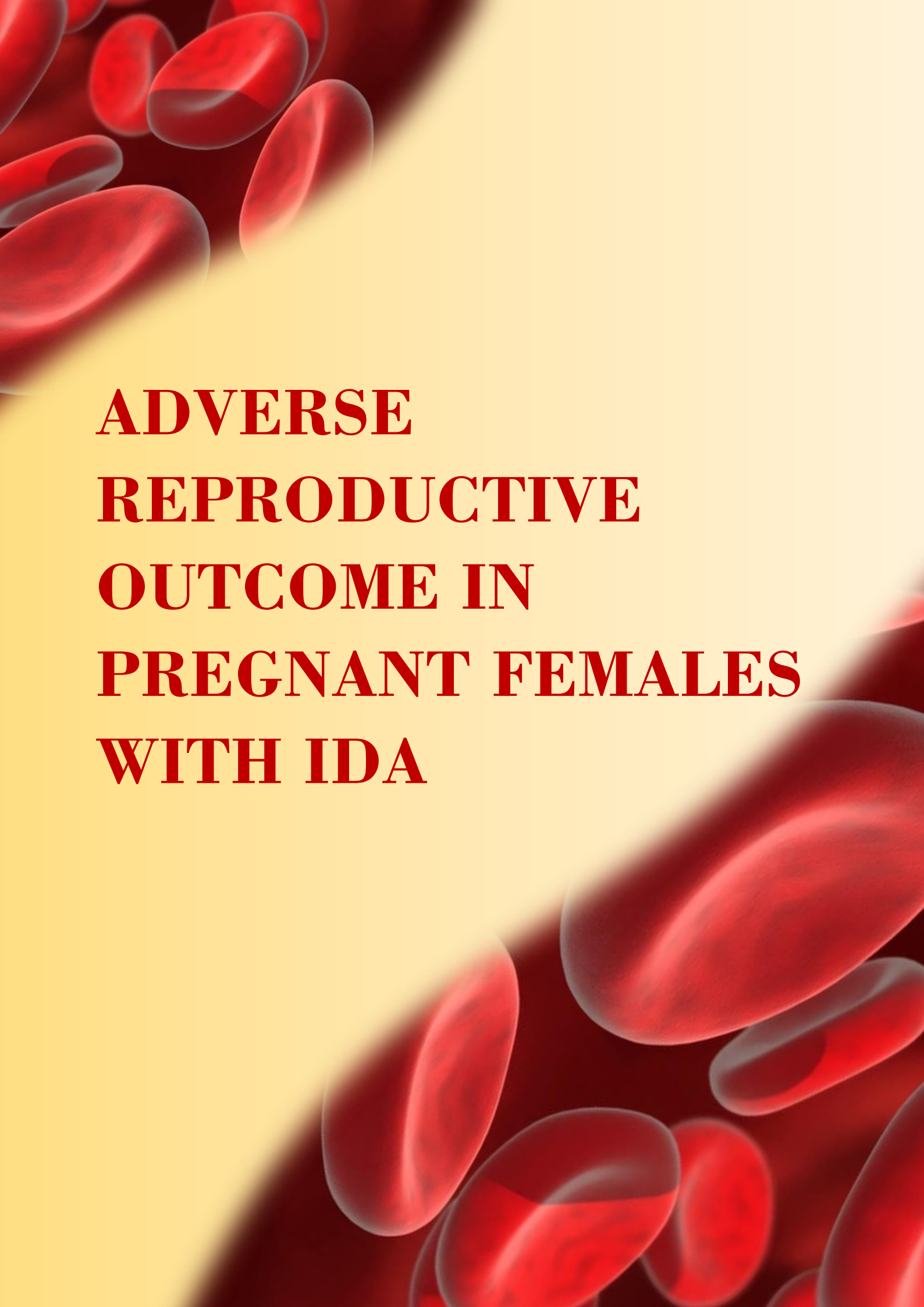

ADVERSE REPRODUCTIVE OUTCOME IN PREGNANT FEMALES WITH IDA

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Background and Objective of the Survey

Iron deficiency anemia (IDA) during pregnancy can significantly impact both maternal health and fetal development, potentially leading to adverse reproductive outcomes. Firstly, pregnant women with IDA are at higher risk of complications such as preterm birth, low birth weight, and postpartum hemorrhage. These complications can pose serious health risks for both the mother and the newborn, requiring close monitoring and management by healthcare providers. Secondly, iron is essential for fetal growth and development, particularly in the later stages of pregnancy when iron requirements increase substantially. IDA during pregnancy can lead to impaired fetal growth and intrauterine growth restriction (IUGR), potentially resulting in long-term developmental consequences for the child. Additionally, iron deficiency in early pregnancy has been linked to an increased risk of congenital anomalies and neural tube defects, further highlighting the importance of adequate iron intake during pregnancy.

Furthermore, infants born to mothers with IDA may experience neonatal complications such as respiratory distress syndrome, hypoglycemia, and neonatal jaundice, particularly if they are born preterm or with low birth weight. These complications can require intensive medical intervention and may have long-term implications for the health and well-being of the newborn. Additionally, iron deficiency during pregnancy has been associated with cognitive and behavioral effects in children, including poorer cognitive function, lower IQ scores, and an increased risk of developmental disorders such as autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD). These findings underscore the importance of addressing iron deficiency early in pregnancy to optimize maternal and fetal health outcomes and reduce the risk of adverse reproductive outcomes. Routine screening for anemia and appropriate iron supplementation are essential components of prenatal care to ensure the best possible outcomes for both mother and baby.

The objective of the survey is:

To study the adverse reproductive outcome in pregnant females with IDA

Methodology of the Survey

A survey was conducted to study the adverse reproductive outcome in pregnant females with IDA. A total of 150 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- Iron Balance: An Overview
- Iron Requirements during Pregnancy
- Benefits And Risks of Iron Supplementation During Pregnancy
- Pregnancies in Iron-Sufficient Populations
- Approach to Iron Administration in Pregnancy

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Literature Review

Introduction[1]

Anemia with a hemoglobin (Hb) concentration no lower than 10 g/dL at term, occurs in nearly all pregnancies, and in the majority of cases reflects a physiologic process (discussed below) rather than a deficiency state or underlying hematologic disorder. Significant anemia in pregnancy (defined as a Hb concentration <11 g/dL in the first trimester or <10 g/dL in the second and third trimesters) occurs with a prevalence ranging between 2% and 26%, depending upon the population studied. Anemia is a major contributor to maternal and fetal morbidity and mortality, particularly in less developed countries. Of the pathologic causes of anemia in pregnancy, anemia due to iron deficiency (IDA) is the most common, particularly in more developed countries, where contributions from other anemia-producing disorders such as malaria or hemoglobinopathies are less significant.

Anemia in pregnancy, and particularly IDA, is both a long-standing scholarly interest and an element of my practice as a hematologist. In preparing for this review, PubMed searches using the terms “pregnancy” and “iron deficiency” were performed. A date range was not specified, but the focus was on papers 2015 and later. Specific searches for subtopics included “hepcidin”, and “guidelines”. Approximately 71 reports, reviews, or studies new to the author were identified through this process.

The effects of ID on red cell production occur in the context of what is usually called the *physiologic anemia of pregnancy*. This is a phenomenon that is conserved across mammalian species, and it is hypothesized that the physiologic anemia of pregnancy serves the purpose of enhancing placental perfusion by reducing maternal blood viscosity and facilitating oxygen and nutrient delivery to the fetus by expanding the erythrocyte mass. Beginning approximately the sixth week of pregnancy, the plasma volume increases disproportionately to the erythrocyte mass, reaching a maximum value at approximately 24 weeks’ gestation. At maximum, the plasma volume is 40%50% higher than at the start of pregnancy.

Since the parameters used to identify anemia in clinical practice (the hematocrit (Hct), the blood Hb concentration, and the circulating erythrocyte count) are expressed as concentrations based on whole blood volume, the expanded plasma volume causes them to decrease and hence

produces “anemia”. While Hb concentration, Hct, and to a lesser degree erythrocyte count, are the anemia indicators used in practice, these parameters are only surrogates for the actual definition of anemia: a reduction in erythrocyte mass per unit body weight. By this criterion, the physiologic anemia of pregnancy is not actually anemia: a 15%25% increase in the erythrocyte mass occurs in pregnancy but is concealed by the dilutional effect of the increase in plasma volume. This is driven by an increase in serum erythropoietin concentrations during the late second and early third trimesters and is facilitated or potentially limited by iron availability. Pregnant women using iron supplementation have a greater increase in erythrocyte mass than women not using supplemental iron, and women with compromised iron stores at outset of pregnancy will have a limited increase in erythrocyte mass. The upper limit of erythrocyte mass increase in the presence of adequate iron is, however, regulated through erythropoietin control and is not raised by increased iron availability: pregnant women in the Bantu tribe, who have both an iron-rich traditional diet and a genetic predisposition to increased dietary iron absorption, do not increase Hb concentration or Hct with supplementation.

As a result of the reset balance between plasma volume and erythrocyte mass, it is generally considered that a Hb concentration <11 g/dL in the late first trimester and <10 g/dL in the second and third trimesters should be investigated for a cause other than the physiologic anemia of pregnancy.

Maternal plasma volume generally decreases during the final weeks of pregnancy, and consequently the Hct, Hb, and circulating erythrocyte count increase. The maternal blood volume generally returns to prepregnancy levels within one to six weeks after delivery and maternal erythropoiesis increases late in gestation and returns to normal by about one month after delivery.

Iron Balance: An Overview[1]

A detailed discussion of the regulation of iron balance is outside the scope of this review, and the reader is referred to recent reviews. Iron content in the human body is carefully regulated and is normally maintained at about 40 mg/kg in women and about 50 mg/kg in men. Since humans are unable to excrete excess iron in a regulated manner, iron balance is controlled at the levels of iron absorption by enterocytes in the duodenum, and of iron mobilization from liver parenchyma and macrophages. These processes are regulated by hepcidin, a small peptide produced in the liver. Hepcidin binds to a cellular iron export protein, ferroportin, causing its

internalization. When hepcidin levels are increased, iron is retained in enterocytes or macrophages and is not available for red cell production. When hepcidin is decreased, either because of ID or by increased erythropoiesis, absorbed iron in the enterocytes or stored iron in macrophages are mobilized into the circulation.

