A cross-sectional study in non-anaemic pregnant women in Turkey to assess necessity of iron supplementation

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Abstract

Background: Iron deficiency is the most common cause of anaemia in pregnancy. Guidelines recommend different threshold values for iron supplementation.

Aims: To determine trimester-specific reference ranges for haematological values (haemoglobin, hematocrit and ferritin) in healthy pregnant women who have not used any iron supplementation during pregnancy to guide future iron treatment.

Methods: A prospective cross-sectional study was carried out on 168 pregnant women aged 18–45 years, with singleton pregnancies in the first trimester, Hb ≥ 11 g/dL and ferritin ≥ 12 µg/L, and not using iron supplementation. Multiple pregnancies, pregnancies with obstetric complications and smokers were excluded from the study. Mean haemoglobin (Hb) and ferritin values, trimester-specific reference ranges and percentile values of Hb and ferritin were determined for each trimester. The normality of the variables was tested using the Kolmogorov–Smirnov test.

Results: Mean Hb decreased significantly between trimesters from 12.6 to 11.9 and then 11.5 g/dL. In addition, Hb, hematocrit and ferritin decreased significantly from the first to the second trimester ($P < 0.001$ for all) but stayed comparable between the second and third trimesters ($P = 0.246$, $P = 0.575$, $P = 0.408$, respectively). The lower reference value for Hb was calculated as 10.67, 10.08 and 9.18 g/dL for 10–14, 20–24 and 30–34 gestational weeks respectively.

Conclusion: This pioneer study allows us to understand that iron supplementation may not be needed as any decrease is due to physiological haemodilution. These results may prevent unnecessary iron prescription during pregnancy.

Keywords: iron deficiency anaemia, antenatal care, dietary supplementation, pregnancy, haemoglobin threshold

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Introduction

Anaemia is the most common haematological problem in pregnancy (*1*) and iron deficiency is the most common cause (*2*). Pregnancy increases iron demand, as it affects both maternal and fetal health. On the other hand, iron antagonizes the intestinal absorption of other essential divalent cations (zinc, copper, chromium, molybdenum, manganese and magnesium) and increases oxidative stress in both the mother and the fetus. There is, therefore, a dilemma when using iron supplements for purely physiologic anaemia as it risks loading an excessive iron burden on pregnant women.

Iron supplementation is routinely recommended by the World Health Organization (WHO) during pregnancy to prevent anaemia (*3*). The International Federation of Gynecology and Obstetrics also recommends routine iron supplementation in pregnancy (*4*). However, in a systematic review in 2012, it was shown that increases in haematological markers did not result in any clinical improvement to maternal or infant health (*5*). In addition, in the same review, when comparing targeted supplementation and routine supplementation there were no statistical differences between fetal and maternal outcomes. In another systematic review in 2019, no association was found between iron during pregnancy and neurodevelopment of offspring (*6*). In the United Kingdom (UK), routine iron supplementation is not recommended (*7*). It is believed that iron supplementation should be given when there is anaemia present (Hb < 11 g/dL in the first trimester and < 10.5 g/dL in the second and third trimesters) or in non-anaemic women identified to be at risk of iron deficiency and serum ferritin levels < 30 µg/L (*7–9*). However, according to the WHO, only moderate (Hb < 9 g/dL) or severe anaemia (*10*) in pregnancy was associated with an increased risk of adverse effects on both mother and fetus (*3,11*). Besides, unselected screening for serum ferritin and is not recommended by the International Federation of Gynecology and Obstetrics guideline (*4*).

In this study, the primary objective was to determine the specific reference ranges of haematological values [Hb, hematocrit (Hct) and ferritin] in each trimester to guide future iron treatment. We used reference ranges from healthy Turkish women who did not use iron supplementation during pregnancy.

