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Excessive Gestational Weight Gain Precedes Incident HELLP Syndrome Among Nigerian Women

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Abstract: Background: Excessive gestational weight gain (GWG) have been theorized to precede HELLP syndrome (HELLPs) among Caucasian women mostly of western populations. This theory has not been validated among women of Nigerian origin. Hence, the current study evaluated the relationship between excessive GWG and the incidence of HELLPs among Nigerian women. Methods: The retrospective study was conducted among 108 supervised nulliparous pregnant women who were diagnosed with complete HELLPs by term (37-42 gestational age) in the University of Port Harcourt Teaching Hospital from 2011-2020. The relevant data of eligible cases were extracted from case notes, nurses' charts, laboratory, and other medical files using a pre-tested research template and analyzed using the Statistical Package for Social Sciences software version 25. Results: During the study, 108 eligible cases were identified. At booking, the majority of the HELLPs patients were found to be overweight (n=49; 45.4%). At diagnosis by term, the HELLPs patients had markedly higher mean weight compared to their mean booking weight (booking weight: 74.32 ± 7.13 vs. term weight: 105.74 ± 7.59; $p<0.001$). The majority of the HELLPs patients had GWG above the Institute of Medicine (IOM) recommendations (n=67; 62.1%; $p<0.001$) by term. The underweight, ideal weight, overweight, and the obese with GWG below the IOM recommendations were less likely [adjusted odd ratio (aOR)<1.0] to develop HELLPs while those with GWG above the IOM recommendations were more likely (aOR>1.0) to develop HELLPs. However, the lower chance of incident HELLPs among those with GWG below the IOM recommendations was attenuated with increasing BMI status while the more likelihood of incident HELLPs among those with GWG above the IOM recommendations becomes amplified with increasing BMI status. Conclusion: The present study findings indicate that excessive GWG seemed to precede incident HELLPs among at-risk women in Nigeria. However, further studies are recommended to verify the conclusions of this study.

Keywords: Nigeria, HELLP, HELLP Syndrome, Gestational Weight Gain

1. Introduction

The HELLPs (HELLP syndrome), the acronym for Hemolysis, Elevated Liver enzymes, and Low Platelet count syndrome, is a rare but very serious complication of pregnancy [1]. The syndrome is at the severe end of the spectrum of gestational hypertensive disorders of pregnancy [1, 2]. Some experts believe the syndrome is a complication or variant of severe preeclampsia [1-3]. However, some others believe that HELLPs is a distinct disease entity [3].

The syndrome is more common among multiparous Caucasian women [4]. For yet unknown reasons, the incidence of the syndrome has remained relatively low among women within the Negroid race.

To date, the pathophysiology of HELLPs has remained an enigma since it was initially described decades ago by Louis Weinstein [1, 5]. Nevertheless, the basic mechanism underlying HELLPs evolution is thought to be due to abnormal placentation and the subsequent release of factors resulting in placental hypoperfusion, ischemia, and systemic microangiopathies [6].

Moreover, several risk factors of the syndrome have been identified in addition to severe preeclampsia in recent times including advanced maternal age, chronic hypertension, diabetes mellitus, multiple gestations, and pre-existing renal disease [3, 6].

Excessive weight gain has also been theorized to precede HELLPs in most cases regardless of pre-pregnancy BMI status [7]. Nevertheless, evidence of this relationship has not been documented among women of Nigerian origin. Hence, the current study evaluated the relationship between gestational weight gain (GWG) and the incidence of HELLPs among pregnant women in Port Harcourt, Nigeria.

2. Materials and Methods

The study was conducted retrospectively in the University of Port Harcourt Teaching Hospital (UPTH), Nigeria among pregnant women who were diagnosed with HELLPs over 10 years following approval by the Institutional Research Ethics Committee. Archived hospital data of all eligible cases of HELLPs diagnosed and managed in the study center during the period under review were meticulously retrieved and analyzed.

The criteria for inclusion were as follows: data of all booked nulliparous non-edematous pregnant women with term (37-42 weeks gestational age) singleton pregnancies and early pregnancy (<10 weeks) anthropometric parameters [weight, height, body mass index (BMI)] who developed complete HELLPs during the antenatal period at term and subsequently managed in UPTH over 10 years (1st January 2011 to the 31st December 2020).

