ORIGINAL ARTICLE

Utility of new reticulocyte parameters such as reticulocyte hemoglobin and new erythrocyte parameters in detection of subclinical stage of iron deficiency in pregnancy

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Abstract

Background: Deficiency of iron is the most common cause of anemia in pregnancy. It may cause various morbidities in pregnancy. Hemoglobin estimation is the routine investigation employed in antenatal screening where 11g/dl is taken as a cut-off for diagnosis of anemia. With the advancement of technology, new reticulocyte and erythrocyte parameters, such as the percentage hypochromic red blood cells and the percentage Microcytic Red Blood Cells (Micro-R), can assess iron status. Hence, in the present study, utility of these parameters was evaluated to determine the subclinical stage of iron deficit in pregnancy. *Aim and Objectives*: To assess utility of newer reticulocyte and erythrocyte parameters by comparing them with serum iron for detecting subclinical deficiency of iron in pregnancy. *Material and Methods*: Hospital-based, observational study was done on blood samples of non-anemic females of first-trimester pregnancy presenting to the obstetrics and gynecology department for the first time. Unpaired *t*-test and receiver operating characteristic analysis were done to check the relative efficiency. *Results:* Reticulocyte Hemoglobin (Ret-He) showed a sensitivity of 98.0% and specificity of 97.0% at the optimal value of 32.25. The area under the curve for Ret-He indicated it as a discriminator of deficiency of iron with a *p*-value < 0.001. Micro-R percentage at a cut-off of 1.55 showed sensitivity and specificity of 76.9% and 69.9%, respectively, and was statistically significant. *Conclusion:* Ret-He can be an alternative hematological investigation for detecting subclinical deficiency of iron in females during pregnancy.

Keywords: Ret-He, Serum Ferritin, %Micro-R, %Hypo-He

Introduction

Anemia is one of the most common maternal factors, which is significantly associated with low birth weight and preterm birth in 62.8% of pregnant women. Hence, early detection of anemia can help in preventing these morbidities [1]. One of the most common cause of anemia during pregnancy is Iron Deficiency (ID). It may cause various morbidities in pregnancy [2]. Iron Deficiency Anemia (IDA) was considered a significant contributing factor to the global burden of the disease [3-4]. According to the 2010 report by the World Health Organization, anemia accounted for 8.8% of total disability [3]. Main etiological factors for IDA are low intake of iron, low socioeconomic status, malabsorption and increased need for iron in physiological conditions like pregnancy and adolescence [4-5]. Maternal complications like postpartum infections and neonatal complications like babies with low weight, premature birth, and complications in infancy like deficient growth can occur due to ID. These complications can be prevented by early diagnosis of IDA and appropriate treatment [2].

Hemoglobin (Hb) estimation is a routine investigation employed in antenatal screening where Hb values of 11 g/dl are taken as cut-off for diagnosing anemia. However, in the case of IDA, Hb level decreases late during the disease. Thus, estimation of Hb for screening IDA will not be able to detect ID in the early stage. Hence, in asymptomatic pregnant women, a diagnosis of IDA may be missed in screening tests done by Hb estimation [5]. Different serum iron status markers, such as serum transferrin, serum iron, and percentage saturation, are additional parameters that may help in the early detection of IDA. With the advancement of technology, newer parameters of red blood cells and reticulocytes are available on newer analyzers to assess iron status. These parameters include a percentage of Microcytic Red Blood Cells (%Micro-R), percentage of Hypochromic Red Blood Cells (%Hypo-He), and the Hemoglobin content of Reticulocytes (Ret-He). These parameters are not influenced by infection or inflammation. The added advantage is that these parameters can be obtained from the sample, which is used for Complete Blood Count (CBC) analysis [2].

In some studies, Ret-He is proposed as an efficient iron status marker and mentioned that Ret-He indicates a strong correlation with ID erythropoiesis. Their study also mentioned that it could indicate iron status in various conditions, such as patients undergoing dialysis with chronic renal disorders, elderly individuals and pregnant women [2, 4, 6]. Reticulocytes act as an immediate snapshot of iron availability [7]. Ret-He can identify the factors inhibiting erythropoiesis and may aid in checking the response to treatment [8]. Ret-He also helps in deciding the requirement of intravenous iron and responsiveness to it and thus helps to plan the treatment [9]. It was mentioned that these newer parameters show significant differences between iron and non-ID groups that help in the early diagnosis of anemia [2]. Analysis of these parameters in pregnant women has not been explored much in Indian studies. Hence, this study was done to evaluate the utility of newer parameters of erythrocytes and reticulocytes by comparing them with the traditional parameters, such as serum iron study for detecting subclinical ID in pregnant women.

