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STUDY OF CORRELATION BETWEEN FERRITIN, BMI AND CRP IN SAUDI YOUNG FEMALES WITH MILD MICROCYTIC ANEMIA IN AL-GHAD COLLEGE, JEDDAH, KINGDOM OF SAUDI ARABIA

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Abstract

The obesity is rapidly increasing health problem. Evidence suggested obesity-related inflammation alters iron metabolism. This study explored correlation between serum ferritin, body mass index (BMI) along with C-reactive protein (CRP), among young females with or without mild microcytic anemia. The study was conducted on 49 students and staff (17- 36 years old), AL-Ghad College, divided into: GI (n=30) with normal hemoglobin level (≥12 g/dl); GII (n=19), mild microcytic anemia (Hb <12-10g/dl; MCV <80fl), further participants stratification according to their BMI into: underweight (BMI <18.5 kg/m^2); normal weight (BMI ranging 18.5-24.9); overweight and obese (BMI >25) subgroups. Serum ferritin and CRP were performed. Results were statistically analyzed.

The results showed that in GI, those with BMI > 25 kg/m^2 had significantly higher CRP compared to normal and underweight subgroups ($p<0.01$), where GII ($p<0.01$), ($p<0.05$), respectively. In both groups, increased BMI, was associated with statistically insignificant elevated ferritin, which is significantly correlated with CRP ($p< 0.05$), yet not correlated with BMI. However, BMI was significantly correlated with CRP, in both ($p< 0.05$), ($p< 0.01$) respectively.

Key words: Serum ferritin; BMI; CRP; young females; mild microcytic anemia.

Introduction

Iron deficiency and obesity independently constitute major disease burdens affecting significant proportions of the global population (Yanoff *et al,* 2007). Although, obesity has an adverse effect on iron status, it is also, characterized by chronic, low-grade, systemic inflammation, which, in turn, is associated with anemia of chronic disease specifically, elevated serum ferritin and low serum iron, transferrin saturation, and Hb level (Nead *et al,* 2004; Al-Nozha *et al,* 2007). However, association between obesity, CRP and iron deficiency were renewed interest in the area of iron status in the obese, particularly in adults and children (Yoo *et al,* 2015).

Based on the fact that serum ferritin measurement is recommended as the first laboratory test for evaluation of microcytosis. It was hypothesized that, within the same range of hemoglobin among subjects presented with or without mild microcytic anemia, overweight and obese individuals may have higher ferritin levels than expected compared to normal weight counterparts (Abo-Zeid *et al,* 2014) referred to the fact that obesity-related inflammation and considering ferritin as one of the acute phase reactants Consequently, this may mask to what extent the state of hypoferritinaemia which is frequently present in microcytic anemia.

The present study explored correlation between iron statuses defined on basis of serum ferritin along with CRP as an inflammatory biomarker and BMI among young females with or without mild microcytic anemia.

Subjects, Materials and Methods

A total of 56 child bearing age women, undergraduate students and staff, in Al-Ghad College, Jeddah, aged 17- 36 years old, consecutively recruited, and volunteered to participate in this research. They divided into two groups either with or without mild microcytic anemia. Both groups were stratified

subsequently according to their BMI into underweight, normal and overweight / obese subgroups, to assess the potential confounding effect of obesity-related chronic inflammation on the determined ferritin levels among these subjects. Prior to obtain any data, the subjects completed a health questionnaire regarding medical history, medications, and current health conditions. Seven out of the 56 subjects were excluded from the study according to eligibility criteria for participation which were: 1- adolescents, and non-pregnant or lactating women of reproductive age; 2- absence of any chronic illness; 3) negative family history for thalassemia; 4- no intake of medications that may influence weight, iron or inflammatory status; and 5- apparently healthy subjects. All subjects signed an informed consent.

Study Design*:* Subjects were divided into 2 main groups on basis of their hemoglobin levels, in which GI (n=30) included subjects with normal level (≥ 12 g/dl), whereas, GII (n=19) included those with Hb level lying in range of (<12-10g/dl) and (MCV <80ft), denoting mild degree of microcytic anemia (WHO, 2001). Each group subsequently, stratified into 3 subgroups according to their BMI into: 1- underweight subgroups where (BMI <18.5 kg/m^2), 2- normal weight subgroups with (BMI ranged from 18.5-24.9 kg/m^2), which was considered as control for their relevants within the same group, and 3- the overweight and obese subjects subgroups with (BMI ≥25kg/m^2). For all subjects, the following tests were performed.

