in women of childbearing age. A recent report found

INTRODUCTION

maternal and perinatal adverse outcomes.

that 25% of the adult population was obese. The obesity rate has rapidly increased in the general population and in women of childbearing age.^{1,2} Pregnant women constitute an important subpopulation with an elevated risk of obesity due to excessive weight gain. It has been shown that maternal obesity and excessive gestational

Obesity has been frequently cited as a health problem

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A study of maternal and perinatal outcomes due to excessive maternal gestational weight gain in a district hospital in West Bengal – A cross-sectional study

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Background: The weight gain that occurs in pregnancy has the potential to influence a

woman's long-term health by increasing the risk for weight retention and obesity, as well

as related comorbidities such as chronic hypertension (HTN) or Type 2 diabetes mellitus.

Aims and Objectives: The aim of the study was to study maternal and perinatal outcomes associated

with excessive maternal gestational weight gain (GWG). Materials and Methods: The current

study was a cross-sectional study conducted at the Department of Obstetrics and Gynecology,

from October 2018 to October 2019. A total of 91 women attending the antenatal clinic of MR Bangur Hospital and getting admitted for delivery during the study period was considered as the study population. Medical records were maintained for variables of the mothers such as

gestational diabetes mellitus (GDM), gestational HTN, pre-eclampsia, eclampsia, duration of

labor, mode of delivery, indication of cesarean section, Postpartum hemorrhage, and perineal tears. coGuide v.0.01 used for statistical analysis. Results: There were majority of 55 (60.4%) participants reported 18.5–24.9 body mass index (BMI). The difference in the proportion of BMI across maternal weight gain was statistically significant. The difference in the proportion of GDM, duration of labor >18 h, and duration of the second stage of labor >2 h between maternal weight gain were statistically significant. The difference in the proportion of APGAR

score at 1 min, and 5 min between groups of maternal weight gain was statistically significant.

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ABSTRACT

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weight gain (GWG) are associated with adverse obstetric and neonatal outcomes including spontaneous abortion, gestational diabetes mellitus (GDM), cesarean delivery, pre-eclampsia, neonatal macrosomia, and operative and anesthetic complications.³

Whitaker⁴ found that the relative risk of childhood obesity associated with maternal obesity in the first trimester of pregnancy was 2.0 (95% confidence interval [CI], 1.7-2.3) at 2 years of age, 2.3 (95% CI, 2.0-2.6) at 3 years of age, and

Conclusion: Our study suggested that GWG has to be achieved within the Institute of Medicine recommendation according to pre-pregnancy BMI to improve pregnancy outcomes and reduce Key words: Body mass index; Gestational weight gain; Institute of medicine; Obesity

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2.3 (95% CI, 2.0–2.6) at 4 years of age. Birth weight has also been shown to be directly correlated with body mass index (BMI) later in life.⁵ Moreover, observational studies suggest an independent association of maternal obesity with excessive fetal growth^{6,7} and childhood obesity. Alarmingly, increasing obesity trends are now observed early in life, even among young infants,⁸ pointing toward harmful changes in the environment in which contemporary children are born and raised.⁹ Women with GDM and excessive GWG have been found to be more likely than women with normal GWG to develop hypertensive disorders of pregnancy and give birth to infants with macrosomia or large for gestational age (LGA).¹⁰

Several observational studies, which have evaluated the relationship between GWG and short-term maternal and neonatal outcomes such as gestational hypertension (HTN), cesarean birth, and macrosomia, have demonstrated positive associations between GWG above the guidelines and these outcomes.^{11,12} There are very few studies from India that have looked at the applicability of the Institute of Medicine (IOM), USA, guidelines in pregnant women.¹³ Previous studies, however, mostly focused on the influence of pre-pregnancy overweight or obesity on pregnancy outcomes. Moreover, in relation to Asian women, only a few studies have evaluated the influence of pre-pregnancy BMI and GWG on perinatal outcomes. The weight gain recommendations by the IOM are in turn, based on Western World Health Organization BMI cutoffs, making it difficult to compare, translate, or generalize their findings to Asian Indians.¹⁴ In particular, there is a paucity of studies conducted on Indian women.

Aims and objectives

The present study was conducted to study maternal and perinatal outcomes associated with excessive maternal GWG.