Material and Methods

This was a hospital-based, prospective, observational study, in which non-anemic females attending the Antenatal Clinic (ANC) in the first trimester were recruited after receiving Institutional Ethical Clearance (IEC/No: 286/2018 dated 17.11.2018) and taking their written informed consent. The study period was from November 2018 to May 2020. Inclusion criterion was pregnant women with Hb more than 11 g/dl. Pregnant women who had undergone blood transfusion in the last 3 months, or were on iron supplements or had manifestations of IDA like pallor, easy fatigability, and breathlessness were excluded from the study.

By referring the study done by Levy *et al.* [2] sample size calculation at 95% confidence level with 6% absolute precision came out to be 279. Hence a total of 280 subjects were recruited to determine the utility of Ret- He, %Micro- R, and %Hypo- He in detecting subclinical ID in pregnant women by comparing with serum ferritin.

Methods of collection of data

Blood samples of these study participants were sent to the haematology section for investigations. In K2 EDTA vacutainers, 2 ml blood samples were collected and processed in Sysmex XN 1000, 5-part fully automated hematology analyzer. An additional 2 ml blood sample was taken in a plain tube for biochemical investigations. Clinical details regarding the present pregnancy, intake of any supplements, or any other additional presenting complaints were recorded. Continuous variables were expressed in mean and standard deviation. To determine the difference in the means of variables between two independent groups, unpaired *t*-test was used. Value of *p* less than 0.05 was considered for statistical significance of the results. Analysis of the data was done using Statistical Package for Social Sciences software v.23 and Microsoft Office.

Results

Maximum cases were between 23 to 27 years, amounting to 137 (48.9%) cases, followed by 18-22 years, amounting to 109 (38.9%) cases. Majority belonged to gravida 1 (G1) and gravida 2 (G2) amounting to 117 (41.7%) cases and 113 (40.3%) cases, respectively. Most of the G1 and G2 cases were 18- 27 years old, amounting to 146 (87.8%) cases. Only two cases were gravida 5 (G5). Out of these two G5 cases, the age of one case was 29 years, and the other was 35 years old.

Based on the serum iron study findings, cases were divided into two groups. Study cases having serum iron less than 40 µg/dl, serum ferritin below 20 ng/ml, and Total Iron Binding Capacity (TIBC) above the level of 400 µg/dl were categorized into the ID group, and cases having serum iron between 40-177 µg/dl, serum ferritin between 20-137 ng/ml and TIBC between 250-400 µg/dl were categorized as normal range and were classified into the non-ID group.

In 18 cases, serum iron was less than 40 µg/dl, amounting to 6.4% and in the normal limit in 262 (93.6%) cases. Increased TIBC was noted in 90 cases (32.1%) cases. In 151 cases, serum ferritin was less than 20 ng/ml, amounting to 53.9%, and it was within the normal limit in 129 (46.1%) cases. Out of 117 cases of G1, the iron level in the serum was below 40 µg/dl in 7 (6%) cases, TIBC was more than the normal range in 32 (27.4%) cases, and ferritin level in the serum was below 20 ng/ml in 52 (44.4%) cases. Out of 113 cases of G2, iron level in the serum was lower than the normal range in 6 (5.3%) cases, TIBC was raised in 36 (31.9%) cases, and serum ferritin was less than the lower limit of the normal range in 58 (51.3%) cases. Out of 36 cases of G3, only 3 (8.3%) cases had low serum iron, 17 (47.2%) cases had high TIBC, and 27 (75%) cases showed low serum ferritin. In all the cases of G4 and G5, serum ferritin values were less than the lower limit of the normal range and were categorized under the ID group. Thus, depending on these three biochemical parameters, maximum cases were classified into the ID group, amounting to 151 (53.9%) cases based on serum ferritin, a gold standard for detecting ID (Table 1).

Out of 280 cases, 32 (11.4%) cases showed Mean Corpuscular Volume (MCV) less than 80 fL, and 248 (88.6%) cases showed normal MCV of 80 to100 fl. In 76 (27.1%) cases, %Micro-R was more than 2.8% and within the range of 0.3 to 2.8 in 204 (72.9%) cases. In 28 (10%) cases, %Hypo-He of more than 1.1% was seen, and these cases were grouped under ID. In the remaining 252 (90%) cases, the %Hypo-He was 0.1% to 1.1%, and these cases were grouped under the non-ID group. Thus, depending on %Micro-R, the ID group cases noted were 76, amounting to 27.1% (Table 2).

