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Inflammation and decreased cardiovagal modulation are linked to stress and depression at 36th week of pregnancy in gestational diabetes mellitus

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Stress and depression have been reported in gestational diabetes mellitus (GDM). Though inflammation and oxidative stress are associated with depression, there are no reports of link of cardiometabolic risks (CMR) to stress and depression in GDM. Normal pregnant women (control group, n = 164) and women with GDM (study group, n = 176) at 36th week of gestation were recruited for the study. Blood pressure (BP), body composition, heart rate variability (HRV), glycated hemoglobin (HbA1C), markers of insulin resistance, oxidative stress, inflammation and endothelial dysfunction, were assessed. Perceived stress score (PSS), quality of life (QoL) scale, Indian diabetic risk score (IDRS) and Edinburg postnatal depression score (EPDS) were assessed. Association of potential contributors to PSS and EPDS were assessed by correlation and regression analyses. There was significant increase in PSS, EPDS, IDRS scores, HbA1C, malondialdehyde (MDA) (oxidative stress marker) and high-sensitive C-reactive protein and interleukin-6 (inflammatory markers), and significant decrease in total power (TP) of HRV (marker of cardiovagal modulation), QoL and nitric oxide (endothelial dysfunction marker) in study group compared to control group. Though many cardiometabolic risk parameters were correlated with PSS and EPDS, the significant independent association was observed for TP, HbA1C, MDA and interleukin-6. However, interleukin-6 had maximum contribution to PSS ($\beta = 0.550$, $p < 0.001$) and EPDS ($\beta = 0.393$, $p < 0.001$) as demonstrated by multiple regression analysis. Inflammation, oxidative stress, glycation status and decreased cardiovagal modulation are associated with stress and depression at 36th week of gestation in GDM.

Abbreviations

| | |
|---------------|-------------------------------------|
| GDM | Gestational diabetes mellitus |
| CMR | Cardiometabolic risks |
| BP | Blood pressure |
| HRV | Heart rate variability |
| HbA1C | Glycated hemoglobin |
| PSS | Perceived stress score |
| QoL | Quality of life |
| IDRS | Indian diabetic risk score |
| EPDS | Edinburg postnatal depression score |
| MDA | Malondialdehyde |
| TP | Total power |
| CV | Cardiovascular |
| TNF- α | Tumor necrosis factor alpha |
| IL-6 | Interleukin-6 |

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| | |
|-------------|---|
| hsCRP | High-sensitive C-reactive protein |
| IADPSG | International association of diabetes and pregnancy study group |
| OGTT | Oral glucose tolerance test |
| BW | Body weight |
| BMI | Body mass index |
| HR | Heart rate |
| SBP | Systolic blood pressure |
| DBP | Diastolic blood pressure |
| MAP | Mean arterial pressure |
| RPP | Rate pressure product |
| BIA | Bioelectrical impedance analysis |
| RM | Resting metabolism |
| BFMI | Body fat mass index |
| FFMI | Fat free mass index |
| LFnu | Low frequency power expressed in normalized units |
| HFnu | High frequency power expressed in normalized units |
| LF–HF ratio | Ratio of low-frequency to high-frequency power |
| SDNN | Mean and standard deviation of RR intervals |
| RMSSD | Square root of the mean of the sum of the squares of differences between adjacent RR interval |
| NN50 | Adjacent RR interval differing more than 50 ms |
| pNN50 | NN50 counts divided by all RR intervals |
| HOMA | Homeostatic model assessment |

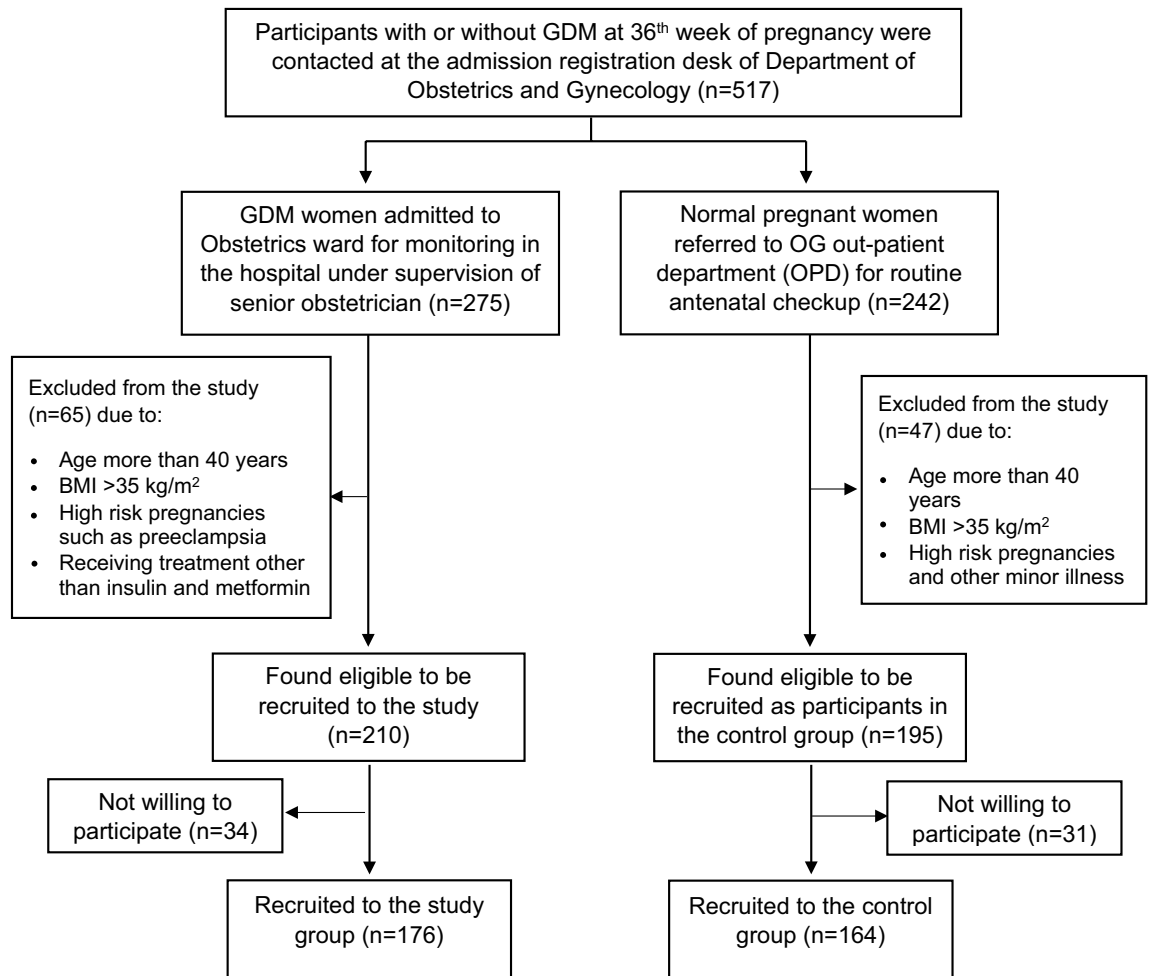
Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with the onset or first recognition during the present pregnancy at 24–28 weeks of gestation¹. In the recent past, there is an increased incidence of diabetes during pregnancy with almost 21 million births (16.2%) affected due to hyperglycemia². Prevalence of GDM in India is 18.9%, ranging between 3.8% to 41% in various parts of the country³. The major maternal and neonatal adverse effects of GDM include increased risk of preterm delivery, pre-eclampsia, caesarean section delivery, development of type 2 diabetes mellitus (T2DM) post-delivery, fetal macrosomia, neonatal hypoglycemia, neonatal respiratory distress, and childhood obesity and insulin resistance, followed by impaired glucose tolerance and T2DM later in life^{4,5}. Women with history of GDM have a sevenfold increased risk of developing T2DM, with 20–70% risk in the first decade after delivery and GDM increases the future cardiovascular disease (CVD) risk by twofold⁶. It is important to note that studies have consistently shown that women with a history of GDM have a higher prevalence of cardiometabolic risk factors, such as dyslipidemia, hypertension, obesity, and metabolic syndrome, compared to their peers. Additionally, by three months postpartum, this adverse cardiovascular risk factor profile is evident⁶.