MATERIALS AND METHODS

The current study was a cross-sectional study conducted at the Department of Obstetrics and Gynecology, MR Bangur Hospital, Kolkata from October 2018 to October 2019. A total of 91 Women attending the antenatal clinic of MR Bangur Hospital and getting admitted for delivery there, during the study period were considered as the study population.

The inclusion criteria for the study were participants between the age group of 18 and 35 years, those with singleton pregnancy, women with no pre-pregnancy highrisk factor, and women with antenatal check-ups from 1st trimester with complete medical records. Those who did not fulfill the inclusion criteria were excluded from the study.

The formula for computing sample size

As per the study by Crane et al., 52.3% of women gained more than the recommended amount of weight during pregnancy (i.e., P=0.523). The number of patients required for this study was 91 with power 80%.

The mother's written informed consent was obtained from each participant before recruitment. Data were collected from the antenatal cards. Every pregnant woman was assessed for height using a measuring scale fixed on a wall, weight using a calibrated electronic weighing machine, and blood pressure (BP) in the seated position with an armrest. Medical, surgical, and obstetric history, personal risk-behavior, and nutrition assessments were done using the study pro forma.

Gestational diabetes

GDM screening was performed an fasting blood sugar (FBS) and prandial blood sugar (PPBS) (2 h after 75 G of oral glucose) in the first visit and subsequently in 24–28 weeks and accordingly if FBS \geq 126 and PPBS \geq 200, we considered them as diabetic (American Diabetic Association).

Gestational hypertension

A sustained rise of BP to 140/90 mm of Hg or more on at least two occasions four or more hours apart beyond 20th week of pregnancy or during the 24 h of delivery in a previously normotensive woman.

Pre-eclampsia

A multisystem disorder of unknown etiology characterized by the development of HTN to the extent of 140/90 mm of Hg or more with proteinuria after the 20^{th} week in a previously normotensive and non-proteinuric patient.

Eclampsia-pre-eclampsia when complicated with generalized tonic-clonic convulsions and/or coma is called eclampsia.

PPH

PPH was taken as blood loss following delivery >500 mL in vaginal delivery and >1000 mL in case of cesarean delivery.

Mode of delivery whether normal vaginal, instrumental or cesarean section (CS) was noted. The indications of CS were noted. Maternal outcome variables included were mean duration of labor (1st and 2nd stage), the prolonged second stage (>2 h), mode of delivery, complications like 3rd or 4th degree perineal tear, and PPH noted.

Fetal growth was assessed through serial ultrasound measurements which were obtained from antenatal records. The first-trimester scan was done at 11–13 weeks of gestation for nuchal translucency and dating of gestational age by measuring crown-rump length. The third-trimester scan was done at 30–35 weeks of gestation. The biparietal diameter, head circumference, abdominal circumference, and femur length were considered and, a combination of these variables was used to derive an estimated fetal weight and growth pattern of the given fetus. Birth weight >2.5 kg was taken as normal, birth weight <2.5 kg irrespective of the gestational age was considered as low birth weight (LBW), and birth weight >4 kg was considered as macrosomia.

The average length of a newborn was taken to be 50 cm. Birth weight was recorded by infant weighing scale and neonatal length was recorded by inch tape. Each baby delivered was examined completely and the Apgar score at 1 min and 5 min was calculated. Babies with birth asphyxia or with poor Apgar score (<7) were followed up in our special newborn care unit (SNCU) for a period as advised by the pediatrician. The final neonatal outcome in terms of neonatal death or discharge was recorded.

Statistical methods

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, and frequency and proportion for categorical variables. Categorical outcomes such as intrauterine fetal demise (IUFD)/stillbirth, APGAR scores, mode of delivery were compared between maternal weight gain groups using the Chi-square test. P<0.05 was considered statistically significant.¹⁵

RESULTS

A total of 91 subjects was included in the final analysis.