Out of 117 G1 cases, low MCV was noted in 5 (4.3%) cases. Increased %Micro-R and %Hypo-He was noted in 22 (18.8%) cases and 9 (7.7%) cases respectively. Out of 113 cases of G2, low

MCV was noted in 21 (18.6%) cases, increased %Micro-R was noted in 33 (29.2%) cases and 11 (9.7%) cases showed an increase in %Hypo-He. In G3 out of 36 cases, 4 (11.1%) cases showed low MCV, 15 (41.7%) cases were with high %Micro-R and in 5 (13.9%) cases high %Hypo-He was noted. Out of 12 cases of G4, low MCV was noted in 1 (8.3%) case, an increased %Micro-R was observed in 4 (33.3%) cases, and 2 (16.7%) cases showed an increased %Hypo-He. One case of G5 showed low MCV and high %Hypo-He. In both cases increased %Micro-R was noted (Table 2).

Table 1: Serum iron parameters distribution in various age groups and gravida

Age (years)	Serum Iron (40 -177 µg/dl)		TIBC (250 -400 µg/dl)		Serum ferritin# (20-137 ng/ml)	
	ID	N-ID	ID	N-ID	ID	N-ID
18-22(n-109)	3	106	37	72	55	54
23-27(n-137)	13	124	41	96	78	59
28-32(n-21)	1	20	8	13	12	9
33-37(n-11)	0	11	3	8	5	6
38-42(n-2)	1	1	1	1	1	1
Total	18	262	90	190	151	129
Gravida						
G1(n-117)	7	110	32	85	52	65
G2(n-113)	6	107	36	77	58	55
G3(n-36)	3	33	17	19	27	9
G4(n-12)	2	10	4	8	12	0
G5(n-2)	0	2	1	1	2	0
Total	18	262	90	190	151	129

**ID – Iron deficient group, N-ID – Non-Iron deficient group, TIBC – Total iron binding capacity*

Table 2: Erythrocyte parameters distribution in various age groups and gravida

Age (years)	MCV (80-100 fL)		%Micro-R (0.3%-2.8%)		%Hypo-He (0.1%-1.1%)	
	ID	**N-ID**	**ID**	**N-ID**	**ID**	**N-ID**
18-22(n-109)	9	100	27	82	10	99
23-27(n-137)	22	115	37	100	16	121
28-32(n-21)	0	21	6	15	1	20
33-37(n-11)	1	10	5	6	1	10
38-42(n-2)	0	2	1	1	0	2
Total	**32**	**248**	**76**	**204**	**28**	**252**
Gravida						
G1(n-117)	5	112	22	95	9	108
G2(n-113)	21	92	33	80	11	102
G3(n-36)	4	32	15	21	5	31
G4(n-12)	1	11	4	8	2	10
G5(n-2)	1	1	2	0	1	1
Total	**32**	**248**	**76**	**204**	**28**	**252**

**ID – Iron deficient group, N-ID – Non-Iron deficient group, MCV – Mean Corpuscular Volume, %Micro-R - Percentage of microcytic red blood cells, %Hypo-He - Percentage of hypochromic red blood cells*

In all 280 cases, reticulocyte count was in the normal range of 0.5 to 2.5%. Ret-He of less than 29 pg was seen in 121 (43.2%) cases. Ret-He was decreased in 39 (33.3%) cases of G1, 50 (44.2%) cases of G2, 22 (61.1%) cases of G3, 8 (66.7%) cases of G4 and 2 cases of G5 respectively. These cases were grouped into ID. Based on the normal range of Ret-He of 29-36 pg, 159 (56.8%) cases were categorized into the non-ID group (Table 3).

Table 3: Reticulocyte parameter distribution

Age (Years)	Ret-He (29-36 pg.)	
	ID	N-ID
18-22(n-109)	47	62
23-27(n-137)	60	77
28-32(n-21)	10	11
33-37(n-11)	3	8
38-42(n-2)	1	1
Total	**121**	**159**
Gravida		
G1(n-117)	39	78
G2(n-113)	50	63
G3(n-36)	22	14
G4(n-12)	8	4
G5(n-2)	2	0
Total	**121**	**159**

**ID – Iron deficient group, N-ID – Non-Iron deficient group, Ret-He - Hemoglobin content of reticulocytes*

The mean RBC count and Hb concentration were in normal range in both iron and non-ID groups. The mean MCV value was normal in both iron and non-ID groups. However, the mean MCV was slightly lesser in both groups, with a statistically significant difference. Red Cell Distribution Width (RDW) and reticulocyte count were within the normal limit in both groups. The mean RDW was slightly higher in the ID group; however, the difference was statistically insignificant. The mean Ret-He values in ID category were lower than non-ID group with a statistically significant difference. The mean of %Micro-R values and %Hypo-He values in the ID group were higher, with significant statistical differences. The mean serum ferritin levels were low, and the TIBC mean was higher in the ID group, with significant statistical differences (Table 4).

