

# Effect of Increased Prepregnancy Body Mass Index on Placental Morphologic Features in Gestational Diabetes

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## ABSTRACT

**Introduction:** Gestational Diabetes Mellitus (GDM) and obesity are both independent and associated risk factors that complicate pregnancy. There has been a worldwide increase in the incidence of GDM. This has been explained by the global epidemic of obesity which has, in turn, resulted in an increase in number of pre-obese and obese women of reproductive age group. Both conditions are associated with metabolic and functional disturbances that affect the placenta. The gross morphologic alterations in gestational diabetic placentae have been extensively studied. The morphopathologic impact of obesity on the gestational diabetic placenta is yet to be explored.

**Aim:** The aim of the present study was to evaluate the changes in placental morphology of GDM pregnancies as compared to placentae from normoglycaemic, normal prepregnancy Body Mass Index (BMI) pregnancies and to further assess the effect of high prepregnancy BMI on the placentae of GDM in comparison with the placentae of GDM with normal prepregnancy BMI.

**Materials and Methods:** The observational cross-sectional comparative study was carried out among women who attended three specialty obstetric clinics in an urban city in central Tamil Nadu, India. The study was carried out between May to August 2016. A total of 95 women, of whom 65 were gestational diabetic participated in the study. The control group comprised of 30 women who had normal prepregnancy BMI and who were normoglycaemic throughout pregnancy. BMI

was calculated from the prepregnancy weight and height. Using Indian standards of BMI classification, the GDM women were grouped into Lean GDM (LG; n=30) and Obese GDM (OG; n=35). At term, the placentae were collected after the delivery from both study and control groups and analysed for gross morphological parameters including placental weight, volume, thickness, diameter, shape and size, number of cotyledons and site of cord insertion. Statistical test ANOVA with post-hoc analysis was used to compare the groups and Pearson's coefficient was used to correlate BMI with placental parameters, using the Statistical Package for Social Sciences (SPSS) version 21.0.0, IBM.

**Results:** Placental weight, volume, thickness and diameter showed a significant increase in the GDM group as compared to control group. There were a higher proportion of irregular placental shapes and marginal and velamentous cord insertion among gestational diabetic placentae. Placental weight, volume and thickness were significantly increased in OG placentae as compared to LG. Pearson's r showed a weak however, significant positive correlation between maternal prepregnancy BMI and placental weight, volume and thickness.

**Conclusion:** Maternal prepregnancy BMI influences gross morphological features of the placenta. The finding is relevant in the context of understanding the response of the placenta to obesity and GDM and in evolving ultrasonographic placental examination criteria that can be used to monitor and safeguard against adverse pregnancy outcomes.

**Keywords:** Maternal, Obesity, Placenta

## INTRODUCTION

The placenta plays a role in mediating foetal growth and viability and it is involved in hormonal and metabolic alterations during pregnancy [1]. Changes in maternal metabolism influence the placental function and morphology, based on the type and timing of the insult [2]. Both GDM and obesity complicate the pregnancy. GDM has been associated with adverse pregnancy outcomes and changes in the normal placental morphology [3,4]. Ultrasonographic studies on the placenta, during pregnancy, report changes in the placental volume, area and perimeter along with altered vascular indices in GDM [5]. It has been proposed that while placental pathology is not diagnostic of GDM, it is nevertheless one of the indicators of abnormal pregnancy environment and foetal growth [6,7]. The changes in the morphology have traditionally been considered pathologic, however, recent research attempts to attribute these changes to adaptive response of the placenta in an effort to offset the adverse metabolic effects [8]. The abnormal placental growth may be construed as compensatory or adaptive to accommodate different maternal risk factors.

There is widespread prevalence of obesity which could explain the worldwide increase in incidence of GDM [9,10]. Obesity and GDM are independent and associated risk factors for the

adverse pregnancy outcomes [11]. The effect of obesity and GDM on pregnancy outcomes is well-documented [12]. Abnormal biochemical and molecular changes in both these conditions cause endothelial dysfunction and a hypoxic condition of the placenta [13,14]. The changes induced by GDM in the placenta have been extensively studied by gestational age, timing of onset of GDM, glycaemic control and other factors [7,15,16]. However, the gross morphologic alteration in the placenta due to obesity alone or the compounding effects of obesity, if any, on the gestational diabetic placenta is under reported in literature.

