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Research Paper

Histo-morphometric vicissitudes in diet-controlled diabetic placenta: A quantitative stereological model

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ABSTRACT

Background: An affordable approach accepted worldwide to successfully treat mild maternal hyperglycemia in gestational diabetes (GDM), is diet-controlled therapy. As no elaborate research was available, this study was crafted to investigate morphometric stereological details and to determine the mean placental oxygen diffusion capacity for patients who were kept on diet therapy for mild gestational hyperglycemia.

Methods: A clinical trial (NCT04907708) was conducted from January 2018 to February 2019. A total of 70 women completed the study, out of which 35 served as healthy controls as Group A and 35 were diagnosed as mild gestational diabetics according to WHO criteria (Group B). These patients were kept on a restricted calorie diet with light exercise during gestation and were followed regularly during gestation. Soon after delivery, conserved placentas underwent complete gross, microscopic, and stereological investigations with the point and intersection -counting methods.

Results: Significant differences were observed for placental width and syncytial knots ($p < 0.010$ and 0.025 respectively) between the groups on gross and light microscopy. Most of the parameters were non-significant, though numerically more in the GDM group. On stereological details, mean placental volume, mean placental components volumes (villi, inter-villous space, fetal capillary, and fetal connective tissue), mean villi and mean fetal capillary diameter, mean villi and capillary surface density and mean morphometric diffusing capacity of placenta showed non-significant results between the groups.

Conclusion: Minimal changes were observed in gross, microscopy, and morphometric stereological details in the placentae of GDM patients managed with nutritional therapy during gestation compared with the healthy controls.

1. Introduction

Diabetes mellitus is a group of metabolic illnesses associated with insulin resistance or secretion abnormalities and is characterized by high blood glucose levels.[1] Insulin resistance escalates throughout pregnancy due to multiple hormonal effects, increasing the chances that expectant mothers are at much higher risk to develop gestational diabetes (GDM). The placenta, an essential organ, a connecting tissue between the mother and the fetus, not only gives the growing sustenance but also gives a clear picture of intrauterine hypoxic conditions during pregnancy. It shows the morphological changes in GDM patients that can lead to undesirable fetal and maternal outcomes.

GDM is a common problem observed during antenatal assessments, affecting 4%~9% of pregnancies in Pakistan. The prevalence has lately risen as a result of a sedentary lifestyle.[2] These factors make it crucial to carefully consider every element of GDM, including the challenges posed by diagnosis, treatment, and screening requirements. Early management of GDM can help to avoid adverse outcomes.[3] The etiology is complex

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and includes multiple risk factors like being overweight or obese, eating poorly, having high blood pressure, not getting enough micronutrients, having endocrine dysfunction, being an older mother, and having a family history of diabetes.[4]

In addition, at times such a high maternal glucose results in numerous microscopic alterations in the placenta, including chorangiosis, immature villi formation, syncytial knots, and zones of fibrosis.[5] The placental physiology is impacted by these alterations.[6] Furthermore, these structural alterations in placental tissue are responsible for the fetus's diminished oxygen supply, particularly when placental relative size is more with the basal membrane thickens in GDM.[7]

The first line of treatment for situations with a slight increase in blood sugar is nutritional therapy, in which the patient is provided suggestions for a special diet with calculated calories.

With nutritional therapy and exercise, the glucose levels are kept close to normal. Therefore, the placenta in patients with a regulated diet should not differ much from normal morphology, but studies have shown that even with careful diet control, still several modifications were observed.[8] Based on gross morphology, the placenta of patients under diet management are known to weigh slightly more. Other cellular alterations reported include, a larger percentage of fibrinoid necrosis, excessive syncytial knots, and cytotrophoblast with moderate edema causing an impact on normal placental physiology.[8] Further no research was available to provide a detailed stereological study in such samples, so this study was crafted to investigate hypoxic, structural, and physiological modifications using stereological methods and to calculate the mean placental morphometric oxygen diffusion capacity for patients who were kept on diet therapy for mild gestational hyperglycemia.