A correlation between %Micro-R and MCV was noted on Receiver Operating Characteristic (ROC) analysis having r = −0.551 at a 95% confidence interval of 0.796 to 0.887 with *p* value less than 0.001. Positive correlation was also found between MCV and Ret-He with r = 0.394 at a 95 % confidence interval of 0.998 to 1.00 with a *p*-value less than 0.001. %Hypo-He was higher in the ID category (0.90 ± 2.2) with a p-value less than 0.018. However, the %Hypo-He did not correlate with MCV (P-0.059). The ROC analysis of the parameters showed cutoff values of 32.25 pg for Ret-He, 1.55% for %Micro-R, 0.25% for %Hypo-He and 15.1ng/ml for ferritin in detection of ID. As per the Ret-He cut-off values, sensitivity was 98%, and specificity was 97%, approximately the same as serum ferritin, amounting to 99.3% and 97.7%, respectively. Ret-He and new erythrocyte parameters %Micro-R and %Hypo-he correlation with serum ferritin showed that Ret-He has sensitivity and specificity same as that of serum ferritin. The ROC analysis for Ret-He was 0.999, with a 95% confidence interval of 0.998-1.000, which shows it as one of the discriminators for deficiency of iron with a *p*-value less than 0.001 (Tables 5 & 6).

Table 4: Comparison of new reticulocyte and erythrocyte parameters with serum iron parameters

Parameters	Reference interval	ID	N-ID	*p*
		Mean ± SD	Mean ± SD	
RBC (× 10 ¹²/L)	3.8 – 4.8	4.3 ± 0.5	4.3 ± 0.5	0.162
Hb (g/dL)	11.0 – 15	12.3 ± 1.1	12.0 ± 1.7	0.098
MCV (fL)	78.9 – 98.5	84.3 ± 5.0	85.7 ± 3.1	0.006*
RDW (%)	12.4 – 17.3	14.1 ± 1.7	13.9 ± 1.2	0.266
Retic count (%)	0.5 – 2.5	1.4 ± 0.4	1.5 ± 1.0	0.207
Ret-He (pg.)	29 – 36	28.3 ± 1.6	33.8 ± 1.6	<0.001*
% Micro-R (%)	0.3 – 2.8	3.9 ± 3.4	1.1 ± 0.6	<0.001*
%Hypo-He (%)	0.1 – 1.1	0.9 ± 2.2	0.4 ± 0.3	0.018*
TIBC (mugm/dl)	265 – 450	391.0	310.4	<0.001*
Fe (mugm/dl)	40 – 177	71.5	70.7	0.814
Ferritin (ng/ml)	20 – 137	14.3	69.1	<0.001*

p-value significant at 5% level of significance (p<0.05)*

**ID – Iron deficient group, N-ID – Non-Iron deficient group, RBC – Red blood cells, Hb – Hemoglobin, MCV – Mean Corpuscular Volume, RDW – Red cell distribution width, Ret-He - Hemoglobin content of reticulocytes, %Micro-R – Percentage of microcytic red blood cells, %Hypo-He - Percentage of hypochromic red blood cells, TIBC – Total iron binding capacity, Fe - Iron*

Table 5: ROC analysis of parameters in predicting iron deficiency

Parameters	Area Under the Curve	Std. Error	*p*	95% CI	
				Lower	Upper
Ret-He (pg.)	**0.999**	0.001	<0.001*	0.998	1.000
% Micro-R (%)	**0.841**	0.023	<0.001*	0.796	0.887
%Hypo-He (%)	**0.546**	0.034	0.184	0.479	0.613
Ferritin (ng/ml)	**0.989**	0.007	<0.001*	0.975	1.000

p-value significant at 5% level of significance (p<0.05)*

Ret-He - Hemoglobin content of reticulocytes, %Micro-R – Percentage of microcytic red blood cells, %Hypo-He - Percentage of hypochromic red blood cells