In the study population, majority of 31 (34.1%) participants were in age group 25–29 and the mean age was 24.07±4.16 with the (Range 18–31), the majority of 87 (95.6%) participants were reported primigravida and majority of 47 (51.6%) were reported 10–12 antenatal visits and the mean number of antenatal visits was 9.63 ± 1.74 with the (Range 7–12). There were majority of 55 (60.4%) participants reported 18.5–24.9 BMI with the mean BMI of the study population being 23.70 ± 2.94 (Range 18.5–31.1). The mean weight (in kg) @1st trimester was 48.41 ± 6.22 (Range 36.3–63.9) and it was mean 58.90 ± 8.66 @ the time of delivery with the (Range 43.8–80.8), majority of 70 (76.9%) participants had normal (8.0–16.0) maternal weight gain, the mean of maternal weight gain (in kg) was 10.49 ± 3.28 (Range 4.9–21.0) (Table 1).

| Table 1: Descriptive analysis of | parameters in |
|----------------------------------|---------------|
| the study population (n=91) | |

| 311 (| • |
|------------------------------------|------------------------------|
| Parameters | Study population (%) |
| Age group (in years) | |
| 18–20 | 23 (25.3) |
| 20–24 | 26 (28.6) |
| 25–29 | 31 (34.1) |
| ≥30 | 11 (12.1 |
| Age | 24.07±4.16 (Range 18–31) |
| Gravida | |
| Multigravida | 4 (4.4) |
| Primigravida | 87 (95.6) |
| Number of antenatal visits group | |
| 7–9 | 44 (48.4) |
| 10–12 | 47 (51.6) |
| Number of antenatal visits | 9.63±1.74 (Range 7–12) |
| BMI (kg/m²) | |
| 18.5–24.9 | 55 (60.4) |
| ≥25.0 | 36 (39.6) |
| BMI (kg/m²) | 23.70±2.94 (Range 18.5–31.1) |
| Weight (in kg) | |
| @1 st trimester | 48.41±6.22 (Range 36.3–63.9) |
| @ The time of delivery | 58.90±8.66 (Range 43.8–80.8) |
| Maternal weight gain (in kg) group | о |
| Low (<8.0) | 11 (12.1) |
| Normal (8.0–16.0) | 70 (76.9) |
| High (>16.0) | 10 (11.0) |
| Maternal weight gain (in kg) | 10.49±3.28 (Range 4.9–21.0) |

The difference in the proportion of age across maternal weight gain was found to be insignificant (P=0.81), with the majority of 25 (35.7%) participants of normal weight gain within the 25–29 years of age group. The majority of 67 (95.7%) participants reported normal weight gain in primigravida. The difference in the proportion of no. of antenatal visits between maternal weight gain was statistically not significant (P=0.55). The difference in the proportion of BMI across maternal weight gain was statistically significant (P<0.001) (Table 2).

In Eclampsia hypertensive disorder, the majority of 9 (12.9%) reported normal weight gain, and 53 (75.7%) were reported with normal BP. The difference in the proportion of GDM, duration of labor >18 h, and duration of the second stage of labor >2 h between maternal weight gain were statistically significant (P<0.05). The difference in the proportion of mal-presentation between groups of maternal weight gain, the majority of 6 (37.5%) participants reported cephalopelvic disproportion indication of lower segment CS (LSCS), 11 (15.7%) were reported in 4th degree perineal tear and 12 (17.1%) were in PPH present (Table 3).

The difference in the proportion of IUFD or stillborn between groups of maternal weight gain was statistically insignificant (P=0.0615). There were 61 (87.1%) participants reported normal weight gain with a normal birth weight of the neonates. The difference in the proportion of APGAR

| Table 2: Comparison of baseline parameters with maternal weight gain in the study population (n=91) | | | | |
|---|-----------------------------------|-------------------|-----------------|---------|
| Baseline parameters | Maternal weight gain | | | P-value |
| | Low (n=11) (%) | Normal (n=70) (%) | High (n=10) (%) | |
| Age (in years) | | | | |
| 18–20 | 2 (18.2) | 18 (25.7) | 3 (30.0) | 0.81 |
| 20–24 | 3 (27.3) | 20 (28.6) | 3 (30.0) | |
| 25–29 | 3 (27.3) | 25 (35.7) | 3 (30.0) | |
| ≥30 | 3 (27.3) | 7 (10.0) | 1 (10.0) | |
| Gravida | | | | |
| Primigravida | 10 (90.9) | 67 (95.7) | 10 (100.0) | * |
| Multigravida | 1 (9.1) | 3 (4.3) | 0 (0.0) | |
| Number of antenatal visits | | | | |
| 7–9 | 4 (36.4) | 36 (51.4) | 4 (40.0) | 0.55 |
| 10–12 | 7 (63.6) | 34 (48.6) | 6 (60.0) | |
| BMI (kg/m ²) | | | | |
| 18.5–24.9 | 5 (45.5) | 42 (60.0) | 8 (80.0) | <0.001 |
| ≥25.0 | 6 (54.5) | 28 (40.0) | 2 (20.0) | |
| *No statistical test was applied due to o | subjects in the calls DMI Deduces | as index | | |