Criteria for exclusion include antecedent or existing liver diseases, hepatobiliary diseases, gallbladder diseases, diabetes, thyroid disorders, chronic renal diseases, hemoglobinopathies, thrombotic microangiopathies, chronic and gestational hypertension, acute fatty liver disease of pregnancy, HIV infected cases, preeclampsia/eclampsia superimposed on chronic hypertension, renal transplant recipients, those diagnosed with drug-induced liver injury, and those who are markedly edematous, those with incomplete, data and those diagnosed outside the study period.

Data was acquired anonymously without any distinguishing identifiers using trained research assistants. Key variables of which data was collected include the number of deliveries within the study period and the number of cases of HELLPs diagnosed within the study period. For each eligible case, all the relevant socio-demographic (age), clinical, anthropometric (weight in kg, height in meters) obstetric, biochemical, and hematological data were abstracted first during the early first trimester at booking and secondly at the point of diagnosis by term.

Complete HELLPs was defined/categorized using laboratory results as recommended by Mississippi triple-class classification system as follows [8]:

Class 1: a. Total plasma bilirubin (TPB) ≥ 1.2mg/dl (20.5 µmol/L) or lactate dehydrogenase (LDH) activity ≥ 600 IU/L

b. Plasma aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activity ≥ 70 IU/L c. PLT count < 50 x 10^9/L. Class 2: a. TPB ≥ 1.2mg/dl (20.5 µmol/L) or LDH of ≥ 600 IU/L b. Plasma AST and ALT activities ≥ 70 IU/L c. PLT count 50-100 x 10^9/L.

Class 3: a. TPB ≥ 1.2mg/dl (20.5 umol/L) or LDH of ≥ 600 IU/L b. Plasma AST and ALT activities ≥ 40 IU/L c. PLT count 100-150 x 10^9/L.

Early (<10 weeks gestational age) pregnancy body mass index (BMI) was calculated as the first measured booking weight in kilogram (kg) divided by height in meter squared (m^2). Patients were further categorized based on BMI into 4 groups as (1) underweight (<18.5), (2) ideal weight (18.5-24.9), (3) overweight (25-29.9), and (4) obese (≥30) based on the World Health Organization's recommendations [9]. GWG was calculated as the difference in kg between the booking weight during the early pregnancy anthropometric measurements and the weight by term just before or during the incident HELLPs as previously described [10]. The GWG at term was defined using the 2009 recommendations of the Institute of Medicine (IOM) and was further categorized into 3 groups such as (1) GWG below, (2) GWG within, and (1) GWG above the IOM recommendations [11].

The acquisition of specimens for all laboratory analyses was carried out using recommended guidelines. The laboratory analysis was done using fully automated chemistry and hematological systems by well-experienced analysts. To evaluate the coefficient of variations during analytical processes, at least two levels of commercially-produced quality control materials were used.

Data were managed using Statistical Package for Social Sciences software version 25. The distribution of continuous data was explored using the Shapiro-Wilk test. Data with non-Gaussian distribution were all logarithmically transformed before analysis and presented as mean ± standard deviation; the comparison was evaluated using the independent-samples t-test or analysis of variance, where necessary. Categorical data were presented as proportions in numbers/percentages; the comparison was made using the Chi-square test or Fisher's exact test and Yate's continuity correction was applied when necessary. Adjusted multiple logistic regression was used to explore the predictive potentials of gestational weight gain on incident HELLPs at 95% confidence intervals (CI). An alpha value <0.05 was chosen as the threshold for statistical significance.

3. Results

During the study period (2011-2020), a total of 128 nulliparous women with booked (supervised) status and singleton pregnancies developed complete HELLPs at term out of a total of 298 HELLPs cases diagnosed during that period. However, data of 108 HELLPs cases met the eligibility criteria for the current study and were subsequently included in the analysis.

Table 1 depicts the recommended ideal term GWG by the

IOM according to pre-pregnancy body BMI status in singleton pregnancies.

At booking, most of the pregnant women were overweight (n=49; 45.4%) while 10 (9.3%), 26 (24.1%), and 23 (21.2%) were underweight, obese, and of ideal weight, respectively (Table 2). Most of the incident HELLPs patients were multigravidas (n=78; 72.3%) and all were nulliparous (n=108; 100%) at booking. At the time of HELLPs diagnosis by term, the HELLPs patients had markedly higher mean weight compared to their mean booking weight (weight at diagnosis: 105.74 ± 7.59 vs. booking weight: 74.32 ± 7.13, kg; p<0.001).

Illustrated in Table 3, majority of the entire study cohorts (n=108) had GWG above the IOM recommendations (n=67; 62.1%; p<0.001) at term. Additionally, the majority of those with pre-pregnancy ideal weight (n=13; 56.6%), overweight (n=34; 69.4%; p<0.001) and obese (n=18; n=66.2%; p=0.017) status also had GWG above the IOM recommendations.