Methods

Study population

This prospective cross-sectional study was conducted in the Department of Obstetrics and Gynaecology at the Faculty of Medicine, Gazi University, Ankara, Turkey between January 2016 and May 2017. All healthy pregnant women satisfying the following inclusion criteria were questioned: aged 18–45 years, singleton pregnancy in the first trimester, Hb ≥ 11 g/dL and ferritin ≥ 12 µg/L (12) (i.e. we included only healthy pregnant women, excluding anaemic patients at the beginning), not using iron supplementation. Multiple pregnancies, pregnancies with obstetric complications such as hypertensive disorder and gestational diabetes, and those with maternal diseases or who smoked tobacco were excluded from the study. Pregnant women who had moderate or severe iron deficiency anaemia (Hb < 9 g/dL) were also excluded from the study and started on iron supplementation during follow-ups. All the patients in the study received the same dietary information to maximize iron intake and absorption (Table 1), and did not use iron supplementation during pregnancy.

Institutional review board approval was obtained from our university (Approval No: E-15-558) and all participants gave informed consent before the study began.

Sample size

In our clinic, approximately 90–100 pregnant patients are examined each day. Sample size was calculated by estimating 14 000 patients would be examined in 7 months. According to the study by Barroso et al., anaemia prevalence was 7% in the first trimester and 12.5% in the third trimester (13). From these findings, accepting a total of 14 000 pregnant patients and anaemia prevalence as 7% in the first trimester, with 95% confidence interval, 5% type-1 error and 80% power, we calculated the sample size as 100 pregnant women. In the third trimester with anaemia prevalence at 12.5%, with 95% confidence interval, 5% type-1 error and 80% power, sample size was calculated as 167 pregnant patients. Sample size was calculated with *OpEnepi* online calculation program, using the formula:

$$n = [\text{DEFF} \times \text{Np}(1-\text{p})]/[(\text{d}^2/\text{Z}^2_{1-\text{a}/2}{}^*(\text{N}-1)+\text{p} \times (1-\text{p})].$$

According to our study protocol, pregnancies in which moderate or severe iron deficiency anaemia (Hb < 9 g/dL) developed would be excluded from the study.

Table 1 Dietary information given to Turkish pregnant women aimed at maximizing iron supplementation

Foods rich in iron	Foods to avoid
Spinach	Tea and coffee
Collard greens	Milk
Broccoli	Whole-grain cereals
Pumpkin seeds	Foods contain tannins, e.g. grapes, corn and sorghum
Pistachios	Foods that contain oxalic acid, e.g. peanuts, parsley and chocolate
Pine nuts	Foods rich in gluten, e.g. pasta and other products made with wheat, barley, rye or oats
Beef	
Lamb	
Sardines	
Tuna	
Salmon	
Halibut	
Perch	
Haddock	
Yogurt	
Cheese	
Chickpeas	
Soybeans	
Orange juice	
Rice	

Blood sampling

Blood samples were collected in the standard fashion, initially at 10–14 gestational weeks then at 20–24 gestational weeks and finally at 30–34 gestational weeks. Blood Hb, Hct and ferritin were analysed: blood was collected into a K2EDTA tube (VSK2E40, Turkey) for a full blood count; Hb was measured on the Cell-Dyn 3500 (Abbott Diagnostics) (Hb in mmol/L 16.115 ¼ Hb in g/L; Hb in g/L 0.062054 ¼ Hb in mmol/L); serum ferritin was measured by microparticle enzyme immunoassay technology (AxSYM Ferritin assay, Abbott Diagnostics).

Statistical analysis

Statistical analyses were performed using *SPSS*, version 21.0, and $P < 0.05$ was defined as statistically significant. Continuous variables are presented as mean and by standard deviation (SD) and median with maximum–minimum. The normality of the variables was tested with the Kolmogorov–Smirnov test. For statistical analysis Friedman's 2-way analysis and Wilcoxon signed rank tests were used. To determine trimester-specific reference ranges for Hb, we calculated mean and 1.96 SD for each trimester. The 2.5th, 5th, 10th, 90th, 95th and 97.5th percentile values of Hb and ferritin were also determined for each trimester.

