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## Review article

## Implementation of early management of iron deficiency in pregnancy during the SARS-CoV-2 pandemic



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## ABSTRACT

Iron deficiency is the commonest cause for anaemia worldwide making it a formidable issue particularly during pregnancy because of increased iron demands. This study looked at establishing a lower limit of normal for haemoglobin concentration (Hb) in our population and to proactively address potentially symptomatic iron deficiency during the current SARS-CoV-2 pandemic. The lower limit of normal for Hb in our 1715 first trimester pregnancy cohort was 116 g/L. This is in contrast with guidance suggesting Hb levels down to 110 g/L are normal. In addition there was evidence of limited testing performed to look for iron deficiency with only 18 % having a serum ferritin checked. Most anaemia was normocytic suggesting that microcytosis is only a late marker of iron deficiency lacking sensitivity. A strategy to avoid hospital contact during the COVID-19 pandemic is proposed.

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## Contents

Authors contribution .....	61
Ethical approval .....	62
Source of funding .....	62
References .....	62

A recent study observed that 42 % of unselected non-anaemic first trimester women were iron deficient using standard cut-offs of transferrin saturation and serum ferritin [1]. Screening for iron deficiency by serum ferritin testing is however not routinely advocated in unselected pregnancies in the United States and UK [2,3]. Our study assessed the prevalence of anaemia in a mixed metropolitan and urban setting in the UK during the first trimester of pregnancy to draw conclusions around managing iron deficiency.

The provision of healthcare has to adapt to new and innovative ways of delivering evidence-based good care in view of the SARS-CoV-2 pandemic. One area where this could be realised is in the management of iron deficiency particularly in pregnancy. There are excellent UK-based guidelines which need not be replaced but rather adapted in the light of current pandemic [3].

Iron deficiency is common, particularly in women of child bearing age predominantly caused by menstrual blood loss and poor oral intake of iron-rich foods [4]. This issue becomes more pronounced during pregnancy with historically around a quarter of UK pregnancies associated with anaemia [5]. The international definition of anaemia during pregnancy is defined as: haemoglobin concentration (Hb) <110 g/L in first trimester and <105 g/L in second and third trimesters and <100 g/L postpartum. It is acknowledged that further work is required to validate these cut-off values [3].

Worldwide the commonest cause of anaemia is iron deficiency. The pathognomonic hallmark is a low serum ferritin, usually <15mcg/L. In addition a serum ferritin of <30mcg/L indicates low iron stores [6]. Around 800–850 mg of body iron is required for foetal development. Women who are already iron deficient and anaemic in early pregnancy will further deplete remaining iron stores and become increasingly anaemic. In those women that are not anaemic but iron deficient further reduction of iron stores will potentially lead to anaemia. Even those women with normal Hb and iron stores run the risk of iron deficiency later in pregnancy.

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UK guidelines recommend the use of Intravenous iron in pregnancy when diagnosed with iron deficiency after 34 weeks gestation and Hb < 100 g/L or when there is intolerance to, or lack of response to oral iron [3]. In contrast, in the United States intravenous iron is more favoured than oral for use in second and third trimester iron deficiency anaemia using the evidence that it improves Hb more rapidly [7–9]. Untreated anaemia at the time of delivery carries a risk of requiring blood transfusion because of further demands such as from blood loss for example. Both intravenous iron and blood transfusion are given within a healthcare setting. In light of the SARS-CoV-2 pandemic this should be avoided if at all possible since it involves therapy within a healthcare setting. Under the current pandemic circumstances a more proactive approach is required.

We studied 1715 pregnancies during the 5 months of November and December 2018, March, April and May 2019. We looked at Haemoglobin (Hb) estimation at those booking prior to 13 weeks gestation. Our population has a very low carriage of haemoglobinopathy.

All full blood counts and serum ferritin assays were assessed on an Abbott Alinity hq and Architect analysers respectively.

One hundred and forty eight (8.6 %) women had Hb concentrations below 120 g/L with 25 (1.5 %) below 110 g/L. Median Hb was 132 g/L; minimum 90 g/L, maximum of 160 g/L. The 95 % lower limit confidence level was 116 g/L.

