THE DETECTION OF IRON DEFICIENCY IN PREGNANCY

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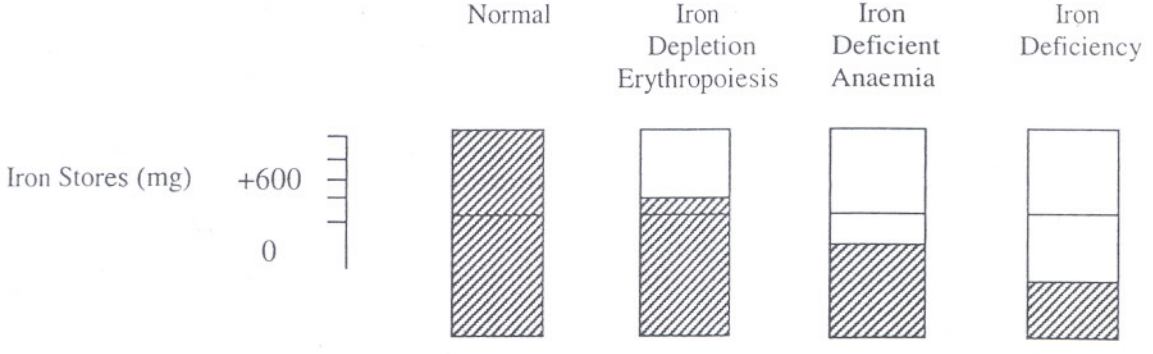
Anaemia is diagnosed if a woman has a haemoglobin (Hb) concentration and haematocrit (Hct) less than the 95% confidence intervals of the respective means expected for her age and period of gestation[1].

As the Hb is maintained within the normal range until the iron stores are depleted the Hb has limitations in the detection of Iron Deficiency (ID) [2,3,4,5,6] (Fig.1) [6].

Table 1- Diagnosis of Anaemia in Pregnancy [1]

	Hb g/L	Hct %
First Trimester	< 110	< 33
Second Trimester	< 105	< 32
Third Trimester	< 110	< 33
4-6 weeks. Post partum	< 120	< 36

Fig. 1 .[6] *Sequential Changes in the development of Iron Deficiency Anaemia.*



	Normal	Iron Depletion Erythropoiesis	Iron Deficient Anaemia	Iron Deficiency
Plasma Ferritin (µg/L)	60	<12	<12	<12
Transferrin (%)	35	35	<16	<16
RBC Protoporphyrin (µg/dl)	30	30	>100	>100
Haemoglobin (g/dl)	>12	>12	>12	<12

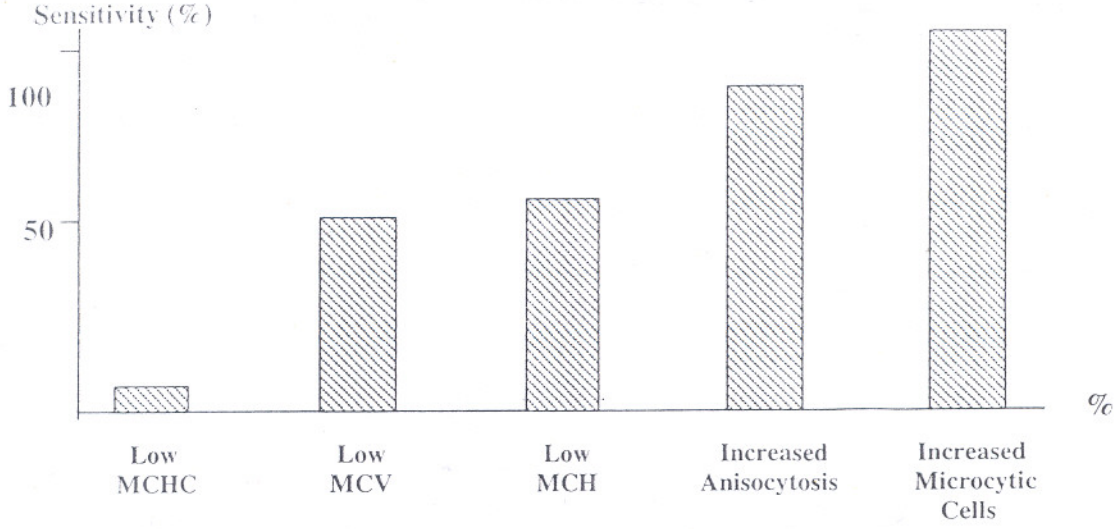
The normal level of serum iron (which includes the free iron as well as the iron bound to transferrin) is approximately 115 µg/dl and levels of < 60 µg/dl suggest iron deficiency. However serum iron depends on mobilization and can be normal or elevated even when the iron stores are depleted. eg during iron supplementation [1,3,4,6].

