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Systematic review of randomized trials of the effect of iron supplementation on iron stores and oxygen carrying capacity in pregnancy

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Abstract

Introduction. Anemia in pregnancy affects 25% of all pregnancies in Europe with iron deficiency affecting even more. Despite supplementation, iron deficiency persists. This review will assess the effect on serum ferritin (iron stores) and hemoglobin (oxygen-carrying capacity) following iron supplementation in pregnant women with anemic and non-anemic iron deficiency. *Material and methods.* A systemic search of electronic databases and trial registers was conducted from inception to January 2014. Randomized controlled trials of iron supplementation that measured serum ferritin and hemoglobin levels before and after supplementation were selected. Two independent reviewers selected studies, extracted data and assessed quality. Descriptive analyses were carried out. *Results.* The review included 23 randomized controlled trials (3525 women). In iron deficiency anemia, more studies described statistically significant increases in serum ferritin levels than in hemoglobin levels following intravenous iron supplementation. In non-anemic iron deficiency there were more statistically significant increases in serum ferritin levels than in hemoglobin levels following oral supplementation. There were no studies reporting maternal quality of life outcomes. *Conclusions.* Serum ferritin appears to change more than hemoglobin following iron supplementation. The clinical effects of this need further investigation.

Abbreviations: IDA, iron deficiency anemia; NAID, non-anemic iron deficiency.

Introduction

Iron deficiency is a leading risk factor for morbidity and mortality worldwide (1). Before developing anemia, sufferers become iron deficient, developing the condition of non-anemic iron deficiency (NAID). There is much

Key Message

Iron supplementation affects serum ferritin levels (iron stores) to a greater degree than hemoglobin levels (oxygen carrying capacity). The clinical effect is unclear and further research on treating non-anemic iron deficiency in pregnancy is required.

debate over the consequences of NAID and whether it should be treated (2,3). The World Health Organization estimates a prevalence of iron deficiency anemia (IDA) as 25% in Europe (>40% worldwide) with a proposed prevalence of iron deficiency being two-fold higher (3,4). Similar prevalence data have been demonstrated in the UK through a large multicenter study (5).

Iron is an essential component of many enzyme-linked processes within the body. It is an integral component of hemoglobin in addition to contributing to immune cell function, DNA synthesis and electron transport (6). About 80% of daily iron requirements are used for erythropoiesis (6). Iron requirements vary in pregnancy, but the World Health Organization recommends a daily intake of 30–60 mg of elemental iron (7,8). In iron depletion, the amount of stored iron is reduced, resulting in a reduction in the serum ferritin. Individuals with iron depletion are not able to mobilize iron stores in the advent of increased demand, such as pregnancy. In IDA, there are reductions in hemoglobin and serum ferritin levels as well as reduced transferrin saturation (2).

Maternal effects of iron deficiency include increased morbidity and mortality resulting from pregnancy and childbirth in addition to fatigue, dyspnea, irritability, poor concentration, low energy, and low mood states (2,9–11). IDA increases the risk of low birthweight and preterm delivery (9,12,13). Women enter a state of NAID before becoming anemic, which means that NAID is a precursor in the pathogenesis of anemia. We postulate that the relation between NAID and IDA is better demonstrated by changes in serum ferritin compared with changes in hemoglobin. We will further explore the effect of iron supplementation on birthweight, gestation at delivery and maternal quality of life. In the review we aimed to assess the effects of iron supplementation on NAID and IDA from data collected in randomized controlled trials.

Material and methods

Data sources

Using recommended methods (14), a search without language restrictions was performed through the following databases: EMBASE (1970 to January 2015), MEDLINE (1970 to January 2015), The Cochrane Library, CINAHL (1970 to January 2015) and AMED (1970 to January 2015). Grey literature was searched using SIGLE (1970 to January 2015).

The searches used subject headings and key words including 'iron deficiency anemia', 'iron deficiency', 'pregnancy', 'ferritin', 'screening', and 'testing'. A hand search of bibliographies of relevant journals was also performed, along with searches of conference proceedings from international conferences in maternal and fetal medicine, to identify articles not electronically cited.