Results

Of the 221 pregnant women who were invited to participate in the study, 168 were included in the final evaluation in accordance with the inclusion and exclusion criteria. Mean age was 32.6 (SD 7.6) years (Table 2). Owing to moderate anaemia development and missed follow-ups, a total of 38 patients (1 had Hb < 9 g/dL and 37 missed the follow-up or had obstetric complications) in gestational week 20–24 and 22 patients (4 had Hb < 9 g/dL and 18 missed the follow-up or had obstetric complications) in gestational week 30–34 were excluded.

In the first trimester, according to the definition of anaemia (3,7), we discovered that 4.76% (8/168) of patients had Hb < 11.g/dL (these were excluded from the study at the beginning), in the second trimester 7.69% of patients (10/130) and in the third trimester 16.66% of patients (18/108) had Hb < 10.5 g/dL. The mean, median and maximum–minimum values are given in Table 3. The differences in Hb, Hct and ferritin values

Table 2 Characteristics of the study sample, 168 healthy Turkish pregnant women, 2016–2017

Characteristic	Mean (SD)
Age at entry of study (years)	32.6 (7.6)
Body mass index (kg/m²)	23 (3.2)
Body height (cm)	162 (5.0)
Parity	1.5 (0.8)

SD = standard deviation.

were statistically significant between trimesters ($P < 0.001$). In addition, Hb, Hct and ferritin decreased significantly from the first to the second trimester ($P < 0.001$ for all) but stayed comparable between the second and third trimesters ($P = 0.246$, $P = 0.575$, $P = 0.408$, respectively). The decrease in Hb was 5.6% between the first and second trimesters and 3.36% between the second and third trimesters.

We found that Hb values were normally distributed according to the definition of anaemia (mean Hb, 1.96 SD), so the lower reference value for our population was calculated as 10.67 g/dL for 10–14 gestational weeks, 10.08 g/dL for 20–24 gestational weeks and 9.18 g/dL for 30–34 gestational weeks.

The 2.5th, 5th, 10th, 90th, 95th and 97.5th percentile values of Hb and ferritin for each trimester are shown in Table 4. Even these patients did not get any iron supplementation: the 50th percentile of the Hb values were not low as expected.

The mean birth weight of the neonates was 3114 (SD 219) g.

Discussion

This study is pioneering in determining the reference intervals for Hb during pregnancy without using any supplementation. Our study showed that with diet alone, without any extra iron supplementation, the lower reference values for Hb were comparable with those suggested by the WHO (2012) and UK guidelines, and the mean birth weight was maintained in the normal range (*3,7*).

Anaemia is defined as occurring when Hb is below 2 standard deviations of the mean of a selected healthy population. Anaemia affects the oxygen-carrying capacity of blood, and even when anaemia is not present, iron deficiency affects enzyme function and cognitive capacity. It is also associated with maternal depression (*14,15*), apathy, impaired thyroid metabolism, low fetal birth weight, preterm birth and neonatal death (*16*).

Although iron deficiency anaemia affects the health of the mother and the fetus in negative ways and may lead to an increased absorption of toxic divalent cations like cadmium and lead (*17*), iron supplementation is not innocent either. Especially if it is given inappropriately, iron can damage the intestinal epithelium by forming free radicals and increasing oxidative stress. For these reasons, normal haematological values should be known for the selected population in order to diagnose iron deficiency anaemia in pregnancy.