Those who had GWG at term above the IOM recommendations were older (31.78 ± 3.73) and had higher systolic blood pressure, diastolic blood pressure, alanine/aspartate aminotransferase, lactate dehydrogenase, creatinine, uric acid, total bilirubin plasma levels/activities but lower plasma albumin, platelet count and parked cell volume compared to those who had term GWG below and above the IOM recommendations (p<0.05) (Table 4).

Illustrated in Table 5, among the entire spectrum of the pre-pregnancy BMI categorized underweight, ideal weight, overweight, and the obese HELLPs cases, those with GWG below the IOM recommendations were less likely [adjusted odd ratio (aOR)<1.0] to develop HELLPs while those with GWG above the IOM recommendations were more likely (aOR>1.0) to develop HELLPs following adjustment for covariates (age, systolic blood pressure, diastolic blood pressure, alanine/aspartate aminotransferase, lactate dehydrogenase, creatinine, uric acid, total bilirubin, albumin plasma levels, platelet count, and packed cell volume) when compared to those with GWG within the IOM recommendations.

However, the less likelihood of incident HELLPs among those with GWG below the IOM recommendations tended to decrease with increasing BMI status from the underweight (aOR: 0.234; 95%CI: 0.112-0.441), to the ideal weight (aOR:0.362; 95%CI:0.183-0.599), to the overweight (aOR:0.488; 95%CI:0.266-0.687), and to the obese (aOR:0.575; 95%CI:0.381-0.792). While the more likelihood of incident HELLPs among those with GWG above the IOM recommendations tended to increase with increasing BMI status from the underweight (aOR:2.011; 95%CI:1.273-3.3871), to the ideal weight (aOR:2.792; 95%CI:1.678-4.272), to the overweight (aOR:3.639; 95%CI:2.230-5.761), and to the obese (aOR:4.993; 95%CI:2.971-6.72).

Table 1. *Ideal term gestational weight gain by categories of pre-pregnancy body mass index.*

Weight status	Pre-pregnancy BMI categories, kg/m²	Ideal term gestational weight gain, kg	
		Lower border	Upper border
Underweight	<18.5	12.5	18.0
Ideal weight	18.5 – 24.9	11.5	16.0
Overweight	25.0 – 29.9	7.0	11.5
Obese	≥30	5.0	9.0

BMI: body mass index.

Table 2. *Descriptive characteristics and comparisons of variables obtained at booking and by term at the time of HELLPs diagnosis.*

Variables	At Booking	At Diagnosis by term	
	M ± SD/n (%)	M ± SD/n (%)	p-value
Age, years	NA	30.90 ± 3.94 (24-39)	NA
Gravidity			
Primigravida	30 (27.70)	NA	<0.001*
Multigravida	78 (72.30)	NA	
Parity			
Nullipara	108 (100.00)	108 (100.00)	NA
Multipara	0 (0)	0 (0)	
Weight, kg	74.32 ± 7.13	105.74 ± 7.59	<0.001*
Height, m	1.68 ± 0.46	NA	NA
BMI, kg/m²	26.31±4.51	NA	NA
BMI status			
<18.5 (Underweight)	10 (9.30)	NA	
18.5-24.9 (Ideal weight)	23 (21.20)	NA	0.002*
25.0-29.9 (Overweight)	49 (45.40)	NA	
≥30.0 (Obese)	26 (24.10)	NA	

*Statistically significant; NA: not applicable; M±SD: mean ± standard deviation;
BMI: body mass Index.

Table 3. *Distribution of categories of body mass index by IOM recommended ideal term gestational weight gain among the HELLPs cases.*

Weight status	Pre-pregnancy BMI categories, kg/m^2	n	Below IOM GWG Reference n (%)	Within IOM GWG Reference n (%)	Above IOM GWG Reference n (%)	p-value
Underweight	<18.5	10	4 (40.0)	4 (40.0)	2 (20.0)	0.060
Ideal weight	18.5 – 24.9	23	4 (17.3)	6 (26.1)	13 (56.6)	<0.001*
Overweight	25.0 – 29.9	49	3 (6.1)	12 (24.5)	34 (69.4)	<0.001*
Obese	≥30	26	2 (7.7)	6 (26.1)	18 (66.2)	<0.017*
Total	NA	108	13 (12.0)	28 (25.9)	67 (62.1)	<0.001*

*Statistically significant; NA: not applicable; IOM: Institute of Medicine; GWG: gestational weight gain; BMI: body mass index.

