UNIVERSIDADE DE BRASÍLIA
FACULDADE DE SAÚDE
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE
TESE DE DOUTORADO

ANA CLAUDIA MORAIS GODOY FIGUEIREDO

ANEMIA MATERNA E PESO AO NASCER

BRASÍLIA, DF
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Tese de doutorado apresentada ao Programa de Pós-Graduação em Ciências da Saúde, Universidade de Brasília, como requisito parcial para obtenção do título de Doutor em Ciências da Saúde.

Área de concentração: Saúde Coletiva

Orientador: Prof. Dr. Maurício Gomes Pereira

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Brasíslia, 23 de fevereiro de 2018.

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BRASÍLIA, DF

2018

*“Às vezes uma pessoa tem capacidade de lidar com o desconhecido, com os mistérios, e isso é **religião**. A **arte** é a capacidade de lidar com a harmonia. A **política** é a capacidade de lidar com a relação entre os seres humanos; e a **ciência** é a capacidade de compreender as leis do universo para que possamos dominá-las e gerar instrumentos, possibilidades de o ser humano lidar melhor com a natureza a fim de melhor aproveitá-la e respeitá-la.*”

Luís Carlos Marques
Nova Acrópole Brasil

Dedico este trabalho às mães, que ao longo da vida cuidam com tanto amor de seus filhos.

AGRADECIMENTOS

À Deus, pela fé que me faz acreditar que o amor é o caminho para um mundo melhor. E à filosofia que me motiva pela busca constante desse caminho.

Aos meus amados pais, Goretti e Godoy, minha fortaleza, e ao meu irmão, Leonardo, por todo carinho ao longo desses anos.

Ao meu marido, José Martins, luz dos olhos meus, por toda paciência, apoio e amor.

Ao meu orientador, professor Maurício, que me guiou com sabedoria durante todo o doutoramento e pela oportunidade do convívio com um renomado epidemiologista.

À querida professora Simone e sua família, por todo carinho e dedicação à minha formação profissional e pessoal ao longo desses 10 anos de amizade.

Ao professor Isaac, pelos conselhos, cuidado, sabedoria e palavras de incentivo durante essa trajetória.

Às participantes da pesquisa original, que foram acolhedoras em um momento singular e delicado de suas vidas.

Ao Núcleo de Epidemiologia e Saúde da Universidade Federal do Recôncavo da Bahia e ao Núcleo de Pesquisa, Prática Integrada e Investigação – NUPPIIM, por todo o apoio logístico para execução da pesquisa original e pelas amizades conquistadas, especialmente à Josicélia e Géssica por toda dedicação.

Aos integrantes do Laboratório de Pesquisas sobre Saúde Baseada em Evidências e Comunicação Científica, pelo aprendizado diário, bem como pelas relações de carinho e amizade construídas. Tenho um agradecimento especial aos estagiários que foram tão colaborativos durante o doutoramento e às amigas de pós-graduação que fizeram esses dias mais leves e felizes.

Aos meus amigos-irmãos que a vida me presenteou: NUFAPOM, pelo amor e respeito que nos permite ser felizes exatamente como somos. Aos demais amigos, que sabem do meu carinho se sintam acolhidos com esse agradecimento.

Às famílias Morais, Ferreira do Vale e Fraga da Costa, por toda torcida e carinho. Amo vocês.

Aos colegas do Hospital Regional de Samambaia e da Gerência de Informação e Análise da Situação de Saúde do Distrito Federal pelo acolhimento e companheirismo durante as etapas do doutorado.

À Fundação de Amparo à Pesquisa do Estado da Bahia (FAPESB) e Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), pelo financiamento da pesquisa original.

À CAPES, pela bolsa de doutorado concedida para o desenvolvimento das atividades propostas.

RESUMO

A anemia é um evento frequente em mulheres que estão no período gestacional devido a alterações fisiológicas provenientes da gravidez, e, possivelmente, fatores causais ainda desconhecidos contribuam para a sua elevada ocorrência durante a gestação, sendo responsável por desfechos indesejáveis, tais como: baixo peso ao nascer, prematuridade e óbito materno-infantil. **OBJETIVO**: Verificar a associação entre anemia materna e peso ao nascer. **MÉTODO: contou com duas partes. Na primeira,** uma Revisão Sistemática foi realizada com estudos de coorte e caso-controle sobre anemia materna e baixo peso ao nascer. Artigos indexados, que atenderam aos critérios de elegibilidade nas principais bases de dados da literatura em saúde foram selecionados. Os descritores utilizados nas estratégias de busca foram: anemia, gestantes, baixo peso ao nascer, estudos de caso-controle e coorte. Não houve limitação de idioma ou de data da publicação. Meta-análises, análises de sensibilidade, subgrupo, meta-regressões e a verificação da existência de viés de publicação foram realizadas. **A segunda parte compreendeu** um estudo de coorte desenvolvido com gestantes que realizavam acompanhamento pré-natal em Unidades de Saúde da Família no município de Santo Antônio de Jesus, na Bahia. As gestantes responderam a um formulário por meio de entrevista para a obtenção de informações socioeconômico-demográficas, relacionadas com estilo de vida e história reprodutiva, e foram classificadas segundo o diagnóstico de anemia materna, valor da hemoglobina menor que 11 g/dl, de acordo com o critério da Organização Mundial de Saúde. Após o parto, essas mulheres foram agrupadas de acordo com o baixo/insuficiente peso ao nascer dos recém-nascidos, menor que 2.999 g. Análise de regressão robusta de Poisson foi realizada para obtenção da medida de associação entre a anemia materna e baixo/insuficiente peso ao nascer, risco relativo e intervalo de confiança, considerando modificadores de efeito e confundidores. **RESULTADOS:** estão apresentados na forma de 3 artigos: 1) Artigo conceitual intitulado: "Anemia materna e anemia ferropriva: suas semelhanças e singularidades", originado da revisão de estudos sobre o tema que abordou aspectos relacionados tanto ao processo de diagnóstico, tratamento e prevenção da anemia durante a gestação quanto à política de combate a anemia materna; 2) Artigo de revisão sistemática que avaliou 71 estudos e concluiu, por meio de meta-análise, que a anemia materna é um forte fator de risco para o baixo peso ao nascer. 3) Artigo intitulado "Anemia materna e baixo peso ao nascer: uma coorte prospectiva" realizada com 622 gestantes e seus recém-nascidos acompanhados até o parto. Os resultados demonstraram

que mães com anemia materna tem maior risco de terem filhos com baixo/insuficiente peso ao nascer que aquelas sem anemia. **CONCLUSÕES:** Os achados obtidos nesta tese indicam que a anemia materna é um evento frequente na população investigada, de ocorrência moderada, bem como é um importante fator de risco para o baixo/insuficiente peso ao nascer, podendo produzir impactos irreversíveis para o binômio materno-infantil e sugerindo a necessidade de medidas de prevenção e controle para a anemia.
Palavras-chave: Anemia; Gestantes; Baixo peso ao nascer; Coorte.

ABSTRACT

Anemia is a common condition amongst pregnant women due to physiological alterations caused by pregnancy. It is possible that still unknown causal factors contribute to the high incidence of anemia during pregnancy. Furthermore, anemia might be responsible for undesirable outcomes such as low birth weight, prematurity, and maternal-infant mortality. **OBJECTIVE:** To verify the association between maternal anemia and birth weight. **METHOD:** It consisted of two parts. **In the first**, a systematic review was conducted with cohort and case-control studies on maternal anemia and low birth weight. Indexed articles, which met the eligibility criteria in the main databases of the health literature were selected. The descriptors used in the search strategies were: anemia, pregnant women, low birth weight, case-control studies and cohort. There was no limitation on language or date of publication. Meta-analyzes, sensitivity, subgroups analyzes, meta-regressions and verification of the existence of publication bias were performed. **The second part comprised** a cohort study developed with pregnant women who underwent prenatal follow-up at Family Health Units in the city of Santo Antônio de Jesus, Bahia. The pregnant women answered a questionnaire through an interview to obtain socioeconomic-demographic information, related to lifestyle and reproductive history. They were classified according to the diagnosis of maternal anemia, hemoglobin value less than 11 g / dl, according to the criteria of the World Health Organization. After delivery, these women were grouped according to the low / insufficient birth weight of the newborns, less than 2,999 g. Robust Poisson regression analysis was performed to obtain the association measurement between maternal anemia and low / insufficient birth weight, relative risk and confidence interval, considering effect modifiers and confounders. **RESULTS:** are presented in the form of three articles. 1) Conceptual article entitled: "Maternal anemia and iron deficiency anemia: their similarities and singularities", originated from the review of studies on the theme that addressed aspects related to both the diagnosis, treatment and prevention process of anemia during pregnancy in relation to the policy to combat maternal anemia. 2) A systematic review paper that evaluated 71 studies and concluded, through meta-analysis, that maternal anemia is a strong risk factor for low birth weight. 3) Article entitled "maternal anemia and low birth weight: a prospective cohort study" conducted with 622 pregnant women and their newborns followed up until delivery. The results showed that mothers with

maternal anemia are at higher risk of having children with low / insufficient birth weight than those without anemia. **CONCLUSIONS:** The findings obtained in this thesis indicate that maternal anemia is a frequent event in the investigated population, of moderate occurrence, as well as being an important risk factor for low / insufficient birth weight. It may produce irreversible impacts to the maternal-infant binomial, which suggests the need for prevention and control measures.
Keywords: Anemia; Pregnant women; Low birth weight; Cohort.

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1 APRESENTAÇÃO

O peso ao nascer pode ser determinado por vários fatores de ordem biológica, socioeconômica e relacionados ao estilo de vida materno. Sabe-se que dois processos fisiológicos podem causar o baixo peso ao nascer: a prematuridade e o retardo do crescimento intrauterino (1). No entanto, embora haja um grande volume de publicações sobre o baixo peso ao nascer na literatura, sua etiologia não é completamente conhecida. Nesse sentindo, investigar possíveis determinantes do baixo peso ao nascer é de suma importância para a Saúde Pública, sendo relevante para produção de ações direcionadas à promoção e prevenção na área da saúde materno-infantil.

A anemia em gestantes, conhecida como anemia materna, é um problema de saúde pública, devido às graves consequências geradas ao binômio mãe-filho (1). A anemia pode produzir desfechos indesejáveis para mãe, a exemplo da mortalidade, e para criança, como prematuridade, retardo do crescimento intrauterino, baixo peso ao nascer e menor concentração de hemoglobina no recém-nascido (2, 3).

Apesar de a anemia durante a gestação ser considerada um dos distúrbios nutricionais mais frequentes no Brasil e no mundo, há um grande esforço das entidades governamentais em buscar o controle desta condição (4). Os estudos existentes ainda são insuficientes para definir seguramente os fatores de risco para anemia (3,5) desse modo, necessitando de métodos mais rigorosos que visem buscar fatores relacionados à ocorrência de anemia materna.

Paralelamente, também são adotadas diversas medidas para diminuição dos indicadores do baixo peso ao nascer. Portanto, é importante compreender o processo saúde-doença-cuidado relacionado à gestação, na tentativa de minimizar situações desfavoráveis à criança. Há estudos que defendem a hipótese de a anemia ser um dos determinantes do baixo peso ao nascer (3, 5). Observa-se, no entanto, que a anemia é um evento frequente em mulheres e passível de controle e prevenção antes, durante e após o período gestacional (4).

Diante do apresentado, considerando-se a escassez de dados robustos, a ausência de dados locais e na perspectiva de se conhecer mais acerca da relação entre anemia em gestantes e peso ao nascer, justifica-se o interesse em abordar o referido tema nesta tese de doutorado.

A presente tese teve como objetivo compreender os efeitos da anemia materna na redução do peso ao nascer. Para tanto, foram desenvolvidos três artigos sobre o tema estudado:

1) Artigo 01 - Anemia materna e anemia ferropriva: suas semelhanças e singularidades. Neste artigo foram abordados aspectos teóricos da anemia, bem como o entendimento da política de combate utilizada rotineiramente para tratar anemia materna, recomendada por instituições internacionais, a exemplo da Organização Mundial de Saúde. O enfoque principal é voltado para a ideia de que anemia ferropriva não é condição *si ne qua non* para definição de anemia materna, mas sim, que existem outros tipos de anemia que podem ocorrer na gravidez. Outro ponto abordado foi à disparidade entre a prevalência de anemia materna e anemia ferropriva na população mundial e a ausência da aplicação do diagnóstico diferencial dos tipos de anemia nos estudos que tratam sobre o tema.

2) Artigo 02 - Anemia materna e baixo/insuficiente peso ao nascer: uma revisão sistemática com meta-análise. Este estudo teve como propósito avaliar sistematicamente a relação da anemia materna e o baixo peso ao nascer em diversas investigações que utilizaram os delineamentos metodológicos de caso-controle e coorte, assim, possibilitando a compreensão da magnitude do evento em todo o mundo. Utilizou-se, para elaboração do artigo, o guia para relatos de revisão sistemática: MOOSE e foi verificado conforme o check list PRISMA (6).

3) Artigo 03 - Anemia materna e baixo/insuficiente peso ao nascer Trata-se de uma coorte realizada com gestantes atendidas em unidades de saúde na cidade de Santo Antônio de Jesus, na Bahia, que teve como objetivo verificar a associação entre anemia em gestantes e o peso ao nascer inferior a 3000 gramas. Este artigo foi produzido conforme o guia para relato de estudos observacionais: STROBE (7). Neste trabalho, serão apresentados resultados relacionados à anemia materna, peso ao nascer e associação entre a exposição e desfecho investigado. Ressalta-se, que essa investigação contou com o apoio do Núcleo de Epidemiologia e Saúde da Universidade Federal do Recôncavo da Bahia (NES-UFRB), coordenado por Professora Simone Seixas da Cruz, o qual obteve financiamento de pesquisa junto a Fundação de Amparo à Pesquisa do Estado da Bahia (FAPESB) e ao Conselho Nacional de Desenvolvimento Científico e Tecnológico– CNPq, bem como do Núcleo de Pesquisa, Prática Integrada e Investigação Multidisciplinar (NUPPIIM) da Universidade Estadual de Feira de Santana (UEFS).

Os três artigos produzidos estão disponíveis respectivamente nas seções 3, 4 e 5 desta tese. Os principais aspectos conceituais sobre a exposição e o desfecho investigados neste trabalho, bem como a relação entre anemia materna e a redução do peso ao nascer.

1.1 ANEMIA MATERNA

Segundo a Organização Mundial de Saúde, a anemia materna é definida como a redução da concentração de hemoglobina em níveis inferiores a 11g/dl e/ou hematócrito inferior a 33%, com ou sem a presença de hemácias normocíticas. No entanto, alguns estudos recomendam que o ponto de corte para dosagem de hemoglobina deveria ser de 10 a 10,5 g/dl (8-12) e que outros critérios diagnósticos, a exemplo da quantidade de hemácias circulantes e dosagem de ferritina, teriam que ser considerados para definição de anemia (13).

A prevalência de anemia materna no mundo é da ordem de 38% (IC95% 33%-43%) (4). Porém, os indicadores ainda são pouco consistentes devido à variabilidade metodológica dos estudos que avaliam esse evento em gestantes. No Brasil, a prevalência oscila entre 30 a 40% nas diferentes regiões (1). Comumente, relaciona-se a anemia materna à anemia ferropriva, uma vez que a deficiência de ferro é considerada uma disfunção hematológica comum em gestantes (14). No entanto, a prevalência da ferropenia, ainda, não é amplamente conhecida na literatura (15). Estima-se que 5% do PIB de países em desenvolvimento é utilizado para combater a anemia por deficiência de ferro, ainda que não se conheça claramente a ocorrência desse evento na população. No Brasil, isso representa mais de cem bilhões de reais por ano (16).

Disfunções hematológicas, especialmente as anemias, podem produzir efeitos deletérios para as mães e os recém-nascidos. No grupo materno, favorece quadros de eclâmpsia, depressão, estresse, fadiga e tontura. Para a criança, pode acarretar mortalidade perinatal, diminuição da hemoconcentração, distúrbios cognitivos e psicomotores, bem como restrição do crescimento intrauterino, prematuridade e baixo peso ao nascer (17, 18)**.**

1.2 PESO AO NASCER

O baixo peso ao nascer (BPN) pode ser definido como aquele inferior a 2.500 gramas, para o peso insuficiente o ponto de corte é entre 2500 e 2999 gramas (19). O peso

reduzido do recém-nascido é considerado um importante preditor da morbimortalidade infantil. Estima-se que o risco de uma criança com baixo peso vir a óbito é 20 vezes maior em relação ao recém-nascido de peso normal (20, 21).

A ocorrência global de baixo peso ao nascer é 15% (22). Esse indicador tem uma tendência a ser maior nos países com situação econômica desfavorável, como Índia (33%) e Bangladesh (50%). Em países europeus as estimativas do BPN são em torno de 4 a 5% (23). No Brasil, aproximadamente, 8% das crianças nascem com peso inferior a 2.500g (24). Relatos sobre a distribuição do peso insuficiente no mundo são escassos.

A causalidade da redução do peso ao nascer ainda não é plenamente conhecida. No entanto, diferentes fatores têm sido indicados como relevantes na sua determinação, a saber: a prematuridade (idade gestacional < 37 semanas) e o crescimento intrauterino restrito, também conhecido como desnutrição fetal, que ocorre quando a criança nasce com peso abaixo do valor-limite para a sua idade gestacional (25). O peso ao nascer reduzido favorece o desenvolvimento de eventos indesejáveis para os recém-nascidos, a saber: infecções, disfunções no trato respiratório e intestinal, obesidade, doenças cardiovasculares, diabetes, síndrome metabólica e paralisia cerebral (25, 26).

1.3 RELAÇÃO ENTRE ANEMIA MATERNA E PESO AO NASCER

A anemia materna predispõe o recém-nascido à prematuridade e à restrição do crescimento intrauterino, consequentemente pode influenciar no peso insuficiente ou baixo peso ao nascer (27). Fisiologicamente, a mulher no período gravídico, a partir da metade do segundo trimestre, produz em média de 30 a 40 ml de plasma por kilograma que corresponde a hipovolemia. Porém, quando paralelamente a esse processo não ocorre o aumento da quantidade de células hematológicas, resulta-se na hemodiluição e possivelmente na anemia materna (28).

Desse modo, níveis baixos de hemoglobina e ferro estimulam alterações no processo de angiogênese placentária e favorecem a diminuição de oxigênio disponível para o feto. O resultado consiste na hipóxia fetal e restrição do crescimento uterino(29). A depleção de hemoglobina no parto prematuro age no aumento da produção de células inflamatórias, como fator de necrose tumoral - alfa (TNF-α), interleucina-1 (IL-1) e interleucina-6 (IL-6) e diminuição da IL-10, responsáveis pelo início do trabalho de parto (30)

Outra linha de atuação da deficiência de ferro é por meio de um peptídeo. A hepcidina tem o papel de regular a homeostase de ferro no sangue materno, atuando também no sistema imune, uma vez que a IL-6 é responsável pela regulação desse hormônio (31). A IL-6 estimula as células hepáticas a metabolizarem proteínas inflamatórias que interferem na captação de ferro e por consequência diminui a produção de eritrócitos (32-34). Desse modo, com o aumento da hepcidina ocorre diminuição dos níveis de ferro na circulação favorecendo o desenvolvimento da hipóxia e prematuridade (32, 30).

Concomitantemente, valores de hemoglobina acima de 13g/dl também podem produzir efeitos deletérios para o grupo materno-fetal. Mulheres grávidas que utilizam a suplementação de ferro excessiva podem ter aumento da hemoconcentração no momento do parto (35, 36) e tal evento eleva a chance de hipertensão, trombose, restrição do crescimento uterino, prematuridade e nascimento de crianças com insuficiente/baixo peso ao nascer (35, 37).

1.4 REFERÊNCIAS

1. Batista Filho M, Souza AI, Bresani CC. Anemia como problema de saúde pública: uma realidade atual. Ciência & Saúde Coletiva. 2008;13:1917-22.

2. Allen LH. Biological mechanisms that might underlie iron's effects on fetal growth and preterm birth. J Nutr. 2001;131(2S-2):581S-9S.

3. Peña-Rosas JP, De-Regil LM, Dowswell T, Viteri FE. Daily oral iron supplementation during pregnancy. Cochrane Database Syst Rev. 2012;12:CD004736.

4. WHO. The global prevalence of anaemia in 2011. Geneva: World Health Organization; 2015.

5. Peña-Rosas JP, De-Regil LM, Garcia-Casal MN, Dowswell T. Daily oral iron supplementation during pregnancy. Cochrane Database Syst Rev. 2015(7):CD004736.

6. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.

7. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007;335(7624):806-8.

8. Bresani CC, Souza AId, Batista-Filho M, Figueiroa JN. Anemia e ferropenia em gestantes: dissensos de resultados de um estudo transversal. Rev Bras Saúde Matern Infant. 2007;Supl.1:S15-S22.

9. Milman N, Byg KE, Agger AO. Hemoglobin and erythrocyte indices during normal pregnancy and postpartum in 206 women with and without iron supplementation. Acta Obstet Gynecol Scand. 2000;79(2):89-98.

10. Yip R. Significance of an abnormally low or high hemoglobin concentration during pregnancy: special consideration of iron nutrition. Am J Clin Nutr. 2000;72(1 Suppl):272S-9S.

11. Centers for Disease Control and Prevention. CDC criteria for anemia in children and childbearing-aged women. MMWR Morb Mortal Wkly Rep. 1989;38(22):400-4.

12. Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States. Centers for Disease Control and Prevention. MMWR Recomm Rep. 1998;47(RR-3):1-29.

13. Matos JF, Dusse LMSA, Gomes KBG, Stubert RVB, Ferreira MdFR, Moreira RCNM, et al. O hemograma nas anemias microcíticas e hipocrômicas: aspectos diferenciais. J Bras Patol Med Lab. 2012;48(4):255-8.

14. Uchimura TT, Szarfarc SC, Latorre MR, Uchimura NS, de Souza SB. [Anemia and birthweight]. Rev Saude Publica. 2003;37(4):397-403.

15. Souza AId, Batista-Filho M. Diagnóstico e tratamento das anemias carências na gestação: consensos e controvérsias. Rev Bras Saúde Matern Infant. 2003;3(473-479).

16. Barros FC, Victora CG, Horta BL. Ethnicity and infant health in Southern Brazil. A birth cohort study. International Journal of Epidemiology. 2001;30(5):1001-8.

17. Brasil. PORTARIA Nº 1247, DE 10 DE NOVEMBRO DE 2014. In: Saúde Md, editor. Brasília2014.

18. Rahman MM, Abe SK, Rahman MS, Kanda M, Narita S, Bilano V, et al. Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: systematic review and meta-analysis. Am J Clin Nutr. 2016;103(2):495-504.

19. World Health Organization. Meeting of Advisory Group on Maternal Nutrition and Low Birthweight; Geneva: World Health Organization; 2002.

20. Moraes AB, Zanini RR, Giugliani ER, Riboldi J. [Trends in the proportion of low birth weight from 1994 to 2004 in Rio Grande do Sul State, Brazil: a multilevel analysis]. Cad Saude Publica. 2011;27(2):229-40.

21. Nascimento LF, Costa TM, Zöllner MS. Spatial distribution of low birthweight infants in Taubaté, São Paulo, Brazil. Rev Paul Pediatr. 2013;31(4):466-72.

22. UNICEF. Low Birthweight: Country,regional and global estimates. New York: UNICEF; 2004.

23. UNICEF. The state of the world´s children 2000. New York: UNICEF; 2000.

24. Brasil. Ministério da Saúde. DATASUS. Informações relacionadas à saúde: indicadores de saúde (nascidos vivos), 2015. 2015 [Available from: http://tabnet.datasus.gov.br/cgi/idb2015/c01.htm.

25. Viana KeJ, Taddei JA, Cocetti M, Warkentin S. [Birth weight in Brazilian children under two years of age]. Cad Saude Publica. 2013;29(2):349-56.

26. Silvestrin S, Silva CH, Hirakata VN, Goldani AA, Silveira PP, Goldani MZ. Maternal education level and low birth weight: a meta-analysis. J Pediatr (Rio J). 2013;89(4):339-45.

27. Harrison KA, Ibeziako PA. Maternal anaemia and fetal birthweight. J Obstet Gynaecol Br Commonw. 1973;80(9):798-804.

28. Hutter D, Kingdom J, Jaeggi E. Causes and mechanisms of intrauterine hypoxia and its impact on the fetal cardiovascular system: a review. Int J Pediatr. 2010;2010:401323.

29. Stangret A, Wnuk A, Szewczyk G, Pyzlak M, Szukiewicz D. Maternal hemoglobin concentration and hematocrit values may affect fetus development by influencing placental angiogenesis. J Matern Fetal Neonatal Med. 2016:1-6.

30. Dória MT, Spautz CC. Trabalho de parto prematuro: predição e prevenção Femina. 2011;39(9):443-49.

31. Grotto HZ. Anaemia of cancer: an overview of mechanisms involved in its pathogenesis. Med Oncol. 2008;25(1):12-21.

32. De Domenico I, Vaughn MB, Paradkar PN, Lo E, Ward DM, Kaplan J. Decoupling ferritin synthesis from free cytosolic iron results in ferritin secretion. Cell Metab. 2011;13(1):57-67.

33. De Domenico I, Zhang TY, Koening CL, Branch RW, London N, Lo E, et al. Hepcidin mediates transcriptional changes that modulate acute cytokine-induced inflammatory responses in mice. J Clin Invest. 2010;120(7):2395-405.

34. De Domenico I, Kaplan J. A new wrinkle in the fold: hepcidin links inflammation to the unfolded protein response. Cell Metab. 2009;10(4):245-6.

35. Aranda N, Ribot B, Viteri F, Cavallé P, Arija V. Predictors of haemoconcentration at delivery: association with low birth weight. Eur J Nutr. 2013;52(6):1631-9.

36. Arija V, Ribot B, Aranda N. Prevalence of iron deficiency states and risk of haemoconcentration during pregnancy according to initial iron stores and iron supplementation. Public Health Nutr. 2013;16(8):1371-8.

37. Peña-Rosas JP, Viteri FE. Effects and safety of preventive oral iron or iron+folic acid supplementation for women during pregnancy. Cochrane Database Syst Rev. 2009(4):CD004736.

2 OBJETIVOS

– Analisar a relação da anemia materna e baixo/insuficiente peso ao nascer, por meio de revisão sistemática e estudo original;

– Mensurar a frequência de anemia materna e do baixo/insuficiente peso ao nascer na cidade de Santo Antônio de Jesus nos anos de 2013 a 2017;

– Caracterizar a amostra investigada em relação aos aspectos sociodemográficos, gestacionais e reprodutivos.

3 ARTIGO: MATERNAL ANEMIA AND IRON DEFICIENCY ANEMIA: SIMILARITIES AND SINGULARITIES

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 as well as the policies addressing it will be presented. In addition, iron deficiency anemia will be considered a proxy for maternal anemia. In previous studies, the concepts of maternal anemia and iron supplementation during pregnancy 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.

3.1 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 (5, 13-15), other studies show that the frequency of iron deficiency is lower when diagnosed using both hemoglobin and ferritin levels (6, 7, 16) . Therefore, there is no consensus that maternal anemia has a frequency similar to that of iron deficiency anemia (5-7, 13-17)

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.

3.2 MATERIAL 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 language 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 descripted and summarized in figures.

3.3 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 (18, 21) 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). 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).

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 (1), regardless of the gestational trimester or type of anemia, which differs from those of previous investigations (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 (25, 28) or two or less standard deviations from the mean of hemoglobin and/or hematocrit (26).

Iron deficiency anemia is characterized by ferritin levels of less than 15 femtoliters 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, (15) the global frequency of iron deficiency anemia in pregnant women was 19.2% (95% CI: 17.1% - 21.5%). 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 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).

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 (48) and, that in the absence of laboratory tests that allow for differential diagnosis, the women would be diagnosed with iron deficiency anemia (1). 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 (4), this would entail a health cost

of approximately 50% more than necessary (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 (49), requiring confirmation by the level of ferritin (<15 femtoliters) for diagnosis (50, 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 disagree 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, 53) than studies that used only hemoglobin levels (5, 13–15).

The WHO maternal anemia criteria are considered inappropriate by some authors (2, 4, 6, 7, 21), when there is the intention to estimate iron deficiency anemia. 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).

3.4 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.

