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Submitting author: Associate Professor Alicia Dennis

Department of Anaesthesia

The Royal Women's Hospital, Locked Bag 300,

Cnr Grattan St & Flemington Rd,

Parkville, Australia 3052

Melbourne, Australia

Review article

Defining peri-operative anaemia in pregnant women – challenging the status quo*

M.T. Ferguson[1] and A.T. Dennis[2]

1 Anaesthesia Fellow, 2 Consultant Anaesthetist, Department of Anaesthesia, Royal Women's Hospital, Melbourne, Australia

Correspondence to: A. Dennis

Email: alicia.dennis@thewomens.org.au

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Twitter: @dr_mferguson @aliciatdennis

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Short title:

Peri-operative anaemia in pregnancy

Summary

Peri-operative anaemia is a significant risk factor for peri-operative morbidity and mortality. Anaemia during pregnancy is associated with adverse maternal and neonatal outcomes, and postpartum haemorrhage remains a leading cause of maternal mortality worldwide. Caesarean section is an operation incurring moderate risk of bleeding, and rates are rising globally. Recent international consensus guidelines recommend targeting a preoperative haemoglobin > 130 $g.l^{-1}$ for all patients having surgery with moderate-to-high risk of bleeding, regardless of gender. It is unclear how this recommendation translates to pregnant women, where anaemia is defined at a much lower haemoglobin level of < 110 $g.l^{-1}$. Longstanding definitions of anaemia during pregnancy are likely to be the result of flawed sampling of a so-called 'normal' but anaemic female population, given the high prevalence of iron deficiency and anaemia in healthy menstruating women. Contemporary data suggest that haemoglobin values in iron-replete pregnant women are higher than previously thought. The definition of anaemia has significant clinical implications, particularly peri-operatively for women undergoing caesarean section. In addition, we should differentiate between lower reference values and optimal haemoglobin targets. The haemoglobin level associated with optimal obstetric and neonatal outcomes requires further investigation in pregnant women.

Caesarean section is one of the most commonly performed operations globally, with almost 23 million performed annually [1]. In low income countries, caesarean section accounts for almost one-third of all surgical procedures performed [1]. Anaemia is increasingly recognised as an important and modifiable peri-operative risk factor, and is particularly relevant in the obstetric population where postpartum haemorrhage remains a leading cause of maternal mortality, particularly in low-income countries [2]. Anaemia in pregnant women is common, with 38% of all pregnant women worldwide being anaemic, increasing to > 50% in regions such as South Asia and Central and West Africa [3]. The high prevalence of anaemia, combined with increasing global rates of caesarean section, mean that peri-operative anaemia in pregnant women is a significant worldwide health issue.

Maternal anaemia is associated with adverse neonatal outcomes including low birthweight, preterm birth, and possibly perinatal mortality [4-6]. Antenatal anaemia is also associated with adverse maternal outcomes including postpartum infection and transfusion [7], and severe anaemia is a risk factor for postpartum haemorrhage [4], pre-eclampsia [8] and maternal mortality [9]. Anaemia is also associated with fatigue, limited exertional tolerance, dizziness, headaches, and reduced cognitive performance [10, 11], which may significantly impair a new mother’s ability to care for an infant. Iron status correlates with maternal health-related quality of life parameters such as general health, physical energy, and mental health parameters [12].

Post-partum anaemia, defined as a haemoglobin concentration < 120 $g.l^{-1}$, is associated with a higher burden of depressive symptoms [13] and adverse mother-infant interactions [14]. Maternal iron deficiency may also lead to adverse neurocognitive effects in the infant. Maternal ferritin levels correlate with neonatal ferritin levels, and iron-dependent neurogenesis is maximum during the third trimester and in early neonatal life [15, 16]. Fetal and neonatal iron deficiency may therefore result in deficits affecting memory, cognition, and behaviour [17].

Despite the recognised importance of anaemia peri-operatively, defining anaemia is challenging because of the high prevalence of undiagnosed anaemia in unselected patient populations [18]. We have reviewed the evidence behind current definitions of anaemia during pregnancy and the postpartum period, and existing guideline recommendations.

Methods

We performed a search for relevant literature including systematic reviews, meta-analyses, randomised controlled trials, and cohort studies. Sources included PUBMED, MEDLINE, Google Scholar, using the following key words: anaemia, hemoglobin/ haemoglobin, normal values, parturient, pregnant, obstetric.