Anthropometric measurements: Height and weight were measured and BMI was calculated with the well-known formula (WHO, 2006): BMI =weight/height^2, where weight was in kilogram and height in meter

Laboratory analysis: Venous blood samples were collected from all subjects, in which, 2ml in EDTA and 3ml in sterile plain vacutainer. The EDTA anti-coagulated sample was used for performing complete blood pictures immediately, using Cell counter (Boule Medical AB Domnarvsgatan, Sweden). The total red cell count, hemoglobin and hematocrit were estimated, and also red cell indices including, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW). The other 3ml of blood, on plain vacutainer tube, were kept at room temperature for nearly an hour and centrifuged to separate sera. Further aliquoted and frozen at -80°C until assessment of serum ferritin concentrations using Module cobas e 601 (cobas®6000 analyzer series; Roche Diagnostics, USA), an electrochemiluminescence immunoassay "ECLIA", also, quantitative CRP Module cobas e 501 using "ECLIA", and determined turbid-metrically.

Also, Giemsa stained blood smears were examined for malignant malaria and stool to exclude intestinal hookworms and schistosomiasis by thick smear (Katz *et al*, 1972).

Statistical analysis: Data were expressed as mean ± standard deviation (SD). Comparison between variables in groups was done using one way ANOVA followed by Tukey's test as a post hoc test if significant results were obtained. Correlation between different variables was done using Pearson correlation coefficient test. Statistical Package for Social Sciences (SPSS) version (19 windows) was used. P value ≤ 0.05 was significant and < 0.01 was highly significant.

Results

The results are shown in tables (1, 2, 3, 4 & 5) and figures (1, 2 & 3).

Table 1: Distribution of population according to BMI in GI and GII.

Parameters	GI Normal Hb (n= 30)	G II Mild microcytic Hb (n= 19)
Underweight (n= 10)	6 (20.0%)	4 (21.1%)
Normal BMI (n= 23)	14 (46.7%)	9 (47.4%)
Overweight & obese (n= 16)	10 (33.3%)	6 (31.6%)

Table 2: Haematological characteristics, Ferritin and CRP among subjects (n= 30) with normal Hb (≥ 12 g/dl) stratified according to BMI.

Parameters	Under weight (n= 6)	Normal weight (n= 14)	Overweight & obese (n= 10)	*P value*
Age (yrs.)	20.83 ± 1.17	21.93 ± 3.56	26.20 ± 8.22	0.098
Height (cm)	160.67 ± 5.61	161.18 ± 8.51	158.00 ± 4.67	0.531
Weight (kg.)	41.95 ± 2.46	56.08 ± 8.05 [a]	74.40 ± 12.57 [aa, bb]	0.001**
BMI (kg/m^2)	16.27 ± 1.13	21.47 ± 1.57 [aa]	29.68 ± 4.05 [aa, bb]	0.001**
Hemoglobin (g/dl)	13.60 ± 1.59	12.99 ± 0.74	13.60 ± 1.12	0.318
MCV (fl)	83.83 ± 5.09	81.57 ± 6.25	81.37 ± 4.22	0.642
RBC (x10^{12}/L)	4.72 ± 0.65	4.63 ± 0.56	5.12 ± 0.51	0.114
Hematocrit (%)	39.43 ± 4.89	37.47 ± 2.71	41.16 ± 4.82	0.096
MCH (g/dl)	29.27 ± 1.41	28.35 ± 2.48	27.16 ± 1.42	0.127
MCHC (%)	34.63 ± 1.14	34.75 ± 1.26	33.78 ± 1.46	0.197
RDW (%)	14.00 ± 0.35	14.28 ± 0.89	14.73 ± 0.92	0.216
Platelet	231.83 ± 33.39	275.50 ± 71.16	232.40 ± 47.25	0.146
WBCs	6.93 ± 1.92	7.47 ± 2.13	8.44 ± 4.04	0.563
S. Ferritin (ng/ml)	17.72 ± 9.31	40.70 ± 31.82	46.48 ± 1.31	0.261
CRP	0.50 ± 0.22	0.41 ± 0.23	1.02 ± 0.54 [aa,bb]	0.001**

p> 0.05= NS= not significant; **p< 0.01= highly significant. [a]p< 0.05 ; [aa]p< 0.01 relative to underweight group. [b]p< 0.05[bb]p< 0.01 relative to normal weight group.