3.5 REFERENCES

1. World Health Organization (2015). The global prevalence of anaemia in 2011. Geneva: World Health Organization. 48 p.

2. Batista-Filho M, Souza AI, Bresani CC. Anemia as a public health problem: the current situation (2008). Ciênc. Saúde coletiva. 13:1917-22. doi: 10.1590/S1413-81232008000600027

3. UNICEF (1990). Strategy for improved nutrition of children and women in developing countries. New York: UNICEF. 38p.

4. Bresani CC, Souza AI, Batista-Filho M et al (2007). Anemia and iron deficiency in pregnant women: disagreements among the results of a cross-sectional study. Rev Bras Saúde Matern Infant. 7:S15-S21. doi: 10.1590/S1519-38292007000600002

5. Banjari I, Kenjerić D, Mandić ML (2015). What Is the Real Public Health Significance of Iron Deficiency and Iron Deficiency Anaemia in Croatia? A Population-Based Observational Study on Pregnant Women at Early Pregnancy from Eastern Croatia. Cent Eur J Public Health. 23:98-103. doi: 10.21101/cejph.a3962

6. Vandevijvere S, Amsalkhir S, Van Oyen H et al (2013). Iron status and its determinants in a nationally representative sample of pregnant women. J Acad Nutr Diet. 113:659-66. doi: 10.1016/j.jand.2012.10.021

7. Bencaiova G, Breymann C (2014). Mild anemia and pregnancy outcome in a Swiss collective. J Pregnancy. 2014:1-7. doi: 10.1155/2014/307535

8. Barroso F, Allard S, Kahan BC et al (2011). Prevalence of maternal anaemia and its predictors: a multi-centre study. Eur J Obstet Gynecol Reprod Biol.159: 99-105. doi: 10.1016/j.ejogrb.2011.07.041

9. Eisele L, Dürig J, Broecker-Preuss M et al (2013). Prevalence and incidence of anemia in the German Heinz Nixdorf Recall Study. Ann Hematol. 92:731-7. doi: 10.1007/s00277-013-1697-1

10. Harvey T, Zkik A, Auges M et al (2016). Assessment of iron deficiency and anemia in pregnant women: an observational French study. Womens Health (Lond). 12:95-102. doi: 10.2217/whe.15.91.

11. Jwa SC, Fujiwara T, Yamanobe Y et al (2015). Changes in maternal hemoglobin during pregnancy and birth outcomes. BMC Pregnancy Childbirth. 15:80. doi: 10.1186/s12884-015-0516-1

12. Lopez A, Cacoub P, Macdougall IC et al (2016). Iron deficiency anaemia. Lancet. 387:907-16. doi: 10.1016/S0140-6736(15)60865-0

13. Casanova BF, Sammel MD, Macones GA (2005). Development of a clinical prediction rule for iron deficiency anemia in pregnancy. Am J Obstet Gynecol. 193:460-6. doi: 10.1016/j.ajog.2004.12.008

14. Aikawa R, Ngyen CK, Sasaki S et al (2006). Risk factors for iron-deficiency anaemia among pregnant women living in rural Vietnam. Public Health Nutr. 9:443-8.

15. Black RE, Victora CG, Walker SP et al (2013). Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet. 82:427-51. doi: 10.1016/S0140-6736(13)60937-X

16. Menon KC, Ferguson EL, Thomson CD et al (2016). Effects of anemia at different stages of gestation on infant outcomes. Nutrition. 32:61-5. doi: 10.1016/j.nut.2015.07.009

17. Donovan A, Roy C, Andrews N (2006). The ins and outs of iron homeostasis. Physiology. 21:115-23. doi: 10.1152/physiol.00052.2005

18. Taylor DJ, Mallen C, McDougall N et al (1982). Effect of iron supplementation on serum ferritin levels during and after pregnancy. B J Obstet Ginecol. 89:1011-1017.

19. Tapia ME (2010). Prevalência de anemia nas gestantes atendidas no Sistema Unico de Saúde – Secretaria Municipal de Saúde – Prefeitura de Belo Horizonte. Rev. bras. anal. clin. 42: 277-81.

20. Souza AI, Batista-Filho M (2003). Dianosis and treatment of nutritional anemia in pregnancy: consensus and controversies. Rev Bras Saúde Matern Infant. 3:473-479. doi: 10.1590/S1519-38292003000400012.

21 Bresani CC, Braga MC, Felisberto DF et al (2013). Accuracy of erythrogram and serum ferritin for the maternal anemia diagnosis (AMA): a phase 3 diagnostic study on prediction of the therapeutic responsiveness to oral iron in pregnancy. BMC Pregnancy Childbirth. 13:13. doi: 10.1186/1471-2393-13-13.

22. World Health Organization (2003). The clinical use of blood in medicine obstetrics, paediatrics surgery and anaesthesia and trauma and burns. Geneva: World Health Organization. 344. p.

23. Cançado RD, Chiattone CS. Anemia of chronic disease (2002). Rev Bras de Hematol e Hemot. 24:127-36. doi: 10.1590/S1516-84842002000200009

24. Hoffbrand A, Pettit F, Moss P. Essential Haematology. 5 ed. Oxford (UK): Blackwell Publishing; 2006.

25. Milman N, Byg KE, Agger AO (2000). Hemoglobin and erythrocyte indices during normal pregnancy and postpartum in 206 women with and without iron supplementation. Acta Obstet Gynecol Scand. 79: 89-98.

26. Yip R (2000). Significance of an abnormally low or high hemoglobin concentration during pregnancy: special consideration of iron nutrition. Am J Clin Nutr. 72: 272S-9S.

27. Centers for Disease Control and Prevention (CDC) (1989). CDC criteria for anemia in children and childbearing-aged women. MMWR Morb Mortal Wkly Rep. 38 :400-4.

28. Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States (1998). Centers for Disease Control and Prevention. MMWR Recomm Rep. 47:1-36.

29. Peña-Rosas JP, De-Regil LM, Dowswell T et al (2012). Daily oral iron supplementation during pregnancy. Cochrane Database Syst Rev. 12:CD004736. doi: 10.1002/14651858.CD004736

30. Weiss G, Goodnough LT (2005). Anemia of chronic disease. N Engl J Med. 352:1011-23. doi: 10.1056/NEJMra041809

31. Gessner BD. Geographic and racial patterns of anemia prevalence among low-income Alaskan children and pregnant or postpartum women limit potential etiologies (2009). J Pediatr Gastroenterol Nutr. 48:475-81. doi: 10.1097/MPG.0b013e3181888fac

32. Montoya-Romero Jde, Castelazo-Morales E, Valerio-Castro, et al (2012). Review by expert group in the diagnosis and treatment of anemia in pregnant women. Federación Mexicana de Colegios de Obstetricia y Ginecología. Ginecol Obstet Mex. 80 9:563-80.

33. Pita GM, Jiménez S, Basabe B et al (2014). Anemia in children under five years old in Eastern Cuba, 2005-2011. MEDICC Rev. 16:16-23.

34. Munares-García O, Gómez-Guizado G, Barboza-Del Carpio J et al (2012). Hemoglobin levels in pregnant women seen in health care centers of the Peruvian Ministry of Health, 2011. Rev Peru Med Exp Salud Publica. 29:329-36. doi: 10.1590/S1726-46342012000300006

35. Adanikin AI, Awoleke JO, Olofinbiyi BA et al (2015). Routine Iron Supplementation and Anaemia by Third Trimester in a Nigerian Hospital. Ethiop J Health Sci. 25: 305-12.

36. Demmouche A, Lazrag A, Moulessehoul S (2011). Prevalence of anaemia in pregnant women during the last trimester: consequense for birth weight. Eur Rev Med Pharmacol Sci. 15: 436-45.

37. Smithers LG, Gialamas A, Scheil W et al (2014). Anaemia of pregnancy, perinatal outcomes and children's developmental vulnerability: a whole-of-population study. Paediatr Perinat Epidemiol. 28:381-90. doi: 10.1111/ppe.12149

38. Tuinakelo LR, Tayler-Smith K, Khogali M et al (2013). Prevalence of anaemia, syphilis and hepatitis B in pregnant women in Nausori, Fiji. Public Health Action. 3:72-5. doi: 10.5588/pha.12.0069

39. Calje E, Skinner J (2017). The challenge of defining and treating anemia and iron deficiency in pregnancy: A study of New Zealand midwives' management of iron status in pregnancy and the postpartum period. Birth. 44:181-90. doi: 10.1111/birt.12282.

40. Martí-Carvajal A, Peña-Martí G, Comunian G, Muñoz S, E et al (2002). Prevalence of anemia during pregnancy: results of Valencia (Venezuela) anemia during pregnancy study. Arch Latinoam Nutr. 52 1:5-11.

41. Hyder SM, Persson LA, Chowdhury M et al (2004). Anaemia and iron deficiency during pregnancy in rural Bangladesh. Public Health Nutr. 7:1065-70. doi: 10.1079/PHN2004645

42. Toteja GS, Singh P, Dhillon BS et al (2006). Prevalence of anemia among pregnant women and adolescent girls in 16 districts of India. Food Nutr Bull. 27:311-5. doi: 10.1177/156482650602700405

43. Treister-Goltzman Y, Peleg R, Biderman A (2015). Anemia among Muslim Bedouin and Jewish women of childbearing age in Southern Israel. Ann Hematol. 94:1777-84. doi: 10.1007/s00277-015-2459-z

44. Pinho-Pompeu M, Surita FG, Pastore DA et al (2017). Anemia in pregnant adolescents: impact of treatment on perinatal outcomes. J Matern Fetal Neonatal Med. 30: 1158-62. doi: 10.1080/14767058.2016.1205032

45. Massucheti LM, Corso ACTC, Moreira EAM (2009). Prevalence of anemia in pregnant women assisted in public health services in Florianópolis municipalty (SC). Cad Saúde Colet. 10:427-32.

46. Smagulova IE, Sharmanov TSh, Balgimekov SA (2013). The prevalence of anemia among children and women of reproductive age in Kazakhstan and basis of its prevention. Vopr Pitan. 82:58-63.

47. World Health Organization (2016) World Health Organization recommendations on antenatal carefor a positive pregnancy experience. Geneva: World Health Organization. 172 p.

48. Qi L, Van Dam RM, Rexrode K et al (2007). Heme iron from diet as a risk factor for coronary heart disease in women with type 2 diabetes. Diabetes Care. 30:101-6.

49. Matos JF, Dusse LMSA, Gomes KBG et al. Blood tests in microcytic and hypochromic anemias: differential aspects (2012). J Bras Patol Med Lab. 48:255-8. doi: 10.1590/S1676-24442012000400004

50. Milman N (2011). Iron in pregnancy: How do we secure an appropriate iron status in the mother and child? Ann Nutr Metab. 59:50-4. doi: 10.1159/000332129

51. Portaria nº 1247, de 10 de novembro de 2014. Brasília: Ministério da Saúde, Brasil; 2014. 18 p.

52. U.S. Preventive Services Task Force (2013). Screening for Iron Deficiency Anemia--Including Iron Supplementation for Children and Pregnant Women. United States: U.S. Preventive Services Task Force. 4 p.

FIGURES

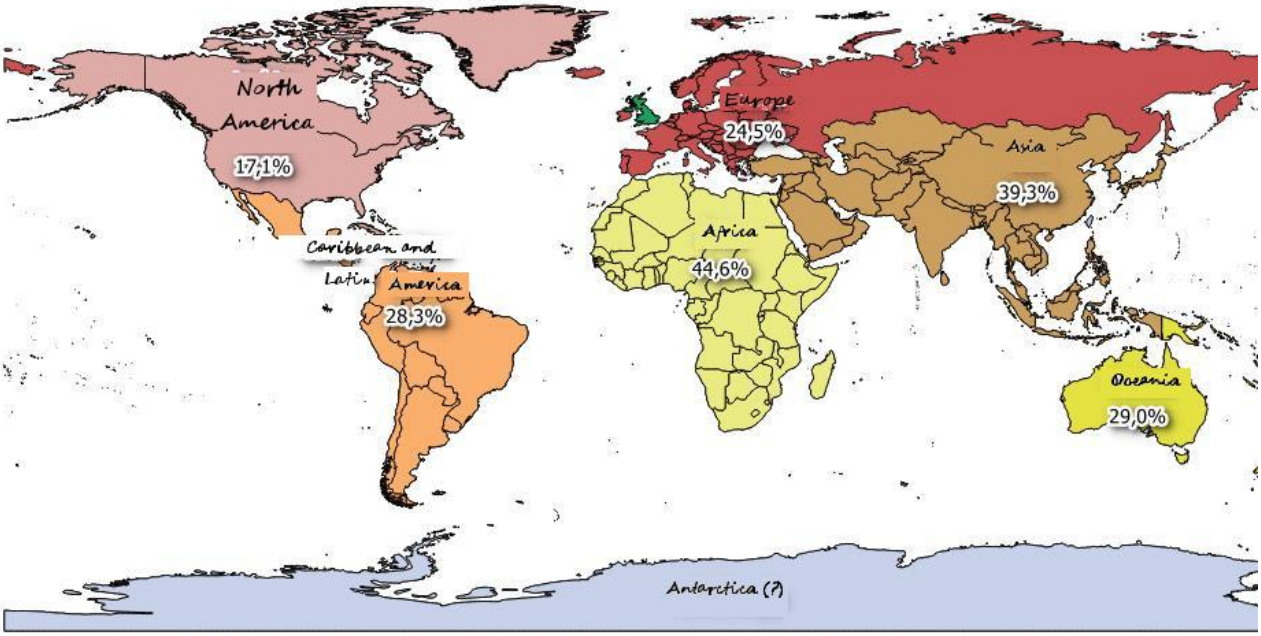

Figure 1. Prevalence of maternal anemia worldwide, 2011. Source: World Health Organization, 2015 (1).

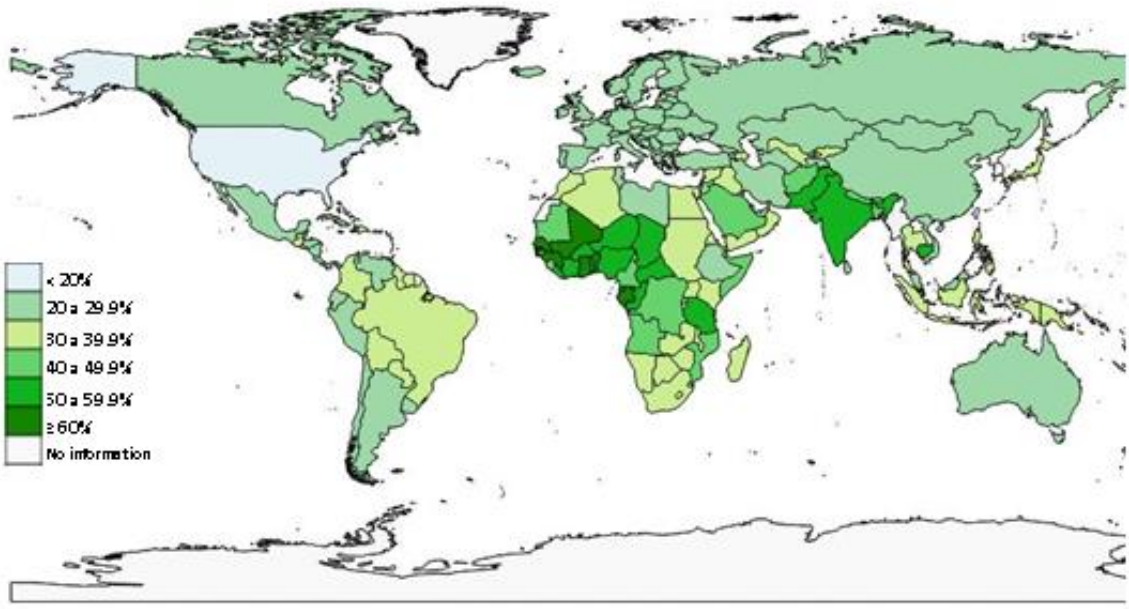

Figure 2. Prevalence of maternal anemia worldwide according to occurrence levels, 2011. Source: World Health Organization, 2015(1).

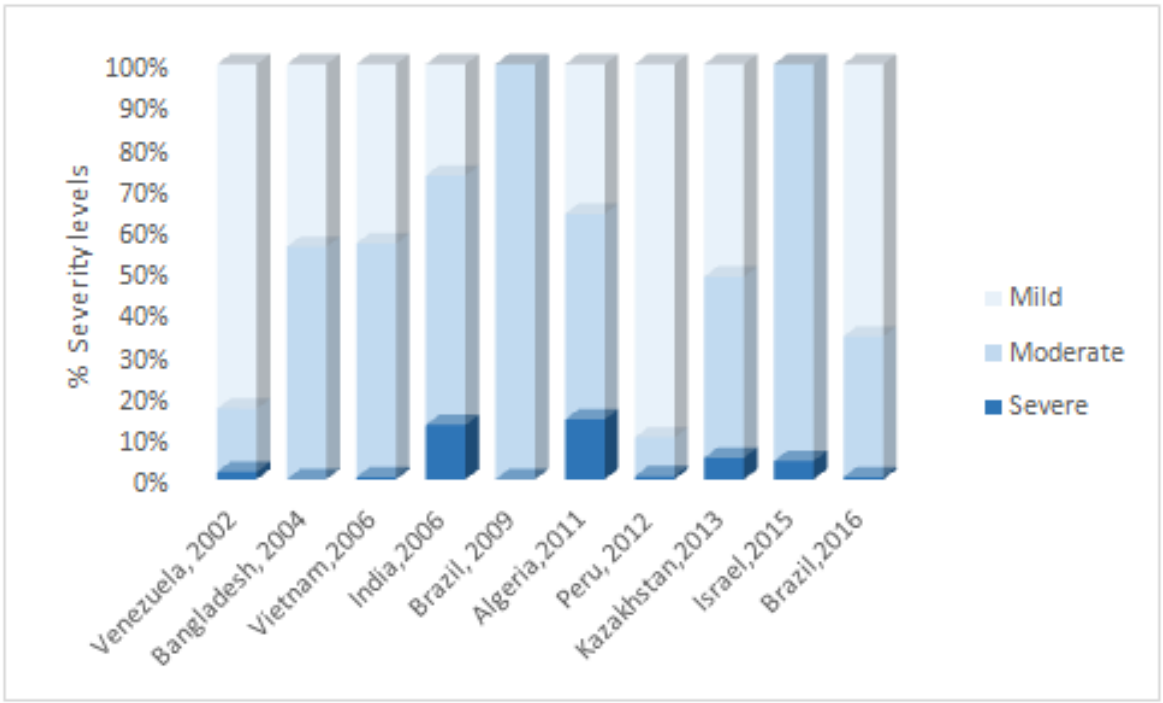

Figure 3. Diagnosis of maternal anemia in different countries by severity,with their respective percentages (14, 39, 41, 44, 48-53).

4 ARTIGO: MATERNAL ANEMIA AND LOW BIRTH WEIGHT: A SYSTEMATIC REVIEW AND META-ANALYSIS.

ABSTRACT

Objective: To systematically analyze the relationship between maternal anemia and low birth weight. Methods: A search of studies was conducted in the main databases (Medline, Embase, Scopus, Web of Science, SciELO and Lilacs), the gray literature and the reference lists of selected articles. Cohort and case-control studies that met the eligibility criteria were included in the review. There was no limitation on the language or date of publication. Article selection and data extraction were performed by two independent reviewers. Meta-analyzes with random effects, subgroup analyses and meta-regressions were performed. Publication bias was measured using Egger regression and visual funnel plot inspection. Results: A total of 7243 articles were found, of which 71 comprised the systematic review and 68 were included in the meta-analyses. Maternal anemia was associated with low birth weight with an adjusted OR: 1.23 (95% CI: 1.06-1.43) and I2: 58%. The meta-regressions confirmed that the sample size and the methodological quality may partially explain the statistical heterogeneity. Conclusion: Maternal anemia was considered a risk factor for low birth weight.

Keywords: Anemia; Pregnancy; Low birth weight; Cohort study; Systematic review

4.1 INTRODUCTION

Worldwide, approximately 7-15% of all live births each year are of low birth weight, a gestational outcome that is considered a major public health problem and is more prevalent in countries with fewer financial resources (1).

Children born weighing less than 2,500 grams are more prone to infant morbidity and mortality (2, 3). Inadequate biological, social, economic, environmental and lifestyle factors, either prior to or during pregnancy, may favor low birth weight (2, 4, 5). Some nutritional aspects, such as a low nutritional diet and inadequate weight gain during pregnancy, contribute to a lower intake of the nutrients considered important for fetal growth, such as B vitamins and iron (6).

Ionic iron is the mineral that promotes the formation of new hemoglobin and is the main source of energy and oxygen transportation to the organs of the body (6). Maternal anemia can develop due to both the unavailability of this element in the extracellular environment for erythropoiesis and the presence of infectious processes, which may influence the metabolism of new hemoglobin (7). In general, the diagnosis of maternal anemia is defined by hemoglobin levels below 11 g / dl (8-10).

Reduced levels of hemoglobin favor changes in placental angiogenesis, limiting the availability of oxygen to the fetus and, consequently, causing potential restriction of intrauterine growth and low birth weight (11). Pregnant women with hemoglobin levels below 11 g / dl are at higher risk of having low birth weight children compared with women who do not have anemia during pregnancy (12).

The most recent data for overall prevalence of maternal anemia, estimated in 2011, was 38.2%. The event occurs throughout the world, and only in North America is its prevalence less than 20%. The prevalence of maternal anemia is distributed among the continents as follows: Europe (24.5%), Latin America and the Caribbean (28.3%), Oceania (29%), Asia (39.3%) and Africa (44.6%) (8). Due to the worldwide occurrence of this disease, maternal anemia demands attention, not only because it affects the health condition of the mother but also because it is related to undesirable gestational outcomes (8).

Despite the need to investigate maternal anemia and low birth weight, there are few robust reviews that include women from diverse countries and socioeconomic conditions. Only one systematic review was found, and it was limited to cohort studies developed up to 2014 and evaluated various gestational outcomes in women residing in low- and middle-income countries (12). Another systematic review on maternal anemia and gestational outcomes published in 2013 was identified; it used both cohort and case-control investigations conducted up to 2010 (13). In addition, other systematic reviews, published in 2012 and 2015, proposed to evaluate the impact of iron sulfate supplementation on low birth weight (14-16).

In view of the scarcity of recent review studies regarding the association between maternal anemia and low birth weight that include information from different continents, this article aimed to systematically assess the relationship between maternal anemia and low birth weight through cohort and case-control studies carried out in several countries around the world.

4.2 METHODS

Registration and protocol

A search for systematic reviews on the subject was conducted in the International Prospective Register of Systematic Reviews (PROSPERO) database, and no records were found. The systematic review was registered in PROSPERO under protocol number CRD42017069451.

Eligibility criteria for the studies

The eligibility criteria consisted of cohort and case-control studies assessing the relationship between maternal anemia (hemoglobin levels <11 g / dl) and low birth weight (< 2500 g). Investigations involving women diagnosed with anemia of a genetic origin or with self-reported exposure or outcomes were excluded. There was no restriction on the date of publication or the language used.

Information sources

The search for information was performed up to January 15, 2018. The electronic databases used were Medline, Embase, Scopus, Web of Science, SciELO and Lilacs. The reference lists of the articles selected for the systematic review were examined to locate citations of references. Additionally, abstracts from congresses and specific databases containing gray literature texts that met the eligibility criteria established in this review were examined.

Search strategies

The descriptors used and their synonyms were identified in the Medical Subject Headings (MeSH). The uniterms and Boolean operators in English used in the search strategies were (anemia OR anaemia OR haemoglobin OR hemoglobin OR haematocrit OR hematocrit) AND (Pregnancy OR Pregnant women OR Gravidity OR Maternal exposure OR Mother OR Pregnant OR Gravid OR Obstetric OR Antenatal OR Antepartum OR Gestation) AND (Infant, Low birth weight) AND (Case-control studies

OR Retrospective studies OR Case-control study OR Study, Case-control OR Studies, case-control OR Case-comparison studies OR 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 OR Case control OR Meta-analysis). The search strategy was adapted for the other electronic databases used (Apêndice A).

Studies selection

Two reviewers (ACMGF and PPSP) selected articles by reading titles and abstracts. During the article selection process, the researchers were not aware of the decisions one another made. After this phase, two researchers (ACMGF and RBS) independently read the full text of the previously selected articles. Articles that met the eligibility criteria were included in the systematic review. In cases where there was divergence between the researchers, the inclusion or exclusion of the articles was decided by consensus (ACMGF, PPSP and RBS).

Extraction of data

Data were extracted from the included articles by two independent researchers (ACMGF and RBS) and subsequently confronted. The data were entered into an electronic form in Excel containing the following fields: author's name, year of publication, place and year of study, objective, study design, sample size, data collection location, data source, criteria for anemia diagnosis, frequency of maternal anemia, percentage of low birth weight infants, association measurements and confidence intervals, and confounding covariables. When the data were not available in the articles, the authors of the studies were contacted.

Evaluation of study quality

The quality of the selected studies was assessed using the Newcastle-Ottawa instrument (17) recommended by the Cochrane Collaboration for cohort and case-control observational studies. It consists of eight questions composed of three axes: study selection, comparability and verification of exposure and outcome investigated. This

instrument has a classification system in which an article receives stars for each criterion met (Additional file 2). The categories of quality classification for studies are 1) low quality - when the article receives up to 3 stars, 2) moderate quality - from 4 to 6 stars, and 3) high quality - from 7 to 9 stars.

Data analysis

A statistical description of the studies and the results related to maternal anemia and low birth weight was performed. Statistical heterogeneity was measured using the chi-square test ($p < 0.10$) and the Higgins and Thompson I-square (I2), and the magnitude of the inconsistency was evaluated (18). I2 values above 50% were considered high, values of 25% to 50% were considered moderate, and values less than 25% were considered low (18).

The summary of exposure and outcome frequency was calculated with 95% confidence intervals using the Freeman-Tukey double arcsine transformation technique (19). The DerSimonian-Laird method was used for the random-effects meta-analysis to obtain the global association measurement, odds ratios and 95% confidence intervals (18). When the cohort study findings were shown to have relative risk, this association measurement was converted to an odds ratio according to criteria defined by Zhang (20). To evaluate the mean difference in birth weight, the nonstandard technique was used in the meta-analysis of random effects.

Publication bias was analyzed using Begg's funnel plot and Egger regression with a significance level of 5% (18). The trim-and-fill test was performed to identify the possible effects of the absence of studies related to the summary association measurement in the meta-analysis.

Sensitivity analysis, subgroup analyses and meta-regressions were also performed to verify the source of heterogeneity in the studies used in the systematic review. In the subgroup analyses and meta-regressions, the following covariables were used: study design (prospective cohort, retrospective cohort, case-control), data collection location (hospital, primary health units, community), differential diagnosis of maternal anemia (maternal anemia, iron deficiency anemia), hemoglobin levels (< 11 g / dl; < 10.6 g / dl; <10 g / dl; <8 g / dl), severity levels of maternal anemia as classified in the study (mild, moderate, severe), gestational trimester when maternal anemia was diagnosed (first, second, third), magnitude of the association measurement (< 2; ≥ 2), Human

Development Index (very high, high, medium, low), geographic region (America, Africa, Asia, Europe, Oceania), sample size (<1000; ≥ 1000) and the year the research was initiated (<1990, 1990-2000, 2001-2010, 2011-2017). Data analysis was performed using the statistical package STATA® version 15.

4.3 RESULTS

Selected studies

From the database searches, 7243 records were identified. After duplicates were removed and titles and abstracts were read, 534 articles were selected for full reading. Only 71 texts met the eligibility criteria of this systematic review (Figure 1). The publication period for the evaluated investigations was from 1986 to 2017.

General characteristics and quality of studies

The population included in this review consisted of 916,990 pregnant women with a mean age of 26 years. Of the total number of selected studies, 54 cohort studies and 17 case-control studies (Table 1) were identified. Much of the research was conducted between 2000 and 2010 in Asian countries with a high Human Development Index, and in a hospital environment.

The definition of maternal anemia used in most studies was hemoglobin levels below 11 g / dl, and more than half of the studies collected this information from medical records. Only 20 studies included information regarding the severity of maternal anemia, and of the six studies that diagnosed pregnant women with iron deficiency anemia, only three reported the ferritin level to confirm the differential diagnosis. The methodological quality of the studies was considered moderate (mean: 6.6), and no selected articles were of low quality (Apêndice A).

For the meta-analysis of maternal anemia proportion, 50 studies were included. To estimate the overall frequency of low birth weight, 51 studies were selected as they contained all the information necessary to generate the summary measurement. Three of the studies included in this review (21-23) (APÊNDICE A) did not include the association measurement and mean birth weight in their findings. However, the authors stated that maternal anemia was considered a risk factor for low birth weight.

To generate the summary association measurement, 56 studies were included in the meta-analysis as they presented association measurements or information that made the calculation of the odds ratio possible. Of these, 36 presented only crude measurements, 19 presented crude and adjusted measurements, and one investigation included only the adjusted measurement. Among these investigations, the covariables most frequently considered in adjustment of the association measurements were maternal age, maternal level of education, hypertensive gestational disease and gestational age.

For the summary measurement of the mean difference in birth weight, only 12 studies were selected for the meta-analysis. Although 14 studies measured mean birth weight according to the presence of maternal anemia, two of these were not considered eligible because they did not present sufficient data to calculate the overall measurement (24, 25) (APÊNCIDE A).

Maternal anemia and low birth weight

The summary frequencies of exposure and outcome, calculated using proportional meta-analysis, were 34% (95% CI: 29%; 40%) and 14% (95% CI: 12%; 15%), respectively (Supplementary File 5).

In this systematic review, the meta-analysis summarized the crude odds ratio as 1.49 (95% CI: 1.36, 1.63) and I2 as 86% (Figure 2), which represents a statistically significant association between maternal anemia and low birth weight, although with high heterogeneity. The Egger test ($p < 0.01$) and the funnel plot showed publication bias for the crude association measurement (Figure 3). If there had been no publication bias, the expected association measurement would be 1.18 (95% CI: 1.07;1.29) according to the trim-and-fill test.

The overall association estimate for the adjusted odds ratio was 1.23 (95% CI: 1.06, 1.43), with 58% heterogeneity (Figure 4) and no publication bias (Egger's test: $p = 0.72$). This finding was confirmed by the trim-and-fill test, which showed that the number of publications and the association measurement expected consistent with the estimate measured in the present systematic review.

