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RESEARCH ARTICLE

Comparative Study Evaluating the Effectiveness of Oral Iron (Ferrous Bisglycinate) and Intravenous Iron (Ferric Hydroxide Saccharate Complex) in Management of Iron Deficiency Anemia in Pregnant Women.

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Abstract

More than 1.6 billion people, almost a quarter of the world's population, are anemic. Despite considerable economic and scientific advancement during recent decades, there has been, at best, only marginal reduction in the global prevalence of anemia. The World Health Organization (WHO) estimates that worldwide, 42% of pregnant women, 30% of non-pregnant women (aged 15 to 50 years), 47% of preschool children (aged 0 to 5 years), and 12.7% of men older than 15 years are anemic [1]. Iron deficiency is not the only cause of anemia, but also other micronutrient deficiencies such as (zinc, copper, folic acid and vitamin B complex) are incorporated as a cause of anemia. Anemia, defined by low hemoglobin or hematocrit, which are commonly used to assess the severity of iron deficiency in pregnant women.

Objective: The present study was designed to compare the efficacy and tolerability of oral iron preparation ferrous bisglycinate elemental iron 27 mg and intravenous iron (Ferric hydroxide saccharate complex100 mg /Ampoule) in the prevention of iron deficiency (ID) and iron deficiency anemia (IDA) in pregnant women.

Method: Descriptive case series. The study was carried out in the department of Obstetrics and Gynecology at Fayoum general hospital over a period of 6 months from 09-2014 to 03-2015. Cases with proven iron deficiency with Hb ≥ 7gm% were included in the study. Total iron deficit was calculated using a standard formula. Target hemoglobin was 10gm %.The pregnant women (n=200) were divided into two groups of pregnant women (n=100). After 28 weeks of gestation, each group was treated with one type of iron. First group, ferrous bisglycinate 27 mg (Pharaferro 27), second group, Intravenous (IV) iron (Ferric hydroxide saccharate complex100 mg /Ampoule) respectively. Follow-up was done for one month. Hemoglobin level (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), reticulocyte count (RC), and serum ferritin were assessed after four weeks. Adverse effects were monitored at end of evaluation period.

Results: The two groups were comparable in terms of both anthropometric and biologic data, distribution of cases by economic status showed non-significant increase in Hb, serum ferritin, MCH, MCHC was seen in all two groups a ($p < 0.05$). Nausea, vomiting, epigastric pain did not significantly coexist with ferrous bisglycinate group, while myalgia and allergic reaction were significantly noticed in IV iron when compared with oral iron.

Conclusions: It can be concluded that oral iron Pharaferro 27mg (ferrous bisglycinate, zinc, copper, folic acid and vitamin B complex) is the same the result in restored iron stores and increase in Hb when compared with IV iron (Ferric hydroxide saccharate complex) so can be considered the best effective medication with tolerable side effects for treatment as well as prevention of iron deficiency anemia during pregnancy.

Introduction:-

Iron deficiency is the most common cause of anemia worldwide and is frequently seen in general practice. Iron deficiency anemia is caused by defective synthesis of hemoglobin, resulting in red cells that are smaller than normal (microcytic) and contain reduced amounts of hemoglobin (hypochromic) [2].

Pregnant women are particularly at high risk for iron deficiency and iron deficiency anemia because of increased iron needs during pregnancy [3].

In Egypt, particularly in rural areas, the prevalence of iron deficiency anemia is relatively high. According to a study done by The Egyptian Nutrition Institute (1993), the prevalence of iron deficiency anemia in rural population was 22% to 30%. With primary affected groups including; children below 5 years old, pregnant and lactating women. One of the major causes of such high prevalence was due to insufficient intake of iron [4].

Morbidity, such as infections, prolonged hospital stays, and general recuperative health problems, has also been associated with preexistent anemia. On the other hand, patients with hemoglobin levels below 4 to 6 g/dl may face life threating problems owing to high output congestive heart failure with decreased oxygenation of cardiac tissue. Anemia has been associated with prematurity, low-birth-weight infants, abortions and fetal deaths, even when the process is mild (hemoglobin levels 8 to 11 g/dl). Moreover, mild deficiency states have been related to decreased birth weight or fetal loss[5].