Absorption of dietary iron is also affected by the iron source and duodenal conditions, such as pH. The proportion of iron absorbed from heme iron and non-food sources such as iron salts or saccharates is approximately 10%15% of elemental iron, while less than 2% of elemental iron from vegetable sources is absorbed. ID may double the percent iron absorption from any given source.

Iron is transported from the enterocyte to the plasma iron transport protein transferrin. The amount of iron bound to transferrin and in circulation is approximately 0.2 mg/kg under normal circumstances. Storage iron resides in macrophages of the spleen, bone marrow, or liver, and in liver parenchymal cells (5–6 mg/kg in women, 10–12 mg/kg in men). Macrophage iron is largely derived from recycling of senescent erythrocytes while liver parenchymal cells receive or release iron from or to transferrin. The largest pool of iron in the body is in circulating erythrocytes and erythroid precursors in the bone marrow (approximately 28 mg/kg in women and 32 mg/kg in men). Nearly all of this erythrocyte iron is in the form of Hb.

Iron Requirements during Pregnancy[1]

It is generally considered that a normal singleton pregnancy carried to term requires a transfer of 500–800 mg of maternal iron. It is estimated that the demand for absorbed iron increases from 0.8 mg/day in early pregnancy to 7.5 mg/day in late pregnancy, with an average requirement over the entire course of pregnancy of 4.4 mg/day. In a study of healthy pregnant women in Denmark, the 5th percentile Hb value of subjects receiving supplementation with 66 mg elemental iron/day was consistently higher than that of the subjects receiving placebo. Differences were small in the first trimester (0.1 mg/dL Hb higher) and gradually increased into the second (0.1–0.4 mg/dL Hb higher) and third trimesters (0.3–0.9 mg/dL Hb higher) and the postpartum period (1 mg/dL Hb higher). The relatively small difference in the first trimester likely reflects a high incidence of ID or marginal iron stores in both groups and the steadily increasing gap reflects the increasing iron requirements of pregnancy that are not being met in the placebo group. In a large review of premenopausal women, only 20% had presumed iron reserves of >500 mg (defined as a serum ferritin concentration >70 µg/L), and would

potentially be able to go through pregnancy without iron supplementation. This is consistent with an earlier study in which women who received or did not receive iron supplementation during pregnancy underwent bone marrow evaluation after delivery. Only 16% of women not supplemented with oral iron had stainable iron in bone marrow aspirates after delivery at term, although their mean Hb concentration (10.9 g/dL) was in the expected range for the third trimester.

Benefits And Risks Of Iron Supplementation During Pregnancy[2]

Physiologic Considerations

Pregnancy poses a large risk of negative iron balance to a woman. Compared with the nonpregnant state, iron demands are greatly amplified for two reasons. First, the fetoplacental unit requires a large amount of iron for its own growth and development during gestation. One gram of iron needs to be accreted by the mother during pregnancy—of which 360 mg is transferred from the mother to the fetus, particularly during the third trimester when growth is most rapid—in order to maintain a content of 75 mg of iron per kg body weight of the fetus. The pregnant woman expands her own plasma and blood volumes to maintain proper circulation and oxygen delivery to her own organs as well as to the placenta. The blood volume expansion consumes 450 mg of the 1 g of additional iron required during pregnancy. Decreasing hepcidin concentrations during pregnancy indicate the pregnant woman's need to absorb more iron for both her own hemoglobin synthesis as well as for transport across the placenta to the highly metabolic and growing fetus. Iron deficiency is generally acknowledged as a greater risk than iron overload during human pregnancy.

The goals of maintaining iron sufficiency during pregnancy are to reduce maternal morbidity, promote fetal health, and to set up the newborn with adequate nutrient stores for early postnatal life. Increasing evidence supports the concept that postnatal iron status at 9 months of age depends on proper fetal iron loading during pregnancy. The risk of postnatal iron deficiency in infants is reduced when neonatal iron stores are normal following gestation, delayed cord clamping is practiced, and postnatal growth rate is not excessive. It is also likely that proper loading of the newborn via the maternal–fetal route reduces the need for excessive early iron supplementation of the infant postnatally in certain iron-sufficient populations.

Pregnancies in Iron-Deficient Populations

There is little debate that iron-deficient women have an increased risk of adverse pregnancy outcomes, that is, those that affect the woman, her fetus, or, consequently, her offspring. Most studies utilize hemoglobin as the biomarker for iron status because of the ubiquitous availability of this measurement and because iron deficiency is the most common cause of anemia in most populations. However, anemia and iron deficiency are not synonymous, which makes interpreting the outcomes of these studies problematic. Anemia at various time points in pregnancy is associated with an increased risk of preterm birth, birth weight <2,500 grams, and low weight for gestational age. In most studies, supplementation of anemic women with iron during pregnancy reduces the rate of iron-deficiency anemia and nonanemic iron deficiency at term, and in some studies, it reduces the risk of adverse outcomes, suggesting that supplementation in this population is beneficial.

Table 1. Interpretation and risk–benefit analysis of maternal iron supplementation during pregnancy based on whether hemoglobin or ferritin was used as the primary biomarker to assess iron status and the information added by a second biomarker

Primary marker	***Literature interpretation***	***Biochemical interpretation with second biomarker***	***Agreement between literature and biochemical finding?***	***Low hepcidin (likely response to therapy)***	***Estimate of risk-benefit of routine supplementation*** [a]
Hemoglobin					
Low	Iron-deficiency anemia	Low ferritin: iron-deficiency anemia	Low ferritin: yes	Low ferritin: yes	B ≫ R
		Normal ferritin: anemia	Normal ferritin:	Normal ferritin: no	Unknown, but R > B because iron

		of inflammation	unknown because total-body iron is unmeasurable		will not be absorbed in high hepcidin state
		High ferritin: anemia of inflammation	High ferritin: unknown because total-body iron is unmeasurable	High ferritin: no	
Normal	Iron sufficient	Low ferritin: low-iron state	Low ferritin: no	Low ferritin: yes	B > R
		Normal ferritin: iron sufficient	Normal ferritin: yes	Normal ferritin: no	Unknown
		High ferritin: iron overload	High ferritin: no	High ferritin: no	R > B
High	Iron sufficient	Low ferritin: polycythemia by volume contraction or other non-iron-	Low ferritin: nonanemia iron deficiency	Low ferritin: yes	R > B

		related condition			
		Normal ferritin: polycythemia by volume contraction or other non-iron-related condition	Normal ferritin: iron overload	Normal ferritin: no	R > B
		High ferritin: iron overload	High ferritin: iron overload	High ferritin: no	R > B
Ferritin					
Low	Low-iron state	Low hemoglobin: iron-deficiency anemia	Low hemoglobin: partly	Low hemoglobin: yes	B ≫ R
		Normal hemoglobin: nonanemia iron deficiency	Normal hemoglobin: yes	Normal hemoglobin: yes	B > R
		High hemoglobin: polycythemia by volume contraction or other non-iron-	High hemoglobin: no	High hemoglobin: no	R > B

		related condition			
Normal	Iron sufficient	Low hemoglobin: anemia of inflammation	Low hemoglobin: no	Low hemoglobin: no	R > B
		Normal hemoglobin: iron sufficient	Normal hemoglobin: yes	Normal hemoglobin: no	Unknown
		High hemoglobin: polycythemia by volume contraction or other non-iron-related condition	High hemoglobin: no	High hemoglobin: no	R > B
High	Iron sufficient	Low hemoglobin: anemia of inflammation	Low hemoglobin: no	Low hemoglobin: no	R > B
		Normal hemoglobin: iron overload	Normal hemoglobin: no	Normal hemoglobin: no	R > B
		High hemoglobin: iron overload	High hemoglobin: no	High hemoglobin: no	R > B

Abbreviations: B, benefit; R, risk.

[a]Estimate of whether the risk (R) of adverse outcomes or the benefit (B) associated with iron supplementation is greater, given each combination of iron markers.

A minority of clinical studies that assessed outcomes as a function of iron status used iron-specific biomarkers as opposed to or in conjunction with hemoglobin concentrations. Iron-specific markers can be problematic for routine screening for analytic and interpretative reasons. The limited availability of the analytic equipment needed to measure specific iron parameters—especially serum ferritin, percent total iron-binding capacity saturation, soluble transferrin receptor, or hepcidin—is a major hurdle, particularly in low-resource countries. An ideal biomarker would index the risks of negative iron balance before physiologic consequences are present. Serum ferritin, which typically indexes iron stores, could theoretically serve this purpose since there are no known consequences of low iron stores, per se, as long as adequate iron is available to support hematopoiesis, tissue-level iron proteins (e.g., cytochromes), and iron transport to the fetus. However, ferritin acts as an acute-phase reactant to infection and inflammation, which undermines its effectiveness as a screening tool. Nevertheless, a meta-analysis of pregnancy outcomes as a function of iron stores demonstrated that low iron stores, particularly during the first trimester, are associated with a greater risk of low birth weight, prematurity, and small size for dates.

Clinical studies have also assessed maternal iron status exclusively as a function of dietary iron intake during pregnancy. This approach has potential drawbacks, including the inherent variability of dietary recall and, more importantly, the question of whether dietary intake is tightly linked to actual iron accretion. This linkage can be tenuous because multiple inflammatory events during pregnancy could result in relatively less absorption of dietary iron due to activation of hepcidin by proinflammatory cytokines, including interleukin-6. Furthermore, dietary iron intake gives no information about the distribution of iron between mother and fetus. Nevertheless, a meta-analysis of studies of maternal iron intake in iron-deficient populations shows that iron supplementation of iron-deficient populations is beneficial. Neurobehavioral pathologies in offspring related to low maternal iron intake during critical periods of pregnancy include increased risks of schizophrenia and autism.

Overall, clinical studies support iron supplementation of pregnant women with iron deficiency defined by any of the three biomarker approaches (i.e., hemoglobin, serum ferritin, or dietary intake). Little discordance exists among the three biomarkers, except in the case of active inflammatory processes.