Table 4. *Descriptive comparison of key variables obtained among the HELLPs cases at diagnosis by IOM-defined term gestational weight gain recommendations.*

Variables	Below IOM GWG Reference, n=13 n (%)	Within IOM GWG Reference, n=28 n (%)	Above IOM GWG Reference, n=67 n (%)	p-value
Age, years	27.43 ± 3.30	28.69 ± 3.46	31.78 ± 3.73	0.014*
Gravidity	1.43 ± 0.66	2.22 ± 0.45	2.94 ± 0.88	0.063
SBP, mmHg	151. 41 ± 7.34	154.71 ± 6.98	159.65 ± 8.33	<0.001*
DBP, mmHg	102. 44 ± 4.89	109. 62 ± 4.56	117.96 ± 5.21	0.023*
ALT, U/L	217.66 ± 9.87	236.76 ± 10.45	276.91 ± 11.56	<0.001*
AST, U/L	164.73 ± 6.88	178.42 ± 7.88	201.54 ± 9.44	0.035*
LDH, U/L	789.21 ± 13.45	729.45 ± 13.62	874.24 ± 14.34	0.016*
Total protein	60.93 ± 5.89	59.68 ± 6.42	61.23 ± 6.12	0.160
Plasma albumin, g/L	29.37 ± 4.23	30.44 ± 4.51	26.45 ± 5.07	0.003*
Creatinine, umol/L	119.81 ± 5.63	126.76 ± 6.72	136.93 ± 7.49	<0.001*
Uric acid, mmol/L	1.87 ± 0.51	2.14 ± 0.67	2.96 ± 0.63	<0.001*
Total bilirubin, umol/L	54.36 ± 5.17	59.13 ± 6.44	79.77 ± 7.01	<0.001*
Plasma sodium, mmol/L	135.89 ± 8.94	136.92 ± 9.66	137.08 ± 7.88	0.107
Plasma potassium, mmol/L	4.27 ± 1.08	4.31 ± 1.07	4.56 ± 1.10	0.074
Plasma bicarbonate, mmol/L	21.74 ± 3.04	20.19 ± 2.45	19.55 ± 2.63	0.523
Plasma urea, mmol/L	3.08 ± 0.96	3.60 ± 1.10	4.88 ± 1.23	0.069
Platelet count, x 10^9 /L	89.61 ± 6.99	81.47 ± 6.75	71.43 ± 5.71	<0.001*
PCV, %	27.05 ± 3.06	29.54 ± 3.43	26.02 ± 3.49	0.009*

*Statistically significant; IOM: Institute of Medicine; GWG: gestational weight gain; SBP: systolic blood pressure; DBP: diastolic blood pressure; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; PCV: packed cell volume.

Table 5. *HELLP syndrome prediction by the IOM GWG references among the pre-pregnancy BMI categories of patients with HELLPs.*

	Underweight, n=10	Ideal weight, n=23	Overweight, n=49	Obese, n=26
IOM GWG Targets	aOR** (95% CI)	aOR** (95% CI)	aOR** (95% CI)	aOR** (95% CI)
Within IOM GWG Reference	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Below IOM GWG Reference	0.234 (0.112-0.441)	0.362 (0.183-0.599)	0.488 (0.266-0.687)	0.575 (0.381-0.793)
Above IOM GWG Reference	2.011 (1.273-3.871)	2.792 (1.678-4.272)	3.639 (2.230-5.761)	4.893 (2.971-6.72)

*Statistically significant; aOR: adjusted odd ratio; IOM: Institute of Medicine; GWG: gestational weight gain;
CI: confidence interval; **adjusted for age, systolic blood pressure, diastolic blood pressure, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, lactate dehydrogenase, creatinine, uric acid, total bilirubin, albumin plasma levels, platelet count, and packed cell volume.

4. Discussion

4.1. Principal Findings

The current study is the first to evaluate the effects of excessive GWG on the incidence of complete HELLPs among Nigerian women. At booking, most of the patients at risk for HELLPs were found to be overweight. While at diagnosis of HELLPs by term, these patients with HELLPs had markedly higher mean weight compared to their mean booking weight. The majority of the HELLPs patients had excessive GWG compared to the IOM recommendations. The HELLPs cases with pre-pregnant underweight, ideal weight, overweight, and the obese status with GWG below the IOM recommendations were less likely to develop HELLPs while those with GWG above the IOM recommendations were had a higher likelihood of developing HELLPs. Moreover, the lower chance of incident HELLPs among those with GWG below the IOM recommendations becomes less pronounced with increasing BMI status while the more likelihood of incident HELLPs among those with GWG above the IOM recommendations becomes more pronounced with increasing BMI status.

