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Iron Deficiency in Pregnancy: A Brief Review

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ABSTRACT

This paper highlights iron deficiency anaemia in pregnancy; its prevalence, causes, screening, and management. Iron deficiency is a spectrum that ranges from iron depletion to iron deficiency anaemia. Iron deficiency is the most common and leading cause of anaemia in pregnancy both in developed and underdeveloped countries. The incidence of iron deficiency anaemia varies worldwide depending on differences in race, socioeconomic factors, nutritional status, health condition, and the frequency of parasitic illnesses. Untreated Iron deficiency has significant adverse foetal and maternal consequences. The management of iron deficiency anaemia includes education regarding dietary modification, specifically ways to enhance iron absorption and iron supplementation. Although oral supplementation is typically the mainstay of treatment, more severe cases of iron deficiency anaemia may require intravenous supplementation.

Introduction

Anaemia is a worldwide public health problem, affecting more than 50% of pregnant women globally and about 90% in low-resourced countries [1]. Iron deficiency (ID) is the depletion of total-body iron, especially of macrophage and hepatocyte iron stores [2]. Because the largest amount of iron is consumed for haemoglobin (Hb) synthesis to produce 200 billion erythrocytes daily, anaemia is the more evident sign of iron deficiency, and iron deficiency anaemia (IDA) is often considered synonymous with iron deficiency [3]. However, iron deficiency is a broader condition that often precedes the onset of anaemia or indicates a deficiency in organs/tissues other than those involved in erythropoiesis, such as skeletal muscles and the heart. The heart is highly iron-dependent for myoglobin and energy production to sustain mechanical contraction [4]. ID was reported as the most prevalent nutrient disorder in both low-and-middle incomes as well as developed countries [5]. Due to regular menstrual flow, and increased iron requirement during pregnancy, women of reproductive age are at a higher risk of ID [6]. Because of the high iron demand to support the placenta and foetus during pregnancy, ID stands to be one of the problems associated with low PCV and decrease blood volume in pregnant women [7]. Fatigue, fever, pagophagia, and restless legs syndrome are considered the symptoms of ID in pregnancy. Pregnant women with ID are at a higher risk of preterm delivery [5]. Children whose mothers had ID in pregnancy are more likely to be born with cognitive impairment in addition to decreased language motor function and learning [8]. Anaemia is a haematological disorder that is common among pregnant women in many developing/low-income countries. It is a public health problem contributing to high maternal/perinatal morbidity and mortality in most low-income countries [9]. It is a condition of low circulating haemoglobin in which concentration has fallen below a threshold lying at two standard deviations below the median of a healthy population of the same age, sex, and stage of pregnancy, causing decreased oxygen-carrying capacity in a pregnant woman [7]. This reduced oxygen-carrying capacity may affect the oxygen supply to the mother, especially in severe anaemia and resulting in shortness of breath, dizziness and fatigue [4]. In developing countries, it is of serious concern as it has adverse effects on the mother and the foetus and contributes to maternal mortality [10]. It increases the risk of preterm delivery and postpartum maternal infections [6]. Iron deficiency anaemia is a shortage in iron stores, transport, and functional iron causing low haemoglobin (Hb), low serum ferritin, low transferrin saturation, and high erythrocyte protoporphyrin concentration [11]. The World Health Organization (WHO) defines anaemia as haemoglobin value <13g/dL and <12 g/dL in men and women who are not pregnant respectively. A serum iron and ferritin below 7.1µg/L and 30ng/l respectively or a transferrin saturation less than 15% is considered as iron deficiency [5,12–13]. Anaemia in pregnancy is defined as a haemoglobin level of less than 11 g/dL. However, a serum ferritin of <30ng/mL or transferrin saturation <20% is associated with a 98% sensitivity and 92% specificity for absent marrow hemosiderin. [5,14], a haemoglobin value of less than 10 g/dL is considered in most developing countries because previous studies report no significant harm to the foetus until the haemoglobin concentration drops below 10 g/dL [15].

Anaemia has many causes. Direct causes can be largely categorized as deficiency, or abnormal production of red blood cells; excessive destruction of red blood cells; and excessive loss of red blood cells [16]. Contributing causes include insufficient dietary intake, diet quality, hygiene, health performances, adverse environmental situations, deficiency of health facilities, socio-economic status of the family, traditional dietary habits of the area, and irregular eating habit [17]. This paper provides a brief review on IDA in pregnancy, its prevalence, causes, and management.

Methodology

Articles were sought from Google scholar, PubMed, Science direct and Web of Science databases using the following keywords; iron deficiency, Anaemia, iron deficiency anaemia, iron deficiency in pregnancy, anaemia in pregnancy, effects anaemia in pregnancy, causes of anaemia, causes of anaemia in pregnancy, prevalence of anaemia, anaemia screening and diagnosis, treatment of anaemia, management of anaemia, oral and parenteral iron supplementation etc. The articles on anaemia /iron deficiency, iron supplementation/therapy, bioavailability of iron supplements, risk factors of anaemia, diagnosis and management of anaemia, and effects of iron supplementation were selected for the review.