2. Materials and methods

2.1. Study subjects

From January 2018 to February 2019 this trial was carried out at the basic medical sciences institute of Jinnah Postgraduate Medical Centre (JPMC) in conjunction with the Department of Gynecology andObstetrics of JPMC, following approval from the Institutional Review Board, Jinnah Postgraduate Medical Centre, Karachi (NO.F.2-81/2017-GENL-IRB/1511/JPMC dated:29-12-2017), and board of advance studies and research, University of Karachi (registration with Clinicaltrial.gov. NCT04907708). A total of 136 high–risk females with previous history of GDM, strong familial diabetic history, recurrent abortions and patients with history of unexplained still births, were evaluated in diabetic and obstetric out-patient department and only 77 patients were recruited after providing written informed consent, of whom 35 were normal pregnant women who served as healthy controls with no comorbids and were negative in assessment for GDM in Group A, and 42 were assigned to Group B (Fig. 1). Group B patients were diagnosed GDM who met the WHO criteria [fasting blood sugar (FBS) > 100 mg/dl, random blood sugar (RBS) > 126 but less than 130 mg/dl] further confirmation with oral glucose tolerance test (OGTT) in which fasting glucose more than 95 mg/dl, or at least two of three glucose values that slightly exceeded the following after 100 g sugar load: 1-h of 180 mg/dl, 2-h 155 mg/dl, 3-h 140 mg/dl with RBS from 126 to 130 mg/dl, confirms the mild hyperglycemia of pregnancy.[9] These patients in group B, were further provided thorough dietary counseling, and specific nutrient advice. They were required to have only a controlled caloric diet (diet therapy 1800–2000 Kcal/day) and advise for light exercise (30-min walk) at least thrice a week.[9]

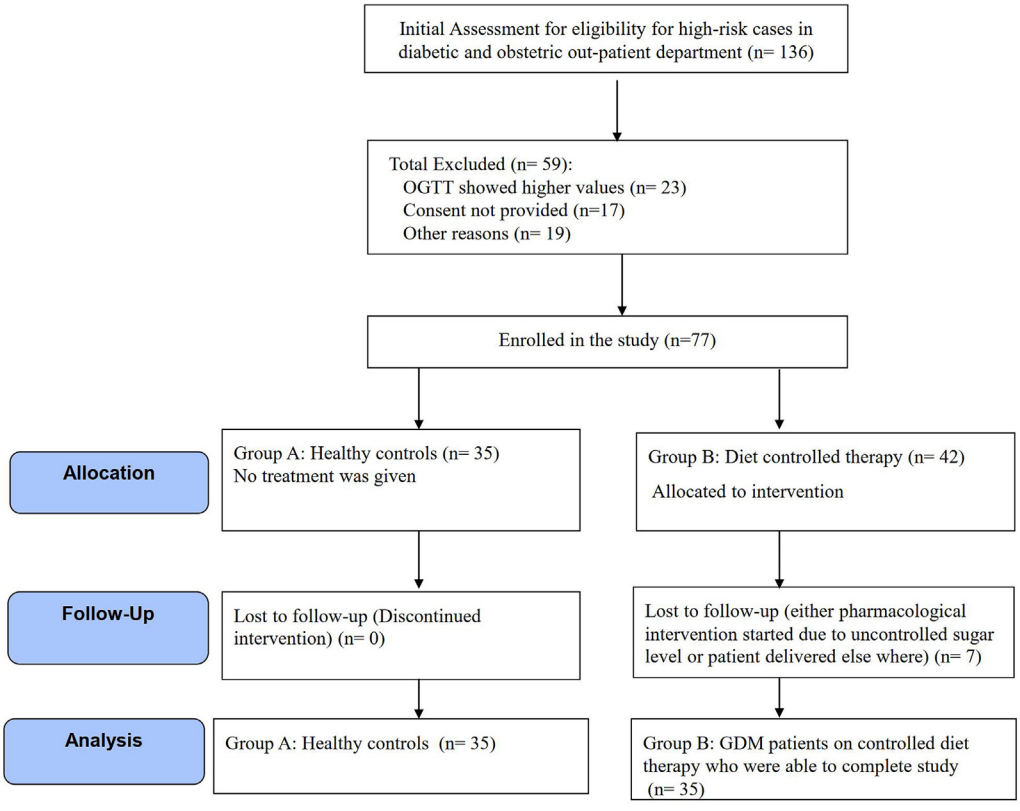

Fig. 1. Flow diagram of the inclusion of participants.