In pregnancy, because of physiological changes, there are variabilities between trimesters and it is difficult to define normal haematological reference intervals for pregnant women (*18*). Furthermore, the boundaries between physiological and pathological anaemia are not clear (*19*) and normal Hb levels are subject to racial differences (*20*), which must be taken into account. Therefore, in order to prevent complications from iron supplementation, treatment should be given based on the normal Hb levels for any population. In a study by Milman et al., normal Hb ranges in the early third trimester amongst Caucasians were reported as between 10.4 g/dL and 13.5 g/dL (*21*). Garn et al. also discovered that Europeans had lower optimum Hb than Africans (*19*). The

Table 3 Mean and median blood test values among Turkish pregnant women for the first, second and third trimesters, 2016–2017

Test	1st trimester (n = 168)		2nd trimester (n = 130)		3rd trimester (n = 108)		P
	Mean (SD)	Median (min–max)	Mean (SD)	Median (min–max)	Mean (SD)	Median (min–max)	
Hb (g/dL)	12.61 (0.97)	12.71 (9.70–15.30)	11.90 (0.91)	12.00 (9.40–14.10)	11.50 (1.16)	11.60 (8.20–13.70)	< 0.001 < 0.001[a] 0.246[b] < 0.001[c]
Hct (%)	37.87 (2.54)	37.95 (30.00–45.20)	35.64 (2.58)	36.00 (26.00–41.00)	34.55 (3.30)	35.10 (24.70–41.60)	< 0.001 < 0.001[a] 0.575[b] < 0.001[c]
Ferritin (µg/L)	30.80 (25.56)	24.50 (4.60–185.00)	20.20 (12.37)	16.35 (5.00–59.00)	19.72 (15.50)	16.20 (5.20–87.0)	0.001 < 0.001[a] 0.408[b] 0.220[c]

Hb = haemoglobin.
Hct = hematocrit.
[a]*Comparison of first and second trimesters.*
[b]*Comparison of second and third trimesters.*
[c]*Comparison of first and third trimesters.*

Table 4 **Percentiles of Hb (g/dL) and ferritin (µg/L) values in each trimester, Turkey 2016–2017**

Percentile	1st trimester		2nd trimester		3rd trimester	
	Hb	Ferritin	Hb	Ferritin	Hb	Ferritin
2.5	10.0	6.0	9.8	6.8	8.8	5.2
5	10.8	6.5	10.2	8.4	9.3	6.4
10	11.4	8.4	10.7	9.1	9.8	7.7
50	12.7	24.5	12.0	16.2	11.6	16.0
90	13.8	61.5	13.0	40.2	12.8	35.0
95	14.1	81.3	13.3	44.7	13.1	58.8
97.5	14.4	94.2	13.6	53.3	13.4	97.7

current research is a pioneering study that has formed a nomogram for each trimester and iron deficiency anaemia prevalence among healthy Turkish pregnant women who were not using iron supplementation.

Iron deficiency anaemia in pregnancy can be detected using several parameters: a full blood count (especially by Hb value), serum ferritin, serum iron and total binding capacity, zinc protoporphyrin, soluble transferrin receptor and bone marrow iron. Among these parameters, the gold standard is bone marrow iron, but it is too invasive and impractical in pregnancy, and serum ferritin is considered to be the best test to assess iron deficiency in pregnancy (7). However, serum ferritin is itself an acute phase reactant and could rise with infection and inflammation. In the current study, we analysed full blood count and ferritin values among all these parameters for a nomogram. According to WHO and Royal College of Obstetricians and Gynaecologists guidelines for collecting a normal healthy population in the first trimester, we took the anaemia cut-off as 11 g/dL. We excluded and gave supplementation to patients whose Hb level was ≤ 9 g/dL in the second and third trimesters because moderate and severe anaemia is associated with an increased risk of adverse effects to both mother and fetus (3,11).

Although there was a statistically significant decrease in ferritin values between 10–14 and 20–24 gestational weeks, there was no significant difference between 20–24 and 30–34 weeks. From this point of view, the Hb value decrease between the second and third trimesters could be because of dilutional anaemia. Although the pregnancy outcomes were not investigated in detail in the study, fetal birth weights were all within the normal range (> 10% for gestational age). This result shows that dilutional anaemia in the third trimester may not affect the outcome of the pregnancy and likewise, in a study by Steer et al., the highest birth weight was at maternal Hb values of 8.6–9.5 g/dL and the lowest low birth weight was at maternal Hb value 9.6–10.5 g/dL (22). Similarly in a study by the National Collaborative Perinatal Project, low birth weight was minimal at maternal Hb value 10.5–12.5 g/dL in Caucasian women (19). In addition, Whittaker et al. also suggested that low Hb values (10–11 g/dL) in late pregnancy reflect changes in plasma volume, and Hb values < 10 g/dL reflected inadequate maternal nutritional status (23).