Studies were included in the systematic review when the following criteria were met: (i) the population of interest was pregnant women at any gestation with NAID and/or IDA, as defined by authors in prespecified values for serum ferritin and hemoglobin; (ii) the intervention was iron supplementation (oral, including fortified water, intravenous or intramuscular); (iii) the comparator was placebo, or oral or intramuscular iron preparations; (iv) the trial design was a randomized controlled trial; and, (v) the outcomes of interest were post-supplementation serum ferritin and/or hemoglobin, maternal quality of life, birthweight and gestation at delivery.

Study selection

Two authors (JD and NAMC) independently reviewed the titles and abstracts retrieved by the electronic searches and identified citations, which fulfilled the selection criteria. Following this, the full text manuscripts of the selected citations were reviewed to assess their suitability for inclusion in the review. Studies were excluded if authors had not prespecified values for anemia (hemoglobin level) or iron deficiency (serum ferritin) before administering an intervention or if they did not measure serum ferritin levels at baseline. Studies where iron supplementation occurred in conjunction with other minerals were excluded. In instances where data were collected but not published, authors were contacted with some authors providing data (15) and others not (16). In cases where data were presented in graphical form only, we extracted the data if this could be done accurately. If not, these studies were excluded if the authors did not respond when contacted (17). Any disagreements regarding study eligibility were resolved by consensus. A κ coefficient of inter-rater reliability was calculated (18). The study selection process was documented as per the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).

The data from selected studies were independently extracted by both reviewers using a predefined, piloted data extraction form. Data were collected on patient characteristics (number of participants, age and gestation at inclusion), study characteristics (study design, location, setting, randomization, blinding and participant recruitment to assess for selection bias) and the outcomes assessed (hemoglobin, serum ferritin, birthweight and gestation at delivery). The Jadad method was used to assess study quality and was carried out independently by both reviewers (19,20); a score of >3 equated to good quality. Differences in quality assessment where studies compared

oral with intravenous or intramuscular supplementation and which could not be blinded due to their study design, were taken into consideration when assessing the quality of included studies.

The results were tabulated. Studies varied on how they reported changes in serum ferritin and hemoglobin following intervention, both in terms of units of measurement and the time point of reporting. All measurements were standardized and converted to μg/L for serum ferritin and g/dL for hemoglobin. Results were presented as descriptive outcomes because meta-analysis was not possible (14). The review was registered prospectively with PROSPERO (CRD42013006578).

Results

In all 1094 studies were identified following the electronic search. Of these, 54 were eligible for full text review, after which 23 were included in the systematic review. The κ statistic was calculated as 0.75 representing good agreement (14). The search strategy is shown in Figure 1.

Twenty-three studies were included in the systematic review (see Table S1). Six studies compared intravenous supplementation with oral iron supplementation; six compared oral iron supplementation with placebo; three compared weekly with daily oral iron supplementation; two studies compared different doses of oral supplementation; three compared different types of oral supplementation; one study compared intravenous with intramuscular supplementation; one study compared oral with intramuscular supplementation and one study compared iron-fortified water with placebo.

There were differences in quality between those studies looking at oral iron supplementation compared with intravenous or intramuscular supplementation. These studies could not be blinded by the nature of their design (Table 1, Figure 2).

Due to the variation in participants, trial methods and timing of assessments, the studies were too heterogeneous for meta-analysis to be conducted and included in this review. Preliminary meta-analysis demonstrated significant heterogeneity, despite subgroup analysis by intervention (oral or paternal) and gestation.

Search terms:
#1. pregnancy [mesh] pregn* Pregnant woman [mesh]
#2. iron deficiency [mesh] iron defic*
#3. Hemoglobin [mesh] hemoglob*
#4. Blood cell count [mesh] full blood count [mesh]
#5. Ferritin [mesh] serum ferrit*
#6. Anemia [mesh] anaem* Anemia [mesh] anem*

Figure 1. Search strategy for systematic review of the use of serum ferritin in assessing the effect of iron supplementation in pregnancy.

Effect of supplementation on pregnant women with IDA

Parenteral supplementation. Six studies compared intravenous with oral iron supplementation (Table 2). There was a statistically significant increase in serum ferritin and hemoglobin from baseline levels in all six studies comparing intravenous with oral supplementation (21–26). When comparing serum ferritin and hemoglobin increases between oral and intravenously supplemented groups, there was a significant increase in hemoglobin in the intravenous group compared with the oral group in three studies (24–26), but when looking at serum ferritin there was a statistically significant increase in five out of the six studies (22–26). In one study there was a 22-fold increase in the serum ferritin in the intravenously supplemented group (26). Figure 3 details these results.