The meta-analysis of global mean difference showed that the children of pregnant women with maternal anemia presented a mean reduction of 60.55 g (95% CI: -111.38, -9.71, I2: 96%) in birth weight compared with the children of women with normal hemoglobin levels, and there was no publication bias (Egger: $p = 0.611$). The trim-and-

fill test confirmed that the findings presented are similar to the expected mean difference (Supplementary File 6).

The sensitivity analysis identified 9 studies that were considered outliers and that produced distortion in the crude (83-85) and adjusted (24, 40, 42, 48, 72, 83, 86) summary measurements, although they were included in the qualitative evaluation of the investigations. The subgroup analysis for the crude and adjusted odds ratio indicated that for most of the variables evaluated, the association measurement continued to be associated with low birth weight, even after stratification (Table 2). Multiple meta-regressions for the crude association measurement confirmed that the strength of the association measurement ($p < 0.01$), geographic location ($p = 0.02$) and sample size ($p < 0.01$) may have been the possible causes of heterogeneity. For the adjusted association measurement, the sample size ($p=0.01$) and the methodological quality of the studies ($p=0.01$) were the possible explanation.

4.4 DISCUSSION

The main findings of this systematic review show that maternal anemia is a risk factor for low birth weight. These results were confirmed through a meta-analysis of the mean difference in birth weight, which showed that the children of women with maternal anemia had a reduction in birth weight compared with those whose mothers did not develop anemia. The methodological quality of the longitudinal studies used in this systematic review, which included case-control and cohort designs, was considered moderate to high, and the studies were performed in different countries across all continents.

Of the previous systematic reviews on the subject, four corroborated the present findings. They also showed moderate and high heterogeneity in their meta-analyses; however, they only used longitudinal studies to evaluate the relationship between maternal anemia and neonatal events and did not focus specifically on low birth weight (12, 13, 27, 87). Rahman et al (12) evaluated exposure and outcomes in 17 cohort studies with high methodological quality, but only included data from low- and middle-income countries. Sukrat et al (13) used only two databases to track their studies on this topic, and to perform the meta-analysis, they included association measurements from only 10 longitudinal studies according to a cutoff point based on hemoglobin levels.

The other two reviews (27, 87) included cross-sectional investigations in addition to cohort and case-control studies. This fact may have contributed negatively to the results of their meta-analyses since the temporality of the events was not considered in the estimation of the summary association measurement. Only Ahankari and Leonardi-Bee (27) corroborated the present review's findings from the meta-analysis of the mean difference in birth weight; however, they used a small sample size of only five studies.

This systematic review also provided an estimation of the global frequency of maternal anemia originating from the proportional meta-analysis, which corroborates the most recent official data (8). Although there is significant regional variation in the occurrence of maternal anemia, the summary measurement presented in this systematic review was able to reproduce this proportion more reliably at the global level because it included studies from countries on all continents, regardless of their socioeconomic conditions. Similarly, the overall percentage of low birth weight children is similar to that reported by the World Health Organization for various countries (88).

Most of the studies in this systematic review presented findings based on a diagnosis of maternal anemia that used a lower severity cutoff. This fact shows how a narrow diagnosis of maternal anemia predominates in the studies. In the present systematic review, the positive association between maternal anemia and low birth weight was verified using subgroup analyses that included both the presence of anemia and its severity level due to the need for more accurate anemia diagnosis.

Another important issue is the high heterogeneity found among the studies, which could be attributed to regional differences in research; to specific characteristics of populations, such as health, socioeconomic and nutritional status; or to the different diagnostic definitions of maternal anemia (6, 89).Countries with a low Human Development Index show an increase in the magnitude of the association between maternal anemia and low birth weight; this association is supported by the findings of this review and justifies the high heterogeneity encountered in the present study.

Of the variables mentioned above, only the Human Development Index was identified as a source of heterogeneity in the subgroup analysis of the present systematic review. Multiple meta-regression showed that the high I2 in the crude association measurement could be partially explained by geographic region, sample size and the strength of the association measurement of the studies used in the meta-analysis. For the adjusted measurement, the sample size and methodological quality of the studies were possible explanations for the high heterogeneity observed.

Regarding the limitations of this review, the publication bias of the crude association measurement stands out, despite a wide search in several databases that had not been previously investigated in other systematic reviews. In an attempt to minimize bias, texts from the gray literature were inserted, and the authors of the published articles that did not provide some data considered relevant for this review were contacted.

To identify the possible effects of the absence of studies from the meta-analysis of the summary association measurement, the trim-and-fill test for the crude association measurement was used. As a result, a 19% reduction in the odds ratio was observed, together with the need for an additional 14 articles to be added to the meta-analysis to correct this measurement. In the present review, 71 studies were included, but only 58 presented sufficient information to calculate the crude summary measurement of the meta-analysis, demonstrating that 13 studies may have shown reporting bias. Of these, three were excluded because they were considered outliers and may have led to an overestimation of the meta-analytic odds ratio. However, when the publication bias was evaluated with and without the inclusion of these outliers, no change in the results was observed.

The difference between the crude and adjusted summary association measurement was lower than 17%, showing that although there one of the measurements showed publication bias, the studies findings point in the same direction: namely, they indicate that maternal anemia may be an important risk factor for low birth weight. However, this result should be interpreted with caution due to the high heterogeneity among the studies, which can be considered an indicator of inconsistency (90-95).

Another limitation was the use of different risk measurements (relative risk and odds ratios) in the meta-analysis. To correct the possible effects of this combination of measurements, all relative risks were converted into odds ratios. To verify the effect of this conversion on the meta-analysis, a sensitivity analysis was performed, and the articles that presented a relative risk and an outcome occurrence higher than 10% were excluded (20). However, the difference was insignificant. Another aspect that reinforces this finding is that the two types of association measurements have a tendency to present similar results since the outcome investigated is considered rare, which minimizes the possible impact of this measurement difference (20).

The strengths of this review include the high number of databases employed, the use of research techniques and validated instruments, such as the Newcastle Quality Survey Scale-Ottawa (17) and the Meta-analysis of observational studies in epidemiology

(MOOSE), to evaluate the studies and draft the systematic reviews (96). In addition, the subgroup analyses to measure possible associations between exposure and outcome used covariables that are considered epidemiologically important.

In terms of minimizing the information bias, another positive aspect was the use of original surveys that obtained information from reliable exposure and outcome measures, such as laboratory tests and medical records, rather than self-reported data.

To the best of our knowledge, this is the first systematic review to include research on the subject conducted in all continents using a large number of longitudinal studies. Although the present findings indicate that maternal anemia is associated with low birth weight, they also signal the need for further longitudinal research on this topic, with an evaluation of the various types of anemia in pregnant women. The relationship between anemia and low birth weight could be better understood through more robust methods, which would improve the quality of scientific evidence on the topic and provide more effective preventive and health-promotion measures for mothers and children.

Conflicts of Interest

The authors declare that they have no conflicts of interests.

4.5 REFERENCES

1. UNICEF. Low Birthweight: Country,regional and global estimates. New York: UNICEF; 2004.

2. Lawani LO, Iyoke CA, Onoh RC, Nkwo PO, Ibrahim IA, Ekwedigwe KC, et al. Obstetric benefits of health insurance: A comparative analysis of obstetric indices and outcome of enrollees and non-enrollees in southeast Nigeria. J Obstet Gynaecol. 2016;36(7):946-9.

3. Petrou S. Economic consequences of preterm birth and low birthweight. BJOG. 2003;110 Suppl 20:17-23.

4. Bird AL, Grant CC, Bandara DK, Mohal J, Atatoa-Carr PE, Wise MR, et al. Maternal health in pregnancy and associations with adverse birth outcomes: Evidence from Growing Up in New Zealand. Aust N Z J Obstet Gynaecol. 2017;57(1):16-24.

5. Harvey EM, Strobino D, Sherrod L, Webb MC, Anderson C, White JA, et al. Community-Academic Partnership to Investigate Low Birth Weight Deliveries and

Improve Maternal and Infant Outcomes at a Baltimore City Hospital. Matern Child Health J. 2017;21:260-6.

6. Brannon PM, Taylor CL. Iron Supplementation during Pregnancy and Infancy: Uncertainties and Implications for Research and Policy. Nutrients. 2017;9(12).

7. Grotto HZW. Metabolismo do ferro: uma revisão sobre os principais mecanismos envolvidos em sua homeostase. Rev Bras Hematol Hemoter 2008;30(5):390-97.

8. WHO. The global prevalence of anaemia in 2011. Geneva: World Health Organization; 2015.

9. Centers for Disease Control and Prevention C. Recommendations to prevent and control iron deficiency in the United States. Centers for Disease Control and Prevention. MMWR Recomm Rep. 1998;47(RR-3):1-29.

10. CDC. CDC criteria for anemia in children and childbearing-aged women. MMWR Morb Mortal Wkly Rep. 1989;38(22):400-4.

11. Stangret A, Wnuk A, Szewczyk G, Pyzlak M, Szukiewicz D. Maternal hemoglobin concentration and hematocrit values may affect fetus development by influencing placental angiogenesis. J Matern Fetal Neonatal Med. 2016:1-6.

12. Rahman MM, Abe SK, Rahman MS, Kanda M, Narita S, Bilano V, et al. Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: systematic review and meta-analysis. Am J Clin Nutr. 2016;103(2):495-504.

13. Sukrat B, Wilasrusmee C, Siribumrungwong B, McEvoy M, Okascharoen C, Attia J, et al. Hemoglobin concentration and pregnancy outcomes: a systematic review and meta-analysis. Biomed Res Int. 2013;2013:769057.

14. Peña-Rosas JP, De-Regil LM, Garcia-Casal MN, Dowswell T. Daily oral iron supplementation during pregnancy. Cochrane Database Syst Rev. 2015(7):CD004736.

15. Peña-Rosas JP, De-Regil LM, Gomez Malave H, Flores-Urrutia MC, Dowswell T. Intermittent oral iron supplementation during pregnancy. Cochrane Database Syst Rev. 2015(10):CD009997.

16. Peña-Rosas JP, De-Regil LM, Dowswell T, Viteri FE. Daily oral iron supplementation during pregnancy. Cochrane Database Syst Rev. 2012;12:CD004736.

17. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. The
Ottawa Hospital: Research Institute; 2014.

18. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58.

19. Freeman MF, Tukey JW. Transformations related to the angular and the square root. Annals of Mathematical Statistics. 1950;21:607-11.

20. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA. 1998;280(19):1690-1.

21. Buzyan LO. Mild anemia as a protective factor against pregnancy loss. Int J Risk Saf Med. 2015;27 Suppl 1:S7-8.

22. Rizvi SA, Hatcher J, Jehan I, Qureshi R. Maternal risk factors associated with low birth weight in Karachi: a case-control study. East Mediterr Health J. 2007;13(6):1343-52.

23. Rodriguez OTS, Szarfarc SC, d'Aquino Benicio MH. Anemia e desnutrição maternas e sua relação com o peso ao nascer. Rev Saúde públ. 1991;25(3):193-7.

24. Malhotra M, Sharma JB, Batra S, Sharma S, Murthy NS, Arora R. Maternal and perinatal outcome in varying degrees of anemia. Int J Gynaecol Obstet. 2002;79(2):93-100.

25. Duthie SJ, King PA, To WK, Lopes A, Ma HK. A case controlled study of pregnancy complicated by severe maternal anaemia. Aust N Z J Obstet Gynaecol. 1991;31(2):125-7.

26. Abeysena C, Jayawardana P, de A Seneviratne R. Maternal haemoglobin level at booking visit and its effect on adverse pregnancy outcome. Aust N Z J Obstet Gynaecol. 2010;50(5):423-7.

27. Anand A, Jo L-B. Maternal hemoglobin and birth weight: systematic review and meta-analysis. Int J Med Sci Public Health. 2015;4:435-45.

28. Ahmad Z, Jaafar R, Hassan MHM, Othman MS, Hashim A. Anaemia during pregnancy in rural Kelantan. Mal J Nutr. 1997;3:83-90.

29. al-Sibai MH, Khwaja SS, al-Suleiman SA, Magbool G. The low birth-weight infants of Saudi adolescents: maternal implications. Aust N Z J Obstet Gynaecol. 1987;27(4):320-2.

30. Ali AA, Rayis DA, Abdallah TM, Elbashir MI, Adam I. Severe anaemia is associated with a higher risk for preeclampsia and poor perinatal outcomes in Kassala hospital, eastern Sudan. BMC Res Notes. 2011;4:311.

31. Bakacak M, Avci F, Ercan O, Köstü B, Serin S, Kiran G, et al. The effect of maternal hemoglobin concentration on fetal birth weight according to trimesters. J Matern Fetal Neonatal Med. 2015;28(17):2106-10.

32. Bakhtiar UJ, Khan Y, Nasar R. Relationship between maternal hemoglobin and Perinatal outcome. RMJ. 2007;32(2):102-4.

33. Bhalerao A, Kawthalkar A, Ghike S, Joshi S. Anemia during Pregnancy: Most Preventableyet most Prevalent. Journal of South Asian Federation of Obstetrics and Gynaecolog. 2011;3(2):75-7.

34. Bian Y, Zhang Z, Liu Q, Wu D, Wang S. Maternal risk factors for low birth weight for term births in a developed region in China: a hospital-based study of 55,633 pregnancies. J Biomed Res. 2013;27(1):14-22.

35. Bodeau-Livinec F, Briand V, Berger J, Xiong X, Massougbodji A, Day KP, et al. Maternal anemia in Benin: prevalence, risk factors, and association with low birth weight. Am J Trop Med Hyg. 2011;85(3):414-20.

36. Bondevik GT, Lie RT, Ulstein M, Kvåle G. Maternal hematological status and risk of low birth weight and preterm delivery in Nepal. Acta Obstet Gynecol Scand. 2001;80(5):402-8.

37. Chang SC, O'Brien KO, Nathanson MS, Mancini J, Witter FR. Hemoglobin concentrations influence birth outcomes in pregnant African-American adolescents. J Nutr. 2003;133(7):2348-55.

38. Cosme JAG, Hechavarría EM, Miralles RMF, Isaac RC, Blanco YV. Factores de riesgo del bajo peso al nacer en el hospital materno de Palma Soriano durante un trienio Risk factors of low birth weight in Palma Soriano Maternal Hospital during a triennium. MEDISAN 2009;13(2). 2009;13(2):1-7.

39. El Guindi W, Pronost J, Carles G, Largeaud M, El Gareh N, Montoya Y, et al. Anémies maternelles sévèreset issues de grossesse. J Gynecol Obstet Biol Reprod. 2004;33:506-9.

40. Elhassan EM, Abbaker AO, Haggaz AD, Abubaker MS, Adam I. Anaemia and low birth weight in Medani, Hospital Sudan. BMC Res Notes. 2010;3:181.

41. Gaillard R, Eilers PH, Yassine S, Hofman A, Steegers EA, Jaddoe VW. Risk factors and consequences of maternal anaemia and elevated haemoglobin levels during pregnancy: a population-based prospective cohort study. Paediatr Perinat Epidemiol. 2014;28(3):213-26.

42. Ganesh Kumar S, Harsha Kumar HN, Jayaram S, Kotian MS. Determinants of low birth weight: a case control study in a district hospital in Karnataka. Indian J Pediatr. 2010;77(1):87-9.

43. Geelhoed D, Agadzi F, Visser L, Ablordeppey E, Asare K, O'Rourke P, et al. Maternal and fetal outcome after severe anemia in pregnancy in rural Ghana. Acta Obstet Gynecol Scand. 2006;85(1):49-55.

44. Hämäläinen H, Hakkarainen K, Heinonen S. Anaemia in the first but not in the second or third trimester is a risk factor for low birth weight. Clin Nutr. 2003;22(3):271-5.

45. Heredia-Olivera K, Munares-García O. Factores maternos asociados al bajo peso al nacer. Rev Med Inst Mex Seguro Soc. 2016;54(5):562-7.

46. Hirve SS, Ganatra BR. Determinants of low birth weight: a community based prospective cohort study. Indian Pediatr. 1994;31(10):1221-5.

47. Hosain GM, Chatterjee N, Begum A, Saha SC. Factors associated with low birthweight in rural Bangladesh. J Trop Pediatr. 2006;52(2):87-91.

48. Ilunga PM, Mukuku O, Mawaw PM, Mutombo AM, Lubala TK, Shongo Ya Pongombo M, et al. Risk factors for low birth weight in Lubumbashi, Democratic Republic of the Congo. Med Sante Trop. 2016;26(4):386-90.

49. Knottnerus JA, Delgado LR, Knipschild PG, Essed GG, Smits F. Haematologic parameters and pregnancy outcome. A prospective cohort study in the third trimester. J Clin Epidemiol. 1990;43(5):461-6.

50. Koura GK, Ouedraogo S, Le Port A, Watier L, Cottrell G, Guerra J, et al. Anaemia during pregnancy: impact on birth outcome and infant haemoglobin level during the first 18 months of life. Trop Med Int Health. 2012;17(3):283-91.

51. Kumar A, Chaudhary K, Prasad S. Maternal indicators and obstetric outcome in the north Indian population: a hospital-based study. J Postgrad Med. 2010;56(3):192-5.

52. Lee HS, Kim MS, Kim MH, Kim YJ, Kim WY. Iron status and its association with pregnancy outcome in Korean pregnant women. Eur J Clin Nutr. 2006;60(9):1130-5.

53. Levy A, Fraser D, Katz M, Mazor M, Sheiner E. Maternal anemia during pregnancy is an independent risk factor for low birthweight and preterm delivery. Eur J Obstet Gynecol Reprod Biol. 2005;122(2):182-6.

54. Lone FW, Qureshi RN, Emanuel F. Maternal anaemia and its impact on perinatal outcome. Trop Med Int Health. 2004;9(4):486-90.

55. Masukume G, Khashan AS, Kenny LC, Baker PN, Nelson G, Consortium S. Risk factors and birth outcomes of anaemia in early pregnancy in a nulliparous cohort. PLoS One. 2015;10(4):e0122729.

56. Mir MK, Yousaf S, Ilyas A, Tahir S. Maternal Anemia is a Risk Factor for Low Birth Weight Babies at Term. PJMHS. 2016;10(3):741-3.

57. Misra A, Ray S, Patrikar S. A longitudinal study to determine association of various maternal factors with neonatal birth weight at a tertiary care hospital. Med J Armed Forces India. 2015;71(3):270-3.

58. Msuya SE, Hussein TH, Uriyo J, Sam NE, Stray-Pedersen B. Anaemia among pregnant women in northern Tanzania: prevalence, risk factors and effect on perinatal outcomes. Tanzan J Health Res. 2011;13(1):33-9.

59. Nasiri-Amiri F, Hajiahmadi M, Basirat Z. Maternal hematocrit status affecting pregnancy outcome. IRCMJ. 2007;9(2):104-8.

60. Negandhi PH, Negandhi HN, Zodpey SP, Ughade SN, Biranjan JR. Risk factors for low birth weight in an Indian urban setting: a nested case control study. Asia Pac J Public Health. 2014;26(5):461-9.

61. Padhi BK, Baker KK, Dutta A, Cumming O, Freeman MC, Satpathy R, et al. Risk of Adverse Pregnancy Outcomes among Women Practicing Poor Sanitation in Rural India: A Population-Based Prospective Cohort Study. PLoS Med. 2015;12(7):e1001851.

62. Patabendige M, Dias T, Gunasena J, Motha CMB, Palihawadana T, Herath RP, et al. Retrospective study on anaemia in pregnancy: effect on fetal and labour outcomes. RCOG world congress 2017; Cape Town, South Africa, 2017.

63. Perveen S, Soomro TK. Sideropaenic anaemia: Impact on perinatal outcome at tertiary care hospital. J Pak Med Assoc. 2016;66(8):952-6.

64. Ren A, Wang J, Ye RW, Li S, Liu JM, Li Z. Low first-trimester hemoglobin and low birth weight, preterm birth and small for gestational age newborns. Int J Gynaecol Obstet. 2007;98(2):124-8.

65. Sananpanichkul P, Rujirabanjerd S. Association between maternal body mass index and weight gain with low birth weight in eastern Thailand. Southeast Asian J Trop Med Public Health. 2015;46(6):1085-91.

66. Scholl TO, Hediger ML, Fischer RL, Shearer JW. Anemia vs iron deficiency: increased risk of preterm delivery in a prospective study. Am J Clin Nutr. 1992;55(5):985-8.

67. Sekhavat L, Davar R, Hosseinidezoki S. Relationship between maternal hemoglobin concentration and neonatal birth weight. Hematology. 2011;16(6):373-6.

68. Sharma SR, Giri S, Timalsina U, Bhandari SS, Basyal B, Wagle K, et al. Low birth weight at term and its determinants in a tertiary hospital of Nepal: a case-control study. PLoS One. 2015;10(4):e0123962.

69. Shobeiria F, Begumb K, Nazari M. A prospective study of maternal hemoglobin status of Indian women during pregnancy and pregnancy outcome. Nutrition Research. 2006;26:209-13.

70. Shobeiri F, Begumb K, Nazari M. A prospective study of maternal hemoglobin status of Indian women during pregnancy and pregnancy outcome. Nutrition Research. 2006;26:209-13.

71. Singh A, Arya S, Chellani H, Aggarwal KC, Pandey RM. Prediction model for low birth weight and its validation. Indian J Pediatr. 2014;81(1):24-8.

72. Smithers LG, Gialamas A, Scheil W, Brinkman S, Lynch JW. Anaemia of pregnancy, perinatal outcomes and children's developmental vulnerability: a whole-of-population study. Paediatr Perinat Epidemiol. 2014;28(5):381-90.

73. Stanisic DI, Moore KA, Baiwog F, Ura A, Clapham C, King CL, et al. Risk factors for malaria and adverse birth outcomes in a prospective cohort of pregnant women resident in a high malaria transmission area of Papua New Guinea. Trans R Soc Trop Med Hyg. 2015;109(5):313-24.

74. Tzur T, Weintraub AY, Sergienko R, Sheiner E. Can anemia in the first trimester predict obstetrical complications later in pregnancy? J Matern Fetal Neonatal Med. 2012;25(11):2454-7.

75. Vural T, Toz E, Ozcan A, Biler A, Ileri A, Inan AH. Can anemia predict perinatal outcomes in different stages of pregnancy? Pak J Med Sci. 2016;32(6):1354-9.

76. Xiong X, Buekens P, Fraser WD, Guo Z. Anemia during pregnancy in a Chinese population. Int J Gynaecol Obstet. 2003;83(2):159-64.

77. Yazdani M, Tadbiri M, Shakeri S. Maternal hemoglobin level, prematurity, and low birth weight. Int J Gynaecol Obstet. 2004;85(2):163-4.

78. Yildiz Y, Özgü E, Unlu SB, Salman B, Eyi EG. The relationship between third trimester maternal hemoglobin and birth weight/length; results from the tertiary center in Turkey. J Matern Fetal Neonatal Med. 2014;27(7):729-32.

79. Yousaf F, Haider G, Shaikh RB, Haider A, Muhammad N. Impact of maternal anemia on perinatal outcome. Pakistan Armed Forces Medical Journal. 2011(4):1-3.

80. Zhou LM, Yang WW, Hua JZ, Deng CQ, Tao X, Stoltzfus RJ. Relation of hemoglobin measured at different times in pregnancy to preterm birth and low birth weight in Shanghai, China. Am J Epidemiol. 1998;148(10):998-1006.

81. Dal Pizzol TS, Giugliani ERJ, Mengue SS. Associação entre o uso de sais de ferro durante a gestação e nascimento pré-termo, baixo peso ao nascer e muito baixo peso ao nascer. Cad Saúde Pública. 2009;25(1):106-68.

82. Lone FW, Qureshi RN, Emmanuel F. Maternal anaemia and its impact on perinatal outcome in a tertiary care hospital in Pakistan. East Mediterr Health J. 2004;10(6):801-7.

83. Rukuni R, Bhattacharya S, Murphy MF, Roberts D, Stanworth SJ, Knight M. Maternal and neonatal outcomes of antenatal anemia in a Scottish population: a retrospective cohort study. Acta Obstet Gynecol Scand. 2016;95(5):555-64.

84. Steer P, Alam MA, Wadsworth J, Welch A. Relation between maternal haemoglobin concentration and birth weight in different ethnic groups. BMJ. 1995;310(6978):489-91.

85. López JI, Botell ML, Echevarría SMM, Pérez CG, Valdés-Dapena DP. Algunos factores de riesgo relacionados con el bajo peso al nacer. Revista Cubana de Ginecología y Obstetricia. 2012;38(1):45-55.

86. Bánhidy F, Acs N, Puhó EH, Czeizel AE. Iron deficiency anemia: pregnancy outcomes with or without iron supplementation. Nutrition. 2011;27(1):65-72.

87. Rahmati S, Delpishe A, Azami M, Hafezi Ahmadi MR, Sayehmiri K. Maternal Anemia during pregnancy and infant low birth weight: A systematic review and Meta-analysis. Int J Reprod Biomed (Yazd). 2017;15(3):125-34.

88. World Health Organization. WHO Global Nutrition Targets 2025: Low Birth Weight Policy Brief. In: Organization WH, editor. 2014. p. 7.

89. Friedrisch JR, Friedrisch BK. Prophylactic Iron Supplementation in Pregnancy: A Controversial Issue. Biochem Insights. 2017;10:1178626417737738.

90. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.

91. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. J Clin Epidemiol. 2011;64(12):1303-10.

92. Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. J Clin Epidemiol. 2011;64(12):1277-82.

93. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011;64(4):380-2.

94. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol. 2011;64(4):407-15.

95. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-94.

96. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008-12.

TABLES

Table 1. Study characteristics

Characteristic	N	%
Study design		
Prospective cohort	38	53.6
Retrospective cohort	16	22.5
Case-control	17	23.9
Location of data collection		
Hospital	58	81.7
Primary health units	7	9.9
Community	3	8.4
Differential diagnosis of exposure		
Maternal anemia	65	91.6
Iron deficiency anemia	6	8.4
Hemoglobin levels*		
< 11 g / dl	54	77.1
< 10 g / dl	10	14.3
< 8 g / dl	6	8.6
Geographic region		
America	9	12.7
Africa	6	8.4
Asia	44	62.0
Europe	8	11.3
Oceania	4	5.6
Sample size		
≤ 1000	43	60.6
> 1000	28	39.4
Methodological quality of the studies		
Moderate	40	56.3
High	31	43.7
Year the research was initiated **		
Before 1990	8	14.0

1990-2009	12	21.0
2000-2009	25	44.0
2010-2017	12	21.0
Control for confounding		
Yes	20	28.2
No	51	71.8

* One study did not present the definition but affirmed that there was a reduction in birth weight.
** Some studies did not report the start date of the survey.

Table 2. Subgroup analysis and meta-regression of the crude and adjusted effect measurement.

Variable	N	Crude OR (95% CI)	Heterogeneity (I^2)	Meta-regression p value*	N	Adjusted OR (95% CI)	Heterogeneity (I^2)	Meta-regression p value*
Study design								
Prospective cohort	30	1.51 (1.29-1.76)	83.8%		6	1.38 (0.96-2.01)	46.7%	
Retrospective cohort	13	1.18 (1.08-1.28)	72.7%	0.03	5	1.24 (1.04-1.49)	70.8%	0.56
Case-control	12	2.29 (1.51-3.47)	82.8%		2	0.85 (0.37-2.00)	79.4%	
Data collection location								
Hospital	44	1.54 (1.39-1.71)	85.4%		10	1.30 (1.06-1.59)	63.4%	
Primary health units	6	1.28 (1.02-1.61)	68.9%	0.28	2	1.05 (0.77-1.42)	55.2%	0.50
Community	5	1.40 (1.09-1.78)	60.4%		1	-	-	
Differential diagnosis of exposure								
Maternal anemia	51	1.47 (1.34-1.61)	86.8%	0.54	12	1.21 (1.04-1.42)	60.0%	0.53
Iron deficiency anemia	4	1.89 (1.10-3.27)	60.9%		1	-	-	
Hemoglobin levels (g / dl)								
< 11	33	1.48 (1.32-1.66)	86.7%		10	1.25 (1.04-1.49)	50.3%	
< 10.6	5	2.58 (1.69-3.94)	72.4%	0.87	1	-	-	0.84
< 10	7	1.25 (1.02-1.52)	86.2%		2	1.04 (0.79-1.37)	64.0%	
< 8	3	1.72 (1.10-2.69)	33.6%		0	-	-	
Severity levels of maternal anemia								
Mild	7	1.14 (0.99-1.31)	66.3%		0	-	-	
Moderate	9	1.39 (1.11-1.74)	49.0%	0.61	2	1.16 (1.04-1.29)	0.0%	-
Severe	9	2.31 (1.47-3.63)	82.7%		4	2.24 (1.35-3.71)	0.0%	

Strength of the association								
< 2	34	1.15 (1.06-1.25)	80.1%	<0.01	10	1.14 (0.99-1.30)	47.8%	0.02
≥ 2	21	2.85 (2.48-3.27)	16.0%		3	1.87 (1.42-2.45)	0.0%	
Maternal anemia by gestational trimester								
First	3	1.51 (0.94-2.42)	55.7%		0	-	-	
Second	3	0.98 (0.56-1.68)	61.5%	-	0	-	-	-
Third	3	0.88 (0.53-1.48)	72.2%		0	-	-	
Human Development Index								
Very high	12	1.24 (1.03-1.49)	88.4%		3	1.25 (1.03-1.51)	0.0%	
High	15	1.30 (1.14-1.49)	82.0%	0.02	6	1.15 (0.92-1.44)	64.8%	0.92
Medium	21	1.82 (1.46-2.27)	77.3%		4	1.30 (0.87-1.94)	72.4%	
Low	7	2.28 (1.23-4.21)	89.5%		1	-	-	
Geographic region								
America	4	1.38 (1.00-1.91)	0.0%		1	-	-	
Africa	6	3.07 (1.60-5.89)	83.9%		1	-	-	0.76
Asia	38	1.44 (1.31-1.58)	83.7%	0.30	9	1.20 (1.02-1.40)	58.2%	
Europe	4	0.94 (0.47-1.89)	87.4%		1	-	-	
Oceania	3	1.51 (1.23-1.85)	16.0%		1	-	-	
Sample size								
≤ 1000	34	1.84 (1.46-2.33)	79.0%	0.02	6	1.46 (1.00-2.16)	57.2%	0.15
< 1000	21	1.24 (1.13-1.35)	86.8%		7	1.15 (1.02-1.31)	44.1%	
Year the research was initiated								
Before 1990	4	0.96 (0.58-1.60)	91.5%		1	-	-	
1990-1999	9	1.34 (1.10-1.64)	81.1%	0.36	4	1.22 (1.00-1.50)	64.6%	0.08
2000-2009	22	1.75 (1.44-2.13)	82.3%		6	1.40 (1.16-1.69)	16.0%	

2010-2017	11	1.32 (1.09-1.60)	87.2%		0	-	-	
Methodological quality of the studies								
Moderate	30	1.65 (1.42-1.91)	83.2%	0.25	2	0.52 (0.26-1.04)	0.0%	0.05
High	25	1.49 (1.36-1.63)	87.0%		13	1.27 (1.10-1.46)	56.6%	

* P value < 0.05. The p value represents the difference between the characteristics.

