Bariatric Surgery and Pregnancy deleteriously affect Women's Hematological Milieu. Is Iron Supplemental Therapy may be beneficial?

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Abstract

Objectives: to evaluate the impact of bariatric surgery (BS) on hematological status of women who got pregnant and the effect of iron supplemental therapy (IST) of these impacts.

Patients & Methods: 57 women had previous BS (group B) and 119 women (Group A) had no previous BS were evaluated at 1st trimester for their hemoglobin concentration (HB conc.) and serum levels of ferritin (SF), hepcidin and interleukin-6 (IL-6). Women had iron deficiency anemia (IDA) received IST in the form of sucrosomial oral cap 100 mg once daily. HB conc. and SF were re-evaluated at the 2nd and 3rd trimester and HB deficit was calculated. Study outcome included the impact of IST on frequency and severity of anemia.

Results: HB conc. and SF of all women decreased progressively during pregnancy course with significantly lower estimates in women of group B compared to group A. Frequency of anemic women was significantly higher in group B at the first two trimesters, but was non-significantly higher at 3rd trimester compared to group A, while frequency of women had ID was significantly higher at 1st trimester but was non-significantly higher at the 2nd and 3rd trimesters in group A than group B. At the 3rd trimester, 56 women had increased; while 116 women had decreased HB conc. with significantly higher frequency of women had increased HB conc. among women of group B. Serum hepcidin levels were significantly higher, while serum IL-6 levels were non-significantly higher in women of group B. Percentage of change of HB conc. at 3rd trimester was positively correlated with presence of BS, while negatively correlated with 1st trimester HB conc. and presence of chronic inflammatory anemia. Regression analysis defined presence of CIA, 1st trimester HB conc., the use of IST and previous BS as significant predictors for possible change of HB conc. at the 3rd trimester.

Conclusion: Women had BS were always anemic and had micronutrient deficiencies that must be corrected prior getting pregnant to avoid aggravation. IST started since 1st trimester allowed improvement of anemia especially for women had BS. Sucrosomial oral iron allowed increased HB conc. in 31.8% of studied women.

Keywords: Bariatric surgery, Pregnancy, Anemia, Iron supplemental therapy, Hepcidin, Interleukin-6.

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INTRODUCTION

Obesity originates from an imbalance between caloric intake and energy expenditure that promotes adipose tissue expansion, which is necessary to buffer nutrient excess [1]. Adipose tissue functions as an active endocrine organ, has key role in immunity and inflammation, and type 1 or type 2 immune responses and their respective cytokines have been linked to white or brown adipose tissue, respectively [2].

Obesity is associated with iron deficiency anemia (IDA) [3] and/or chronic inflammatory anemia (CIA) [4]. Bariatric surgery (BS) is considered as the most effective treatment of obesity with long lasting weight loss and improvement of metabolic disorders [5] but BS induces progressive increase of the frequency and severity of IDA, despite of decreasing the frequency of CIA [6].

Anemia is a common problem in obstetrics and perinatal care [7] and is mainly secondary to nutritional deficiencies [8]. Iron deficiency (ID) is the most common micronutrient deficiency worldwide with >20% of women experiencing ID during their reproductive lives [9]. Anemia affects about 50% of pregnant women and is associated with adverse outcomes for mother and child [10]. During pregnancy, trans-placental iron transfer systems include binding transferrin-bound iron to its receptor [11], uptake into an endosome, acidification, release of iron through divalent metal transporter 1 [12], efflux across the basolateral membrane through ferroportin and oxidation to ferrous ion [13].

Iron supplemental therapy (IST) during pregnancy is still a matter of discrepancy [14] because its clinical value for both the mother and newborn is still to some extent unclear [15], despite of the improved maternal hematological indexes [16]. Additionally, how to supply iron is also a matter of debit because high intake of heme iron was found to be associated with high risk of gestational diabetes [17], intolerability of multiple oral iron preparations and the risks and side effects of intravenous iron [18].

Hypothesis

Considering the high prevalence of iron and micronutrient deficiencies among women had BS [6], the prevalence of iron deficiency during pregnancy [10] and the low knowledge among women in childbearing period about the necessity of pre-conception medical evaluation to diagnose and treat deficiencies and systemic diseases [19], the current study hypothesized the necessity of evaluation of these deficiencies in women attending the obstetric outpatient clinic (OUC) for diagnosis or follow-up of pregnancy and the effect of IST during pregnancy on hematological measures.