Anemia leads to an increased risk of blood transfusion during the peripartum period. Iron therapy before delivery may reduce the transfusion rate for the iron-deficient women[6]. However, there may not be enough time for the treatment of anemia until term. Intravenous iron does not induce an erythropoietic response more rapidly than oral iron replacement while use of iron requires several weeks after administration of injectable iron. Thus, the rise in hemoglobin concentration is only slightly faster than that after oral iron treatment. In recent years, few studies compared intravenous iron treatment with oral iron treatment during pregnancy [7].

Since the 1980s, many studies have examined ferrous bisglycinate chelate fortification of different foods[8-11]. these studies showed that ferrous bisglycinate chelate is 2.5 -to-3.4 fold more bioavailable[12], that its absorption is controlled by body iron storage[9], and that it causes fewer side effects[8-11].In addition, it has been hypothesized that iron amino acid chelates prevent iron from binding to inhibitors in food[13]and, in deprived areas in Egypt, food is composed basically of rice, beans, and vegetables, rich sources of phytates. Therefore, it was thought worthwhile to study the effects of one standard conventional oral iron preparation – ferrous bisglycinate– as a fully reacted amino acid chelate that has shown great efficacy, less GI irritation, and more absorption.

Material and Methods:-

Study sample:-

The study was conducted in Fayoum general hospital, gynecology & obstetric department, Cairo, Egypt over 6 months from 9- 2014 till 3- 2015. It was designed as a comparative study with 200 pregnant women who were attending out –patient clinic, their ages ranged 18 –45 years, that participated in an antenatal checkup program after 28 weeks gestation having Hb more than 7gm/dl and that were diagnosed microscopically to have microcytic hypochromic anemia. The study protocol was approved by the institutional ethics committee at Beni Suef University hospital, gynecology & obstetric department. After informing, written authorization was taken from the patients, they were randomly allocated into 2 groups (each n=100). The duration of study for each patient was 30 days (one month). The dropout patients were replaced by new patients in the study.

Exclusion criteria:-

Pregnant women with Hb < 7gm/dl, history of severe oral intolerance, excessive emesis, bleeding piles, active peptic ulcer, high obstetric risk associated with hypertension, diabetes, twins pregnancy, hepatic, renal diseases or any other GIT problems.

Medication:-

Study medication was supplied in the form of tablets.

Group I: received a combination of ferrous bisglycinate containing 27mg elemental iron once daily (PharaFerro27).

Group II: received a combination of intravenous iron on saline (Ferric hydroxide saccharate complex100 mg /Ampoule) twice weekly.
After recruitment, the patients were supplied with the respective medication and asked to follow-up after week (7 days). During each follow-up visit, they were subjected to general and obstetric examination and supplied with study medication for the next 3 weeks. Compliance was checked by verbal enquiry and verified by checking empty or used packets of the drug brought by the patients. Patients were also informed and given a reminder on the phone of the date of the next visit as well as a confirmation of the need to adhere to the given medication. Investigations: Samples for blood investigation were collected at day 0 (before starting medication) and day 30 (end of month). The amount of blood collected at each visit was 4 to 5 ml. The parameters of Hb, MCV, MCHC, reticulocyte count, and Serum ferritin were assessed at day 0 and at the end of month. Parameters like Hb, MCV and MCHC were done on automatic cell counter (sysmax).

Safety measures:-
Patients were trained to record and observe the adverse effects and instructed to report immediately if serious adverse reaction occurs. Any adverse events like metallic taste, epigastric distress, abdominal pain, nausea, vomiting, diarrhea and constipation, were recorded on a case record form. Also, during follow-up visits, patients were evaluated for the following symptoms associated with iron deficiency anemia, fatigue, malaise, loss of appetite, breathlessness, palpitation, giddiness, and irritability.

Statistical methods:-
All statistical calculations were done using computer programs. SPSS (statistical package for the social science version 20.00) statistical programs were used at 0.05level of probability[14].A comparison of the percentage was done using the chi square (X^2) test. t test, paired t- test were presented using percentage, mean ± standard deviation. Receiver operating characteristic (ROC curve) is a graphical plot that illustrates the performance of a binary classifier system as its discrimination threshold is varied[15].