FIGURES

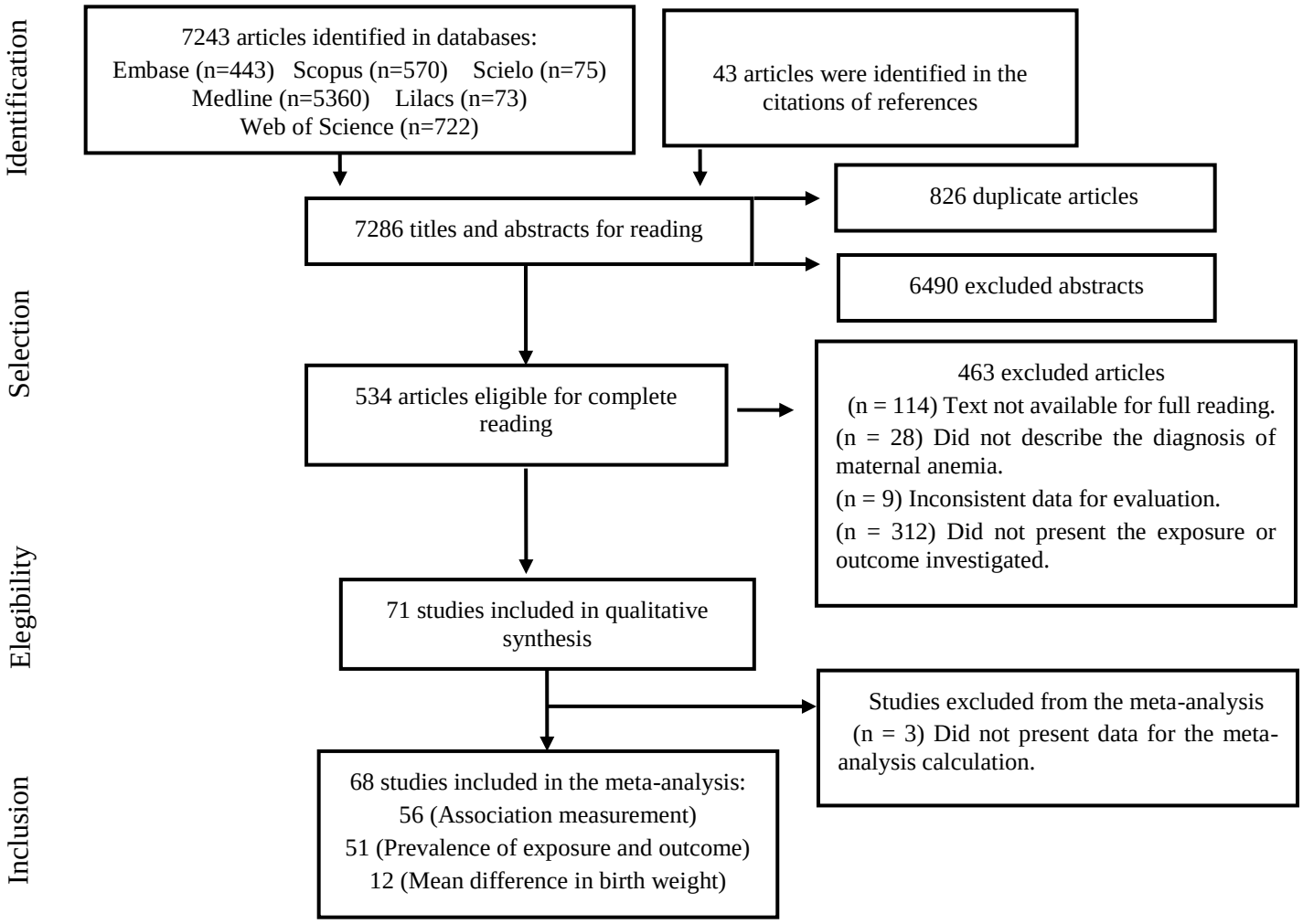

Figure 1. Flowchart of the search, selection and inclusion of the studies.

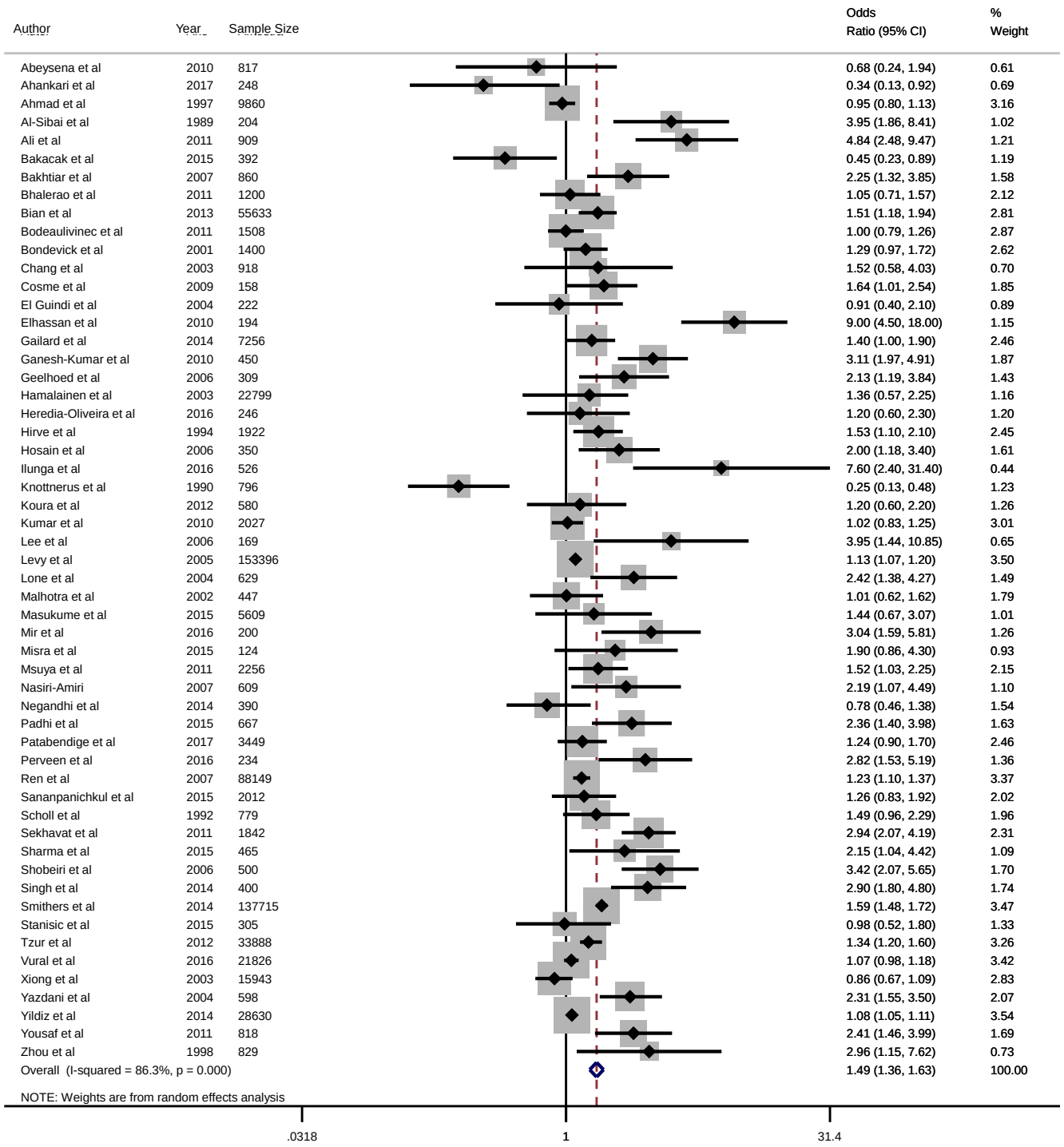

Figure 2. Meta-analysis with crude effect measurement for the evaluated studies and 95% confidence intervals.

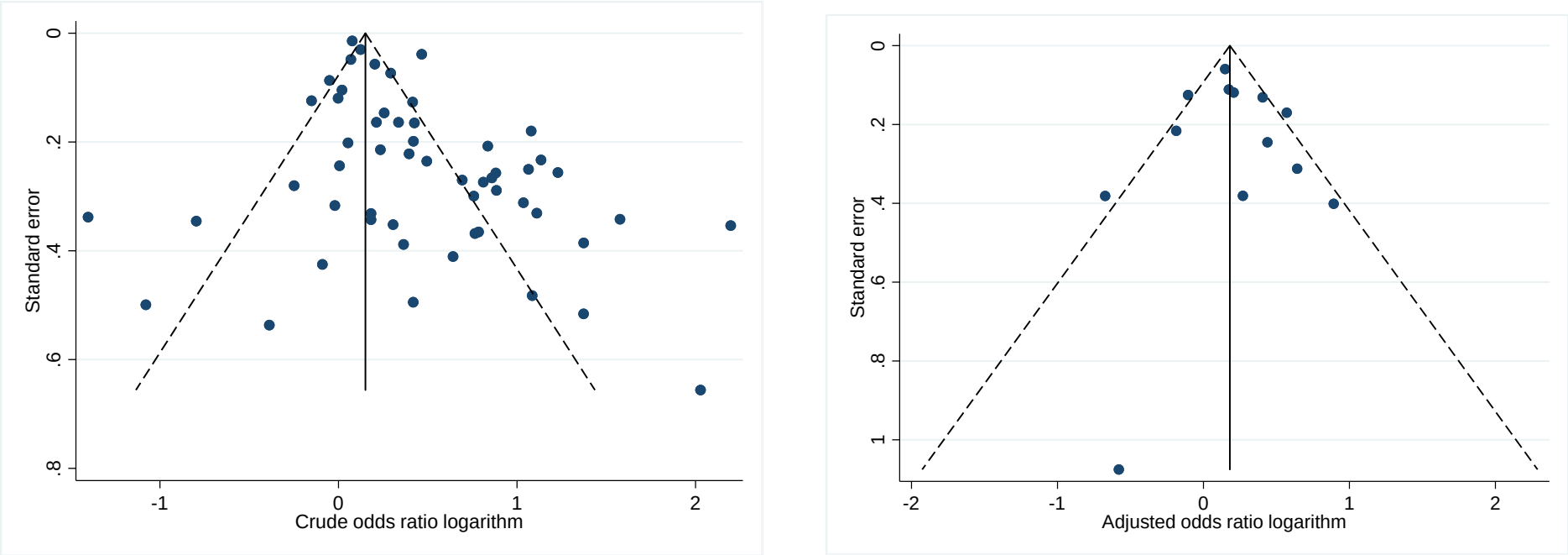

Figure 3. Publication bias

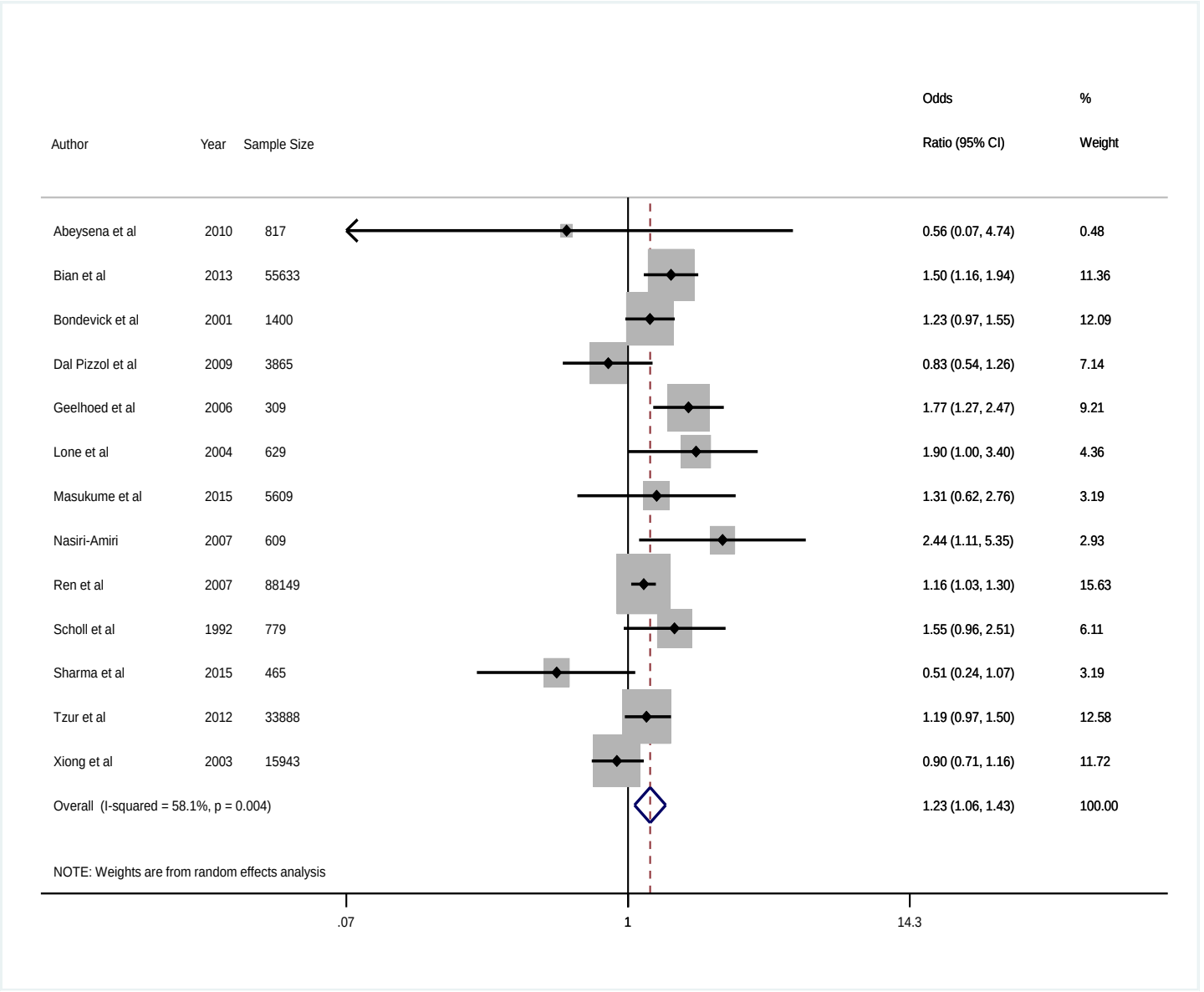

Figure 4. Meta-analysis with adjusted effect measurements for the evaluated studies and 95% confidence intervals.

5 ARTIGO: MATERNAL ANEMIA AND BIRTH WEIGHT: A PROSPECTIVE COHORT STUDY

ABSTRACT

BACKGROUND: Transformations provoked by pregnancy can promote imbalances resulting in significant changes to both the mother and growing child, and maternal anemia and low or insufficient birth weight are prime examples. **OBJECTIVE:** To verify the association between maternal anemia and low/insufficient birth weight. **DESIGN:** A prospective cohort study of pregnant women who underwent prenatal care at the healthcare units in a municipality of northeast Brazil together with their newborn infants was carried out. The pregnant women were classified as having anemia when the hemoglobin level was below 11 g/dl. Infants who were born full term weighing less than 3000 g were allocated to the low/insufficient weight group. The occurrence of maternal anemia and its association with birth weight was verified using crude and adjusted Relative Risk (RR) estimates with their corresponding 95% confidence intervals (95%CIs). **RESULTS:** Maternal anemia was considered a risk factor for low/insufficient birth weight, after adjusting the effect measurement for maternal age, family income, urinary infection, parity, alcoholic beverage consumption during pregnancy and gestational body mass index: $RR_{adjusted}$ = 1.38 [95% CI: 1.07 to 1.77]. **CONCLUSIONS:** Maternal anemia was associated with low/insufficient birth weight, representing a risk factor for the gestational outcomes studied.

Keywords: Anemia; Pregnant women; Birth weight; Cohort; Prospective

5.1 INTRODUCTION

Low birth weight has been widely studied and is an important risk factor for infant morbidity and mortality (1-4). However, insufficient weight has received little attention (5-8), even though three decades ago, children with birth weights less than 3000 grams were considered to have a risk of mortality that was three times higher during the first year of life than that of children whose weights were above or equal to this cutoff point (9,10).

The classic risk factors for low birth weight are associated with unfavorable biological, social and environmental conditions that may occur before or during the pregnancy period (4, 11-13). Nutritional determinants, such as pre-gestational weight and weight gain during

pregnancy, influence birth weight. Thus, inadequate maternal caloric intake, which may be the result of a diet that is nutritionally poor, leads to lower absorption of essential micronutrients, such as vitamin B12 and iron, for fetal growth (14).

Although the determinants of both low and insufficient weight at birth are similar, the mechanism that links maternal anemia to insufficient birth weight is not fully known. Few prospective cohort studies have analyzed the association between maternal anemia and low birth weight (15-27). Indeed, after a rigorous search of previous investigations on the topic, only two retrospective cohort studies, from Colombia and Finland, that addressed the relationship between nutritional exposure and insufficient birth weight were identified (5, 6).

Given the relevance of the theme and the knowledge that the association between maternal anemia and birth weight is affected by demographic and socioeconomic factors, an investigation of this relationship in diverse populations is necessary to identify the groups at greatest risk. The objective of this study was to verify the frequency of maternal anemia and its association with low/insufficient birth weight in users of the public health service from a population in northeastern Brazil.

5.2 METHODS

Study design/population

A prospective analytical cohort study was carried out with pregnant women, who underwent prenatal follow-up at healthcare units in the urban area of Santo Antônio de Jesus, Bahia, Brazil, and their newborns. The data collection period was from January 2013 to March 2017.

Eligibility criteria

Inclusion criteria

The pregnant women in this study had the following: pregnancy with fetal gestational ages between 8 and 32 weeks, assistance from the public health system, prenatal care from the selected healthcare units, live births, full-term births, and children available for the study.

Exclusion criteria

Women were excluded from the study if they had a twin pregnancy or a history of bleeding that required hospital treatment for at least 24 hours.

Data collection procedures

Information concerning the pregnant women was first obtained through interviews. Then, trained researchers performed blood collections, and oral examinations were performed by a dentist. The data that could not be obtained during the interview were acquired from the patient's chart and/or pregnancy card. During the postpartum period, information on birth weight was collected from the Declaration of Live Births.

Data collection tools

The questionnaire form was divided into six sections: 1) identification, socioeconomic-demographic data and environmental data; 2) nutritional information; 3) gynecological-obstetric history; 4) drug information; 5) variables related to the anthropometry of the pregnant woman; and 6) information concerning childbirth, which was collected from the Declaration of Live Births.

Blood collection for laboratory tests

The blood collection followed the standard criteria of collection and storage (28) to obtain the complete blood count and ferritin dosage.

Oral examination

The oral evaluation was performed by examining all of the teeth of each participant. Periodontitis was diagnosed according previous studies on the topic (29, 30).

Birth weight

Birth weight was measured immediately after delivery on a precise scale and subsequently recorded in the Declaration of Live Birth by a health professional who participated in the birth (31).

Criteria for the definitions of exposure and outcome

Exposure: Maternal anemia

Study participants were diagnosed as having maternal anemia when the hemoglobin level was below 11 g/dl or when the hematocrit was less than 33% (32). Additionally, the participants were diagnosed with iron deficiency anemia when the reference value for serum ferritin was less than 15 femtoliters and the mean corpuscular volume (MCV) was less than 80 femtoliters (32). Participants were diagnosed with anemia of chronic disease when the MCV was normal, from 80 to 96 femtoliters, and when they had the aforementioned hemoglobin level (32).

Outcome: Low/insufficient birth weight

The classification of birth weight was defined according to the criteria of the World Health Organization (2). Newborns with birth weights less than 2500 grams were classified as low birth weight, and those weighing between 2500 and 2999 grams were classified as insufficient weight. Children born with weights above or equal to 3000 grams were allocated to the group of newborns with satisfactory weights.

Procedure for analyzing the data

Descriptive analysis for all selected variables was performed, according to the relative and absolute frequency. The Kolmogorov-Smirnov test (33) was applied, and histogram inspection was performed to verify the normality of the continuous variables. Student's t-test (34) or the Mann-Whitney U test (35) was used, according to the normality test of the variable, employing the mean, median and standard deviation to verify the differences between the groups. Categorical covariables were also evaluated for distribution, the presence of maternal anemia and weight less than 3000 grams using the chi-square test (36) or Fisher's exact test (37), with a significance level of 5%.

The investigation of the association between maternal anemia and low/insufficient birth weight was performed by estimating the crude and adjusted relative risk (RR), with their 95% confidence intervals and a significance level of 5% by robust Poisson regression analysis, using backward elimination.

Potential confounding factors and effect modification for the selected covariables were identified by stratified analysis. The interaction identification was performed using the maximum likelihood ratio test, according to the definition of the saturated and reduced models for each of the possible effect modifier variables. A covariable was considered confounding when, after being eliminated from the saturated model, the covariable promoted a variation in the effect measurement that was greater than 10%compared to the main association measurement. In addition, the criterion of epidemiological importance for the selection of confounding covariables was adopted during modeling. The diagnosis of the model was performed using the Hosmer-Lemeshow test (38).

To evaluate the relationship between hemoglobin levels and the outcome, the multicollinearity test was performed, followed by univariate and multiple linear regression analysis using the common minimum squares technique (39). For the adjusted model, the covariables that were considered to be confounders were used. These covariables included those that altered the parameters of the null model based on the statistical criteria ($p < 0.20$) and those of epidemiological relevance. Stata® software, version 15, was used for data processing and analysis (40).

Sample size

To calculate the sample size, the following parameters were used: an Odds Ratio of 2.36 (26), the frequency of the rarest outcome, a low-birth-weight incidence of 8.29% in the group of pregnant women without anemia (26) and a ratio of exposed *versus* not exposed to anemia of 1:3. A study power of 80%, alpha error of 5% and the 95% confidence interval were also considered. Thus, the minimum estimated sample size was 141 pregnant women in the group diagnosed with anemia and 421 in the non-anemic group. In addition, 10% was added to the sample size to correct for possible losses, with a minimum sample calculation of 618 pregnant women. The sample size was calculated using Epi Info (StatCalc), version 7 (27).

The present study was approved by the Research Ethics Committee of Feira de Santana State University. All pregnant women voluntarily participated in the study and signed the Free Consent Form.

5.3 RESULTS

The sample consisted of 622 pregnant women who utilized the public health service of the municipality of Santo Antônio de Jesus, BA. The mean age of the participants was 25.5 years (± 6.5 SD), with a median of 25 years and a range of 13 to 46 years. The refusal rate was 2%.

The pregnant women were classified into two groups per the maternal anemia diagnostic criteria: 24.9% (n = 155) with anemia and 75.1% (n = 467) without anemia. Regarding the severity of maternal anemia, 20.1% of the pregnant women were diagnosed with mild anemia, and 4.8% were diagnosed with moderate anemia; there was no record of severe maternal anemia. The frequency of iron deficiency anemia was 6.0% among the participants, whereas the frequency of anemia of chronic disease was 18.9%. Ferropenia was present in 16.4% of the pregnant women.

The socioeconomic-demographic data are described in Table 1, and the data related to the maternal condition are shown in Table 2. Among the characteristics, only urinary infection, parity and the late onset of prenatal care showed statistically significant differences between the women with anemia and those without anemia, indicating that for most covariables, the comparison groups were homogeneous.

Regarding birth weight, 29.4% (183) of the participants had children with birth weights less than 3000 g, with 3.4% of the live births being classified as low birth weight and 26% being classified as insufficient birth weight. The frequency of mothers who had children of satisfactory weight was 70.6% (439).

The central tendency measures of the descriptors used for the diagnosis of maternal anemia, according to birth weight, are summarized in Table 3. Notably, statistically significant differences were evident only for the mean values of hemoglobin ($p = 0.03$) and hematocrit ($p = 0.02$).

Women diagnosed with maternal anemia showed a significantly higher incidence of children with birth weights<3000 g than the women who were not exposed to anemia during pregnancy ($RR_{\mathbf{crude}} = 1.36$; 95% CI: 1.06 to 1.76). According to the multiple-adjusted model, pregnant women with anemia had a 38% higher risk of having children with low/insufficient weight at birth than the women without anemia ($RR_{\mathbf{adjusted}} = 1.38$; 95% CI: 1.07 to 1.77; Table 4). The model was adjusted for the following confounders: maternal age, family income, urinary infection, parity, alcoholic beverage consumption during pregnancy and gestational body mass

index . The quality of this model was considered good because the null hypothesis was rejected ($p = 0.74$).

The linear regression analysis showed that on average, there was a 21-g decrease ($p = 0.03$) in the weight of the newborn per 1 g/dl of reduced maternal hemoglobin during the gestational period. In the saturated model, which was adjusted for the above-mentioned confounders, there was a 0.20-g decrease ($p = 0.05$) in birth weight per 1 g/dl of maternal hemoglobin lost during pregnancy.

5.4 DISCUSSION

Despite a rigorous search of a large number of electronic databases, only two cohort studies were found that discussed the relationship between maternal anemia and insufficient birth weight (5, 6). Studies addressing anemic exposure and low birth weight were more frequent. Regardless of the lack of previous investigations on the topic, the main results of the present investigation highlighted maternal anemia as a risk factor for low/insufficient birth weight, which was consistent with data from a previous study by Raisanen et al. (2014) (5). Thus, these findings contribute to current knowledge concerning this important public health problem. Other findings from the present study confirmed the above association since women with hemoglobin depletion had children with significantly reduced birth weights. Only one investigation had contrasting findings (6), showing no association between maternal anemia and low/insufficient birth weight. In addition, the incidence of maternal anemia in the current sample was approximately 25%, corroborating the frequency found in other studies (17, 41-43). Among these women, the incidence of children with low/insufficient birth weight was approximately 37%, whereas in children without anemia, the incidence was 27%.

The biological plausibility of the association between maternal anemia and low/insufficient birth weight is not fully understood (44, 45). However, previous studies have argued that maternal anemia predisposes the fetus to intrauterine growth restriction and may consequently influence the birth weight (9, 46). Physiologically, beginning during the middle of the second trimester of pregnancy, women produce an average of 30 to 40 ml of plasma per kilogram, corresponding to hypervolemia. However, when the number of hematological cells does not increase in parallel with this process, hemodilution occurs, and maternal anemia may develop (47).

Thus, low hemoglobin levels may stimulate changes in placental angiogenesis and favor fetal hypoxia. According to this theory, a reduction in nutrients and oxygen to the fetus due to

deficits in placental transport may result from hemoglobin depletion. The potential framework of uterine growth restriction begins with a reduction in blood perfusion in the uterus, an elevation in vascular resistance and growth restriction of the trophoblastic surface, which is responsible for ejecting maternal arterial blood into the placenta. These events may result in the restriction of gas exchange within the maternal-fetal complex and, consequently, in low/insufficient birth weight (48).

Within the scope of the present investigation, the findings of only one study clearly point to the association between maternal anemia and a birth weight of less than 3000 g (5) since this exposure is often studied only in terms of its relationship with low birth weight (49-51), without the inclusion of insufficient weight.

Multiple investigations have shown that maternal anemia is associated with low birth weight (52-54). Conversely, several other studies that included only low birth weight as the outcome refuted the hypothesis under investigation (23, 55, 56), making the association controversial. Although discussions about the damage from insufficient birth weight have been carried out for more than 30 years, few studies have evaluated the relationship between insufficient weight and various undesirable gestational events (8-10, 57), emphasizing only the extreme ranges of birth weight, such as low weight and macrosomia (49-51).