Depression during pregnancy has been reported to adversely affect women and their children^{7,8}. Anxiety, psychological stress and depression are associated with GDM^{9–12}. Psychological stress and depression in GDM severely affect the maternal and fetal outcomes^{13,14}. Also, it has been reported that the prenatal depression in GDM is linked to post-partum depression for a longer duration and adverse cardiovascular (CV) consequences^{15,16}. Recently we have reported the decreased heart rate variability (HRV) and cardiovagal modulation associated with depression in women during antenatal period, which exposes them to CV risks¹⁷. However, till date the mechanism that causes CV risks in GDM have not been well studied and the association of CV risks to mental illness in GDM has not been reported. It is important for healthcare workers to know the relationship between stress and depression with fetomaternal outcomes, and if the depression-associated problems can be prevented in the perinatal period. In a recently conducted pilot study at 36th week of gestation in 15 women having GDM, we observed that cardiometabolic risks, adverse fetomaternal outcomes and poor psychophysical health were improved by practice of short course of yoga¹⁸. But, in this study due to less sample size, we could not assess the enormity of cardiometabolic risks, the mechanisms that could lead to development of these risks and the link of depression to the risks and the maternal–fetal outcomes.

Inflammation has long been proposed as a pathophysiologic mechanism of depression¹⁹. There is accumulating evidence that anti-inflammatory interventions could be promising antidepressants, particularly in patients with increased peripheral inflammatory biomarkers^{19,20}. Elevated C-reactive protein (CRP), tumor necrosis factor alpha (TNF- α), and interleukin-6 (IL-6) are the major molecular inflammatory signature associated with depression in general population^{21,22}. Among the chemical mediators, high-sensitive C-reactive protein (hsCRP) and IL-6 are mainly reported to be associated with GDM^{23–25}. However, till date the association of CRP and IL-6 with depression and cardiometabolic risks in GDM has not been studied. Oxidative stress and endothelial dysfunction have also been implicated in the pathophysiology of GDM^{26,27}. But the association of oxidative stress and endothelial dysfunction with stress and depression-mediated increased cardiometabolic risks in GDM has not been reported yet.

We have reported the decreased HRV as an indicator of reduced cardiovagal modulation and sympathovagal imbalance as a marker of CV risk in various disorders including diabetes^{28–34}. In a recent study, we have demonstrated the link of decreased level of nitric oxide as marker of endothelial dysfunction with reduced HRV in gestational hypertension³⁵. However, the extent of HRV and cardiovagal modulation and their link to depression in GDM has not been reported till date. In GDM, a cardiometabolic risk intensifies in later part of pregnancy. We have investigated the link of retrograde inflammation, oxidative stress, endothelial dysfunction and decreased cardiovagal modulation to stress and depression at 36th week of pregnancy in gestational diabetes mellitus.

Recruitment flow chart:



Methods

Study design. The present descriptive-analytical study was conducted in the Department of Physiology in collaboration with the Department of Obstetrics and Gynaecology (OG), and Biochemistry, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India from October, 2020–April, 2022 after obtaining approval from Scientific Advisory Committee and Ethics Committee of JIPMER, Puducherry. All the methods were performed in accordance with the institutional guidelines and regulations. A total of 517 pregnant women registered at admission counter of OG department of JIPMER hospital were screened. Following inclusion and exclusion criteria, 176 GDM women and 164 normal pregnant women at 36th week of gestation were recruited (as depicted in the recruitment flow-chart below).

Written informed consent was obtained from all the participants prior to the initiation of the study. All the investigations were done at the bedside of the subjects in the OG Ward. GDM was diagnosed based on the International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria in which 75-gm oral glucose tolerance test (OGTT) was done at 24–28 weeks in fasting and GDM was diagnosed if any one of the following cut-off is met i.e. ≥ 92 mg/dl (≥ 5.2 mmol/l) or 1-h ≥ 180 mg/dl (≥ 10 mmol/l) or 2-h ≥ 153 mg/dl (≥ 8.5 mmol/l)³⁶.

Sample size calculation. Sample size was calculated using G*Power 3.1.9.7. Based on the previous report of PSS in GDM³⁷, sample size was calculated with 90% power to detect the difference between means of PSS in GDM and normal pregnant women with a significance level of (alpha) 0.01. The minimum sample size was calculated to be 106 in each group. However, since stress levels are highly subjective and HRV parameters have wider variations in pregnancy, the sample size was kept at minimum 160 in each group, in the present study.

Grouping of subjects

Study group (n = 176). Subjects of study group were pregnant women diagnosed with gestational diabetes and admitted to OG ward of JIPMER hospital at 36th week of gestation.

Inclusion criteria. GDM women at 36th gestational weeks between the age of 18 and 40 years, and receiving insulin and/or oral anti-diabetic agents as part of anti-diabetic treatment protocol practiced in JIPMER hospital

| Sl. no | Control group (n = 164) (normal pregnant women) | Study group (n = 176) (women with GDM) |
|--------|---|--|
| 1 | Standard antenatal medications for healthy pregnant women (i) Tab. Folate—5 mg, once daily (ii) Tab. FST—200 mg, twice daily (iii) Tab. Calcium—500 mg, once daily (iv) Tab. Vitamin C—100 mg, once daily | Standard antenatal medications for women with gestational diabetes admitted to JIPMER hospital (i) Tab. Folate—5 mg, once daily (ii) Tab. FST—200 mg, twice daily (iii) Tab. Calcium—500 mg, once daily (iv) Tab. Vitamin C—100 mg, once daily |
| 2 | No medication | (i) Only insulin ^a —104 patients (ii) Both insulin ^a and OAD ^b —47 patients (iii) Only OAD ^b —25 patients |
| 3 | No diet restriction | Diabetic diet (composition of diabetic diet was given in the table below) |
| 4 | Routine antenatal counseling | Routine antenatal counseling |

Table 1. Treatment received by pregnant women in control group and study group. ^aRI: 4U–10 U, NPH: 4U–12U, Actrapid: 6U–20U, Insulatard: 14U–18U, Mixtard: 6U–14U. ^bTab. Metformin 500 mg. *GDM* gestational diabetes mellitus, *FST* ferrous sulphate tablets, *OAD* oral anti-diabetic drug.

| | Quantity | 1500 calorie | 1800 calorie | 2000 calorie |
|--|------------------|----------------------------|----------------------------|----------------------------|
| Morning 6.30 AM | | | | |
| Tea/milk without sugar | 1 | 100 ml | 150 ml | 150 ml |
| Breakfast | | | | |
| Rice/wheat/raggi (idly/dosai/upma) | 1 | 50 g raggi | 60 g raggi | 60 g raggi |
| Sambar/chutney (tomato/onion/coriander/mint/curry leaves) | 2 table spoon | 15 g dal 50 g vegetable | 20 g dal 50 g vegetable | 25 g dal 50 g vegetable |
| Morning | | | | |
| Buttermilk/coconut water/soup (vegetable, mushroom, corn, dal) | 1 glass | 200 ml | 200 ml | 200 ml |
| Lunch | | | | |
| Rice/chappathi | 225 g | 75 g | 75 g | 80 g |
| Rasam/sambar | ¼ cup | 5 g dal | 10 g dal | 10 g dal |
| Chicken/fish/egg/dal | 1 piece/1 katori | 40 g 13 g | 60 g 15 g | 75 g 15 g |
| Greens | ½ cup | 100 g | 100 g | 100 g |
| Vegetable curry | 2 katoris | 100 g | 100 g | 100 g |
| Buttermilk | 1 glass | 150 ml | 150 ml | 150 ml |
| Evening | | | | |
| Tea/milk (without sugar) | 1 glass | 100 ml | 150 ml | 150 ml |
| Vegetable sandwich/sundal | ¼ cup | 30 g | 45 g | 50 g |
| Dinner | | | | |
| Chappathi/wheat rice | 2 | 50 g | 70 g | 75 g |
| Dal/sambar | 1 katori | 10 g | 10 g | 10 g |
| Vegetable curry | 2 katoris | 150 g | 150 g | 150 g |
| Night | | | | |
| Milk | ½ glass | 100 ml | 100 ml | 150 ml |
| Fruit | 1 | 50 g | 75 g | 100 g |
| Total oil quantity | | 20 g | 20 g | 25 g |
| Total butter quantity | | | | 10 g |
| Total salt intake | | Less than 6 gm | | |