In our study, according to the UK guidelines for the definition of iron deficiency anaemia (7), without iron supplementation in the first trimester only 4.76% had Hb < 11.00g/dL. In the second trimester 7.69% and in the third trimester 16.66% had Hb < 10.5 g/dL. In a multicentre study by Barroso et al. in the UK, the anaemia percentages were 7.0%, 19.0% and 12.5% in the first, second and third trimesters respectively (13). Our findings are comparable with the UK prevalence, although in the UK study the selected population received iron supplementation. In our study, mean values of Hb and ferritin levels in the first, second and third trimesters were 12.61–30.8, 11.90–20.2, and 11.50–19.72 respectively. In a study from China, 240 consecutive healthy patients with iron supplementation were followed and mean Hb values were 12.2, 11.3 and 11.5 g/dL in the first, second and third trimesters, respectively (24). These values are also lower than our values. In the same study, lower reference values of Hb were reported as 10.4, 9.5 and 9.6 g/dL in the first, second and third trimesters respectively, lower than those suggested by the WHO and UK guidelines (3,7). In the current study, we also determined lower reference values of Hb as 10.67, 10.08 and 9.18 g/dL in the first, second and third trimesters, respectively. Compared with the results from the China study, our base reference value of Hb in the third trimester was lower. This may be due to iron supplementation during pregnancy in their study. In our study, even though the patients did not use supplementation during pregnancy, the anaemia percentages were lower. This could be because our selected population paid attention to the dietary advice given; it could also, hypothetically, be related to the high altitude (938 m) of the location of the study.

Our study is particularly important because the selected healthy population did not use iron supplementation that could change the Hb and ferritin values. It is also especially valuable because this was the first prospective study in Turkey where the same population (nonanaemic at the beginning of the pregnancy) was followed up until birth. The study population was representative of the breadth of the Turkish population, thus our clinic was a reference hospital in Turkey and included several patients from

different areas of the country. According to studies (*25,26*), a minimum of 120 consecutive measurements is sufficient for the statistical significance of a study and in our method we followed up 160 patients.

In conclusion, the results of the current study may help prevent unnecessary iron usage during pregnancy especially during embryogenesis and we believe that further studies with larger patient groups must be planned in order to reach more definative conclusions.

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Competing interests: None declared.

Étude transversale auprès de femmes enceintes non anémiques en Turquie pour évaluer la nécessité d'une supplémentation en fer

Résumé

Contexte : La carence martiale est la principale cause d'anémie pendant la grossesse. Les lignes directrices recommandent différentes valeurs seuils pour la supplémentation en fer.

Objectifs : Déterminer des intervalles de référence par trimestre pour les valeurs hématologiques (hémoglobine, hématocrite et ferritine) chez les femmes enceintes en bonne santé qui n'ont pas été supplémentées en fer pendant leur grossesse, afin d'orienter un futur traitement martial.

Méthodes : Une étude transversale prospective a été conduite auprès de 168 femmes enceintes âgées de 18 à 45 ans menant des grossesses uniques, se trouvant au premier trimestre de leur grossesse et non supplémentées en fer (hémoglobine ≥ 11 g/dl et ferritine ≥ 12 µg/l). Les grossesses multiples, les grossesses avec complications obstétricales et les fumeuses ont été exclues de l'étude. On a établi des valeurs moyennes d'hémoglobine (Hb) et de ferritine, des intervalles de référence par trimestre et des valeurs percentiles relatives à l'hémoglobine et à la ferritine pour chaque trimestre. La normalité des variables a été évaluée à l'aide du test de Kolmogorov-Smirnov.

