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SYSTEMATIC REVIEWS/META-ANALYSIS

Parenteral Versus Oral Iron for Treatment of Iron Deficiency Anaemia During Pregnancy and post-partum: A Systematic Review

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Abstract

Introduction The burden of iron deficiency anaemia during pregnancy and post-partum continues to remain high especially in India. Challenges to treatment include gastrointestinal side effects and non compliance to oral iron therapy. Newer parenteral formulations need to be explored as alternatives.

Methods Meta-analysis of randomized controlled trials published between years 2011 and 2018 comparing anaemic pregnant and post-partum women treated with intravenous iron sucrose versus oral iron was performed. The primary outcomes were mean maternal haemoglobin,

serum ferritin and haematocrit at the end of 1st, 2nd, 4th and 6th weeks and comparison of adverse effects.
Results Eighteen studies including 1633 antenatal women were randomly assigned to intravenous iron sucrose (n = 821) or oral iron [ferrous sulphate, ferrous ascorbate or fumarate] group (n = 812) in ten trials . Another eight studies compared iron sucrose infusion with oral iron in 713 post-partum women who were randomly assigned to intravenous iron sucrose group (n = 351) or oral iron group (n = 362). Cumulative analysis of all the time points indicates that the estimated mean values of Hb in the intravenous iron sucrose and oral iron groups were 10.11 g/dl and 9.33 g/dl, respectively, in antenatal group, while it was 10.57 g/dl and 9.74 g/dl in post-partum. The estimated mean ferritin level from first week to six weeks was 63.1 µg/l and 28.6 µg/l, respectively, in intravenous and oral iron groups. Cumulative estimate of haematocrit in the intravenous sucrose and oral iron over 6 weeks showed that the mean values in the respective groups were 30.5% and 29.5% in antenatal and 33.8% and 31.6%, respectively, in post-partum groups. Sensitivity analysis confirmed the reliability and consistency of the results. Oral iron was associated with significant gastrointestinal side effects. There was no significant difference in birthweight between the groups.
Conclusion This meta-analysis demonstrates that intravenous iron sucrose is more effective than oral iron therapy for pregnant and post-partum women with iron deficiency anaemia. It is an effective and safe alternative to address the problem of iron deficiency especially in those who require rapid replacement of iron stores though medical personnel for intravenous administration of drug is required.
Trial registration CRD42015024343

Keywords Iron deficiency anaemia · Intravenous iron · Oral iron · Pregnancy · post-partum

Abbreviations

IDA	Iron deficiency anaemia
WHO	World Health Organization
NFHS-4	National Family Health Survey-4
OR	Odds ratio
IVS	Intravenous iron sucrose
OIG	Oral iron group
PCV	Packed cell volume
MD	Mean difference
CI	Confidence interval
Hb	Haemoglobin
ANC	Antenatal clinic
QOL	Quality of life
LMIC	Low–middle-income countries

Background

Iron deficiency anaemia (IDA) is defined by World Health Organization (WHO) as haemoglobin less than 11 g/dL [1]. Causes of IDA include poor nutrition, malaria, infestations and chronic infections [2, 3]. More than two-thirds of pregnant women in developing countries suffer from anaemia of which 95% are due to iron deficiency [4]. About 84% women are iron deficient in the first post-partum week [5]. According to National Family Health Survey-4 (NFHS-4, 2015–2016), 45.7% (urban) and 52.1% (rural) antenatal women in India are anaemic [6]. Globally, IDA is considered directly (20%) and indirectly (50%) responsible for maternal death [7] and feto-maternal morbidity [8]. Oral iron results in haemoglobin rise of 0.3–1.0 g per week [9, 10]. Its limitation includes poor compliance (22–64%) due to gastrointestinal side effects [8, 10, 11].

Iron requirement during pregnancy is about 4–6 mg/day. At least 40–60 mg of dietary iron is required to meet this demand since iron absorption is less than 10% [12]. Government of India recommends universal oral iron–folic acid supplementation for antenatal and post-partum women [13].

Of the two parenteral formulations which hold promise due to safety and ease of administration (ferric carboxymaltose and intravenous iron sucrose (IVS)), only IVS is approved for use in both antenatal and post-partum periods in India.

IVS is a complex of polynuclear iron (III) hydroxide in sucrose. Following intravenous administration, it is dissociated by reticuloendothelial system into iron and sucrose. It is quickly cleared from serum with terminal half-life of approximately 5–6 h and, hence, is more rapidly available for erythropoiesis [14–17].

Our aim was to study the place of iron sucrose in the management of iron deficiency anaemia in pregnant and post-partum women and explore the possibility of its use on mass scale. Preliminary literature search revealed that studies addressing this issue were mainly published after 2011. This systematic review includes literature published in the period 2011 to 2018.

Objectives

The overall objective of this review is to confirm the safety and efficacy of intravenous iron sucrose compared to oral iron for treatment of IDA in antenatal and post-partum women.

1. To compare efficacy of oral and parenteral iron in treatment of iron deficiency anaemia during antenatal period for improvement in haematological indices, i.e.

Hb, ferritin and PCV at 1st, 2nd, 4th and 6th week post-treatment.
2. To compare efficacy of oral and parenteral iron in treatment of iron deficiency anaemia during post-partum period for improvement in haematological indices, i.e. Hb, ferritin and PCV at 1st, 2nd, 4th and 6th week post-treatment.
3. To compare the adverse effects of oral and parenteral iron.