Table 2. Diet given to GDM women admitted to obstetrics ward of JIPMER hospital. Three different calories of food items were given according to their individual requirements, as prescribed by the hospital nutritionist monitored on daily basis.

(Table 1) and followed by others³⁸, in addition to the routine diabetic diet for GDM management (Table 2) and those willing to participate in the study, were included.

Exclusion criteria. GDM women with severe anemia, polyhydramnios, multiple pregnancy, pregnancy-induced hypertension, cardiac problems, history of depression, GDM women with history of PCOS on metformin treatment and body mass index (BMI) > 35 kg/m² were excluded from the study³⁹.

Control group (n = 164). Normal pregnant women at 36th week of gestation, attending OG out-patient department (OPD) for 3rd trimester antenatal check-up, were recruited as control group participants. Subjects having BMI > 35 kg/m², age more than 40 years, previous history of depression and not willing to participate were excluded from the study.

Procedure

Anthropometric measurements. All the subjects' body weight (BW) in kg and height in cm were measured and body mass index (BMI) was calculated by Quetelet's index formula.

Blood pressure-related parameters. Following 10 min of supine rest in their bed, heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were recorded using automated blood pressure monitor (Omron automatic blood pressure monitor HEM-8712, Omron Healthcare Company Ltd, Tokyo, Japan). Mean arterial pressure (MAP) and rate pressure product (RPP) were calculated. RPP, an index of myocardial work stress⁴⁰ was calculated using the formula, $RPP = (BHR \times SBP) \times 10^{-2}$.

Body composition parameters. Body composition was assessed Bodystat[®] (Model QuadScan 4000[®], Isle of Man, United Kingdom) which works based on the bioelectrical impedance analysis (BIA). Body composition was measured following the procedure as described earlier³⁰. Subjects were rested in supine position. The recording electrodes were positioned on the dorsal surface of hand proximal to metacarpal–phalangeal and on the foot proximal to metatarsal–phalangeal joints. Body composition parameters included total body fat, visceral fat, resting metabolism (RM), subcutaneous fat (whole body) and skeletal muscle (whole body), lean body mass, body fat mass index (BFMI), fat-free mass index (FFMI), and ratio of RM to body weight.

Gestational weight gain observed during pregnancy is associated with an increase in the maternal, foetal and placental tissue, changes in the amniotic and extracellular fluid, and blood volume expansion. It seems that BIA has a better prognostic potential for gestational and post-partum outcomes than body mass index⁴¹. It has been observed that the BIA method can be successfully used to study the effect of excessive gestational weight gain in pregnancy on the development of obstetric complications, including gestational diabetes mellitus⁴².

HRV recording. Following 10 min of rest in supine position, short-term HRV was recorded based on the recommendation of Task Force on HRV⁴³ and as described earlier³⁵. ECG electrodes were connected and Lead II ECG was acquired for 15 min at a rate of 20,000 samples/sec using BIOPAC MP 46 data acquisition system (BIOPAC Inc., USA). The data were transferred from BIOPAC to a laptop with Biopac Student Lab (BSL) software. With due care, ectopics and artifacts were meticulously removed from the recorded ECG. By using the R wave detector in the BSL software, the extraction of RR tachogram was done from the edited 900 s ECG. HRV analysis was done by using software (Kubios HRV standard, version 3.5.0) that analyzes the frequency spectral components and time-domain components using Fast Fourier transformation in the RR trend. The frequency-domain indices of HRV recorded were total power (TP), component of low frequency expressed as normalized unit (LFnu), component of high frequency expressed as normalized unit (HFnu), and LF–HF ratio. The time-domain indices of HRV included square root of the mean of the sum of the squares of differences between adjacent RR interval (RMSSD), mean and standard deviation of RR intervals (SDNN), adjacent RR interval differing more than 50 ms (NN50), and NN50 counts divided by all RR intervals (pNN50).

Perceived stress scale. Perceived Stress Scale (PSS) was used to determine the stress level of the subjects^{17,44}. The questionnaire consists of 10 questions with a score of 0–4 each. The score ranges from 0 to 40. A score of 0–13 is low stress, 14–26 is moderate stress and 27–40 is considered as high stress.

Edinburgh postnatal depression scale. Edinburgh Postnatal Depression Scale (EPDS) was used to assess the participant mood in the past 1 week^{17,45}. It entails ten questions with a score of 0–3 each question. The score of EPDS ranges from 0 to 30. The higher the scores, risk of depression is high and a score of 10 or greater indicates possible depression.

Flanagan's quality of life. In the present study, Flanagan Quality of Life (QoL) scale was used to assess the quality of life of the participants⁴⁶. The questionnaire comprises of 16 items covering five aspects including physical and Material well-being; relations with other people; social, community and civic activities; personal development and fulfilment; and recreation. The score ranges from 16 to 112.

Participants were not asked to fill the questionnaires on their own. However, to avoid biased information, an independent researcher was assigned for the task. Time taken to fill the above-mentioned three set of questionnaires was about 15 to 20 min.

Estimation of biochemical parameters. Five ml of fasting blood samples were collected and serum was separated and stored at –80 °C for further analysis. Fasting blood glucose (FBG) was noted from the patients' case records. Insulin was measured using enzyme linked immunosorbent assay (ELISA) (Calbiotech, USA). For determination of insulin resistance, homeostatic model assessment (HOMA) of insulin resistance was calculated [$HOMA-IR = FBG \text{ (mg/dL)} \times \text{Insulin } (\mu\text{IU/L}) / 405$]. HbA1c was determined from whole blood using commercial kits for turbidimetric immunoassay (Quantia, Tulip diagnostics). Malondialdehyde (MDA), the oxidative stress marker was measured by colorimetric assay kit (Elabscience, USA) and inflammatory markers such as interleukin-6 (IL-6) (Diaclone, France) and high sensitive C-reactive protein (hsCRP) (Calbiotech, USA) were

measured by ELISA kits according to the manufacturer instructions. Nitric oxide derivatives (nitrate and nitrite) were estimated by colorimetric method using microplate reader (Elabscience, USA).

Statistical analysis. Statistical Package for the Social Sciences (SPSS) version 13 (SPSS Software Inc., Chicago, IL, USA) was used for statistical analysis. Normality of data was tested by Kolmogorov–Smirnov test and accordingly data were expressed as mean \pm SD and median (interquartile range) for parametric and non-parametric data respectively. For comparison of data between control and study groups, the level of significance was tested by unpaired *t* test for parametric data, Mann–Whitney U test for non-parametric data. The association of PSS and EPDS with various parameters was assessed by Spearman correlation analysis. The independent contribution of various parameters to PSS and EPDS was assessed by multiple regression analysis. The *p* value less than 0.05 were considered statistically significant.