Table 6: Cut-off values with sensitivity & specificity of the parameters

Parameters	Cutoff value	Sensitivity	Specificity
Ret-He (pg.)	32.25	98.0%	97.0%
% Micro-R (%)	1.55	76.9%	69.9%
%Hypo-He (%)	0.25	63.9%	39.1%
Ferritin (ng/ml)	15.1	99.3%	97.7%

Ret-He - Hemoglobin content of reticulocytes, %Micro-R - Microcytic red blood cells, %Hypo-He - Percentage of hypochromic red blood cells

1 A 1B

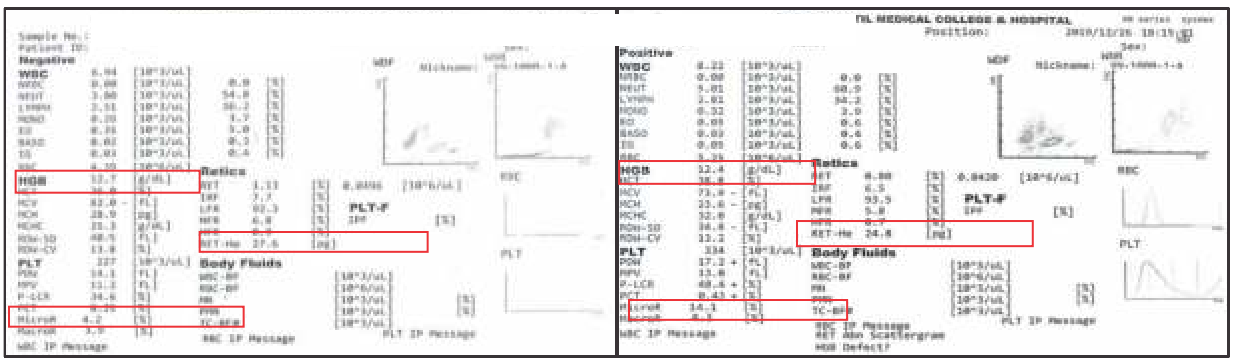

Figure 1A: The hematology analyzer report shows normal hemoglobin and normal MCV but increased %Micro-R and decreased Ret-He

Figure 1B: Hematology analyzer report showing normal Hb and decreased MCV, increased %Micro-R and decreased Ret-He

Discussion

One of the routine investigations done during pregnancy in antenatal checkups is CBC. MCV and RDW investigations are also done for IDA screening. However, these parameters do not help in identifying patients with subclinical anemia. If there is a suspicion of IDA, the subsequent investigations of choice are biochemical tests to assess the serum iron status. The most commonly used parameters to rule out IDA are serum iron, TIBC and ferritin. Serum iron and TIBC show changes once the disease is advanced. Serum ferritin, which is considered the gold standard, is affected by ongoing inflammation/infection and gives falsely high results. Serum transferrin saturation, though a reliable test, is expensive. Hence, there has been a need for reliable and cost-effective parameters to identify IDA in subclinical anemia. The newer parameters introduced in the recent hematology analyzers like Ret-He, %Micro-R and %Hypo-He have been studied extensively to evaluate their efficacy by comparing them to the existing gold standard parameters [1, 10]. These parameters give information about iron availability for erythropoiesis of reticulocytes and RBCs. Biochemical tests are affected by infection and inflammation, but new reticulocyte and erythrocyte parameters are unaffected. These additional tests can be done on the sample collected in an EDTA tube for CBC. A study conducted by Schapkaitz [11] stated that Ret-He can be measured on K2 EDTA specimens maintained at 4° to 8°C for up to 72 hours. Storage at the above-mentioned temperature causes swelling of RBCs. Hence, it is not a viable option for estimating erythrocyte parameters such as %Hypo-He and % Micro-R. The erythrocyte parameters should be evaluated within 12 hours for reliable results [11]. In the present study, erythrocyte parameters were evaluated within 2 hours of collection in all cases.

Women are likely to develop IDA due to pregnancy, menstruation and insufficient nutritional intake [10]. The relation between parity and IDA was studied by Prasad [12] in 200 pregnant women, of which 108 were primigravida, and 92 were multigravida. Of the multi-gravida group, 40.2% had mild anemia, 30.5% had moderate anemia, and 7.6% had severe anemia. Whereas in the primigravida group, 54.6% did not have anemia. Based on these findings, the author concluded that an increase in parity increases the risk of IDA. Similarly, Al-Farsi *et al*., [13] also showed an increase in anemia with an increase in parity. However, they also noted considerably high ID cases in primigravida. In the indexed study, 117 were primigravida; out of which 52 (44%) were ID and 113 were second gravida, of which 58 (51.3%) were ID. Women with gravida 3 were 36 cases, of which 27 (75%) were ID. All the gravida 4 and 5 cases were classified under the ID group, unlike the primigravida, having almost equal distribution between the ID and non-ID groups.