Method

Design and Search Strategy

Comprehensive literature search was performed independently by two reviewers (VG and AGR), for English literature published in the period 1 August 2011 to 31 March 2018. Online electronic databases including Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, MEDLINE, MedIND were searched using defined search strategy (Annexure 1 of Electronic Supplementary Material). We identified newly published articles on PubMed using the 'related articles' feature. For unpublished and grey literature and ongoing trials, we searched the following databases:

Metaregister (http://www.isrctn.com/search?q=iron+deficiency+anemia), Physician Data Query (http://www.nci.nih.gov), http://www.clinicaltrials.gov, https://www.ctri.nic.in and National Medical Library (NML), Delhi, India. Electronic databases ZETOC (http://zetoc.mimas.ac.uk) and WorldCat Dissertations were searched for conference proceedings and abstracts. Two independent reviewers (AGR and VP) screened the titles and abstracts of retrieved articles for relevance, deleted duplicates, screened and marked studies as excluded or requiring further assessment. Full-text articles of shortlisted abstracts were obtained. Further, bibliographies of retrieved articles and previous reviews were manually scrutinized to identify additional eligible studies. Discrepancies regarding search results were resolved through discussion with third reviewer (AS). Authors of included studies were contacted when required.

Inclusion and Exclusion Criteria

Covidence platform was used by reviewers (AGR, AS) to decide on inclusion of studies for the review as per set criteria. Inclusion criteria included: (1) published and unpublished randomized controlled trials (RCTs) or quasi-randomized studies in the period from 1 August 2011 to 31 March 2018; (2) pregnant and post-partum women diagnosed with IDA; (3) treatment intervention comprised of intravenous iron sucrose versus oral iron supplement; and (4) trial outcome record available in any three points of follow-up periods: 1st, 2nd, 4th or 6th week.

Exclusion criteria were: (1) non-RCT studies and commentaries; (2) studies involving non-pregnant women; and (3) anaemia not due to iron deficiency.

Outcome Measures

The primary outcome measures were (1) effect of treatment for IDA in pregnant and post-partum women on mean haemoglobin (g/dl), haematocrit/packed cell volume (PCV) (%) and serum ferritin level (μg/l), (2) change in quality of life and (3) adverse events with treatment. The secondary outcomes were (1) requirement of blood component therapy and (2) neonatal outcome measured by foetal birthweight.

Data Extraction

Two reviewers AGR and VP independently extracted the data which were then cross-checked. Following information was extracted from each trial: first author, year of publication, study design, study population characteristics and relevant outcome data. The data entered into Covidence software and then transferred to Revman 5.3 for further analysis [18]. Disagreements were resolved through discussion with third investigator (AS).

Quality Assessment of Studies

We used Cochrane Risk of Bias for methodological quality assessment of included studies. Data were assessed for the following biases: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants), detection bias (blinding of outcome assessors), attrition bias (completeness of data including attrition and exclusions from analyses), reporting bias (selective outcome reporting) and other biases (any important concerns about other possible sources of bias). Publication bias was assessed by testing the intercept of Egger regression at all time points.

Statistical Analysis

The statistical analysis was performed by (VP, AGR) using latest version of Revman [18] from Cochrane. Heterogeneity across studies was tested by using the I^2 statistics, (quantitative measure of inconsistency across studies). I^2 statistics of greater than 50% was considered significant heterogeneity. Mantel–Haenszel Chi-square test and random effects model were used for further calculations in

significant heterogeneity. At each time point, mean differences (MD) between IVS and oral iron group (OIG) were evaluated for continuous variables, accompanied by 95% confidence intervals (CIs). Percentage improvement from baseline to post-treatment of the outcome measures was calculated to assess clinical significance. Sensitivity analysis was also carried out to assess the validity and consistency of findings. A two-tailed probability of P value < 0.05 was considered to be statistically significant.

Results

Study Selection

We identified 892 and 9 studies through electronic search and hand search, respectively (total 901). With 65 duplicates removed, 836 records were screened. Further 803 records were removed after review of titles and abstracts. Of the remaining 33 studies, 14 studies were excluded after full-text reading with justifications (PRISMA flow chart, Annexure 2). Data extraction was done from remaining 19 RCTs [19–37]. One study (Mumtaz et al. [37]) was excluded as it did not report minimum required data such as mean, standard deviation and number of observations in each group and the authors could not be contacted. Finally, 18 studies were included for analysis. Of these, one study [28] contributed data both to antenatal and post-partum periods. Hence, a total of 11 and eight studies in antenatal and post-partum, respectively, were included.

Overall, 1633 *antenatal* women were randomly assigned to IVS ($n = 821$) or oral iron [ferrous sulphate, ferrous ascorbate or fumarate] group ($n = 812$) in ten trials [19–28] and 713 *post-partum* women were randomized to IVS ($n = 351$) or OIG ($n = 362$) in eight studies [29–36]. Summary of characteristics of included studies is presented in Boxes 1 and 2 below. The intercept of Egger regression at all time points for identifying publication bias was not statistically significant implying that there was publication bias. Due to inadequate number of studies, publication bias was not assessed for ferritin and PCV in post-partum period.