The role of inflammation in confounding iron status assessments is important. Inflammation activates hepcidin and thereby countermands the normal increase in iron accretion mediated by

low hepcidin concentrations during pregnancy. Hepcidin increases iron in the storage pool, as evidenced by high serum ferritin concentrations, while shortchanging iron availability for hemoglobin synthesis by reducing intestinal iron absorption. Chronic inflammation results in reduced total-body iron during pregnancy and less iron availability for the fetus, yet the condition may be interpreted as iron overload or iron sufficiency if ferritin is the only biomarker used by the clinician to assess iron status.

Although chronic low-grade inflammation may be relatively common in austere settings, the most common inflammatory condition worldwide during pregnancy is malaria. Worldwide, approximately 35 million pregnant women are at risk of *Plasmodium falciparum* malaria each year. The vast majority of populations at risk for malaria live in regions where iron deficiency is endemic. Iron supplementation in areas where both iron deficiency and malaria are endemic must be viewed within in the context of the 2006 landmark study on Pemba Island, Tanzania, that found that universal, daily supplementation with iron and folic acid increased the risk of hospitalization and death in young children. Subsequent cross-sectional studies seemed to support this association in pregnant women, finding a lower prevalence of placental malaria among women with iron-deficiency anemia. In vitro studies have provided apparent mechanistic support of these findings, demonstrating that red blood cells taken from both anemic children and anemic pregnant women support a lower rate of *Plasmodium* growth than nonanemic red blood cells. Iron supplementation without treatment of malaria leads to increased parasite growth in red blood cells from both children and women.

However, two recent randomized placebo-controlled trials have not supported a harmful link between healthy iron status and the risk of malaria in pregnant women. The trials demonstrate the importance of treating the malaria first and then addressing iron status. In the first study, 1,500 HIV-uninfected pregnant Tanzanian women with serum ferritin concentrations >12 μg/L and hemoglobin concentrations >85 g/L were enrolled before 27 weeks' gestation and were randomized to 60 mg of daily iron as ferrous sulfate or to placebo. All women received monthly prenatal health checks that included malaria screening, intermittent presumptive treatment for malaria, and antimalarial treatment if needed. Iron supplementation was not associated with an increased risk of placental malaria or other adverse events, and while iron did not increase birth weight, hemoglobin concentration and iron status as measured by serum ferritin concentration were greater among women in the iron-supplemented group. Although this study was conducted in an urban setting with a relatively low risk of malaria, a subsequent study in a malaria-endemic area of rural Kenya had similar findings. In that randomized placebo-

controlled trial, daily supplements of 60 mg iron as ferrous fumarate given to pregnant women between the ages of 15 and 46 years, with no other inclusion criteria, did not increase the risk of maternal malaria and were associated with greater birth weight, lower risk of premature birth, longer length of gestation, and higher maternal and infant iron stores 1 month after birth when compared with placebo.

After the Pemba study, all iron supplementation trials in malaria-endemic areas have included a malaria control component for ethical reasons. These findings support the current World Health Organization (WHO) recommendation for universal daily supplementation with 30 to 60 mg elemental iron during pregnancy in regions where the prevalence of anemia is 20% or higher, with a stipulation in malaria-endemic areas that supplementation should be given in conjunction with “adequate measures to prevent, diagnose and treat malaria”.

Pregnancies in Iron-Sufficient Populations

Further controversy with respect to the accurate diagnosis of iron status and subsequent iron supplementation surrounds the routine iron supplementation of apparently iron-sufficient (i.e., non-iron-deficient) women during pregnancy. The US Preventive Services Task Force stated that there was insufficient evidence to advocate routine iron supplementation during pregnancy. A similar statement from the European Food Safety Authority concluded that iron supplementation during pregnancy should be reserved for those at risk for or with documented iron deficiency. The controversy stems from the difficulty in demonstrating any added benefit versus any potential risks of iron supplementation.

The majority of this literature defines iron status by measuring maternal hemoglobin concentration. However, precisely defining iron status in the context of what is termed the physiologic anemia of pregnancy is problematic. The physiologic anemia of pregnancy occurs because of a disproportionately greater expansion of the plasma volume (+50%) than of the red cell mass (+25%), leading to a dilutional reduction in hemoglobin concentration. Maternal hemoglobin concentrations between 95 and 110 g/dL have been associated with the best pregnancy outcomes and, thus, would be considered normal. Hemoglobin concentrations higher than this range have been associated with higher rates of preeclampsia, prematurity, and fetal growth restriction. A smaller number of trials have assessed the effect of iron supplementation on women with high hemoglobin concentrations (i.e., >132 g/L) and found an increased rate of maternal preeclampsia and fetal growth restriction.

A nonanemic hemoglobin concentration would typically be considered a biomarker of iron sufficiency in nonpregnant women, whereas excessively high hemoglobin would be consistent with total-body iron overload, given that iron is predominantly found in red cells. Alternatively, elevated hemoglobin concentrations during pregnancy may not indicate iron overload but instead reflect low plasma volume expansion, that is, cases in which the 2:1 ratio of plasma volume to red cell mass expansion is not achieved. In that circumstance, serum ferritin may be normal or even low. Thus, an elevated hemoglobin concentration may be misinterpreted as iron overload. Studies that associate high hemoglobin concentrations during pregnancy with poorer outcomes should be interpreted cautiously as to whether the mechanistic causes of the poorer outcomes are a fundamental gestational pathology that leads to low plasma volume expansion, true iron overload, or both. The possibility that iron plays a primary role in plasma volume dysregulation must be considered because such information would have a direct impact on the decision to offer iron supplementation to women with normal or high hemoglobin concentrations. The lack of adequate studies hinders the ability to provide guidelines regarding universal iron supplementation in nonanemic pregnant women.

Future studies could avoid dividing pregnant women into the two traditional hemoglobin categories, anemic or nonanemic, and instead consider a three-group model: anemic, normal, and polycythemic. Data support this approach since a U-shaped risk curve of pregnancy complications as a function of hemoglobin concentration has been described. Moreover, women with normal hemoglobin concentrations may have preanemic iron deficiency. Women with high hemoglobin concentrations may be iron-sufficient, but not iron overloaded, if the high hemoglobin concentration is due solely to the failure of plasma volume expansion.

Assessing pregnancy outcomes as a function of iron-specific biomarkers could potentially provide more direct insight than measuring hemoglobin alone. In turn, these markers could be used to identify candidates for supplementation during pregnancy. Among these markers, serum ferritin has been most often utilized in outcome studies. WHO recently assessed its usefulness as a screening tool. Clinical interpretation of ferritin concentrations relies on the understanding that if iron stores are replete, sufficient iron is present to support iron-dependent cellular processes at the tissue level. Serum ferritin is an excellent specific metric for low-iron states because no condition other than iron deficiency results in low serum ferritin concentrations. Interpreting high serum ferritin concentrations is more problematic with respect to understanding serum ferritin’s relationship to tissue iron status. High ferritin concentrations could indicate iron overload or, alternatively, a shift of iron into

reticuloendothelial cell storage as part of a response to inflammation. Mathematical correction of ferritin concentrations for the degree of inflammation as indexed by an inflammatory biomarker has been proposed, but has not been widely implemented.

The majority of published studies on pregnancy outcomes as a function of maternal iron status utilized serum ferritin as the biomarker. They reported that higher ferritin concentrations early in pregnancy were associated with more positive pregnancy outcomes, whereas higher ferritin concentrations in the third trimester were associated with poorer outcomes, including premature delivery and low birth weight. Interpreting these studies is difficult because it is unclear whether the high ferritin concentrations during the third trimester indexed increased total-body iron or a shift of iron into the storage pool due to inflammation. There is a great need for a sensitive and specific biomarker that indexes tissue iron status and is not influenced by inflammation.

Assessing iron status by quantifying iron intake has yielded mixed results with respect to pregnancy and offspring outcomes. On one hand, iron intake in non-iron-deficient mothers early in pregnancy appears to protect against autism in the offspring, and iron intake during the third trimester induces a more mature gray matter pattern on diffusion tensor imaging in term infants. Conversely, iron supplementation in women with high hemoglobin concentrations (i.e., >132 g/L) during the second trimester leads to even higher hemoglobin concentrations in the mother, but a greater risk of fetal growth restriction, most likely due to maternal hypertension. Iron supplementation in pregnant women has also been linked in observational studies to a greater risk of gestational diabetes mellitus.

Approach to Iron Administration in Pregnancy[1]

At present, neither the US Preventive Services Task Force nor the American College of Obstetricians and Gynecologists (ACOG) take a position on routine iron supplementation in pregnancy, and society guidelines in the UK recommend against it. Both the ACOG and the UK guidelines recommend screening for anemia as a surrogate for detecting ID. The recommended standards at which anemia should be investigated from both societies are generally consistent with the earlier discussion in this review of the expected degree of anemia from the physiologic anemia of pregnancy: 11.0 g/dL in the first and third trimesters, and 10.5 g/dL in the second trimester (ACOG), or 11.0 g/dL in the first trimester and 10.5 g/dL in subsequent trimesters (UK). Both guidelines suggest a trial of iron as the initial step, with

subsequent investigation for other causes if there is an insufficient response. This approach poses a risk of missing individuals who are iron deficient but not anemic as well as the early stages of ID. It has been suggested, based upon cross-sectional studies of reproductive age women who are not pregnant, that a hemoglobin threshold of 12.8 g/dL (higher than the World Health Organization standard of 12.0 g/dL) is a more appropriate cut off for identifying women at risk for ID. Neither the ACOG nor UK guidelines recommend routine screening with iron studies, but the UK guidelines recommend measuring serum ferritin in women perceived to be at high risk for ID, even if they are not anemic. The most effective approach to anticipating and managing ID risk in pregnancy is a critical topic for future research.