There were two studies looking at intramuscular supplementation compared with either oral or intravenous supplementation (Table 2). In both studies there was a significant rise in serum ferritin from the baseline level in the intervention arms (27,28). There was a significant rise in hemoglobin from the baseline level in the study comparing intravenous and intramuscular iron supplementation in both treatment groups (27). On comparing changes in serum ferritin between comparator arms, there was no significant change in serum ferritin between intravenous and intramuscular iron supplementation (27); however, there was a significant change in hemoglobin in the intravenous group compared with the intramuscular group in this study (27). Figure 3 details these results.

Oral supplementation. There were three studies comparing weekly with daily oral iron supplementation (29–31); three studies comparing alternative oral preparations with a commonly used preparation (ferrous sulfate of varying doses); two studies comparing different doses of oral iron supplementation; one study comparing iron fortified water with placebo (32) and one study comparing oral supplementation with placebo (32,33) (Table 2).

In the studies comparing oral supplementation at weekly compared with daily intervals there was a significant increase in serum ferritin from baseline in both the intervention and control arms in two of the three studies (30,31) and a significant increase in hemoglobin from the baseline level in one of the studies between the intervention and control arms (31). In two of these three studies there was a significant increase in serum ferritin in the group supplemented daily compared with weekly. There

Table 1. Methodological quality assessment (Jadad scoring system) (19) of studies included in the systematic review of iron supplementation in iron deficiency in pregnancy.

Study (reference)	Randomized	1±[a]	Double blind	1+	Withdrawals and drop outs	Total	Quality
Al 2005 (21)[b]	1	1	0	0	1	3	High[b]
Bayoumeu 2002 (22)[b]	1	1	0	0	1	3	High[b]
Cogswell 2003 (15)	1	1	1	1	1	5	High
Dhanani 2012 (27)	1	1	0	0	1	3	High[b]
Falahi 2011 (41)	1	−1	1	1	0	2	Low
Froessler 2013 (23)[b]	1	1	0	0	1	3	High[b]
Hyder 2003 (30)	1	−1	0	0	1	1	Low
Khalafallah 2010 (24)[b]	1	1	0	0	1	3	Low
Kochhar 2013 (25)[b]	1	1	0	0	1	3	Low
Krafft 2005 (39)	1	1	1	1	1	5	High
Kumar 2005 (28)	1	0	0	0	1	2	Low
McKenna 2003 (32)	1	1	1	1	1	5	High
Meier 2003 (33)	1	0	1	1	1	4	High
Milman 2006 (35)	1	0	1	0	1	3	Low
Mumtaz 2000 (31)	1	1	1	1	1	5	High
Nappi 2009 (36)	1	1	1	1	1	5	High
Ortiz 2011 (38)	1	1	0	0	1	3	Low
Ridwan 1996 (29)	1	−1	0	0	1	1	Low
Siega-Riz 2006 (43)	1	1	1	1	1	5	High
Saha 2007 (37)	1	0	1	1	0	3	Low
Singh 1998 (26)[b]	1	0	0	0	0	1	Low
Thomsen 1993 (34)	1	0	0	0	1	2	Low
Ziaei 2008 (40)	1	1	1	0	1	4	High

[a]This refers to description of randomization and blinding. If methods are described and deemed adequate a point is added, if deemed inadequate a point is subtracted.

[b]Studies including intravenous supplementation in addition to oral supplementation, which could not be blinded.

were no statistically significant changes between the groups seen with respect to hemoglobin (30,31) (Figure 3).

In the studies comparing different doses of oral supplementation, there was a significant decrease in serum ferritin in both studies when comparing the lowest dose of supplementation with the higher doses (34,35). There was a significant increase of hemoglobin from baseline in the higher dose of iron supplementation in one study but not in the groups receiving lower doses of iron supplementation (34) (Figure 3).

In the three studies comparing different oral preparations, there was a statistically significant increase in serum ferritin from the baseline in all three studies in both the intervention and comparator arms (36–38). There was a significant increase from the baseline in hemoglobin in both intervention and control arms in two of the three studies (36,37). When comparing one oral iron preparation with another, there was a significant increase in the serum ferritin in the intervention group in two studies (36,37). There were no significant changes in hemoglobin when comparing one oral iron preparation with another (Figure 3).