Results

Current definitions of anaemia in pregnancy

The most widely cited definition of anaemia is from the World Health Organization (WHO), which defines anaemia as a haemoglobin < 120 $g.l^{-1}$ for women, and < 110 $g.l^{-1}$ for pregnant women [19]. Severe anaemia during pregnancy is defined as haemoglobin < 70 $g.l^{-1}$. These definitions of anaemia were first published in 1968, and have not been revised. Most other definitions of anaemia by major guideline groups are similar to the WHO definition of anaemia (Table 1).

The WHO definitions of anaemia have been criticised because the data were obtained from a small number of unselected subjects, and used outdated methods of haemoglobin measurement [20, 21]. The WHO guidelines refer to four original scientific papers published during the 1950s and 1960s [22-25]. Two of these did not include pregnant women [24, 25].

The two studies that included pregnant women had small sample sizes of 82 [23] and 149 [22], limiting the conclusions that can be made regarding reference ranges. Both studies were designed to assess the impact of iron supplementation during pregnancy, and both suggested that iron supplementation increased haemoglobin concentration at term and postpartum, although these conclusions were limited by a lack of randomisation and blinding. The first of these studies measured haemoglobin values in healthy women divided into four groups (control; intramuscular iron supplementation; twice-daily oral iron supplementation; and daily oral iron supplementation) [23]. The mean haemoglobin values in each group at three months gestation were 125 $g.l^{-1}$, 131 $g.l^{-1}$, and 114 $g.l^{-1}$, respectively, with data not reported for the fourth group. At six months, the mean values were 114 $g.l^{-1}$, 118 $g.l^{-1}$, and 118 $g.l^{-1}$ respectively, with data not reported for the fourth group. At term, the mean values were 109 $g.l^{-1}$, 127 $g.l^{-1}$, and 124 $g.l^{-1}$, and 123 $g.l^{-1}$, respectively. Measures of spread were not reported. There was a greater increase in haemoglobin mass in women receiving iron supplementation of 32%, compared with 15% in controls. The second of these studies measured haemoglobin values during the first trimester and at term, and women were divided into three groups (control; oral iron supplementation; i.v. iron supplementation) [22]. The mean haemoglobin during the first trimester was 121 $g.l^{-1}$ before iron supplementation. At term, haemoglobin values were 114 $g.l^{-1}$, 120 $g.l^{-1}$, and 121 $g.l^{-1}$ in each group, respectively.

Updated definition of anaemia

More recently, the use of a lower haemoglobin threshold to define anaemia in the female population has been challenged. A lower haemoglobin threshold during pregnancy has significant implications for diagnosis and management. A 2017 international consensus statement on peri-operative anaemia recommended that patients undergoing major surgery, including the obstetric population, undergo investigation and treatment for anaemia with the aim of achieving a haemoglobin level > 130 $g.l^{-1}$, regardless of sex [26]. Similarly, Butcher et al. recommend a haemoglobin threshold < 130 $g.l^{-1}$ to trigger investigation and optimisation pre-operatively, regardless of sex, although they do not discuss the implications of redefining anaemia in the obstetric population [21].

Evidence behind currently accepted reference ranges

Reference values to define anaemia during pregnancy should be based on haemoglobin values in healthy women without pre-existing haematinic deficiencies [18].

There is a high prevalence of anaemia in otherwise healthy menstruating women of child-bearing age. For example, almost 29% of non-pregnant women are anaemic globally [3], and 45% of women of reproductive age have low or absent iron stores [17]. Cohort studies not screening for anaemia will therefore include iron deficient women. Based on a small sample of healthy women who underwent bone marrow aspirate during pregnancy, 29% of women had depleted iron stores early in pregnancy [23], Similarly, 18% of pregnant women had absent estimated total body iron stores using the serum ferritin and soluble transferrin receptor ratios [27].

Normal pregnancy and childbirth are associated with increased iron requirements to facilitate haematopoiesis (570 mg), fetal iron stores (300 mg), and iron loss related to delivery blood-loss (280 mg) [23]. Only 15-20% of women have adequate iron stores to meet the net iron requirements of pregnancy (~580 mg) [17, 28]. Without iron supplementation, 84% of healthy women have absent bone marrow iron stores at term pregnancy, and this persists for up to six months postpartum in 75% of women [23]. Any laboratory reference range that is calculated from an unselected sample of women will thus include a significant proportion of anaemic and/or iron deficient women, and result in biased ‘normal’ reference ranges.