A similarity does exist between low birth weight and insufficient weight, but the former is considered more serious than the latter for the newborn. However, the unfavorable effect produced by insufficient birth weight cannot be ignored since this condition may contribute to inadequate cognitive development and infant growth and increase the morbidity and mortality of this age group (3).

The findings of the present investigation are relevant in that they contribute to a better understanding of the importance of insufficient birth weight to pediatric health, and several method-related parameters, such as the sample size, diagnostic criteria for maternal anemia and treatment of confounders, should be carefully evaluated when comparing these results to those of previous studies on the topic.

The sample size of the present study exceeded the minimum calculated sample size to estimate the effect measurement. The total number of pregnant women involved in the study by Mesa et al. (2012) (6) was approximately half of that employed in the present investigation and may explain the non-association, which was probably due to the lack of power in the study, found between maternal anemia and low/insufficient birth weight. However, Raisanen et al. (2014) (5) evaluated a large sample comprising 290,622 pregnant women and found a positive association, corroborating the findings of the present study.

Regarding the diagnosis of anemia in the present investigation, to improve internal validity, a laboratory test was used to define maternal anemia, establishing a hemoglobin reference value <11 g/dl and confirming the result with a hematocrit <33%. These criteria are recommended by the World Health Organization (32). Mesa et al. (2012) (6) used the same criteria, although the authors did not confirm the diagnosis of maternal anemia by hematocrit. However, Raisanen et al. (2014) (5) defined anemia using only the information contained in the hospital chart.

The subclassification of maternal anemia is highly valuable to ensure the adequate monitoring of pregnant women. For example, the diagnosis of iron deficiency anemia may facilitate therapy for the disease with iron supplementation. Increasingly, iron deficiency anemia has been classified as maternal anemia since multiple reports in the literature support the hypothesis that the primary cause of anemia in pregnant women is ferritin deficiency (17, 58-61). This notion conflicts with the findings presented in this study because most women with the anemia were diagnosed with anemia of chronic disease (18.9%), with a low frequency of iron deficiency anemia (6.0%), thus corroborating other studies (62-64).

Regarding severity levels, the participants in this study had a higher frequency of mild anemia. This severity was expected because much of the research converges in this direction (60, 65-68).

In the present investigation, the effect measurement was adjusted by confounders, due to knowledge of the possible effects of these covariables on both the exposure factor and the outcome. This criterion was also used in the study by Raisanen et al. (2014) (5), which corroborated the findings of this study. In contrast, Mesa et al. (2012) (6) did not adjust for the confounding covariables, and this lack of adjustment may explain why their findings contrasted the association verified in the present research.

According to the conceptual framework adopted here and the multicausality involved in the association between maternal anemia and low/insufficient birth weight, the following covariables were considered in the adjustment of the final model: maternal age, family income, urinary infection, parity, alcoholic beverage consumption during pregnancy and gestational BMI.

Unfavorable socioeconomic-demographic factors can influence both the exposure and the gestational outcome of interest. Maternal age, in its extreme age ranges, is a classical confounding variable because younger women do not have complete biological maturity for gestation and because older women are more likely to have comorbidities, such as maternal

anemia (25, 64). Regarding family income, pregnant women who have lower purchasing power are more vulnerable in terms of poor living conditions and, consequently, health (42, 54).

Infectious processes, such as urinary infection, influence the metabolism of new hemoglobin, leading to the development of maternal anemia (16), and intrauterine growth restriction, contributing to low/insufficient birth weight. Another relevant factor is parity since multiparity is a condition that can favor both low/insufficient birth weight and maternal anemia (25, 42).

Alcoholic beverage consumption during pregnancy can cause inflammatory disorders that restrict intrauterine growth, a contributing factor to low/insufficient birth weight (69, 70). Alcohol consumption can also compromise caloric intake, making it insufficient and, consequently, favoring the development of maternal anemia (69, 70). Women with inadequate nutrition are susceptible to both maternal anemia and having low/insufficient-birth-weight children, probably due to the poor dietary intake of essential micronutrients during pregnancy (42, 69).

Regarding the limitations of this investigation, the self-reported information may have produced calibration bias. Although the sample is representative of the urban population of the municipality investigated, caution should be exercised when interpreting the results by extrapolating them to other locations that do not have a population group that is similar to the one in this study. As in any other investigation, the possibility of residual confounding remains since some factors may not have been measured in the present study.

Finally, this research can contribute information that has not previously been elucidated toward confirming the hypothesis. The temporality of the events, namely, the order of the exposure relative to the outcome, is established since the laboratory tests for the diagnosis of maternal anemia preceded delivery and birth. Possible sample losses were measured prior to the study, which assures the representativeness and power of the sample size and the reliability of the presented findings. The adoption of these criteria also minimizes the possibility of a spurious association. Furthermore, the use of validated instruments by the researchers, who were previously trained, strengthens the internal validity of this study.

Based on the method employed and the limitations described, the exposure investigated was confirmed as a risk factor for low/insufficient birth weight. Given the findings, a far-reaching measure in public health would be the implementation of healthcare actions for the prevention and control of maternal anemia, aiming to reduce unfavorable gestational outcomes.

Conflicts of Interest

The authors declare that they have no conflicts of interests.

5.6 REFERENCES

1. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bull World Health Organ. 1987;65(5):663-737.

2. World Health Organization. Meeting of Advisory Group on Maternal Nutrition and Low Birthweight Genebra: WHO; 2002 Internet: http://www.who.int/nutrition/topics/lbw_strategy_background.pdf (accessed 23 august 2017).

3. Moraes IB. Risk factors for underweight at birth. Campinas, São Paulo: Universidade Estadual de Campinas, 2001.

4. UNICEF. Low Birthweight: Country,regional and global estimates. New York: UNICEF; 2004.

5. Raisanen S, Kancherla V, Gissler M, Kramer MR, Heinonen S. Adverse perinatal outcomes associated with moderate or severe maternal anaemia based on parity in Finland during 2006-10. Paediatr Perinat Epidemiol. 2014;28(5):372-80. DOI: 10.1111/ppe.12134.

6. Mesa SLR, Sosa BEPS, Gómez JA, López NZ, Díaz CAG, Moreno CMR, Alarca NAC, Vásquez LEE. Maternal nutritional status and its relationship with birth weight of the newborn, pregnant women study Public Network of Medellín, Colombia Perspect Nutr Humana. 2012;14(201):199-208.

7. Barros MAR, Holanda MAGd, Lopes KRL, Nicolau AIO. Obstetric factors associated with weight of newborn at term not gemelar. Rev enferm UFPE. 2013;7(12):6821-7.

8. Costa RSC, Caldevilla DE, Gallo PR, Sena BF, Leone C. Incidence and characteristics of insufficient birth weight Newborns from a cohort of neonates in a public regional Hospital of a metropolitan area. Journal of Human Growth and Development. 2013;23(2):238-44.

9. Puffer RR. Patterns of birthweights: a summary. Bull Pan Am Health Organ. 1987;21(2):185-95 (abrst).

10. Rees JM, Lederman SA, Kiely JL. Birth weight associated with lowest neonatal mortality: infants of adolescent and adult mothers. Pediatrics. 1996;98(6 Pt 1):1161-6.

11. Carniel EF, Zanolli ML, Antônio MRGM, Morcillo AM. Determinants for low birth weight according to Live Born Certificates. Rev. bras. epidemiol. 2008;11:169-79. DOI: http://dx.doi.org/10.1590/S1415-790X2008000100016

12. Melo ASO, Assunção PL, Gondim SSR, Carvalho DF, Amorim MMR, Benicio MHDA, Cardoso, MAA. Estado nutricional materno, ganho de peso gestacional e peso ao nascer. Rev. bras. epidemiol. 2007;10:249-57. DOI: http://dx.doi.org/10.1590/S1415-790X2007000200012

13. Geib LTC, Fréu CM, Brandão M, Nunes ML. Social and biological determinants of infant mortality in population cohort in the city of Passo Fundo, Rio Grande do Sul State. Ciênc. saúde coletiva. 2010;15:363-70. DOI: http://dx.doi.org/10.1590/S1413-81232010000200011.

14. Bresani CC, Souza AId, Batista-Filho M, Figueiroa JN. Anemia and iron deficiency in pregnant women: disagreements among the results of a cross-sectional study. Rev Bras Saúde Matern Infant. 2007; Supl.1:S15-S22. DOI: http://dx.doi.org/10.1590/S1519-38292007000600002.

15. Yip R. Significance of an abnormally low or high hemoglobin concentration during pregnancy: special consideration of iron nutrition. Am J Clin Nutr 2000; 72: 272S-9S.

16. Donovan A, Roy C, Andrews N. The ins and outs of iron homeostasis. Physiology. 2006 21:115-23. DOI: 10.1152/physiol.00052.2005

17. World Health Organization. The global prevalence of anaemia in 2011. Geneva: World Health Organization; 2015.

18. Batista Filho M, Souza AI, Bresani CC. Anemia as a public health problem: the current situation) Ciênc. saúde coletiva. 2008; 13:1917-22. DOI: http://dx.doi.org/10.1590/S1413-81232008000600002.

19. Peña-Rosas JP, De-Regil LM, Dowswell T, Viteri FE. Intermittent oral iron supplementation during pregnancy. Cochrane Database Syst Rev. 2012(7):CD009997.

20. Rahman MM, Abe SK, Rahman MS, Kanda M, Narita S, Bilano V, Ota E, Gilmour S, Shibuya K. Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: systematic review and meta-analysis. Am J Clin Nutr. 2016;103(2):495-504. DOI:10.3945/ajcn.115.107896.

21. Rocha DS, Netto MP, Priore SE, Lima NMM, Rosado LEFPL, Franceschini SCC. Nutritional status and iron-deficiency anemia in pregnant women: relationship with the weight of the child at birth. Rev Nutr. 2005;18(4):481-9. DOI: http://dx.doi.org/10.1590/S1415-52732005000400004.

22. Grotto HZ. Anaemia of cancer: an overview of mechanisms involved in its pathogenesis. Med Oncol. 2008;25(1):12-21. DOI: 10.1007/s12032-007-9000-8.

23. Abeysena C, Jayawardana P, de A Seneviratne R. Maternal haemoglobin level at booking visit and its effect on adverse pregnancy outcome. Aust N Z J Obstet Gynaecol. 2010;50(5):423-7. DOI: doi 10.1111/j.1479-828X.2010.01220.x.

24. Bakacak M, Avci F, Ercan O, Köstü B, Serin S, Kiran G, Bostanci MS, Bakacak, Z. The effect of maternal hemoglobin concentration on fetal birth weight according to trimesters. J Matern Fetal Neonatal Med. 2015;28(17):2106-10. DOI: 10.3109/14767058.2014.979149.

25. Koura GK, Ouedraogo S, Le Port A, Watier L, Cottrell G, Guerra J, Choudat I, Rachas A, Bouscaillou J, Massougboji A, et al. Anaemia during pregnancy: impact on birth outcome and infant haemoglobin level during the first 18 months of life. Trop Med Int Health. 2012;17(3):283-91. DOI: 10.1111/j.1365-3156.2011.02932.x.

26. Padhi BK, Baker KK, Dutta A, Cumming O, Freeman MC, Satpathy R, Das BS, Panigrahi P. Risk of Adverse Pregnancy Outcomes among Women Practicing Poor Sanitation in Rural India: A Population-Based Prospective Cohort Study. PLoS Med. 2015;12(7):e1001851. DOI: 10.1371/journal.pmed.1001851. eCollection.

27. CDC. Epi info, version 7. Centers for Disease Control and Prevention. 2017 Internet: https://www.cdc.gov/epiinfo/index.html. (accessed 02 august 2017).

28. Andriolo A, Ballarati CAF, Galoro CAO, Mendes ME, Melo MR, Sumita, NM. Collection and Preparation of the Biological Sample. Barueri, São Paulo: Minha Editora, 2014.

29. Gomes Filho IS, Macedo TCN, Cruz SS, Soledade KR, Trindade SC, Sarmento VA. Comparison of clinical diagnosis criteria to establish periodontal disease. Rev odonto ciênc. 2006;21(51).

30. Gomes-Filho IS, Cruz SS, Rezende EJ, Dos Santos CA, Soledade KR, Magalhães MA, et al. Exposure measurement in the association between periodontal disease and prematurity/low birth weight. J Clin Periodontol. 2007;34(11):957-63.

31. Brasil. Manual de instruções para o preenchimento da declaração de nascido vivo. Language in Portuguese. (Instruction manual for filling in the declaration of live birth) 3 ed. Brasília: Ministério da Saúde, 2001.

32. World Health Organization. Iron Deficiency Anaemia:Assessment, Prevention, and Control: A guide for programme managers. Geneva: World Health Organization, 2001.

33. Ong LD, LeClare PC. The Kolmogorov-Smirnov test for the log-normality of sample cumulative frequency distributions. Health Phys. 1968;14(4):376.

34. Satterthwaite FE. An approximate distribution of estimates of variance components. Biometrics. 1946;2(6):110-4.

35. Mann H, Whitney D. On a test whether one of two random variables is stochastically larger than the other. Annals of Mathematical Statistics. 1947;18:50-60.

36. Pearson K. On the criterion that a given system of deviations from the probable in the case of a correlated system of variables is such that it can be reasonably supposed to have arisen from random sampling. Philosophical Magazine Series 5. 1900;50(302):157-75.

37. Fisher RA. On the interpretation of $\chi 2$ from contingency tables, and the calculation of P. Journal of the Royal Statistical Society. 1922;85(1):87-94.

38. Hosmer DW, Lemeshow S, Sturdivant RX. Applied Logistic Regression . New York: Wiley, 2013.

39. Davidson R, MacKinnon JG. Estimation and Inference in Econometrics. New York: Oxford University Press, 1993.

40. STATA. Data analysis and statistical software, version 15. Serial number: 401506208261. 2017.

41. Vural T, Toz E, Ozcan A, Biler A, Ileri A, Inan AH. Can anemia predict perinatal outcomes in different stages of pregnancy? Pak J Med Sci. 2016;32(6):1354-9. DOI: 10.12669/pjms.326.11199.

42. Bener A, Salameh KM, Yousafzai MT, Saleh NM. Pattern of Maternal Complications and Low Birth Weight: Associated Risk Factors among Highly Endogamous Women. ISRN Obstet Gynecol. 2012;2012:540495.

43. Sekhavat L, Davar R, Hosseinidezoki S. Relationship between maternal hemoglobin concentration and neonatal birth weight. Hematology. 2011;16(6):373-6. DOI: 10.1179/102453311X13085644680186.

44. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75-84. DOI: 10.1016/S0140-6736(08)60074-4.

45. De Domenico I, Vaughn MB, Paradkar PN, Lo E, Ward DM, Kaplan J. Decoupling ferritin synthesis from free cytosolic iron results in ferritin secretion. Cell Metab. 2011;13(1):57-67. DOI: 10.1016/j.cmet.2010.12.003.

46. Harrison KA, Ibeziako PA. Maternal anaemia and fetal birthweight. J Obstet Gynaecol Br Commonw. 1973;80(9):798-804.

47. Hutter D, Kingdom J, Jaeggi E. Causes and mechanisms of intrauterine hypoxia and its impact on the fetal cardiovascular system: a review. Int J Pediatr. 2010; 2010:401323. DOI: 10.1155/2010/401323.

48. Stangret A, Wnuk A, Szewczyk G, Pyzlak M, Szukiewicz D. Maternal hemoglobin concentration and hematocrit values may affect fetus development by influencing placental angiogenesis. J Matern Fetal Neonatal Med. 2017; 30(2):199-204.

49. Ali AA, Rayis DA, Abdallah TM, Elbashir MI, Adam I. Severe anaemia is associated with a higher risk for preeclampsia and poor perinatal outcomes in Kassala hospital, eastern Sudan. BMC Res Notes. 2011;4:311. DOI: 10.1186/1756-0500-4-311.

50. Misra A, Ray S, Patrikar S. A longitudinal study to determine association of various maternal factors with neonatal birth weight at a tertiary care hospital. Med J Armed Forces India. 2015;71(3):270-3. DOI: 10.1016/j.mjafi.2015.03.001.

51. Trojner Bregar A, Blickstein I, Bržan Šimenc G, Janša V, Verdenik I, Lučovnik M, Tul N. Perinatal Advantages and Disadvantages of Being Underweight before Pregnancy: A Population-Based Study. Gynecol Obstet Invest. 2017; 82(3):303-6. DOI: 10.1159/000447557

52. Peña-Rosas JP, De-Regil LM, Gomez Malave H, Flores-Urrutia MC, Dowswell T. Intermittent oral iron supplementation during pregnancy. Cochrane Database Syst Rev. 2015 (10):CD009997.

53. Lone FW, Qureshi RN, Emmanuel F. Maternal anaemia and its impact on perinatal outcome in a tertiary care hospital in Pakistan. East Mediterr Health J. 2004;10(6):801-7.

54. Msuya SE, Hussein TH, Uriyo J, Sam NE, Stray-Pedersen B. Anaemia among pregnant women in northern Tanzania: prevalence, risk factors and effect on perinatal outcomes. Tanzan J Health Res. 2011;13(1):33-9.

55. Abioye AI, Aboud S, Premji Z, Etheredge AJ, Gunaratna NS, Sudfeld CR, Mongi R, Meloney L, Darling AM, Noor RA et al. Iron Supplementation Affects Hematologic Biomarker Concentrations and Pregnancy Outcomes among Iron-Deficient Tanzanian Women. J Nutr. 2016;146(6):1162-71. DOI: 10.3945/jn.115.225482.

56. Rukuni R, Bhattacharya S, Murphy MF, Roberts D, Stanworth SJ, Knight M. Maternal and neonatal outcomes of antenatal anemia in a Scottish population: a retrospective cohort study. Acta Obstet Gynecol Scand. 2016;95(5):555-64. DOI: 10.1111/aogs.12862.

57. Viana KJ, Taddei JA, Cocetti M, Warkentin S. Birth weight in Brazilian children under two years of age. Cad Saude Publica. 2013;29(2):349-56.

58. Banjari I, Kenjerić D, Mandić ML. What Is the Real Public Health Significance of Iron Deficiency and Iron Deficiency Anaemia in Croatia? A Population-Based Observational Study on Pregnant Women at Early Pregnancy from Eastern Croatia. Cent Eur J Public Health. 2015;23(2):98-103.

59. Casanova BF, Sammel MD, Macones GA. Development of a clinical prediction rule for iron deficiency anemia in pregnancy. Am J Obstet Gynecol. 2005;193(2):460-6.

60. Aikawa R, Ngyen CK, Sasaki S, Binns CW. Risk factors for iron-deficiency anaemia among pregnant women living in rural Vietnam. Public Health Nutr. 2006;9(4):443-8.

61. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, Onis M, Ezzati M, Grantham-McGregor S, Kartz J, Martorell R et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. The Lancet. 2013; 382(9890):427-451. DOI: 10.1016/S0140-6736(13)60937-X.

62. Barroso F, Allard S, Kahan BC, Connolly C, Smethurst H, Choo L, Khan K, Stanworth S. Prevalence of maternal anaemia and its predictors: a multi-centre study. Eur J Obstet Gynecol Reprod Biol. 2011;159(1):99-105. DOI: 10.1016/j.ejogrb.2011.07.041.

63. Vandevijvere S, Amsalkhir S, Van Oyen H, Egli I, Ines E, Moreno-Reyes R. Iron status and its determinants in a nationally representative sample of pregnant women. J Acad Nutr Diet. 2013;113(5):659-66. DOI: 10.1016/j.jand.2012.10.021

64. Bencaiova G, Breymann C. Mild anemia and pregnancy outcome in a Swiss collective. J Pregnancy. 2014;2014:307535. DOI: 10.1155/2014/307535.

65. Pita GM, Jiménez S, Basabe B, García RG, Macías C, Selva L, Hernández C, Cruz M, Herrera R, O´Farril R et al. Anemia in children under five years old in Eastern Cuba, 2005-2011. MEDICC Rev. 2014;16(1):16-23.

66. Treister-Goltzman Y, Peleg R, Biderman A. Anemia among Muslim Bedouin and Jewish women of childbearing age in Southern Israel. Ann Hematol. 2015;94(11):1777-84. DOI: 10.1007/s00277-015-2459-z.

67. Pinho-Pompeu M, Surita FG, Pastore DA, Paulino DS, Pinto E Silva JL. Anemia in pregnant adolescents: impact of treatment on perinatal outcomes. J Matern Fetal Neonatal Med. 2016;1-5. DOI: 10.1080/14767058.2016.1205032.

68. Smagulova IE, Sharmanov TSh, Balgimekov SA. The prevalence of anemia among children and women of reproductive age in Kazakhstan and basis of its prevention. Vopr Pitan. 2013;82(5):58-63.

69. Masukume G, Khashan AS, Kenny LC, Baker PN, Nelson G, Consortium S. Risk factors and birth outcomes of anaemia in early pregnancy in a nulliparous cohort. PLoS One. 2015;10(4):e0122729. DOI: 10.1371/journal.pone.0122729. eCollection

70. Mohamed MA, Ahmad T, Macri C, Aly H. Racial disparities in maternal hemoglobin concentrations and pregnancy outcomes. J Perinat Med. 2012;40(2):141-9. DOI: 10.1515/jpm.2011.137.

TABLES

Table 1. Number (n) and percentage (%) of the socioeconomic-demographic characteristics of the sample, according to the presence of anemia. Santo Antônio de Jesus, Bahia, Brazil, 2017 (n = 622).

CHARACTERISTICS	Maternal Anemia		p*
	Yes	No	
	n (%)	n (%)	
	155 (24.9)	467 (75.1)	
AGE (years)			
18-35	120 (24.0)	380 (76.0)	
<18	21 (33.9)	41 (66.1)	0.09
>35	14 (23.3)	46 (76.7)	0.91
EDUCATION LEVEL (years)			
≥8	108 (24.2)	338 (75.8)	
< 8	47 (26.7)	129 (73.3)	0.52
CONJUGAL STATUS			
With partner	140 (25.0)	419 (75.0)	
Without partner	15 (23.8)	48 (76.2)	0.83
RACE/SKIN COLOR			
Not black	91 (24.0)	288 (76.0)	
Black	64 (26.3)	179 (73.7)	0.51
CURRENT OCCUPATION			
Paid	65 (23.0)	218 (77.0)	
Unpaid	90 (26.6)	249 (73.4)	0.30
FAMILY INCOME[1]			
> 2 minimum wages	51 (27.4)	135 (72.6)	
≤ 2 minimum wages	104 (23.9)	332 (76.1)	0.35

HOUSEHOLD DENSITY (number of people per household)			
≤ 4	132 (25.8)	379 (74.2)	
>4	23 (20.7)	88 (79.3)	0.26

1- Minimum wage values (per month) at the time of collection: 2013, R $ 678.00; 2014, R $ 724.00; 2015, R $ 788.00; 2016, R $ 880.00; 2017, R $ 937.00.

* P value: level of significance ≤ 0.05.

Table 2. Number (n) and percentage (%) of the characteristics related to the health and lifestyle of the sample, according to the presence of maternal anemia. Santo Antônio de Jesus, Bahia, Brazil, 2017 (n = 622).

	Maternal Anemia		
CHARACTERISTICS	Yes	No	p*
	n (%)	n (%)	
	155 (24.9)	467 (75.1)	
SEX OF THE NEWBORN			
Male	70 (22.9)	236 (77.1)	0.25
Female	85 (26.9)	231 (73.1)	
URINARY INFECTION			
No	141 (24.1)	445 (75.9)	
Yes	14 (38.9)	22 (61.1)	0.05
PERIODONTITIS**			
No	111 (23.5)	361 (76.5)	0.68
Yes	23 (25.6)	67 (74.4)	
MATERNAL ARTERIAL HYPERTENSION			
No	151 (25.0)	454 (75.0)	
Yes	4 (23.5)	13 (76.5)	0.89

ABORTION			
No	128 (25.2)	380 (74.8)	
Yes	27 (23.7)	87 (76.3)	0.74
GESTATIONAL BMI[1]			
Proper weight	72 (25.3)	213 (74.7)	
Low weight	32 (27.6)	84 (72.4)	0.63
Overweight	40 (26.9)	109 (73.1)	0.72
Obese	11 (15.3)	61 (84.7)	0.08
PARITY			
> 2 children	118 (33.5)	234 (66.5)	0.01
≤ 2 children	65 (24.1)	205 (75.9)	
BEGINNING OF THE PRENATAL ACCOMPANIMENT			
≤ 3 months	128 (23.4)	419 (76.6)	0.02
> 3 months	27 (36.0)	48 (64.0)	
MATERNAL SMOKING HABIT**			
No	140 (24.6)	429 (75.4)	0.89
Yes	38 (25.5)	38 (74.5)	
ALCOHOLIC BEVERAGE CONSUMPTION DURING PREGNANCY			
No	124 (25.1)	371 (74.9)	0.54
Yes	24 (22.2)	84 (77.8)	
FERROUS SALT SUPPLEMENTATION DURING PREGNANCY			
No	30 (20.0)	120 (80.0)	
Yes	125 (26.5)	347 (73.5)	0.11

1 - The Atalah curve was employed to calculate this covariable;

* P value: level of significance ≤ 0.05;

** There were deficits in this information.

Table 3. Central tendency and dispersion measurements of the descriptors used to evaluate maternal anemia, according to the newborn weight, in users of the public health system in Santo Antônio de Jesus, Bahia, Brazil, 2017 (n = 622).

Descriptors	Weight < 3000 g		Weight ≥ 3000 g		
	Mean (±SD*)	Median	Mean (±SD*)	Median	p**
Hemoglobin level (g/dl)	11.6 (±1.1)	11.6	11.8 (±1.1)	11.9	0.03
Red blood cell count (millions)	4.1 (±0.4)	4.1	4.6 (±8.7)	4.2	0.14
Hematocrit (%)	35.1 (±3.2)	35.2	36.0 (±4.2)	36.3	0.02
Ferritin level (femtoliters)	44.8 (±38.9)	31.8	45.2 (±40.2)	32.2	0.89
Mean Corpuscular Volume - MCV (femtoliters)	85.9 (±7.1)	85.0	87.0 (±5.5)	86.4	0.06

* SD: Standard deviation;

** P value: level of significance ≤ 0.05;

*** Reference value: Hemoglobin: ≥ 11 g / dl; Blood cell count: > 4 million; Hematocrit: ≥ 33%; Ferritin: ≥ 15 femtoliters; MCV = 80-96 femtoliters.

Table 4. Crude and adjusted Relative Risk (RR) of the association between maternal anemia and low/insufficient birth weight with the corresponding 95% confidence intervals (95% CI).

Maternal anemia	Birth weight									
	<3000 g		≥3000 g		RR_{crude}	95% CI	p*	$RR_{adjusted**}$	95% CI	p*
	N	%	N	%						
Yes	57	36.8	98	63.2	1.36	1.06 to 1.76	0.02	1.38	1.07 to 1.77	0.01
No	126	27.0	341	73.0						

* P value: level of significance ≤ 0.05;

**Adjusted by maternal age, family income, urinary infection, parity, alcoholic beverage consumption during pregnancy and gestational BMI. Model fit test (Hosmer-Lemeshow): p = 0.74.