Box 1 Characteristics of included studies (antenatal period)

Total of 710 participants in the IVS group were compared with 729 participants in the OIG for rise in hematological indices, adverse effects, requirement for blood transfusion and fetal outcomes. For further details authors may be directly contacted

Box 2 Characteristics of included studies (post-partum period)

Total of 377 participants in the IVS group were compared with 374 participants in the OIG for rise in hematological indices, adverse effects, requirement for blood transfusion. For further details authors may be directly contacted

Antenatal Period

1. Mean Maternal Haemoglobin (Hb) (Fig. 1)

Overall, baseline mean values of Hb for studies included in ANC period were 7.88 g/dl and 7.99 g/dl in IVS and OIGs, respectively, with no significant intergroup difference. Impact of treatment in the first week showed that mean difference (MD) was statistically significant in three studies [24, 31, 35] in favour of IVS though one study [23] did not show significant impact. Overall, the difference of MD was not statistically significant between groups implying that at the first week of evaluation both treatments have similar impact. At 2 weeks, seven out of nine studies showed statistically significant ($P < 0.05$) increase in Hb with IVS. Overall MD at 2 weeks of evaluation (0.79 g/dl; 95% CI 0.38–1.20 g/dl) was statistically significant ($Z = 3.77$; $P < 0.001$) implying that the rise in Hb is higher for IVS compared to oral iron. At 4 weeks, all the eight studies showed significant increase in Hb with IVS. Overall MD (0.93 g/dl; 95% CI 0.52–1.35 g/dl) was significant ($Z = 4.46$; $P < 0.001$) with rise in Hb in favour of IVS. Significant positive impact towards IVS treatment continued at 6 weeks; most studies (7/9) showed significant increase in Hb, overall MD (0.66 g/dl; 95% CI 0.29–1.04 g/dl) which was statistically significant ($Z = 3.46$; $P = 0.002$).

Cumulative analysis of all time points indicates that the estimated mean values of Hb in IVS and OIGs were 10.11 g/dl and 9.33 g/dl, respectively. The MD (0.78 g/dl; 95% CI 0.57–1.00 g/dl) was statistically significant ($Z = 7.08$; $P < 0.001$). Improvement (baseline to post-evaluation) in Hb was 28.3% in IVS and 16.8% in OIG. At the end of 6 weeks of evaluation with 95% confidence, minimum MD and maximum MD in Hb of IVS and oral iron were 0.25 g/dl and 2.55 g/dl, respectively.

2. Mean Maternal Ferritin Level (Fig. 2)

Of 11 studies in ANC period, seven assessed ferritin levels at specific time. The baseline mean value of serum ferritin was 10.51 μg/l in IVS and 11.13 μg/l in the OIG with no significant difference. The only two studies [24, 35] that presented evaluation at the end of first week showed significant increase in ferritin with overall MD (21.25 μg/l; 95% CI 6.63–35.87 μg/l) being statistically significant ($Z = 2.85$; $P = 0.004$). At the end of second week, four study results showed that overall MD (49.63 μg/l; 95% CI 26.01–73.25 μg/l) was statistically significant ($Z = 4.12$; $P < 0.001$). In the fourth week, all the five studies showed

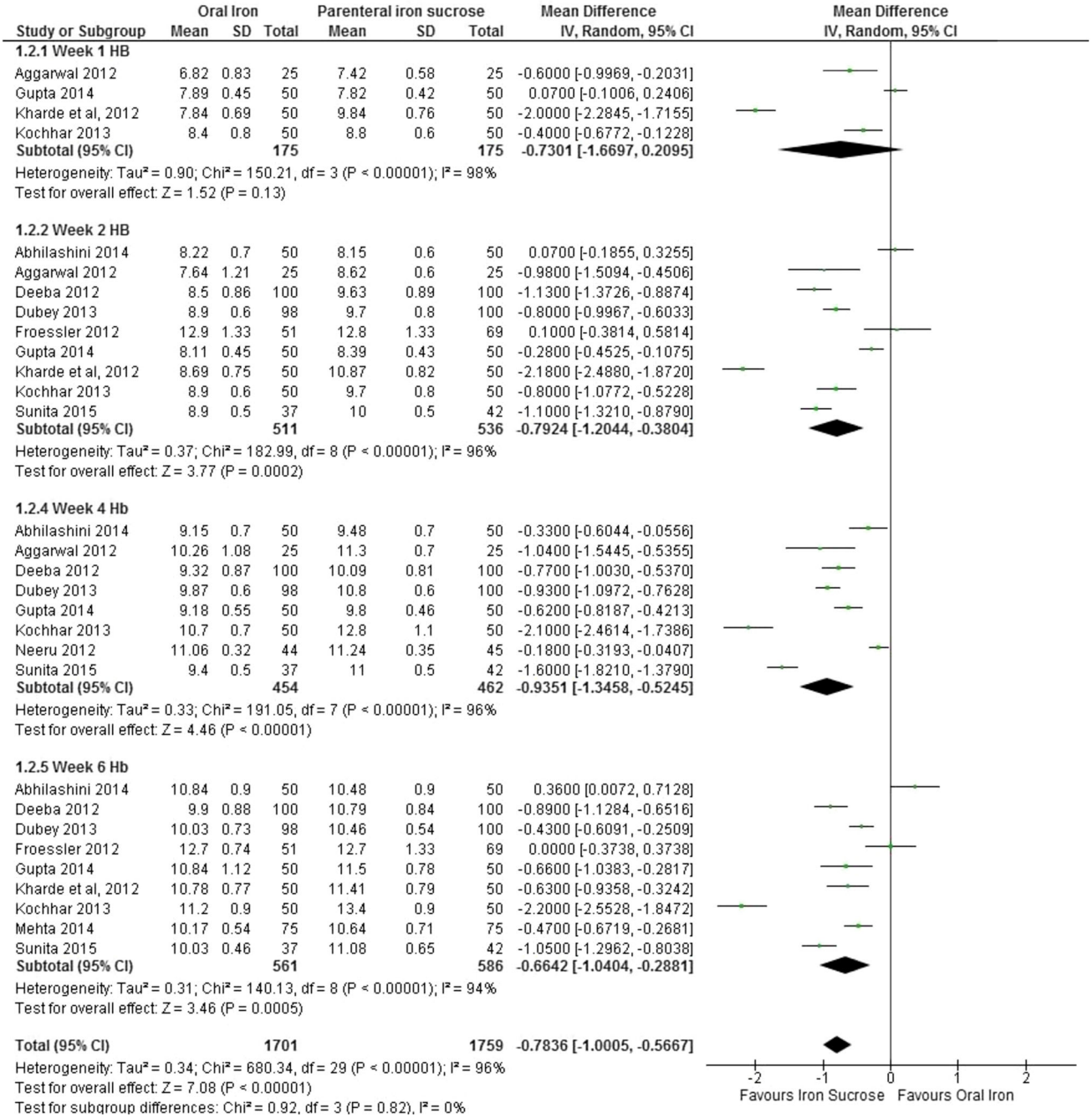

Fig. 1 Impact of oral iron and parenteral iron during ANC period (Hb)