Ethics approval and consent to participate. Approval was obtained from Institute Ethics Committee (Human studies) of JIPMER (Reference number: JIP/IEC/2020/09). All the methods were performed in accordance with the institutional guidelines and regulations. Individual written informed consent was obtained from the participants before recruiting into the study.

Results

There was no significant difference in age between the subjects of control group and study group. There was a significant increase ($p < 0.001$) in the body weight and BMI in the study group compared to control group (Table 3).

Body composition parameters such as total body fat, visceral fat, RM, BFMI, FFMI ($p = 0.001$), subcutaneous fat and RM/BW were found to be significantly increased ($p < 0.001$) and body lean, skeletal muscle and RM/BF were found to be significantly decreased ($p < 0.001$) in study group compared to control group (Table 3). HR, SBP, DBP, MAP, and RPP of study subjects were significantly increased ($p < 0.001$) in study group compared to the control group subjects (Table 3).

Among the frequency domain indices of HRV, TP and HFnu were significantly reduced ($p < 0.001$), and LFnu and LF–HF ratio were significantly increased ($p < 0.001$) in study group compared to control group subjects. Time domain indices such as SDNN, RMSSD, NN50 and pNN50 were significantly reduced ($p < 0.001$) in subjects of study group compared to control group (Table 4).

PSS score, EPDS and IDRS were significantly increased in study group ($p < 0.001$) when compared to compared group, whereas QoL score was significantly reduced ($p < 0.001$) in study group than control group subjects (Table 4).

Glucose-related parameters such as FBG, insulin, HOMA-IR and HbA1C were significantly increased ($p < 0.001$) in study group compared to control group. Inflammatory markers such as IL-6 and hsCRP, and the

| Parameters | Control group (n = 164) | Study group (n = 176) | <i>p</i> value |
|-----------------------------------|-------------------------|------------------------|----------------|
| Age (years) | 27.35 (24.00–30.00) | 27.50 (25.00–30.00) | 0.764 |
| Body weight (kg) | 65.41 \pm 8.78 | 71.04 \pm 12.37 | < 0.001 |
| BMI (kg/m ²) | 25.80 (22.70–28.80) | 28.29 (26.22–31.37) | < 0.001 |
| Body composition parameters | | | |
| Total body fat (%) | 27.12 \pm 4.38 | 33.10 \pm 5.55 | < 0.001 |
| Visceral fat (%) | 5.86 \pm 2.10 | 7.91 \pm 2.71 | < 0.001 |
| Body lean (%) | 72.85 \pm 7.15 | 66.17 \pm 6.80 | < 0.001 |
| RM (kcal/day) | 1245.70 \pm 136.90 | 1424.03 \pm 182.60 | < 0.001 |
| BFMI (kg/m ²) | 7.38 \pm 0.88 | 9.67 \pm 1.08 | < 0.001 |
| FFMI (kg/m ²) | 19.75 \pm 1.37 | 20.26 \pm 1.42 | 0.001 |
| Subcutaneous fat (%) | 27.70 (22.50–33.20) | 31.50 (26.40–35.67) | < 0.001 |
| Skeletal muscle (%) | 26.77 \pm 2.95 | 24.49 \pm 2.98 | < 0.001 |
| RM/BW (kcal/kg) | 19.03 \pm 1.85 | 20.49 \pm 2.56 | < 0.001 |
| RM/BF (kcal/kg) | 71.02 \pm 7.45 | 60.56 \pm 6.10 | < 0.001 |
| Blood pressure related parameters | | | |
| HR (per min) | 80.12 \pm 7.30 | 90.15 \pm 10.07 | < 0.001 |
| SBP (mmHg) | 111.00 (103.00–119.00) | 120.00 (110.00–125.00) | < 0.001 |
| DBP (mmHg) | 71.00 (65.00–79.00) | 78.00 (70.00–83.00) | < 0.001 |
| MAP (mmHg) | 84.95 (77.50–92.80) | 91.67 (83.75–96.33) | < 0.001 |
| RPP (mmHg) | 90.85 (78.85–105.20) | 106.09 (98.28–116.61) | < 0.001 |

Table 3. Comparison of anthropometric, body composition and blood pressure-related parameters in normal pregnant women (control group) and women with GDM (study group) at 36th week of gestation. The data presented are mean \pm SD and median (IQR). Comparison was done by unpaired *t* test for parametric data and Mann–Whitney U test for non-parametric data. *P* value < 0.05 was considered statistically significant. *BMI* body mass index, *RM* resting metabolism, *BFMI* body fat mass index, *FFMI* fat-free mass index, *BW* body weight, *BF* body fat, *HR* heart rate, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MAP* mean arterial pressure, *RPP* rate pressure product.

| Parameters | Control group (n = 164) | Study group (n = 176) | p value |
|------------------------------|-------------------------|------------------------|---------|
| HRV frequency domain indices | | | |
| TP (ms ²) | 950.74 (610.20–1310.20) | 506.50 (393.00–597.00) | < 0.001 |
| LFnu | 50.50 (38.70–62.36) | 62.04 (51.85–65.56) | < 0.001 |
| HFnu | 46.90 (40.25–61.86) | 37.74 (33.65–47.93) | < 0.001 |
| LF–HF ratio | 1.10 (0.72–1.40) | 1.62 (1.08–1.93) | < 0.001 |
| HRV time domain indices | | | |
| SDNN (ms) | 40.10 (27.35–52.10) | 21.20 (17.40–29.70) | < 0.001 |
| RMSSD (ms) | 45.32 (31.20–58.80) | 23.70 (18.40–30.30) | < 0.001 |
| NN50 | 33.15 (25.20–43.62) | 28.00 (22.00–32.00) | < 0.001 |
| pNN50 (%) | 10.27 (7.10–13.20) | 6.05 (4.59–6.88) | < 0.001 |
| Stress and risk scores | | | |
| PSS score | 14.30 (11.50–17.80) | 24.00 (21.00–27.75) | < 0.001 |
| EPDS score | 7.60 ± 1.80 | 10.57 ± 2.21 | < 0.001 |
| Flanagan QoL score | 105.00 (93.00–113.50) | 90.00 (82.25–95.00) | < 0.001 |
| IDRS | 40.00 (35.20–45.80) | 60.00 (50.00–70.00) | < 0.001 |

Table 4. Comparison of frequency domain and time domain indices of heart rate variability, perceived stress scale, quality of life and Indian diabetic risk score in normal pregnant women (control group) and women with GDM (study group) at 36th week of gestation. The data presented are mean ± SD and median (IQR). Comparison was done by unpaired *t* test for parametric data and Mann Whitney U test for non-parametric data. *P* value < 0.05 was considered statistically significant. *TP* total power of HRV, *LFnu* low-frequency power normalized, *HFnu* high-frequency power normalized, *LF–HF ratio* ratio of LF to HF, *SDNN* standard deviation of normal to normal (NN) interval, *RMSSD* square root of the mean of the sum of the squares of the differences between adjacent NN intervals, *NN50* number of interval differences of successive NN intervals greater than 50, *pNN50* NN50 counts divided by all RR intervals, *PSS* perceived stress scale, *EPDS* Edinburgh postnatal depression scale, *QoL* quality of life, *IDRS* Indian diabetic risk score.

| Parameters | Control group (n = 164) | Study group (n = 176) | p value |
|--------------------------------|-------------------------|-----------------------|---------|
| Glucose-related parameters | | | |
| FBG (mg/dL) | 86.17 ± 12.45 | 116.86 ± 16.62 | < 0.001 |
| Insulin (uIU/ml) | 10.60 (5.10–16.80) | 23.85 (16.38–31.29) | < 0.001 |
| HOMA-IR | 3.20 (1.10–5.20) | 6.33 (4.16–9.03) | < 0.001 |
| HbA1C (gm%) | 5.18 ± 0.86 | 6.81 ± 1.19 | < 0.001 |
| Oxidative stress marker | | | |
| MDA (μmol/L) | 15.10 (11.20–19.80) | 22.95 (17.62–25.60) | < 0.001 |
| Inflammatory markers | | | |
| IL-6 (pg/mL) | 12.45 ± 3.05 | 20.12 ± 5.34 | < 0.001 |
| hsCRP (μmol/L) | 3.10 (2.15–5.10) | 7.28 (4.71–9.65) | < 0.001 |
| Endothelial dysfunction marker | | | |
| NO (μM/L) | 30.80 ± 3.80 | 25.43 ± 2.83 | < 0.001 |