Table 3: Haematological characteristics, serum ferritin level and CRP among subjects in GII with mild microcytic anemia (Hb <12-10g/dl; MCV < 80fl) stratified according to BMI.

Parameters	Under weight (n= 4)	Normal weight (n= 9)	Overweight & obese (n= 6)	*P value*
Age (yrs.)	20.00 ± 1.63	23.44 ± 6.00	25.50 ± 5.75	0.310
Height (cm)	159.00 ± 11.94	159.00 ± 5.57	161.33 ± 7.50	0.831
Weight (kg.)	46.50 ± 4.65	52.52 ± 6.42	80.00 ± 14.57 [aa, bb]	0.001**
BMI (kg/m^2)	17.83 ± 1.56	20.83 ± 1.36	30.48 ± 3.43 [aa, bb]	0.001**
Hemoglobin (g/dl)	10.35 ± 2.10	11.18 ± 0.80	10.50 ± 0.91	0.413
MCV (fl)	71.03 ± 12.14	75.32 ± 7.29	73.65 ± 8.81	0.724
RBC (x10^{12}/L)	4.40 ± 0.35	4.41 ± 0.29	4.42 ± 0.46	0.999
Hematocrit (%)	31.45 ± 5.08	32.37 ± 2.09	32.32 ± 3.16	0.883
MCH (g/dl)	23.60 ± 5.32	25.44 ± 2.60	24.02 ± 2.90	0.587
MCHC (%)	33.03 ± 2.57	34.67 ± 1.16	32.52 ± 0.82 [b]	0.030*
RDW (%)	16.03 ± 2.82	14.87 ± 1.34	16.18 ± 1.01	0.278
Platelet	264.25 ± 76.80	296.33 ± 120.35	298.00 ± 45.91	0.830
WBCs	6.60 ± 1.28	6.82 ± 1.99	7.85 ± 2.21	0.528
S. Ferritin (ng/ml)	5.61 ± 1.48	12.55 ± 14.83	15.28 ± 9.49	0.387
CRP	0.36 ± 0.08	0.28 ± 0.13	1.20 ± 0.74 [a,bb]	0.002**

p> 0.05= NS= not significant;*p< 0.05= significant;**p< 0.01= highly significant. [a]p< 0.05 ; [aa]p< 0.01 relative to underweight group. [bb]p< 0.01 relative to normal weight group.

Table 4: Correlative study between BMI and Ferritin levels with different parameters in GI (n= 30) with normal hemoglobin group.

Items	BMI		Ferritin	
	Pearson Correlation	p value	Pearson Correlation	p value
Hb	0.050	0.791	-0.208	0.457
RBC	0.343	0.064	-0.039	0.889
MCV	-0.103	0.588	-0.244	0.381
HCT	0.270	0.149	-0.246	0.377
MCH	-0.316	0.089	-0.281	0.310
MCHC	-0.168	0.376	0.065	0.819
RDW	0.240	0.201	-0.032	0.909
WBC	0.108	0.570	0.411	0.128
PLT	0.019	0.919	0.283	0.308
Ferritin	0.206	0.461	---	--
CRP	0.398	0.029*	0.561	0.030*

p> 0.05= NS= not significant. *p< 0.05= significant. **p< 0.01= highly significant.

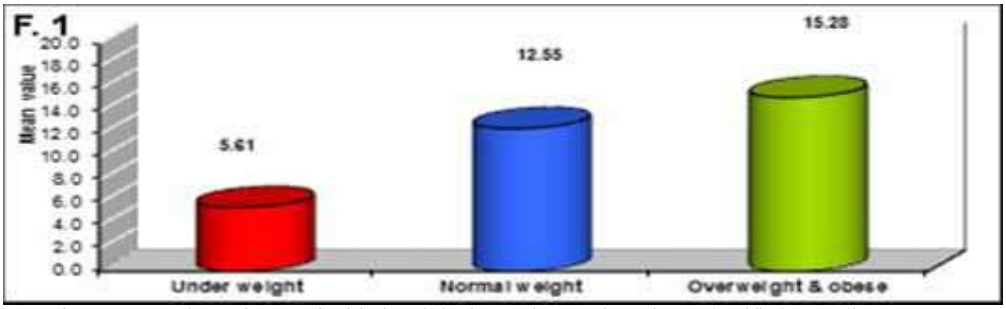

Fig 1: Mean values of serum ferritin in mild microcytic anemia patients classified according to BMI.