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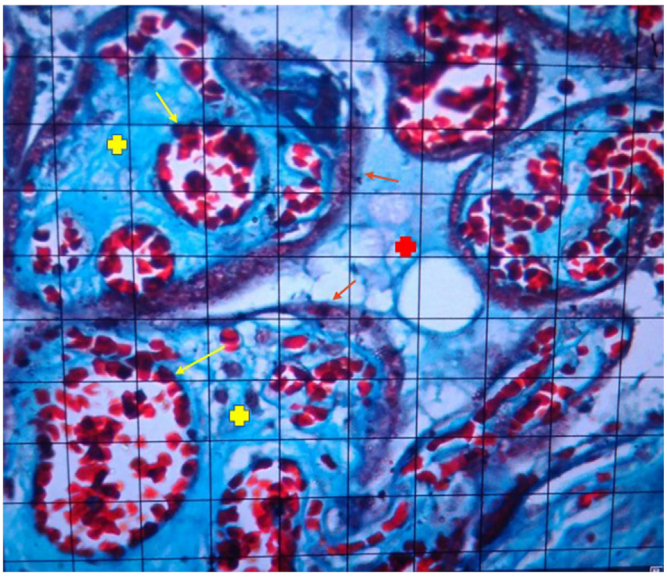

Fig. 2. Point counting method (diet-controlled placenta) × 40
Red arrow: points towards placental villi on microscopic section; Red cross: represents the intervillous space between the villi; Yellow arrow: points towards fetal capillaries within villi, Yellow cross: represents the fetal stroma between the fetal capillaries within the villi.

Initial parameters of all enrolled women in both the groups, including weight, age, FBS, RBS, and HbA1c (glycated hemoglobin) at enrollment and at term were noted down. They were examined during the entire gestational process, and following delivery, conserved placentas were stored in formalin for histological procedures.[10] Over the course of gestation we lost to follow 7 patients in Group B either due to the addition of pharmacological intervention for uncontrolled sugar level or they delivered elsewhere.

2.2. Morphometric and stereological measurements of the placenta

The data evaluated and analyzed for this study involved 35 placentas in each group, for females who were able to complete the study. Blocks and slides were made as per histological parameters for light microscopic analysis after a gross evaluation. The villus immaturity, chorangiosis, villus fibroid necrosis, calcification, and syncytial knots of these slides were all evaluated under the light microscope.[11]

Stereology is the study of detailed histological analysis for counting important structures on microscopic sections.[12] This method applies a grid with counted points or lines to the microscopic field to calculate the structural densities and numerical evaluations of biological organelles.[13] Thus, it provides a clear picture of extensive tissue analysis histologically on the microscope.

With the Nikon (Eclipse 50i) microscope connected to the DSL2, DS-camera control unit placentas were examined for component volumes. Randomly chosen ten of the microscopic fields were obtained from two selected slides, from each placenta at the 12 o'clock, 6 o'clock, or center positions. These fields were carefully examined using a point-counting technique to determine the volume of placental components. A grid of 100 squares with 1 cm in each square, positioned above the microscopic fields to calculate the density of the placental structures. Keeping the microscopic magnification of 40, points of intersection of horizontal and vertical lines of the grid lying on each placental component (including villi, fetal capillaries, inter-villous space, and fetal connective tissue) were counted separately to estimate the component volumes[14,15]

The observed number of points was divided by the total number of points on the grid (100) to get volume densities (Vd) (Fig. 2). Volume density = total points on the object of interest/total points applied on section. Further, with a known placental density (D) of 1.05 gm^3, the placental volume was calculated by V=W/D, where W is the placental weight measured on gross examination.[14,15] The total volume for all 4 placental components was further computed using the formula (Vd × V) where Vd is the volume density of the placental components and V indicates the calculated volume of the whole placenta.[14,15]

The surface areas of the placental villi (S. A villi) and capillaries (S. A cap) were determined using a grid of horizontal lines with the intersection-counting method, keeping the microscopic magnification at 10 (Fig. 3). S.A villi = [2 × Iv/Lt)], "Iv" is the mean of the intersections of the villi with the horizontal lines, and "Lt" is the overall length of the horizontal lines in the grid.[14,15]

S. A cap = [2 × Ic/Lt)], "Ic" is the mean of the intersections of the fetal capillaries with the horizontal lines, and "Lt" is the overall length of the horizontal lines in the grid applied.[15]

