The prevalence of Gestational Diabetes Mellitus among pregnant women with varied hemoglobin concentrations and in relation to the use of Iron Supplemental Therapy

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Abstract

Objectives: To determine the prevalence of gestational diabetes mellitus (GDM) among pregnant women with varied hemoglobin concentrations (HC).

Patients & Methods: 847 newly pregnant women underwent estimation of HC, evaluation of insulin resistance (IR) using the homeostasis model assessment of IR (HOMA-IR) score and glucose tolerance using 75-oral glucose tolerance test (OGTT) at the 6th, 13th, 24th, and 36th gestational week (GW). Women were categorized according to the 6th GW HC into Low (<11 g/dl), Normal (11-<13 g/dl), and High HC (>13 g/dl). Women who had LHC received iron supplemental therapy (IST) till HC was adjusted, and IST was stopped. The study outcome is the incidence of IR and/or GDM among the studied women, and the predictability of the 6th GW HC for the oncoming development of IR and/or GDM.

Results: This is a cross-sectional study conducted at a University Hospital in the time period from January 2017 to June 2018, with the aim to evaluate cases presenting with a confirmed diagnosis of perforated IUCD.

Results: At the 6th GW the frequency of LHC, NHC, and HHC was 22%, 64%, and 14%, respectively. During pregnancy, the frequency of NHC women decreased, while that of HHC women increased. The frequency IR and HOMA-IR score progressively increased during pregnancy in all women with significantly higher frequency and score among HHC women. At the 24th and the 36th GW, 75 and 71 women developed GDM with significantly higher frequency among HHC women than LHC and NHC women and in LHC women compared to NHC women. Statistical analyses defined high HC at the 6th GW as the significant predictor for the development of GDM at the 24th GW, while high BMI at the 6th GW and multiparity as predictors for high HOMA-IR score.

Conclusion: Preconception evaluation of HC is mandatory to define women with low or high HC. Women who had low HC must be managed cautiously using IST till having NHC and IST must be stopped. HHC early in pregnancy

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could predict the oncoming development of IR and GDM.

Keywords: Hemoglobin concentration, Pregnancy, Insulin resistance, Gestational Diabetes mellitus.

Introduction

Gestational glucose intolerance with onset or first recognition during pregnancy is an abnormal initial gestational diabetes mellitus (GDM) screening test (1). Glucose intolerance during pregnancy, even if it did not progress to GDM, is associated with a risk of obstetric and neonatal complications [(2)].

Increased rates of obesity among women of reproductive age, rising maternal age, and the implementation of diagnostic criteria and procedures for GDM lead to a continuously rising international prevalence of GDM (1). The screening of GDM depends mainly on the oral glucose tolerance test (OGTT) at 24-28 gestational weeks (GW); however, early diagnosis and intervention of GDM may limit the development of or improve the previously documented adverse pregnancy outcomes [(3)].

Anemia is a global health concern, and iron deficiency anemia (IDA) affects about 50% of cases especially pregnant women [(4)] due to depletion of body iron stores to cope with the high demand for iron to maintain fetal and placental iron metabolism [(5)]. Thus, maintaining adequate iron status during pregnancy through replenishment of maternal iron stores is mandatory for both the mother and the developing fetus [(6)].

The normal iron content in adults is about 60 g/dl; however, iron overload has deleterious effects and is involved in the development of cancer, type 2 diabetes, and cardiovascular conditions [(7)], and can affect the normal functioning of the innate and adaptive immune responses [(8)], promote the generation of reactive oxygen species and cell oxidative stress [(9)] and brain iron accumulation causes neurodegenerative diseases [(10)].

Gestational IDA and DM are two prevalent pregnancy-induced complications that affect maternal and neonatal outcomes. On the other side, the need for iron supplemental therapy (IST) to correct IDA is essential but as previously documented iron overload may induce the development of DM; such dilemma requires to be explored. Thus, the current study aimed to determine the prevalence of GDM among pregnant women with varied hemoglobin concentrations (HC).

Design

A prospective interventional comparative study.

Setting

Department of Obstetrics & Gynecology, Faculty of Medicine, Benha University.

Ethical consideration

The study protocol was approved by the Local Ethical Committee at Benha Faculty of Medicine by approval number: RC: 4-2-2022.