The total iron binding capacity increases as a result of increased demand for iron as seen in pregnancy. The transferrin saturation is normally approximately 35% and levels of <16% are suggestive of iron deficiency [1,3,4,6]. The red cell distribution width is an index of anisocytosis but is not a commonly used index now [7].

The erythrocyte protoporphyrin level is a good indicator of ID. Its normal levels are approximately 30 µg/L and in the presence of ID it increases to >100 µg/L [1,3,4,6].

It has been shown that even a low serum iron, a low MCV, TfS <16% and the red cell distribution width are poor indices for the detection of iron deficiency during pregnancy [4]. It has also been shown that the detection of increased anisocytosis and microcytosis in a peripheral blood film has a better sensitivity of detecting low transferrin saturation (TfS <16%) than a low mean corpuscular haemoglobin concentration (MCHC), mean corpuscular volume (MCV) or mean corpuscular haemoglobin (MCH) (Fig.2)[7].

Fig.2 [7] Sensitivities of Haematological Indices in detecting low TfS (< 16 %)



During pregnancy there may be a coexisting folate (or rarely even vitamin B_{12}) deficiency which results in macrocytosis. Many women with ID have already been on some iron supplement before they come to an obstetrician and this too would result in an overactive bone marrow releasing immature macrocytes into the peripheral circulation. This would result in a dimorphic peripheral blood picture. Since the MCH, MCHC and the MCV are all indices which are calculated averages of the red cell population the dimorphism will be masked and the ID may be missed [8].

Serum Ferritin (SF) [1,3,4,5] and more recently serum transferrin receptors (STfR) [1,9,10] have been recommended as better indices of ID.

The SF has been shown to have a good correlation with iron stores in the body [3,4,5]. Each microgram of SF per litre of plasma is thought to be equivalent to approximately 10 mg of storage iron [3,11]. The SF can be increased due to acute or cronic inflammation [11]. Hence a normal SF level may be found during an infection although the iron stores are depleted. A low SF level however is found only with iron deficiency [3,4,5,11]. ID is diagnosed when the SF is <12µg / L and levels of <10µg / L are associated with virtual exhaustion of iron stores [3,5,11]. Low SF levels correlate with absent bone marrow iron, a common finding in pregnancy [5,11]

More recently however, it has been shown that. iron status indices (including SF) demonstrate within subject day to day biological variations [12] Since this variability also should be taken into consideration a single measurement of any index can be misleading. Haemodilution too can result in misleading results.

The transferrin receptor controls the flow of transferrin iron into the cells and a soluble form of this receptor is found in the serum [9]. The serum transferrin receptor (STfR) concentration is a sensitive index of tissue iron deficiency and is relatively unaffected by inflammation or the period of gestation. STfR concentrations increase even in mild iron deficiency of recent onset. It is an index of functional ID.

Hence it can be of great value in the diagnosis of iron deficiency in pregnancy [10]. A STfR level of >8.5 mg / L indicates tissue iron deficiency [1,10]. Some women with moderately low SF levels appear to be able to adapt themselves to this moderate ID and do not show any clinical signs of ID. These women have been found to have normal STfR [9,10].

In clinical practice however, SF and STfR would be unavailable and a MCV of less than 80 fl is considered as a relatively reliable index of Iron Deficiency Anaemia (IDA) [1,3,4], although it could be unreliable in the presence of a dimorphic blood picture as mentioned earlier [8]. The Hb, Hct, and MCV should be checked at booking, at approximately 28 weeks of gestation and in high-risk cases 4-6 weeks after the delivery [1]

A cross sectional study was carried out on 236 consecutive women attending the university antenatal clinic (UANC) in Galle for booking. The Hb was measured by the cyanmethhaemoglobin method and the SF was measured by an immunoradiometric assay technique. It was found that although only 56% had IDA as diagnosed by a Hb < 110g/l, 69% had ID as detected by SF < 12µg/l [2]. (Tables 2 & 3).

Table 2. The distribution of subjects according to their Hb & SF levels [2].

	SF <12 µg / L	>12 µg / L	
Hb <110 g / L	102	31	133
Hb >110 g / L	60	43	103
	162	74	236

Table 3. The ability of the Hb (< 110 g / L) to detect or exclude iron deficiency

(SF< 12 g / L) [2].	Hb <110 g / L
Sensitivity	63 %
Specificity	58 %
Positive Predictive Value	77 %
Negative Predictive Value	42 %
Accuracy	61 %

On the basis of these findings it was concluded that the Hb, which is the standard screening test for anaemia has limitations in its ability to detect or exclude ID during pregnancy [2].