*No statistical test was applied due to o subjects in the cells, BMI: Body mass index

| Table 3: Comparison of maternal factors with maternal weight gain in the study population (n=91) | | | | | |
|--|----------------------|-------------------|-----------------|--------|--|
| Maternal factors | Maternal weight gain | | | | |
| | Low (n=11) (%) | Normal (n=70) (%) | High (n=10) (%) | | |
| Hypertensive disorders | | | | | |
| Eclampsia | 0 (0.0) | 2 (2.9) | 1 (10.0) | * | |
| Gestational HTN | 1 (9.1) | 9 (12.9) | 3 (30.0) | | |
| Pre-eclampsia | 0 (0.0) | 6 (8.6) | 1 (10.0) | | |
| Normal BP | 10 (90.9) | 53 (75.7) | 5 (50.0) | | |
| GDM | () | | | | |
| Present | 2 (18.2) | 4 (5.7) | 3 (30.0) | 0.0341 | |
| Absent | 9 (81.8) | 66 (94.3) | 7 (70.0) | | |
| Mal-presentation | | | | | |
| Present | 2 (18.2) | 11 (15.27) | 2 (20.0) | 0.93 | |
| Absent | 9 (11.8) | 59 (77.6) | 8 (10.5) | | |
| Duration of labor >18 h | () | | | | |
| Present | 2 (22.2) | 4 (44.4) | 3 (33.3) | 0.0341 | |
| Absent | 9 (11.0) | 66 (80.5) | 7 (8.5) | | |
| Duration of the second stage of labor >2 h | () | | () | | |
| Present | 1 (9.1) | 2 (2.9) | 2 (20.0) | 0.044 | |
| Absent | 10 (9.1) | 68 (97.1) | 8 (80.0) | | |
| Mode of delivery | | | | | |
| LSCS | 2 (18.2) | 16 (22.9) | 6 (60.0) | | |
| OVD | 1 (9.1) | 2 (2.9) | 1 (10.0) | 0.042 | |
| VD | 8 (72.7) | 52 (74.3) | 3 (30.0) | | |
| Indication of LSCS | | - (-) | | | |
| CPD | 1 (50.0) | 6 (37.5) | 3 (50.0) | * | |
| Eclampsia | 0 (0.0) | 1 (6.3) | 0 (0.0) | | |
| FD | 0 (0.0) | 2 (12.5) | 0 (0.0) | | |
| NPOL | 0 (0.0) | 2 (12.5) | 1 (16.7) | | |
| Obstructed labor | 0 (0.0) | 1 (6.3) | 0 (0.0) | | |
| Unfavorable cervix, post-dated with high PP | 0 (0.0) | 0 (0.0) | 1 (72.7) | | |
| Pre-eclampsia | 0 (0.0) | 1 (6.3) | 1 (16.7) | | |
| IUGR | 1 (50.0) | 0 (0.0) | 0 (0.0) | | |
| PROM with high PP | 0 (0.0) | 3 (18.8) | 0 (0.0) | | |
| 4 th degree perineal tear | | | | | |
| Present | 0 (0.0) | 11 (15.7) | 2 (20.0) | * | |
| Absent | 11 (100.0) | 59 (84.3) | 8 (80.0) | | |
| PPH | (/ | () | - (/ | | |
| Present | 0 (0.0) | 12 (17.1) | 2 (20.0) | * | |
| Absent | 11 (100.0) | 58 (82.9) | 8 (80.0) | | |

*No statistical test was applied due to o subjects in the cells, HTN: Hypertension, BP: Blood pressure, GDM: Gestational diabetes mellitus, LSCS: Lower segment cesarean section, VD: Vaginal delivery, OVD: Operative vaginal deliveries, IUGR: Intrauterine growth restriction, PROM: Premature rupture of membranes, PPH: Postpartum hemorrhage

score at 1 min, and 5 min between groups of maternal weight gain was statistically significant (P<0.001). The difference in the proportion of SNCU admission and final outcome after SNCU between maternal weight gain was statistically significant (P<0.05) (Table 4).

