SPECIAL ARTICLE

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Funding: This research was partially funded by the Fogarty International Center, the National Institute on Aging (NIA) and the National Institute of Environmental Health Sciences (NIEHS) under the Global Environmental and Occupational Health Program No. 5U01TW010107.

Conflicts of interest: The authors declare that they have no conflicts of interest.

Received: 27 September 2023

Accepted: 10 October 2023

Online publication: 6 December 2023

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Cite as: Gonzales GF, Ordoñez-Aquino C, Vásquez-Velásquez C. Considerations on gestational and newborn anemia in Peru: a narrative review. Rev peru ginecol obstet. 2023;69(4). DOI: https://doi.org/10.31403/rpgo.v69i2569

Considerations on gestational and newborn anemia in Peru: a narrative review

Consideraciones sobre la anemia en la gestación y el recién nacido en el Perú: revisión narrativa

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DOI: https://doi.org/10.31403/rpgo.v69i2569

ABSTRACT

Anemia during pregnancy is considered a public health problem, due to the alarming prevalence worldwide. The measure chosen by various governments is massive iron supplements. However, there is currently contradictory evidence on iron intake, excess consumption, and potential risks during pregnancy for both the mother and child. For gestation, an additional 1 gram of iron is required for the mother, fetus, placenta, and delivery. This generates an increase in red mass of 20% but to avoid hemoconcentration the plasma volume expands by almost 50% generating a physiological hemodilution. For pregnant women, no criteria have been established to differentiate iron deficiency anemia and physiological anemia due to the normal process of hemodilution. In the case of Peru and countries with high altitude resident population, there is an additional problem, the hemoglobin correction factor for high altitude residence, which is a mathematically and arbitrarily determined value. Recent evidence suggests that this factor should be reevaluated because it does not consider ethnicity and generational time of residence at high altitude. The present review provides an update and discussion of the diagnostic criteria for anemia, iron supplementation, the hemoglobin correction factor for altitude of residence, and the impact of environmental pollution on the gestation process.

Key words: Pregnant women, Anemia, Iron, Hemodilution, Altitude

RESUMEN

La anemia durante la gestación es considerada un problema de salud pública debido a las prevalencias alarmantes que se presentan a nivel mundial. La medida optada por los diversos gobiernos es la administración masiva con suplementos de hierro. Sin embargo, actualmente existe evidencia contradictoria sobre el consumo de hierro, el exceso de su consumo y los potenciales riesgos durante la gestación tanto para la madre como para el producto. Para la gestación se requiere de 1 gramo adicional de hierro para la madre, el feto, la placenta y el parto. Esto genera un aumento de la masa roja del 20%; pero, para evitar la hemoconcentración el volumen plasmático se expande casi el 50%, generando una hemodilución fisiológica. Para la gestante no se ha establecido un criterio que permita diferenciar la anemia por deficiencia de hierro, de la anemia fisiológica debido al proceso normal de hemodilución. En el caso de Perú y de países con población residente de altura, se suma una problemática adicional, el factor de corrección de hemoglobina por residencia en la altura, el cual es un valor determinado de forma matemática y arbitraria. Las evidencias recientes sugieren que este factor debe ser reevaluado, debido a que no considera la etnia y el tiempo generacional de residencia en la altura. La presente revisión muestra una actualización y discusión de los criterios de diagnóstico de anemia, la suplementación con hierro, el factor de corrección de hemoglobina por altura de residencia y el impacto de la contaminación ambiental sobre el proceso de gestación.

Palabras clave: Gestantes, Anemia, Hierro, Hemodilución, Altura

Introduction

Gestational anemia continues to be a public health burden worldwide. Despite numerous interventions, in all populations in most countries, the prevalence of mild anemia has changed little, whereas moderate and severe anemia decreased significantly[(1,2)]. However, global anemia prevalences have remained stagnant over the past two decades.

The World Health Organization (WHO) recognizes that the results of iron intervention over the past 20 years have been unsatisfactory and that strategies to reduce these high rates should be comprehensive and not only focused on supplementing populations with iron[3]. The diagnosis of anemia is based on the measurement of hemoglobin (Hb) alone[4], which makes it impossible to determine its cause or etiology.

