**Comparison of different doses of daily iron supplementation for anemia prophylaxis in pregnancy: A systematic review**

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**ABSTRACT**

Different doses of iron are used for oral supplementation during pregnancy throughout the world. This objective of this review is to describe the effectiveness and side effect profile of different doses of oral iron supplementation for prophylaxis of anemia among pregnant women. Published literature was searched using keywords “iron,” “pregnancy,” and “supplementation” and related terms. Gray literature was searched in medical libraries including National Medical Library, Dr. B. B. Dikshit library, and library of ICMR. Intervention studies comparing different doses of oral iron given as prophylaxis for anemia during pregnancy, published till December 2017, were retrieved. Studies done only among anemic patients, and studies comparing oral iron with placebo were excluded. In total, 1588 studies were obtained and 11 of them met the objectives. In global studies, prophylactic dose of 30 mg and above is shown to maintain normal hemoglobin. Among the studies from India, prophylactic dose of 120 mg showed consistent results and 60 mg showed inconsistent results in increasing both hemoglobin and ferritin levels. No significant difference in side effects was reported up to 80 mg iron in global studies and the side effects were comparable with 60 to 240 mg doses in Indian studies. It was evident from the review that a state of clinical equipoise exists for the ideal dose of iron supplementation for the prevention of anemia in pregnancy in terms of efficacy and side effect profile. Robust clinical trial as well as technical consultation is required, especially in Indian setting to explore this question further.

**Keywords:** Anemia, iron and folic acid, pregnancy, prophylaxis, supplementation

**Introduction**

Anemia is considered as one of the major public health challenges in almost every part of the world especially the developing countries. The global prevalence of anemia in pregnancy is estimated to be 38% which translates as 32 million pregnancies⁴. India is no exception with latest National Family Health Survey-4 showing almost 50% of pregnant women to be anemic.⁵ Studies have documented a consistent link between anemia in pregnancy with adverse outcomes like low birth weight, preterm delivery, and increasing maternal mortality and morbidity.⁶⁻⁸ To tackle such a widespread problem, many strategies were devised, out of which iron folic acid tablets supplementation is considered one of the best strategies in Indian setting. Starting from the national anemia control program of 1971, it was recommended that all pregnant women be given iron supplementation with specific doses. The aim was to prevent anemia and improve maternal and neonatal outcome. In India, iron supplementation is started from 12 weeks of pregnancy and continued up to delivery. The dose of iron used in India is 200 mg daily from 40 weeks of pregnancy and 120 mg daily from 28 weeks of pregnancy. However, the efficacy and side effect profile of these doses are not well described. The present study aims to provide a systematic review of the literature on the available data from different doses of iron supplementation for prophylaxis of anemia during pregnancy.

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the latest guidelines recommending a 60 mg of elemental iron for the same.\[9\] Even though over 3 decades have passed since the idea of prophylactic iron supplementation was conceived and implemented, the prevalence of anemia among pregnant women in India has remained almost stagnant. This calls for a better understanding of the complexities involved and sometimes revisiting the established evidence.

Newer evidences are coming up which show harmful effect of excess iron in body and debate continues over the adverse outcomes when given in malaria-endemic regions. A large systematic review taken up by WHO in 2009 has highlighted the lack of evidence showing maternal and child benefit with iron supplementation.\[7\] On a further note, the review also cautions about the side effects and hemoconcentration with iron supplementation and calls for the review of the dose of iron prescribed which is generally 60 mg and above of elemental iron. An update of the review has maintained the stand of low clarity on evidence for maternal and child benefit.\[8\] Adding to the problem is the lack of consensus among different guidelines regarding the iron dose needed for prophylaxis. WHO recommends a dose of 30 mg to 60 mg elemental iron for prophylaxis among pregnant women.\[8\] India has followed a dose of 100 mg elemental for anemia prophylaxis in pregnancy which was recently revised to 60 mg elemental iron.\[9\] The rationale and evidence for recommendations in Indian setting should be reviewed considering newer evidence.