There are two general approaches to iron supplementation in pregnant women who are not anemic. These are selective supplementation, typically guided by laboratory values or by patient demographics in high-risk areas; and routine or universal supplementation. One well-described approach to selective supplementation is based on estimation of iron stores by serum ferritin. When the serum ferritin is greater than 70 µg/L, iron stores are considered adequate to support pregnancy and no supplementation is given. When serum ferritin is less than 30 µg/L, iron stores are considered absent or nearly absent, and the patient is treated with 80–100 mg elemental iron/day orally. Women whose ferritin values are between these points receive low-dose supplementation of 30–40 mg/day. A recent systematic review supports the concept that intermittent iron supplementation in pregnancy (2–3 times weekly, as opposed to daily) is as effective as daily supplementation, and associated with fewer side effects and presumably, higher compliance.

By those criteria, more than 75% of the women participating in the Third NHANES study overall would require supplementation at some level, and more than 90% of Latina women would require supplementation. For this reason, many physicians utilize routine or universal iron supplementation in all pregnant women.

An alternate approach to selective supplementation has been proposed using hepcidin as the indicator of early ID and a need for therapy. A recent report comparing a hepcidin-guided supplementation approach to a universal prophylaxis approach showed similar patient outcomes in both groups. This study was performed in a high-risk population in Gambia, and this approach may have different outcomes in other venues.

One reason to avoid routine supplementation in the less developed world is concern that iron supplementation will increase risk of infection with iron dependent microorganisms and

parasites, including malaria. A study in Papua New Guinea found that the benefits of iron supplementation on maternal anemia and birthweight exceeded potential risk, although the benefits were most pronounced in patients who had some degree of ID. In general, iron supplementation is considered low risk, and an iron supplement of 65 mg elemental iron mg/day beginning at or before 20 weeks' gestation generally is adequate to prevent ID during pregnanc. However, one of the arguments against routine iron supplementation, particularly in the less-developed world, is that benefits on infant neurocognitive development (as distinct from benefits on maternal anemia and iron stores) have not been demonstrated clearly, as was discussed earlier.

In keeping with the UK and ACOG guidelines, investigation for an etiology of anemia would occur if Hb were below the levels described. At this point, the focus moves beyond supplementation (which could be regarded as providing the additional iron required for gestation to a person with adequate iron stores) to the treatment of IDA. The objective in the treatment of IDA is correction of anemia and also repletion of absent iron stores. If initiated early in pregnancy, therapy will need to accommodate the 500–800 mg of iron that will be transferred to the newborn as well as maintaining the maternal Hb/Hct and repleting iron stores. A reasonable approach to therapy is to provide 60–100 mg of elemental iron per day. A variety of oral iron preparations are available and patient preference and, in some cases, considerations of the financial cost to the patient, can govern choices. Traditionally, ID was treated with oral iron three times daily. Subsequent studies investigating the interaction of oral iron therapy with the hepcidin axis led to the recognition that the hepcidin increment caused by therapeutic doses of iron salts or saccharates decreases absorption for approximately 24 h, implying that once daily oral iron therapy is as effective or more effective than the traditional twice or three times daily dosing. Failure to respond to oral iron should lead to a re-assessment of iron status. This would be to address problems with iron absorption leading to a poor response or (more commonly) lack of compliance with iron therapy, but also to consider other potential etiologies of anemia in pregnancy. Oral iron therapy for IDA in pregnancy should continue until the Hb/Hct and MCV are in the normal range, and until the serum ferritin has also returned to a solidly normal value (certainly higher than 30 µg/L and probably higher than 50 µg/L) indicating adequate iron stores.

Most pregnant patients are able to tolerate oral iron, particularly when given once daily or on an intermittent schedule. However, if the patient is unresponsive to oral iron, or unable/unwilling to take iron orally, intravenous iron therapy is safe and effective. An

advantage of intravenous iron therapy is that it corrects Hb/Hct and iron stores concurrently and rapidly. Recent systematic reviews indicate that intravenous iron therapy in pregnancy allows more complete achievement of desired Hb concentrations. A number of intravenous iron preparations are available, with different dosing schedules, and a detailed discussion of these is outside the scope of the current review. In most cases, the total dose to be administered intravenously is 1000–1500 mg elemental iron.

In the absence of gastrointestinal signs or symptoms, endoscopic evaluation of the gastrointestinal tract is unlikely to identify a lesion accounting for blood loss in premenopausal women with ID, and can be deferred safely in favor of a trial of iron replacement. As noted earlier, failure to respond to iron therapy should prompt evaluation for either ongoing sources of blood loss if there is persisting evidence of ID, or consideration of other etiologies of anemia.

References:

1. Means RT. Iron Deficiency and Iron Deficiency Anemia: Implications and Impact in Pregnancy, Fetal Development, and Early Childhood Parameters. *Nutrients*. 2020;12(2):447.
2. Georgieff MK, Krebs NF, Cusick SE. The Benefits and Risks of Iron Supplementation in Pregnancy and Childhood. *Annu Rev Nutr*. 2019;39:121-146.

Survey Form

1) How frequently do you encounter pregnant females with iron deficiency anemia (IDA) in your clinical practice?

a. Very frequently
b. Frequently
c. Occasionally
d. Rarely

2) When managing pregnant females with IDA, what is your preferred form of iron supplementation?

a. Elemental iron
b. Iron salts (ferrous sulfate, ferrous gluconate, etc.)
c. Iron polysaccharide complex
d. Other

3) In your experience, how often do you observe adverse reproductive outcomes in pregnant females with IDA?

a. Very often
b. Often
c. Occasionally
d. Rarely

4) What adverse reproductive outcomes have you commonly observed in pregnant females with IDA?

a. Preterm birth
b. Low birth weight
c. Developmental delays in infants
d. Maternal complications

5) How confident are you in the efficacy of elemental iron supplementation in reducing adverse reproductive outcomes in pregnant females with IDA?

a. Very confident
b. Confident
c. Neutral
d. Not confident

6) When initiating iron supplementation in pregnant females with IDA, what factors influence your choice of dosage and duration?

a. Severity of anemia
b. Patient's compliance history
c. Presence of comorbidities
d. Other

7) How do you monitor the response to elemental iron supplementation in pregnant females with IDA?

a. Regular blood tests (hemoglobin levels)
b. Clinical assessment of symptoms
c. Patient-reported improvements
d. Combination of the above

8) Have you encountered any challenges or concerns related to patient compliance with elemental iron supplementation during pregnancy?

a. Yes, frequently
b. Occasionally
c. Rarely
d. No, not at all

9) In your opinion, what are the main barriers to optimal iron supplementation in pregnant females with IDA?

a. Gastrointestinal side effects
b. Taste and palatability of iron supplements
c. Lack of awareness among patients
d. Other

10) How often do you educate pregnant females with IDA about the importance of consistent and timely iron supplementation?

a. Always
b. Often
c. Occasionally
d. Rarely or never

11) Do you routinely recommend dietary changes in conjunction with elemental iron supplementation for pregnant females with IDA?

a. Yes, always
b. Yes, often
c. No, not routinely
d. Not applicable

12) How do you handle situations where pregnant females express concerns about the potential taste or aftertaste of elemental iron supplements?

a. Recommend flavored formulations
b. Provide additional information on the benefits of supplementation
c. Adjust dosage or switch to a different formulation
d. Not applicable, as taste concerns are not a common issue

13) How do you address concerns about potential side effects, such as constipation, associated with elemental iron supplementation in pregnant females?

a. Adjust dosage or switch to a different formulation
b. Recommend lifestyle modifications (e.g., increased water intake, dietary fiber)
c. Provide additional medications to manage side effects
d. Not applicable, as side effects are not a common concern

14) In your clinical practice, how often do you encounter pregnant females with IDA who have received iron supplementation before their pregnancy?

a. Very often
b. Occasionally
c. Rarely
d. Not applicable

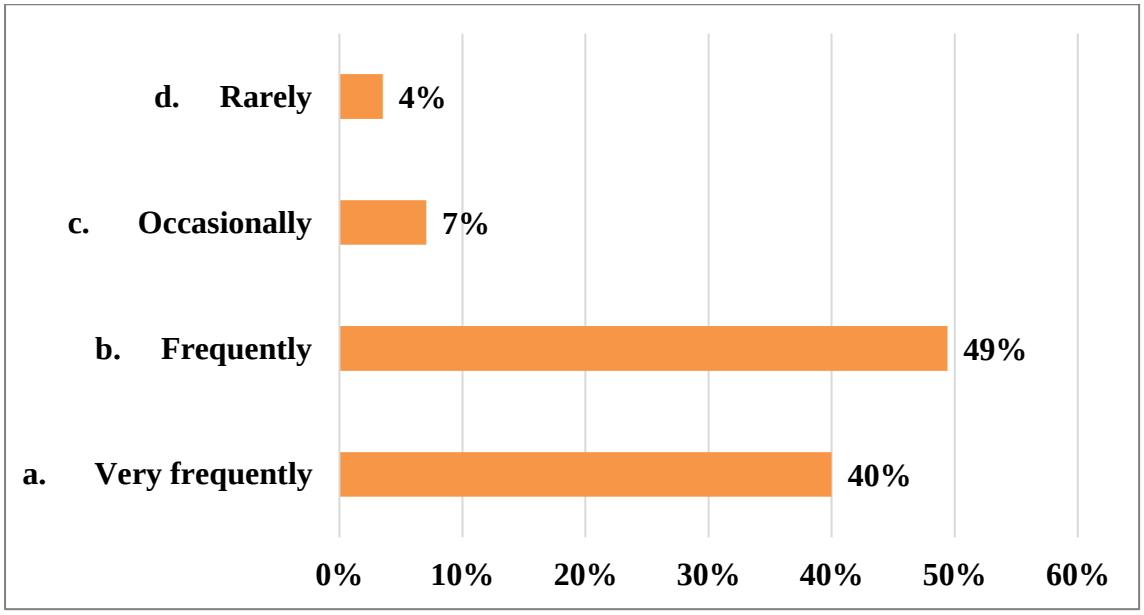
15) Overall, how satisfied are you with the clinical outcomes of elemental iron supplementation in pregnant females with IDA in your practice?

a. Very satisfied
b. Satisfied
c. Neutral
d. Unsatisfied

Survey Findings

1) How frequently do you encounter pregnant females with iron deficiency anemia (IDA) in your clinical practice?