Results:-

Table 1.clinical features of patient groups*

		Groups		Significant test	P value
		Oral iron (Ferrous bisglycinate 27 mg)	**IV iron (Ferric Hydroxide saccharate complex100 mg /Ampoule)**		
Age		29.50 ± 4.70	28.86 ± 4.88	t = 0.944	0.346 ^{NS}
Gestational age		31.14 ± 2.95	31.97 ± 4.17	t = 0.529	0.598 ^{NS}
BMI		28.41 ± 4.36	29.08 ± 4.39	t = 1.080	0.282 ^{NS}
Pulse pretreatment		104.37 ± 9.50	101.87 ± 7.54	t = 1.008	0.315 ^{NS}
Pulse post treatment		78.54 ± 6.21	77.73 ± 5.69	t = 0.202	0.840 ^{NS}
History of blood transfusion	**Absent**	96 (96%)	90 (90%)	X^2 =2.765	0.096 ^{NS}
	Present	4 (4%)	10 (10%)		

NS = non-significant at P value > 0.05.
BMI= body mass index
* Values are numbers of patients or means ± SD

Pregnant women characteristics are presented in Table 1**.** There were no statistically significant differences between groups upon entry into the study. In general, both groups of patients had no gastrointestinal complaints after using ferrous bisglycinate or ferric hydroxide saccharate complex.

Table 2. Differences in hematological parameters according to baseline values during the study period.

	Groups		t test	P value
	Oral iron (Ferrous bisglycinate 27 mg)	**IV iron (Ferric Hydroxide saccharate complex100 mg /Ampoule)**		
Hb(g /dl) Pre-treatment	8.73 ± 1.40	8.62 ± 1.10	1.069	0.274 ^{NS}
Hb(g /dl) After treatment	10.59 ± 1.11	10.32 ± 1.38	1.215	0.226 ^{NS}
Serum ferritin(µg/l) Pre-treatment	33.86 ± 3.95	34.08 ± 5.65	0.328	0.743 ^{NS}
Serum ferritin(µg/l) After treatment	51.83 ± 3.88	53.19 ± 5.55	2.010	0.054 ^{NS}
MCV (fL) Pre-treatment	73.12 ± 1.13	76.54 ± 1.56	0.105	0.345 ^{NS}
MCV (fL) After treatment	74.83 ± 1.03	75.05 ± 1.47	0.643	0.521 ^{NS}
MCHC (pg) Pre-treatment	19.45 ± 1.39	19.32 ± 1.46	0.638	0.524 ^{NS}
MCHC (pg) After treatment	28.74 ± 1.45	27 .54 ± 1.08	0.329	0.743 ^{NS}

NS = non-significant at P value > 0.05; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume.

Hemoglobin levels, serum ferritin, MCV and MCHC at baseline and 4thweek and at term are summarized in [Tables 2/Figs 1&2]. The mean difference in hemoglobin at baseline and 4th week were found to be significant statistically when compared between the two groups, also the mean differences of serum ferritin MCV and MCHC were significant. Improvement of hemoglobin, serum ferritin in iron ferrous bisglycinate group was much better than that of IV (Ferric Hydroxide saccharate complex) iron group at 4th week. The difference in improvement in MCV were almost similar in both the groups at the end of 4th week.