Table 5. Comparison of insulin resistance markers, oxidative stress marker and inflammatory markers in normal pregnant women (control group) and women with GDM (study group) at 36th week of gestation. The data presented are mean ± SD and median (IQR). Comparison was done by unpaired *t* test for parametric data and Mann Whitney U test for non-parametric data. *P* value < 0.05 was considered statistically significant. *FBG* fasting blood glucose, *HOMA-IR* homeostatic model assessment-insulin resistance, *HbA1C* glycated hemoglobin, *MDA* malondialdehyde, *IL-6* interleukin-6, *hsCRP* high sensitive c-reactive protein, *NO* nitric oxide.

oxidative stress marker, MDA were significantly increased ($p < 0.001$), while NO was significantly decreased ($p < 0.001$) in the subjects of study group compared to control group (Table 5).

Except EPDS and QoL, there was no significant correlation of PSS with any of the parameter in the subjects of control group. However, the correlation of RPP ($r = 0.193$, $p = 0.010$), RM ($r = 0.151$, $p = 0.045$), HRV parameters [TP ($r = -0.167$, $p = 0.027$; Fig. 1), LFnu ($r = 0.235$, $p = 0.002$), LF–HF ratio ($r = 0.184$, $p = 0.014$)], HbA1C ($r = 0.336$, $p < 0.001$; Fig. 2), oxidative stress marker [MDA ($r = 0.410$, $p < 0.001$; Fig. 3)], inflammatory marker, IL-6 ($r = 0.428$, $p < 0.001$; Fig. 4), endothelial dysfunction marker, NO ($r = -0.381$, $p < 0.001$) and depression and risk scores such as EPDS ($r = 0.582$, $p < 0.001$), QoL ($r = -0.299$, $p < 0.001$) and IDRS ($r = 0.195$, $p = 0.009$) with PSS were significant in the study group (Table 6).

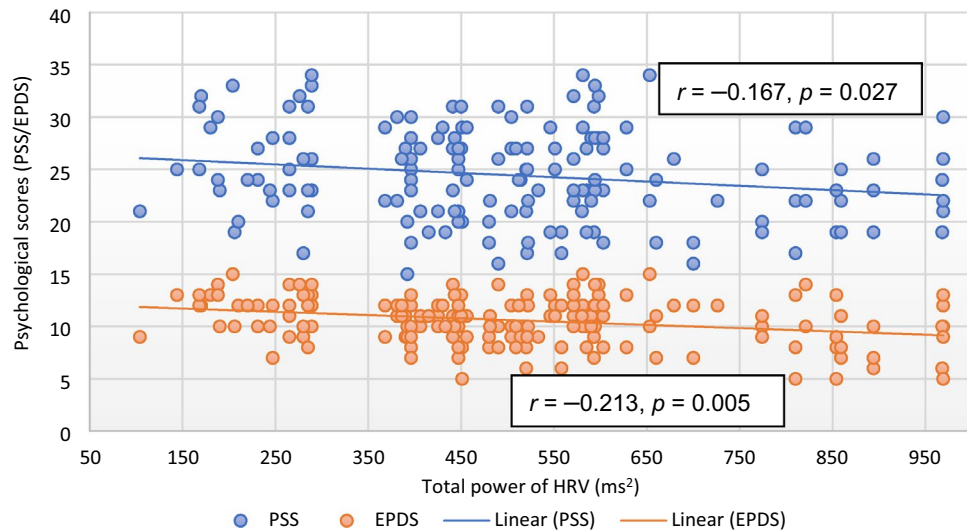


Figure 1. Correlation of total power of heart rate variability with psychological scores. *EPDS* Edinburgh postnatal depression scale, *HRV* heart rate variability, *PSS* perceived stress scale.

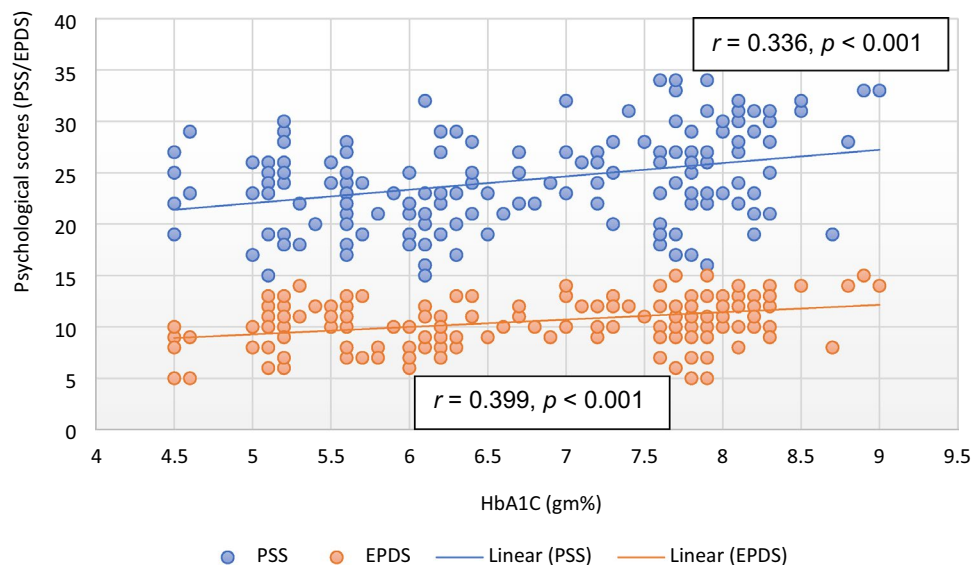


Figure 2. Correlation of glycated hemoglobin with psychological scores. *EPDS* Edinburgh postnatal depression scale, *HbA1C* glycated hemoglobin, *PSS* perceived stress scale.

Except *PSS*, none of the parameters were significantly correlated with *EPDS* in the subjects of control group. In study group subjects, *BMI*, *HR*, *SBP* and *DBP* were not significantly correlated with *EPDS* scores, however, *RPP* ($r = 0.168, p = 0.026$) and *RM* ($r = 0.153, p = 0.043$) showed significant positive correlation to *EPDS* scores (Table 7).

IL-6 ($r = 0.439, p < 0.001$; Fig. 4), *MDA* ($r = 0.452, p < 0.001$; Fig. 3), *HbA1C* ($r = 0.399, p < 0.001$; Fig. 2), *hsCRP* ($r = 0.186, p < 0.013$), were positively correlated and *NO* ($r = -0.419, p < 0.001$) was negatively correlated with *EPDS* scores in subjects of study group. Among *HRV* parameters, *TP* ($r = -0.213, p = 0.005$; Fig. 1) and *HFnu* ($r = -0.201, p = 0.007$) were negatively correlated and *LFnu* ($r = 0.287, p < 0.001$) and *LF-HF* ratio ($r = 0.236, p < 0.002$) were positively correlated with *EPDS* scores. *PSS* ($r = 0.582, p < 0.001$) and *IDRS* ($r = 0.178, p = 0.018$) were positively correlated and *QoL* ($r = -0.163, p = 0.035$) was negatively correlated with *EPDS* (Table 7).