4.2. Results in the Context of Scientific Literature

While reports on the impact of GWG on preeclampsia have been well-documented in the literature [12, 13], that of its influence on HELLPs is very limited in the literature with virtually none reported from our poor-resource setting. Of those few reports on the impact of GWG on HELLP, most have emanated from the western populations, however, with

inconsistent conclusions [14-17]. Martin Jr and colleagues evaluated the impact of GWG on preeclampsia,/eclampsia, and HELLPs in a retrospective study of 434 pregnant women and concluded that GWG was associated with preeclampsia but not HELLPs [14]. Leeners and colleagues had explored obesity as a risk factor in a retrospective study of women with a history of hypertensive diseases in pregnancy, and later in a cohort study of women with HELLP syndrome during the first pregnancy [15, 16]. BMI cut-off values of ≥ 25 kg/m^2 and ≥ 30 kg/m^2 were applied as the threshold of potential risk for incident HELLPs. The authors in both studies surmised that obesity was not a risk factor for HELLP syndrome. The reports of Martin Jr and colleagues and that of Leener and colleagues contrast with our findings which may be due to differences in study methodologies or study population characteristics [14-16]. In stark contrast to these three previous aforementioned studies [14-16], Malmstrom and colleagues showed in a similar study that GWG was a risk factor for HELLPs in the first but not in the second pregnancy and also concluded that the effect of GWG was marked at BMI ≥ 30 which becomes more pronounced with increasing BMI status [17]. These conclusions reported by Malmstrom and colleagues concur with the finding of the current study.

4.3. Mechanisms

Although the physiological mechanisms surrounding HELLP are not fully understood to date. Adipose tissue is hormonally active tissue and produces, for example, several inflammatory mediators that can act to alter endothelial function which remains the hallmark of the pathophysiology of HELLPs [18]. Adiposity has been postulated to result in the production of elevated C-reactive protein and inflammatory cytokines as well as contributing to increased levels of oxidative stress in HELLPs [19]. This may partly explain the association between excess GWG and the onset of HELLPs that may be mediated by these physiologic alterations. This mechanism may also explain the observed risk among women who exhibited excessive GWG in this study. As reported, the current study showed a higher likelihood of HELLPs with increasing GWG.

4.4. Clinical Implications

The primary preventive measures by pre-pregnancy weight reduction, the modification of pre-pregnancy BMI before pregnancy, and close monitoring of GWG among at-risk pregnant women are measures that may prevent or reduce the incidence of this syndrome.

5. Limitations

The study was limited to some extent by a few factors worthy of note. First, its retrospective structure may have led to the under-reporting of the actual number of cases of HELLPs cases identified during the study. Secondly, as a hospital-based study, its conclusions may be limited by its

lack of generalizability to the entire large population within the sampled location. Hence, the study conclusions should be interpreted with caution including its clinical application.

6. Conclusion

The current study evaluated the effects of excessive GWG on the incidence of complete HELLPs among Nigerian women. At booking, most of the patients at risk for HELLPs were found to be overweight. While at diagnosis of HELLPs by term, the HELLPs patients had markedly higher mean weight compared to their booking mean weight. The majority of the HELLPs patients had excessive GWG compared to the IOM recommendations. The HELLPs cases with pre-pregnant underweight, ideal weight, overweight, and the obese status with GWG below the IOM recommendations were less likely to develop HELLPs while those with GWG above the IOM recommendations were had a higher likelihood of developing HELLPs. Moreover, the lower chance of incident HELLPs among those with GWG below the IOM recommendations became less pronounced with increasing BMI status while the more likelihood of incident HELLPs among those with GWG above the IOM recommendations became more pronounced with increasing BMI status.

Statement of Ethics

The ethical approval of the study was obtained from the Research Ethics Committee of UPTH. Following the review of the study protocols and the study was executed in compliance with the principles embodied in the Helsinki Declaration.

Disclosure Statement

The authors declare that they have no competing interests.

Author Contributions

All the authors were involved substantially in the concept and design of the study, data acquisition, analysis and interpretation of the data, drafting the article, revising the article critically for its intellectual content, and in the final approval of the version to be published.

Data Availability

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author (CA) upon reasonable request.

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