Thus, it is ideal and prudent that we objectively review the available literature for understanding and identifying the best-recommended dose range for iron supplementation which minimize the harm due to excess iron but preserving the prophylactic action of iron supplements especially in Indian setting. This review is an attempt for the same with special focus on studies comparing different doses of iron for prophylaxis. Efficacy and side effect profile of different doses of iron are studied.

**Materials and Methods**

A systematic search was conducted to identify primary research articles which compare different doses of iron used in prophylaxis of anemia in pregnancy. The inclusion criteria were intervention studies as well as observational studies which compare different doses of iron given as daily supplement to pregnant women with singleton pregnancy. Studies were excluded if they recruited only anemic patients and if the comparison group has placebo. The primary outcome must be change in hemoglobin or ferritin values. Compliance and side effects if reported were also compared.

The search was carried out primarily using PubMed. Other search engines like Google scholar, IndMed, WHO website, and ResearchGate which provide access to full-text research articles were searched. Citations of articles were also reviewed for finding the articles. To identify gray literature, manual search was conducted in libraries which include National Medical Library, Dr. B. B. Dikshit library, and ICMR library situated in New Delhi. In PubMed, Medical Sub Headings (MeSH) for iron and anemia were identified and used. Keywords included “iron” “anaemia”, “anemia” “pregnancy” “supplement.” Truncation was used for terms like “pregnancy” and “supplement” to widen the search and include all relevant keywords. The Boolean function “OR” was used to find articles which use different spellings for anemia. The only filter applied was to include human studies. No limitation to the date of publishing was applied and articles up to December 2017 were included. All the articles were reviewed by two independent authors.

Initially all the articles in search results were screened for inclusion into the study based on title and abstract. Full-text articles of these shortlisted articles were obtained described as Indian and foreign studies for better understanding in local context. Excluded articles were further reviewed for retrieving information regarding side effects and compliance with iron supplementations.

**Results**

In total, 1588 records were identified of which 57 articles described the effect of different doses of elemental iron (18 mg to 240 mg) in different settings and conditions. [Figure 1]. Of these, 18 articles had control group to compare different doses of iron as supplementation. Finally, 11 articles met the inclusion criterion, and were tabulated [Tables 1 and 2] to describe the details. Out of 11 studies, 7 were done outside India. Of the seven, five were randomized controlled trials (RCT), one quasi RCT, and one longitudinal study. All four Indian studies were RCTs and all were included in the analysis, irrespective the inclusion criteria, due to paucity of articles. All studies had either hemoglobin and/or ferritin as outcomes measures. Ferrous fumarate or ferrous sulfate salts are used in studies and most of the iron supplementation were supervised.

Chanarin and Rothman\[10\], in 1971, conducted a study in an antenatal clinic, London and concluded that 30 mg was a good enough dose for anemia prophylaxis. But, the study was a quasi-RCT with a high risk of bias. In 1972, Brown and Dawson conducted an RCT\[11\] which recommend 50 mg elemental iron for prophylaxis of anemia. There were no reporting of side effects or compliance and iron intake was supervised in both the studies. The third study included was done by Thane-Toe and Thein-Than in Burma.\[12\] It stated that both 60 mg and 120 mg elemental iron were almost similar as far as maintaining hemoglobin and final ferritin values. But, the control group taken for the study included males and cannot be considered as an ideal control group.

Among nonanemic pregnant women, Thomsen et al. reported higher doses ranging from 50 mg to 100 mg elemental iron would be a better choice for prophylaxis as 18 mg iron was inadequate.\[13\] Lee et al. conducted a study in 2015 with\[14\] objective to find the
best time and dose for iron supplementation. The study had a relatively low risk of bias and demonstrated the ability of low doses of iron to maintain hemoglobin concentration in pregnancy especially when started early.

Milman et al.\textsuperscript{[15]} reported both the dose and side effect profile along with compliance to iron supplementation. A dose of 40 mg was identified as the ideal dose for prophylaxis. No significant difference was found in side effects and compliance between the doses. The final study included was a longitudinal study which divided the participants into groups based on their iron consumption.\textsuperscript{[16]} It was found that 60 mg iron was unable to raise the serum ferritin levels and 120 mg seemed to be the ideal compromise. This conclusion was arrived by comparing the side effect profile, which increased with increasing dose.