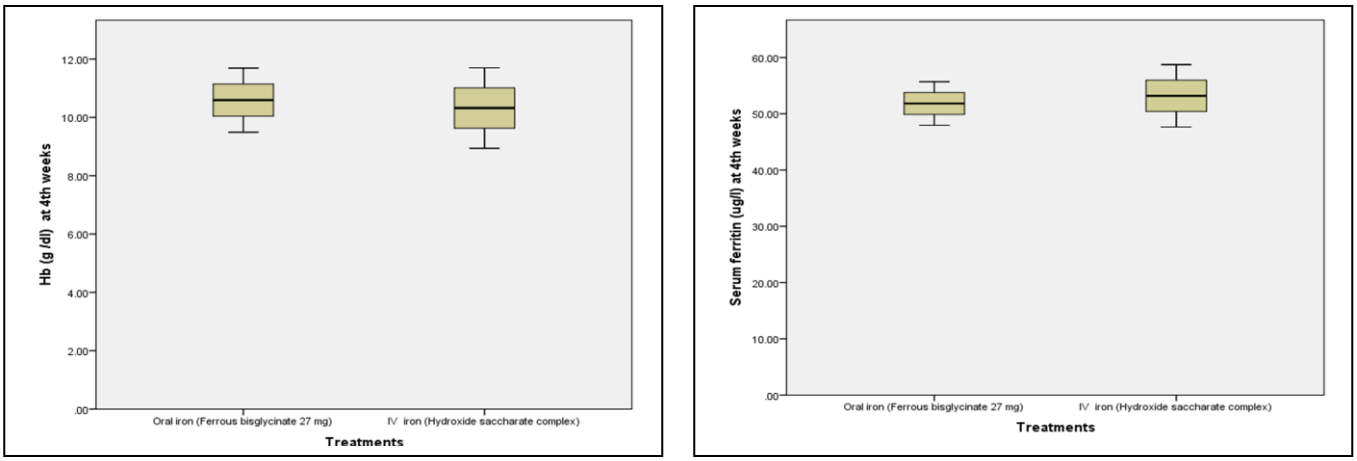
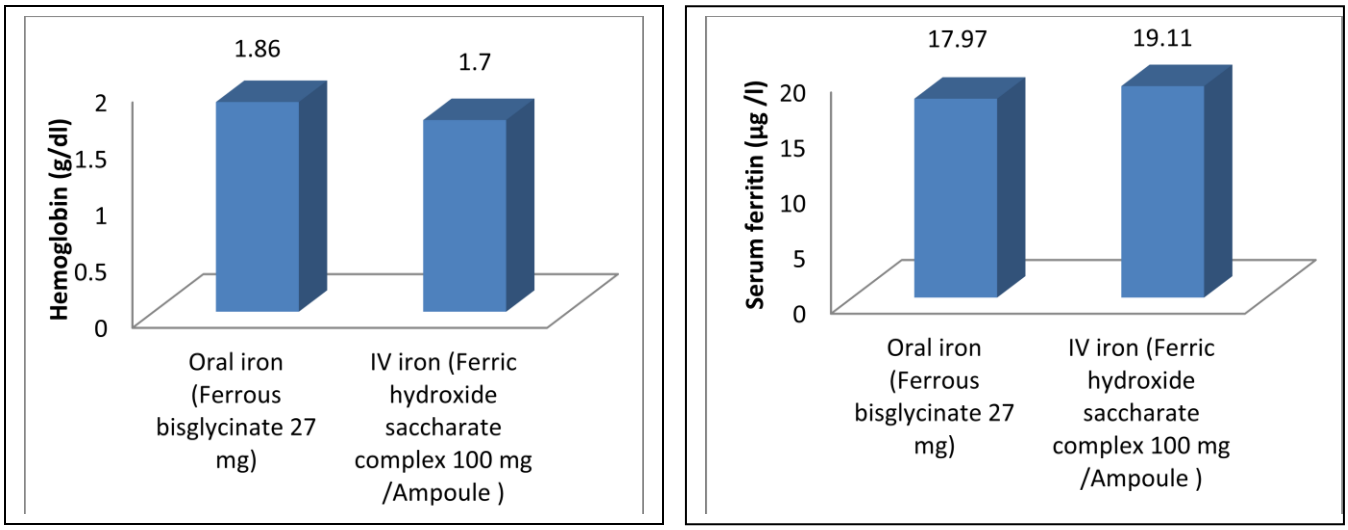


Figure (1): Box plot of hemoglobin, serum ferritin concentrations in women during pregnancy in the two iron supplementation groups: ferrous bisglycinate 27 mg elemental iron; Intravenous iron (Ferric hydroxide saccharate complex 100 mg /Ampoule).