The measurement scale built-in the computer and microscope was used to gauge the diameter of the fetal capillary and the placental villi. Using the same scale orthogonal intercepts were also measured using the 100- square grid. Orthogonal intercepts are the horizontal or vertical lines drawn from the fetal capillary surface perpendicular to the villous membranes. This is the area in which oxygen has to travel from maternal blood in intervillous space to fetal blood in fetal capillaries. The arithmetic mean is the simple average of the lengths, whereas the harmonic mean calculated is the reciprocal of the arithmetic means of the intercept lengths. To calculate it in random plane sectioning for membrane thickness, multiply the harmonic mean by 0.848.[15] (Fig. 4)

Furthermore, the following formula was used to determine the mean oxygen diffusion capacity across the villous:[15,16]Mean oxygen diffusion capacity of villi (MDC villi) = Surface area of exchange (S. A villi + S. A cap) × Krogh's constant for O^2 (2.3×10^{-8})/2 × Harmonic mean thickness. This formula provides more than 90% of the oxygen's maximal capacity for diffusion across the placental membrane.[16]

2.3. Statistics

Following the data collection, additional in-depth microscopy, stereological calculations, and statistical analysis using appropriate statistical tests were applied for numerical and categorical values. The statistical analysis was completed using the "Statistical Package for Social Science (SPSS)" version 26.0. Continuous and categorical variables were displayed as mean with SD and frequencies respectively. The normal distribution of the data was confirmed using the Kolmogorov-Smirnov test. The appropriate statistical, parametric, and nonparametric tests, such as the Mann-Whitney test or Student's T test, were used to analyze the data between the two groups whilst a value of less than 0.05 was considered significant.

3. Results

When results were evaluated for the placentae in two groups, it was evident that both the groups were comparable for age (28.57 ± 4.93 vs 30.37 ± 3.6 years old) and weight (77.40 ± 10.80 kg vs 77.27 ± 7.50 kg) of the patients (p = 0.08, p = 0.92 respectively) while significant differences were observed for FBS-1, RBS, HbA1c-1, and HbA1c-2 (p<0.001, 0.021, <0.01, <0.01 respectively) between the groups (Table 1).

On gross morphology size of the placenta and weight were non-significant whereas the placental width was significant between the groups (p< 0.01) (Table 2). 35 placentas each in two groups were

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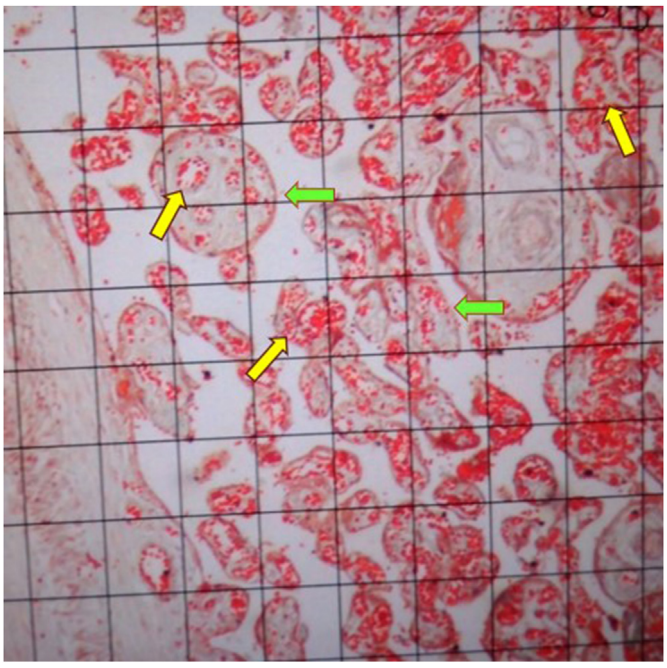

Fig. 3. The intersection-counting method (diet-controlled placenta) × 10
Green arrows show placental villi, yellow arrows represent fetal capillaries with red blood cells within them.