significant increase in ferritin with IVS treatment and overall MD 45.98 μg/l (95% CI 26.58–65.37 μg/l) was statistically significant ($Z = 4.65$; $P < 0.001$). Four of the six studies which recorded the impact of ferritin at the end of 6 weeks showed a significant ($P = 0.05$) increase in ferritin level in IVS group. The overall MD 20.7 μg/l (95% CI 2.90–38.5 μg/l) was also statistically significant ($Z = 2.28$; $P < 0.05$). Estimated mean ferritin level from first to six weeks was 63.1 μg/l and 28.6 μg/l in IVS and OIGs, respectively. The MD (34.5 μg/l; 95% CI 26.15–42.86 μg/l) was statistically significant ($Z = 8.09$; $P < 0.001$). Percentage improvement from baseline to post-evaluation was 500% and 157% in IVS and oral group, respectively.

3. Maternal Packed Cell Volume PCV (%)

Of the ten studies, only four had studied the impact on PCV. Baseline mean PCV values in IVS and OIG were

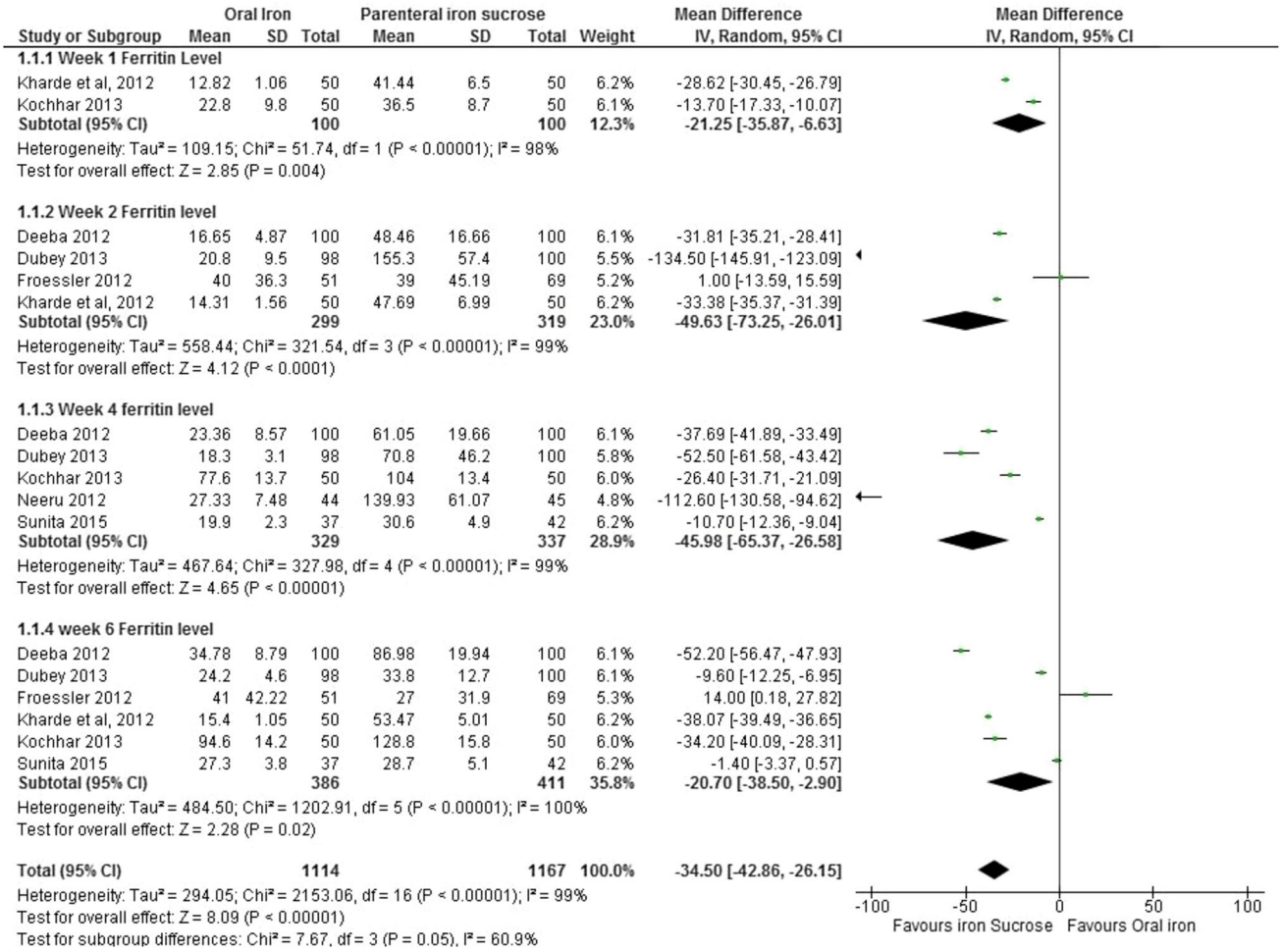

Fig. 2 Comparison of oral iron vs parenteral iron during ANC (ferritin)

23.9% and 24.2%, respectively. Though MD values observed individually at follow-up weeks were not statistically significant, the cumulative effect over a period of 6 weeks showed that the mean values in the respective groups were 30.5% and 29.5%. The resulting MD (1.00%; 95% CI 0.31–1.7%) was statistically significant ($Z = 2.83$; $P < 0.01$) in favour of IVS. The percentage improvement in IVS (28%) and OIG (22%) confirmed the clinical significance of IVS treatment.