The WHO recommends since 2016 that in the second trimester a value of 10.5 g/dL should be considered as the cut-off point for Hb to define anemia, and for the first and third trimester a value of 11 g/dL[5]. As pregnancy is a new condition and where a new life develops, an additional 1,040 mg of iron is required for erythropoiesis, placenta, fetus, and delivery[6]. For this purpose, from the second trimester on, the levels of the hormone hepcidin decrease and with it the absorption of iron increases, which allows increasing the production of red blood cells that increases the red mass by 20%, and to avoid hemoconcentration the vascular volume expands to 50%, a process that allows generating hemodilution, so that the concentration of hemoglobin and ferritin are reduced.

The WHO prioritizes the diagnosis of anemia using the automated hemogram in venous blood, because the measurement in capillary blood is inaccurate[7]. In general, Hb measurement in different countries is done using the hemoglobinometer called HemoCue. A meta-analysis study shows that Hb measurements with HemoCue® Hb 301 result in higher concentrations than measurements with HemoCue® Hb 201+ in non-pregnant women[8]. These differences should be considered when comparing anemia prevalence between different regions or between different times in the same region.

Several studies have shown that iron deficiency anemia (IDA) would not be the main cause of anemia in low- and middle-income countries and have established that where infections and parasitism are endemic, inflammatory anemia predominates. Therefore, anemia control programs should be region-specific[9].

Pregnancy is characterized by a reduced immune response, which makes women more susceptible to infections[10]. Another aspect to consider is that depending on ethnicity there are differences in anemia rates and adverse outcomes[11].

In pregnant women who begin pregnancy with normal Hb and serum ferritin (SF) values, when evaluated prospectively, their concentrations decrease in the second and third trimester and then recover at the end of pregnancy, which suggests that iron supplementation (IS) is not required[12]. In recent years there has been great concern about iron excess, due to the risk of tissue overload, since in non-anemic pregnant women with IS, adverse effects are observed with a dose of 45 mg/day.

Erythrocytosis or Hb > 13 g/dL during gestation causes high blood viscosity, resulting in reduced oxygen supply to tissues and health complications[13]. The association between Hb levels and gestational outcomes is U-shaped[14]. Severe anemia and in some cases also moderate anemia are the only ones associated with damage to maternal and/or newborn health[15,16].

The present review will discuss the role and outcomes associated with hemodilution, IDA, and erythrocytosis in gestation, Hb correction for altitude, and the impact of environmental air pollution on Hb concentration during gestation.

Evaluation of hematologic criteria for defining anemia: use of automated complete blood count (CBC).

In 2016, WHO notified that pregnant women should be evaluated quarterly using automated blood count[5]. Alteration of three to four of the normal values for mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and erythrocyte distribution width coefficient of variation (RDW-CV) and Hb<11 g/dL are qualified as IDA, whereas with Hb<11 g/dL and all four normal markers is qualified as hemodilution anemia[17].

The concentration of the soluble transferrin receptor (sTfR) in hemodilution is like that observed in normal or in pregnant women with erythrocytosis, indicating that they are not ID and do not require increased erythropoiesis. Three models for diagnosing severe IDA, total IDA and hemodilution anemia were analyzed using the ROC curve. The results show that the criteria used allow differentiation between IDA (total and severe) and hemodilution anemia (Table 1). These results are like those observed in another study in 2,100 pregnant women[18].

Table 1. Areas under the ROC curve with respect to each biomarker of iron status or inflammation.

	Adjusted model		
	Severe IDA	Total IDA	Hemodilution
EPO (mU/mL)	0.95 (0.90-1.00)	0.79 (0.66-0.92)	0.67 (0.54-0.80)
sTfR (µg/mL)	0.92 (0.78-1.00)	0.87 (0.77-0,97)	0.63 (0.49-0.76)
sTfR/logF	0.94 (0.82-1.00)	0.87 (0.78-0.96)	0.74 (0.63-0.85)
Hep (ng/mL)	0.92 (0.83-1.00)	0.76 (0.64-0.88)	0.78 (0.67-0.89)
Hep/SF*100	0.92 (0.83-1.00)	0.76 (0.78-0.96)	0.55 (0.41-0.69)
Hep/EPO	0.98 (0.95-1.00)	0.77 (0.65-0.90)	0.83 (0.73-0.93)
SF (ng/mL)	0.69 (0.51-0.88)	0.79 (0.68-0.91)	0.75 (0.63-0.87)

EPO: erythropoietin; sTfR: soluble transferrin receptor; Log F: log ferritin, Hep: hepcidin, SF: serum ferritin. Adjusted model: controlled for parity, gestational age and inflammation. Source:[45].