Multiple regression analysis revealed significant individual contribution of *RPP* ($\beta = 0.154, p = 0.021$), *TP* ($\beta = -0.182, p = 0.005$), *HbA1C* ($\beta = 0.386, p = 0.016$), *MDA* ($\beta = 0.345, p = 0.004$) and *IL-6* ($\beta = 0.550, p < 0.001$) to *PSS* in study group. Though *RM* and *NO* were correlated with *PSS*, its independent contribution to *PSS* was not significant (Table 8). *TP* ($\beta = -0.286, p < 0.001$), *HbA1C* ($\beta = 0.237, p = 0.004$), *MDA* ($\beta = 0.337, p < 0.001$) and *IL-6* ($\beta = 0.393, p < 0.001$) significantly contributed to *EPDS* in study group (Table 9).

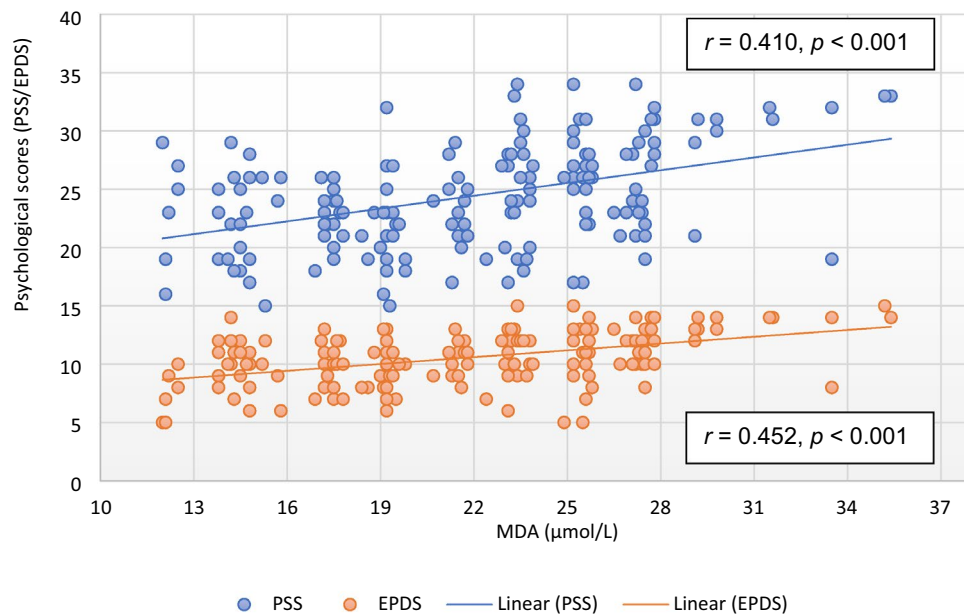


Figure 3. Correlation of malondialdehyde with psychological scores. *EPDS* Edinburgh postnatal depression scale, *MDA* malondialdehyde, *PSS* perceived stress scale.

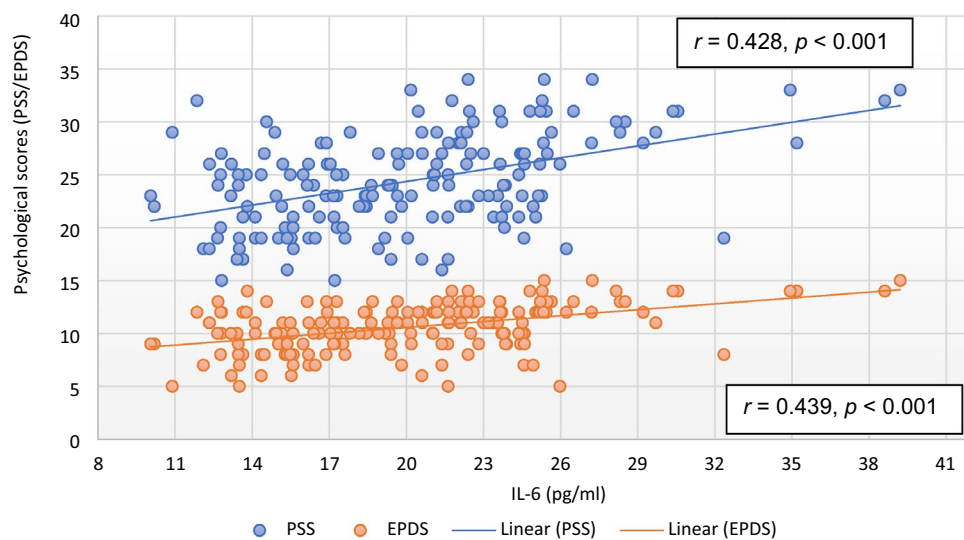


Figure 4. Correlation of interleukin-6 with psychological scores. *EPDS* Edinburgh postnatal depression scale, *IL-6* interleukin-6, *PSS* perceived stress scale.

Discussion

The participants of study group of the present study were GDM patients admitted to obstetrics ward of JIPMER hospital, which is a tertiary healthcare center of central government of India. Usually, the GDM patients admitted to this tertiary care hospital few weeks before delivery are those who have poor glycemic control inspite of treatment or those who are at risk of developing complications during delivery; otherwise they come for delivery just a couple of days before the expected date of delivery or after developing the labour pain. Thus, the GDM women in the study group had relatively less glycemic control in their 3rd trimester of pregnancy inspite of receiving antidiabetic treatment since the diagnosis of GDM. In the present study, the stress and depression scores were significantly increased in study group subjects compared to control group subjects depicting that the perceived psychological stress and depression are more in 36th week of gestation in pregnant women diagnosed with GDM. Earlier report³⁷ suggests that pregnant women with GDM experience higher levels of anxiety and stress compared to non-pregnant women and healthy pregnant women. Diagnosis of GDM in pregnant women increases their anxiety, resulting in 2–4 times susceptibility to have antenatal or postnatal depression than women without

| Parameters | Control group at 36th week | | Study group at 36th week | |
|-------------|----------------------------|---------|--------------------------|---------|
| | r value | p value | r value | p value |
| BMI | -0.045 | 0.398 | 0.013 | 0.867 |
| HR | 0.109 | 0.185 | 0.120 | 0.114 |
| SBP | -0.145 | 0.095 | 0.090 | 0.235 |
| DBP | -0.102 | 0.197 | 0.077 | 0.310 |
| RPP | -0.152 | 0.085 | 0.193 | 0.010 |
| RM | 0.115 | 0.157 | 0.151 | 0.045 |
| TP | 0.108 | 0.186 | -0.167 | 0.027 |
| LFnu | 0.099 | 0.192 | 0.235 | 0.002 |
| HFnu | 0.053 | 0.286 | -0.140 | 0.064 |
| LF-HF ratio | -0.098 | 0.217 | 0.184 | 0.014 |
| HbA1C | 0.110 | 0.175 | 0.336 | <0.001 |
| MDA | -0.103 | 0.195 | 0.410 | <0.001 |
| hsCRP | -0.083 | 0.213 | 0.109 | 0.149 |
| IL-6 | -0.110 | 0.183 | 0.428 | <0.001 |
| NO | 0.154 | 0.088 | -0.381 | <0.001 |
| EPDS | 0.198 | 0.024 | 0.582 | <0.001 |
| QoL | 0.162 | 0.048 | -0.299 | <0.001 |
| IRDS | -0.095 | 0.220 | 0.195 | 0.009 |

Table 6. Spearman correlation of PSS with various parameters in control group (n = 164) and study group (n = 176) at 36th week of gestation. The p value < 0.05 was considered significant; r : correlation coefficient. *PSS* perceived stress scale, *BMI* body mass index, *HR* heart rate, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *RPP* rate pressure product, *RM* resting metabolism, *TP* total power of HRV, *LFnu* low-frequency power normalized, *HFnu* high-frequency power normalized, *LF-HF* ratio of LF to HF, *HbA1C* glycated hemoglobin, *MDA* malondialdehyde, *hsCRP* high sensitive c-reactive protein, *IL-6* interleukin-6, *NO* nitric oxide, *EPDS* Edinburgh postnatal depression scale, *QoL* quality of life, *IRDS* Indian diabetic risk score.