DISCUSSION

In this study, we studied the association of seven maternal and neonatal outcomes on GWG and weight gain trajectories during pregnancy. From the results of the current study, we could find that the majority of the women belonged to the age group of 25–29 years. Similar results were obtained by Akgun et al., who found most of the women (82.2%) were 19–30 years old.¹⁶ In a similar study by Restall et al., the mean age was found to be 28.5 years.¹⁷ In another study by Stotland et al., it was seen that women older than 40 years were less likely to have GWG above the IOM guidelines compared with other age categories.¹⁸

In the present study, all the primigravida women showed high GWG. Our results were in sync with a study by Sarkar et al., as they found 58% primigravida and 42% multipara women with high GWG.¹⁹ Similar study on females with excessive GWG by Radhakrishnan et al., it was found that 46% of study subjects were primigravida.¹³

The present research showed a statistical significance of BMI across maternal weight gain. Similarly in a study

when compared with women of normal weight, high pre-pregnancy BMI resulted in a higher risk of CS with an adjusted odds ratio of 1.95 (95% CI being 1.29-2.96) for the overweight group and 3.26 (1.57-6.76) for the obese group.20 Studies by DeVader et al., and Cedergren show similar weight gain (33-43%).^{21,22} In another study by Crane et al., in women with normal pre-pregnancy BMI, excess weight gain was associated with increased rates of gestational HTN (OR 1.27; 95% CI 1.08-1.49), augmentation of labor (OR 1.09; 95% CI 1.01-1.18), and birth weight \geq 4000 g (OR 1.21; 95% CI 1.10–1.34).²³ in a study by Restall et al., the mean BMI of pregnant women with excessive GWG was 25.9 ± 4.8 kg/m². In this study, it was seen that overweight women were at 3 times higher risk of GWG compared to those women who had normal pre-pregnancy BMI and obese women had 2.5 times higher risk of excess GWG.¹⁷ Researchers in previous studies have suggested similar findings regarding this association. However, the effects of GWG on the development of adverse perinatal outcomes are also important for investigation to understand the underlying mechanisms of certain associations. The previous population cohort studies of the relationships between pre-pregnancy BMI and GWG and adverse outcomes were from Western countries.24

There was a significant association between hypertensive disorders in pregnancy and excess GWG (P<0.0001) in the current study. Briese et al., analyzed German perinatal statistics and demonstrated higher rates of HTN, pre-

| Table 4: Comparison of Neonatal factors with maternal weight gain in the study population (n=91) | | | | |
|--|----------------------|-------------------|-----------------|---------|
| Neonatal factors | Maternal weight gain | | | P-value |
| | Low (n=11) (%) | Normal (n=70) (%) | High (n=10) (%) | |
| IUFD or Stillborn | | | | |
| Yes | 1 (9.1) | 4 (5.7) | 2 (20.0) | 0.0615 |
| No | 10 (90.9) | 66 (94.2) | 8 (80.0) | |
| Birth weight of the neonates (in I | kg) | | | |
| LBW | 2 (18.2) | 2 (2.9) | 0 (0.0) | * |
| Normal | 9 (81.8) | 61 (87.1) | 7 (70.0) | |
| Macrosomia | 0 (0.0) | 7 (10.0) | 3 (30.0) | |
| Length of the neonates (in cm) | | | | |
| Low | 3 (27.3) | 3 (4.3) | 1 (10.0) | * |
| Normal | 8 (72.7) | 63 (90.0) | 6 (60.0) | |
| High | 0 (0.0) | 4 (5.7) | 3 (30.0) | |
| APGAR Score at 1 min | | | | |
| Low | 6 (60.0) | 5 (7.6) | 5 (62.5) | <0.001 |
| Normal | 4 (40.0) | 61 (92.4) | 3 (37.5) | |
| APGAR Score at 5 min | | | | |
| Low | 5 (50.0) | 4 (6.1) | 4 (50.0) | < 0.001 |
| Normal | 5 (50.0) | 62 (93.9) | 4 (50.0) | |
| SNCU admission | | | | |
| Required | 3 (30.0) | 2 (25.0) | 5 (7.6) | 0.040 |
| Not Required | 7 (70.0) | 6 (75.0) | 61 (92.4) | |
| Final outcome after SNCU admis | ssion | | | |
| Discharged Alive | 8 (80.0) | 64 (97.0) | 6 (75.0) | 0.018 |
| Died | 2 (20.0) | 2 (3.0) | 2 (25.0) | |