Supplementation in pregnant women with NAID

There were five studies that looked at iron supplementation in pregnant women with NAID (Table 2). The definition of iron deficiency varied between each of these groups (Table 1). These five studies compared oral iron supplementation with placebo. Of the five studies, there were two demonstrating a significant increase in serum ferritin levels in the intervention groups compared with baseline (39,40) and one study showed a significant increase in hemoglobin in the supplemented group compared with the placebo group (40) (Figure 4).

Three studies reported rates of NAID and IDA. Cogswell et al. reported that before delivery 65.1% of the population in the placebo arm of their study were iron deficient and 20.9% had IDA (defined as hemoglobin <11.0 g/dL and serum ferritin <12 μg/L) (15). Similarly, Siega-Riz et al. reported that 65% of the population in their placebo group were iron deficient and 15% had IDA (defined as hemoglobin <11.0 g/dL and serum ferritin <20 μg/L). Falahi et al. also reported an NAID rate of 28% in their non-supplemented study population (41).

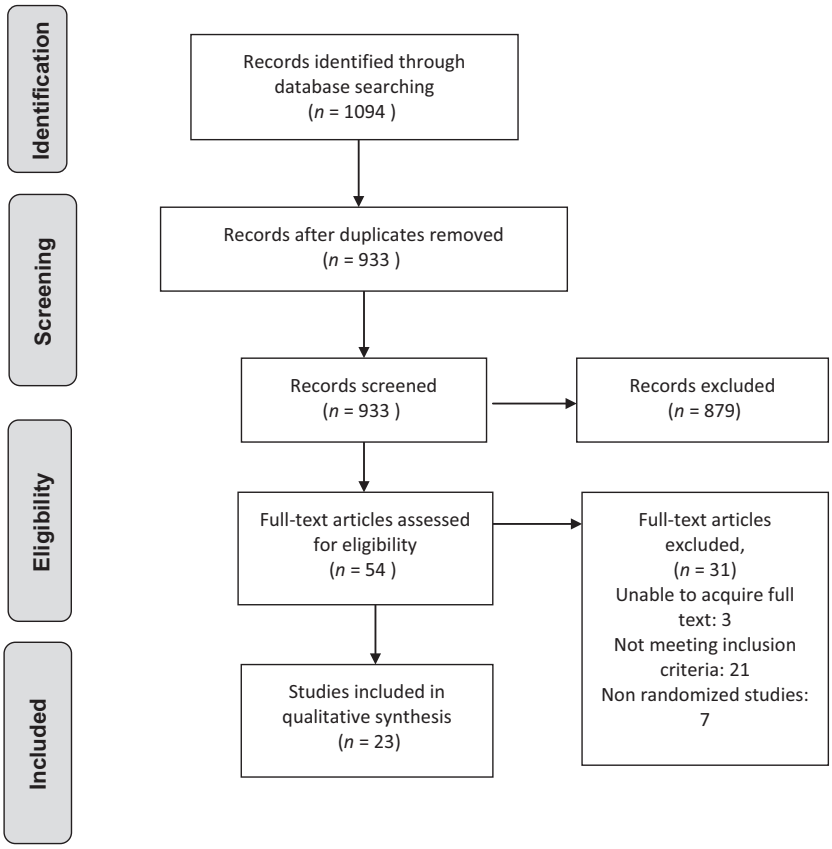

Figure 2. PRIMSA flow diagram: study selection for systematic review of ferritin testing in iron deficiency and iron deficiency anemia in pregnancy.

Neonatal outcomes and maternal quality of life

None of the studies included reported maternal quality of life outcomes. In 2012, Khalafallah et al. published a retrospective quality of life study on some of their study population following their randomized trial in 2009 (42). This was however, separate from their initial study and so has not been included in this review.

There were no statistically significant differences in gestational age at delivery or birthweights when parenteral and oral supplementations were compared. When comparing oral supplementation in anemic iron-deficient women, there were two studies reporting neonatal outcomes but neither found a significant difference between the two groups (33,38).

All of the studies examining oral iron supplementation in non-anemic women reported neonatal outcomes (15,39,41,43,44) and in two of them, there were significant improvements in birthweight seen with oral iron supplementation (43,45).