Automated blood count values can be used to assess ID, inflammation, and macrocytic anemia, which may be indicative of folic acid and vitamin B12 deficiency. There are even automated CBC markers to differentiate thalassemia anemia from IDA. Automated analysis is much more cost effective than hemoglobin measurement alone[19,20].

Hemoglobin cutoff points for the diagnosis of anemia

After the definition in 1967 of the cut-off point for the diagnosis of anemia during gestation (Hb: 11 g/dL), in 2016, the WHO adjusted for pregnant women in the second trimester (Hb: 10.5 g/dL)[5].

The cut-off point for Hb in women of reproductive age has also been a source of discrepancy, due to the low response of iron intervention. Thus, in India it has been shown that the Hb cut-off point for a non-pregnant woman would be 10.8 g/dL and not 12 g/dL as proposed by WHO, and this higher cut-off point would explain the persistently high prevalence of anemia[21]. Although WHO has defined reference values for low Hb levels, it has not done the same for high values[14].

Correction of hemoglobin for residence altitude

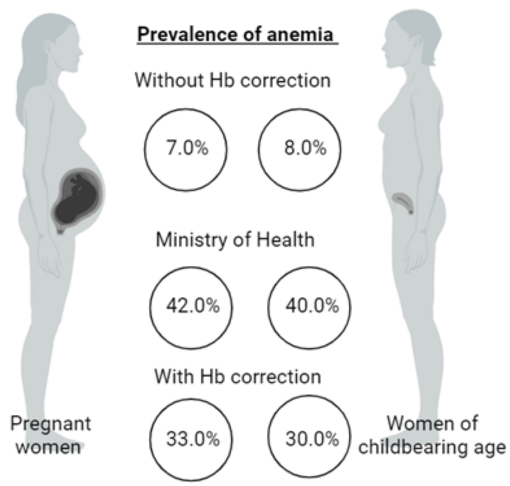
Because Hb concentration increases as the altitude of residence increases, WHO proposes to correct Hb from 1,000 m onwards. This adjustment is proportional to altitude, and when Hb is corrected for altitude, anemia rates increase markedly[22].

A recent review suggests that the diagnostic safety of hemoglobin is greater when no correction for altitude is used[23]. In Peru, Hb correction for altitude increases anemia in women of reproductive age by 3.75 times and the prevalence of anemia in pregnant women by 4.7 times (Figure 1).

This correction criterion consists in the fact that at HA there is a lower arterial oxygen saturation, which, to level it to the sea level value, the Hb concentration should be reduced proportionally. This assumption, however, does not consider that each heme group of the Hb molecule has an iron atom in its interior and that, therefore, if the premise of lower oxygen availability at HA is true, this will not be corrected by the administration of more iron. On the contrary, by increasing iron intake there is a greater possibility of erythrocytosis. Different studies show that the body iron content (BIC) in pregnant women at HA is similar or higher than at sea level[24].

Erythrocytosis is associated with higher blood viscosity and mathematically the Hb value can be reduced by correction for altitude, but this will not change the degree of viscosity, even if the Hb correction brings the pregnant women into the normal Hb category.

Figure 1. Prevalence of anemia with and without hemoglobin correction for height in pregnant women and women of reproductive age.



Iron deficiency anemia, hemodilution anemia and anemia due to other causes in pregnant women

Anemia has a multifactorial origin. However, both in clinical practice and in public health, iron is the first and often the only intervention to treat anemia[3].

According to WHO and for a long time it was established that ID was the cause of 50% of anemia, while 42% was due to inflammatory factors and 8% to other causes. This has now changed, as inflammatory anemia predominates in settings with a high burden of infection[9, 10].

Iron deficiency anemia (IDA)

For the diagnosis of IDA, SF levels accompanied by hematological parameters such as Hb, mean corpuscular volume (MCV), hemoglobin per red blood cell (HBC), Hb concentration per red blood cell (HBCR) and red cell distribution width-coefficient of variation (RDW-CV) are used, all of which are reduced except RDW-CV, which is rather increased[25]. IDA particularly of moderate and severe degree requires treatment with IS.

IS should be oriented to the second and third trimester of pregnancy, while in non-anemic pregnant women it should not be administered. In the first trimester (organogenesis), intestinal iron absorption is quite low because iron is teratogenic, and therefore iron should not be supplemented.

As the trimesters progress, plasma volume increases; in the first trimester it increases by 6%, in the second trimester by 18-29% and in the third trimester by 42-48%[26]. This vascular expansion is dependent on the renin-angiotensin-aldosterone axis. A smaller increase in plasma volume (hemoconcentration) is related to hypertensive alterations of pregnancy.