Résultats : L'hémoglobine moyenne a diminué significativement d'un trimestre à l'autre, passant de 12,6 à 11,9 puis à 11,5 g/dl. En outre, l'hémoglobine, l'hématocrite et la ferritine ont diminué significativement du premier au deuxième trimestre (en tout, $p < 0,001$) mais sont restés stables entre le deuxième et le troisième trimestre ($p = 0,246$; $p = 0,575$ et $p = 0.408$, respectivement). La valeur de référence la plus faible pour l'hémoglobine a été évaluée à 10,67 entre la 10e et la 14e semaine, à 10,08 entre la 20e et la 24e semaine et à 9,18 g/dL entre la 30e et la 34e semaine.

Conclusion : Cette étude pionnière nous montre qu'il n'est pas forcément nécessaire de recourir à une supplémentation en fer car la diminution des valeurs est due à une hémodilution physiologique. Ces résultats pourraient éviter une prescription inutile de fer pendant la grossesse.

دراسة مقطعية على النساء الحوامل غير المصابات بفقر الدم في تركيا لتقييم الحاجة إلى مُكمّلات الحديد

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الخلاصة

الخلفية: يُعد نقصُ الحديد السببَ الأكثر شيوعاً لفقر الدم أثناء الحمل. وتوصِي المبادئ التوجيهية بقيم عتبية مختلفة لمكملات الحديد.

الأهداف: هدفت هذه الدراسة إلى تحديد نطاقات مرجعية لقيم الدم في مراحل الحمل (الهيموجلوبين والهيماتوكريت والفيريتين) لدى النساء الحوامل الأصحاء اللاتي لم يستخدمن أي مكملات حديد أثناء الحمل للاسترشاد بذلك في العلاج بالحديد في المستقبل.

طرق البحث: أُجريت دراسةٌ مقطعية استباقية على 168 امرأة حاملاً تتراوح أعمارهن بين 18–45 سنة، مع حالات حمل فردي في الأشهر الثلاثة الأولى، وقيمة هيموجلوبين ≤ 11 جرام/ ديسيلتر وقيمة فيريتين ≤ 12 ميكروجرام/ لتر، مع عدم استخدام مكملات الحديد. واستُبعدت من الدراسة حالات الحمل المتعدد والحمل المرتبط بمضاعفات عند الولادة والنساء المدخّنات. وحُدِّد متوسط الهيموجلوبين وقيم الفيريتين، والنطاقات المرجعية الخاصة بمراحل الحمل كل ثلاثة أشهر والقيم المئوية للهيموجلوبين والفيريتين لكل ثلاثة أشهر. وتم اختبار الحالة الطبيعية للمتغيرات باستخدام اختبار كولموجوروف سميرنوف.

النتائج: انخفض متوسط الهيموجلوبين على نحوٍ كبير بين مراحل الحمل كل ثلاثة أشهر من 12.6 إلى 11.9 ثم 11.5 جرام/ ديسيلتر. وبالإضافة إلى ذلك، انخفض الهيموجلوبين والهيماتوكريت والفيريتين على نحوٍ كبير من الثلث الأول إلى الثلث الثاني من الحمل ($P < 0.001$ للجميع) ولكن ظلت القيم قابلة للمقارنة بين الثلث الثاني والثالث ($P=0.408$، $P=0.575$، $P=0.246$، على التوالي). واحتُسبت القيمة المرجعية الأقل للهيموجلوبين على أنها 10.67 و10.08 و9.18 جرام/ ديسيلتر لمدة 10–14 و20–24 و30–34 أسبوعاً من الحمل على التوالي.

الاستنتاجات: تتيح لنا هذه الدراسة الرائدة أن نفهم أنه قد لا تكون هناك حاجة إلى مكملات الحديد لأن أي انخفاض يرجع إلى تخفيف الدم الفسيولوجي. وقد تحُول هذه النتائج دون وصف الحديد غير الضروري أثناء الحمل.

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