Antenatal ultrasound examination which evaluates the placental parameters such as the weight, volume and cord insertion has been proven to be of predictive value in the pregnancy outcomes such as foetal weight and adverse effects [5,17,18]. In this context, we sought to examine the gross morphological effects of increasing BMI with the GDM on placental morphology.

## MATERIALS AND METHODS

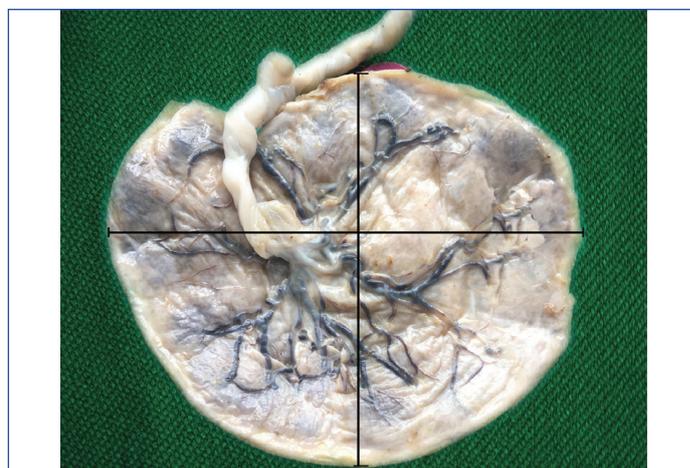
The observational cross-sectional comparative study was carried out among women who attended three specialty obstetric clinics in an urban city in central Tamil Nadu, India. The study was carried out between May to August 2016. 65 women with singleton

pregnancies who had been diagnosed as GDM, based on DIPSI criteria, of more than 140 mg/dL of glucose two hours after a 75 gm oral glucose load at 24-28 weeks were included in the study [19]. Of the 65 women with GDM, 35 were obese (OG group) and 30 had a normal prepregnancy BMI (LG group). Normoglycaemic women with a normal prepregnancy BMI were specifically chosen for control group (n=30). The WHO proposed lower action cut-off points for BMI in Asian populations [20]. Accordingly, the BMI cut-off values that were recommended by the Indian Health Ministry were used to classify participants [21]. BMI of 18.5 to 21.9 is defined as normal BMI (LG and control groups) and above 25 is considered to be obese (OG group) [20,21]. Pregnancies complicated by pre-existing diabetes mellitus, chronic hypertension, other co-morbidities such as anaemia, pre-eclampsia, and substance abuse were excluded. Participants with a total pregnancy weight gain of more than 16 kg in control and LG groups and more than 11.5 kg in OG group were excluded from the study [22]. The level of glycaemic control was considered adequate if the mean fasting glucose levels were  $\leq 90$  mg/dL and two hour postprandial glucose levels were  $\leq 120$  mg/dL [23].

Placentae were collected immediately after delivery. The placenta was washed in running tap water and fixed in 10% formal saline for 2-3 days. Placental membranes were trimmed close to the periphery and the umbilical cord was sectioned 5 cm away from the site of insertion. Placentae were weighed on an electronic scale and the volume was estimated by fluid displacement method [24]. Placental shapes were classified as discoid, ovoid, and irregular, based on modification from previous descriptions of placental shape [25]. The site of cord insertion was noted. The site of cord insertion was categorised into central, eccentric, marginal and velamentous. The different types of placental shapes and cord insertion per group were expressed as percentages. The placenta was categorised into three concentric areas from the centre towards the periphery and thickness was measured by passing a needle through three representative areas [Table/Fig-1]. The mean thickness was calculated [26]. The largest diameter of the placenta was measured (major axis) on the foetal surface. A measurement perpendicular to the largest diameter was taken at the bisection of the major axis (minor axis). The placental diameter was calculated as the mean of the major and minor axes [Table/Fig-2] [26]. The maternal surface was examined for the presence of clots, number of cotyledons, discolouration, calcification, areas of haemorrhage and necrosis. The foetal surface was examined for abnormalities and discolouration. The maternal prepregnancy weight and height and demographic details were obtained from hospital records. The prepregnancy weight was defined as the weight recorded during the first antenatal visit during the first trimester. The study was carried out after obtaining prior approval from the Institutional Ethical committee (CMCH and RC/IEC-No:19/15.04.2016). Informed consent was obtained prior to delivery for collection of data and placenta.