Objectives

Evaluation of the impact of bariatric surgery (BS) on hematological status of women who got pregnant and the effect of iron supplemental therapy (IST) of these impacts

Design

Comparative prospective multicenter interventional study.

Setting

Gynecology & Obstetrics Department at Benha University Hospital in conjunction with multiple private Obstetric centers and clinical pathology department Benha Univerisity.

Patients & Methods

All pregnant women attending the obstetrics OUC during the 1st trimester were eligible for evaluation for inclusion criteria. Women had previous BS and fulfilling inclusion criteria were grouped as group B, while women had no previous BS were grouped as group A. Inclusion criteria included pregnancy in singleton fetus, no uterine or fetal anomalies, no history of cervical incompetence, free of indications for cesarean section, as previous CS, contracted pelvis, abnormal placental location, signed written fully informed consent to participate the study and to attend follow-up visits. Women had uncontrolled chronic systemic diseases, bleeding tendency, endocrinopathyies, maintained on immunosuppressive therapy or therapies affecting bone marrow health were excluded from the study.

According to **Api et al.** [20] iron deficiency and IDA was diagnosed according to sequential estimation of serum ferritin (SF) concentration and hemoglobin concentration (HB conc.) during the

three trimesters. HB conc. of <11, 10.5 and 11 g/dl during 1st, 2nd and 3rd trimesters, respectively indicates presence of anemia and if coupled with SF< 15 ng/ml indicates IDA but if SF was ≥15 ng/ml this points to an inflammatory state inducing iron stores depletion and indicates CIA [20]. All women with IDA diagnosed at time of enrollment or follow-up visits during 2nd and 3rd trimesters received IST using Sucrosomial Iron (Sideral Forte composed of sucrosomial iron® (Sideral® rm) 30 mg and vitamin C 70 mg; PharmaNutra, Via delle Lenze, Pisa, Italy) 100 mg cap to be taken once daily. Hemoglobin deficit at the 3rd trimester was calculated in relation to HB conc. estimated at time of enrolment was calculated.

Investigations

Venous blood samples (5 ml) were collected from the antecubital vein under complete aseptic conditions at time of enrolment and were divided into three parts:

1. The first part was put in EDTA tube (about 1.8 mg trik EDTA/ 1 ml blood) for at once HB conc. estimation by cyanomethemoglobin method [21].
2. The second part of the sample was kept in a plane container and allowed to clot then serum was separated by centrifugation at 3000 rpm for 10 min. Serum was removed and placed in pyrogen-free Eppendorf tubes and stored at -70°C until ELISA assayed by Spectrophotometer for

   a.Serum ferritin concentration using an ELISA kit from Eagle Bioscience Inc., USA (Catalogue No FER31-K01) [22].

   b.Serum hepcidin level using ELISA kit from Calbiotec, A Life Science Co, USA (Catalogue No DHP250) [23].

   c.Serum IL-6 using ELISA kit from Eagle Bioscience Inc., USA (Catalogue No IL631-K01) [24].

Study outcome

1. Primary outcome is the impact of IST on BS-induced and pregnancy-associated anemia (PAA).
2. Secondary outcome is the relation between serum levels of IL-6 and hepcidin and frequency of ID and IDA and HB deficits.

Statistical analysis

Obtained data were presented as mean±SD, numbers, percentages, median and interquartil range (IQR). Results were analyzed using paired t-test, One-way ANOVA Test and Chi-square test (X2 test). Possible relationships were investigated using Spearman's linear regression analysis. Regression analysis (Stepwise method) was used for stratification of studied parameters as specific predictors. Statistical analysis was conducted using the IBM SPSS (Version 23, 2015; IBM, South Wacker Drive, Chicago, USA) for Windows statistical package. P value <0.05 was considered statistically significant.

Results

The study included 176 pregnant women; 57 had previous BS (group B), while the remaining 119 women (Group A) had no previous BS (Fig. 1).