Discussion

This systematic review showed that serum ferritin levels (iron stores) change more than hemoglobin levels (oxygen carrying capacity) in response to iron supplementation in pregnancy. It also demonstrated the wide variation in outcome reporting. Changes in serum ferritin and hemoglobin as outcome measures were not correlated to quality of life or clinical outcomes.

There was variation with regard to participants, methods and outcomes. As a result the preliminary meta-analysis showed significant heterogeneity even when divided by type of intervention (oral or parenteral iron) and gestation. The studies included in this systematic review were heterogeneous in the criteria for participant recruitment with respect to levels of serum ferritin and hemoglobin being used to define iron deficiency (ranging from a serum ferritin <12 μg/L to serum ferritin <20 mg/L; hemoglobin ranging from <11 g/dL to <8.5 g/dL) (26,36). This variation was also seen in current published

Table 2. The effect of iron supplementation on serum ferritin and hemoglobin in women with anemic and non-anemic iron deficiency.

Study (reference)	Intervention and comparator	Significant change in SF from baseline	Significant change in Hb from baseline	Significant difference between intervention and comparator arms for changes in SF	Significant difference between intervention and comparator arms for changes in Hb
Iron deficiency anemia					
Al 2005 (21)	IV vs. oral	Increase	Increase	No difference	No difference
Bayoumeu 2002 (22)	IV vs. oral	Increase	Increase	Increase in IV group	No difference
Froessler 2013 (23)	IV vs. oral	Increase	Increase	Increase in IV group	No difference
Khalafallah 2010 (24)	IV vs. oral	Increase	Increase	Increase in IV group	No difference
Kochhar 2013 (25)	IV vs. oral	Increase	Increase	Increase in IV group	Increase in IV group
Singh 1998 (26)	IV vs. oral	Increase	Increase	Increase in IV group	Increase in IV group
Kumar 2005 (28)	IM vs. oral	Increase	No change	No difference	No difference
Dhanani 2012 (27)	IV vs. IM	Increase	Increase	No difference	Increase in IV group
Meier 2003 (33)	Oral vs. placebo	Increase	Increase	Increase in oral arm	No difference
McKenna 2003 (32)	Fortified water vs. placebo	Decrease	No change	Decrease in fortified arm	No difference
Thomsen 1993 (34)	Different oral doses	Decrease	Increase	No difference	Increase in higher dose arm
Milman 2006 (35)	Different oral doses	Decrease	No change	Decrease in lower dose arm	No difference
Hyder 2003 (30)	Weekly vs. daily	Increase	No change	Increase in daily arm	No difference
Mumtaz 2000 (31)	Weekly vs. daily	Increase	Increase	Increase in daily arm	Increase in daily arm
Ridwan 1996 (29)	Weekly vs. daily	No change	No change	No difference	No difference
Nappi 2009 (36)	Different oral preparations	Increase	Increase	No difference	No difference
Ortiz 2011 (38)	Different oral preparations	Increase	No change	Increase in polymaltose arm	No difference
Saha 2007 (37)	Different oral preparations	Increase	Increase	Increase in polymaltose arm	No difference
Non-anemic iron deficiency					
Cogswell 2003 (15)	Oral vs. placebo	No change	No change	No change	No change
Falahi 2011 (41)	Oral vs. placebo	No change	No change	No change	No change
Siega-Riz 2006 (43)	Oral vs. placebo	No change	No change	No change	No change
Krafft 2005 (39)	Oral vs. placebo	Increase	Increase	Increase in oral arm	Increase in oral arm
Ziaei 2008 (44)	Oral vs. placebo	Increase	Increase	Increase in oral arm	Increase in oral arm

All values refer to significant p values of $p < 0.05$.
Hb, hemoglobin; IV, intravenous; IM, intramuscular; SF, serum ferritin.

guidelines (2,3,46). Iron deficiency in the UK guidelines is defined as serum ferritin <30 μg/L (2), whereas in the USA iron deficiency is set at serum ferritin <15 μg/L (46). These values are based on studies comparing serum ferritin with bone marrow biopsies from a variety of populations and may not be representative of true iron deficiency throughout all the trimesters of pregnancy (47,48). The British Society for Haematology guidelines state that at serum ferritin levels <15 μg/L, there is a complete loss of iron stores from bone marrow and that iron deficiency begins from serum ferritin levels <30 μg/L in pregnancy (2).