**[Table/Fig-1]:** Maternal surface of placenta with cotyledons, showing the three zones (1,2,3), from which thickness was measured.



**[Table/Fig-2]:** Foetal surface of placenta showing measurement of diameter along two axes.

## STATISTICAL ANALYSIS

Data was tabulated and statistical tests of ANOVA with Tukey post-hoc analysis and Pearson's correlation were performed using the SPSS version 21.0.0, IBM. Data on weight, volume, thickness and diameter are expressed as mean $\pm$ standard deviation.

Characteristic	Control (n=30)	Lean GDM (n=30)	Obese GDM (n=35)
<b>Age</b>			
Mean $\pm$ standard deviation	28.83 $\pm$ 3.333	26.83 $\pm$ 3.668	28.49 $\pm$ 2.894
Minimum	24	20	22
Maximum	34	34	33
<b>Prepregnancy BMI</b>			
Mean $\pm$ standard deviation	21.73 $\pm$ 0.97	20.968 $\pm$ 1.38	32.45 $\pm$ 4.20
Minimum	19.3	18.8	27.3
Maximum	22.9	23.9	42
<b>Well controlled glycaemic levels</b>			
Percentage of subgroup (number of participants)	100% (30)	86.67% (26)	85.71% (30)

**[Table/Fig-3]:** Demographic features of the selected sample and the percentage of gestational diabetic who had maintained good glycaemic control.

## RESULTS

### Maternal Demographic Characteristics

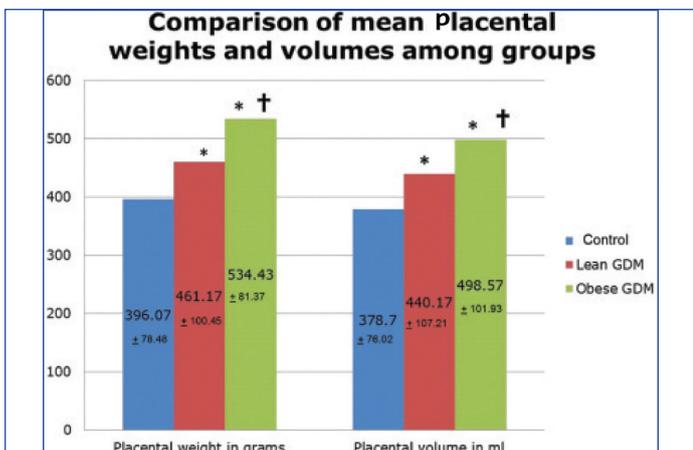
As given in [Table/Fig-3], the age range of the participants of the study was from 20 to 34 years. There was no significant difference in mean age between the three groups. The LG and OG groups differed only by BMI.

### Placental Weight, Volume, Thickness and Diameter

ANOVA results on comparison between the mean placental weight, volume, thickness, diameter and number of cotyledons showed significant differences between the groups ( $p < 0.001$ ).

The mean placental weight in grams in the control group, LG and OG groups was 396.07 $\pm$ 78.48, 461.17 $\pm$ 100.45 and 534.43 $\pm$ 81.37 respectively [Table/Fig-4]. The placental weight in the GDM groups was significantly increased from the control group. Post-hoc analysis using the Tukey Honest Significant Difference (HSD) test shows that the difference in mean placental weight between that of control and LG and between that of control and OG groups was significant at a level of  $p < 0.05$ . There was a significant difference between the LG and OG groups ( $p < 0.05$ ).