Sensitivity Analysis

Sensitivity analysis was performed to assess robustness and consistency of findings. Only the studies that had evaluated the outcomes at all time points (2, 4 and 6 weeks) were considered for sensitivity analysis. Variation due to study subjects in these studies was minimized on account of evaluation from the same cohort at all time points. Accordingly, six [19–24] out of 11 ANC studies evaluated the Hb level at all the three time points. Meta-analysis of results indicates that the overall MD (95% CI) between IVS and OIGs was 0.84 g/dl (0.6–1.09 g/dl). Since the MD 0.84 and its 95% CI were within the confidence limits (0.57–1.0) obtained based on the 11 studies, consistency of findings was established. Only four studies [20, 21, 27, 34] had evaluated ferritin level at 2 and 6 weeks. Meta-analysis based on the four studies indicates that overall MD was 35.9 µg/l (95% CI 23.9–47.9) which corroborates with the MD 34.50 µg/l (95% CI 26.15–42.86) that was based on five studies analysis. There were inadequate number of studies to conduct sensitivity analysis for PCV outcome.

Post-partum Period

1. Mean Maternal Haemoglobin (Fig. 3)

Overall baseline mean value of Hb in IVS and OIG was 7.62 g/dl and 7.64 g/dl, respectively. In two [32, 34] of the four studies that had reported changes in Hb, MD was statistically significant at 1 week post-treatment. However,

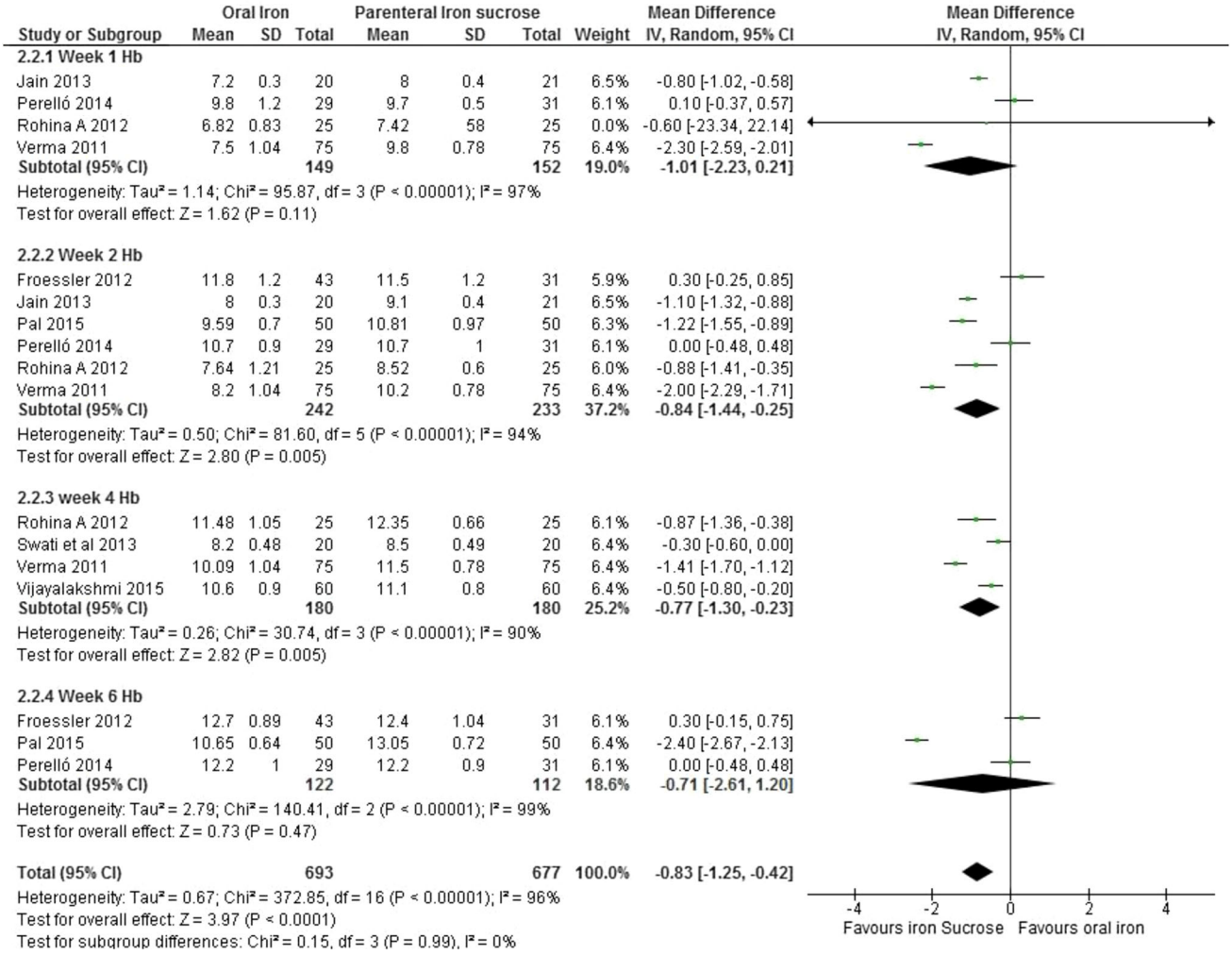

Fig. 3 Comparison of oral iron vs parenteral iron during post-partum period (Hb)