Patients

During the duration of the study since Jan 2019 till Oct 2021, women attended the Antenatal Care Unit, Benha University Hospital for assurance of being pregnant underwent history taking as regards the presence of a history of GDM or IDA during the previous pregnancies, current DM, family history of DM, hormonal disturbances, nutritional deficiencies, bleeding attacks, preconception menstrual disturbances especially polymenorrhagia and menorrhagia, drug intake, food hypersensitivity, previous treatment for any grade of dyspepsia, or maintenance on peptic ulcer treatment. Then, women underwent clinical examination including determination of body height and weight, and body mass index (BMI) was calculated as weight (kg)/ height (m^2) as a baseline BMI.

Exclusion criteria

Exclusion criteria included current DM, previous GDM, multiple pregnancies, fetal abnormalities, BMI of >35 kg/m^2, previous history of bleeding episodes, maintenance on IST, liver, or kidney diseases.

Inclusion criteria

Newly pregnant women with singleton fetuses, free of exclusion criteria and accepted to sign the written fully informed consent to attend the follow-up visits were enrolled in the study.

Evaluation tools

1. Hemoglobin (Hb) hemoglobin concentration was estimated to detect gestational IDA that was defined as HC <11 g/dl in early or late pregnancy or <10.5 g/dl in mid-pregnancy [(11)].
2. The homeostasis model assessment of IR (HOMA-IR) score for detection of IR women using >2 as diagnostic cutoff point [(12)].
3. Glucose intolerance was assessed using the 75-oral glucose tolerance test (75-OGTT) according to the previously documented levels [(13)] as follows: FBG ≥92 mg/dl and 2-hr PPBG ≥153 mg/dl indicated development of GDM.

Investigations

Four blood samples were obtained at the 6th, 13th, 24th and 36th GW and at the start of each trimester for estimation of blood glucose and hemoglobin contractions and ELISA estimation of serum human insulin (catalog no. ab200011, Abcam Inc., San Francisco, USA) [(14)].

Grouping

- According to HC estimated at the 6th GW, the enrolled women were categorized into three groups: low HC (LHC) if HC was <11.0 g/dl, Normal HC (NHC) if HC was in the range of 11-<13 g/dl, and high HC (HHC) if HC was ≥13 gm. %.
- According to the HOMA-IR score determined throughout the pregnancy course, women who had HOMA-IR scores of >2 were diagnosed as IR women.
- According to glucose intolerance as evaluated by 75-OGTT throughout the pregnancy course women were categorized as having GDM or no GDM.

Iron Supplemental therapy

During the duration of the study since Jan Iron supplemental therapy (IST) was provided as ferrous bisglycine sulfate complex (Ferrous glycine sulfate 487 mg equivalent to 80 mg elemental iron + Folic acid 1 mg; Minapharm, Egypt; Schwarz Pharma), which is composed of 2 glycine molecules bound to a ferrous cation to form a double heterocyclic ring compound that can protect the iron from dietary inhibitors of absorption of non-heme iron and intestinal interactions, so it has high bioavailability (15). In addition, vitamin C was given to enhance the bioavailability of iron from the bis-glycine chelate (16). Vitamin C was given as an effervescent tablet (Vitacid C effervescent tablets, Cid Co Egypt), a form that enhances the absorption and metabolism of vitamin C when taken after a meal. Ferrous bisglycine sulfate complex was preferred for the inverse relationship between the absorption of amino-chelated iron with body iron stores (17). However, it was prescribed only to women who had HC <11 g/dl to guard against iron overload, and once HC was adjusted, IST was stopped.

Study outcomes

1. The primary outcome is the incidence of IR and/or GDM among studied women.
2. The secondary outcomes include:

- The relation between HC estimated at the

6th GW and the disturbed glucose homeostasis variables at the 24th GW.

- The predictability of HC was estimated at the 6th GW and preconception patients' data for the disturbed glucose homeostasis variables at the 24th GW.