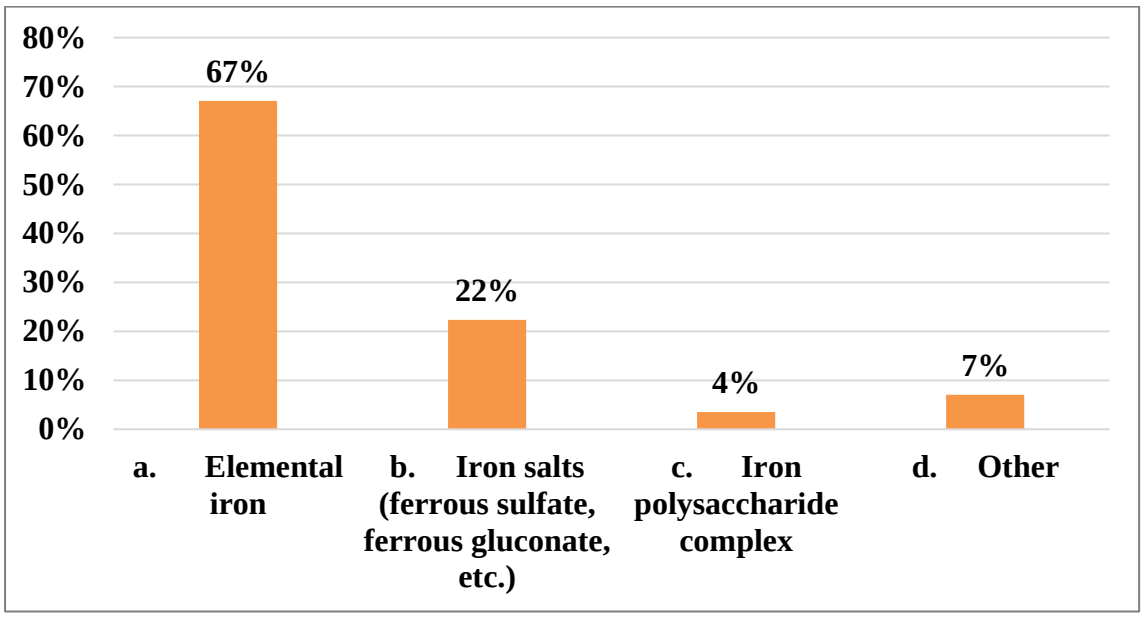
a. Very frequently
b. Frequently
c. Occasionally
d. Rarely



According to 49% of doctors, they frequently encounter pregnant females with iron deficiency anemia (IDA) in their clinical practice.

2) When managing pregnant females with IDA, what is your preferred form of iron supplementation?

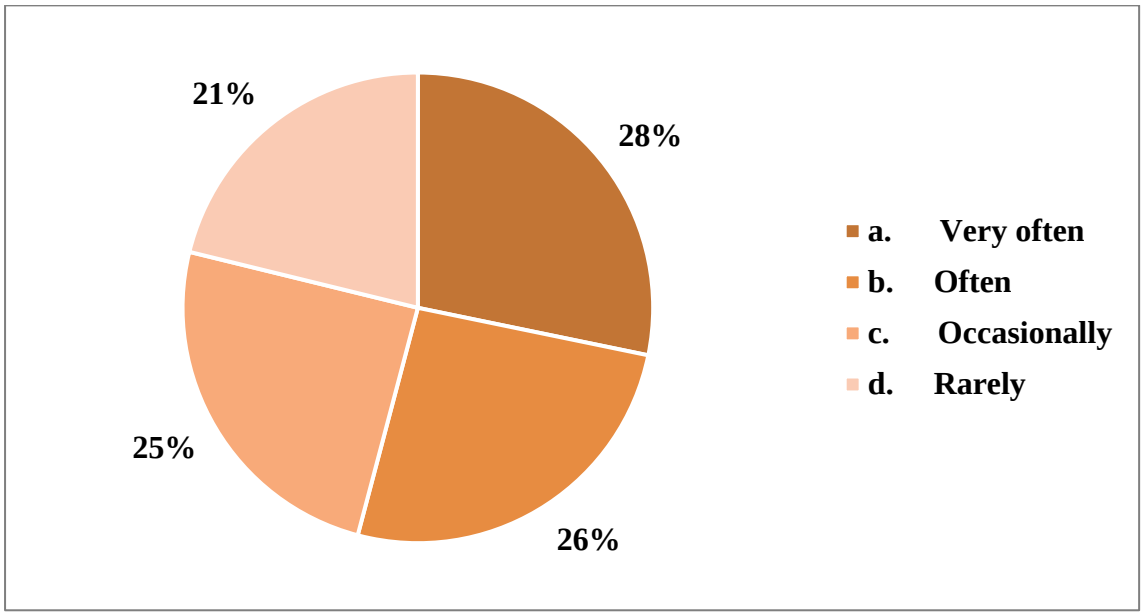
a. Elemental iron
b. Iron salts (ferrous sulfate, ferrous gluconate, etc.)
c. Iron polysaccharide complex
d. Other



Majority of doctors, 67%, prefer elemental iron supplementation when managing pregnant females with IDA.

3) In your experience, how often do you observe adverse reproductive outcomes in pregnant females with IDA?

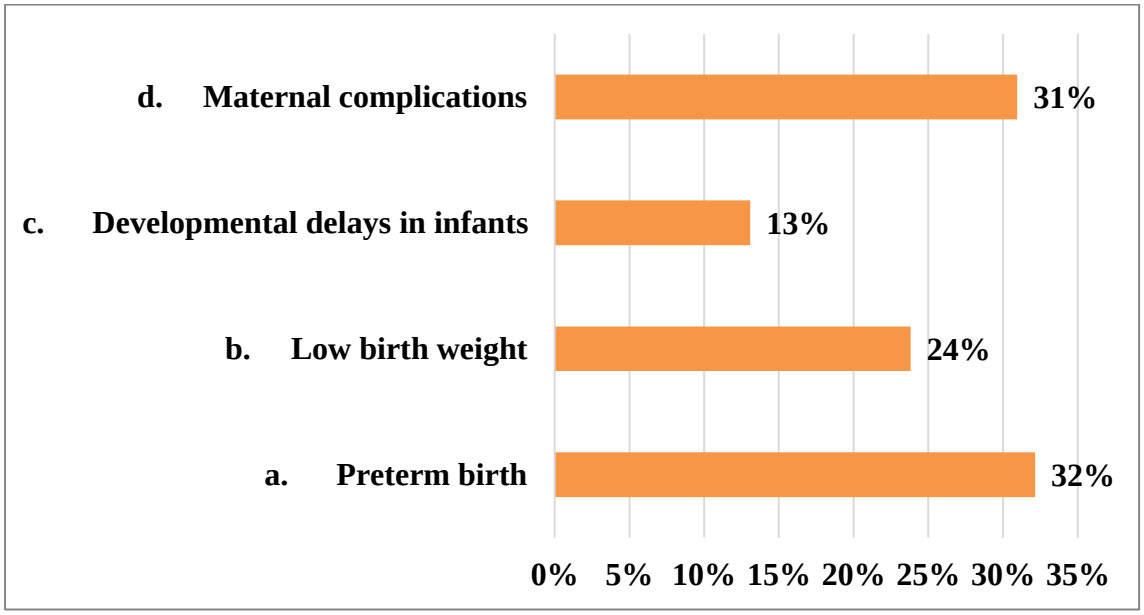
a. Very often
b. Often
c. Occasionally
d. Rarely



In the experience of 28% of doctors, they very often observe adverse reproductive outcomes in pregnant females with IDA.

4) What adverse reproductive outcomes have you commonly observed in pregnant females with IDA?

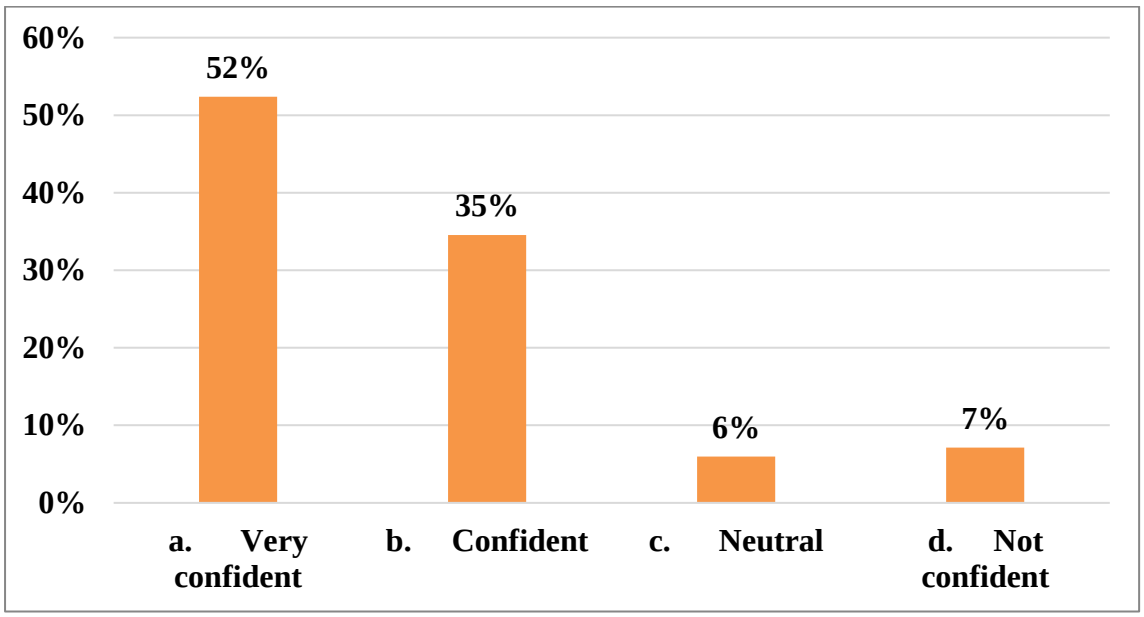
a. Preterm birth
b. Low birth weight
c. Developmental delays in infants
d. Maternal complications



32% doctors have commonly observed adverse reproductive outcomes of maternal complications observed in pregnant females with IDA.