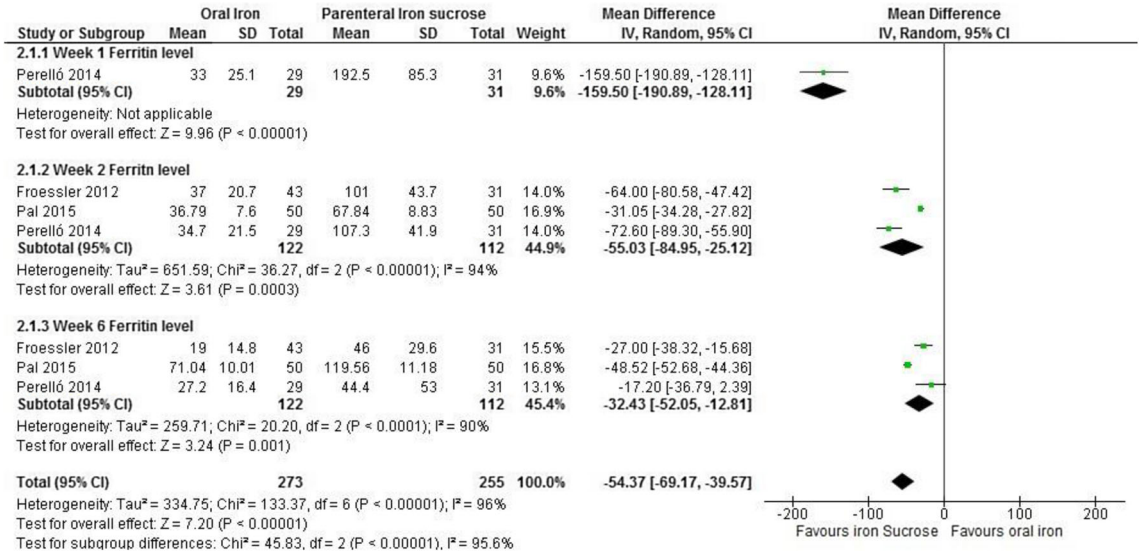

Fig. 4 Comparison of oral iron vs parenteral iron during post-partum period (ferritin level)

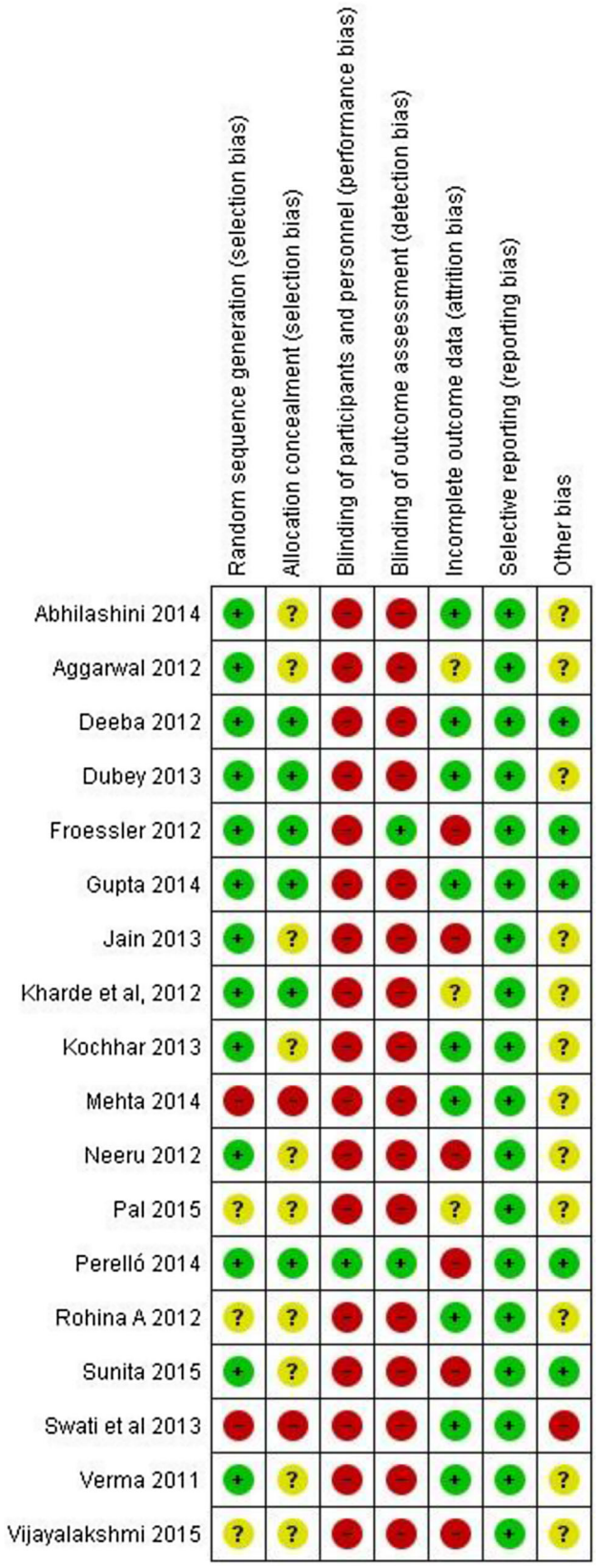

Fig. 5 Risk of bias summary: review of authors' judgements about each risk of bias item for each included study