In some studies, a comparison of the iron stores in marrow was done with serum iron, TIBC and serum ferritin levels. In these studies, it was observed that ferritin level in serum was the best discriminator among the three parameters. Still, it is not practical to perform in all patients, especially in pregnancy, when they do not have any clinical presentation. [14, 15]. Broek *et al*., [14] stated that for serum ferritin, a cutoff of less than 30 µg/dl was significant, whereas in some studies, it was observed that serum ferritin with the start of the disease process at a cut off of less than 25 µg/dl was significant [15]. In one of the studies, cutoffs of less than 15 µg/dl were specific for serum ferritin but not sensitive [16]. In the present study, the IDA cutoff value for serum ferritin was less than 20 µg/dl. Based on this cutoff, out of 280 pregnant women, 151 were classified as ID cases and 129 as non-ID. Based on ROC analysis, serum ferritin at the cutoff of 15.1 µg/dl showed a sensitivity of 99.3% and specificity of 97.7% with area under curve (AUC) of 0.989.

The new erythrocyte parameters %Micro-R and %Hypo-He have been considered in the present study to identify subclinical ID. %Micro-R was statistically significant ($p < 0.001$) whereas %Hypo-He was not. The new reticulocyte parameter, Ret-He, showed statistical significance ($p < 0.001$). The highest sensitivity and specificity of 98% and 97%, respectively, were seen at 32.25 pg and were comparable to that of serum ferritin, which was 99.3% and 97.7% at a cutoff of 15.1 µg/dl.

Levy *et al*., [2] mentioned that newer erythrocyte and reticulocyte parameters help to discriminate

ID from non- ID groups significantly. Ret-He, at a cut-off of less than 31.2 pg, was considered the best discriminator with 62.5% sensitivity and 86.44% specificity. The sensitivity was better at a cut-off of less than 32 pg, but the specificity came down to 67.8%. We observed high sensitivity and specificity at a cut-off value of 32.25 pg. The sensitivity and specificity were best at a cut-off of more than 0.2% and more than 1.4% for %Hypo-he and %Micro-R. The present study showed a sensitivity of 76.9% and specificity of 69.9% at a cutoff of more than 1.55%, which was statistically significant. Whereas %Hypo-He at a cutoff value of more than 0.25 did not show statistical significance.

Urrechaga *et al*., [17] studied healthy premenopausal women to identify latent ID. Ret-He and %Hypo-He were the two parameters considered. Ret-He at a cutoff of less than 29.9 pg showed good sensitivity (86.8%) and specificity (85.7%) with AUC of 0.914 at a 95% CI of 0.824-1.000 and %Hypo-He at a cut-off value of more than 1.6 % showed highest sensitivity and specificity. In the current study Ret-He cut-off showed better sensitivity and specificity at a cutoff of 32.25 pg.

Karunarathne *et al*., [18] studied the effectiveness of Ret-He in diagnosing ID in renal disease on regular hemodialysis and erythropoietin. They could not establish its utility in the diagnosis of ID. However, 72 hours after treatment, Ret-He showed a statistically significant increase. Therefore, they concluded that Ret-He is best used to evaluate the response after iron therapy.

The present study showed maximum sensitivity and specificity at a higher cutoff value of 32.25 pg of Ret-He when compared to other studies, such as Cai *et al.*, [19] which showed the sensitivity and specificity to be highest at a cutoff value of 27.2 pg in their studies. Kumar *et al.*, [20] concluded that a cutoff value of 27.8 pg showed the highest discriminative value with maximum sensitivity and specificity. However, Joosten *et al.* [21] found a cutoff value of 26 pg having better sensitivity and specificity. The present study has the highest sensitivity of 98% and specificity of 97%, with an AUC of 0.99 at a cutoff value of 32.25 pg.

Conclusion

Ret-he can be used as an alternative hematological investigation instead of serum ferritin for the early detection of subclinical IDA in pregnancy due to its cost-effectiveness and as it can be done along with routine hematological investigation such as CBC. This study adds the utility of newer erythrocyte and reticulocyte parameters by comparing them with the traditional parameters for detecting subclinical ID in pregnant women.

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