Iron Deficiency in Pregnancy

Haemoglobin concentration decreases during the first trimester. It is important to note that variations exist within the definition of normal haemoglobin levels during pregnancy; for example, normal haemoglobin levels may differ depending on altitude [5]. During a singleton pregnancy, maternal plasma volume increases by approximately 50% and is accompanied by a modest increase in red blood cell (RBC) mass [18]. These changes are responsible for producing the physiologic anaemia that occurs during pregnancy [2]. Iron requirements peak in the second and third trimesters to support the expansion of maternal blood volume and the development of the foetus and placenta [19]. Individuals at greatest risk for developing IDA during pregnancy include women with pre-conception heavy uterine bleeding, women with shorter inter-pregnancy intervals, women who had insufficient iron stores prior to conception, and women with poor dietary intakes of iron (common in developing countries) [19, 20]. Untreated maternal iron deficiency can negatively impact foetal development, particularly in terms of brain development where iron is required to synthesize the myelin sheath [21].

Prevalence of Iron Deficiency Anaemia in Pregnant Women

The prevalence of IDA varies among countries but is a major public health problem in the developing world, reflecting differences in race, socio-economic factors, nutritional habits, medical care, and the frequency of parasitic illnesses [22]. A previous study reported that anaemia in pregnancy has a prevalence rate of 38% in over 100 countries [9], of whom about 75% were manifested with ID [23]. The prevalence of IDA, the major type of anaemia, appears to vary across regions, from 3% in Europe [17] to over 50% in Africa [24]. **Table 1** highlight the prevalence and risk factors associated with IDA in pregnancy in under-developed and developing countries with more emphasis on Africa and Nigeria.

Causes of Iron Deficiency Anaemia in Pregnancy

The most common cause of IDA in pregnancy is blood loss and/or iron transfer to foetus. Other common contributing factors include nutritional deficiency (when the body is not getting enough iron) and low initial iron stores that cannot adequately support the increasing demand for iron [41]. Menstrual blood loss in excess of iron intake, gastrointestinal blood loss (e.g., intestinal parasites, chronic gastrointestinal diseases), and hereditary haemorrhagic telangiectasia could leads to blood loss over a long time with a resultant depletion of the body's iron stores [41].

Impact of Anaemia in Pregnancy

Anaemia in pregnancy has negative effects on both the woman and the foetus [42; 43]. The clinical presentation and the complications depend on the severity and duration of anaemia. If severe, it is associated with a significant maternal morbidity and mortality [44]. The presence of other risk factors or surgical procedures may disproportionality increase the adverse outcomes [45]. Anaemia has been associated with a neonate's low birth weight and prematurity [1]. Considering high prevalence, significant clinical impact, and many available preventive and treatment options, early recognition, and appropriate classification of anaemia in a pregnant woman is imperative. **Table 2** summarizes the consequences of IDA in pregnancy.

Iron Deficiency Anaemia Screening during Pregnancy

Considering the high prevalence of anaemia in pregnancy and its negative impact on maternal and foetal/neonatal morbidity and mortality, screening for anaemia, particularly IDA is recommended by many agencies [45]. The specific guidelines may vary in different countries, but Hb measurement together with serum ferritin and transferrin saturation once or twice during pregnancy is generally recommended [41]. According to the American College of Obstetrics and Gynaecologists, Centres for Disease Control and Prevention, and United Kingdom guidelines, every pregnant woman should receive a complete blood count (CBC), serum ferritin and transferrin saturation at the initial antenatal visit [41]. Depending on the general population and the prevalence of IDA and other anaemia's, some countries recommend additional screening strategies for other haemoglobin disorders (thalassemia, sickle cell trait/disease) and a possible trial of oral iron supplementation in cases of an unexplained anaemia [48].

Management of Iron Deficiency Anaemia

The goal of IDA treatment is to correct the anaemia and reduce the adverse outcomes of both the iron deficiency and anaemia [49]. The management of IDA includes education regarding dietary modification, specifically ways to enhance iron absorption and iron supplementation [50]. Although oral supplementation is typically the mainstay of treatment, in cases where

Table 1. Studies on the prevalence and risk factors associated with iron deficiency anaemia in pregnancy.