Guidance suggests that Hb values > 110 g/L are adequate in the first trimester [3]. Our data reports that the lower limit of normal in our cohort was 116 g/L. Hypothesising that the first trimester is not physiologically dissimilar to a pre-pregnant state we chose Hb < 120 g/L as our defining threshold for anaemia. Similar challenges of the definition of peri-operative anaemia in pregnant women also suggest targeting a higher Hb may be more appropriate [10].

We further assessed the outcome in pregnancies in November, December and March in those pregnancies where the booking Hb at less than 13 weeks gestation was below 120 g/L. Ninety of 1001 women during these months had Hb < 120 g/L giving a 9% incidence of anaemia by our definition. Of 81 evaluable cases Hb fell from booking to 28 week gestation by a median of 8 g/L (range +39 to –27 g/L) with 33 (41 %) dropping by 10 g/L or more. No data on iron supplementation was collected.

Of the women with Hb < 120 g/L the average MCV and MCH were 87.5 fL and 29 pg respectively. Of these 17 % had an MCV < 80 fL, and 27 % had an MCH < 28 pg. Most therefore had normal red cell indices.

In the 3 months assessed only 16 women (18 %) had their serum ferritin (SF) checked with a median value of 6.5 mcg/L (range 3–45). Thirteen of 16 women had a serum ferritin below 30 mcg/L. Although only a few cases, we saw an average fall in Hb of 3.5 g/L (median rise of 2 g/L, range –22 g/L to +15 g/L). One assumes that in those pregnancies found to have a low serum ferritin, iron supplementation was given. Of note the serum ferritin was only requested at booking if the MCH was found to be < 27 pg (in all but one patient who had a normal MCH) as part of the United Kingdom National Sickle cell and Thalassaemia screening programme.

Only 4 pregnancies were associated with blood transfusions.

Whilst we cannot show that low Hb at booking predicts for a transfusion requirement we can show that the incidence of anaemia in our first trimester population is around 9%. We suggest that Hb values below 120 g/L in the first trimester are not physiologically acceptable. For our cohort there is a fall in Hb between booking and 28 weeks of 8 g/L which would generally be the accepted norm. The fall is less in the small number of cases that were shown to have low serum ferritin and therefore likely treated.

In the light of the current SARS-CoV-2 pandemic our study suggests that for all women at booking with Hb less than 120 g/L we should offer low dose iron supplementation even if they have a normal serum ferritin. If the serum ferritin is below 30 mcg/L irrespective of the Hb iron should also be offered. This means that at least 9% of women will be given iron therapy at booking on the basis of their Hb alone. Using a low MCV or MCH to decide if serum ferritin testing is required seems to be wholly inappropriate since both MCV and MCH are in the majority normal in pregnant women at booking even with iron deficiency.

What do we suggest?

- 1) Universal screening for iron deficiency in the first trimester and treating cases with oral iron. We suggest that all women at booking who have Hb < 120 g/L or have low iron stores (serum ferritin < 30 mcg/L) at booking start low dose oral iron.

Rationale: Most anaemia in pregnancy is due to iron deficiency and there will always be more demand on iron stores as pregnancy progresses. Pairing the full blood count with a serum ferritin avoids the risk of iron supplementation in persons with potential iron overload indicated by a raised serum ferritin. Although tolerability and compliance are potential issues, using a low dose is potentially better tolerated [11]. Starting early improves the chances of having sufficient stores later in pregnancy and attempts to reduce the need for intravenous iron. Low dose oral iron is typically ferrous sulphate 200 mg alternate daily.

- 2) Once started on oral iron there is no requirement to monitor the effect until repeat testing at 28 weeks occurs unless the booking Hb is less than 100 g/L

Rationale: Whilst this seems at variance with standard practice where one would look to always gauge response after 2–4 weeks, the intention is to limit contact with the healthcare system as much as possible. Concerns around not monitoring could be met by telephone contact about symptoms and compliance or performing a full blood count and reticulocyte count on those felt to be at greater risk such as when the booking Hb is less than 100 g/L.