5) How confident are you in the efficacy of elemental iron supplementation in reducing adverse reproductive outcomes in pregnant females with IDA?

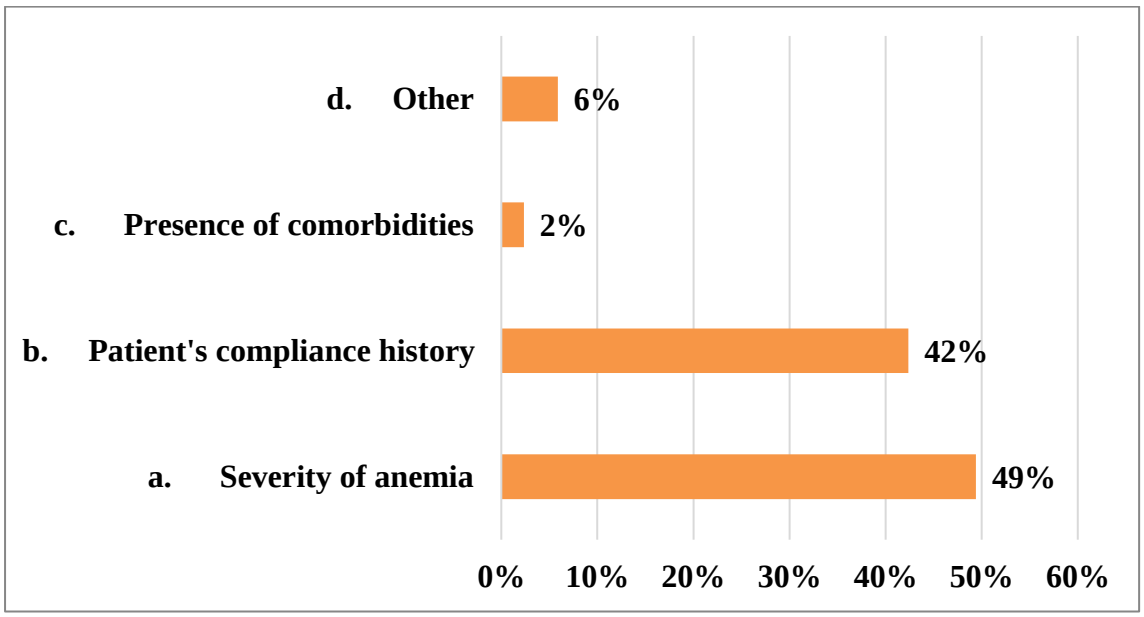
a. Very confident
b. Confident
c. Neutral
d. Not confident



52% of doctors are very confident in the efficacy of elemental iron supplementation in reducing adverse reproductive outcomes in pregnant females with IDA.

6) When initiating iron supplementation in pregnant females with IDA, what factors influence your choice of dosage and duration?

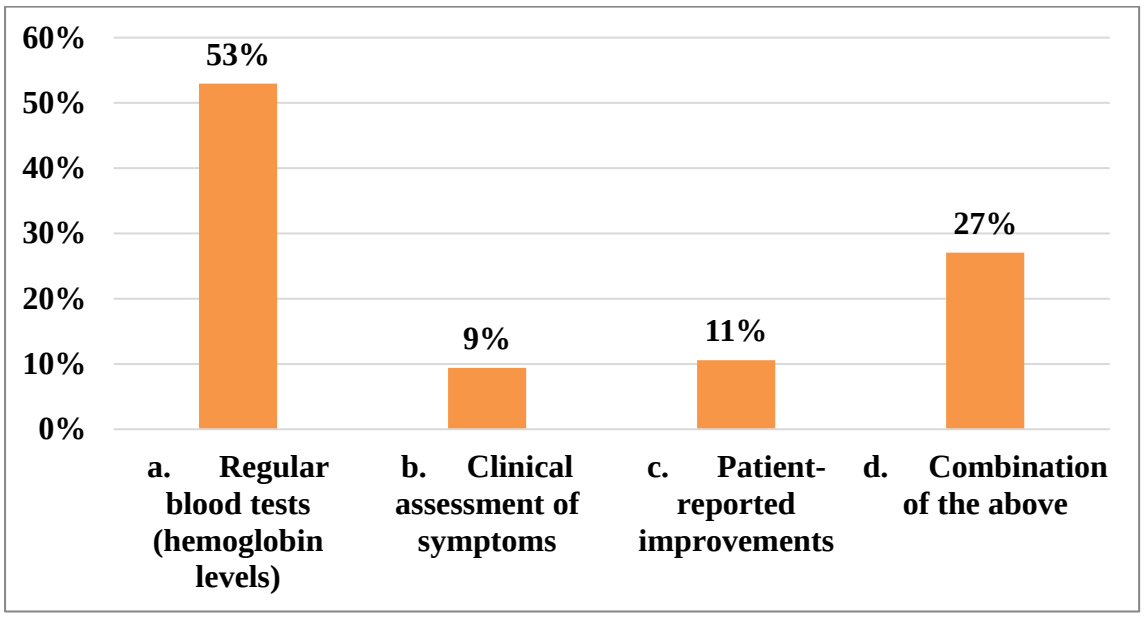
a. Severity of anemia
b. Patient's compliance history
c. Presence of comorbidities
d. Other



According to 49% of doctors, when initiating iron supplementation in pregnant females with IDA severity of anemia influence their choice of dosage and duration.

7) How do you monitor the response to elemental iron supplementation in pregnant females with IDA?

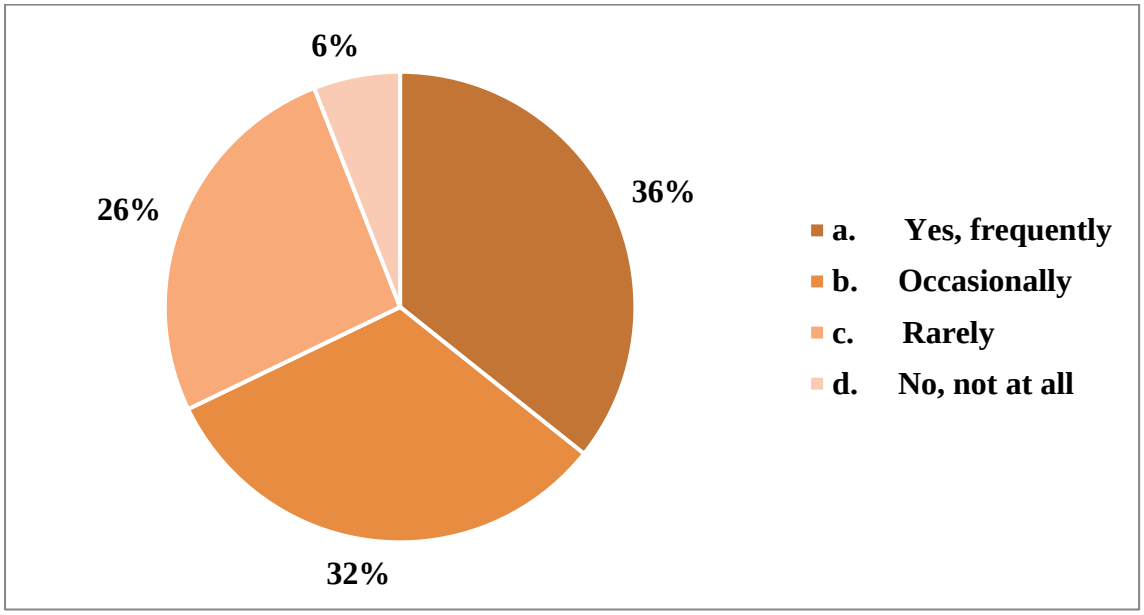
a. Regular blood tests (hemoglobin levels)
b. Clinical assessment of symptoms
c. Patient-reported improvements
d. Combination of the above



53% of doctors monitor the response to elemental iron supplementation in pregnant females with IDA by conducting regular blood tests (hemoglobin levels).

8) Have you encountered any challenges or concerns related to patient compliance with elemental iron supplementation during pregnancy?

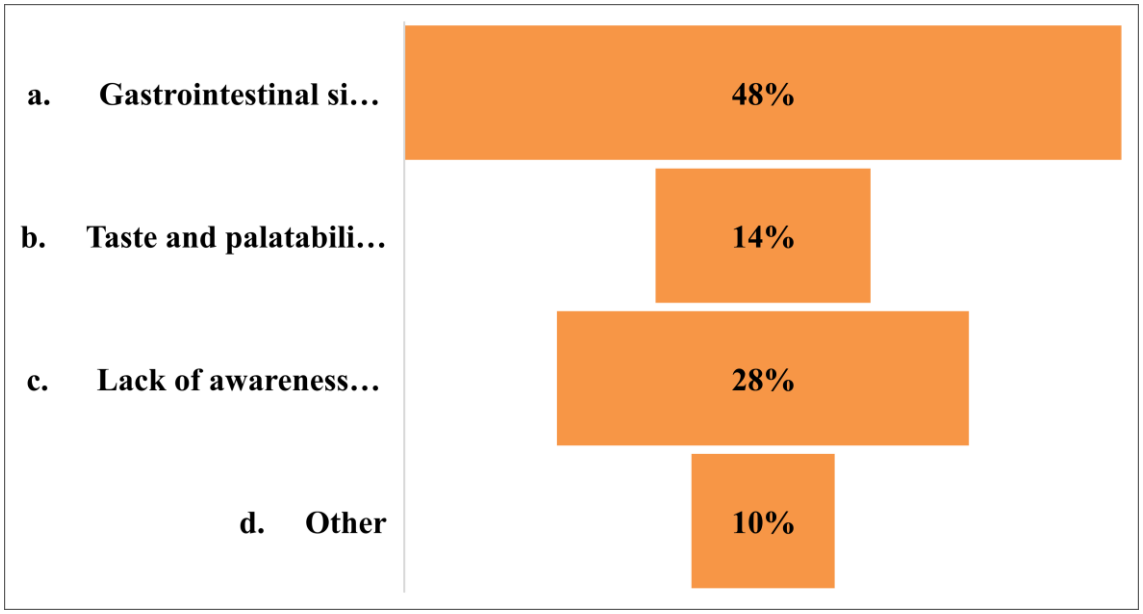
a. Yes, frequently
b. Occasionally
c. Rarely
d. No, not at all



36% of doctors have frequently encountered challenges or concerns related to patient compliance with elemental iron supplementation during pregnancy.