Country/Methodology	Sample size	Result/Conclusion	Reference
Nigeria/ Cross-sectional study	70	Anaemia and iron deficiency anaemia were found to be significantly higher among pregnant women (20.0%, 15.7%) when compared to non-pregnant women. The mean haemoglobin, haematocrit, serum iron, ferritin, and transferrin levels were significantly reduced in pregnant compared to non-pregnant women. Pregnant women in their third trimesters and multigravida had the highest prevalence of iron deficiency and iron deficiency anaemia.	[25]
Nigeria/ Cross-sectional study	2702	Lower prevalence of anaemia at the tertiary hospital may be attributed to the higher socioeconomic status of the clientele. Short-term early antenatal management of anaemia and long-term economic/educational empowerment is advocated.	[26]
Nigeria/ Cross-sectional study	202	The prevalence of IDA was 12.3%. IDA is still a fairly common condition among parturient in Lagos and it's mostly associated with maternal peripartum morbidities.	[27]
Nigeria/ Cross-sectional study	88	The mean values of the haematology and anaemia–related parameters among the pregnant subjects were; haemoglobin (10.14 ± 1.45 g/dL), PCV (30.567± 4.492%), SI (153.55 ± 66.061µg/dl), TIBC (4.33.18 ± 97.248 µg/dl), Serum Ferritin (32.9 ±14.2 ng/mL) and TS (7.69 ± 28.84%). The prevalence of IDA was significantly higher among women in the 3rd trimester of pregnancy compared to the 2nd trimester.	[28]
Nigeria/ Cross-sectional study	90	Serum ferritin among the pregnant and non-pregnant subjects were 26.0 µg/L and 70.3 µg/L, respectively. Even though iron deficiency was observed in 68/90 (75.6%) of pregnant women, it was latent in 61/68(89.7%) of the women while it was frank in 7/68 (10.3%).	[29]
Nigeria/ Cross-sectional study	307	Parity, low educational level, and economic status as factors responsible for IDA. Both serum iron level and haemoglobin concentration can be used to diagnose anaemia.	[30]
Nigeria/ Cross-sectional study	200	A 24.5 % prevalence of anaemia in pregnancy. A significant decrease (p< 0.05) in packed cell volume (PCV) of pregnant women [34.94 ± 4.98%] compared to non-pregnant women (38.11 ± 6.47%). Progressive increase in PCV from the first to the third trimester, while it decreases with advancing maternal age and parity.	[31]
Congo/Cross-sectional study	128	Anaemia is common in pregnant women living in low-income settings compare to pregnant women living in high-income settings. Malaria, large family size, and <18 years of age were associated with anaemia in pregnant women.	[32]
South Africa/ Cross-sectional study	2,000	The prevalence of anaemia in HIV-positive pregnant women was significantly higher relative to HIV-negative pregnant women (71% vs. 28.7%, p<0.0001).	[1]
Russia/ Cross-sectional study	390	The prevalence of anaemia was significantly higher in macro- and micro-somatotype compared to meso-somatotype.	[33]
Ethiopia/ Cross-sectional study	206	Anaemia in pregnant women was significantly (p<0.05) associated with rural dwelling [AOR= 9.17, 95%CI= 2.15–40, p<0.001] and intestinal parasite infection (AOR=55.09, 95%CI=6.88–441.19, p<0.001).	[34]
India/ Community-based study	446	Anaemia was reported as one of the main complication in pregnancy with a frequency of 62%. Other complications such as postpartum haemorrhage, preeclampsia, abortion and still birth ranging from 1.6% to 3.5%.	[35]
East Africa/ Cross-sectional study	8,583	The prevalence of anaemia in pregnancy was estimated at 41.8% in East Africa (95%CI= 40.78, 42.87) with over 23% in Rwanda and about 57% in Tanzania. An increased incidence of anaemia was observed in pregnant women with bad toilet facility (aPR=1.17, 95%CI=1.06, 1.27), women from countries with high illiteracy level (aPR=1.12, 95%CI=1.07, 1.18), and teenage women (aPR=1.22, 95%CI=1.02, 1.40).	[36]
Latin America, Africa, Western Pacific and Southeast Asia/ Cross-sectional study	312,281	Severe Anaemia was associated with maternal death among pregnant women (AOR=1.86, 95%CI=1.39–2.49).	[37]
USA/Population-based cohort study	20,690	Increased odds of postpartum haemorrhage and delivering a small neonate was observed in anaemic pregnant women. Successful treatment of anaemia in pregnant women lead to a significant decrease in odds for preterm birth (5.1% vs. 8.3%, AOR=0.59, 95%CI= 0.47–0.72) and preeclampsia (5.9% vs. 8.3%, AOR=0.75, 95%CI= 0.61–0.91). However, untreated anaemia was associated with increased odds for preterm birth (AOR=1.44, 95%CI= 1.16–1.76) and preeclampsia (AOR=1.54, 95%CI= 1.24–1.89).	[38]
Ghana/Cross-sectional study	400	The incidence of anaemia increased with the trimester of pregnancy. Women in the third trimester were 4 times more susceptible to anaemia relative to those in the first trimester (AOR=3.57, 95%CI= 1.91–6.67). Women's knowledge of anaemia and pregnancy trimester at interview time was associated with their anaemia status.	[39]
China/Retrospective cohort study	18,948,443	Moderate and severe anaemia during pregnancy was associated with increased risk of maternal death, still birth, restricted foetal growth, and maternal shock compared to no anaemia. Mild anaemia was associated with a decreased risk of maternal death, maternal shock, foetal growth restriction and still birth compared to moderate and severe anaemia after adjusting for demography and pregnancy complications.	[40]

Table 2. Consequences of IDA in pregnancy. Source: [49, 50].