| Parameters | Control group at 36th week | | Study group at 36th week | |
|-------------|----------------------------|---------|--------------------------|---------|
| | r value | p value | r value | p value |
| BMI | -0.110 | 0.184 | 0.119 | 0.115 |
| HR | 0.093 | 0.202 | 0.109 | 0.185 |
| SBP | -0.106 | 0.162 | 0.145 | 0.095 |
| DBP | -0.080 | 0.210 | 0.147 | 0.051 |
| RPP | -0.160 | 0.072 | 0.168 | 0.026 |
| RM | 0.102 | 0.195 | 0.153 | 0.043 |
| TP | 0.115 | 0.172 | -0.213 | 0.005 |
| LFnu | 0.090 | 0.192 | 0.287 | <0.001 |
| HFnu | 0.050 | 0.302 | -0.201 | 0.007 |
| LF-HF ratio | -0.090 | 0.232 | 0.236 | 0.002 |
| HbA1C | 0.112 | 0.181 | 0.399 | <0.001 |
| MDA | -0.150 | 0.086 | 0.452 | <0.001 |
| hsCRP | -0.045 | 0.318 | 0.186 | 0.013 |
| IL-6 | -0.142 | 0.112 | 0.439 | <0.001 |
| NO | 0.158 | 0.078 | -0.419 | <0.001 |
| PSS | 0.180 | 0.047 | 0.582 | <0.001 |
| QoL | 0.048 | 0.310 | -0.163 | 0.035 |
| IRDS | -0.175 | 0.052 | 0.178 | 0.018 |

Table 7. Spearman correlation of EPDS with various parameters in control group (n = 164) and study group (n = 176) at 36th week of gestation. The p value < 0.05 was considered significant; r : correlation coefficient. *EPDS* Edinburgh postnatal depression scale, *HR* heart rate, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *RPP* rate pressure product, *RM* resting metabolism, *TP* total power of HRV, *LFnu* low-frequency power normalized, *HFnu* high-frequency power normalized, *LF-HF* ratio of LF to HF, *HbA1C* glycated hemoglobin, *MDA* malondialdehyde, *hsCRP* high sensitive c-reactive protein, *IL-6* interleukin-6, *NO* nitric oxide, *PSS* perceived stress scale, *QoL* quality of life, *IRDS* Indian diabetic risk score.

| Independent variables | Standardized regression coefficient β | 95% C.I. | | p value |
|-----------------------|---|-------------|-------------|-----------|
| | | Lower limit | Upper limit | |
| RPP | 0.154 | 0.007 | 0.085 | 0.021 |
| TP | -0.182 | -0.007 | -0.001 | 0.005 |
| RM | 0.117 | 0.000 | 0.006 | 0.077 |
| HbA1C | 0.386 | -2.560 | -0.270 | 0.016 |
| MDA | 0.345 | 0.096 | 0.492 | 0.004 |
| IL-6 | 0.550 | 0.221 | 0.681 | <0.001 |
| NO | -0.035 | -0.415 | 0.524 | 0.819 |

Table 8. Multiple regression analysis of PSS (as dependent variable) with various parameters (as independent variables) in study group at 36th week of gestation, adjusted for plasma insulin. R: 0.578; R²: 0.334; adjusted R²: 0.307. C.I. confidence interval, PSS perceived stress scale, RPP rate pressure product, TP total power of HRV, RM resting metabolism, HbA1C glycated hemoglobin, MDA malondialdehyde, IL-6 interleukin-6, NO nitric oxide.

| Independent variables | Standardized regression coefficient β | 95% C.I. | | p value |
|-----------------------|---|-------------|-------------|-----------|
| | | Lower limit | Upper limit | |
| RPP | 0.105 | -0.004 | 0.035 | 0.112 |
| TP | -0.286 | -0.005 | -0.002 | <0.001 |
| RM | 0.072 | -0.001 | -0.002 | 0.272 |
| HbA1C | 0.237 | -1.009 | 0.133 | 0.004 |
| MDA | 0.337 | 0.046 | 0.243 | <0.001 |
| IL-6 | 0.393 | 0.048 | 0.277 | <0.001 |
| NO | -0.010 | -0.242 | 0.227 | 0.948 |

Table 9. Multiple regression analysis of EPDS (as dependent variable) with various parameters (as independent variables) in study group at 36th week of gestation, adjusted for plasma insulin. R: 0.591; R²: 0.349; adjusted R²: 0.322. C.I. confidence interval, EPDS Edinburgh postnatal depression scale, RPP rate pressure product, TP total power of HRV, RM resting metabolism, HbA1C glycated hemoglobin, MDA malondialdehyde, IL-6 interleukin-6, NO nitric oxide.

GDM during pregnancy⁴⁷. Pace et al⁴⁸, reported that when pregnant women with GDM become apprehensive of uncontrolled diabetes resulting in adverse maternal and neonatal outcomes, they are more likely to experience antenatal depression, stress and anxiety⁴⁹. In these women, the causes of anxiety and depression could be the inability to manage diabetes, serious concerns about the disease, need for dietary restrictions, insulin treatment and the demand for self-assessment of blood glucose⁵⁰. Also, GDM patients are afraid of treatment and are concerned about the adverse effects of medication on the growth and development of the fetus, resulting in anxiety⁵¹. Additionally, women who received insulin treatment experienced significantly higher levels of stress compared to women who only received dietary treatment alone⁵¹. In the present study, 85.79% GDM patients (151/176) had received insulin therapy in addition to dietary management (Table 1), which could have been a factor for stress and depression in these patients.

In our current study, along with increased stress and depression there was decreased quality of life (QoL) in the study group compared to the control group subjects (Table 4). QoL is the most important indicator for assessing the status of health care in chronic diseases such as diabetes and it has been reported that increased stress is linked to poor QoL in diabetes⁵². Though decreased QoL has been reported in GDM^{53,54}, the relationship of stress to QoL has not been studied in GDM yet. In our study, PSS (Table 6) and EPDS (Table 7) were highly correlated with decreased QoL in GDM women at 36th week of gestation. It has been observed earlier that depression in diabetes is an important comorbidity that requires careful management because of its severe impact on QoL⁵⁵. As such, decreased QoL increases the cardiovascular risk⁵⁶. Therefore, the health care professionals need to consider these findings when treating patients with gestational diabetes. Further, in the present study, IDRS was significantly high in study group compared to control group and IDRS was significantly correlated with PSS (Table 6) and EPDS (Table 7) indicating that GDM women are at the higher risk of developing metabolic syndrome, which is defined as the cluster of conditions consisting of hyperinsulinemia (the upper fourth of the fasting insulin level among nondiabetic subjects) or hyperglycemia (fasting glucose ≥ 110 mg/dl) in addition to at least two of the following: waist girth ≥ 94 cm, dyslipidemia (triglycerides ≥ 150 mg/dl or HDL cholesterol < 40 mg/dl), or BP $\geq 140/90$ mmHg or taking BP medication⁵⁷. Though IDRS is generally used for screening of diabetes in the community⁵⁸, the higher IDRS is reported to be associated with higher risk of metabolic syndrome and CVD

even among people without prediabetes or diabetes⁵⁹. Thus, decreased QoL and increased IDRS as observed in the study group subjects in the present study could increase the risk of developing CVD in women having GDM.