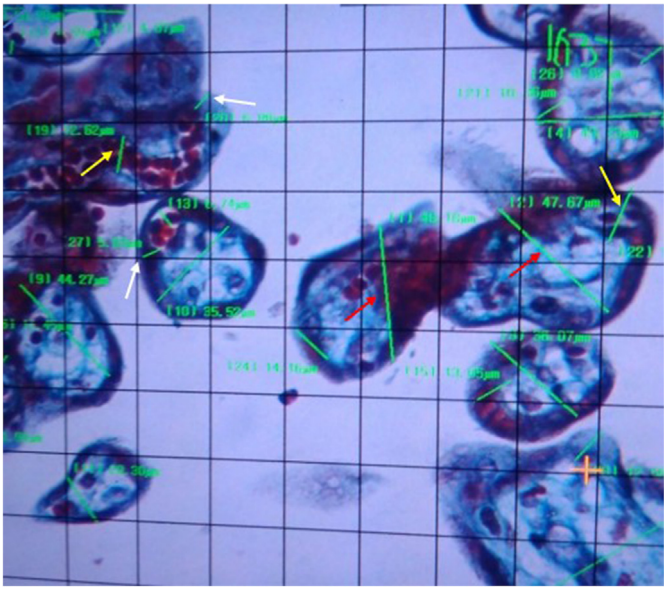

Fig. 4. Measurement of villi and capillaries diameters (diet-controlled placenta) × 40
Red arrow: villi diameter, yellow arrow: capillary diameter, white arrow: orthogonal intercepts measurement.

evaluated for light microscopy and thorough serological investigation. Light microscopic analysis revealed that diabetic placentas had higher numbers for hypo-perfusion parameters, these findings were numerically prominent but not statistically significant. In the placenta of the GDM, villi were more immature. There was a higher incidence of chorangiosis in GDM placentae (14 vs. 8, p = 0.97). 20 GDM placentas and 19 control group placentas, had villus fibrinoid necrosis (p = 0.81). Calcification was found in 11 placentae in the control group and 13 GDM placentas. While syncytial knots were observed in 17 cases compared to 8 from controls; the result was statistically significant (p = 0.025) (Table 2).

Mean volumes of the placenta, villi, inter-villous space, fetal capillary, and fetal connective tissue and mean diameter for villi, and fetal capillaries were not significant between the groups. Similarly, mean surface density for villi and fetal capillaries, harmonic mean, corrected harmonic mean, and mean morphometric diffusing capacity of the placenta also showed non-significant results on stereological morphometry (Table 3).

4. Discussion

Due to an increase in the prevalence of metabolic conditions, studies have investigated placental abnormalities associated with gestational diabetes.[17,18] The maternal and fetal well-being depends on the placental appropriate growth, but metabolic changes in maternal blood such as in gestational diabetes can cause alterations in the morphology increasing the risk of adverse fetal and maternal outcomes.[18] An adaptable and affordable approach is nutrition therapy that successfully regulates maternal glycemia while supporting normal fetal growth. The traditional approach is to strictly control the intake of all forms of carbohydrates. This strategy also is a major way to adhere to possible hypoglycemic pharmacological management when needed.[19] The primary goal of the present study is to assemble data on anatomical placental abnormalities related to diet-controlled GDM.

GDM inhibits placental development not only due to hyperglycemia but also several other unexplained metabolic or endocrine pathways connected to insulin resistance. The effects of metabolic alterations are frequently seen in structural variations such as villous immaturity and vascular dysfunction.

Increasing placental weight and thickness are the two most prominent gross placental morphological alterations associated with diabetes mellitus in pregnancy that have been studied in the literature.[20,21] Our findings from the physical examinations showed that the groups had significantly more placental thickness while the results for weight were non-significant. Though the GDM placental numerical values were high for size and weight in our study. These findings were inconsistence with Souza's extensive description of GDM placentae.[22] Another study by Saini et al. with 40 samples in each diabetic and control group, found that the GDM placentae had a considerably higher mean central thickness than the control group, supporting our results.[23] Kadivar stated that the placental weight and diameter are not altered when diabetes is detected and treated well on time with appropriate glycemic control.[24] Again consistency with our study is that these alterations are less pronounced in pregnant women with well-controlled diabetes especially when the blood glucose values were not deranged much initially. The range of morphological alterations would therefore be directly influenced by glycemic management, metabolic regulation, and other related maternal and fetal factors. According to research done by Jermuzk, levels of severity of diabetes are associated with microscopic changes in placental development and eventual vascular dysfunction. The majority of placentas from the GDM group on microscopy exhibit some typical histological characteristics such as enhanced angiogenesis, chorangiosis, and villous fibrinoid necrosis.[25]