FIGURE

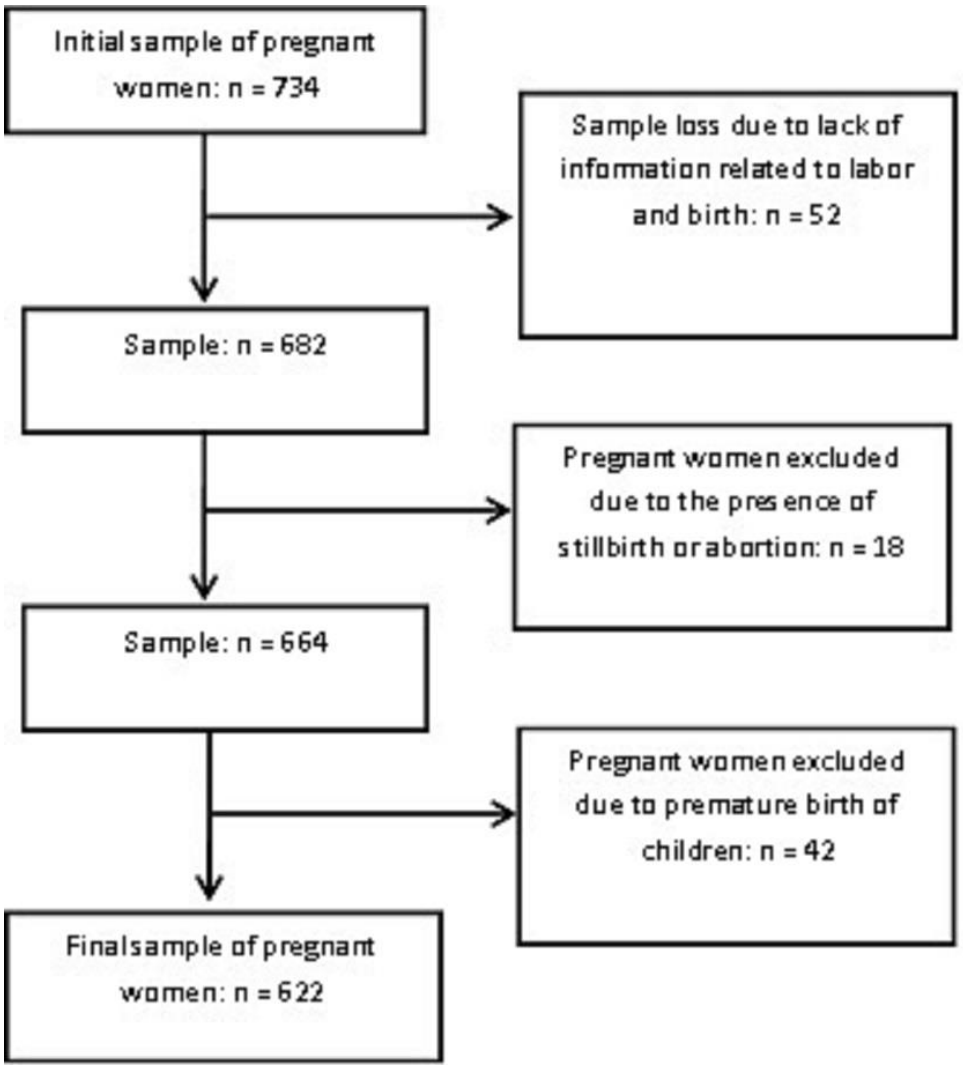

Figure 1. Flowchart of the sample participant selection process

APÊNDICE A- ARQUIVOS SUPLEMENTARES DO ARTIGO: MATERNAL ANEMIA AND LOW BIRTH WEIGHT: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Quadro 1. Estratégias de busca conforme base de dados

Medline (via pubmed) n= 5360	(“anemia” [Title/Abstract] OR "anemia"[MeSH Terms] OR “anaemia” [Title/Abstract] OR “anaemia” [MeSH Terms] OR “haemoglobin” [Title/Abstract] OR “haemoglobin” [MeSH Terms] OR “hemoglobin” [Title/Abstract] OR “hemoglobin” [MeSH Terms] OR “haematocrit” [Title/Abstract] OR “hematocrit” [Title/Abstract] OR “haematocrit” [MeSH Terms] OR “hematocrit” [MeSH Terms]) AND (“Pregnancy” [MeSH Terms] OR “Pregnancy” [Title/Abstract] OR “Pregnant Women” [Title/Abstract])] OR “Pregnant Women” [MeSH Terms] OR “gravidity” [Title/Abstract])] OR “gravidity” [MeSH Terms] OR “maternal exposure” [MeSH Terms] OR “maternal exposure” [Title/Abstract] OR “mother” [Title/Abstract] OR “mother” [MeSH Terms] OR “pregnan” [Title/Abstract] OR “pregnan” [MeSH Terms] OR “gravid” [Title/Abstract] OR “gravid” [MeSH Terms] OR “obstetric” [Title/Abstract] OR “obstetric” [MeSH Terms] OR “antenatal” [Title/Abstract] OR “antenatal” [MeSH Terms] OR “antepartum” [Title/Abstract] OR “antepartum” [MeSH Terms] OR “gestation” [Title/Abstract] OR “gestation” [MeSH Terms]) AND (“Infant, Low Birth Weight” [MeSH Terms] OR “Infant, Low Birth Weight” [Title/Abstract] OR “Low Birth Weight” [Title/Abstract]) AND(“case-control studies” [MeSH Terms] OR “case-control studies” [Title/Abstract] OR “retrospective studies” [Mesh] OR “retrospective studies” [Title/Abstract] OR “case-control study” [Title/Abstract] OR “Study, case-control” [Title/Abstract] OR “Studies, case-control” [Title/Abstract] OR “case-comparison studies” [Title/Abstract] OR “cohort studies” [MeSH Terms] OR “cohort studies” [Title/Abstract] OR “Longitudinal Studies” [MeSH Terms] OR “Follow-Up Studies” [MeSH Terms] OR “Prospective studies” [MeSH Terms] OR “cohort” [Title/Abstract] OR “longitudinal” [Title/Abstract] OR “prospective” [Title/Abstract] OR “retrospective” [Title/Abstract] OR “incidence study” [Title/Abstract] OR “follow up” [Title/Abstract] OR “case control” [Title/Abstract] OR “meta-analysis” [MeSH term])
Scopus n= 570	(TITLE-ABS-KEY(("anemia" OR “anaemia” OR “haemoglobin” OR “hemoglobin” OR “haematocrit” OR “hematocrit”)) AND TITLE-ABS-KEY (("Pregnancy" OR "Pregnant women” OR “gravidity” OR “maternal exposure" OR “Gestation” OR “Prenatal Care” OR “mother” OR “pregnan” OR “gravid” OR “obstetric” OR “antenatal” OR “antepartum” OR “gestation”)) AND TITLE-ABS-KEY (("Infant, Low Birth Weight" OR "Low Birth Weight" OR Low-Birth-Weight Infant)) AND TITLE-ABS-KEY (("retrospective studies" OR "case-control studies” OR “case-comparison studies" OR "cohort studies" OR "prospective studies" OR "longitudinal studies" OR "Incidence studies" OR "Incidence Study" OR “Retrospective Study” OR “Longitudinal Survey” OR “Analysis, Cohort” OR “meta-analysis”)))

Embase (sem medline) n= 443	'anemia'/exp OR 'anemia' OR 'anaemia'/exp OR 'anaemia' OR 'haemoglobin'/exp OR 'haemoglobin' OR 'hemoglobin'/exp OR 'hemoglobin' OR 'haematocrit'/exp OR 'haematocrit' OR 'hematocrit'/exp OR 'hematocrit' AND ('pregnancy'/exp OR 'pregnancy' OR 'pregnant women'/exp OR 'pregnant women' OR 'gravidity'/exp OR 'gravidity' OR 'maternal exposure'/exp OR 'maternal exposure' OR 'environmental exposure'/exp OR 'environmental exposure' OR 'mother'/exp OR 'mother' OR 'pregnan' OR 'gravid' OR 'obstetric' OR 'antenatal' OR 'prenatal care'/exp OR 'prenatal care' OR 'antepartum' OR 'gestation'/exp OR 'gestation') AND ('low birth weight'/exp OR 'low birth weight') AND ('case-control studies'/exp OR 'case-control studies' OR 'retrospective studies'/exp OR 'retrospective studies' OR 'case-control study'/exp OR 'case-control study' OR 'study, case-control' OR 'studies, case-control' OR 'case-comparison studies' OR 'cohort studies'/exp OR 'cohort studies' OR 'prospective studies'/exp OR 'prospective studies' OR 'longitudinal studies'/exp OR 'longitudinal studies' OR 'incidence studies' OR 'studies, incidence' OR 'study, incidence' OR 'cohort study'/exp OR 'cohort study' OR 'cohort analysis'/exp OR 'cohort analysis' OR 'longitudinal study'/exp OR 'longitudinal study' OR 'prospective study'/exp OR 'prospective study' OR 'case control study'/exp OR 'case control study' OR 'retrospective study'/exp OR 'retrospective study' OR 'cohort' OR 'longitudinal'/exp OR 'longitudinal' OR 'prospective' OR 'retrospective' OR 'incidence study' OR 'case' OR 'meta-analysis'/exp OR 'meta-analysis') NOT [medline]/lim
Web of science n= 722	(anemia OR anaemia OR haemoglobin OR hemoglobin OR haematocrit OR hematocrit) AND (Pregnancy OR Pregnant Women OR gravidity OR mother OR pregnan OR gravid OR obstetric OR antenatal OR antepartum OR gestation) AND (Infant, Low Birth Weight OR Low Birth Weight) AND (retrospective studies OR retrospective study OR case-control studies OR case-control study OR case-comparison studies OR case-comparison study OR cohort studies OR cohort study OR prospective studies OR prospective study OR longitudinal studies OR longitudinal study OR Incidence studies OR Incidence Study OR Follow-Up Studies OR cohort OR longitudinal OR prospective OR retrospective OR incidence study OR follow up OR case control OR meta-analysis)
Lilacs n = 73	(Low birth weight) AND (anemia in pregnancy)
SciELO n= 75	(Low birth weight) AND (anemia in pregnancy)

Quadro 2. Critérios de qualidade do instrumento Newcastle-Ottawa (21) para estudos de coorte e caso-controle.

Coorte
1. Seleção: representatividade (*), seleção dos não expostos (*), determinação da exposição(*) e existência anterior do desfecho(*) 2. Comparabilidade: Controle para confundimento (máximo**) 3. Desfecho: fonte para determinar o desfecho(*), tempo de seguimento(*) e adequação do acompanhamento(*).
Caso-controle
1. Seleção: definição do caso(*), representatividade dos casos(*), seleção dos controles(*), definição dos controles(*). 2. Comparabilidade: Controle para confundimento (máximo**). 3. Exposição: fonte de determinação da exposição(*), mesmo método para determinação de casos e controles(*), taxa de não-resposta(*).

Tabela 03. Avaliação da qualidade metodológica dos estudos de coorte

Autor	Reprers entativi dade	Seleção	Determinação da exposição	Desfech o	Comparabi lidade	Determinaçã o do desfecho	Seguiment o	Acompanhamen to	Pontuaçã o
Abeysena et al	0	1	1	1	0	1	1	1	6
Alizadeh et al	0	1	1	1	0	1	1	1	6
Bakacak et al	0	1	1	1	0	1	1	1	6
Bakhtiar et al	0	1	1	1	1	1	1	1	7
Bhalerao et al	0	1	1	1	0	1	1	1	6
Bodeaulivinec et al	0	1	1	1	0	1	1	1	6
Brabin et al	0	1	1	1	0	1	1	1	6
Dal Pizzol et al	1	1	1	1	2	1	1	1	9
Gailard et al	1	1	1	1	0	1	1	1	7
Hirve et al	0	1	1	1	0	1	1	1	6
Hosain et al	1	1	1	1	0	1	1	1	7
Knottnerus et al	0	1	1	1	1	1	1	1	7
Koura et al	0	1	1	1	0	1	1	1	6
Kumar et al	0	1	1	1	1	1	1	1	7
Lao e Ho	1	1	1	1	0	1	1	1	7
Levy et al	1	1	1	1	0	1	1	1	7
Lone et al	0	1	1	1	1	1	1	1	7
Malhotra et al	0	1	1	1	1	1	1	1	7
Mesa et al	1	1	1	1	0	1	1	1	7
Mohamed et al	0	1	1	1	0	1	1	1	6
Msuya et al	1	1	1	1	0	1	1	1	7

Continuação

Continuação

Autor	Reprers entativi dade	Seleção	Determinação da exposição	Desfech o	Comparabi lidade	Determinaçã o do desfecho	Seguiment o	Acompanhamen to	Pontuaçã o
Padhi et al	0	1	1	1	0	1	1	1	6
Rodriguez et al	0	1	1	1	0	1	1	1	6
Sananpanichku l et al		1	1	1	0	1	1	1	6
Scholl et al		1	1	1	2	1	1	1	8
Sekhavat et al		1	1	1	2	1	1	1	8
Sharma et al	0	1	1	1	0	1	1	1	6
Singh et al	0	1	1	1	0	1	1	1	6
Smithers et al	1	1	1	1	2	1	1	1	9
Steer et al	0	1	1	1	2	1	1	1	8
Tzur et al	0	1	1	1	2	1	1	1	8
Xiong et al	0	1	1	1	2	1	1	1	8
Yildiz et al	0	1	1	1	0	1	1	1	6
Yousaf et al	0	1	1	1	0	1	1	1	6
Zhou et al	1	1	1	1	0	1	1	1	7
Ahmad et al	1	1	1	1	0	1	1	1	7
Al-Sibai et al	0	1	1	1	0	1	1	1	6
Bian et al	0	1	1	1	1	1	1	1	7
Chang et al	0	1	1	1		1	1	1	6
El Guindi et al	0	1	1	1	0	1	1	1	6
Geelhoed et al	0	1	1	1	1	1	1	1	7
Lee et al	0	1	1	1	0	1	1	1	6
Masukume et al	1	1	1	1	2	1	1	1	9
Misra et al	0	1	1	1	0	1	1	1	6

Continuação

Autor	Representatividade	Seleção	Determinação da exposição	Desfecho	Comparabilidade	Determinação do desfecho	Seguimento	Acompanhamento	Pontuação
Perveen et al	0	1	1	1	0	1	1	1	6
Ren et al	1	1	1	1	2	1	1	1	9
Rukuni et al	0	1	1	1	2	1	1	1	8
Shobeiri et al	0	1	1	1	0	1	1	1	6
Stanisic et al	1	1	1	1	0	1	1	1	7
Tabrizi et al	0	1	1	1	0	1	1	1	6
Vural et al	0	1	1	1	0	1	1	1	6
Yazdani et al	0	1	1	1	0	1	1	1	6

Tabela 04. Avaliação da qualidade metodológica dos estudos de caso-controle

Autor	Definição dos casos	Representatividade dos casos	Seleção dos controles	Definição dos controles	Comparabilidade	Determinação da exposição	Determinação dos casos e controles	Taxa de não resposta	Pontuação
Ali et al	0	1	0	1	2	1	1	0	6
Banhidy et al	1	0	1	1	2	1	1	0	7
Bondevick et al	1	1	0	1	2	1	1	0	7
Buzyan et al	0	0	1	1	0	1	1	0	4
Cosme et al	1	0	0	1	0	1	1	0	4
Duthie et al	1	0	1	1	0	1	1	0	5
Elhassan et al	1	1	1	1	1	1	1	0	7
Hamalainen et al	0	1	0	1	0	1	1	0	4
Heredia-Oliveira et al	1	1	0	1	0	1	1	0	5
López et al	1	1	0	1	0	0	1	0	4
Nasiri-Amiri	1	0	1	1	2	1	1	0	7
Negandhi et al	1	1	0	1	1	1	1	0	6
Rizvi et al	1	1	0	1	1	1	1	0	6
Sharma et al	1	0	0	1	1	1	1	0	5

Tabela 01. Descrição dos estudos

Primeiro autor, ano	Tamanho da amostra	País	Delineamento	Categorização da anemia materna	Definição da exposição	Resultados principais	Exposição (%)	Desfecho (%)
Alizadeh, 2014	86	Irã	Coorte Prospectiva	**Segundo trimestre:** Hb 9 -10.9g/dl; Hb 7-8.9g/dl; Hb <7g/dl **Terceiro trimestre:** Hb < 11g/dl; Hb 8.5 -10.4g/dl; Hb 6.5-8.4g/dl; Grave: Hb <6.5 g/dl	**Segundo trimestre:** Hb < 10.5g/dl; **Terceiro trimestre**: Hb< 11g/dl		12.8 (segundo trimestre); 27.9 (terceiro trimestre)	16.3
Bhalerao, 2011	1200	Índia	Coorte Prospectiva		Hb< 11g/dl	Houve associação entre a exposição e o desfecho investigados.	65.6	10.3
Koura, 2012	580	Benim	Coorte Prospectiva		Hb< 11g/dl	Não houve associação entre a exposição e o desfecho investigados.	39.5	10.1
Vural, 2016	21826	Turquia	Coorte Prospectiva	Hb 10 a 11 g/dl; Hb <10g/dl	Hb< 11g/dl		25.1 (global); 11.9 (primeiro trimestre);	12.9

							32.1 (segundo trimestre); 33.0 (terceiro trimestre)	
Ahmad, 1997	9860	Malásia	Coorte Retrospectiva	Hb 9-10.9 g/dl; Hb < 9 g/dl	Hb< 11g/dl		47.5	6.0
Bakhtiar, 2007	860	Paquistão	Coorte Prospectiva		Hb< 11g/dl		46.7	7.3
Bodeaulivinec , 2011	1508	Benim	Coorte Prospectiva	Hb 10–10.9 g/dL; Hb 8–9.9 g/dL; Hb < 8 g/dL	Hb< 11g/dl			
Bondevick, 2001	1400	Nepal	Caso-controle	Ht < igual 24 %; Ht 25%–27 %; Ht 28%–30 %; Ht 31%–33%;	Ht <33%	Não houve associação entre a exposição e o desfecho investigados.	55.9	10.2
El Guindi	222	Guiana Francesa	Coorte Retrospectiva		Hb < 8 g/dl		50.0	11.3
Hamalainen, 2003	22799	Finlândia	Coorte Retrospectiva		Hb< 11g/dl	Não houve associação entre a exposição e o desfecho investigados.	2.6	2.9
Heredia-Oliveira , 2016	246	Peru	Caso-controle		Hb< 11g/dl		18 .3	50.0
Hirve, 1994	1922		Coorte Prospectiva		Hb 7 a 9 g/dl	Houve associação entre a		

						exposição e o desfecho investigados.		
Hosain, 2006	350	Bangladesh	Coorte Prospectiva		Hb < 8g/dl	Houve associação entre a exposição e o desfecho investigados.	47.7	24.0
Knottnerus, 1990	796	Países baixos	Coorte Prospectiva	Hb ≤ 6.9 g/dl; Hb 7-7.9g/dl	Hb < igual 8g/dl		5 .5	
Malhotra , 2002	447		Coorte Prospectiva	Hb 9–10.9 g/dl; Hb 7–8.9 g/dl; Hb < 7 g/dl	Hb< 11g/dl		72 .5	
Perveen, 2016	234	Paquistão	Coorte Prospectiva		Hb < 11g/dl e Ferritina < 12g/dl	Houve associação entre a exposição e o desfecho investigados.	50.0	26.9
Scholl, 1992	779	Inglaterra	Coorte Prospectiva		**Primeiro e terceiro trimestre:** Hb < 11g/dl; **Segundo trimestre:** Hb < 10.5 g/dl; Ferritina < 12g/dl	Não houve associação entre anemia materna e baixo peso ao nascer, no entanto a medida de efeito ajustada entre anemia ferropriva e o desfecho	27 .8	

						investigado apresentou-se com significância estatística (OR: 3.10; IC95%: 1.16;4.39).		
Steer , 1995	153602	Inglaterra	Coorte Retrospectiva		Hb < 11g/dl	Houve associação entre níveis de hemoglobina inferiores a 8.5 g/dl e baixo peso ao nascer.	19.3	
Xiong, 2003	15943	China	Coorte Retrospectiva	Hb 8–9 g/dl; Hb < 8 g/dl	Hb < 10g/dl	Não houve associação entre anemia materna e baixo peso ao nascer, mesmo após ajuste da medida de efeito.	18.9	3.1
Yousaf, 2011	818	Paquistão	Coorte Prospectiva		Hb < 11g/dl	Houve associação entre a exposição e o desfecho investigados.	49.8	7.3

Zhou, 1988	829	China	Coorte Prospectiva	Hb 10-10.9 g/dl; Hb 9.0-9.9 g/dl; Hb <9.0g/dl	Hb < 11g/dl	Houve associação entre a exposição e o desfecho investigados, conforme os níveis de gravidade da anemia materna.	48.7	
Abeysena , 2010	817	Sri Lanka	Coorte Prospectiva		Hb < 11g/dl	Não houve associação entre anemia materna e baixo peso ao nascer, mesmo após ajuste da medida de efeito.	7.1	11 .8
Ali, 2011	909	Sudão	Caso-controle	Hb 7-10.9 g/dl; Hb < 7g/dl	Hb < 11g/dl		41.9	10.6
Banhidy, 2011	38151	Hungria	Caso-controle		Hb < 11g/dl	Houve associação entre a exposição e o desfecho investigados, mesmo após ajuste da	16.7	5.7

						medida de efeito.		
Bian, 2013	55633	China	Coorte Retrospectiva		Hb < 10.5		4.9	1.7
Buzyan,2015	421	Rússia	Caso-controle		Hb < 11g/dl	Não houve associação entre anemia materna e baixo peso ao nascer, porém não apresenta a medida de efeito.	90.3	
Chang,2033	918	Estados Unidos da América	Coorte Retrospectiva		Primeiro trimestre: Hb < 11 g/dl ; Segundo trimestre: Hb < 10.5 g/dl	Não houve associação entre anemia materna e baixo peso ao nascer.	13.0	
Elhassan, 2010	194	Sudão	Caso-controle	Hb 9-10.9 g/dl; Hb 7 - 8.9 g/dl; Hb < 7 g/dl	Hb < 11g/dl	Houve associação entre a exposição e o desfecho investigados, mesmo após ajuste da medida de efeito.	47.4	12.6

Geelhoed,2006	309	Gana	Coorte Retrospectiva	Hb < 8g/dl	Valores de hemoglobina superiores a 7g/dl não foram associados ao desfecho. Foi encontrada associação entre exposição e desfecho, quando os níveis de hemoglobina foram menores ou iguais a 6 g/dl.	50.8	12.9
Lee,2006	169	Coreia	Coorte Prospectiva	Hb < 10.5 g/dl	Média geral da dosagem de ferritina: 89.4 g/dl; 30,4% das gestantes foram diagnósticadas com anemia ferropriva.		
Levy,2005	153396	Israel	Coorte Retrospectiva	Hb < 10g/dl		8 .6	9.5

Lone,2004	629	Paquistão	Coorte Prospectiva		Hb < 11g/dl	Houve associação entre a exposição e o desfecho investigados na medida bruta, após o ajuste do modelo houve perda da significância.	49.8	9.7
Masukume,2015	5609	Multicêntrico: Nova Zelândia, Austrália, Inglaterra e Irlanda	Coorte Prospectiva		Hb < 11g/dl	Não houve associação entre anemia materna e baixo peso ao nascer, mesmo após ajuste da medida de efeito.	2.2	5.2
Misra,2015	124		Coorte Prospectiva		Hb < 11g/dl	Não houve associação entre anemia materna e baixo peso ao nascer.	45.5	26.6
Mohamed, 2012		Estados Unidos da América	Coorte Retrospectiva	Hb 10 - 10.9 g/dl; Hb 9 - 9.9g/dl; Hb <9g/dl	Hb < 11g/dl	Houve associação entre a exposição e o	4.7	13.7

						desfecho investigados.		
Msuya, 2011	2256	Tanzânia	Coorte Prospectiva	Hb 9 - 10.9 g/dl; Hb 7 - 8.9 g/dl; Hb <7g/dl	Hb < 11g/dl		47.4	
Negandhi, 2014	390	Índia	Caso-controle		Hb < 10g/dl	Não houve associação entre anemia materna e baixo peso ao nascer.	30.5	36.9
Padhi,2015	667	Índia	Coorte Prospectiva		Hb < 11g/dl		63.9	14.2
Ren, 2007	88149	China	Coorte Retrospectiva		Hb < 11g/dl	Houve associação entre a exposição e o desfecho investigados, mesmo após ajuste da medida de efeito.	21.9	1.9
Rizvi, 2007		Paquistão	Caso-controle		Não define a classificação de anemia materna	Informa que a média dos níveis de hemoglobina materna foi mais baixa (9.4 +-1.7) no grupo de		

					crianças com baixo peso quando comparadas as crianças com peso normal (10.6+-1.4).		
Rukuni, 2016	80422	Escócia	Coorte Prospectiva	< 10g/dl	Houve associação entre a exposição e o desfecho investigados, mesmo após ajuste da medida de efeito.	9.3	6.2
Sananpanichkul , 2015	2012	Tailândia	Coorte Retrospectiva	Ht < 33%		13.2	1.4
Sharma, 2015	465	Nepal	Caso-controle	Hb < 11g/dl	Não houve associação entre anemia materna e baixo peso ao nascer, mesmo após ajuste da medida de efeito.	89.2	33.3
Singh ,2014	400	Índia	Caso-controle	Hb < 11g/dl			

Stanisic,2015	305	Papua-Nova Guiné	Coorte Prospectiva		Hb < 11g/dl		28.2	16.7
Tabrizi,2015	1405	Irã	Coorte Prospectiva	Hb 8.1 -10 g/dl; Hb 6.5 - 8.0 g/dl; Hb < 6.5 g/dl	Hb <10 g/dl		20.2	
Tzur	33888		Coorte Retrospectiva		Hb < 10g/dl		5.1	9.1
Yazdani,2004	598	Irã	Coorte Prospectiva		Hb < 10.5 g/dl		30.1	13.2
Yildiz,2014	28630	Turquia	Coorte Retrospectiva	Hb < 10g/dl; Hb 10 - 11g/dl	Hb < 11g/dl	Houve associação entre a exposição e o desfecho investigados.		
Al-Sibai,1989	204	Arábia Saudita	Coorte Retrospectiva		Hb < 10.6 g/dl		8.3	21.6
Brabin, 1990		Papua-Nova Guiné	Coorte Prospectiva		Hb< 8g/dl		46.1	
Cosme, 2009	158	Cuba	Caso-controle		Hb < 11g/dl	Houve associação entre a exposição e o desfecho investigados.		33.1
Dal Pizzol, 2009	3865	Brasil	Coorte Prospectiva		Hb < 11g/dl	Não houve associação entre anemia materna e baixo peso ao	31.2	8.0

						nascer, mesmo após ajuste da medida de efeito.		
López, 2012	632	Cuba	Caso-controle		Hb<11 g/dl ou Ht < 34%		6.5	6.5
Mesa, 2012	336	Colômbia	Coorte Retrospectiva		Hb < 11g/dl		15.1	
Rodriguez,1991	691	Brasil	Coorte Prospectiva		Hb < 11g/dl	A anemia materna não foi associada ao baixo peso ao nascer, no entanto não foi apresentada a medida de efeito.	29.2	12.9
Gailard,2014	7256	Holanda	Coorte Prospectiva		Hb <11 g/dl ou Ht <=33%	Não houve associação entre anemia materna e baixo peso ao nascer.	13.6	4.8
Guindi	222	Guiana Francesa	Coorte Retrospectiva		Hb < 8g/dl		46.0	
Bakacak,2015	329	Turquia	Coorte Prospectiva	Hb 9-11 g/dl; Hb <9g/dl	Hb < 11g/dl			
Duthie,1991	96	China	Caso-controle		Hb < 8g/dl	63,5% das gestantes tinham	-	-

						ferropenia, embora não seja relatado se foi realizado a dosagem de ferritina ou transferritina.		
Lao, 2004	726	China	Caso-controle		Hb < 10g/dl			
Nasiri-Amiri, 2007	609	Irã	Coorte Prospectiva	Ht < 25%; Ht 25-33,9%	Ht <34%	Houve associação entre a exposição e o desfecho investigados, mesmo após ajuste da medida de efeito.	11.3	8.9
Sekhavat, 2011	1842	Irã	Coorte Prospectiva		Hb <10g/dl	Houve associação entre a exposição e o desfecho investigados.	21.6	9.2
Sharm, 2008		Nova Deli	Coorte Prospectiva	Hb 8 - 10.9 g/dl; Hb 5 -7,9g/dl	Hb < 11g/dl		88.8	
Shobeiri, 2006	500	Índia	Coorte Prospectiva	**Primeiro trimestre:** Hb 8 - 8.9 g/d; Hb 6 -7.9g/dl; Hb < 6.0 g/dl.	Hb < 10.5g/dl		45.6 (primeiro trimestre); 49.4	

				Segundo trimestre: Hb 8.5-10.4 g/dl; Hb 8.5 - 10.4 g/dl; Hb <6.5 g/dl			(segundo trimestre); 16.2 (terceiro trimestre)	
Smithers, 2014	137715	Austrália	Coorte Prospectiva		Hb < 11g/dl	Não houve associação entre anemia materna e baixo peso ao nascer, mesmo após ajuste da medida de efeito.	7.0	6.3
Kumar, 2010	2027	Índia	Coorte Prospectiva		Hb < 10 g/dl	Houve associação entre anemia materna e baixo peso ao nascer, mesmo após ajuste da medida de associação.	99.3	-

Tabela 02. Características dos estudos

Autor	Ano de publicação	Fonte dos dados	Desfecho principal investigado	Exposição principal investigada	Periodo da Pesquisa	Local da coleta dos dados	Fonte da coleta dos dados	Fonte das informações para determinar anemia materna	Diagnóstico diferencial para anemia materna
Alizadeh et al	2014	Embase	Peso ao nascer e Apgar	Anemia materna		Hospital	Entrevista	Exame laboratorial	Não
Bhalerao et al	2011	Embase	Desfechos gestacionais	Anemia materna	Janeiro a dezembro de 2009	Hospital	Entrevista	Exame laboratorial	Não
Koura et al	2012	Embase	Desfechos gestacionais	Anemia materna	Junho de 2007 a julho de 2008	Hospital	Entrevista	Exame laboratorial	Não
Vural et al	2016	Embase	Desfechos gestacionais	Anemia materna	Janeiro de 2011 a setembro de 2014	Hospital	Prontuário	Exame laboratorial	Não
Ahmad et al	1997	Outras fontes	Desfechos gestacionais	Anemia materna	Agosto de 1992 a julho de 1993	Unidade de Saúde primária	Prontuário	Prontuário	Não
Bakhtiar et al	2007	Outras fontes	Desfechos gestacionais	Anemia materna	Janeiro de 2004 a dezembro de 2005	Hospital	Prontuário	Prontuário	Não
Bodeaulivinec et al	2011	Outras fontes	Baixo peso ao nascer	Anemia materna	Julho de 2005 a	Hospital	Prontuário	Exame laboratorial	Não

					abril de 2008				
Bondevick et al	2001	Outras fontes	Baixo peso ao nascer	Níveis de hemoglobina	Agosto de 1994 a julho de 1995	Hospital	Prontuário	Exame laboratorial	Não
Hamalainen et al	2003	Outras fontes	Baixo peso ao nascer	Anemia materna	1990-2000	Hospital	Prontuário	Prontuário	Não
Heredia-Oliveira et al	2016	Outras fontes	Peso ao nascer	Fatores de risco	2010-2011	Hospital	Prontuário	Prontuário	Não
Hirve et al	1994	Outras fontes	Peso ao nascer	Fatores de risco			Prontuário	Exame laboratorial	Não
Hosain et al	2006	Outras fontes	Baixo peso ao nascer	Fatores de risco	2000-2001	Unidade de Saúde primária	Prontuário	Prontuário	Não
Knottnerus et al	1990	Outras fontes	Desfechos gestacionais	Níveis de hemoglobina	Julho de 1985 a maio de 1986	Hospital	Prontuário	Prontuário	Não
Kumar	2010	Outras fontes	Desfechos gestacionais	Fatores de risco	2005 a 2006	Hospital	Prontuário	Prontuário	Não
Malhotra et al	2002	Outras fontes	Desfechos gestacionais	Anemia materna	Janeiro 2001 a setembro 2001		Prontuário	Prontuário	Não
Perveen et al	2016	Outras fontes	Desfechos gestacionais	Anemia ferropriva materna	Fevereiro de 2011 a agosto de 2011	Hospital	Prontuário	Prontuário	Sim (dosagem de ferritina)
Scholl et al	1992	Outras fontes	Prematuridade	Anemia materna		Hospital	Prontuário	Prontuário	Sim (dosagem de ferritina)