Statistical analysis

Results were analyzed using paired t-test, One-way ANOVA, Chi-square (X2 test) and Mann-Whitney tests by IBM® SPSS® software (Version 22, 2015; Armonk, USA). Spearman's correlation analysis was applied to evaluate correlations between patients' data and HC estimated at the time of pregnancy diagnosis (the 6th GW) and the disturbed glucose homeostasis variables at the 24th GW. The ROC curve was used to determine the predictors of the development of GDM among patients' data and the 6th GW HC. The Regression analysis using the Stepwise method was applied to determine the predictability of the correlated variables for the disturbed glucose homeostasis variables. Significance was documented if P-value was <0.05.

Results

During the duration of the study, the data of 847 women were analyzed. Estimated HC at the 6th GW defined 186 women with low HC (LHC), 542 women had normal HC (NHC) and 119 women had high HC (HHC; Fig. 1); demographic and clinical data that were obtained at the 6th GW were shown in table 1.

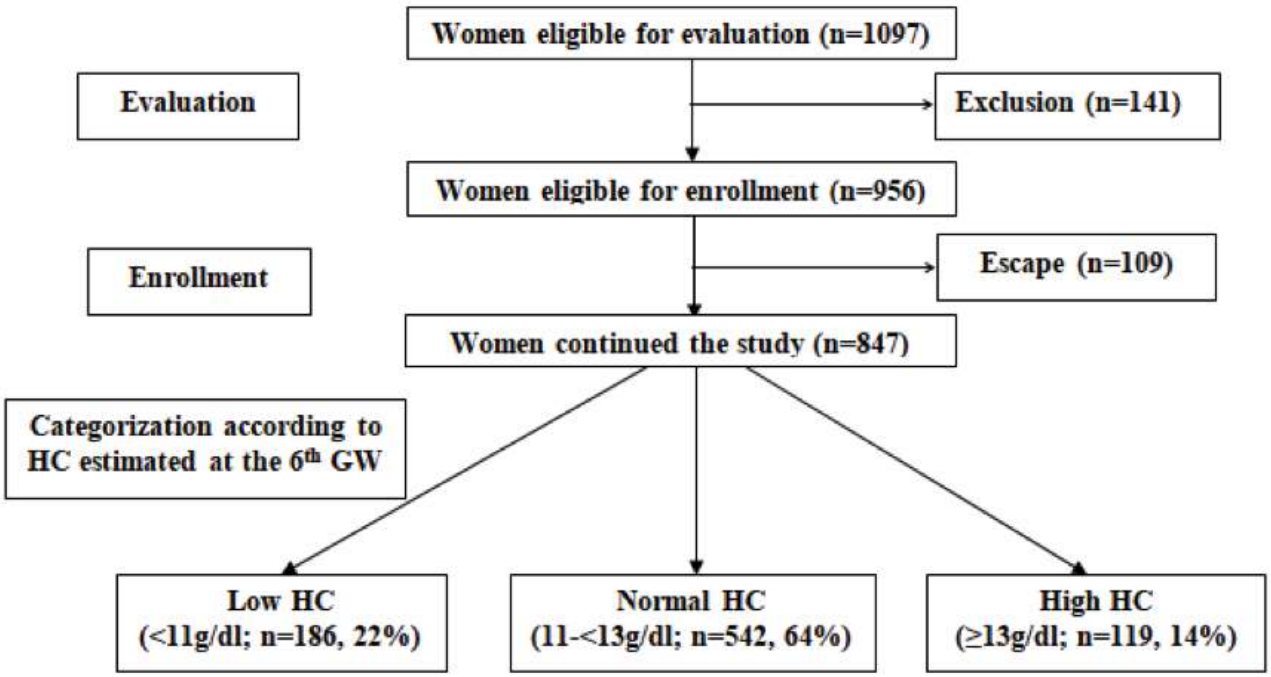

Fig. (1): Study Flow Chart

Table 1: Demographic and clinical data of studied women

Data	Findings
Age (years)	28 (2.8)
Weight (kg)	82.9 (6.4)
Height (cm)	169.7 (3.4)
Body mass index (kg/m^2)	28.8 (2.2)
Gravidity	2 [1-2]
Parity	1 [1-2]
Systolic blood pressure (mmHg)	114.7 (7.7)
Diastolic blood pressure (mmHg)	75.9 (5.7)

Pregnancy affected hemoglobin concentration (HC) in various directions, but the frequency of women who had NHC decreased with the progress of pregnancy with a significantly lower frequency of women who had NHC at the 13th, 24th, and 36th GW in comparison to the frequency at the 6th GW. The frequency of women who had LHC fluctuates during pregnancy reaching a summit at the 13th GW. As a consequence of IST, the frequency of women had HHC increased progressively reaching a summit at the 24th GW (Table 2).