Paried t test p > 0.05

Figure (2) Comparison between groups as regards hemoglobin and serum ferritin and their statistical difference

Table 3. Comparison between Estimated fetal weight in both groups

		Groups				Chi square	P value
		Oral iron (Ferrous bisglycinate 27 mg)		IV iron (Ferric hydroxide saccharate complex 100 mg / Ampoule)			
		n	%	n	%		
Estimated fetal weight	Normal weight	90	90	94	94	1.087	0.297^{NS}
	Low of birth weight	10	10	6	6		

NS = non-significant at P value > 0.05.

Result between oral and injectable iron with estimated fetal weight revealed statistically non-significant difference (p > 0.05) (Table 3, figure 3).

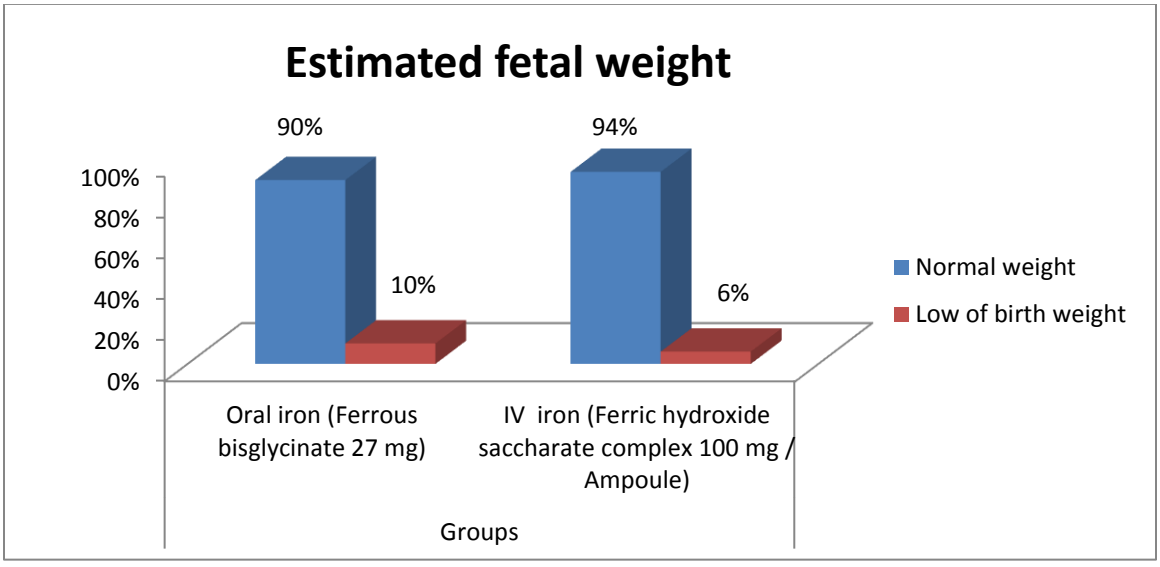


Figure (3): Comparison between both groups as estimated fetal weight and their statistical significance.

Table 4. Comparison of side effect profile between oral and IV iron group.

	Groups				Chi square	P value
	Oral iron (Ferrous bisglycinate 27 mg) N = 100		IV iron (Ferric hydroxide saccharate complex 100 mg /Ampoule) N = 100			
	n	%	n	%		
Nausea	3	3	0	0	3.046	0.081 NS
Vomiting	0	0	0	0	--------	--------
Dyspepsia	1	1	0	0	1.005	0.316 NS
Constipation	3	3	0	0	3.046	0.081 NS
Metallic taste	4	4	0	0	4.082	0.043 S
Diarrhea	2	2	0	0	2.020	0.155 NS
Allergic reaction	0	0	9	9	9.424	0.002 S
Discontinued	5	5	7	7	0.355	0.552 NS

NS = non-significant at P value > 0.05, S = significant at P value < 0.05.

Side effects are summarized in [Table 3]. Gastrointestinal side effects were not seen in women on intravenous iron therapy. All Patients were compliant with oral iron therapy and intravenous iron. Twenty two percent of patients in the oral iron group had gastrointestinal side effects but they were not severe enough to affect the compliance.

This table shows there is non-significant difference between ferrous bisglycinate and IV iron (Ferric hydroxide saccharate complex) in nausea, vomiting, dyspepsia, and diarrhea. While there is significant difference between oral and IV in myalgia allergic reaction ($p < 0.05$).