Steer et al	1995	Outras fontes	Peso ao nascer	Niveis de hemoglobina	1988-1991	Hospital	Prontuário	Prontuário	Não
Xiong et al	2003	Outras fontes	Desfechos gestacionais	Anemia materna	Janeiro de 1989 a dezembro de 1990	Hospital	Prontuário	Prontuário	Não
Yousaf et al	2011	Outras fontes	Desfechos gestacionais	Anemia materna	Março a dezembro de 2007	Hospital	Prontuário	Prontuário	Não
Zhou et al	1998	Outras fontes	Baixo peso ao nascer	Anemia materna	Junho de 1991 a junho de 1992	Unidade de Saúde primária	Entrevista e prontuário	Prontuário	Não
Abeysena et al	2010	Pubmed	Desfechos gestacionais	Anemia materna	Maio de 2001 a abril de 2002	Hospital	Prontuário	Exame laboratorial	Não
Ali et al	2011	Pubmed	Desfechos gestacionais	Anemia materna	Janeiro de 2008 a dezembro de 2010	Hospital	Banco de dados secundários	Prontuário	Não
Al-Sibai et al	1989	Pubmed	Baixo peso ao nascer	Fatores de risco	1981-1985	Hospital	Prontuário	Prontuário	Não
Banhidy et al	2011	Pubmed	Desfechos gestacionais	Anemia materna	1980-1996	Hospital	Banco de dados secundários	Prontuário	Não
Bian et al	2013	Pubmed	Baixo peso ao nascer	Fatores de risco	2001 a 2008	Hospital	Prontuário	Prontuário	Não

Brabin et al	1990	Pubmed	Desfechos gestacionais	Anemia materna	Julho de 1985 a junho de 1987	Hospital	Entrevista e prontuário	Exame laboratorial	Não
Buzyan et al	2015	Pubmed	Desfechos gestacionais	Anemia materna leve	Janeiro a março de 2014	Hospital	Prontuário	Prontuário	Não
Chang et al	2003	Pubmed	Desfechos gestacionais	Níveis de hemoglobina	1990 a 2000	Hospital	Prontuário	Exame laboratorial	Não
Elhassan et al	2010	Pubmed	Baixo peso ao nascer	Anemia Materna	Agosto a outubro de 2009	Hospital	Entrevista e prontuário	Exame laboratorial	Não
Geelhoed et al	2006	Pubmed	Desfechos gestacionais	Anemia materna grave	Janeiro de 1999 a janeiro de 2000	Hospital	Prontuário	Prontuário	Não
Lee et al	2006	Pubmed	Desfechos gestacionais	Anemia materna		Hospital	Entrevista e prontuário	Exame laboratorial	Sim (dosagem de ferritina)
Levy et al	2005	Pubmed	Baixo peso ao nascer	Anemia materna	1988 a 2002	Hospital	Prontuário	Prontuário	Não
Lone et al	2004	Pubmed	Desfechos gestacionais	Anemia materna	Outubro de 2001 a outubro de 2002	Hospital	Entrevista e prontuário	Prontuário	Não
Masukume et al	2015	Pubmed	Desfechos gestacionais	Anemia materna	Novembro de 2004 a fevereiro de 2011		Prontuário	Exame laboratorial	Não

Misra et al	2015	Pubmed	Peso ao nascer	Fatores de risco		Hospital	Prontuário	Prontuário	Não
Mohamed et al	2012	Pubmed	Peso ao nascer	Níveis de hemoglobina	Janeiro de 1990 a dezembro de 2003	Hospital	Prontuário	Prontuário	Não
Msuya et al	2011	Pubmed	Desfechos gestacionais	Anemia materna	Junho de 2002 a março de 2004	Unidade de Saúde primária	Entrevista	Exame laboratorial	Não
Negandhi et al	2014	Pubmed	Baixo peso ao nascer	Fatores de risco		Hospital	Entrevista	Exame laboratorial	Não
Padhi et al	2015	Pubmed	Desfechos gestacionais	Fatores de risco		Hospital	Entrevista e prontuário	Prontuário	Não
Ren et al	2007	Pubmed	Pequeno para idade gestacional	Anemia materna	1995 a 2000	Unidade de Saúde primária	Prontuário	Exame laboratorial	Não
Rizvi et al	2007	Pubmed	Baixo peso ao nascer	Fatores de risco		Hospital	Prontuário	Prontuário	Não
Rukuni et al	2016	Pubmed	Desfechos gestacionais	Anemia materna					
Sananpanichkul et al	2015	Pubmed	Baixo peso ao nascer	Índice de Massa Corporea Gestacional	1 de janeiro a 30 de junho de 2013	Hospital	Prontuário	Prontuário	Não
Sharma et al	2015	Pubmed	Baixo peso ao nascer	Fatores de risco		Hospital	Prontuário	Prontuário	Não

Singh et al	2014	Pubmed	Baixo peso ao nascer	Fatores de risco	Abrila a agosto de 2011	Hospital	Prontuário	Prontuário	Não
Stanisic et al	2015	Pubmed	Desfechos gestacionais	Fatores de risco para malária	Setembro de 2005 a outubro de 2007	Unidade de Saúde primária	Entrevista	Exame laboratorial	Não
Tabrizi et al	2015	Pubmed	Peso ao nascer	Anemia materna	2015-2015	Hospital	Prontuário	Exame laboratorial	Não
Tzur et al	2012	Pubmed	Desfechos gestacionais	Anemia materna		Hospital	Prontuário	Exame laboratorial	Não
Yazdani et al	2004	Pubmed	Baixo peso ao nascer	Anemia materna	Agosto de 2001 a setembro de 2002	Hospital	Prontuário	Prontuário	Não
Yildiz et al	2014	Pubmed	Peso ao nascer	Anemia materna	Janeiro de 2010 a dezembro de 2011	Hospital	Prontuário	Prontuário	Não
Cosme et al	2009	Scielo	Baixo peso ao nascer	Fatores de risco	Janeiro de 2005 a dezembro de 2007	Hospital	Prontuário	Prontuário	Não
Dal Pizzol et al	2009	Scielo	Prematuridade e baixo peso ao nascer	Uso de sais de ferro	Fevereiro de 1991 a junho de 1995	Unidade de Saúde primária	Entrevista e prontuário	Exame laboratorial	Não

López et al	2012	Scielo	Baixo peso ao nascer	Fatores de risco	Janeiro de 2003 a dezembro de 2008	Hospital	Prontuário	Prontuário	Não
Mesa et al	2012	Scielo	Baixo peso ao nascer	Condição nutricional materna	Janeiro a dezembro de 2007	Hospital	Entrevista e prontuário	Exame laboratorial	Não
Rodriguez et al	1991	Scielo	Peso ao nascer	Anemia materna		Hospital	Prontuário	Exame laboratorial	Não
Gailard et al	2014	Scopus	Desfechos gestacionais	Anemia materna		Comunidade	Entrevista	Exame laboratorial	Não
Guindi et al	2004	Scopus	Desfechos gestacionais	Anemia materna	Janeiro de 1999 a dezembro de 2000	Hospital	Prontuário	Exame laboratorial	Sim (92.7% < 20g/l)
Bakacak et al	2015	Web of Science	Peso ao nascer	Anemia materna	Janeiro de 2013 a janeiro de 2014	Hospital	Prontuário	Prontuário	Não
Duthie et al	1991	Web of Science	Desfechos gestacionais	Anemia materna	1985-1989	Hospital	Prontuário	Prontuário	Sim (não específica)
Lao e Ho	2004	Web of Science	Diabetes Mellitus	Deficiência de ferro		Comunidade	Prontuário	Prontuário	Sim (não específica)
Nasiri-Amiri	2007	Web of Science	Desfechos gestacionais	Anemia materna	Dezembro de 2001 a dezembro de 2002	Hospital	Entrevista e prontuário	Exame laboratorial	Não
Sekhavat et al	2011	Web of Science	Baixo peso ao nascer	Anemia materna	2009 a 2010	Hospital	Entrevista e	Exame laboratorial	Não

							prontuário		
Sharma et al	2008	Web of Science	Desfechos gestacionais	Anemia materna	Abril de 2005 a dezembro de 2006	Hospital	Prontuário	Exame laboratorial	Não
Shobeiri et al	2006	Web of Science	Desfechos gestacionais	Anemia materna		Hospital	Entrevista	Exame laboratorial	Não
Smithers et al	2014	Web of Science	Desfechos gestacionais	Anemia materna	1999 a 2005	Comunidade	Banco de dados secundários	Prontuário	Não

PRISMA CHECKLIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	43
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	43
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	43
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	44
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	45
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	45
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	45
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	45
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	46
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	46
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	47

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	48
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	47
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	47
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	47
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	47 and 48
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	48
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	48
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2 and Figure 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	49
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	48 and Figure 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	50 amd Table 2
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	50
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	51 and 52
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	53

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	-

APÊNDICE B - ARQUIVOS SUPLEMENTARES DO ARTIGO: MATERNAL ANEMIA AND BIRTH WEIGHT: A PROSPECTIVE COHORT STUDY.

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Você está sendo convidada a participar do Projeto de Pesquisa intitulado "**Determinantes estruturais, socioeconômicos, demográficos, nutricionais e gineco-obstétricos da anemia em gestantes usuárias do Programa de Saúde da Família do município de Santo Antônio de Jesus - Bahia**". Sua participação é muito importante, porém, você só deve participar se assim desejar. As informações deste estudo são confidenciais e, em nenhum momento, serão divulgados nomes e características que possam identificar as participantes do estudo. Leia atentamente as informações abaixo e faça as perguntas que achar necessárias para qualquer esclarecimento. O objetivo desta pesquisa é identificar os fatores que podem estar associados à anemia em gestantes atendidas em unidades de Saúde da Família. Ao concordar em participar, vocêirá responder um questionário, em que serão feitas perguntas a respeito do seu estado de saúde e seus hábitos de vida mas lembre-se: você pode recusar responder a algumas questões, se assim o desejar. O risco em participar desta pesquisa envolve o constrangimentoque poderá ser evitado utilizando uma sala reservada ou um espaço afastado de outras pessoas. Além disso, sua altura e seu peso corporal serão verificados e anotados em uma ficha da pesquisa. Para verificar a existência ou não da anemia, uma amostra do seu sangue será coletada através da punção de um acesso venoso periférico realizado por uma pessoa da equipe previamente treinada. Como medida protetora, este acesso será realizado respeitando os cuidados de higiene e segurança para não haver risco de contaminação e, eventualmente, poderá causar dor leve, arroxeamento, calor e vermelhidão no local, semelhante às coletas de sangue que são feitas para realização de exames de laboratório rotineiros da gravidez. As anotações presentes no seu cartão da gestante e no seu prontuário também poderão ser consultadas. Você terá acesso aos resultados da pesquisa, visto queserão apresentados à Secretaria Municipal de Saúde e divulgados em forma de artigo, servindo para todos os profissionais de saúde que atuam nas unidades de saúde da família, assim como os gestores em saúde compreender melhor quais os fatores poderão estar relacionados com a existência de anemia em gestantes. Como benefícios, com a realização da pesquisa, será possível conhecer melhor a condição de saúde da gestante, e contribuir para que haja desenvolvimento de ações voltadas para prevenção dessa doença e promoção da saúde.Suas informações serão confidenciais e de responsabilidade dos profissionais que trabalharão na pesquisa, sendo guardadas no Núcleo de Epidemiologia e Saúde UEFS por um período de 5 anos, após esse período o material será destruído. As informações adquiridas serão utilizadas nesta pesquisa e poderá contribuir para futuros estudos sobre o tema.Caso haja despesas decorrentes da sua participação na pesquisa, você receberá de volta o que pagou, assim como se houver qualquer dano comprovadamente decorrente da pesquisa, você será indenizado, sendo de responsabilidade de nós, pesquisadores, a garantia do seu acompanhamento, até a resolução do seu problema. Caso você, ou o seu responsável não deseje participar do estudo, terão liberdade de recusar ou abandonar a participação a qualquer momento, sem qualquer prejuízo. Portanto, atenção: sua participação em qualquer tipo de pesquisa é voluntária.Duas vias serão assinadas e uma via será retida pelo participante da pesquisa. __/__/__, _____

_____ _____

Nome da voluntária **Assinatura da voluntária ou responsável**

_____

Pesquisadora responsável: Renata Marques da Silva

_____

Universidade Estadual de Feira de Santana – UEFS – Av. Transnordestina, S/N – Novo Horizonte – Feira de Santana – BA – Módulo 6 – Prédio de Pós Graduação em Saúde Coletiva – Núcleo de Epidemiologia e Saúde (75) 3161-8095

FICHA DE COLETA DE DADOS

Nº do questionário: _____ Unidade Básica de Saúde:_____

Dados da Gestante:

Nome**:**_____

Endereço completo:_____

Bairro:_____ Como se chega lá?_____

_____

Telefone de contato:_____ Apelido:_____

O nome completo de outro parente ou amigo (a) sua?

Alguém que no caso de mudança, possa nos informar notícias suas?

Nome:_____

Endereço completo:_____

Bairro:_____ Como se chega lá?_____

_____

Telefone de contato:_____ Apelido:_____

CARACTERÍSTICAS SÓCIO-DEMOGRÁFICAS

1- Estudou/estuda? □ Sim (1) □ Não (2)

2- Até que ano da escola completou? Série_____ Total de anos de estudo:_____

3- Estado civil:

□ Solteira (1) □ Casada (2) □ Mora com companheiro (3) □ Divorciada (4) □Viúva (5) □ Separada (6)

4- Situação de emprego: □ Sim (1) □ Não (2)

5- Última profissão exercida:_____ □ NSA

6- Cor da sua pele:

□ Amarela (1) □ Branca (2) □ Parda (3) □ Preta (4) □ Indígena (5) □Não sabe

7- Já fumou? □ Sim (1) □ Não (2) Período (meses):_____ □ NSA

8- Fuma/fumou na gravidez? □ Sim (1) □ Não (2) Período (meses):_____ □ NSA

9- Bebida alcoólica? □ Sim (1) □ Não (2)

10- Bebeu na gestação? □ Sim (1) □ Não (2) Período (meses):_____ □ NSA

11- Está praticando regularmente alguma atividade física?□ Sim (1) □ Não (2)

12- Qual é a sua religião?

□ Católica (1) □ Protestante (2) □ Espírita (3) □ Religiões brasileiras(4) □ Sem religião(5) □ Outras(6) □ Não Sabe

13- Raça/cor do companheiro: □ Amarela (1) □Branca (2) □ Parda (3) □ Preta (4) □ Indígena (5) □ Não sabe

14-Ocupação/profissão do companheiro:_____

15- Renda familiar:R$_____ SM:_____ (no momento da coleta)

16- Recebe algum auxílio ou beneficio do Governo? □ Sim (1) □ Não (2)

17- Se sim, qual? _____□ NSA

18- Quantas pessoas moram na sua casa?_____

POSSE DE ITENS	**QUANTIDADE DE ITENS**				
	0	**1**	**2**	**3**	**4 ou +**
1. Televisão a cores	0	1	2	3	4
2. Rádio	0	1	2	3	4
3. Banheiro (com vaso sanitário e descarga)	0	4	5	6	7
4. Automóvel (não considerar se or para uso profissional/meio de renda)	0	4	7	9	9
5. Empregada mensalista (que trabalham pelo menos cinco dias por semana)	0	3	4	4	4
6. Máquina de lavar (não considerar tanquinho, se responder assim)	0	2	2	2	2
7. DVD	0	2	2	2	2
8. Geladeira	0	4	4	4	4
9. Freezer (aparelho independente ou parte da geladeira)	0	2	2	2	2

Grau de instrução da pessoa com maior renda	
Analfabeto/primário incompleto/Até 3ª série do ensino fundamental	0
Primário completo/Ginasial incompleto/Até 4ª série do ensino fundamental	1
Ginasial completo/Colegial incompleto/Fundamental completo	2
Colegial completo/Superior incompleto/Médio completo	4
Superior completo	8
Total de pontos: (____)Classe:_____ Classe A 35-45 Classe B 23-34 Classe C 14-22 Classe 8 -13 Classe E 0-7	

INFORMAÇÕES NUTRICIONAIS

18- Peso pré-gestacional (anotar em Kg) |___||___||___|,|___| □ Não sabe

19- Nesta USF você recebeu alguma orientação alimentar e nutricional? □ Sim (1) □ Não (2)

20- Nesta USF você recebeu alguma orientação sobre aleitamento materno? □ Sim (1) □ Não (2)

INFORMAÇÕES GINECOLOGICO-OBSTETRICA

21- Esta com quantas semanas gestacionais:_____ semanas (trimestre da atual gestação □ 1º □ 2º □ 3º)

DUM:____/____/____ (verificar com o cartãoda gestante) DPP: ____/____/____

22- Qual a sua data de nascimento? ____/____/____23- Qual a sua idade? _____ anos

24- Idade do pai do bebê? _____ anos □ Não sabe

25- Planejou esta gravidez? □ Sim (1) □ Não (2)

26- Estava utilizando algum método anticoncepcional? □ Sim (1) □ Não (2)

27- Se sim, qual?_____

28- Quantas vezes ficou grávida?_____

29- Já teve algum aborto? □ Sim (1) □ Não (2) Quantos?_____

30- Teve hemorragia no ultimo aborto? □ Sim (1) □ Não (2) □ NSA

31- Tomou transfusão de sangue no ultimo aborto? □ Sim (1) □ Não (2) □ NSA

32- Quantos filhos nasceram? (vivos e mortos)_____ filhos □ NSA

33- Número de partos: _____ vaginais_____ cesarianas □ NSA

34- Idade do ultimo filho: □ Menos de dois anos (1) □ Mais de dois anos (2) □ NSA

35- Você amamentou o ultimo bebê? □ Sim (1) □ Não (2) □ NSA

36- Algum dos seus filhos teve problemas respiratórios? □ Sim (1) □ Não (2) □ NSA

37- Algum nasceu com menos de 2,500g? □ Sim (1) □ Não (2) □ NSA

38- Algum filho nasceu prematuro? □ Sim (1) □ Não (2) □ NSA

39- Teve alguma gestação gemelar? □ Sim (1) □ Não (2) □ NSA

40- Fez as consultas depois do parto? □ Sim (1) □ Não (2) □ NSA

41- Tomou vitamina A na alta hospitalar do último parto? □ Sim (1) □ Não (2) □ NSA

42- Teve alguma hemorragia no último parto? □ Sim (1) □ Não (2) □ NSA

43- Recebeu algum sangue no último parto? (transfusão de sangue) □ Sim (1) □ Não (2) □ NSA

44- Teve anemia na última gravidez? □ Sim (1) □ Não (2) □ NSA

45- Se sim, fez tratamento? □ Sim (1) □ Não (2) □ NSA

46- Com quantos meses de gravidez fez a 1ª consulta? _____ □ NSA

47- Realizou quantas consultas de pré-natal nesta gestação?_____ 48- Realizou alguma USG? □ Sim (1) □ Não (2)

49- Primeira USG □ 1º□ 2º □ 3º Trimestre (____ semanas _____ dias) □ NSA

50- Tem algum problema de saúde? □ Sim (1) □ Não (2) Qual?_____

51- Precisou ficar internada por algum problema de saúde? □ Sim (1) □ Não (2)

52- Nesta gestação, você está com algum sintoma/queixa? □ Sim (1) □ Não (2)

□ Náuseas/enjoo(1) □ Vômitos (2) □ Dor (3) □ Febre (4) □ Gases (5) □ Azia (6) □ Inflamação (7)

□ Prisão de ventre (8) □ Dor de cabeça (9) □ Cólica abdominal (10) □ Diarreia (11) □ Falta de apetite (11) □ Outras (12)

53- Se outras, quais?_____ □ NSA

54- Como tem sido a sua saúde nos últimos 15 dias?□ Excelente (1) □ Muito boa (2) □ Boa (3) □ Ruim (4) □ Muito Ruim (5)

55- Está tomando alguma vitamina? □ Sim (1) □ Não (2) Qual? _____

56- Tomou a vacina Antitetânica? □ Sim (1) □ Não (2)

57- Se sim, quantas doses? □ Primeira (1) □ Segunda (2) □ Terceira (3) □Reforço (4) □ NSA

Exames	Data	Resultado		
Hemoglobina:				
Hematócrito: %				
VCM:				
Glicemia: (mg/dL)				
Dosagem de ferritina:				
Exames	Data	Positivo	Não Reage	NR
HIV		1	2	3
HTLV		1	2	3
VDRL		1	2	3
Citomegalovírus		1	2	3
Toxoplasmose		1	2	3
Hepatite B (HBV)		1	2	3
Hepatite C (HBV)		1	2	3
Rubéola		1	2	3
Parasitológico de fezes		1	2	3

Especificar parasito:_____ □ NSA

58- Realizou outros exames: □ Sim (1) □ Não (2) Idade gestacional:_____ □ NSA

INFORMAÇÕES MEDICAMENTOSAS

59- Você estava usando algum remédio, **antes da gravidez**? □ Sim (1) □ Não (2)

60- Qual? _____

61- Para que usou este medicamento?_____

62- Quem indicou o medicamento?

□ Farmacêutico (1) □Balconista (2) □Parente, amigo, vizinho (3) □Conta própria (4) □ Propaganda (5)

□ Enfermeiro (6) □ Dentista (7) □ Outro (8) □ NSA (9) □Médico (10)

63- Você está usando algum remédio, **nesta gravidez**? □ Sim (1) □ Não (2)

64- Qual? _____

65- Para que usou este medicamento?_____

66- Quem indicou o medicamento?

□ Farmacêutico (1) □Balconista (2) □ Parente, amigo, vizinho (3) □ Conta própria (4)

□Propaganda (rádio, tv, revista) (5) □Enfermeiro (6) □ Dentista (7) □ Outro (8) □ NSA (9) □Médico (10)

ANTROPOMETRIA

67- Peso:_____ 68- Peso do cartão da gestante:_____

69- Altura:_____ 70- Altura do cartão do gestante: _____

71 – Índice de Atalah: _____

INFORMAÇÕES DO PARTO E NASCIMENTO

72 – Sexo □ feminino (1) □ masculino (2)

73 – Peso ao nascer: _____ g

74 – Idade gestacional:_____ semanas

75 – Apgar:

76 – Tipo de parto: □ Vaginal (1) □ Cesáreo (2)

FICHA PARA AVALIAÇÃO PERIODONTAL

Nº:____ **Data da Coleta:___/___/_____**

Nome: _____ **Diagnóstico da doença**: _____

Data de nascimento:___/___/_____ **Idade:** ____A _____M **Idade aprox. em anos:_____**

Sinais clínicos do uso do cigarro: _____

Dente	IR-H						Profundidade de Sondagem						Indice de Sangramento						NIC					
	disto-v	médio-v	mesio-v	disto-l	médio-l	mesio-l	disto-v	médio-v	mesio-v	disto-l	médio-l	mesio-l	disto-v	médio-v	mesio-v	disto-l	médio-l	mesio-l	disto-v	médio-v	mesio-v	disto-l	médio-l	mesio-l
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Nomenclatura dentária segundo o sistema FDI.

Nomenclatura dentária segundo o sistema FDI.

Nota: A aproximação da idade segue o seguinte critério: até 6 meses aproxima para a idade anterior; acima de 6 meses aproxima para a idade seguinte. NIC: nível de inserção clínica nas faces vestibular e lingual (mm)

IR-H: índice de recessão ou hiperplasia (mm) Profundidade de sondagem nas faces vestibular e lingual (mm) Índice de sangramento nas faces vestibular e lingual: 0=ausente; 1=presente

RESULTADOS DAS COVARIAVIES COM PESO AO NASCER

Tabela 5. Medidas de tendência central e dispersão dos descritores empregados para avaliação da anemia materna em usuárias do Sistema Único de Saúde em Santo Antônio de Jesus, Bahia, Brasil, 2017 (N=622).

	Diagnóstico de Anemia						
	Sim N = 156			**Não N = 578**			
Descritores	**Média**	**Desvio Padrão**	**Mediana**	**Média**	**Desvio Padrão**	**Mediana**	**p***
Dosagem hemoglobina (g/dl)	10,30	0,52	10,40	12,24	0,82	12,20	≤0,01
Dosagem hemácias (milhões)	3,76	0,40	3,80	4,56	7,57	4,30	≤0,01
Hematócrito (%)	32,12	2,95	31,90	36,84	3,43	36,90	≤0,01
Dosagem de Ferritina (fentolitros)	40,96	42,47	25,00	47,31	40,71	35,10	0,49
Volume Corpuscular Médio –VCM (fentolitros)	85,51	8,21	85,25	88,30	31,74	85,99	≤0,01

* Valor de p. Nível de significância: ≤ 0,05.

* Valor de referência dos indicadores: Hemoglobina: > 11 g/dl / Hemácias: > 4 milhões / Hematócrito: > 33% / Ferritina: > 15 fentolitros / VCM: 80-96 fentolitros.

Tabela 6. Número (n) e percentual (%) das características socioeconômico-demográficas da amostra de gestantes, conforme peso do recém-nascido. Santo Antônio de Jesus, Bahia, Brasil, 2017 (n=622).

CARACTERÍSTICAS	**Peso ao nascer**		**p***
	<3000g	**≥ 3000g**	
	n (%)	**n (%)**	
	183 (29,92)	**439 (70,58)**	
IDADE			
18-35 anos	149 (29,80)	351 (70,20)	
<18 anos	22 (35,48)	40 (64,52)	0,360
>35 anos	12 (20,00)	48 (80,00)	0,116
NÍVEL DE ESCOLARIDADE (em anos de estudo)			
≥8 anos	134 (30,04)	312 (69,96)	

< 8 anos	49 (27,84)	127 (72,16)	0,587
SITUAÇÃO CONJUGAL			
Com companheiro	160 (28,62)	399 (71,38)	
Sem companheiro	23 (36,51)	40 (63,49)	0,193
RAÇA/COR DA PELE			
Não preta	105 (27,70)	274 (72,30)	
Preta	78 (32,10)	165 (67,90)	0,241
OCUPAÇÃO ATUAL			
Remunerada	90 (31,80)	193 (68,20)	
Não remunerada	93 (27,43)	246 (72,57)	0,234
RENDA FAMILIAR[1]			
> 2 salários mínimos	62 (33,33)	124 (66,67)	
≤ 2 salários mínimos	121 (27,75)	315 (72,25)	0,162
DENSIDADE DOMICILIAR (número de pessoas por domicílio)			
≤ 4 pessoas	152 (29,75)	359 (70,25)	
>4 pessoas	31 (27,93)	80 (72,07)	0,703

1- Valores do salário mínimo na época da coleta: 2013: R$ 678,00; 2014: R$ 724,00 ; 2015: R$ 788,00; 2016: R$ 880,00; 2017: R$ 937,00.

* Valor de p. Nível de significância: ≤ 0,05.

** Houve perdas de informação

Tabela 7. Número (n) e percentual (%) das características relacionadas aos nascidos vivos e à condição de saúde e estilo de vida da amostra de gestantes, conforme peso do recém-nascido. Santo Antônio de Jesus, Bahia, Brasil, 2017 (n=622).