Table 2: Women distribution according to estimated levels of HC during the pregnancy course

		Time of estimation				Actual P-value for differences					
		6th GW	13th GW	24th GW	36th GW	6th vs. 13th	6th vs. 24th	6th vs. 36th	13th vs. 24th	13th vs. 36th	24th vs. 36th
LHC	Frequency	186 (22%)	217 (25.6%)	177 (20.9%)	195 (23%)	0.077	0.594	0.601	0.021	0.213	0.291
	HC (g/dl)	10 (0.37)	10.1 (0.49)	9.97 (0.6)	10.02 (0.52)	0.275	0.855	0.997	0.047	0.375	0.754
NHC	Frequency	542 (64%)	488 (57.6%)	501 (59.1%)	497 (58.7%)	0.0072	0.041	0.025	0.522	0.886	0.658
	HC (g/dl)	12 (0.54)	12 (0.59)	12.05 (0.56)	12.03 (0.54)	0.766	0.220	0.391	0.392	0.712	0.664
HHC	Frequency	119 (14%)	142 (16.8%)	169 (20%)	155 (18.3%)	0.122	0.0012	0.0175	0.091	0.406	0.387
	HC (g/dl)	14 (0.58)	13.9 (0.62)	14.11 (0.6)	13.99 (0.58)	0.834	0.171	0.985	0.0208	0.633	0.324

HC: Hemoglobin concentration; LHC, NHC, HHC: Low, Normal, and High HC

The calculated HOMA-IR score showed a progressive increase in the frequency of IR women and a score with the progress of pregnancy in all studied women. Interestingly, at the 6th GW, there were 77 IR women (9.1%); 11 LHC women (5.9%), 35 NHC women (6.5%), and 31 HHC women (26.1%) with significantly (P<0.001) higher frequency of IR women among HHC women at the time of diagnosis of pregnancy in comparison to frequency among LHC and NHC women, despite the non-significantly higher score in comparison to score determined for LHC (P1=0.083) and NHC (P2=0.823). At the 13th GW, 140 women were IR (16.5%) with significantly (P<0.001) higher frequency among HHC women in comparison to LHC and NHC women and significantly higher score in comparison to LHC (P1=0.031) and NHC (P2=0.021) scores. At the 24th and the 36th GW, 262 (30.9%) and 299 women (35.3%),

respectively, became IR with significantly (P<0.001) higher frequency and score among HHC women in comparison to women of other groups and significantly (P1<0.001) higher score among NHC women compared to LHC women (Table 3).

At the 6th and 13th GW, no case of GDM was reported, while at the 24th GW, 75 women (8.85%) developed GDM with significantly higher frequency among HHC women in comparison to LHC women (P1=0.0022) and NHC women (P2<0.001) and significantly (P1=0.015) higher frequency of women who developed GDM among LHC women compared to NHC women. At the 36th GW, 146 women (17.2%) became diabetic with significantly higher frequency among HHC women compared to the frequency among LHC (P1=0.0001) and NHC women (P2<0.001) and significantly (P1=0.037) higher frequency among LHC women compared to NHC women. At the 6th GW, the estimated levels of FBG and 2-hr PPBG showed non-significant differences between the studied women. At the 13th and 24th GW, both FBG and PPBG measures were significantly lower in LHC women in comparison to NHC and HHC women, with non-significantly higher FBG, but significantly higher PPBG measures in HHC women compared to NHC women. At the 36th GW, both FBG and PPBG measures were significantly higher in HHC women in comparison to LHC and NHC women with significantly higher BG measures in NHC women compared to LHC women (Table 3).

Table 3: Insulin resistance and glucose intolerance data reported during pregnancy course of studied women.