In another study the Hb, Hct, MCV, MCH, MCHC & red blood cell count (RBCC) were estimated by an automated haematology analyser and compared with SF levels measured by immuno radiometric assay in two groups of women; 156 women (group A)in the second trimester (T_2) and 47 women (group B) in the third trimester (T_3) of pregnancy. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of detecting ID, and the Kappa Statistic [13] were calculated for the accepted cut points for each haematological index using a SF<12μg/L as the diagnostic criterion for ID[14].

The accepted cut points used for each index are shown in Table 4

Table 4. Cut points for detection of ID

Index \ Trimester		T_2	T_3
Hb	g/L	105	110
Hct.	%	32	33
MCV	fl	80	80
MCHC	%	30	30
MCH	pg/L	30	30
RBCC	per mm^3	$4.1x10^6$	$4.1x10^6$

ID (SF<12μg/L) was found in 62 (40%) of subjects in group A (n =156, T_2) and 22 (46%) in group B (n =47, T_3). In the detection of ID the indices having high specificities were the Hct (97% in T_2 and 96% in T_3), MCV (98% in T_2 and 96% in T_3) and the MCHC (97% in T_2 and 100% in T_3) The Hb had a specificity of 87% in T_2 and 92% in T_3. The sensitivity was poor in all the indices except the MCH, which had sensitivity of 92% and 86% in T_2 and T_3 respectively. Except for MCHC, which had a moderate agreement (Kappa 0.41, p=0.00) none of the other indices had any agreement with the SF levels in the detection of ID.

The results of this study suggested that in T_2 a Hct <32%, MCV <80 fl and a MCHC <30% could be used to detect ID while a MCH >30% could be used to exclude ID. In T_3, a Hb <110 g/L, MCV <80 fl and a MCHC <30% could be used to detect ID.

None of the indices could reliably exclude ID in T_3 as their negative predictive values were all < 70% [14].

In clinical practice it is often observed that haematological indices obtained from a laboratory are not compatible with the clinical impression of the degree of anaemia in a patient.

In the second part of this study the Hb and Hct were also measured by conventional methods. (cyanmethhaemoglobin and haematocrit tubes respectively) in two other laboratories.The agreement between the values obtained by the two methods and in different laboratories was evaluated using the Kappa statistic. The data was further analysed graphically [15,16,17].

The discrepancies in the values obtained in the three laboratories were clearly seen when the values were plotted graphically.

Both in T_2 and T_3 the Hb levels obtained by automated haematology analyser in one laboratory differed significantly from the values obtained by conventional methods in the two other laboratories [15].

We concluded that the significant differences in the measurement of Hb in the three laboratories were probably due to technical errors (bias) in the three laboratories [15].

Conclusion

In clinical practice, especially in government hospitals in Sri Lanka, often it is only the Hb that is measured to detect or exclude anaemia. Furthermore clinical management is often based on a single Hb measurement. It should be kept in mind that the Hb not only has limitations in detecting iron deficiency but also that a single measurement can be erroneous.

In the 3rd trimester of pregnancy, a full blood count should be interpreted with caution as none of the commonly measured haematological indices can reliably excludes iron deficiency.

If the clinical picture is not compatible with the laboratory report, the haematological assessment should be repeated.
A minimum of two haematological indices should be assessed. eg. Hb and Hct. In a full blood count the more reliable indices such as the Hb, Hct, MCV and MCHC should all be taken into consideration when interpreting the report.

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How I'd like to be treated if I was terminally ill

I would want to be able to choose a consultant who would sit on my bed, without his (or her) entourage,unafraid of what I might ask him and be prepared to explain to me, repeatedly, in words of one syllable, what I cannot grasp – and then do it all over again in one week or two weeks or one month later with a gentle consistency and sensitive honesty that leaves me in no doubt as to the truth of the facts of the matter.

I would want to benefit from the wisdom of an old fashioned general practitioner who has a broad mind to think around the problem of drug administration and be unafraid of titrating the drug against the symptom to be controlled , perhaps in larger doses than he is used to, remembering that there is no ceiling to the dose of opiates he might use, and translate that into a tablet here, a subcutaneous infusion there, a transdermal patch if feasible, a suppository only if absolutely necessary. May he remember to prescribe the laxative with the first dose of opiate and save me the indignity and embarrassment of the high, hot, and helluva lot of enema required to shift faecal impaction otherwise caused.

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