	Peso ao nascer		
CARACTERÍSTICAS	**< 3000g n (%)**	**≥ 3000g n (%)**	**p***
	183 (29,92)	**439 (70,58)**	
SEXO DO RÉCEM-NASCIDO			
Masculino	89 (28,16)	227 (71,84)	0,485
Feminino	94 (30,72)	212 (69,28)	
INFECÇÃO URINÁRIA MATERNA			
Não	176 (30,03)	410 (69,97)	
Sim	7 (19,44)	29 (80,56)	0,176
PERIODONTITE MATERNA**			
Não	151 (27,31%)	402 (72,69%)	0,212

Sim	25 (40,32%)	37 (59,68%)	
HIPERTENSÃO ARTERIAL MATERNA			
Não	177 (29,26)	428 (70,74)	
Sim	6 (35,26)	11 (64,71)	0,590
ABORTO			
Não	151 (29,72)	357 (70,28)	
Sim	32 (28,07)	82 (71,93)	0,726
IMC GESTACIONAL[1]			
Peso adequado	84 (29,47)	201 (70,53)	
Baixo peso	47 (40,52)	69 (59,48)	0,033
Sobrepeso	33 (22,15)	116 (77,85)	0,104
Obesidade	19 (26,39)	53 (73,61)	0,606
PARIDADE			
> 2 filhos	118 (33,52)	234 (66,48)	0,010
≤ 2 filhos	65 (24,07)	205 (75,93)	
INÍCIO DO ACOMPANHAMENTO PRÉ-NATAL			
≤ 3 meses	156 (28,52)	391 (71,48)	0,182
> 3 meses	27 (36,00)	48 (64,00)	
HÁBITO DE FUMAR MATERNO**			
Não	165 (29,00)	404 (71,00)	0,721
Sim	16 (31,37)	35 (68,63)	
CONSUMO DE BEBIDA ALCÓOLICA MATERNO			
Não	143 (27,82)	371 (72,18)	0,056
Sim	40 (37,04)	68 (62,96)	
SUPLEMENTAÇÃO DE SAIS DE FERRO MATERNO			
Não	40 (26,67)	110 (73,33)	
Sim	143 (30,30)	329 (69,70)	0,395

1 - O método de Atalah foi empregado para o cálculo desta covariável.
* Valor de p. Nível de significância: ≤ 0,05.
** Houve perdas de informação

STROBE STATEMENT—CHECKLIST OF ITEMS THAT SHOULD BE INCLUDED IN REPORTS OF OBSERVATIONAL STUDIES

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes
Methods			
Study design	4	Present key elements of study design early in the paper	Yes
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Yes
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Yes
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes
Bias	9	Describe any efforts to address potential sources of bias	Yes

Study size	10	Explain how the study size was arrived at	Yes
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes
		(*b*) Describe any methods used to examine subgroups and interactions	Yes
		(*c*) Explain how missing data were addressed	Yes
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Yes
		(*e*) Describe any sensitivity analyses	Yes
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes
		(b) Give reasons for non-participation at each stage	Yes
		(c) Consider use of a flow diagram	Yes
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	Yes
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	No
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Yes

		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes
Discussion			
Key results	18	Summarise key results with reference to study objectives	Yes
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes

ANEXO A - INTERNATIONAL PROSPECTIVE REGISTER OF SYSTEMATIC REVIEWS

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

Maternal anemia and low birth weight: systematic review and meta-analysis

ANA CLAUDIA MORAIS FIGUEIREDO, MAURÍCIO GOMES PEREIRA, FABIANA DA MATA, PRISCILLA PEREIRA, ROBERTA BORGES SILVA, SIMONE SEIXAS DA CRUZ, ISAAC SUZART GOMES-FILHO

Citation

ANA CLAUDIA MORAIS FIGUEIREDO, MAURÍCIO GOMES PEREIRA, FABIANA DA MATA, PRISCILLA PEREIRA, ROBERTA BORGES SILVA, SIMONE SEIXAS DA CRUZ, ISAAC SUZART GOMES-FILHO. Maternal anemia and low birth weight: systematic review and meta-analysis. PROSPERO 2017 CRD42017069451 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017069451

Review question

Is maternal anemia a risk factor for low birth weight?

Searches

We will search the following databases: MEDLINE, EMBASE, Scopus, Web of Science, SciELO and LILACS. Reference lists from eligible articles will be checked for additional records.
Cohort and case-control studies evaluating the relationship between maternal anemia and low birth weight will be considered eligible for inclusion. We will not include studies with women diagnosed with genetic anemia.

Types of study to be included

We will consider for inclusion cohort and case-control studies to evaluate risk factors for low birth weight

Condition or domain being studied

Anemia during pregnancy is a frequent event that occurs due to physiologic alterations necessary to the fetus growth. Gestational anemia may cause intrauterine growth restriction and, consequently, undesired gestational outcomes such as low birth weight.

Participants/population

Pregnant women and newborns

Intervention(s), exposure(s)

Inclusion criteria: women diagnosed with maternal anemia, with serum hemoglobin below 11g/dl.
Exclusion criteria: women diagnosed with genetic anemia, such as sickle cell anemia.

Comparator(s)/control

For both cohort and case-control designs: we will compare women with maternal anemia with those who are not diagnosed with maternal anemia.

Primary outcome(s)

Low birth weight

Secondary outcome(s)

Birth weight mean difference

Data extraction (selection and coding)

The following information will be extracted from articles: authorship, year of publication, year of data collection, diagnostic criteria for anemia, birth weight, association measures (risk ratio, odds ratio), contingence table, methodological quality within studies, sample size.
Data extraction will be performed by two reviewers, independently, using a standardized spread sheet.

Risk of bias (quality) assessment
Risk of bias assessment will be taken using the NOS - Newcastle-Ottawa checklist for critical appraisal of cohort and case-control studies. The checklist comprises 3 sections: selection, comparability and exposures/outcomes. Each section has questions regarding methodological characteristics. At the end of the evaluation, a score is given for each study.

Strategy for data synthesis
Qualitative synthesis will be taken and information will be presented in a table with studies/participants characteristics.
Quantitative synthesis: meta-analysis will be performed using random effects method.

Analysis of subgroups or subsets
We will perform subgroup analysis with the following variables: geographic region, year of publication, sample size and study design.

Contact details for further information
Miss Figueiredo
aninha_m_godoy@hotmail.com

Organisational affiliation of the review
University of Brasilia
http://www.unb.br/

Review team members and their organisational affiliations
Miss ANA CLAUDIA MORAIS FIGUEIREDO. UnB
Dr MAURÍCIO GOMES PEREIRA. UnB
Miss FABIANA DA MATA. UnB
Dr PRISCILLA PEREIRA. UnB
Miss ROBERTA BORGES SILVA. UnB
Dr SIMONE SEIXAS DA CRUZ. UFRB
Dr ISAAC SUZART GOMES-FILHO. UEFS

Anticipated or actual start date
13 January 2017

Anticipated completion date
15 December 2017

Funding sources/sponsors
University of Brasilia

Conflicts of interest
None known

Language
English

Country
Brazil

Stage of review
Review_Completed_not_published

Subject index terms status
Subject indexing assigned by CRD

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

Subject index terms
Infant, Low Birth Weight; Anemia; Infant, Newborn; Humans\

Date of registration in PROSPERO
13 June 2017

Date of publication of this version
23 January 2018

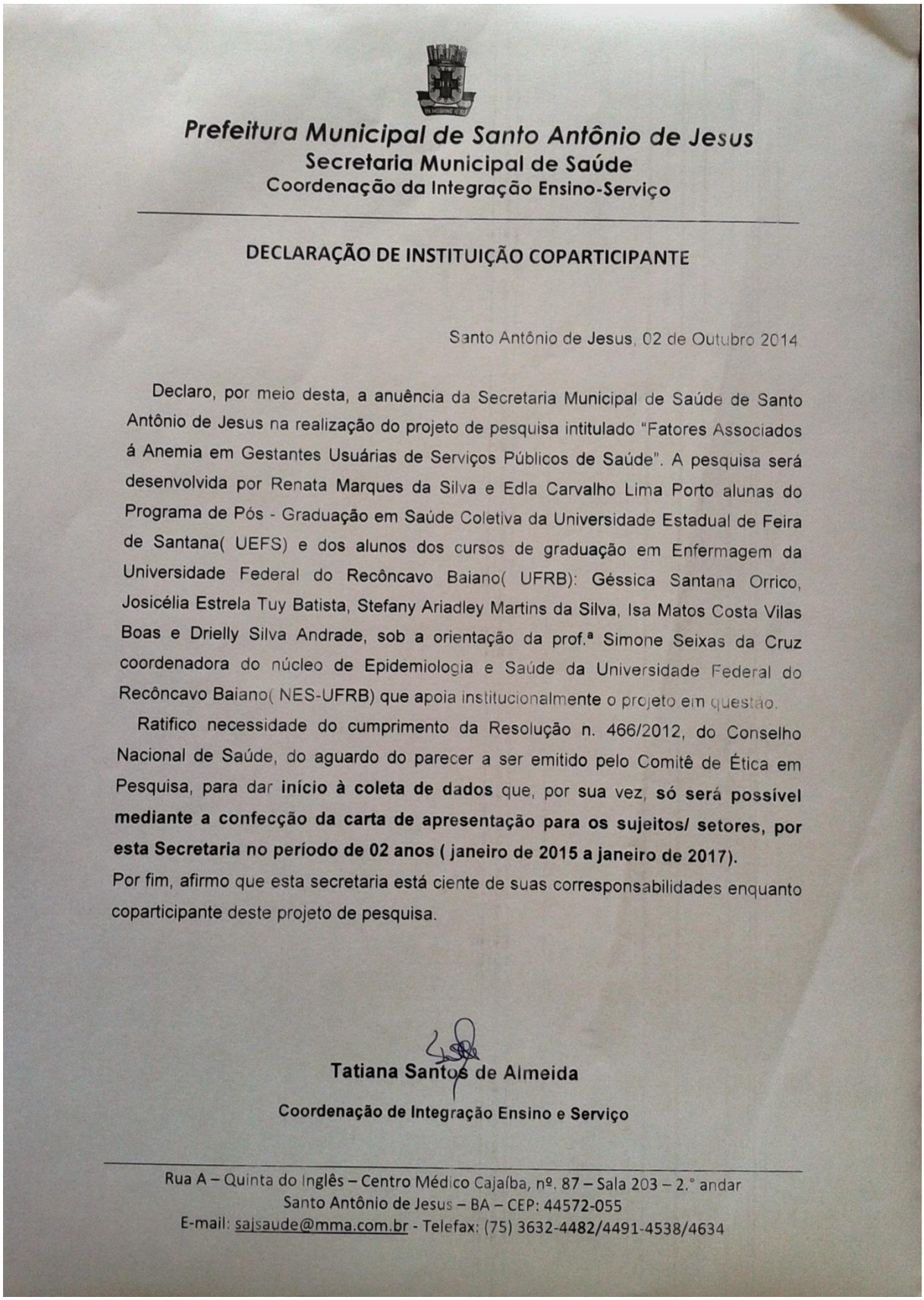
Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Versions
13 June 2017
23 January 2018

ANEXO B – CARTA DE ANUÊNCIA DA SECRETARIA DE SAÚDE DE SANTO ANTÔNIO DE JESUS - BA



Prefeitura Municipal de Santo Antônio de Jesus
Secretaria Municipal de Saúde
Coordenação da Integração Ensino-Serviço

DECLARAÇÃO DE INSTITUIÇÃO COPARTICIPANTE

Santo Antônio de Jesus, 02 de Outubro 2014

Declaro, por meio desta, a anuência da Secretaria Municipal de Saúde de Santo Antônio de Jesus na realização do projeto de pesquisa intitulado "Fatores Associados á Anemia em Gestantes Usuárias de Serviços Públicos de Saúde". A pesquisa será desenvolvida por Renata Marques da Silva e Edla Carvalho Lima Porto alunas do Programa de Pós - Graduação em Saúde Coletiva da Universidade Estadual de Feira de Santana(UEFS) e dos alunos dos cursos de graduação em Enfermagem da Universidade Federal do Recôncavo Baiano(UFRB): Géssica Santana Orrico, Josicélia Estrela Tuy Batista, Stefany Ariadley Martins da Silva, Isa Matos Costa Vilas Boas e Drielly Silva Andrade, sob a orientação da prof.ª Simone Seixas da Cruz coordenadora do núcleo de Epidemiologia e Saúde da Universidade Federal do Recôncavo Baiano(NES-UFRB) que apoia institucionalmente o projeto em questão.

Ratifico necessidade do cumprimento da Resolução n. 466/2012, do Conselho Nacional de Saúde, do aguardo do parecer a ser emitido pelo Comitê de Ética em Pesquisa, para dar **início à coleta de dados** que, por sua vez, **só será possível mediante a confecção da carta de apresentação para os sujeitos/ setores, por esta Secretaria no período de 02 anos (janeiro de 2015 a janeiro de 2017).**

Por fim, afirmo que esta secretaria está ciente de suas corresponsabilidades enquanto coparticipante deste projeto de pesquisa.

Tatiana Santos de Almeida
Coordenação de Integração Ensino e Serviço

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Santo Antônio de Jesus – BA – CEP: 44572-055
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ANEXO C – APROVAÇÃO DO COMITÊ DE ÉTICA

UNIVERSIDADE ESTADUAL DE FEIRA DE SANTANA - UEFS

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: FATORES ASSOCIADOS À ANEMIA EM GESTANTES USUÁRIAS DE SERVIÇOS PÚBLICOS DE SAÚDE

Pesquisador: Renata Marques da Silva

Área Temática:

Versão: 2

CAAE: 34111914.3.0000.0053

Instituição Proponente: Universidade Estadual de Feira de Santana

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 927.520

Data da Relatoria: 29/12/2014

Apresentação do Projeto:

Trata-se de um estudo de Mestrado em Saúde Coletiva proposto por Renata Marques da Silva, sob a orientação da Prof.ª Dra. Simone Seixas da Cruz e co-orientação do Prof. Dr. Isaac Suzart Gomes Filho. Definida pelo projeto como "uma alteração no tamanho das hemácias acompanhada da redução ou não da concentração de hemoglobina", a anemia é "a deficiência nutricional mais prevalente no mundo pelo fato de qualquer grupo etário ser vulnerável a essa deficiência, sobretudo as mulheres, que devido à menstruação, por exemplo, possuem fisiologicamente, menor reserva de ferro que os homens [...] As gestantes se destacam como um dos grupos mais suscetíveis à ocorrência de anemia, devido, entre outros fatores, à elevada necessidade de ferro exigida pelo crescimento acentuado dos tecidos para o desenvolvimento do feto, da placenta e do cordão umbilical, pela produção de hemácias e elevação de cerca de 50% do volume plasmático que é necessário para suprir a demanda do sistema vascular hipertrofiado de um útero aumentado, sendo ainda maior no terceiro trimestre gestacional" (Informações Básicas/Plataforma Brasil, p. 02). Segundo a autora, a pesquisa será do tipo transversal, descritivo e de caráter exploratório contará com uma

amostra composta por 363 gestantes "que realizam acompanhamento pré-natal nas unidades de saúde da família, nos municípios de Juazeiro e Santo Antônio de Jesus no estado da Bahia que

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atenderem aos critérios de elegibilidade. O tamanho dessa amostra foi "calculado a partir da prevalência da anemia no Brasil, e será levada em conta a população total de habitantes" (Informações Básicas/Plataforma Brasil, p. 03).

Apresenta cronograma detalhado e orçamento estimado em R$ 17.096,10, com contrapartida dos seguintes núcleos: Núcleo de Epidemiologia e Saúde da Universidade Federal do Recôncavo da Bahia (NES-UFRB); Núcleo de Epidemiologia e Saúde da Universidade Federal do Vale do São Francisco (NES-UNIVASF) e Núcleo de Pesquisa, Prática Integrada e Investigação Multidisciplinar (NUPPIIM) da Universidade Estadual de Feira de Santana (UEFS).

Objetivo da Pesquisa:

O projeto descreve os seguintes objetivos:

GERAL: "Verificar os fatores associados à anemia e aos seus diferentes níveis de gravidade em gestantes atendidas em Unidades de Saúde nos municípios de Juazeiro e Santo Antônio de Jesus no estado da Bahia" (Informações Básicas/Plataforma Brasil, p. 02; Projeto completo, p. 05).

ESPECÍFICOS: "Estimar a prevalência e a gravidade da anemia, leve, moderada e grave, em gestantes atendidas em Unidades de Saúde nos municípios de Juazeiro e Santo Antônio de Jesus – BA. Identificar: Fatores socioeconômicos e demográficos; Fatores relacionados à reprodução das gestantes anêmicas; e Fatores relacionados ao estilo de vida e a ocorrência de anemia em gestantes atendidas em Unidades de Saúde nos municípios de Juazeiro e Santo Antônio de Jesus – BA" (Informações Básicas/Plataforma Brasil, p. 02-03; Projeto completo, p. 05).

Avaliação dos Riscos e Benefícios:

RISCOS:

"O risco em participar desta pesquisa envolve o constrangimento que poderá ser evitado utilizando uma sala reservada ou um espaço afastado de outras pessoas. Além disso, sua altura e seu peso corporal serão verificados e anotados em uma ficha da pesquisa. Para verificar a existência ou não da anemia, uma amostra do seu sangue será coletada através da punção de um acesso venoso periférico realizado por uma pessoa da equipe previamente treinada. Como medida protetora, este acesso será realizado respeitando os cuidados de higiene e segurança para não haver risco de contaminação e, eventualmente, poderá causar dor leve, arroxeamento, calor e vermelhidão no local, semelhante às coletas de sangue que são feitas para realização de exames de laboratório rotineiros da gravidez." (TCLE)

BENEFÍCIOS:

"Como benefícios, com a realização da pesquisa, será possível conhecer melhor a condição de saúde da gestante, e contribuir para que haja desenvolvimento de ações voltadas para prevenção dessa doença e promoção da saúde." (TCLE)

"Os resultados da pesquisa servirão para todos os profissionais de saúde que atuam nas unidades de saúde da família, assim como os gestores em saúde compreenderem melhor quais os fatores poderão estar relacionados com a existência de anemia em gestantes. Dessa forma, colaborar para conhecer melhor a condição de saúde dessa mulher, e contribuir para que haja desenvolvimento de ações voltadas para prevenção dessa doença e promoção da saúde" (Informações Básicas/Plataforma Brasil, p. 03).

Comentários e Considerações sobre a Pesquisa:
O estudo é exequível e o projeto de pesquisa está bem estruturado e detalhado.

Considerações sobre os Termos de apresentação obrigatória:
Protocolo completo.

Recomendações:

Conclusões ou Pendências e Lista de Inadequações:
Após o atendimento das pendências, o Projeto está aprovado para execução, pois atende aos princípios bioéticos para pesquisa envolvendo seres humanos, conforme a Resolução nº 466/12 (CNS).

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

Considerações Finais a critério do CEP:
Tenho muita satisfação em informa-lhe que o seu Projeto de Pesquisa satisfaz às exigências da Res. 466/12. Assim, seu projeto foi Aprovado, podendo ser iniciada a coleta de dados com os participantes da pesquisa conforme orienta o Cap. IX.3, alínea 5a - Res. 466/12.
Relembro que conforme institui a Res. 466/12, Vossa Senhoria deverá enviar a este CEP relatórios anuais de atividades pertinentes ao referido projeto e um relatório final tão logo a pesquisa seja concluída. O não cumprimento poderá implicar no impedimento de apreciação de novos projetos

do pesquisador.

Em nome dos membros CEP/UEFS, desejo-lhe pleno sucesso no desenvolvimento dos trabalhos e, em tempo oportuno, um ano, este CEP aguardará o recebimento dos referidos relatórios.

FEIRA DE SANTANA, 29 de Dezembro de 2014

Assinado por:
ANDRÉA SILENE ALVES FERREIRA MELO
(Coordenador)

UNIVERSIDADE ESTADUAL DE FEIRA DE SANTANA - UEFS

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: A influência da Periodontite mediada pela Anemia Materna no Baixo Peso ao Nascer

Pesquisador: Gessica Santana Orrico
Área Temática:
Versão: 2
CAAE: 74302717.9.0000.0053
Instituição Proponente: Universidade Estadual de Feira de Santana
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.455.751

Apresentação do Projeto:
Projeto de Dissertação apresentado ao Programa de Pós graduação em Saúde Coletiva – Mestrado Acadêmico da Universidade Estadual de Feira de Santana (UEFS), desenvolvido pela mestranda Géssica Santana Orrico, orientado pela Prof. Dra. Simone Seixas da Cruz (pesquisadora colaboradora), tendo como coorientador o Prof. Dr. Isaac Suzart Gomes Filho (pesquisador colaborador). São também pesquisadoras colaboradoras Ana Cláudi Morais Godoy Figueiredo, Edla Carvalho Lima Porto e Josecélia Estrela Tuy Batista.

Trata-se de um estudo observacional, longitudinal, analítico, que se caracteriza pelo acompanhamento das gestantes até o momento do parto e nascimento. Na primeira etapa, as participantes são gestantes que buscaram atendimento pré-natal nas unidades de saúde da família no município de Santo Antônio de Jesus/Bahia. As informações relacionadas ao período gestacional estão disponíveis em um banco de dados da pesquisa intitulada "Estado nutricional e condição bucal em gestantes usuárias do serviço público de saúde: associação entre periodontite e anemia" que já foi aprovado pelo comitê de ética em pesquisa sob CAAE – 31581114.7.0000.0053/2014. O banco de dados da primeira etapa foi disponibilizado pelo Núcleo de Epidemiologia e Saúde (NES/UFRB) em parceria com o Núcleo de Pesquisa, Pratica Integrada e Investigação Multidisciplinar (NUPPIM/UEFS). Está sendo submetido ao Comitê de Ética em Pesquisa da UEFS para a avaliação da segunda etapa de coleta de dados, referente ao

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levantamento de dados secundários acerca das variáveis contidas no banco do Sistema de Informação Sobre Nascidos Vivos (SINASC). Desta forma, justifica-se o pedido de dispensa do Termo de Consentimento Livre e Esclarecido na segunda etapa (coleta de dados no SINASC). Em relação à primeira etapa já aprovada pelo CEP a gestante foi informada do objetivo da pesquisa e caso concorde em participar, foi solicitado a assinatura do
Termo de Consentimento Livre e Esclarecido – TCLE pela própria ou seu responsável (no caso das gestantes menores de 18 anos), em duas vias, em que uma fica com o pesquisador e a outra com a participante.

Na segunda etapa, por sua vez, serão coletadas informações secundárias referentes ao binômio mãe/filho, no Sistema de Informação Sobre Nascidos Vivos (SINASC), acessados na Secretaria Municipal de Saúde de Santo Antônio de Jesus. As informações que constam no SINASC são oriundas da Declaração de Nascidos Vivos emitida imediatamente após o nascimento. Serão coletados do SINASC alguns dados do binômio mãe/filho, tais como: peso ao nascer, tipo de parto, idade gestacional e sexo do recém-nascido.

Critério de definição do desfecho: Peso ao Nascer (Variável Dependente): A classificação do peso ao nascimento foi definida conforme critério da Organização Mundial de Saúde (OMS, 2002). O recém-nascido com peso inferior a 2.500 gramas foi considerado de baixo peso. As crianças que nasceram com peso superior ou igual a 2500 gramas foram alocadas no grupo de nascidos vivos com peso satisfatório.

Aspectos éticos: A metodologia empregada e os critérios estabelecidos nesta pesquisa estão de acordo com a Resolução 466/12 do Conselho Nacional de Saúde (CNS).
Critério de Inclusão: Serão incluídas nesse estudo as informações, contidas no banco de dados, das gestantes que participaram da pesquisa intitulada "Estado nutricional e condição bucal em gestantes usuárias do serviço público de saúde: associação entre periodontite e anemia". Os critérios que atendem o projeto supracitado são: gestantes atendidas nas Unidades de Saúde da Família de Santo Antônio de Jesus, idade gestacional de 08 a 32 semanas, bem como realização de consulta pré-natal nas Unidades de Saúde envolvidas no estudo. Critério de Exclusão: Foram considerados: gravidez gemelar, número de dentes presentes inferior a quatro, ter diagnóstico de alguma enfermidade que necessite de profilaxia antibiótica prévia ao exame periodontal, casos de aborto recente (menos de oito semanas), de sangramento que implicava tratamento hospitalar de

pelo menos 24 horas, cardiopatias descompensadas, bem como doenças renais (uréia acima de 50mg/dL, creatinina acima de 1,6 mg/dL)". Página 3 do Projeto simplificado.

Apresenta cronograma, com coleta prevista, possivelmente, para ser iniciada em junho de 2017 e orçamento estimado em R$16.357,50.

Objetivo da Pesquisa:
PRIMÁRIO: - Investigar a associação entre à periodontite e o baixo peso ao nascer em mulheres gestantes com e sem o diagnóstico de anemia materna em usuárias do serviço público de saúde no município de Santo Antônio de Jesus (BA) (Informações básicas/Plataforma Brasil, p. 03; Projeto completo, p. 10).

SECUNDÁRIOS: - Estimar a ocorrência de periodontite em gestantes atendidas no serviço público de saúde de Santo Antônio de Jesus (BA); - Estimar a ocorrência de BPN entre os nascidos vivos das gestantes atendidas no serviço público de saúde de Santo Antônio de Jesus (BA) (Informações básicas/Plataforma Brasil, p. 03; Projeto completo, p. 10)

Avaliação dos Riscos e Benefícios:
RISCOS: "Os riscos assumidos nesse estudo foram previstos no projeto intitulado "Estado nutricional e condição bucal em gestantes usuárias do serviço público de saúde: associação entre periodontite e anemia." (CAAE – 31581114.7.0000.0053/2014). Já na segunda etapa serão utilizados apenas os dados secundários do SINASC" (Informações básicas/Plataforma Brasil, p. 03).

BENEFÍCIOS: "Os resultados da pesquisa servirão para os profissionais de saúde que atuam nas Unidades de Saúde da Família, assim como os gestores em saúde para melhor compreenderem a associação de periodontite e baixo peso ao nascer mediada pela anemia materna" (Informações básicas/Plataforma Brasil, p. 03).

Comentários e Considerações sobre a Pesquisa:
Trata-se de um tema com grande relevância, ficando clara a importância da saúde bucal para a gestante. Na autorização da Prefeitura de Santo Antônio de Jesus, para a coleta dos dados secundários existe a informação de que este projeto é coordenado pela Profª Simone Seixas da Cruz coordenadora do Núcleo de Epidemiologia e Saúde da Universidade Federal do Recôncavo da

Bahia (NES-UFRB).

Neste projeto é solicitada uma dispensa do TCLE vez que os dados referentes ao parto e nascimento que serão coletados são de origem secundária e estão disponíveis no Sistema de Informação Sobre Nascidos Vivos (SINASC) na Secretaria Municipal de Saúde de Santo Antônio de Jesus.

Considerações sobre os Termos de apresentação obrigatória:

Protocolo completo, fazendo-se necessários alguns ajustes para atender às exigências da Resolução 466/12. Foram anexados os seguintes documentos:

1) Folha de rosto;
2) Projeto completo;
3) Anuência da Secretaria Municipal de Saúde de Santo Antonio de Jesus;
4) Declaração dos pesquisadores colaboradores se comprometendo em observar a Resolução 466/12;
5) Parecer CAAE – 31581114.7.0000.0053/2014;
6) Dispensa de TCLE.

Conclusões ou Pendências e Lista de Inadequações:

Após o atendimento das pendências, o Projeto está aprovado para execução, pois atende aos princípios bioéticos para pesquisa envolvendo seres humanos, conforme a Resolução nº 466/12 (CNS).

Considerações Finais a critério do CEP:

Tenho muita satisfação em informar-lhe que seu Projeto de Pesquisa satisfaz às exigências da Res. 466/12 e 510/2016. Assim, seu projeto foi Aprovado, podendo ser iniciada a coleta de dados com os participantes da pesquisa conforme orienta o Cap. X.3, alínea a - Res. 466/12 e Cap II da Res 510/2016. Relembro que conforme institui a Res. 466/12 e 510/2016, Vossa Senhoria deverá enviar a este CEP relatórios anuais de atividades pertinentes ao referido projeto e um relatório final tão logo a pesquisa seja concluída. Em nome dos membros CEP/UEFS, desejo-lhe pleno sucesso no desenvolvimento dos trabalhos e, em tempo oportuno, um ano, este CEP aguardará o recebimento dos referidos relatórios.

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Continuação do Parecer: 2.455.751

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_934420.pdf	20/11/2017 22:58:53		Aceito
Outros	Oficio_CEP_1124.docx	20/11/2017 22:57:26	Gessica Santana Orrico	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_Gessica_CEP_1125.docx	20/11/2017 22:56:50	Gessica Santana Orrico	Aceito
Declaração de Instituição e Infraestrutura	Autorizacao_SAJ.pdf	24/08/2017 13:52:42	Gessica Santana Orrico	Aceito
Declaração de Pesquisadores	DECLARACAO_SIMONE.pdf	29/07/2017 21:53:55	Gessica Santana Orrico	Aceito
Declaração de Pesquisadores	DECLARACAO_JOSI.pdf	29/07/2017 21:53:39	Gessica Santana Orrico	Aceito
Declaração de Pesquisadores	DECLARACAO_ISAAC.pdf	29/07/2017 21:53:24	Gessica Santana Orrico	Aceito
Declaração de Pesquisadores	DECLARACAO_EDLA.pdf	29/07/2017 21:53:10	Gessica Santana Orrico	Aceito
Declaração de Pesquisadores	DECLARACAO_ANA.pdf	29/07/2017 21:52:30	Gessica Santana Orrico	Aceito
Folha de Rosto	FOLHA_ROSTO.pdf	06/07/2017 16:47:26	Gessica Santana Orrico	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

FEIRA DE SANTANA, 22 de Dezembro de 2017

Assinado por:
Pollyana Pereira Portela
(Coordenador)

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ANEXO D – ARTIGO ACEITO PARA PUBLICAÇÃO

Health Care: Current Reviews
ISSN: 2375-4273

Figueiredo et al., Health Care Current Reviews 2018, 6:1
DOI: 10.4172/2375-4273.1000217

Review Article Open Access

Maternal Anemia and Iron Deficiency Anemia: Similarities and Singularities

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[3]*Department of Epidemiology, Federal University of Recôncavo da Bahia*

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.