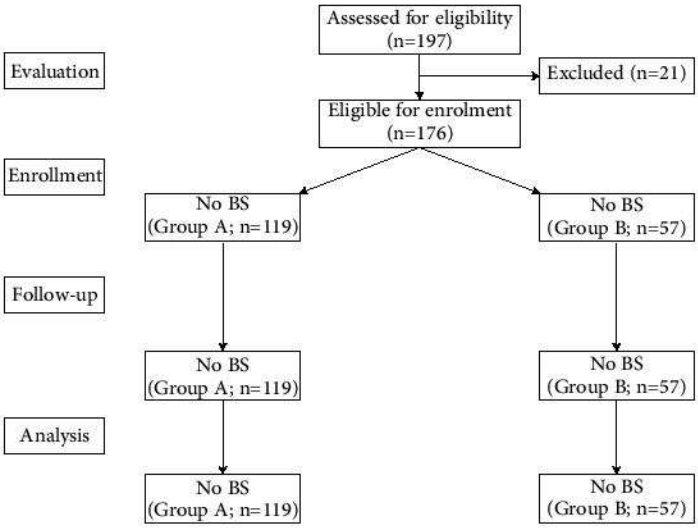

Figure 1: Consort Flow sheet

Women of Group B had significantly higher BMI with higher frequency of women had BMI>30 than women of group A. Moreover, blood pressure measures and fasting blood glucose level estimated at time of enrolment were significantly higher in women of group B compared to women of Group A (Table 1)

Table (1): Patients' data determined at time of enrolment

Data		Group A (n=119)	Group B (n=57)	P value
Age (years)		28±2.6	28.7±2.4	0.086
Body weight (kg)		80.1±5.3	88.9±4.2	<0.001
Height (cm)		169±3.4	168.2±3.4	0.729
Body mass index (kg/m^2)	<30	110 (92.4%)	38 (66.7%)	<0.001
	>30	9 (7.6%)	19 (33.3%)	
	Mean (±SD)	28.1±2	31.4±1.6	<0.001
Gravidity		2.2±0.8	2.1±0.8	0.328
Parity		1.2±0.8	1±0.8	0.119
Blood pressure (mmHg)	Systolic	115.6±4.6	119.6±8.9	0.013
	Diastolic	73.1±6.1	76.2±10.6	0.015
Fasting blood glucose (mg/dl)		108±11.5	115±7.5	0.023

Data are presented as mean±SD, numbers, percentages

HB conc. of women of group A showed progressive and significant decrease during pregnancy, while in group B, HB conc. was non-significantly higher at the 3rd trimester compared to at 1st and 2nd trimesters despite of being significantly lower than HB conc. estimated in women group A during pregnancy course (Fig. 2). On contrary, estimated levels of serum ferritin (SF) showed progressive and significant decrease in patients of both groups throughout pregnancy course with significantly lower SF levels in patients of group B than patients of group A at 1st trimester, but the difference was non-significant at the 2nd and 3rd trimester estimations. The frequency of anemic women was significantly higher in group B at the 1st and 2nd trimesters, but was non-significantly higher at the 3rd trimester compared to group A (Fig. 2). On contrary, the frequency of women had ID with SF level of <15 ng/ml was significantly higher at the 1st trimester, but was non-significantly higher at the 2nd and 3rd trimesters in women of group A than women of group B (Table 2, Fig. 3).

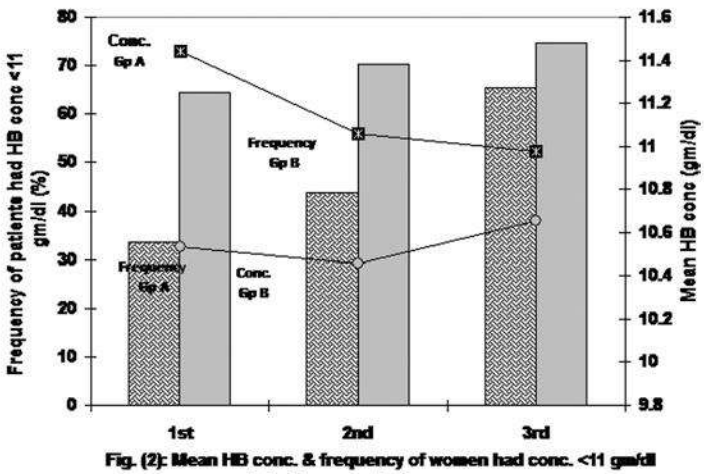

Fig. (2): Mean HB conc. & frequency of women had conc. <11 gm/dl in both groups during pregnancy