*No statistical test was applied due to o subjects in the cells, IUFD: Intrauterine fetal demise, LBW: Low birth weight: SNCU: Special newborn care unit

eclampsia, gestational diabetes, fetal macrosomia, fetal structural anomalies, and low neonatal Apgar score in obese than in normal-weight women.²⁵ Bhattacharya et al., who compared 1,857 obese pregnant women with 14,076 normal pregnant women, reported that obese pregnant women had significantly higher frequencies of pre-eclampsia, gestational HTN, emergency CS, preterm delivery at <33 weeks of gestation, and birth weight over 4000 g.26 In a study by Arora et al., 3.9% of the women with excess GWG had pre-eclampsia and there was a significant association between excess GWG and risk of development of preeclampsia (P<0.001).²⁷ Women who develop pre-eclampsia have reduced plasma volume expansion in early pregnancy compared with women who remain normotensive. However, studies have suggested that this is due to increased capillary permeability and a redistribution of plasma to interstitial fluid.^{28,29} In a study by Arora et al., 2013, among the women with excessive GWG than IOM recommendation, 48% of them underwent LSCS. Of pregnant women who had normal GWG, 37.8% had LSCS, and for those with inadequate GWG, 27.3% had LSCS. There was a significant association between GWG and mode of delivery (P<0.001).²⁷ In a study by Su et al., 2019, women who had excessive GWG had a 1.43 times higher risk of undergoing LSCS than those who had normal GWG and those who had inadequate GWG (0.9 times the risk of LSCS).³⁰

In the present study, there was a significant association between the birth weight of the neonate and GWG (P=0.033), with excess GWG having a positive association with macrosomia. Results obtained by Shrestha et al., showed the mean weight gain of the mothers was 9.48 (SD=3.41) kg, and the mean birth weight of the infants was found to be 2965.66 (SD=364.37) G. Multiple liner regression models showed the effect of GWG, age, and parity on the birth weight of the infant. Step-wise multiple regressions gave rise to models that showed the effect of GWG and age on the birth weight of the infants.³¹ Similar results were obtained in a nationwide cohort study. It was found that after 22 weeks, GWG was greater in the subjects who delivered macrosomia infants and lower in the subjects who delivered LBW infants. The GWG from pre-pregnancy to the first, second, and third trimesters and to delivery were categorized into quartiles (Quartiles 1, 2, 3, and 4); subsequently, a multiple logistic regression analysis was performed to assess the risk of LBW or macrosomia associated with GWG from pre-pregnancy.32 Maternal BMI is consistently reported as an independent risk factor for both pre-eclampsia and gestational HTN.33 In a study by Radhakrishnan et al., among women with excess GWG 14.57% had given birth to LGA babies and the mean birth weight of the babies born to such mothers was 3.07 kg. There was a significant association between GWG and the birth weight of the babies.13

Limitations of the study

The limitations of the current study were a smaller sample size and it was conducted only in one center. We also suspect hospital bias due to the place of the study.

CONCLUSION

The current study showed that GWG is an important determinant of pregnancy outcomes. Excessive GWG was found to be associated with increased maternal complications in the form of post-inflammatory hyperpigmentation, GDM, prolonged labor, and increased CS rates. It was also associated with increased adverse neonatal outcomes such as IUFD or stillborn, macrosomia, LGA, poor APGAR score at 1–5 min, and increased SNCU admission rates due to complications such as hypoglycemia, myoclonic-atonic seizures, and seizures.

Hence, our study suggested that GWG has to be achieved within the IOM recommendation according to prepregnancy BMI to improve pregnancy outcomes and reduce maternal and perinatal adverse outcomes.

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SCM- Conceptualized the study and played a primary role in compiling, analyzing, and interpreting the data. AB, SCM, and MC- Contributed to fine-tuning the proposal and contributed to data collection and entry. Reviewed the results and contributed to the preparation and review of drafts. All the authors have read and approved the final version of the manuscript. All the authors take complete responsibility for the content of the manuscript.

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