It has been suggested to systematically perform a hemogram in the first trimester of pregnancy because the measurement of Hb in that period is the best predictive biomarker of anemia in the third trimester, with a cut-off value of 12 g/dL[27]. IDA is diagnosed when SF levels are below normal and sTfR values are elevated. BIC assessment using the logarithm of the sTfR to ferritin ratio [Log (R/F)] has also been described. IDA is considered when BIC values are less than -4 mg/kg[24].

The WHO gives reference values for iron deficiency only in the first trimester with SF values <15 ng/mL. It then indicates that this threshold is modified, although it does not establish figures, both by the effect of a physiological increase in acute phase proteins secondary to pregnancy, increase in plasma volume in the second trimester and changes in inflammatory measures in the third trimester of gestation[28]. The sTfR/LogSF index according to some authors is a better predictor of ID in subjects with inflammatory processes[29].

In Peru, programs to reduce anemia through IS have been ineffective, particularly in high-altitude populations, where serum levels of hepcidin are similar or higher, as has been demonstrated in pregnant women in Ayacucho and Cusco[30], than in those at sea level. This indicates that ID does not occur population-wise in areas at high altitudes. An additional problem is that the frequency of erythrocytosis decreases. At sea level, erythrocytosis is associated with adverse effects such as preeclampsia, gestational diabetes, small for gestational age (SGA) and preterm (PT) delivery. If Hb is corrected for altitude, the rate of erythrocytosis decreases, but health problems will remain.

Gestational anemia due to hemodilution

In pregnant women, plasma volume expansion can reach 50%, a value higher than the increase in red mass (20%)[26].

To differentiate IDA from hemodilution anemia in 183 pregnant women attended at the National Maternal-Perinatal Institute, the diagnosis of severe and total IDA was made with MCV (<84 fL), MCCH (<30 g/100 mL), MCH (<27 pg), RDW-CV (>15%) and Hb (11g/dL) for the first and third trimester and 10.5 g/dL for the second trimester. Hemodilution anemia is diagnosed when there is Hb <11 g/dL associated with all 4 corpuscular values within normal. Pregnant women with hemodilution accounted for 17.3%, and those with IDA accounted for 13.96%.

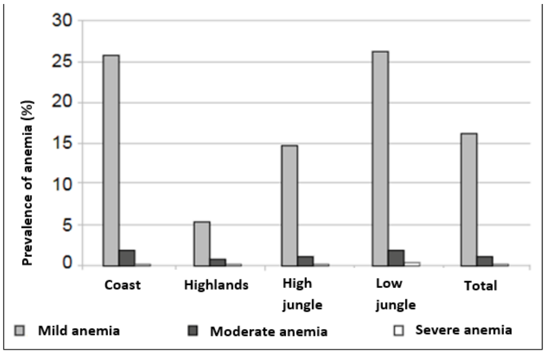
In the diagnosis of severe IDA, total IDA and hemodilution there is a significant decrease versus the normal group of SF and hepcidin markers. sTfR, Index sTfR/Log ferritin and erythropoietin are higher in the severe IDA and total IDA group than in the hemodilution group and the reference group (Table 2). The area under the ROC curve (AUC) for IDA (total anemia and severe anemia) and for hemodilution anemia are presented in Table 1. The regression model adjusted for different variables shows a better AUC ROC for IDA (total or severe), but not for hemodilution anemia. Similarly, in the hepcidin/SF ratio there is a good AUC ROC for IDA (total or severe) but not for hemodilution anemia. This methodology allows differentiating IDA from hemodilution anemia.

Several studies show that mild anemia is associated with favorable perinatal maternal outcomes, which would be associated with hemodilution having normal MCV values. In China, in 18'948,443 pregnant women between 15 and 49 years of age, moderate/severe anemia was associated with adverse outcomes, while mild anemia was associated with better maternal and fetal health[31]. This would allow our country not to consider anemia as a severe public health problem, since severe and moderate anemia do not exceed 10% (Figure 2).

Other causes of anemia

Other causes of anemia include other nutritional deficiencies (vitamins, proteins), infectious and inflammatory conditions, blood loss, and genetic Hb disorders, which may overlap and vary by geography[10].

Figure 2. Prevalence of gestational anemia in different regions of Peru according to degree of anemia (mild, moderate, and severe) and total anemia. The Hb concentration to define anemia has not been corrected for altitude (Own elaboration. Published in the Revista Peruana de Medicina Experimental y Salud Pública)[44].