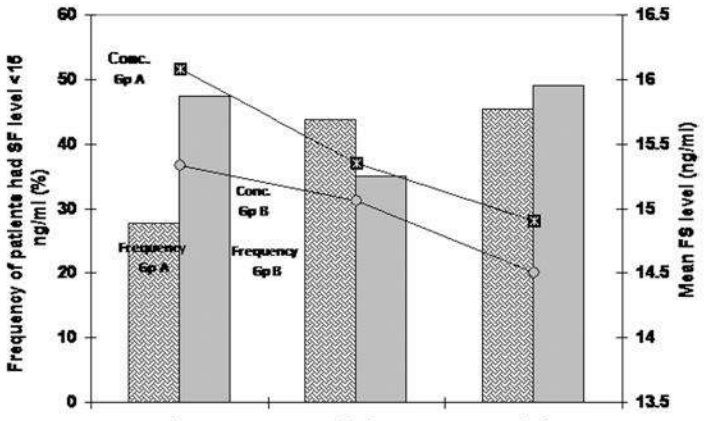

Fig. (3): Mean serum ferritin (SF) level & frequency of women had SF level <15 ng/ml in both groups during pregnancy

During course of pregnancy, 89, 67 and 36 women had no anemia/ID, at 1st, 2nd and 3rd trimesters, respectively with significantly higher frequency among women of group A at 1st and 2nd compared to women of group B, but the difference became non-significant at the 3rd trimester. Interestingly, at 3rd trimester, 56 women (31.8%) had increased; while 116 women (65.9%) had decreased HB conc. in relation to 1st trimester level and only 4 women (2.3%) had stable HB conc. with significantly higher frequency of women had increased HB conc. among women of group B. Moreover, the median value of change was -6.1 and 0.935 for women of groups A and B, respectively (Table 2). Serum hepcidin levels were significantly higher, while serum IL-6 levels were non-significantly higher in women of group B compared to women of group A (Table 2, Fig. 4)

Table (2): Laboratory findings of women of both groups determined during course of pregnancy

Time			Group A (n=119)	Group B (n=57)	P value
1st trimester	HB conc. (gm/dl)	<11	40 (33.6%)	37 (64.5%)	0.0009
		>11	79 (66.4%)	20 (35.5%)	
		Mean (±SD)	11.4±1	10.5±1.25	0.0002
	SF (ng/ml)	<15	33 (27.7%)	27 (47.4%)	0.011
		>15	86 (72.3%)	30 (52.6%)	
		Mean (±SD)	16.08±1.65	15.33±1.71	0.0061
	IDA		27 (22.7%)	23 (40.4%)	0.0005
	CIA		13 (10.9%)	14 (24.6%)	
	ID		6 (5%)	4 (7%)	
	No anemia/ID		73 (61.4%)	16 (28%)	
	Serum Hepcidin (ng/ml)		20.9±4.8	25±5.8	0.0007
	Serum IL-6 (ng/ml)		38.8±13.4	42.8±12	0.053
2nd trimester	HB conc. (gm/dl)	<11 gm	52 (43.7%)	40 (70.2%)	0.001
		>11 gm	67 (56.3%)	17 (28.8%)	
		Mean (±SD)	11.1±0.88	10.5±0.9	0.0009
	SF (ng/ml)	<15	43 (43.7%)	20 (35.1%)	0.277
		>15	76 (56.3%)	37 (64.9%)	
		Mean (±SD)	15.35±1.6	15.06±1.54	0.255
	IDA		35 (29.4%)	29 (50.9%)	0.0008
	CIA		17 (14.3%)	11 (19.3%)	
	ID		8 (6.7%)	9 (15.8%)	
	No anemia/ID		59 (49.6%)	8 (14%)	
3rd trimester	HB conc. (gm/dl)	<11 gm	78 (65.5%)	44 (74.6%)	0.117
		>11 gm	41 (34.5%)	13 (25.4%)	
		Mean (±SD)	10.9±0.9	10.65±0.58	0.028
	SF (ng/ml)	<15	54 (45.4%)	28 (49.1%)	0.641
		>15	65 (54.6%)	29 (50.9%)	
		Mean (±SD)	14.9±1.52	14.5±1.59	0.186
	IDA		41 (34.5%)	23 (40.4%)	0.453
	CIA		37 (31.1%)	21 (36.8%)	
	ID		13 (10.9%)	5 (8.8%)	
	No anemia/ID		28 (23.5%)	8 (14%)	
HB change at 3rd trimester in relation to 1st trimester		Increased	25 (21%)	31 (54.3%)	0.0005
		No change	3 (2.5%)	1 (1.8%)	
		Decreased	91 (76.5%)	25 (43.9%)	
		Median (IQR)	-6.1 (31.959)	0.935 (32.918)	0.0001