ROC curves were drawn to look at maximum sensitivity and specificity for indices which showed statistically significant correlation with serum ferritin and also to see which one gave maximum area under curve (AUC). Table [5] shows the area under ROC curves for various red cell indices for diagnosis of iron deficiency in pregnant women. ROC for Hb was found to give the maximum area under its curve and it was seen that Hb< 8.95 g/dL can predict iron deficiency anemia in the second and third trimester with a sensitivity of 100% and specificity of 99 % (Fig. 4).

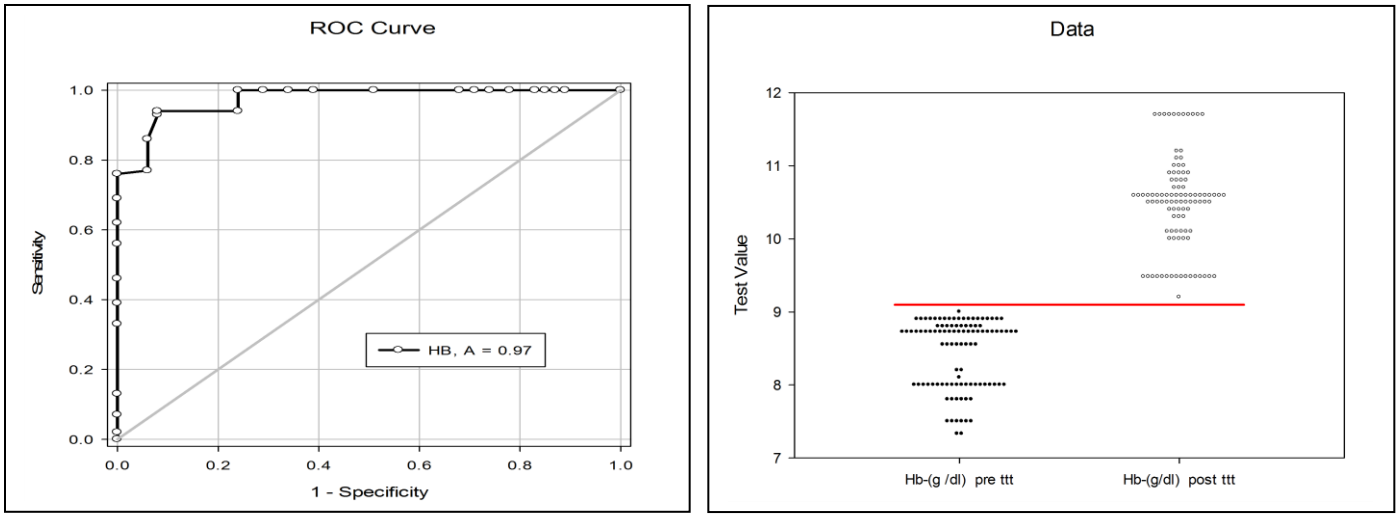


Fig. (4): ROC curve for hemoglobin in predicting iron deficiency anemia. Area under curve (0.915). The best cut-off is Hb < 8.95 gm/dL with a sensitivity of 100% and specificity of 99%

Table 5. Area under ROC curve and the best cut-off for various red cell indices for diagnosis of iron deficiency in pregnant women

Index	Area under the curve	Best cut off	Sensitivity	Specificity	PV +	PV -
Hb	0.891	<8.95	0.7600	1.0000	1.0000	0.9875

Discussion:-

Iron-deficiency anemia is a major health problem worldwide, but responds well to iron supplementation. The responsible constellation factors producing iron deficiency anemia generally precedes the pregnancy, including diet poor in iron content coupled with menstrual losses and a rapid succession of pregnancies in which supplemental iron was not provided. Most women begin their pregnancy with partially or completely depleted iron reserves. Thus, the severity of the anemia is inversely related to the amount of iron reserves [16].

The purpose of this study was to assess the currently available preparations for iron supplementation during pregnancy in terms of frequency of use, rate of side effects and discontinuation rate.