		6th GW	13th GW	24th GW	36th GW
Insulin resistance as judged by HOMA-IR score					
LHC	Frequency	11 (5.9%)	34 (15.7%)	44 (24.9%)	47 (24.1%)
	Score	0.96 (0.4)	1.18 (0.48)	1.29 (0.6)	1.55 (0.65)
NHC	Frequency	35 (6.5%)	57 (9.7%)	115 (23%)	133 (26.8%)
	P1 value	0.732	0.334	0.607	0.884
	Score	1 (0.32)	1.2 (0.4)	1.57 (0.53)	1.87 (0.51)
	P1 value	0.271	0.988	0.0001	0.0001
HHC	Frequency	31 (26.1%)	49 (34.5%)	103 (60.9%)	119 (76.8%)
	P1 value	0.00022	0.0005	0.00001	0.00014
	P2 value	0.00015	0.00026	0.00001	0.00019
	Score	1.11 (0.62)	1.3 (0.66)	1.81 (0.78)	2.28 (0.74)
	P1 value	0.083	0.031	0.0008	0.00001
	P2 value	0.823	0.021	0.061	0.00011
Total frequency of IR		77 (9.1%)	140 (16.5%)	262 (30.9%)	295 (34.8%)
Glucose intolerance and development of GDM as judged by 75-OGTT					
LHC	Frequency*	0	0	16 (9%)	34 (17.4%)
	FBG	77.8 (7.8)	79 (6.7)	83.1 (7.4)	87.5 (8.2)
	2hr PPBG	118.5 (5.4)	119 (8.1)	127.6 (13.1)	135.1 (15.5)

NHC	Frequency*	0	0	24 (4.8%)	57 (11.5%)
	P1 value	-	-	0.015	0.037
	FBG	79.2 (4.6)	82.5 (4.3)	85.8 (5.8)	88.6 (6.7)
	P1 value	0.063	<0.001	<0.001	0.094
	2hr PPBG	117.7 (7.7)	125.7 (7.8)	133.3 (9.7)	141.4 (12)
	P1 value	0.982	0.00085	0.00072	0.0009
HHC	Frequency*	0	0	35 (20.7%)	55 (35.5%)
	P1 value	-	-	0.0022	0.0001
	P2 value	-	-	0.0001	0.00001
	FBG	78.8 (5.4)	82.1 (5)	88.8 (7.5)	92.6 (8.9)
	P1 value	0.274	0.0009	0.00016	0.00001
	P2 value	0.615	0.886	0.521	0.00001
	2hr PPBG	118 (6.8)	127.5 (7.6)	138.1 (15.8)	152.1 (16.4)
	P1 value	0.722	0.0007	0.00012	0.00001
	P2 value	0.827	0.032	0.0096	0.00001
Total frequency of GDM		0	0	75 (8.85%)	146 (17.2%)

P1 value indicates the significance of difference versus LHC women; P2 value indicates the significance of difference versus NHC women

Spearman's correlation analysis showed a positive significant correlation between the development of GDM and women's age, BMI, parity, and the 6th GW HC, in increasing order of significance. The 24th GW FBG and PPBG levels and the calculated HOMA-IR score showed a positive significant correlation with BMI and the 6th GW HC, while the calculated HOMA-IR score also showed a positive significant correlation with parity (Table 4). ROC curve analysis defined high 6th GW HC as the highly significant predictor for the development of GDM at the 24th GW with AUC= 0.653 (SE= 0.039, P-value <0.001; 95% CI: 0.576-0.729), followed by high BMI with AUC= 0.584 (SE= 0.036, P-value =0.015; 95% CI: 0.513-0.655), high parity rate with AUC= 0.419 (SE= 0.036, P-value =0.019; 95% CI: 0.347-0.490), and finally higher age with AUC=0.420 (SE= 0.033, P-value =0.021; 95% CI: 0.354-0.485), (Fig. 2). Regression analysis defined high HC estimated at the 6th GW as a significant predictor for high FBG, PPBG, and HOMA-IR score at the 24th GW, while high BMI at the 6th GW was also a predictor for high PPBG and HOMA-IR score, and multiparity as a predictor for high HOMA-IR score (Table 4).

Table (4): Statistical analyses for variables determined at the 6th GW as predictors for disturbed glucose homeostasis at the 24th GW.