Data are presented as mean±SD, numbers, percentages, median, IQR: Interquartile range; HB: Hemoglobin; SF: Serum ferritin; IDA: Iron deficiency anemia (indicates HB conc. <11 gm/dl & SF <15 ng/ml); ID: Iron deficiency (indicates SF <15 ng/ml); CIA: Chronic inflammatory anemia; CIA indicates HB conc. <11 gm/dl & SF >15 ng/ml; No anemia/ID indicates HB conc. >11 gm/dl & SF >15 ng/ml

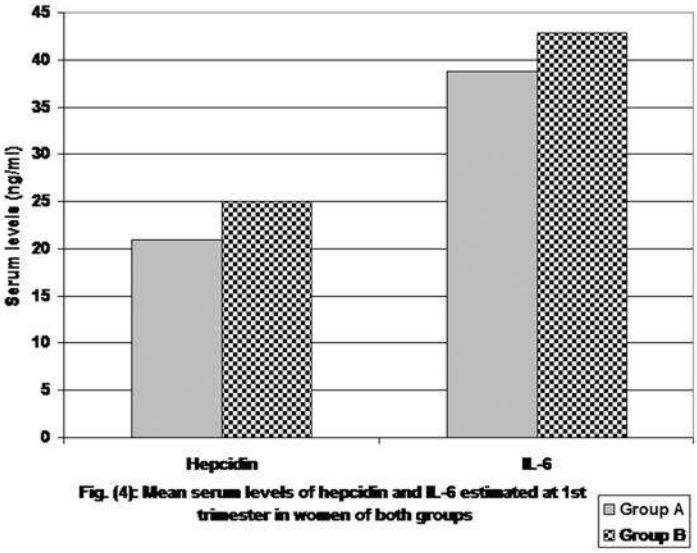

Fig. (4): Mean serum levels of hepcidin and IL-6 estimated at 1st trimester in women of both groups

Spearman correlation analysis showed a negative significant correlation between previous BS and HB conc. (Rho=-0.335, p<0.001) and SF (Rho=-0.208, p=0.006), while showed positive significant correlation with presence of chronic inflammatory anemia (Rho=0.177, p=0.019). Percentage of change of HB conc. at the 3rd trimester showed positive significant correlation with presence of previous BS, while showed negative significant correlation with HB conc. at 1st trimester and with the presence of CIA. Elevated serum hepcidin and IL-6 levels were positively correlated (Rho=0.628, p<0.001) and both showed positive significant correlation with presence of CIA (Rho=0.544 & 0.542, p<0.001), while showed negative significant correlation with HB conc at 1st trimester (Rho= -0.681 & -0.604, p<0.001). Previous BS showed positive correlation with elevated serum hepcidin (Rho=0.348, p<0.001) and IL-6 (Rho=0.137, p=0.069), (Table 3). Regression analysis defined presence of CIA (β:-0.662, p<0.001), HB conc. estimated at 1st trimester (β:-0.280, p<0.001), the use of IST (β: 0.404, p<0.001) and previous BS (β: 0.203, p<0.001) as significant predictors for possible change of HB conc. at the 3rd trimester.

Table (3): Spearman correlation between studied variables

Variables	Bariatric surgery		HB conc.		Hp		CIS anemia	
	Rho	p	Rho	p	Rho	p	Rho	p
HB conc.	-0.335	<0.001					-0.423	
SF	-0.208	0.006	0.606	<0.001	-0.405	<0.001	-0.308	<0.001
Hepcidin	0.348	<0.001	-0.681	<0.001			0.544	<0.001
IL-6	0.137	0.069	-0.604	<0.001	0.628	<0.001	0.542	<0.001
CIS anemia	0.177	0.019						
% of HB change at 3rd trimester	0.295	<0.001	-0.315	<0.001	0.169	0.103	-0.423	<0.001

HB: Hemoglobin; SF: Serum ferritin; Hp: Hepcidin, IL-6: Interleukin-6; CIS: Chronic inflammatory state

Discussion

Bariatric surgery had negative impact on patients' iron status as manifested by the significantly higher number of patients had iron deficiency anemia (IDA) with significantly lower HB conc. and serum ferritin (SF), at 1st trimester, in women had BS than control women. These results coincided with recent studies reported that iron deficiency (ID) is frequent in obese people and exacerbates by bariatric surgery [6, 25] and that reported a risk for cumulative iron, vitamin B_{12} deficiency, and anemia of 20%, 48%, and 28%, respectively after BS [26], irrespective of the undertaken surgical procedure [27].