Erythrocytosis in pregnancy

Both low and high maternal Hb concentrations are strong predictors of adverse maternal and infant health outcomes[14].

In a recent study, obesity was associated with erythrocytosis[32]. This may be due to hemoconcentration in the obese pregnant woman. Erythrocytosis (Hb >13 g/dL) is associated with a reduction in newborn weight greater than 100 g than when maternal Hb is 10 g/dL[33], and with an increased risk of gestational diabetes[34]. There are several potential mechanisms for how erythrocytosis is generated, including decreased plasma volume expansion; increased iron status; and life at high altitude. National studies have shown that in pregnant women in Cusco (3,400), the BIC was higher than in Lima[24]. Sherpas have a higher plasma volume because of better adaptation than Andean natives[35].

Table 2. Serological biomarkers according to categories defined by hematological parameters.

Biomarkers		Categories based on complete blood count			
		Severe iron deficiency anemia (N=4)	Total iron deficiency anemia (N=25)	Hemodilution (N=31)	Normal (N=123)
Iron	Serum ferritin (ng/mL)	10.84±1.59*	11.60±1.57*	10.70±1.23*	20.33±1.66
	Hepcidin (ng/mL)	1.16±0.13*	3.65±0.17#	2.29±0.37*	5.97±0.17
	sTfR (µg/mL)	6.97±1.95*	7.54±1.09*	2.66±0.26#	2.19±0.17
	Index sTfR /log(ferritin)	6.33±1.35*	6.01±1.51*	2.98±0.43#	1.93±0.19
Erythropoiesis	EPO (mU/mL)	28.98±4.26*	21.33±2.61*	17.10±2.90*,#	10.98±1.3
	Testosterone (ng/mL)	0.43±0.003	0.44±0.009	0.50±0.05	0.59±0.04
	Estradiol (pg/mL)	119.76±1.69	163.50±1.78	146.17±3.93	155.47±8.5
	Index (T/E)**	0.137±0.001*	0.021±0.001*,#	0.013±0.005#	0.006±0.0005
Inflammation	IL- 6 (pg/mL)	24.85±1.84	14.94±2.47	22.75±0.90	22.89±2.14

*Data are means ± SE.** Values reported per 10. ANOVA *p<0.05 with respect to normal pregnant women. # p<0.05 with respect to severe iron deficiency in pregnant women. EPO: Erythropoietin; IL-6: Interleukin 6. Source[45].*

Gestational anemia and its association with air pollutants

Air pollutants cause changes in iron homeostasis, culminating in inflammation and fibrosis[36]. Excess iron in tissues can affect their function and even produce ferroptosis, iron-dependent programmed cell death and lipoperoxidation.

Iron can also be part of particulate matter (PM2.5 and PM10) and thus cause an excess at the respiratory level and a greater influx via the olfactory route to the brain. In cases of inflammation there may be IDA with high iron load in tissues that are sequestered by the increase in hepcidin levels generated by inflammation. There is evidence of an association between exposure to air pollution and adverse effects in pregnancy such as low birth weight, small for gestational age, preterm birth and even fetal death[37]. The fetus is most vulnerable during early development to death associated with PM2.5 exposures[38].

Prenatal exposure to air pollution, especially in weeks 21 to 24 of pregnancy, is associated with the risk of premature rupture of membranes (PROM), which is partially mediated by low maternal Hb levels. IS in anemic pregnant women may prevent the risk of PROM associated with exposure to air pollution[39].

A study between 2015 and 2021 with 6,824 pregnant women from three hospitals in China found that for every 10 μg/m3 increase in PM2.5 and PM10, and for every 5 μg/m3 increase in SO2 and for every 0.1 mg/m3 increase in CO during the second and third trimester are associated with lower maternal Hb levels[40].

Similarly, for every interquartile range (IQR) increase in PM2.5, black carbon, nitrate (NO3-), and organic matter (OM) there is a decrease in Hb[40]. And in Ethiopia, in 1,088 pregnant women it was shown that the use of kerosene and charcoal for cooking was associated with anemia (OR: 4.6; 95% CI: 1.41-18.35); being higher in those in the third trimester (Table 3), while other studies find that exposure to PM2.5 is associated with reduced fetal growth due to erythrocytosis[41].

These contradictory results show the need for further research on the impact of air pollutants at different stages of pregnancy on Hb concentration, including PM and its constituents.