The growth of the immature villus results in decreased oxygen transfer from the mother's blood to the fetus. In other investigations, GDM placentae showed an increase in the amounts of syncytial knots, peri-villous fibrin depositions, the basal membrane thickness of the trophoblast, fibrosis of the villous stroma, villous edema, thickening of the vasculature, and the presence of nucleated fetal erythrocytes. The characteristics of immature intermediate villi that set them apart from mature ones include a large stroma, loose reticular visible channels, and

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Table 1
Baseline details of the patients (n = 70) (Mean ± SD).

Characteristics	Group A (n = 35)	Group B (n = 35)	*P* value
Age (years)	28.57 ± 4.93	30.37 ± 3.60	0.086
Weight (kg)	77.40 ± 10.80	77.27 ± 7.50	0.920
FBS-1 (mg/dl)	79.62 ± 18.63	93.77 ± 15.98	<0.001*
RBS (mg/dl)	126.42 ± 32.97	145.45 ± 34.32	0.021*
HbA1c-1 (%)	5.00 ± 0.49	5.45 ± 0.44	<0.010*
HbA1c-2 (%)	5.06 ± 0.43	5.71 ± 0.48	<0.010*

Group A:non-diabetic pregnancies, Group B: diabetic pregnancies with diet control.
FBS: fasting blood sugar at enrolment; RBS: Random blood sugar at enrolment.
HbA1c-1: glycated hemoglobin at enrolment; HbA1c-2: Glycated hemoglobin at 36 weeks.
* Statistically significant (independent T-test applied).

Table 2
Placental gross and microscopic morphology (n = 70).

Characteristics	Group A (n = 35)	Group B (n = 35)	*P* value
Gross Morphology (Mean ± SD)			
Placental surface size 1 (cm)	15.74 ± 2.39	14.7 ± 2.34	0.070
Placental surface size 2 (cm)	13.80 ± 1.74	13.74 ± 2.30	0.480
Placental width (cm)	2.08 ± 0.49	2.65 ± 0.63	<0.010*
Placental weight (g)	576.20 ± 136.80	579.10 ± 128	0.928
Microscopic Morphology (n)			
Villous immaturity			
Present	11	17	0.140
Absent	24	18	
Chorangiosis			
Present	8	14	0.970
Absent	27	21	
Villous fibrinoid necrosis			
Present	19	20	0.810
Absent	16	15	
Calcification			
Present	11	13	0.610
Absent	24	22	
Syncytial knots			
Present	8	17	0.025*
Absent	27	18	

Group A: non-diabetic pregnancies, Group B: diabetic pregnancies with diet control.
Size 1 indicates X-axis horizontal measurement, and size 2 represents Y-axis vertical length measurement for the placental diameter.
* Statistically significant (independent T-test, Mann-Whitney test and chi-square applied accordingly).

Hoffbauer cells. However, it should be highlighted that only 80% of placentas from GDM pregnancies at or near term exhibited normal histologic findings (lack of any form of pathological lesions).[26]

GDM placentas had considerably shown greater incidences of chorangiosis (a greater number of capillary densities in terminal villi) with thrombotic vasculopathy than simple pregnancies in many of the prospective trials involving over a thousand patients. Although the majority of GDM-placentas at term lack these lesions significantly as a result, these placental abnormalities do not always result in bad outcomes.[20,26] Several researchers have reported similar findings as in our study, demonstrating that GDM placentas exhibit more syncytial knots and chorangiosis than controls.[27] Syncytial knots increase in frequency as healthy placentas get older, but too many are associated with defective oxygen placental perfusion.[28]

For stereological parameters, when compared to the healthy group, most of the criteria for diet-controlled GDM were non-significant, though

Table 3
Stereological measurements (n = 70).