overall MD was not statistically significant ($P = 0.11$). At the end of 2 weeks, majority of studies (4/6) [30, 31, 33, 34] showed statistically significant MD ($P < 0.05$) with positive impact on Hb with IVS. Overall MD (0.84 g/dl; 95% CI 0.25–1.44 g/dl) was also statistically significant ($Z = 2.80$; $P < 0.01$). Similar trend was observed at 4 weeks with overall MD (0.77 g/dl; 95% CI 0.23–1.3 g/dl) which was statistically significant ($Z = 2.82$; $P < 0.01$). Though MD was not statistically significant at 6 weeks, the cumulative estimate of mean values in the respective groups was 10.57 g/dl and 9.74 g/dl, and MD 0.83 g/dl (95% CI 0.42–1.25) from first to six weeks of observation, was statistically significant ($Z = 3.97$; $P < 0.001$). *Upper limit of cumulative MD (1.25 g/dl) was higher in post-partum period compared to that of ANC period (1.00 g/dl).* Improvement of Hb from baseline to post-evaluation was 39% and 28% in IVS and OIG, respectively. Clinical significance of IVS treatment for post-partum IDA is clearly evident.

2. Mean Maternal Ferritin Level (Fig. 4)

Overall baseline ferritin levels were 22.02 µg/l and 24.0 µg/l in IVS and OIG, respectively.Three out of four studies [28, 32, 33] reported ferritin levels. Only one study [32] reported evaluation at the first week in which MD (159.5 µg/l; 95% CI 128.11–159.5) was statistically significant ($Z = 9.96$; $P < 0.001$). The values of MD at 2 weeks (55.03 µg/l; 95% CI 25.12–84.95) and 6 weeks (32.43 µg/l; 95% CI 12.81–52.05) were statistically significant ($P \leq 0.001$). Cumulative mean estimate in the respective group was 90.5 µg/l (IVS) and 36.1 µg/l (OIG). The MD (54.4 µg/l; 95% CI 39.57–69.17) from first to six weeks of observation was statistically significant ($Z = 7.2$; $P < 0.001$) with *larger positive impact implying that for post-partum IDA, IVS treatment is a better choice* as evidenced by 311% improvement with IVS versus 50% with oral iron.

3. Maternal PCV

Overall baseline mean value of PCV in IVS (21.7%) and OIG (22.1) was not significantly different.Three studies reported changes in PCV in post-partum period. At the end of 2 weeks, overall MD (2.09%; 95% CI 0.25–3.93) of all three studies was statistically significant ($Z = 2.22$; $P = 0.03$). Since only one of two studies reported the changes in PCV at one or more time points, there was no strong evidence to comment on the impact. However, cumulative estimate of PCV in the IVS and OIG was 33.8% and 31.6%, respectively. The MD (2.24%; 95% CI 0.40–4.08) from first to six weeks was statistically significant ($Z = 2.38$; $P = 0.02$). Improvement in the respective groups was 56% (IVS) and 43% (OIG). *Meta-*

Table 1 Summary of findings

Comparison of parenteral iron with oral during antenatal period for treatment of iron deficiency with respect to haemoglobin and ferritin			
Patient or population: antenatal mother			
Setting: hospital			
Intervention: parenteral iron (IVS)			
Comparison: oral iron			
Outcomes	Anticipated absolute effects* (95% CI) Risk with comparison of oral iron	No of participants (studies)	Quality of the evidence (GRADE)
Ferritin level	MD 34.5 lower (42.86 lower to 26.15 lower)	2281 (7 RCTs)	⊕⊕⊕⊕ HIGH[1,2]
Ferritin level at 6 weeks	MD 20.7 lower (38.5 lower to 2.9 lower)	797 (6 RCTs)	⊕⊕⊕⊕ HIGH
Haemoglobin level	MD 0.78 lower (1 lower to 0.57 lower)	3460 (11 RCTs)	⊕⊕⊕⊕ HIGH
Haemoglobin level at 6 weeks	MD 0.66 lower (1.04 lower to 0.29 lower)	1147 (9 RCTs)	⊕⊕⊕⊕ HIGH
Comparison of parenteral iron with oral iron during with respect to haemoglobin and ferritin			
Patient or population: post-partum woman			
Post-natal period for [health problem]			
Setting: India			
Intervention: parenteral iron (IVS)			
Comparison: oral iron			
Outcomes	Anticipated absolute effects* (95% CI) Risk with comparison of oral iron	No of participants (studies)	Quality of the evidence (GRADE)
Ferritin level	MD 54.37 lower (69.17 lower to 39.57 lower)	528 (3 RCTs)	⊕⊕⊕⊖ Moderate[1,2,3]
Ferritin level at 6 weeks	MD 32.43 lower (52.05 lower to 12.81 lower)	234 (3 RCTs)	⊕⊕⊕⊖ Moderate
Haemoglobin level	MD 0.83 lower (1.25 lower to 0.42 lower)	1370 (8 RCTs)	⊕⊕⊕⊖ Moderate
Haemoglobin at 6 weeks	MD 0.71 lower (2.61 lower to 1.2 higher)	234 (3 RCTs)	⊕⊕⊕⊖ Moderate

[1]Not blinded

[2]The confidence intervals do not overlap

[3]Negative and low-quality reports not represented well but funnel plot cannot be made

GRADE working group grades of evidence: High quality: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

analysis indicates that the effect of IVS is more significant during both ANC and post-partum periods.