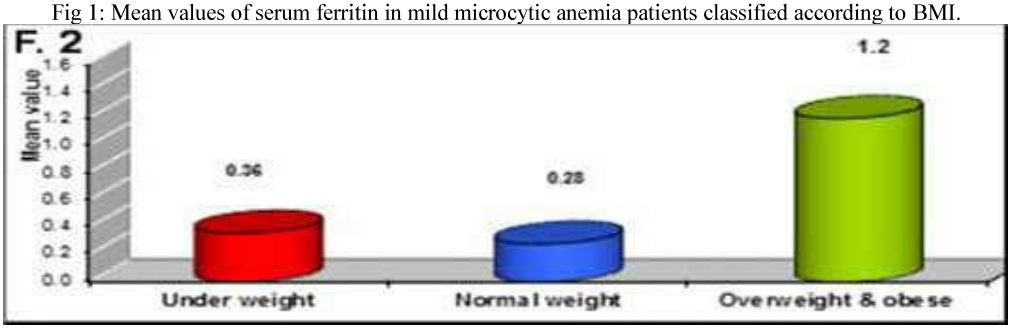

Fig 2: Mean values of CRP in mild microcytic anemia patients classified according to BMI.

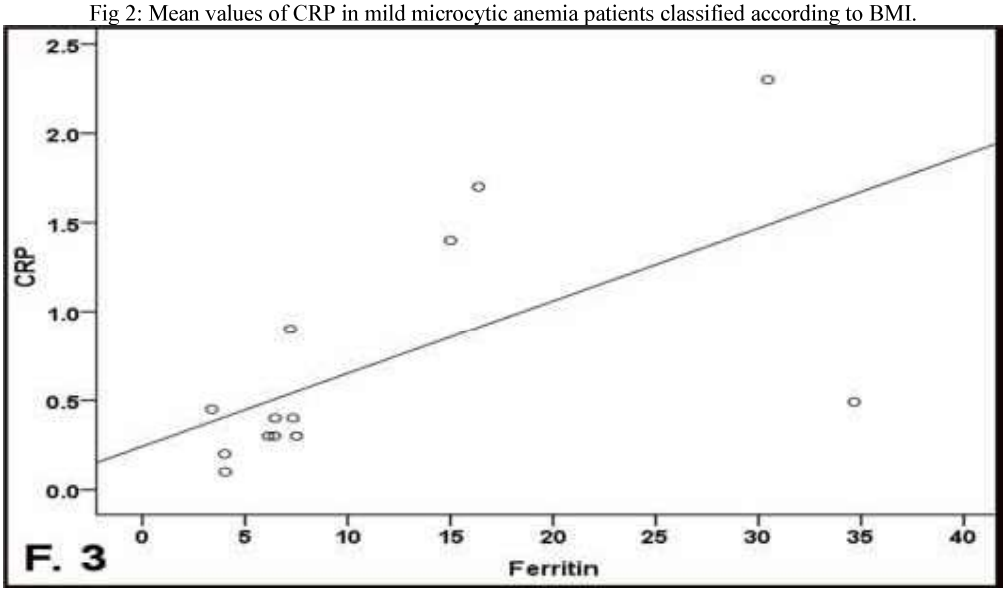

Fig. 3: Correlation between ferritin and CRP in mild microcytic anemia group (r= 0.616; p= 0.025).

Table 5: Correlative study between BMI and ferritin with different studied parameters GII (n= 19) with mild microcytic anemia group.

Items	BMI		Ferritin		CRP	
	Pearson Correlation	p value	Pearson Correlation	p value	Pearson Correlation	p value
Hb	-0.129	0.599	-0.154	0.616	-0.147	0.547
RBC	0.112	0.647	0.053	0.863	0.041	0.866
MCV	-0.040	0.870	-0.131	0.670	-0.035	0.886
HCT	0.075	0.759	-0.148	0.630	0.025	0.918
MCH	-0.154	0.529	-0.150	0.625	-0.117	0.632
MCHC	-0.434	0.063	-0.013	0.966	-0.370	0.119
RDW	0.196	0.421	-0.090	0.771	0.140	0.569
WBC	0.226	0.353	0.149	0.626	0.177	0.468
PLT	0.097	0.692	-0.141	0.647	-0.104	0.671
Ferritin	0.464	0.110	---	---	0.616	0.025*
CRP	0.818	0.001**	0.616	0.025*	---	---

p> 0.05= NS= not significant. *p< 0.05= significant.**p< 0.01= highly significant.