Parameter	Group A (n = 35)	Group B (n = 35)	*P* value
Villi volume (%)	54.11 ± 10.61	55.10 ± 9.42	0.682
Inter-villous space volume (%)	48.20 ± 14.73	49.13 ± 12.56	0.776
Fetal capillaries volume (%)	16.03 ± 3.90	14.90 ± 2.97	0.176
Fetal connective volume (%)	38.66 ± 8.86	38.18 ± 8.77	0.822
Placental volume (cm^3)	569.41± 117.2	557.90 ± 129.68	0.698
Total volumes of placental villi (cm^3)	307.56 ± 73.6	308.66 ± 82.13	0.953
Total volume of Inter-villous area (cm^3)	261.66 ± 92.88	259.48 ± 72.5	0.913
Total volume of fetal capillaries (cm^3)	81.55 ± 25.4	81.50 ± 22.08	0.927
Total volume of fetal connective tissue (cm^3)	237.13 ± 53.89	227.36 ± 63.99	0.492
Mean villi diameter (μm)	52.42 ± 14.12	55 ± 10.93	0.395
Mean fetal capillary diameter (μm)	20.46 ± 6.59	20.62 ± 7.64	0.927
Villous surface density (g/cm^3)	7.54 ± 2.47	7.38 ± 2.5	0.796
Capillary Surface density (g/cm^3)	8.50 ± 3.14	8.06 ± 2.97	0.550
Harmonic mean thickness of Villous membrane (μm)	7.72 ± 2.35	7.96 ± 2.35	0.673
Corrected harmonic mean(μm)	6.56 ± 1.99	6.85 ± 2.02	0.555
Morphometric diffusing capacity ($cm^2.min^{-1}.\ mmHg^{-1}$)	2.95 ± 0.81	2.83 ± 1.44	0.672

Group A: non-diabetic pregnancies; Group B: diabetic pregnancies with diet control.

more numerically. A study by Jirkovská, with 17 diabetic and 14 control placentas, found that the capillary diameter was slightly increased in GDM placentae.[29] Similarly, when Higgins evaluated 10 controls vs 18 women with GDM in 2011, he also found that the capillary capacity was increased in GDM pregnancies.[7] Though in our study mean fetal capillary diameter was not different in GDM from the control group. Whereas mean villi diameter was slightly more in the GDM placenta though statistically non-significant. Later on, Bhanu studied 96 placentas, of which 48 had gestational diabetes mellitus and 48 were controls. He documented that the mean diameter of the villi in GDM placentae was slightly more and the results were in favor of our findings.[30] Another study states that placental morphometric features were considerably elevated in the mild to moderate hyperglycemia group and the capillarization index was statistically comparable to the control group, but the overall area of placental terminal villi was more significantly.[31] The divergence of the results of this study from our findings could be due to the difference in sample size and considerably different HbAIc at 36 weeks. In our study, these less documented microscopic changes can be one of the factors of similar physiology, that is comparable mean morphometric diffusion capacity of oxygen in our study between the two groups. GDM-related changes in placental structures and function, as well as many of the mechanisms causing these changes, are highly complicated. The likelihood of histopathological alterations would increase with the early onset of severe hyperglycemia in the initial trimester. However, some investigations declared that few of the placental abnormalities persist even after improvements in maternal glycemic control or vice versa, suggesting that hyperglycemia is not only the main cause of these changes.[32] and this narrative still has many unrevealed details.

This is a single-centred study. In the future, multicentred trials can be carried out with some added groups such as a non-diet controlled mild hyperglycaemic GDM group for better comparison. Further immunohistochemical studies and detailed electron-microscopy can be done to visualize concealed information between the groups and is an open

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avenue for new researchers to follow.

5. Conclusion

Minimal changes were observed on microscopy and morphometric stereological details in the placentae of GDM patients with mild hyperglycemia during gestation, managed with nutritional therapy.

Contributions

RA presented the main concept, did sampling, drafted the article, did a literature search, the whole of the research project, and main write-up. EA helped in the recent Literature search, and write-up. AKP helped in the analysis, and presentation of data for this manuscript and revise the manuscript critically for the final version to be published. TM did supervision for histopathological work and approved the histological analysis.

Ethical approval

Institutional Review Board, JPMC, Karachi (NO.F.2-81/2017-GENL-IRB/1511/JPMC dated:29-12-2017)

Consent to participate from patients

A well-informed documented consent was taken before enrolment in the study.

Consent for publication

Patients and authors have provided the consent for publication of this data and research.

Availability of data and materials

Prepared and analyzed data sets for the current study are available from the corresponding author upon reasonable request.

Declaration of competing interest

There is no conflict to declare by the authors involved in the research.

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