In the present study, there were no significant differences in hematological status between the oral iron and IV iron groups during the entire pregnancy. Iron status variables were similar at baseline and at 27–28 weeks of gestation. At 36–37 weeks of gestation, the bisglycinate group had slightly lower mean transferrin saturation and geometric mean ferritin than the IV iron group. However, the prevalence of ID and IDA was almost similar in the two groups.

Regarding many studies showing favorable results with ferrous bisglycinate chelate, the present study demonstrated that patients using ferrous bisglycinate showed decreased level of anemia when compared with patients using IV iron. There was a marked improvement in laboratory parameters observed for patients using ferrous bisglycinate. This was shown by increases in hemoglobin, serum iron, transferrin saturation, and serum ferritin to normal levels at the end of the study. Analysis of individual patients confirmed the mean data, mainly through the following findings: only five patient using ferrous bisglycinate discontinued treatment at the end of the study and seven patients using IV iron.

By drawing ROC curves for various red cell indices for diagnosis of IDA, we found that the maximum area to be for Hb and a cut-off < 8.95 g/dL had a sensitivity of 100% and a specificity of 99 % in the diagnosis of Egyptian pregnant women. This was mainly similar to the cut-off of 9.7 g/dL given in the study among African Americans in USA[17&18].Though all indices had a statistically significant correlation with ferritin for IDA can help in the diagnosis of iron deficiency anemia in Egyptian pregnant women in the second and third trimester.
In these cases the ferrous bisglycinate chelate it is more stable and has high bioavailability to ensure less GIT irritation and so that absorption of bisglycinate is not affected by phytates in food[19]. Ferrous bisglycinate chelate has been used successfully for iron fortification. As a supplement it has been tested in many countries and has shown a great efficacy in reducing iron deficiency anemia[20].

Many studies have shown that treatment with ferrous bisglycinate resulted in significant increase in hemoglobin (Hb) levels, the mean increase in Hb of the group receiving ferrous bisglycinate (22.72%) was significantly higher than that of the group receiving another oral iron (18.66%) [21&22].

In our study a comparative study between ferrous bisglycinate and IV iron, it is reported that both group showed significant increase in Hb, plasma ferritin level.

Oral iron (ferrous bisglycinate) treated iron deficiency anemia of pregnancy and restored iron stores faster and more effectively with no serious adverse reaction. Ferrous bisglycinate also has the advantage in that it is considered a 'natural' product [23].

The success of oral iron (ferrous bisglycinate) treatment depends on various factors. Especially, the patient's dietary habits influence the success of treatment because the nature of the meal affects absorption. Absorption not effect when iron (ferrous bisglycinate) is taken after or during meal[16].
Oral Iron (ferrous bisglycinate) was well tolerated with no serious adverse effects. It has a lower incidence of adverse metallic taste, however IV iron more rapid effects but causing adverse effects. It has a higher incidence of adverse myalgia and allergic reactions.

The review by William Sand Wheby[24], note that several studies considered anemia to be a risk factor for low birth weight. Fetal birth weight was not different between groups in the current study. However, IV iron don't contain component that required for treatment anemia as oral iron (ferrous bisglycinete) which contain iron, zinc, copper, vitamin B complex, vitamin C and folic acid.

Oral Iron (ferrous bisglycinete) iron is a safe and effective alternative to intravenous iron in treatment of iron deficiency anemia of pregnancy. It restores blood stores more rapidly, and a significant increase in hemoglobin may be achieved. It may reduce the blood transfusion rates in pregnant women who have severe anemia near term. Major disadvantages of injectable Iron are the cost, need for hospitalization or an outpatient setting, and the invasive nature of the procedure.

Conclusions:-

Oral iron (Ferrous bisglycinate) has tolerable adverse effects, and it increases iron stores significantly. Ferrous bisglycinate also increases Hb and produces less adverse effects than the IV iron. Thus, ferrous bisglycinate could be considered as an effective treatment for prevention of iron deficiency anemia during pregnancy as well as prevention of iron deficiency anemia.

Recommendations:-

All pregnant women after 13th weeks should be supplied with oral iron (Ferrous bisglycinate) which is more efficient in increasing Hb, MCV, MCHC and iron stores. At the same time, it has tolerable adverse effects and high compliance.

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