9) In your opinion, what are the main barriers to optimal iron supplementation in pregnant females with IDA?

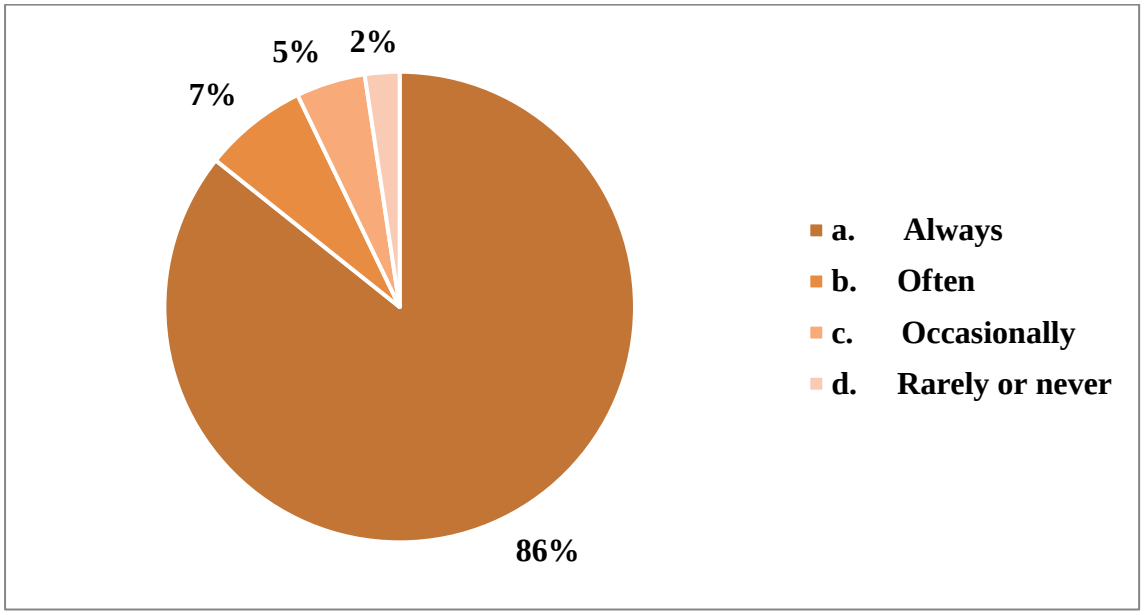
a. Gastrointestinal side effects
b. Taste and palatability of iron supplements
c. Lack of awareness among patients
d. Other



In the opinion of 48% of doctors, the main barriers to optimal iron supplementation in pregnant females with IDA is gastrointestinal side effects.

10) How often do you educate pregnant females with IDA about the importance of consistent and timely iron supplementation?

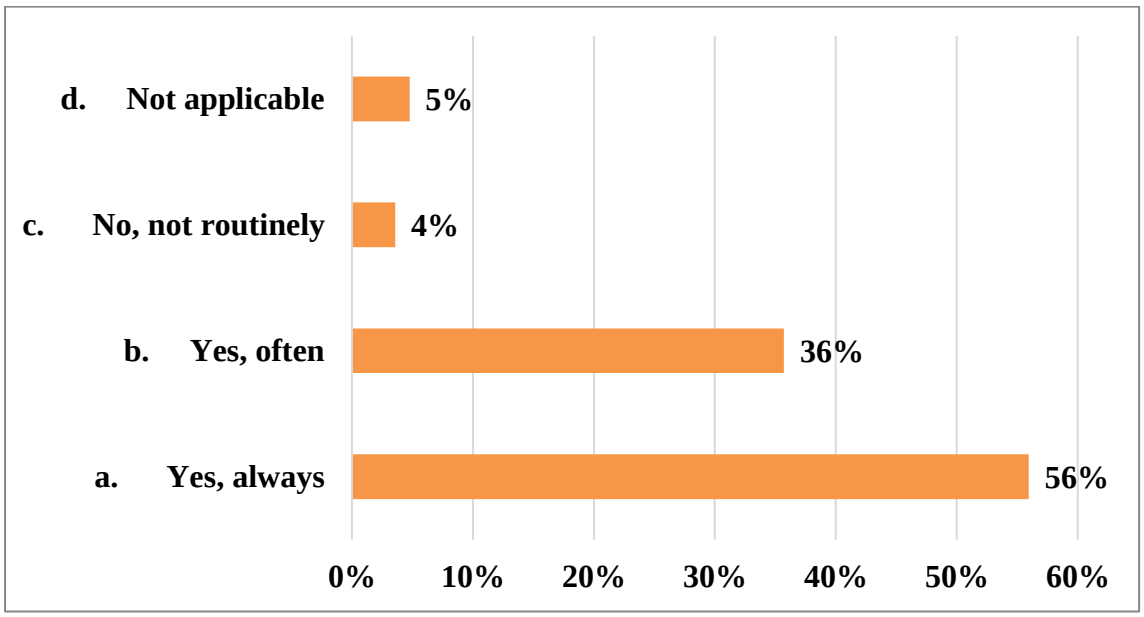
a. Always
b. Often
c. Occasionally
d. Rarely or never



Majority of doctors, 86%, always educate pregnant females with IDA about the importance of consistent and timely iron supplementation.

11) Do you routinely recommend dietary changes in conjunction with elemental iron supplementation for pregnant females with IDA?

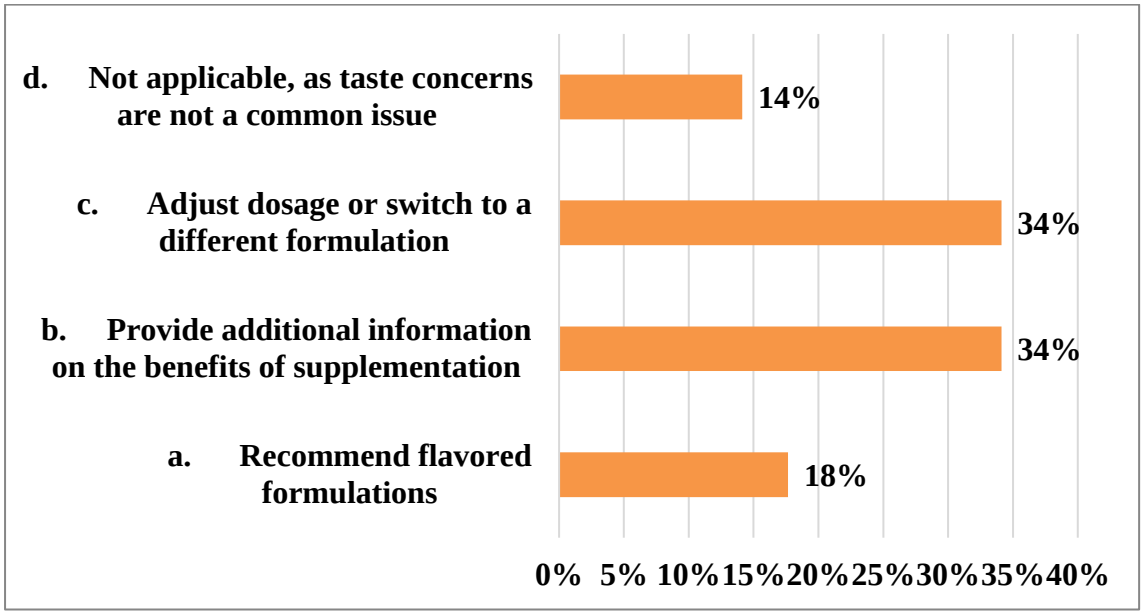
a. Yes, always
b. Yes, often
c. No, not routinely
d. Not applicable



Majority of doctors, 56%, always routinely recommend dietary changes in conjunction with elemental iron supplementation for pregnant females with IDA.

12) How do you handle situations where pregnant females express concerns about the potential taste or aftertaste of elemental iron supplements?

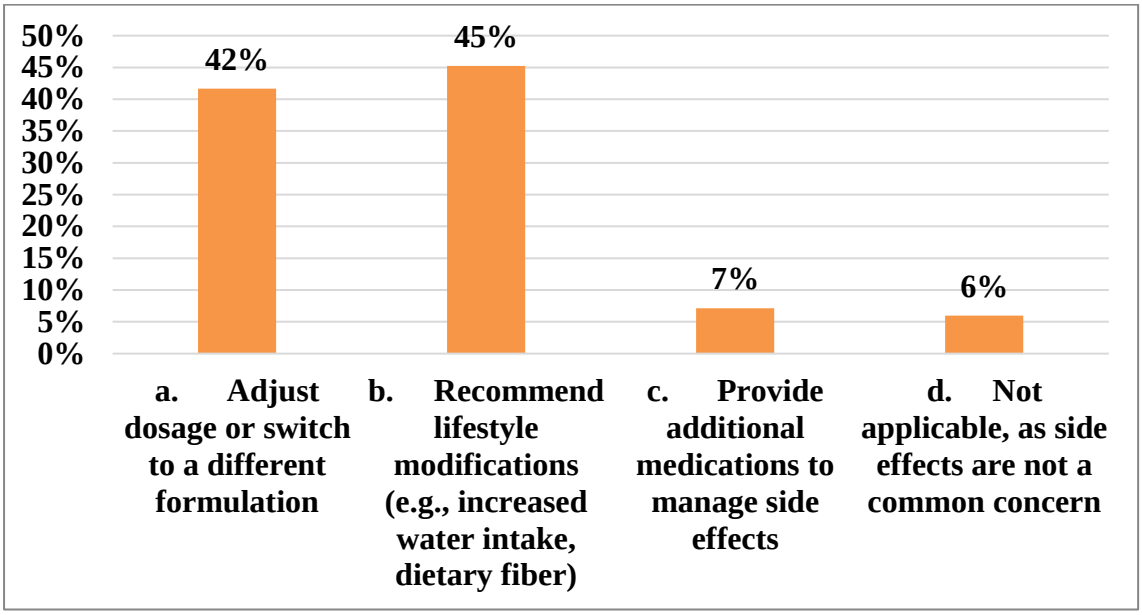
a. Recommend flavored formulations
b. Provide additional information on the benefits of supplementation
c. Adjust dosage or switch to a different formulation
d. Not applicable, as taste concerns are not a common issue



According to 34% of doctors, where pregnant females express concerns about the potential taste or aftertaste of elemental iron supplements, they handle situations by adjusting dosage or switching to a different formulation, whereas another 34% of doctors handle by providing additional information on the benefits of supplementation.