- 3) Women with persistent iron deficiency despite oral iron or intolerance to oral iron should be considered for intravenous iron at the earliest opportunity. Iron deficiency at or beyond 34 weeks and Hb < 70 g/L would be a strong indication for intravenous iron regardless of prior oral iron intake [3]. It should be considered for similar cases with Hb < 100 g/L but alternatives should be considered if symptoms allow for those persons iron deficient with Hb > 100 g/L.

Rationale: One major aim is to reduce the need for intravenous iron for only those where all other choices have been explored. Alternative iron preparations may be considered, but one must recognise that there is no credible evidence that one oral formulation is better than any other. Ultimately intravenous iron may be the only option. Initial iron therapy orally is appropriate but recourse to intravenous iron is advised if severely iron deficient anaemic (Hb < 70 g/L) or there is insufficient time for oral iron to work or be compliant with.

#### Authors contribution

All authors contributed equally to the final manuscript. TS, JL, and DWT performed the data analysis. DWT, DT-J and JL formulated the study concept. All authors (TS, JL, DT-J and DWT) agreed the final manuscript prior to submission.

## Ethical approval

Ethics approval was not required since the study was a retrospective analysis of data already collected and used for the purposes of the UK National Antenatal Haemoglobinopathy screening programme. No additional blood samples were required for the study.

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## Declaration of Competing Interest

We, the authors, Disclosure no conflict of interests. This includes: relevant financial, personal, political, intellectual or religious interests.

## References

- [1] Auerbach Michael, Abernathy Jessica, Juul Sandra, Short Vanessa, Dernan Richard. Prevalence of iron deficiency in first trimester, nonanemic pregnant women. *J Matern Fetal Neonatal Med* 2019;1–4 Jun 3.
- [2] Sui Albert, on behalf of the U.S. Preventative Services Task Force. Screening for iron deficiency anemia and iron supplementation in pregnant women to improve maternal health and birth outcomes: U.S. preventative services task force recommendation statement. *Ann Intern Med* 2015;163(7):529–36.
- [3] Pavord Sue, Daru Jan, Prasannan Nita, Robinson Susan, Stanworth Simon, Girling Joanna, et al. UK guidelines on the management of iron deficiency in pregnancy. *Br J Haematol* 2020;188:819–30.
- [4] WHO Guideline: daily iron supplementation in adult women and adolescent girls. Geneva: World Health Organization; 2016.
- [5] Barroso F, Allard S, Kahan BC, Barroso F, Allard S, Kahan BC, et al. Prevalence of maternal anaemia and its predictors: a multi-centre study. *Eur J Obstet Gynecol Reprod Biol* 2011;159:99–105.
- [6] Van Den Broek NR, Letsky EA, White SA, Shenkin A. Iron status in pregnant women: which measurements are valid? *Br J Haematol* 1998;103:817–24.
- [7] Al RA, Unlubilgin E, Kandemir O, Yalvac S, Cakir L, Haberal A. Intravenous versus oral iron for treatment of anemia in pregnancy: a randomised trial. *Obstet Gynecol* 2005;106(6):1335–40.
- [8] Shepshelovich D, Rozen-Zvi B, Avni T, Gafter U, Gafter-Gvili A. Intravenous versus oral iron supplementation for the treatment of anemia in CKD: an updated systematic review and meta-analysis. *Am J Kidney Dis* 2016;68(5):677–90.
- [9] Achebe Maureen M, Gafter-Gvili Anat. How I treat anemia in pregnancy: iron, cobalamin, and folate. *Blood* 2017;129(8):940–9.
- [10] Furguson MT, Dennis AT. Defining peri-operative anaemia in pregnant women -challenging the status quo. *Anaesthesia* 2019;74:237–45.
- [11] Moretti Diego, Goede Jeroen S, Zeder Christophe, Jiskra Markus, Chatzinakou Vaiya, Tjalsma Harold, Melse-Boonstra Alida, Brittenham Gary, Swinkels Dorine W, Zimmermann Michael B. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. *Blood* 2015;126(17):1981–9.