Though stress and depression have been highly documented in GDM, the pathophysiologic mechanisms of development of these mental illnesses in women with GDM have not been well studied till date. In the present study, the markers of inflammation were significantly increased in study group population (Table 5). Reports of animal studies and clinical trials indicate that among pro-inflammatory cytokines, IL-6 plays a unique role in the pathophysiology and somatic consequences of depression, and also mediate the effects of treatment of depressive disorder^{60,61}. The IL-6 was highly correlated with PSS ($r=0.428, p<0.001$; Table 6) and EPDS ($r=0.439, p<0.001$; Table 7) (Fig. 4) and among all the parameters, IL-6 had highest independent contribution to PSS ($\beta=0.550, p<0.001$, Table 8) and EPDS ($\beta=0.393, p<0.001$, Table 9). Thus, findings of our study indicate that inflammation is associated with GDM, and IL-6 could be the potential contributor to the development of stress and depression in GDM. It has been stated earlier that elevated IL-6 activity may lead to depression through stimulation of hypothalamic–pituitary–adrenal axis or by influencing the metabolism of neurotransmitters^{60,62}. Other suggested mechanisms are that IL-6 may increase the activity of indoleamine-2,3-dioxygenase (IDO), which catalyses tryptophan that in turn activate kynurenine pathway and reduce availability of serotonin in the brain^{63,64}. As a result, quinolinic acid, 3-hydroxy kynurenine, and the neurotoxic *N*-methyl-*D*-aspartate glutamate agonist are produced, which causes oxidative stress and contributes to the neurodegeneration and depression. IL-6 is also reported to be involved of in neuro-inflammation and brain-derived neurotrophic factor (BDNF)-mediated depression in various mental disorders⁶⁵. Therefore, future studies should focus on the association of IL-6 with BDNF and brain activity of serotonin and IDO to understand the role of neuro-inflammation in the causation of depression in GDM.

Malondialdehyde, the marker of oxidative stress was significantly increased in study group compared to control group. Malondialdehyde was significantly correlated with stress and depression (Fig. 3) and had independent contribution to both PSS (Table 8) and EPDS (Table 9). These findings indicate the possible role of oxidative stress in causation of stress and depression in GDM. Though oxidative stress has been implicated in poor fetomaternal outcomes in GDM⁶⁶, its role in pathophysiology of stress and depression in GDM has not been reported yet. Nitric oxide, the marker of endothelial dysfunction was significantly increased in study group and was substantially correlated with both stress and depression (Tables 6 and 7). However, nitric oxide had no independent association with PSS (Table 8) and EPDS (Table 9). Though nitric oxide is known to be involved in the pathophysiology of cardiometabolic risks in GDM both in antepartum and postpartum periods⁶⁷, from the finding of the present study it appears that endothelial dysfunction is unlikely to be linked to stress and depression in GDM.

FBG and HbA1C were significantly high in study group compared to control group, indicating that glycemic control was not effective inspite of antidiabetic treatment given to all GDM patients (Table 1). Glycated hemoglobin was strongly correlated with both stress and depression (Tables 6 and 7; Fig. 2) and had strong independent association with both the parameters. The level of glycated hemoglobin generally reflects the glycemic status in last three months period of a person and a higher glycated hemoglobin represents the poor diabetic control and increased cardiovascular risk⁶⁸. The higher blood glucose and HbA1C levels has been reported to be associated with higher stress in pregnant women⁶⁹. Thus, it appears that disease severity (level of glycemic status) could be an indicator of stress and depression in GDM and higher glycated hemoglobin level could herald the onset of depression and cardiovascular disease in GDM. As 151 out of 176 GDM patients received insulin therapy (Table 1), HOMA-IR was not considered for correlation and regression analysis. Also, plasma insulin was adjusted in the multiple regression models (Tables 8 and 9).

Spectral analysis of HRV has been used for assessment of autonomic functions and dysfunctions in health and diseases^{28–31} and decreased HRV is a known marker of CVD risk^{33,34,70}. In the present study, TP of HRV was considerably decreased in study group and control group (Table 4) and TP had significant correlation (Tables 6 and 7; Fig. 1) and independent association with stress and depression scores (Tables 8 and 9). TP of HRV reflects the overall magnitude of variability of heart rate and the vagal drive of cardiac modulation^{43,71}. Decreased TP is an established marker of CVD risk⁷¹. Decrease in time domain indices of HRV also reflects decreased cardiac vagal modulation⁷¹. The time-domain indices were significantly decreased in study group subjects (Table 4). Thus, findings of the present study reveal the decreased cardiovagal modulation at 36th week of gestation in women with GDM, which is linked to increased stress and depression in women those who have been receiving antidiabetic treatment for GDM. Increased LF–HF ratio, the marker of sympathovagal imbalance was prominently higher in study group compared to control group, indicating a severe state of autonomic dysregulation in women with GDM. To best of our knowledge, the present study is the first of its kind linking the reduction in HRV and cardiometabolic risks with depression in GDM.

In the present study, RPP was significantly more in study group subjects, and increased RPP was significantly correlated (Tables 6 and 7) and independently associated (Tables 8 and 9) with PSS and EPDS. Increase in RPP physiologically indicates myocardial work stress⁴⁰. Increase in RPP and heart rate has reported to be associated with CVD risks and sudden cardiac death, especially in individuals having high BP⁷². In the present study, HR and SBP were significantly more in study group subjects compared to control group subjects. Thus, findings of the present study indicate the presence of increased myocardial work stress in GDM and its possible link to stress and depression in GDM. Though BMI, body fat%, visceral fat%, BFMI, FFMI and resting metabolism were significantly high in the study group compared to control group (Table 3), the body composition and metabolism had no influence on stress and depression (Tables 8 and 9).

All the patients were followed upto delivery and their two important fetomaternal outcomes were noted. In control group, 82.92% (136/164) had normal delivery and 17.08% (28/164) had caesarean delivery, whereas in study group, 55.11% (97/176) had normal delivery and 44.89% (79/176) had caesarean delivery. The birth weight was normal (with reference to Indian standard birth weight of 2.7 kg to 3.1 kg in females, and 2.8 kg to

3.2 kg in males) in 92.68% (152/164) neonates in control group (birth weight 2.94 ± 0.24 kg) and there was no incidence of macrosomia. In study group, 64.77% (114/176) neonates had normal birth weight (2.97 ± 0.27 kg) and 48 neonates had macrosomia, i.e., more than 3.5 kg as per Indian birth weight reference⁷³. Thus, it appears that fetomaternal outcomes were poor in women with GDM.

Persistent increase in IL-6 has been reported in stress reactions and in patients with depression. In the present study, the increased IL-6 were found to be strongly associated with stress and depression in GDM women receiving antidiabetic treatment. All these evidence suggest for future studies to address if restoration of IL-6 level could be the key to treatment of depression associated with inflammation in GDM. In developing countries like India, the glycemic control and fetomaternal outcomes are poor in GDM due to various socio-economic factors that include poor compliance to treatment^{54,73}. Therefore, studies should be designed to assess if non-pharmacological interventions like yoga instituted early in the pregnancy can improve cardiovagal modulation and prevent the development of stress and depression in GDM.

Limitations. The major limitation of the study is that we did not recruit the subjects in 24th to 28th week of gestation to assess the cardiometabolic risks in GDM women when they were diagnosed with the disease. Also, we have not assessed the details of fetomaternal outcomes. However, the present study reports the cardiometabolic risks in GDM women at 36th week of pregnancy, and their potential contributions to stress and depression in GDM.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Received: 23 August 2022; Accepted: 21 June 2023

Published online: 26 June 2023

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Acknowledgements

Authors acknowledge the support given by JIPMER Authority to the first author as part of her PhD intramural grant, for conduct of this study.

Author contributions

G.K.P., L.C., N.N., K.T.H. and M.R. designed the protocol. M.R. conducted investigations. G.K.P., L.C., N.N. and K.T.H. assisted in conduct of work. G.K.P. supervised the work. M.R. performed biochemical estimations in guidance with N.N. and D.T. G.K.P., M.R., N.N. and K.T.H. did the data analysis. G.K.P. and M.R. prepared manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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