The National Health and Nutrition Examination Survey recruited 1171 pregnant women aged 15-39 years old between 1999-2006 [27]. The mean (95%CI) haemoglobin concentration was 124.6 (123.3 - 125.9) $g.l^{-1}$. However, the gestation at which haemoglobin was measured was not specified, and 18% of pregnant women had absent total body iron stores. This large cohort study suggests that the reference range for pregnant women is significantly higher than the haemoglobin threshold of 110 $g.l^{-1}$ defined by the World Health Organisation and others. However, this may still underestimate ‘normal’ haemoglobin values during pregnancy, due to the inclusion of women with pre-existing haematinic deficiencies, most commonly iron deficiency.

While it is difficult to recruit women who are known to be iron-replete prior to pregnancy, several cohort studies have measured haemoglobin trends in otherwise healthy women receiving iron supplementation (Table 2). The Centre for Disease Control published aggregate data from four studies investigating the effect of varying doses of oral iron supplementation during pregnancy during the 1970s and 1980s [29]. Sjostedt et al. studied 300 healthy pregnant Finnish women receiving 100 - 200 mg oral iron supplementation commenced at between 12 - 16 weeks gestation [30]. Haemoglobin values did not differ between groups receiving different oral iron doses, reaching a nadir of 116 - 117 $g.l^{-1}$ during the second trimester, and then rising to 128 - 129 $g.l^{-1}$ at term.

The three other studies were small randomised trials investigating the effect of oral iron supplementation during pregnancy on haematological parameters. Taylor et al. randomly allocated 45 healthy pregnant women in the UK to oral iron and folate supplementation (n=21) or control (n=24) [31]. At term, women receiving oral iron supplementation had a trend towards higher serum ferritin (17 μmol.l^{-1} vs. 6 μmol.l^{-1}) and haemoglobin levels (126.8 vs. 111.5 g.l^{-1}), although these differences were not compared for statistical significance. Svanberg et al. randomly allocated 60 healthy Swedish women in their first pregnancy with a baseline haemoglobin value of ≥ 120 g.l^{-1} to receive either oral iron (n=24) or placebo (n=26) (10 women who discontinued the study were excluded from analysis) [32]. Both groups showed a decline in haemoglobin values up to 28 weeks gestation, reaching a nadir of 116 g.l^{-1} and 113 g.l^{-1}, respectively. Haemoglobin values in the iron-supplemented group then increased to 124 g.l^{-1} at 35 weeks, while in the placebo group haemoglobin values plateaued at 114 g.l^{-1}. Puolakka et al. randomly allocated 32 healthy Finnish women with baseline haemoglobin values of ≥110 g.l^{-1} to received either oral iron (n=16) or placebo (n=16) in early pregnancy [33]. Similarly, haemoglobin values reached a nadir at 28 weeks gestation (115 g.l^{-1} vs. 109 g.l^{-1}, respectively), and mean haemoglobin values at term were higher in women receiving iron supplementation (132 g.l^{-1} vs. 111 g.l^{-1}). At two months postpartum, iron stores were absent in 80% of women who did not receive iron supplementation, compared with 7% in women randomly allocated to oral iron. Expanding upon these small studies, Milman et al. randomly allocated 206 healthy Danish women to receive oral iron (n=99) or placebo (n=107) [34]. The daily oral iron dose used in this study of 66 mg was slightly lower than that used in previous investigations. In the placebo group, haemoglobin values reached a nadir of 114 g.l-1 at 31-34 weeks gestation, whereas in the iron-treated group the nadir haemoglobin was 118 g.l-1 at 23-26 weeks. Similar to the findings from earlier smaller randomised trials, the mean haemoglobin at term was also higher in iron-treated women (129 g.l^{-1} vs. 119 g.l^{-1}; $p < 0.0001$). Following on from this earlier work, in 2007, Milman et al. studied 434 healthy Danish women receiving varying daily doses of between 20-80 mg oral iron supplementation during pregnancy [35]. Haemoglobin values did not differ significantly between groups receiving different oral iron doses, although serum ferritin was significantly lower in those receiving the lower 20mg dose. In 2010, Klajnbard et al. studied 391 healthy Dutch and Danish women with uncomplicated pregnancies receiving 50-70 mg oral iron daily [36]. Haemoglobin reference ranges at term were similar between these two later studies, at 108 – 140 $g.l^{-1}$, and 110 – 147 $g.l^{-1}$, respectively [35, 36].