Variables	Development of Gestational diabetes		24th GW fasting blood glucose		24th GW Post-prandial blood glucose		24th GW Insulin resistance score	
Spearman's correlation analysis								
	Rho.	P-value	Rho.	P-value	Rho.	P-value	Rho.	P-value
Age	0.080	0.019	0.042	0.217	0.043	0.214	0.011	0.869
BMI	0.083	0.015	0.080	0.020	0.072	0.035	0.105	0.002
Gravidity	0.027	0.435	0.019	0.591	0.013	0.845	0.067	0.051
Parity	0.086	0.012	0.053	0.124	0.023	0.508	0.115	0.001
6th GW HC	0.151	0.00087	0.197	0.0009	0.307	0.00014	0.230	0.0001
Regression analysis								
	24th GW FBG				24th GW PPBG		24th GW HOMA-IR score	
	β		P-value		β	P-value	β	P-value
Age	0.062		0.067		0.033	0.312	0.002	0.962
BMI	0.061		0.073		0.079	0.018	0.102	0.001
Gravidity	0.315		0.010		0.762	0.021	0.710	0.315
Parity	0.022		0.514		0.018	0.587	0.084	0.013
6th GW HC	0.196		0.0005		0.263	0.00034	0.231	0.00041

GW: Gestational week; BMI: Body mass index; HC: Hemoglobin concentration

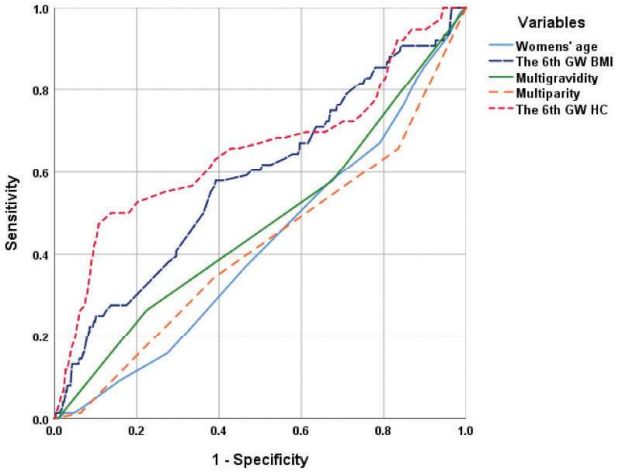

Fig. (2): ROC curve analysis of women's data determined at the 6th GW as predictors for oncoming GDM.

Discussion

Estimation of hemoglobin concentration (HC) at the time of diagnosis of pregnancy (the 6th GW) defined a prevalence of women who had low HC of 22%. This figure is coincident with that recently detected in multiple surveys in varied countries all over the world (18-20) and indicated the necessity of preconception evaluation of HC to allow correction of anemia before getting pregnant. On the other side, the current study detected a prevalence of high hemoglobin concentration (HHB) of 14%; a figure that is in agreement with that recently detected by Amarasinghe et al. [20].

Evaluation of insulin resistance (IR) at the 6th GW detected an incidence of IR of 9.1% despite the blood glucose (BG) measures being within normal range and lower than that defined by IADPSG for diagnosis of diabetes. Moreover, the incidence of IR early in pregnancy was positively correlated with body mass index (BMI) and increased progressively during the pregnancy course, so there were 299 IR women (35.3%) at the 36th GW. Also, the obtained results of the 75-OGTT at the 24th and 36th GW defined 75 and 71 women had developed GDM for a total incidence of 17.2%.

These findings spotlight a fact that pregnancy per se is a diabetogenic state of the type-2 category because it is associated with IR as evidenced by the positive relation between FBG levels estimated at the 24th and 36th GW and HOMA-IR score and with at the 6th GW BMI. In line with these findings and assumptions, Gorkem et al. [21] reported significantly higher serum insulin levels and HOMA-IR values in GDM women than in control pregnant women. Thereafter, Psoinos et al. [22] detected a high incidence of pre-pregnancy subclinical IR with a positive association between HOMA-IR and BMI, amount of subcutaneous fat, high serum inflammatory markers, and high possibility of complicated pregnancy. Also, Bano et al. [23] detected a prevalence of IR, gestational glucose intolerance, and GDM among their series of pregnant women of 27.9%, 22.05%, and 52.2% and detected a significant correlation between IR, BMI, and GDM.