In the placenta of the diabetic, the placental volume was increased (440.17 $\pm$ 107.21 mL in the LG group and 498.57 $\pm$ 101.93 mL in the OG group) compared to the control (378.70 $\pm$ 76.02 mL) group ( $p < 0.05$ ). The placentae in the LG group had a significantly lesser



**[Table/Fig-4]:** Comparison of the placental mean placental weights and volume among groups.

\*indicates values significantly different from control  
†indicates significant difference between the lean GDM and obese GDM groups. ANOVA with post-hoc analysis was used to test for differences between means of groups

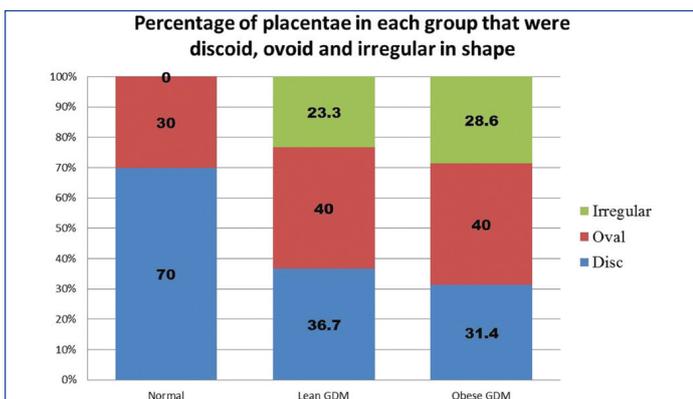
volume than the placentae in the OG group ( $p < 0.05$ ) [Table/Fig-4]. The mean thickness and the mean diameter of placenta from the LG and OG groups were significantly increased compared to the mean

Group	Mean placental thickness in cm	Significance ( $p < 0.05$ ) by post hoc analysis	Mean placental diameter in cm	Significance ( $p < 0.05$ ) by post hoc analysis
Control	2.38±0.26		15.95±1.64	
Lean GDM	3.18±0.60*	LG and CL; $p=0.001^*$ LG and OG; $p=0.431$	17.95±2.82*	LG and CL; $p=0.001^*$ LG and OG; $p=0.991$
Obese GDM	3.34±0.61*	OG and CL; $p=0.001^*$	17.87±3.09*	OG and CL; $p=0.001^*$

**[Table/Fig-5]:** Comparison of the placental mean thickness and diameter between groups.

\*indicates values significantly different from control. ANOVA with post-hoc analysis was used to test for differences between means of groups

thickness and the mean diameter of placentae of the control group ( $p < 0.05$ ). While the mean thickness of placenta was increased in the OG group as compared to the LG group, the difference was not statistically significant. The mean diameter of the placentae of the OG group did not show statistically significant difference from that of the LG group [Table/Fig-5].



**[Table/Fig-6]:** Increased incidence of irregular and oval shaped placentae in the GDM groups compared to control.

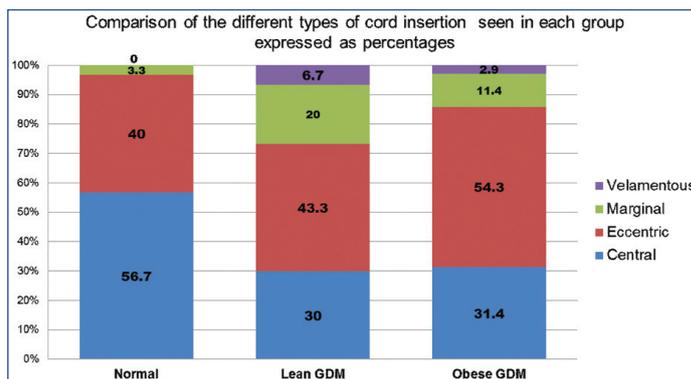
### Morphological Features of Placenta: Shape and Umbilical Cord Attachment

The GDM group had a higher percentage of ovoid and irregular placentae than the control group [Table/Fig-6]. Irregular placentae were noted to be higher in the OG group than the LG group [Table/Fig-7a]. There were two placentae each in the LG and OG group that were lobed [Table/Fig-7b].