A notable study from India, the ICMR task force study, (1987 to 1989) formed the basis for revision of supplement dose from 60 mg to 100 mg.\textsuperscript{[20]} It was multicentric study conducted at 6 centers with primary objective to compare the effect of 60 mg, 120 mg, and 180 mg iron along with side effects. The conclusion drawn was that 120 mg is an ideal dose for prophylaxis. The article also mentions that 60 mg has lesser side effects and adequate efficacy to prevent anemia and can be considered for prophylactic dose. However, there were high number of dropouts and noncompliance in the study. Madan et al.\textsuperscript{[21]} conducted an RCT comparing 60 mg, 120 mg, and 240 mg of iron and concluded both 60 mg and 120 mg were adequate for improving hemoglobin. However, a significant rise in ferritin was observed with 120 mg iron.

**Indian studies on iron dose**

The earliest Indian study to investigate the effect of different doses of iron was done by Sood et al.\textsuperscript{[18]} A minimum of 120 mg was found to be the best dose. But the major drawback included loss to follow-ups and the comparison group had Vitamin B12 supplemented along with iron. Another study done in 1989 compared different doses of iron (60 mg, 120 mg, and 240 mg).\textsuperscript{[19]} It was found that 60 mg iron was unable to raise the serum ferritin levels and 120 mg seemed to be the ideal compromise. This conclusion was arrived by comparing the side effect profile, which increased with increasing dose.
Table 1: Global studies comparing different iron doses

| Author (year)             | Study setting and Participants                                                                 | Study methodology                        | Results and Comments                                                                 |
|---------------------------|------------------------------------------------------------------------------------------------|------------------------------------------|---------------------------------------------------------------------------------------|
| Chanarin and Rothman[10]  | 251 women attending antenatal clinic at St Mary's Hospital, London, United Kingdom before 20th week of gestation | Group 1: 30 mg of elemental iron daily    | Hb value (g/dL) on 20 weeks and 37 weeks                                              |
|                           |                                                                                               | Group 2: 60 mg of elemental iron daily    | 30 mg: 11.8±0.10 to 12.4±0.14                                                        |
|                           |                                                                                               | Group 3: 120 mg of elemental iron daily   | 60 mg: 11.7±0.12 to 12.1±0.16                                                         |
|                           |                                                                                               | Group 4: Placebo                         | 120 mg: 11.6±0.12 to 12.2±0.26                                                        |
|                           |                                                                                               | Group 5: IV iron                         | Remarks:                                                                              |
|                           |                                                                                               | Iron formulation: Ferrous fumarate        | Compliance not reported                                                                |
| Brown and Dawson[11]      | 181 pregnant women attending an antenatal clinic before 32 weeks of gestation                  | RCT with 3 groups                        | Supplementation started at 20 weeks, 30 mg was found to be adequate for maintaining normal Hb |
|                           |                                                                                               | Group A: 50 mg elemental iron with reminder | Group A: 12.7 to 13.0                                                                 |
|                           |                                                                                               | Group B: 50 mg elemental iron            | Group B: 12.8 to 12.7                                                                   |
|                           |                                                                                               | Group C: 100 mg elemental iron           | Group C: 12.6 to 13                                                                    |
| Thane-Toe and Thein-Than[12]| 135 healthy pregnant women attending antenatal clinic in Burma Gestation of 22-28 weeks      | RCT                                       | - Compliance and side effect not reported                                              |
|                           |                                                                                               | Three intervention group who were given doses of 60 mg, 120 mg, and 240 mg daily | - Dose of 50 mg is adequate for prophylaxis                                             |
| Thomsen et al[13]         | 52 healthy nonanemic nulliparous women with normal singleton pregnancy and serum ferritin levels above 15 mg/L at 16th week in Helve, Denmark | Group 1: 18 mg elemental iron with 0.3 mg folic acid | Before and after supplementation                                                       |