Moreover, the detection of 71 GDM women at the 36th GW indicated the necessity of continuous follow-up of pregnant women for the disturbed glucose homeostasis variables till the end of pregnancy without reliance only on estimations determined at the 24th GW. In hand with this finding and suggestion, multiple recent studies [24-26] indicated the necessity of the detection of late-pregnancy GDM because it is associated with adverse fetomaternal outcomes.

Multiple studies tried to explore the underlying mechanisms for the development of gestational IR and DM, whereas Gorkem et al. [21] attributed the development of gestational IR and DM to the detected higher levels of serum placental growth factor that was positively correlated with serum insulin levels and HOMA-IR scores. Recently, gestational IR was attributed to adipose tissue inflammation and endoplasmic reticulum stress which promote adiponectin degradation [27]. Another recent study attributed IR during pregnancy to the development of non-alcoholic fatty liver secondary to mitochondrial dysfunction causing oxidative stress and to epigenetic mechanisms related to alterations in genes involved in lipid metabolism, and inflammation [28].

Interestingly, women with at the 6th GW HHC showed the highest prevalence of GDM that was significantly higher than its prevalence in women with LHC or NHC. Moreover, there was a positive significant correlation between 6th GW-HC and FBG estimated at the 24th GW and statistical analyses defined HHC early in pregnancy as a significant predictor for oncoming development of GDM. In support of these results, an early study suggested that HHC during early pregnancy can predict the risk of GDM [29] and a meta-analysis detected that women with LHC are 39% less likely to develop GDM than women with NHC or HHC [30]. In line with the obtained results, Abumohsen et al. [31] found women who had HHC in the 1st trimester were at higher risk of high FBS, and Li et al. [32] documented that HHC is a risk factor for developing GDM than NHC with increased risk of GDM with higher HBC.

Recently, Sissala et al. [33] found mothers with GDM had higher HBC than controls, and HBC is positively associated with preconception BMI, FBG, and glucose levels at the time of diagnosis of GDM and using multivariable regression analysis HBC remained an independently associated parameter for GDM. Also, Eidgahi et al. [34] found hematocrit value, HBC, and FBG estimated in the 1st and 2nd pregnancy trimesters were significantly higher in GDM women in comparison to non-GDM women and the concurrent use of these variables could predict GDM with AUCs of 87%, 70%, and 83%.

The reported progressively increasing prevalence of IR from 5.9% at the 6th GW (5.9%) to 24.1% at the 36th GW and of GDM from 9% at the 24th GW to 17.4% at the 36th GW among LHC women, who received iron supplemental therapy (IST),

points to a diabetogenic effect of IST and support the relation between HHC and GDM. Similarly, Zhang et al. [35] documented that long-duration peri-conception IST for anemic pregnant women is associated with increased GDM risk. Recently, Rajendran et al. [36] found IST in anemic pregnant women improves hematological status and decreased inflammation, but once these women became non-anemic, continued IST increases oxidative stress and inflammation.

The pathogenic mechanisms for the relation between HHC and development of IR and type-2 diabetes mellitus was still a matter of debate; however, an earlier study attributed this coincidence to the impaired function of pancreatic islet β cells that affects insulin secretion [37]. Another study attributed the IR to the altering effect of iron on the expression of insulin receptors in hepatocytes [38]. A more recent study had focused on the relationship between iron overload and increased oxidative stress which inhibits insulin internalization and function leading to hyperinsulinemia and IR with HHC [41]. Recently, genetic evidence was provided to support a causal link between increased systemic iron status and increased risk of type-2 diabetes [40].

Conclusion

Variability of HC among newly pregnant women is evident and necessitates preconception evaluation to define women with low or high HC. Women who had low HC must be managed cautiously using IST till having NHC and IST must be stopped. HHC early in pregnancy could predict the oncoming development of IR and GDM even in normoglycemic women.

Limitation

Evaluation of pregnancy outcome and the effect of hemoglobin variability, IR, and GDM on maternal and fetal welfare

Recommendation

Judicious use of IST during pregnancy is mandatory to reduce the incidence of IR and/or GDM and improve maternal and fetal outcomes. Evaluation of glucose homeostasis parameters must be continued till the end of pregnancy to detect the development of late GDM.

Acknowledgment

The author thank the staff member of the Clinical Pathology Department, Benha University, for performing the required investigations.

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