**[Table/Fig-7]:** a) An irregularly shaped placenta; b) Lobed placenta.

Higher incidence of marginal and eccentric umbilical cord insertion were noticed in the GDM group [Table/Fig-8,9a]. Velamentous insertion was also seen [Table/Fig-9b]. Among the placenta from OG group, one showed velamentous insertion and four had marginal insertions. Among the LG group, there were two velamentous insertions and six placentae with marginal insertion of umbilical



**[Table/Fig-8]:** Different types of umbilical cord insertion in each group.



**[Table/Fig-9]:** a) Marginal insertion of cord; b) Velamentous or membranous insertion.

cord. In comparison, there were no velamentous insertions of the umbilical cord in the control group and a single placenta had marginal insertion. The mean number of cotyledons in LG, OG, control groups were  $17.47 \pm 2.46$ ,  $17.06 \pm 2.43$  and  $14.87 \pm 1.14$  respectively. The number of cotyledons was increased in the GDM group. There was a significant difference ( $p < 0.05$ ) between the control and LG and between the control and OG groups ( $p < 0.05$ ).

Parameters	Pearson's coefficient	Significance ( $p < 0.05$ )
Placental weight	0.382	$p=0.001$
Placental volume	0.324	$p=0.001$
Mean placental thickness	0.305	$p=0.003$

**[Table/Fig-10]:** Pearson's coefficient of correlation of placental parameters that showed significant association with BMI.

### Correlation with Increased BMI

As given in [Table/Fig-10], the Pearson's co-efficient  $r$ , showing association of BMI with weight, volume and mean thickness of placenta, was 0.382, 0.324 and 0.305 respectively. There was a significant yet weak positive correlation between the increasing maternal BMI and the placental parameters such as weight, volume and thickness ( $p < 0.01$ , two tailed).

### DISCUSSION

Metabolic derangements cause morphological and functional changes in the placenta. Based on the timing of the onset of GDM,

the changes in the placenta may be functional and morphological or only functional [2]. These changes, that are seen in a placenta, have been attributed by researchers as an attempt to compensate for the abnormal metabolic and cellular derangements [8,27].

GDM has been associated with increased weight, central thickness and diameter of the placenta along with increased volume [2,3,15,28-30]. Along with the above mentioned changes, studies also report an increase in the number of cotyledons and circumference [30,31]. The findings in present study corroborate with these studies, in that GDM placentae were heavier and thicker with an increased volume and diameter. A study reported increased placental hypertrophy in overweight and obese pregnancies and found that higher placental weight was associated with higher rates of caesarean section, post dates and increased foetal weight [32]. Increased or decreased placental weight was found to be an independent risk factor for adverse pregnancy outcome [33]. A study found an increase in mean placental weight over the years [34]. The authors hypothesised that this change in standard normal placental weights could be correlated to the increasing BMI trends [34]. The present study shows increase in placental weight, thickness and diameter along with volume in GDM pregnancies. There was significant increase in placental weight and volume in the OG group as compared to the LG group.

GDM might cause vascular dysfunction by means of the hyperglycaemia and hyperinsulinemia [35]. Placentae with increased weight were found to be associated with adverse neonatal clinical outcomes [36]. The placental thickness has a weak positive correlation with birth weight [37]. GDM and obesity are involved in hypoxic stress generation in the placenta [14]. The increase in placental weight is accompanied by an increase in surface area for diffusion [38]. These changes may be interpreted as pathologic changes caused due to the increased metabolic insult in obese GDM pregnancies. They may also be interpreted as an attempt by the placenta to increase placental function in order to compensate for metabolic derangement. The increase in weight might reflect an attempt in increasing placental efficiency.