|                           |                                                                                               | Group 2: 100 mg elemental iron with 0.3 mg folic acid | Hb                                                                                     |
| Lee et al[14]             | 154 apparently healthy pregnant women attending antenatal clinic in Gwangju, South Korea. Pregnant women in first trimester were recruited | RCT                                       | 60 mg: 10.9±0.20 to 11.2±0.27                                                         |
|                           |                                                                                               | Group 1: 30 mg elemental iron+0.17 mg folic acid from first trimester to delivery | 120 mg: 10.9±0.14 to 11.3±0.15                                                        |
|                           |                                                                                               | Group 2: 60 mg elemental iron+0.35 mg folic acid from first trimester to delivery | 240 mg (+FA): 10.5±0.34 to 11.1±0.12                                                    |
|                           |                                                                                               | Group 3: 30 mg elemental iron+0.17 mg folic acid from 20 weeks of gestation to delivery | Serum Ferritin (Difference) | 60 mg: +7.61                                                                            |
|                           |                                                                                               | Group 4: 60 mg elemental iron+0.35 mg folic acid from 20 weeks of gestation to delivery | 120 mg: +9.24                                                                           |
|                           |                                                                                               | Group 5: Control group (No supplements)  | 240 mg (+FA): +21.02                                                                   |
|                           |                                                                                               | Iron formulation: Ferrous sulfate        | Remarks:                                                                              |
|                           |                                                                                               |                                            | - Iron supplementation supervised                                                      |
|                           |                                                                                               |                                            | Hemoglobin maintained in all groups                                                     |
|                           |                                                                                               |                                            | Final serum ferritin same with 60 mg and 120 mg iron.                                  |
| Milman et al[15]          | 427 healthy Danish pregnant women Copenhagen County, Denmark                                   | RCT                                       | Hb (1st trimester and delivery)                                                        |
|                           |                                                                                               |                                            | 30 mg group: 13.2±1.2 to 11.1±1.5                                                     |
|                           |                                                                                               |                                            | 60 mg group: 13.5±1.0 to 12.2±1.3                                                     |
|                           |                                                                                               |                                            | 80 mg group: 13.3±1.1 to 12.7±1.3                                                     |
|                           |                                                                                               |                                            | Hematocrit (%) (1st trimester and delivery)                                           |
|                           |                                                                                               |                                            | 30 mg group: 39.9±3.3 to 33.9±3.9                                                     |
|                           |                                                                                               |                                            | 60 mg group: 42.1±5.1 to 36.7±4.2                                                     |
|                           |                                                                                               |                                            | sTfR (1st trimester and delivery)                                                     |
|                           |                                                                                               |                                            | 30 mg group: 145.7±75.1 to 347.8±140.6                                                |
|                           |                                                                                               |                                            | 60 mg group: 148.3±90.2 to 274.5±153.7                                               |