13) How do you address concerns about potential side effects, such as constipation, associated with elemental iron supplementation in pregnant females?

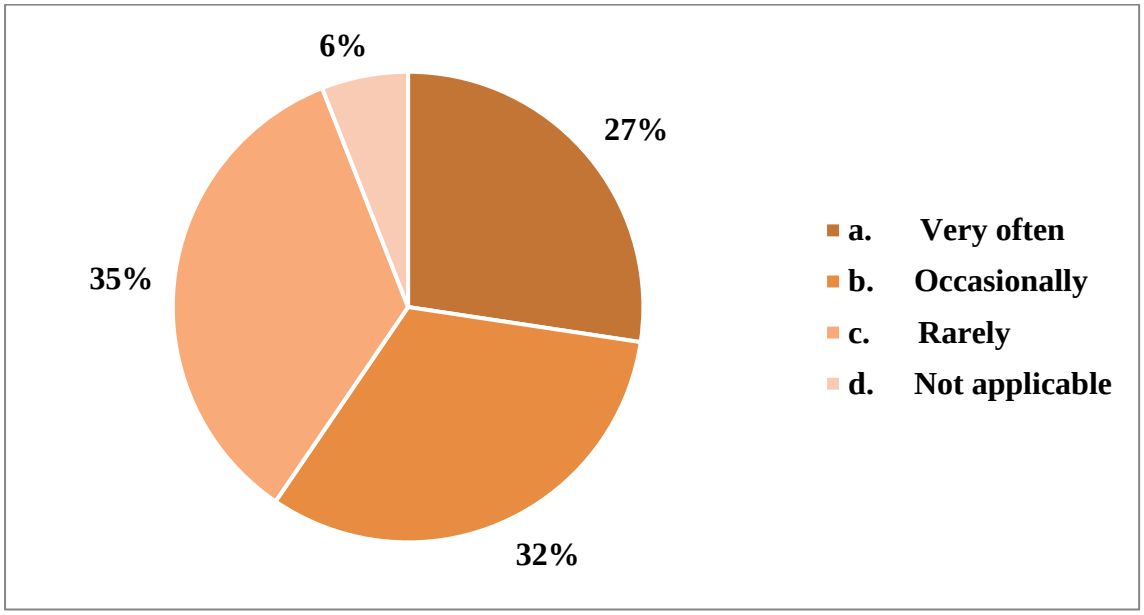
a. Adjust dosage or switch to a different formulation
b. Recommend lifestyle modifications (e.g., increased water intake, dietary fiber)
c. Provide additional medications to manage side effects
d. Not applicable, as side effects are not a common concern



45% of doctors address concerns about potential side effects, such as constipation, associated with elemental iron supplementation in pregnant females by recommending lifestyle modifications (e.g., increased water intake, dietary fiber).

14) In your clinical practice, how often do you encounter pregnant females with IDA who have received iron supplementation before their pregnancy?

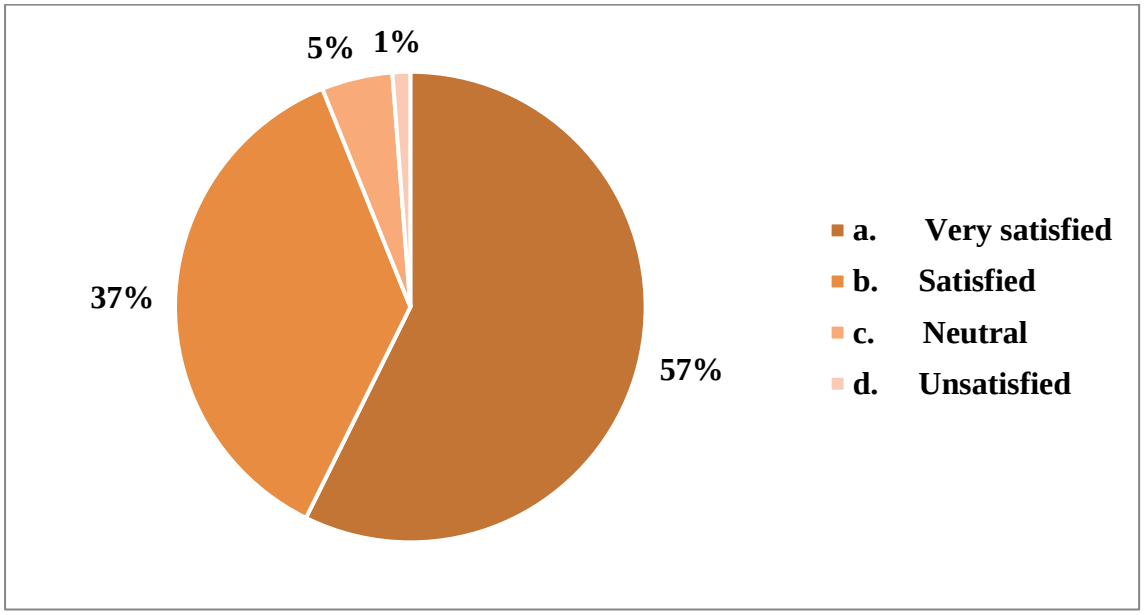
a. Very often
b. Occasionally
c. Rarely
d. Not applicable



In the clinical practices of 35% of doctors, they rarely encounter pregnant females with IDA who have received iron supplementation before their pregnancy.

15) Overall, how satisfied are you with the clinical outcomes of elemental iron supplementation in pregnant females with IDA in your practice?

a. Very satisfied
b. Satisfied
c. Neutral
d. Unsatisfied



Majority of doctors, 57%, are very satisfied with the clinical outcomes of elemental iron supplementation in pregnant females with IDA in their practice.

Summary

- According to 49% of doctors, they frequently encounter pregnant females with iron deficiency anemia (IDA) in their clinical practice.
- Majority of doctors, 67%, prefer elemental iron supplementation when managing pregnant females with IDA.
- In the experience of 28% of doctors, they very often observe adverse reproductive outcomes in pregnant females with IDA.
- 32% doctors have commonly observed adverse reproductive outcomes of maternal complications observed in pregnant females with IDA.
- 52% of doctors are very confident in the efficacy of elemental iron supplementation in reducing adverse reproductive outcomes in pregnant females with IDA.
- According to 49% of doctors, when initiating iron supplementation in pregnant females with IDA severity of anemia influence their choice of dosage and duration.
- 53% of doctors monitor the response to elemental iron supplementation in pregnant females with IDA by conducting regular blood tests (hemoglobin levels).
- 36% of doctors have frequently encountered challenges or concerns related to patient compliance with elemental iron supplementation during pregnancy.
- In the opinion of 48% of doctors, the main barriers to optimal iron supplementation in pregnant females with IDA is gastrointestinal side effects.
- Majority of doctors, 86%, always educate pregnant females with IDA about the importance of consistent and timely iron supplementation.
- Majority of doctors, 56%, always routinely recommend dietary changes in conjunction with elemental iron supplementation for pregnant females with IDA.
- According to 34% of doctors, where pregnant females express concerns about the potential taste or aftertaste of elemental iron supplements, they handle situations by adjusting dosage or switching to a different formulation, whereas another 34% of doctors handle by providing additional information on the benefits of supplementation.

- 45% of doctors address concerns about potential side effects, such as constipation, associated with elemental iron supplementation in pregnant females by recommending lifestyle modifications (e.g., increased water intake, dietary fiber).
- In the clinical practices of 35% of doctors, they rarely encounter pregnant females with IDA who have received iron supplementation before their pregnancy.
- Majority of doctors, 57%, are very satisfied with the clinical outcomes of elemental iron supplementation in pregnant females with IDA in their practice.

Consultant Opinion

Market Opportunities: Recognize the high prevalence of pregnant females with IDA as an opportunity for pharmaceutical companies to develop and market more effective and tolerable iron supplementation products tailored specifically for this population.

Value for Healthcare Professionals: Provide healthcare professionals with updated guidelines and educational materials on the management of IDA in pregnant females, emphasizing the importance of early detection, appropriate supplementation, and monitoring to reduce adverse reproductive outcomes.

Adverse Effect Management: Invest in research and development efforts to create iron supplementation formulations with improved tolerability profiles, minimizing gastrointestinal side effects that often lead to poor patient compliance.

Withdrawal Management: Develop strategies and resources to address challenges related to patient compliance with iron supplementation during pregnancy, such as providing alternative formulations, dosage adjustments, and ongoing education and support.

Market Positioning: Position iron supplementation products as essential components of prenatal care, highlighting their role in preventing adverse reproductive outcomes and ensuring the health and well-being of both mothers and babies.

Personalized Treatment Decisions: Encourage healthcare providers to individualize iron supplementation regimens based on the severity of anemia, patient preferences, and potential side effects, optimizing treatment adherence and efficacy.

Improving Patient Outcomes: Promote patient education and counseling about the importance of consistent and timely iron supplementation during pregnancy, emphasizing the benefits of treatment for both maternal and fetal health outcomes.

Innovation and Research: Support research initiatives aimed at developing novel iron supplementation formulations that are better tolerated, more bioavailable, and easier to administer, ultimately improving treatment adherence and clinical outcomes in pregnant females with IDA.

By addressing these aspects, both healthcare professionals and pharmaceutical companies can collaborate to optimize the management of IDA in pregnant females, leading to improved patient care and outcomes during pregnancy and beyond.

NOTES

NOTES

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Developed by:

Weston Medical Education Foundation of India

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