Another factor contributing to the heterogeneity were the time points at which measurements were taken following supplementation and this resulted in a large variation in the total duration and dose of iron supplementation. None of the included studies provided any justification as to why particular time points were chosen for the measurement of hematological parameters. The physiological expansion of plasma volume in the third trimester of pregnancy and its contribution to lower serum ferritin and hemoglobin levels should be taken into account (2,49). The variations in doses and forms of iron may be linked to a lack of international consensus on the amount and preparations for iron administration. The British Society for Haematology have provided guidance on the dose of elemental iron, based on the level of iron deficency and IDA in pregnant women (2).

Outcome reporting was deficient in many aspects. IDA and iron deficiency are known to adversely affect mood, concentration and exercise tolerance (50), although these are factors that can also be altered by pregnancy. However, data in this area are lacking. Maternal quality of life outcomes were not reported. Some studies looked at the gastrointestinal adverse effects of oral supplementation, but none examined improvement in symptoms of iron deficiency, leaving a significant gap in assessment of the effect of iron supplementation (11,42,51).

Within previous reviews, there have been discrepancies regarding the effect of supplementation on birthweight and gestation at delivery (52–54). There is concern about the possibility of routine supplementation leading to adverse neonatal outcomes, therefore it is proposed that iron supplementation should be titrated against set

		Change in hemoglobin levels between intervention and comparator arms		
		+	0	–
Change in serum ferritin between intervention and comparator arms	+	3	7	
	0	2	4	
	–		2	

Figure 3. Permutations representing significant changes in hemoglobin and the serum ferritin change between the intervention and comparator arms in studies looking at parenteral and oral iron supplementation in pregnant women with iron deficiency anemia (IDA) included in this systematic review. Numbers in the cells are the number of studies relevant to each permutation. Key: +, increase; 0, no change; –, decrease.

		Change in hemoglobin levels between intervention and comparator arms		
		+	0	–
Change in serum ferritin between intervention and comparator arms	+	2		
	0		3	
	–			

Figure 4. Permutations representing significant changes in hemoglobin and the serum ferritin change between the intervention and comparator arms in studies looking at iron supplementation in pregnant women with non-anemic iron deficiency (NAID) included in this review. Numbers in the cells are the number of studies relevant to each permutation. Key: +, increase; 0, no change; –, decrease.

hematological parameters (12,55). Birthweight at delivery is affected by both IDA and NAID in pregnant women, but observational studies show that birthweight follows a U-shaped distribution in relation to maternal iron levels (12,56,57) with low birthweight associated with both anemia and iron overload (9,55,57). However, large meta-analyses have found conflicting data on whether a link between anemia and low birthweight or preterm delivery exists (52,54). Little is known about whether iron supplementation in NAID in pregnancy will affect birthweight adversely (12) or beneficially (45). A recently published randomized controlled trial demonstrated that low-dose iron supplementation in iron-replete women does not result in low birthweight at delivery (58).

Non-anemic iron deficiency is a disease in its own right, as discussed in other recent publications (59). The effects of NAID on pregnancy outcomes are debated (2,12). There was a significant change in serum ferritin and hemoglobin levels following iron supplementation in NAID in two of the five studies included in this review (Figure 4). This is an area for future research.

The results of supplementation in NAID demonstrate that there are still many unanswered questions and the current published literature is equivocal on whether supplementation is of benefit. Despite this, the debate over routine supplementation continues, so titrating supplementation to serum ferritin levels rather than using hemoglobin levels as a guide should be studied further in clinical trials (12,52,60,61). To assess the cost-effectiveness of such an intervention a full cost-analysis would need to be performed.

Conclusions

Iron supplementation affects serum ferritin levels to a greater degree than hemoglobin levels in both IDA and NAID in pregnancy. Further assessment of whether serum ferritin can be used as screening tool or to titrate iron supplementation is required before it can be implemented. No recommendations on the treatment of NAID can be made from this review.

The heterogeneity of the timings and the outcomes reported in this systematic review demonstrates the need for a defined set of core outcomes for iron deficiency in pregnancy to be used in future work (62). Further work on NAID and IDA in pregnancy is needed, including correlation of hematological parameters to clinical outcomes including maternal quality of life.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Table of characteristics of studies included in systematic review of serum ferritin testing in iron supplementation in pregnancy.