Sensitivity Analysis

To assess consistency and reliability of findings, sensitivity analysis was carried out using the same criteria in earlier analysis. Four studies [30–32, 34] evaluated the impact of treatment on Hb at two time points (1st and 2nd weeks). Meta-analysis of these four studies resulted in an overall MD (95% CI) of 1.0 g/dl (0.43–1.6), which was found to be close to 0.83 g/dl and within the confidence limits (0.42–1.25) obtained based on all time points. Sensitivity analysis for ferritin in post-partum period was carried out based on three studies [28, 32, 33] that evaluated the ferritin at two time points (2 and 6 weeks). The overall MD (95% CI) was 43 μg/l (30.7–55.1) and found to be within the confidence limits (39.57–69.17). Due to inadequate number of studies, sensitivity analysis for PCV could not be carried out.

Adverse Reactions

Adverse events were reported in all trials. Gastrointestinal symptoms such as metallic taste, nausea, vomiting, dyspepsia, epigastric discomfort, constipation and diarrhoea were commonly observed in the OIG. Three studies reported higher percentage of patients reporting adverse

effects, i.e. 16–18% [21, 22] in OIG, while no difference was observed in two studies [24, 27]. Dropout of 2% in OIG due to side effects (25%) was recorded in one study [21].

With IVS use, adverse events included metallic taste, nausea, dizziness, hot flushes, arthralgia, pruritus and pain at injection site. Thrombophlebitis was reported in one patient. There were no serious adverse effects.

Secondary Outcomes

Requirement for blood transfusion was mentioned in three studies [21, 24, 28]. Transfusion rates were same in the two groups in Frossler's study [28], two patients OIG versus none in IVS received transfusion in one study [24], and there was no difference in the study by Dubey et al. [21].

Foetal outcomes were reported in four studies [19, 21, 23, 24]. No statistically significant difference was observed in birthweight between the two groups. The average baby weight was 2.6–2.8 kg.

Quality of Life (QOL)

The only study which compared the effect on post-partum depression did not find statistically significant results at any time point [32].

Risk of Bias Assessment (Fig. 5)

Five trials [32–36] satisfactorily described the randomisation sequence generation. Three studies [34–36] reported adequate allocation concealment. Relevant information in remaining RCTs was not available. Blinding was reported in one study only [32]. Intention-to-treat analysis was used in five trials [32–37] to assess outcome measures. All studies had loss to follow-up and dropout rates less than 20%. The summary of findings table generated using Grade profiler software is attached in Table 1.

Discussion

IDA accounts for 75–80% of anaemia in young women [38]. Iron requirement in pregnancy is increased by about 1000 mg [39]. Adverse feto-maternal effects due to anaemia include increased risk of maternal blood transfusion, preterm births, caesarean deliveries and higher admission to neonatal intensive care [8]. Significant improvement in birthweight following iron supplementation was found by Haider et al. [40].

Regular as well intermittent supplementations have a place for treatment of IDA [41]. Poor compliance to oral iron due to gastrointestinal side effects has led to failure of prevention and treatment strategies. Parenteral formulations include intramuscular and intravenous preparations. Intramuscular iron is associated with side effects such as pain, staining at injection site and severe arthralgia [42]. The newer parenteral preparations, e.g. iron sucrose, ferric carboxymaltose and low molecular weight iron dextran, are found to be safe though limited by cost [2]. Anaphylactic reactions are virtually unknown with iron sucrose, the reported incidence being 0.002% [43].

In a systematic review of 43 trials [44] comprising of 6831 adult participants on oral iron, ferrous sulphate supplementation significantly increased risk of GI side effects compared to placebo and IVS. Non-compliance to oral iron in pregnant women may be up to 50% leading to significant treatment failures [45].

The systematic review by Shi et al. [46] concluded that for pregnant women who could not tolerate the side effects of oral iron treatment or required a rapid replacement of iron stores, IVS was more effective with fewer adverse events.

Health-related QOL during after pregnancy is improved significantly in anaemic pregnant women by repletion of their iron stores through supplementation. Improvement in QOL has been observed with parenteral iron preparations (ferrous polymaltose) [43]. No significant difference on post-partum depression between the IVS and OIGs was noted by the only study which reported this outcome in our analysis [32]. Following total dose infusion, there is restoration of body iron (including stores) within a short time as is also demonstrated in our analysis. This obviates long-term oral iron intake.

IVS also has a role in patients with refractory anaemia not responding to oral iron, e.g. chronic infections, chronic kidney disease, inflammatory bowel disease, chemotherapy-induced anaemia and peri-partum period [47, 48]. This is especially important in low-resource countries with high prevalence of chronic diseases like TB and endemic malaria.

Our systematic review has the following limitations:

(1) There is a large statistical heterogeneity in our meta-analyses (hence, random effect modelling was done). The reasons for this heterogeneity could be the differences in settings, use of different oral iron preparations. Since we included several quasi-randomized studies, there was risk of bias observed on account of inadequately described randomization sequence generation and allocation concealment, and blinding was not possible in majority of studies due to the nature of interventions.
(2) We may have missed negative trials since there is publication bias.

(3) We could not report on the quality of life as only one study reported this outcome.

Strength of our study is that it synthesizes evidence from recently conducted trials in developing countries. Policymakers often like to look at local evidence before recommending an alternate treatment modality for national programs. We hope that results of our systematic review would give an opportunity for mainstreaming parenteral treatment for IDA.

Conclusion

IVS is an effective and safe alternative to address the problem of IDA in India. Through this systematic review of RCTs conducted mostly in LMICs, we hope to draw the attention of policy makers to this important and feasible treatment of iron-deficient pregnant and post-partum women.

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Compliance with Ethical Standards

Conflicts of interest The authors declare no conflict of interest.

Ethical statement This article does not contain any studies with human or animal subjects performed by the any of the authors.

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