Moreover, women who had BS had higher frequency of chronic inflammatory anemia (CIA) with significantly higher serum levels of hepcidin than control women. On the other hand, there was non-significant difference between serum IL-6 levels estimated at 1st trimester between women of both groups; a finding indicating ameliorating effect of BS on the obesity-induced inflammatory state. These results go in hand with **Coimbra et al**. [28] who found weight loss after BS is associated with an improvement in inflammation with reduction in IL-6 serum levels and **Hohensinner et al.** [29] who reported decreased serum levels of CRP and IL-6 by 83% and 55%, respectively, after BS. Also, **Askarpour et al.** [30] out of systemic review of published literature documented that BS significantly lowered serum levels of inflammatory factors; CRP, IL-6 and TNF-α.

Pregnancy also imposed a deleterious effects on patients' hematological milieu as manifested by the progressively increasing number of anemic women on the 2nd (109/176) and 3rd (140/176) trimester compared to number of anemic women determined at 1st trimester (87/176). In support of this finding, multiple recent studies documented that the prevalence of anemia in pregnant women at the 2nd and 3rd trimesters of pregnancy was higher than that at 1st trimester of pregnancy [31, 32, 33].

Interestingly, the number of patients had inflammatory anemia was 2-fold higher at the 3rd trimester than its number at 1st and 2nd trimesters. This finding indicated that pregnancy induced anemia of inflammatory state that may be attributed to iron delocalization despite of cellular/tissue overload [34] or to increased levels of inflammatory cytokines that shorten erythrocyte lifespan by activating macrophages through Toll-like receptor activation [35], prioritize leukocyte production in the marrow, and induce hepcidin to increase plasma transferrin saturation and the concentration of non-transferrin-bound iron [36].

These data points to the vicious circle affecting pregnant women who had BS where on one-side; obesity initiates a low-grade inflammatory status [37] with high hepcidin [38] and inflammatory cytokines serum levels [39, 40] with aggravation of iron and micronutrient deficiency [6, 25, 26] and also hepcidin reduces iron utilization thus aggravating the already present IDA (38). On the other side, pregnancy also induces a state of low-grade inflammation and depletion of maternal iron stores to fulfill fetal requirements [41] leading to aggrevation of both CIA and IDA.

Iron supplemental therapy provided since 1st trimester did well for the studied population of pregnant women; especially those had bariatric surgery as manifested by the increased HB conc. at the 3rd trimester compared to 1st trimester concentration and by the significantly higher number of women who developed increased HB conc. than control women. These findings illustrated the need of patients had bariatric surgery to supplemental iron therapy and go in hand with previous studies evaluated the supplemental therapy for patients had bariatric surgeries [42, 43, 44].

The IST was provided as sucrosomial oral iron for its unique structural, physicochemical and pharmacokinetic characteristics, together with high iron bioavailability and excellent gastrointestinal tolerance [45]. Unfortunately, no previous studies evaluated the use of sucrosomial oral iron for correction of pregnancy-induced anemia, however, the efficacy and safety of sucrosomial iron was approved experimentally where increased bone marrow iron availability was detected 5-hr after single dose of sucrosomial [46] and it was found to provide absorption pharomacodynamics similar to ferrous sulfate without inducing inflammatory responses [47]. Clinically, sucrosomial oral iron provides increases in HB levels and response similar to intravenous iron in cancer patients, but with higher tolerability and without risks or side effects [48]. Also, sucrosomial oral iron can provide iron effectively even in difficult-to-treat populations especially patients with IDA, inflammatory bowel disease and iron sulfate intolerance [49, 50]. Moreover, sucrosomial oral iron was used as effective alternative to parenteral iron after bariatric surgery [51].

Conclusion

Women had BS were always anemic and had micronutrient deficiencies that must be corrected prior getting pregnant to avoid aggravation of their disturbed hematological milieu. Iron supplemental therapy started since 1st trimester allowed improvement of anemia especially for women had BS for being in more need for IST. sucrosomial oral iron is appropriate form for IST that allowed increased HB conc. in 31.8% of studied women. Wider scale comparative studies are mandatory to establish the efficacy of sucrosomial oral iron than other forms of IST.

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