Contd...
Discussion

This review is an attempt to understand the dose of elemental iron which is best for prophylaxis of anemia in pregnancy in India. To put this in context, we need to take a look at the evolution of guidelines in India. In the beginning of National Nutritional Anemia Prophylaxis Program in 1970, a dose of 60 mg was used for daily supplementation. An evaluation of NNAPP by ICMR task force later found the program to be ineffective and gave its recommendations for major changes in the program. One of the factors recommended was to revise the iron dose. Subsequently, field-based supplementation trial with different iron doses was conducted by ICMR task force. In 1991, NNAPP was changed to National Anemia Control Program and a revised dose of 100 mg elemental iron was recommended as supplementation dose. However, the study used iron tablets with 120 mg of elemental iron and no study was conducted to assess the effect of 100 mg of iron compared to other dosage formulations in India. In the following years, the program was modified and integrated with other national programs. In 2018, Intensified-National Iron Plus Initiative (I-NIPI) guidelines were released which changed the dose of elemental iron back to 60 mg, in line with current WHO recommendation. The current recommendation for anemia prophylaxis in pregnant women in India is 60 mg elemental iron with 0.5 mg of folic acid given as single tablet daily from second trimester and continued for 180 days or more.

It has been more than two decades since the national anemia control program came into effect; however, the prevalence of anemia has almost remained unchanged. Various reasons can be identified for the same which includes a low program coverage, inadequate supply of iron tablets, low bio-availability of iron in Indian diets, presence of factors decreasing iron absorption, high prevalence of infections like hookworm, malaria and low compliance to iron tablets. Compliance is defined as the extent to which a patient's behavior coincides with medical advice. Low compliance with iron folic acid tablets among pregnant women has been identified as one of the reasons for the failure of supplementation programs. Major reasons for women not consuming iron tablets are poor access to supplies (i.e. low utilization of antenatal care services

| Author (year) | Study setting and Participants | Study methodology | Results and Comments |
|---------------|-------------------------------|-------------------|----------------------|
| Ribot et al.[16] 2012 | 358 pregnant women were followed up from their first prenatal care appointment (gestational week 10) until delivery at the Obstetrics and Gynecology Unit of the Hospital Universitari Sant Joan de Reus (Catalonia, Spain) | Longitudinal study: Post completion of study divided into 4 groups Group 1: Nonsupplemented Group 2: Low iron supplemented (<60 mg/day) Group 3: Moderate iron supplemented (between 60 and 100 mg/day) Group 4: High iron supplemented (>100 mg/day). | 20 mg: 1.51±0.296 to 1.19±0.229 40 mg: 1.50±0.299 to 1.35±0.243 60 mg: 1.51±0.273 to 1.36±0.232 80 mg: 1.51±0.316 to 1.43±0.242 Remarks: There were no significant differences in iron status (ferritin, sTfR, and Hb) among group 40 mg, 60 mg, and 80 mg 40 mg is adequate for prophylaxis No significant difference in compliance or gastrointestinal side effects among groups |
| Hb | Group 1: Week 10: 12.5 (12.3, 12.7) Week 34: 11.7 (10.8, 11.4) Group 2: Week 10: 12.5 (12.4, 12.6) Week 34: 11.4 (11.2, 11.6) Group 3: Week 10: 12.3 (12.2, 12.7) Week 34: 11.7 (11.4, 12.0) Group 4: Week 10: 12.4 (12.2, 12.6) Week 34: 11.4 (11.3, 11.4) Ferritin | Group 1: Week 10: 28.6 (27.8, 29.4); Week 34: 7.7 (7.1, 8.3) Group 2: Week 10: 29.2 (28.2, 30.1) Week 34: 9.3 (8.6, 10.0) Group 3: Week 10: 26.4 (25.6, 27.2) Week 34: 13.2 (12.6, 13.8) Group 4: Week 10: 26.7 (25.9, 27.5) Week 34: 14.9 (14.2, 15.6) Remarks: -Higher the iron dose, lower the Iron deficiency anemia (P<0.001) and high iron supplementation group has 27.6% of risk of hemoconcentration at partum. -Supplementation with iron at daily doses of between 60 mg and 100 mg appears to be the most beneficial for the health of mother and child. |
or inadequate supplies of facilities), the pharmacological characteristics of the of tablets (i.e. unappealing taste, smell, color), side effects (e.g. gastrointestinal problems), fear (e.g. increased birth weight of the babies, difficult delivery, harm to fetus), recovery (i.e. discontinuation of supplement as a result of improvement in symptom), and behavior (i.e. forgetting or not wanting to take tablets).

Addressing each of these issues is crucial for control of anemia in India, especially at primary health care where the actual service delivery happens. According to NFHS 4, 85% of pregnant women registered for ANC services. However, only 30% have consumed at least 100 IFA tablets in the same survey. Hence, identifying optimal IFA dose and solutions expected to overcome the expected side effects is essential to improve service delivery for pregnant women at primary health care level and also at higher levels of the health care system.
A study conducted in secondary care center in Ballabgarh, Haryana found that while 100% pregnant women reported receiving IFA supplements, only 45% women completed more than 90 days of iron-folic acid tablets supplementation. A study by Shatrugna et al. in 2013 among pregnant women at 16–30 weeks at an antenatal clinic, Haryana reported that 14.4% were consumed IFA for less than 90 days and a side effect is a major reason for noncompliance. Similarly, a cross-sectional study was done by Godara et al. in 2013 among pregnant women at 16–30 weeks at an antenatal clinic, Haryana reported that 14.4% were consumed IFA for less than 90 days and a side effect is a major reason for noncompliance.