Discussion

Re-defining anaemia

There is no physiological reason why normal haemoglobin reference values should differ between men and non-pregnant women [37]. In fact, a lower haemoglobin value has elevated significance peri-operatively in women due to their lower total red cell mass, and lower total body iron stores compared with men; thus, the same total blood loss will generally have a proportionally greater effect in women [21]. Even mild anaemia is associated with adverse peri-operative outcomes in women as well as men [38].

In the context of redefining anaemia in non-pregnant women, we should also focus on empirically re-examining normal haemoglobin values during pregnancy. The thresholds and targets (which may differ from the lower reference range) during pregnancy to optimise outcomes are currently unknown. In particular, given that caesarean section is open abdominal surgery with a moderate bleeding risk, should we redefine pre-operative haemoglobin targets in women planned to have caesarean section surgery, similar to recommendations for non-pregnant women undergoing elective surgery with moderate-to-high bleeding risk [26]?

Contemporary data on haemoglobin trends in pregnant women receiving iron supplementation suggest than mean values during pregnancy are significantly higher than the traditional WHO thresholds, and that reference ranges at term are close to those of non-pregnant women. While the studies included in this review recruited healthy women who commenced oral iron supplementation during pregnancy, these studies were likely to have included women who were anaemic prior to pregnancy as part of their ‘normal’ sample, given the high baseline prevalence of anaemia and iron deficiency in otherwise healthy women. In several of these studies, a significant proportion of women still had low ferritin values indicating iron deficiency despite oral iron supplementation [31, 35], and i.v. iron was not used to treat women with persistent iron deficiency. Intravenous iron replacement results in higher rates of anaemia correction and higher final haemoglobin values than oral replacement alone [18].

Haemoglobin values decrease during pregnancy due to ‘dilutional anaemia’ resulting from a proportionately greater rise in plasma volume than red blood cell mass [39]. During the second trimester, haemoglobin values fall by approximately 5 $g.l^{-1}$ [19]. However, this effect decreases towards term, and the degree of dilutional anaemia observed is attenuated with iron supplementation [34, 40]. In the context of the known high prevalence of iron deficiency in women of childbearing age, plus the elevated iron requirements during pregnancy, there is the potential that iron deficiency-limited haematopoiesis contributes to the ‘dilutional anaemia’. The degree of dilutional anaemia that occurs during pregnancy in normal, iron-replete, women is unclear.

Patient blood management in the obstetric population

Pregnant patients are vulnerable to haemorrhage around the time of delivery. Postpartum haemorrhage may occur rapidly and unpredictably, and the principles of optimising haemoglobin stores prior to surgery with intermediate-to-major blood loss risk should also apply to pregnancy and delivery [41]. This is reflected in the publication of several recent obstetric-specific patient blood management guidelines [18, 42]. In Australia and New Zealand and the UK, guidelines recommend measurement of haemoglobin at 28 weeks gestation [43, 44]. This time-point represents an opportunity to investigate and intervene to correct anaemia prior to delivery.

Effective implementation of patient blood management pathways into routine obstetric care can reduce antenatal anaemia and reduce peripartum transfusion rates [45]. This is particularly important when caesarean section is planned because of the higher average blood loss compared with vaginal delivery [46]. Caesarean section results in calculated blood loss ranging from 440 ml [47] to 800 ml [46] – this equates to surgery with moderate-to-high blood loss (> 500 ml) as defined by recent international consensus guidelines [26]. Caesarean delivery is associated with elevated risk of transfusion compared with non-operative vaginal delivery [48], with transfusion rates of 2% to 4% [49].

While the physiological changes associated with pregnancy result in an increased red cell mass, iron stores may easily become depleted due to the elevated physiological demands of pregnancy and blood loss during delivery [17]. By the time anaemia develops, iron deficiency is severe, and total body iron stores are likely to be insufficient to meet the ongoing elevated demands of pregnancy and lactation. Worldwide, approximately 50% of anaemia in pregnancy is responsive to iron supplementation, and this may rise to 70% in high-income countries [3]. Multiparous women may particularly benefit from pre-operative haematinic optimisation. A higher parity is associated with reduced total body iron stores [27], and a history of repeated caesarean section is associated with long-term anaemia [50].