Maternal complications	Foetal outcomes
Preeclampsia	Low birth weight
Intrauterine death	Congenital anomaly
High risk of preterm delivery	Low cognitive development
Antepartum and postpartum haemorrhage	High risk of schizophrenia
Postpartum depression	Neonatal anaemia
Premature membrane rupture	Still birth

oral supplementation is intolerance and/or ineffective, IDA patients may require intravenous (IV) supplementation.

Dietary Advice: Dietary iron occurs in two forms: haem and non-heme. Haem iron has a higher bioavailability than non-heme iron and is only found in meat, poultry, and fish products [51]. Dietary iron absorption is dependent on bioavailability, physiologic requirements, and the presence of absorption promoters (ascorbic acid) or inhibitors such as tannins, calcium, or phytates [52]. Ascorbic acid enhances iron absorption by reducing ferric iron to ferrous iron, allowing for iron uptake by the mucosal cells and forming a chelate with iron to allow for iron absorption in the duodenum [53].

The negative effects of iron inhibitors can be negated with the use of ascorbic acid [53]. The dietary reference intake of dietary iron for pregnant women is 27 mg. Approximately 1 to 2 mg of iron is lost per day due to mucosal shedding in the GI tract [54]. Because pregnant women have increased iron demands, merely increasing their intake of dietary iron may be insufficient to correct their IDA [55]. However, increased dietary iron would be beneficial for pregnant women with iron depletion, rather than IDA, as typically only 10% to 25% of dietary iron is absorbed from the GI tract [54]. This is due to a hormone called hepcidin, which is essential for iron homeostasis by controlling intestinal iron absorption [55].

Oral Iron Supplementation: Oral iron supplements are cheap, convenient, and readily available in different forms, these include ferrous sulphate (20% elemental iron/mg), ferrous gluconate (11% elemental iron/mg), and ferrous fumarate (33% elemental iron/mg) [51]. For pregnant women with IDA, the recommended elemental iron dose is 120 mg per day throughout the period of pregnancy and for at least, 3 months postpartum [56]. However, the bioavailability of oral iron is low especially in healthy individuals with 5% and 5.6% absorption rate in male and females respectively [57,58]. In severe iron deficiency, the absorption may reach 20% [59]. While some previous studies reported a significant decrease in iron absorption following daily administration, other studies report no significant changes [50–62]. Because of the decrease in iron absorption that is associated with daily administration, an alternate day iron supplementation is recommended. The iron that remain in the intestine may cause a change in gut microbiota and promote pathogenic specie growth leading to inflammation and mucosal injury [63]. Hence, parenteral iron supplementation is a better alternative.

Parenteral Iron: Supplemental iron is also available through intravenous (IV). Parenteral iron is a promising method of iron supplementation because it does not affect the intestinal mucosa and can be used to effectively treat severe iron deficiency [5]. Intramuscular iron injection is associated with increased pain, reduced efficacy, and a higher risk for permanent skin staining. Hence, it is not recommended for use [64]. The major benefit for IV iron is that it more effectively corrects IDA. However, infusion reactions and anaphylaxis may occur following IV iron supplementation [65]. Hence, iron formulations with low infusion reaction are required for IV iron [66]. The common formulations with high tolerability include ferric carboxymaltose (FCM), ferric derisomaltose (FDI), and ferrumoxytol (FMX) [67]. In Europe and Asia, FDI is recommended in cases of severe iron deficiency that requires rapid correction while in America and Africa FCM is indicated for patients with chronic kidney disease [68].

Conclusion

In both poor resource and developed countries, the most prevalent and pervasive dietary deficit is ID. Due to recurrent menstrual losses as well as the higher iron demands of pregnancy and lactation, women of reproductive potential are most at risk of ID. The need for the extra iron required to maintain expansion of blood volume/red cell mass and growth of the foetus and placenta during pregnancy increases the risk for ID and IDA. IDA in pregnancy is readily manageable yet an unmet health demand. The management strategy is dependent upon the period of gestation and severity of anaemia. Organization of patient group meetings and the use of social media can spread awareness of this public health issue.

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Conflict of interest statement
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