Iron supplementation: technical standard or physiological criterion

During pregnancy, iron requirements change from 1 mg/day in non-pregnant women to 0.8 mg/day in the first trimester and 7 mg/day in the second and third trimester. As ID has been related to adverse pregnancy outcomes, iron supplementation is a common practice before and during pregnancy, and this occurs in Peru by regulation of the Ministry of Health in 2017, which obliges iron supplementation from the 14th week of gestation, whether or not the pregnant woman is anemic.

The results of our research in Lima and Ayacucho have shown that when a woman is diagnosed as hemodilution anemia, the weight of the newborn is optimal. On the other hand, in cases of mild, moderate, or severe IDA, the weight of the newborn is lower than in the hemodilution anemia group (data in the process of being published).

Table 3. Literature review related to environmental contamination and anemia.

Author	Country	Anemia	Inflammation criteria	Pollutant value	Results
Andarge et al., 2021[36]	Ethiopia	The proportion of anemia in low, medium, and high pollution levels due to fuel use was 13.6%, 46% and 40.9%, respectively.	Type of cooking fuel	High pollution fuels (wood, animal manure and crop residues), medium pollution fuels (kerosene and coal) and low pollution fuels (electricity, liquefied petroleum gas and natural gas).	Kerosene and charcoal for cooking was associated with anemia (OR: 4.6; 95% CI: 1.41-18.35), being higher in those in the third trimester of pregnancy (OR: 1.72; 95% CI: 1.12-2.64).
Xie et al., 2022[40]	China	The prevalence of anemia was 22.2% and 29.2% for primiparous and multiparous pregnant women.	PM2.5, BC, NH4+, NO3-, MO, SO42- and dust	PM2.5, BC, NH4+, NO3-, MO, SO42-, and dust were mean (standard deviation) 69.56 (15.24), 10.02 (2.72), 8.11 (1.77), 14.96 (5,42), 15.36 (4.11), 10.08 (1.20), y 10.98 (1.85) μg/m3, respectively	Anemia was associated with dust (OR: 0.90, 95% CI: 0.82, 0.99, by increase of the IQR) in primiparous pregnant women; in the rest, no association was obtained.

IQR: interquartile range. PM2.5: particulate matter <2.5 μg, BC: black carbon, NH4+: ammonium, NO3-: nitrate, SO42-: sulfate; OM: organic matter. 95%CI: 95% confidence interval.

In young women, oral doses of iron ≥60 mg in ID and ≥100 mg in IDA have been shown to increase serum hepcidin levels that persist 24 h after iron dose administration but decrease 48 h after iron dose administration. To maximize iron absorption, oral doses ≥60 mg should be administered every other day. The circadian increase in serum hepcidin levels is greatest when iron is administered in the morning[42]. In summary, morning doses of 60 to 120 mg of iron as a ferrous salt administered with ascorbic acid (AA), away from meals or coffee, on alternate days, are suggested for women with ID and mild IDA.

Women with SF<30 ng/mL in early pregnancy have been shown in a clinical trial to be at high risk for ID/IDA and should be recommended IS. With increasing iron stores, the need for IS decreases and women with SF≥40 ng/mL rarely develop IDA. Women with SF levels SF≥50 ng/mL have adequate iron stores and do not need IS[43].

Conclusions

For its adequate control, gestational anemia should be diagnosed differentially among the main causes that occur, such as hemodilution anemia, ID anemia, inflammatory anemia, among others. The complete blood count should be used and applied as a priority for evaluation at the national level, as it supports the differential diagnosis of anemia in pregnant women. Hemodilution is a natural process that occurs in gestation and can be identified through the application of five parameters: VCM, HCM, CHCM, RDW-CV and hemoglobin.

Low grade inflammation due to environmental contamination can affect iron availability and can lead to anemia with increased iron stores. Pregestational obesity can cause hemoconcentration in gestation increasing Hb levels.

Iron supplementation is effective in cases of IDA and should be adequately monitored and avoided in cases where the iron reserve is sufficient, as occurs in high-altitude populations.

The scientific evidence presented and compiled worldwide should be used to evaluate and rectify public policies to address anemia as a public health problem. It should be considered that IS should not be the main or obligatory measure for the management of this condition.

Current scientific evidence shows that both moderate/severe anemia and erythrocytosis cause health problems in pregnant women and newborns, so that reference cut-off points for Hb should be established to define anemia and erythrocytosis.

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