Discussion

Iron deficiency affects predominantly children due to increased demand and women of child bearing age due to menstrual blood loss (Ausk and Ioannou, 2008). Studies have demonstrated that, the most significant negative consequence of iron deficiency is iron deficiency anemia (Li *et al,* 2011; Al-Quaiz *et al,* 2012).

In this study, subjects with parasites encountered in Saudi Arabia as malaria (Al-Harthi, 2016) mainly *falciparum* (Al-Farsi *et al*, 2012), intestinal parasites (Taha *et al,* 2013) and/or schistosomiasis (Mohammad, 2014) were excluded. These parasites are known to cause iron deficient anemia. Also, Abd Ellah *et al*. (2915) in Upper Egypt reported that the highest prevalence of schistosomiasis is usually found in school-age children and youth, where it represents the main cause of iron deficiency anemia. They found that the overall pure schistosomiasis was 31.66%. Iron deficiency anemia was 27.7% in non-infected cases and in schistosomiasis patients iron deficiency anemia were found in 43.38% with statistically significant (P value=0.001).

The current study focused on women of child bearing age, as they were likely prone to develop Fe deficiency. A total of 39% (19/49) had mild microcytic anemia. This finding agreed with a study conducted in Riyadh demonstrated that 40% of child bearing age women suffered from anemia and 83% among them of mild type, where their RBCs indices point towards IDA (Al-Johara *et al,* 2013). Fattahi Bafghi *et al*. (2013) in Iranian children reported chronic Malaria disorder characterized by moderate to mild normocytic, normochromic anemia along with microcytic hypochromic cells. Huang *et al.* (2014) in the United Kingdom stated that the acute malarial anemia remains a major public health problem. Hepcidin, the major hormone controlling the availability of iron, was raised during acute and asymptomatic parasitemia. Rodríguez-Guardado *et al*. (2013) reported a case of hookworm in a Spanish patient who before imprisonment had lived in Brazil; diagnosis established a progressive manifestation of asthenia, together with hypochromic microcytic anemia and eosinophilia.

Generally speaking, the increasing in the prevalence of obesity is a global health concern always leading to diabetes mellitus, which is a public health challenge worldwide (El-Tawdi *et al,* 2016). Diabetes mellitus is a public health challenge worldwide, and roughly 25% of diabetes patients in developing countries developed at least one foot ulcer during their lifetime (Melmed *et al*, 2011). Often people with type 2 diabetes have no symptoms (CDC, 2015). Al-Hazzaa (2007) stated that the rising trends in BMI between 1988 and 1996 were indication of increasing obesity among Saudi male adolescents. More attention to the promotion of healthy nutrition and the physical activity throughout childhood and adolescence was required. In Saudi Arabia, based on the National Nutrition Survey in 2007, the prevalence of overweight in the community was determined to be 30.7% for men as compared to 28.4% for women (Al-Dossary *et al,* 2010)..In agreement with previous findings, the current results revealed that the prevalence of those subjects with BMI > 25kg/m^2 among females was nearly 32% (16/49). Moreover, 37.5% (6/16) of them suffered from mild microcytic anemia (Tab. 1).

The present results revealed that in both groups, there was a highly significant difference regarding CRP compared to overweight and obese within groups, as p value <0.01 (Tabs. 2 & 3). The present data went with that denoted significant association between obesity and CRP (Ausk *et al, 2008;* Tussing-Humphreys *et al,* 2009). No doubt, CRP is the main acute phase protein and a sensitive marker of systemic inflammation in man (Moschonis *et al,* 2012) and experimental animals (Torrente *et al*, 2015). Studies have shown that obesity is characterized by a state of low grade inflammation in different tis-

sues and consequently CRP concentration decreases significantly after massive weight reduction. This decrease indicated that fat mass played an important role in the production of CRP (Lecube *et al,* 2006).