Iron supplementation is a low-cost and high-value intervention. A 2015 Cochrane review found that oral iron supplementation improved haemoglobin by 8.9 $g.l^{-1}$ at term, compared with no supplementation [40]. This difference persisted at six weeks postpartum, with a mean difference of 7.6 $g.l^{-1}$. Iron supplementation during pregnancy reduced the risk of maternal anaemia (haemoglobin <110 $g.l^{-1}$) at term from 36% to 13% (relative risk 0.30; 95%CI 0.19 - 0.46), and reduced maternal iron deficiency at term (relative risk 0.43; 95%CI

0.27 - 0.66) [40]. There was also a trend towards reduced rates of low birthweight and preterm birth, although the confidence intervals for these estimates were wide and were not statistically significant [40].

While oral iron is generally recommended as a first-line strategy for treating iron deficiency anaemia during pregnancy, its efficacy is limited by gastrointestinal adverse effects, which may be particularly problematic in the pregnant population [51]. Adequate absorption is indicated by a rise in haemoglobin concentration of ≥ 10 $g.l^{-1}$ after a two week trial of oral iron [51]. Intravenous iron is recommended after the first trimester for pregnant women with hyperemesis gravidarum, gastrointestinal pathology limiting iron absorption (e.g. inflammatory bowel disease, previous bypass surgery), or women unable to tolerate a trial of oral iron [51]. Two small studies have investigated the efficacy of oral compared with i.v. iron for management of postpartum anaemia. Intravenous iron is efficacious in increasing haemoglobin level postpartum, but the findings regarding oral iron are conflicting; one study found no effect and the other study found an increase in haemoglobin values similar to that of i.v. iron [52, 53]. These studies were too small to evaluate safety concerns regarding postpartum iron administration. A large multicentre randomised controlled trial is underway investigating the efficacy of i.v. iron compared with packed red blood cell transfusion for women who are stable (i.e. no ongoing bleeding) after postpartum haemorrhage who have symptomatic anaemia with haemoglobin values between 55-80 $g.l^{-1}$ [54].

While iron supplementation may improve haemoglobin values, the optimal haemoglobin target during pregnancy is unknown. There is limited retrospective cohort study data associating higher haemoglobin values at booking and during early in pregnancy with adverse pregnancy outcomes. For example, booking haemoglobin concentrations > 139 $g.l^{-1}$ have been associated with pregnancy-induced hypertension, gestation diabetes, and low birthweight [55]; and haemoglobin values > 133 $g.l^{-1}$ early in pregnancy have been associated with hypertension during pregnancy, low birthweight, and preterm delivery [56]. A high maternal haemoglobin concentration of ≥ 140 $g.l^{-1}$ at the end of second trimester has been associated with stillbirth [57]. The timing of haemoglobin measurement and outcome may be important, with one large cohort study suggesting that the nadir haemoglobin value has a U-shaped association with perinatal outcomes [58].

It is unclear whether iron supplementation to achieve higher haemoglobin values is associated with harm in certain populations, and whether oral iron and i.v. iron carry different risk profiles. Particular concerns include infection risk, generation of reactive oxygen species, and adverse reactions related to i.v. iron preparations. A large Cochrane review of oral iron supplementation during pregnancy did not demonstrate any increased risk of adverse outcomes, and there was no evidence of increased risk of placental malaria, although only two studies addressed this outcome [40]. Intravenous iron during pregnancy is associated with adverse reactions in 2.2 - 6.7%, although the definitions used are highly variable [59]. Concerns about overcorrection of haemoglobin values were investigated in a retrospective study of pregnant women receiving iron infusions during pregnancy for both non-anaemic iron deficiency and iron deficiency anaemia [60]; haemoglobin values measured at three and six weeks post-infusion did not demonstrate evidence of haemoconcentration.

Conclusion

Caesarean section has moderate-to-high blood-loss risk. Perioperative anaemia in women undergoing caesarean section represents an important global health issue. This is likely to be a more significant problem in low- and middle-income countries where caesarean section accounts for almost one-third of all operations performed, and there is a higher prevalence of anaemia compounded by reduced access to interventions such as iron infusions and blood transfusions.

Future research should focus on prospectively defining normal haemoglobin trends during pregnancy using a cohort of non-iron deficient, non-anaemic women early in pregnancy. In addition to defining true normal reference ranges, the optimal haemoglobin values during pregnancy to reduce maternal and neonatal morbidity and mortality are unknown. This is important in order to guide optimal treatment end-points when implementing patient blood management strategies in the obstetric population. Future studies investigating haemoglobin optimisation during pregnancy should investigate the impact of both anaemia optimisation, and the impact of treating non-anaemic iron deficiency, on patient-centred outcomes such as quality of life in addition to maternal and neonatal morbidity outcomes. Finally, concerns about potential perinatal harm related to higher haemoglobin values during pregnancy require further investigation.