The placental shape is commonly described as discoid or ovoid [25]. A study shows that irregularities in the placental shape, measured quantitatively, had significant correlation with uteroplacental and fetoplacental vascular pathology [39]. A study on foetal programming states that, while placental weight can be correlated with foetal weight, placental shape cannot be correlated with the foetal weight [40]. The altered placental shape can be considered as an adaptive change to the altered maternal and uterine environment [40]. Studies on placental shape in GDM pregnancies report variable findings. Placenta from GDM pregnancies were found to be more ovoid than round [29]. There was incidence of lobed placenta [41]. A study reported that there were no differences in shape [42]. Present study shows that approximately one-fourth of placentas belonging to the GDM groups were irregular in shape. Along with the increased weight and thickness of GDM placentas, this irregularity in shape might reflect an underlying vascular and surface area adaptation. Given the high occurrence of irregular shaped placenta associated with GDM, it could be presupposed that an irregular shaped placenta on ultrasound examination might be indicative of underlying pathology and this would warrant further evaluation and close monitoring of maternal and foetal health.

Insertion of umbilical cord is commonly central or eccentric [25]. Marginal insertion of umbilical cord is seen in approximately 7% of placentas and 1% of them show velamentous or membranous insertion [25]. It has also been stated that the site of insertion of the umbilical cord is often eccentric than central [43]. A study found no difference in umbilical cord insertion in GDM pregnancies [43]. A study reports that deviation from non central or near central insertion site of the umbilical cord negatively impacted transfer capability across the placenta [44]. This was because of disturbances in

the chorionic vasculature, despite a discoid placental shape [44]. Velamentous insertion has been associated with increased foetal risk and ante-natal ultrasonographic evaluation has been of value to provide necessary information about type of umbilical cord insertion [17,18,45,46]. It is significant to note that our results show an increase in both the marginal and velamentous insertion among the GDM placentae compared to controls. This indicates a deviation in normal placental vascularisation. This feature might be taken in combination with other commonly associated placental findings in GDM such as increased weight and thickness, irregularity in shape, and serve to signal an underlying disorder of pregnancy.

The influence of glycaemic control during pregnancy on the clinical outcomes, gross morphological and microscopic features of the placenta, is debated [3,28]. In present study, the majority of the cases had optimal glycaemic control. Several studies have stated that disturbances in placenta do exist independent of the glycaemic control.

Placental weight is a predictor of foetal birth weight and risk of adverse effects [6,33,36]. Placental weight plays a role in mediating the effects of maternal obesity, GDM and gestational weight gain [7]. Placental volume in the second trimester is dependent on maternal weight at first ante-natal visit and pregnancy weight gain [47]. This is, in turn, associated with foetal growth indices [47]. Velamentous and marginal insertion of the umbilical cord are considered abnormal and is evaluated during antenatal ultrasound examination due to their relation with adverse outcomes [48]. The gross morphologic placental changes in association with GDM and obesity might aid in understanding the placental mechanisms at play in response to the metabolic changes in these conditions. These features may be relevant in ultrasonography as a surveillance feature to identify the possible presence of underlying disease.

Increasing BMI and increased placental weight are independent risk factors for adverse pregnancy outcomes [32]. The placental weight and thickness, along with diameter and thickness was increased in the GDM group compared to controls. There is a significant increase in placental weight and volume in the OG group compared to the LG group. Present study results show significant but weak positive correlation of placental weight, volume, thickness with maternal prepregnancy BMI. It can be argued that this feature is more in favor of an attempt at adaptation by the placenta to increase its efficiency in the presence of factors that affect it. The complicating factor of obesity may either exacerbate or dampen this response. However, to definitively comment on such a response, we will require a larger sample size and a study of the foetal and maternal outcomes, microscopic, ultrastructural and molecular mechanisms involved.

The results of the study show changes in the gestational diabetic placentas which are more marked in OG group than in the LG group.

## LIMITATION

The effect of poorly controlled GDM was not studied. Further study on the associated histopathological changes that accompany the gross morphological changes of placenta and the biochemical alterations that are associated with the placental changes will shed light on the mechanisms of placental changes seen in GDM and in obesity.

## CONCLUSION

The present study shows increased placental parameters in the obese GDM group compared to the lean GDM group. Further research is needed to elucidate the underlying pathologic and adaptive changes of the placenta to metabolic insult. Viewed as a combination of findings, these changes may alert the physician or sonographer to the complications of pregnancy and enable more efficient monitoring of such pregnancies to ensure safe pregnancy outcomes.

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