In the current study, there was a non-significant increase in the levels of serum ferritin with increased BMI in both groups, with the greatest level among overweight and obese subjects. Moreover, it was worthy to mention that, this increase in ferritin level, yet still within the reference range in case of GI, and under the reference range in GII, and the wide reference range of serum ferritin level; 15-150µg/l for females (WHO, 2010). This difference in serum ferritin level in the present study although within the same Hb level range may be due to the fact that, obesity is characterized by chronic, low-grade, systemic inflammation, which subsequently, associated with the increase in serum ferritin level being one of the acute phase reactants. Likewise, this elevation in serum ferritin level may either obscure an iron deficiency or indicate a larger iron store than truly exists. On the other hand, the associated decreased ferritin level among underweight subjects, a possible explanation for this might be the important role of fat mass in the production of CRP (Al-Johara *et al,* 2013).

In consistency with the present data, Cheng *et al*. (2012) demonstrated that, increased BMI was associated with higher serum ferritin levels and lower serum levels of iron and transferrin saturation. Nevertheless, hemoglobin concentration was not lower in overweight and obese persons compared with normal-weight persons. However, unpredictably, Ghadiri-Anari *et al*. (2014) conducted a comparative analysis of the association between general obesity (BMI) and visceral obesity (waist circumference) with the iron status among Iranian population, showed that, obese or overweight people are more likely to have iron deficiency, whilst those with raised waist circumference are more likely to have iron overload.

The gold standard of empty iron stores was serum ferritin. Furthermore, a concentration of <12–15ug/l was taken to indicate deficient iron stores and likelihood of development of IDA (Yoo *et al*, 2015). Consequently, it was superior to transferrin saturation or serum iron in the diagnosis of IDA as its concentration correlates with bone marrow iron stores. Nevertheless, developed countries recommended iron supplementation based on serum ferritin levels (Asberg *et al,* 2014). But, in some populations, such as those with inflammatory disease or cirrhosis, these tests must be interpreted slightly differently because ferritin is an acute-phase reactant. Cutoffs for abnormality in these patients generally are higher (Ghadiri-Anari *et al,* 2014).

The present statistical analysis showed a high positive statistical correlation between BMI and CRP as a marker of inflammation where ($p< 0.05$); ($p< 0.01$) in GI and GII respectively. There was a significant correlation between CRP and serum Ferritin level among GII population, females with mild microcytic anemia where ($p< 0.05$), meanwhile no statistical correlation regarding the previous studied parameters in GI (Tabs. 4 & 5).

The current results revealed, in GI, BMI had insignificant negative correlation with MCV, MCH and MCHC and insignificant positive correlation with other studied parameters including ferritin, while CRP mentioned previously. In GII, there was insignificant negative correlation between BMI and Hb, MCV, MCH and MCHC without significant positive correlation with other parameters. The results agreed with those obtained from a cross-sectional study conducted among 406 obese patients (18-65 years old) in Yazd province (Iran) from January 2011 to January 2013 (Ghadiri-Anari, *et al,* 2014).

Conversely, there was a significant correlation (Nead *et al,* 2004; Ausk *et al,* 2008). This discrepancy might be due study population's variability regarding age groups and BMI scoring.

Generally, the present study faced some limitations. Being consecutively recruited, and stratification of subjects had the same range of Hb level according to their BMI resulting in, small sample size of overweight and obese subjects, forcing us to make them in one subgroup where the BMI > 25kg/m^2, regarding both groups.

Conclusion

Serum ferritin cannot be reliable predictor marker identifying iron status due to association of its elevation, with increased BMI although occurrence of mild microcytic anemia and significantly correlated with CRP. Ferritin was significantly correlated with CRP. Undoubtedly, the obesity particularly in females is a predisposing factor to the diabetes mellitus and its risky complications on both the mother and her fetus.

Recommendations

To sum up, particularly, based on the fact that, obesity-related inflammation alters iron metabolism, in the current study, the specifically have selected serum ferritin was considered as the most specific indicator of body iron reserves, alternate to stainable iron in bone-marrow smears, besides being one of the acute phase reactants.

One has to look for the newer surrogate iron biomarkers and inflammatory markers such as soluble transferrin receptor (sTfR), hepcidin markers for reliably predicting iron deficiency, in addition to existing routine iron markers in the present ongoing study.

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