The general trend in recommendation of WHO over the decades is more in favor of decreasing the iron dose for minimizing the side effects and the evidence for the same are mainly from developing countries. To quote the latest guideline from WHO “In settings where anemia in pregnant women is a severe public health problem (i.e. where at least 40% of pregnant women have a blood hemoglobin [Hb] concentration <11.0 g/dL), a daily dose of 60 mg of elemental iron is preferred. If a woman is diagnosed with anemia during pregnancy, her daily elemental iron should be increased to 120 mg until her Hb concentration rises to normal (Hb 11.0 g/dL or higher). Thereafter, she can resume the standard daily antenatal iron dose to prevent recurrence of anemia.” Also, when we look at guidelines of developed countries, a much lower dose like 30 mg is recommended and in United Kingdom prophylaxis is not recommended at all.

The rationale for providing to a specific dose of iron should consider iron and noniron deficiency related anemia in the country/region, availability of anemia testing, type of technology and equipment used, and observer errors in correct estimation of anemia. This is especially important when there are numerous studies both from developed and developing countries shedding light on adverse effects of excess iron dose. Studies have noted adverse outcome in pregnancy and increased oxidative stress related to excess iron in body. When iron is increased in body, the regulator molecule hepcidin can increase which in turn decrease iron absorption. Adding to this is the fact that excess iron in alimentary canal may decrease the absorption of other divalent metal thus resulting in its deficiency. The negative effect of excess iron on alimentary tract and gut bacteria is also found especially in children which may have a similar consequence on pregnant women.

Excess iron can lead to hemoconcentration which in itself can cause adverse pregnancy outcomes like preterm birth, gestational diabetes mellitus, preeclampsia, and complication associated in malaria in endemic regions. Mwangi et al. reported in a review that 60 mg daily antenatal iron supplementation did not increase the risk of Plasmodium infection in low-income countries. However, the authors did not evaluate the effect of iron more than 60 mg in the study. Also, there are other evidences which show a link between iron and increased risk of malaria. Hence, the functionality of existing malaria control program and prophylaxis with iron in malaria-endemic regions

is still a matter of serious debate and beyond the scope of this review. However, the evidence of iron overload among pregnant women in India is limited. Hence, in India, iron supplementation should be followed along with other infection control measures such as the use of insecticide-treated bed nets for the prevention of malaria and deworming.

In a large systematic review done on behalf of WHO, it was clearly mentioned that low doses such as 18 mg and 20 mg iron are inadequate, and two studies report that 30 mg has the potential to prevent fall in hemoglobin. However, doses 40 mg and above consistently have shown to maintain the hemoglobin levels in all the studies from other parts of the world. However, as far Indian studies are concerned, a dose of 120 mg was uniformly recommended as an optimal dose for prophylaxis to maintain both hemoglobin and body iron stores as measured by ferritin. In most global studies taken for this review, data on side effects and harm due to different doses are not clearly reported. The general trend shows a lower dose has lesser side effects.

There are a few limitations for this review. Only a small number of articles were available for comparison and those available had significant bias and less data for comparison. No published literature after 1999 comparing different doses of iron formulations was available, leading to limited knowledge on various iron doses supplementation during pregnancy. All four studies from India were conducted among a small number of pregnant women except ICMR task force studies. The method for estimation of hemoglobin might also have a significant role in the estimation of the outcome.

It is evident from the studies that lower dose of elemental iron, such as 60 mg may be adequate for maintaining the hemoglobin level. However, there was inconsistency in the improvement of hemoglobin among the studies in the lower doses. Hence, more studies with robust methodological rigor and follow-up are essential to provide strong evidence of the required dose of iron among pregnant women in Indian settings. Factors which may have an influence on the hemoglobin levels, etiologies of anemia, and other infectious conditions pertaining to India should be considered while planning such studies.

Conclusion

The review concludes that there are ambiguity and lack of consensus regarding the ideal dose of iron for prophylaxis. There is a paucity of evidence and a state of clinical equipoise exists when it comes to the ideal dose of iron which is adequate for anaemia prophylaxis and causing less harm. Thus, the need of the hour is to generate evidence in the form of a large clinical trial in community and technical consultation, especially in Indian settings to explore this question further.

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