Competing Interests

No external funding and no competing interests declared.

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Table 1 Definitions of anaemia during pregnancy in guidelines.

Reference	*Definition of anaemia*	*Comment*
World Health Organization (WHO), 2011 [19]	Hb < 110 g.l^{-1}	The WHO guidelines do not differentiate haemoglobin cut-offs during different trimesters, but recognise that Hb values may fall by 5 g.l^{-1} during the second trimester.
American College of Obstetricians and Gynaecologists, 2008 [6]	First trimester: Hb <110 g.l^{-1} or Hct < 0.33 Second trimester: Hb <105 g.l^{-1} or Hct < 0.32 Third trimester: Hb <110 g.l^{-1} or Hct < 0.33	Based on data from the Centers for Disease Control and Prevention (see Table 2)
British Committee for Standards in Haematology, 2012 [61]	First trimester: Hb < 110 g.l^{-1} Second trimester: Hb < 105 g.l^{-1} Post-partum: Hb < 100 g.l^{-1}	'In view of the relative plasma expansion being particularly marked in the second trimester, it would seem reasonable to take 105 g.l^{-1} as the cut-off from 12 weeks'.

Australian Patient Blood Management Guideline, 2015 [42]	'There is no agreed normal range for haemoglobin values in pregnant women in Australia… In light of evidence that higher Hb levels may also be associated with adverse pregnancy outcomes, it would seem reasonable to assume that normal pregnancy haemoglobin levels lie between 103 and 146 g.l^{-1}.'

Hb, haemoglobin; Hct, haematocrit

Table 2 Haemoglobin trends during pregnancy in women receiving routine iron supplementation.

Reference	***Study participants***	***Haemoglobin values (g.l^{-1})***	***Comments***
Centre for Disease Control, 1989 [29]	Combined data from four European studies of healthy pregnant women receiving iron supplementation: N=21; 325 mg iron.day.$^{-1}$ [31] N=16; 200 mg iron.day.$^{-1}$ [33] N=24; 200 mg iron.day.$^{-1}$ [32] N=300; 100-200 mg iron.day.$^{-1}$ [30]	**Mean haemoglobin *(5th percentile)*** 12 weeks: 122 (110) 16 weeks: 118 (106) 20 weeks: 116 (105) 24 weeks: 116 (105) 28 weeks: 118 (107) 32 weeks: 121 (110)	Median serum ferritin at 40 weeks gestation was 17 μmol.l^{-1} [31].

		36 weeks: 125 (114) 40 weeks: 129 (119)	
Milman, 2000 [34]	N=99 healthy Danish women Normal singleton pregnancy	**Mean haemoglobin *(+/- 5th to 95th percentile)*** 9-13 weeks: 125.4 (111.2-141.8) 14-18 weeks: 121.9 (108.8-136.2) 19-22 weeks: 119.6 (106.4-137.0) 23-26 weeks: 118.3 (103.1-137.0) 27-30 weeks: 119.1 (104.7-132.1) 31-34 weeks: 120.9 (104.7-138.6) 35-38 weeks: 124.5 (109.6-138.6) 39-43 weeks: 128.9 (115.3-141.8)	Ferrous iron supplementation 66 mg/day. Ferritin values not reported.

Milman, 2007 [35]	N=434 healthy Danish women Normal singleton pregnancy ≥ 37 weeks duration; newborn weight > 2500 g	***Mean haemoglobin (+/- 1.96 x SD)*** 18 weeks: 117.6 (104.7-132.1) 32 weeks: 117.6 (103.1-133.8) 39 weeks: 124.1 (108.0-140.2) 8 weeks postpartum: 132.1 (117.6-146.6)	Variable dose ferrous iron supplementation after 18 weeks (20-80 $mg.day.^{-1}$). Mean serum ferritin was 21 $\mu mol.l^{-1}$ at 39 weeks gestation.
Klajnbard, 2010 [36]	N=391 healthy Caucasian women Uncomplicated pregnancy and vaginal delivery	**2.5^{th} to 97.5^{th} percentile reference range:** 13-20 weeks: 113-147 21-28 weeks: 111-143 29-34 weeks: 109-145 35-42 weeks: 110-147	Variable dose ferrous iron supplementation (50-70 mg/day). Ferritin values not measured.