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*Case Study Article*

# Chemical and Medicinal Impacts of Gestational Diabetes Mellitus on Heart Rate Variability Indices-A Case-Control Study

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**ABSTRACT**

**Background:** Gestational diabetes [GDM] is one of the most common metabolic disorders associated with many adverse maternal and fetal complications including cardiovascular events. This study aimed to evaluate the function of the autonomic nervous system by heart rate variability [HRV] between pregnant women with GDM and healthy pregnant women.
**Methods**: The study was a case-control observational study on 50 pregnant women with GDM and 51 healthy pregnant women. They were assigned to the study at 32-36 weeks of gestational age. Demographic and past medical history and lab findings were gathered. HRV was assessed by a time-domain analysis of 24-hour cardiac Holter monitoring including SDNN-SDANN-rMSSD and pNN50 variables.
**Results:** The mean age of the participants was 28.69 [± 5.5]. Data analysis showed no significant difference in the age [p-value: 0.10], maternal hypothyroidism [p-value: 0.2], and PCO [p-value: 1/000] between two groups. There was no significant difference between SDNN [p-value: 0.21], SDANN [p-value: 0.11], and rMSSD [p-value: 0.87] between two groups. pNN50 in GDM group decreased significantly [P-value = 0.0001].
**Conclusion:** A significant decrease in the pNN50 index in GDM group may be a marker of autonomic dysfunction. Reduced pNN50 could be explained by decreasing parasympathetic activity and sympathetic overcome in pregnancy, especially in pregnancy associated with diabetes, leading to instability of the autonomic nervous system.

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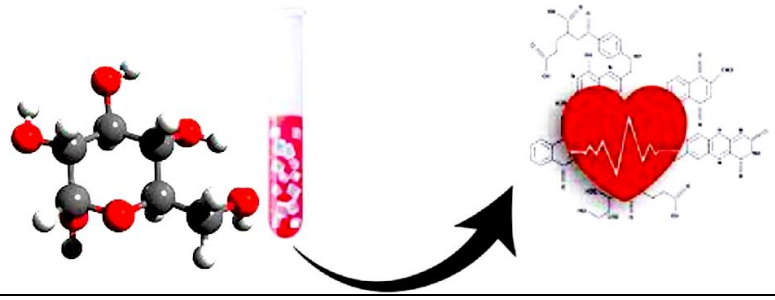
**GRAPHICAL ABSTRACT**



## Introduction

Pregnancy is perceived as a miracle. Many women feel an inner glow and bond to the growing fetus [1]. Glucose intolerance, which is first diagnosed during pregnancy is defined as gestational diabetes [2]. It mostly happens in the second and third trimester [3]. Pregnancy-induced physiological changes in glucose metabolism can lead to glucose intolerance or insulin resistance [4]. Pregnancy incidence of GDM varies from 2% to 14% globally, which is increasing [5], and parallel to the increment in the prevalence of obesity and type 2 diabetes mellitus [6]. Other risk factors related to the incidence of gestational diabetes include a family history of diabetes, high maternal age, low physical activity and dietary habits [7].

Gestational diabetes leads to increased maternal and fetal morbidity and mortality [8]. It is also a risk factor for cardiovascular disease [9]. Cardiac events such as myocardial infarction, heart failure, arrhythmia, and sudden cardiac death occur more frequently in these women [10].

Another important manifestation of cardiovascular disorders in this group of patients is cardiac autonomic neuropathy, which is strongly associated with hyperglycemia and insulin resistance [11]. The autonomic nervous system [ANS] regulates electrical activity and contraction of the heart through the interaction between sympathetic and parasympathetic systems [12]. HRV is a quantitative measure for the autonomic nervous system and its reduction could be representative of cardiac autonomic neuropathy [13].

This study was accordingly designed to evaluate and compare HRV between pregnant women with gestational diabetes and healthy pregnant women in our region.

## Materials and Methods

This inquiry is a case-control study. Pregnant women between 32-36 weeks of pregnancy, who referred to the women's clinic of Shohadye Kargar Hospital, Amir obstetric Clinic, Qaemieh obstetric Clinic, during the first half of 2017, participated in the study. These clinics are public and pregnant women are referred from primary health care centers. The sampling method for control group was simple randomization from all pregnant women who were recruited in these three centers. The cases were gathered by survey method; with all of GDM with inclusion criteria during first half of 2017 in these three centers. The inclusion criteria of case and control groups were: 32-36 weeks pregnant women, age between 18-40 years old, and those who had done oral glucose tolerance test [OGTT] between 24-28 weeks, while the exclusion criteria comprised history or medication of hypertension, cardiovascular disease, preeclampsia, type 1 or 2 diabetes, autonomic neuropathy, epilepsy or seizure, psychological disorders. Group matching of cases and controls were done according to gestational age, maternal age and past medical history.

The sample size of 101 patients was determined based on similar studies findings and according to two group proportion comparisons. Subjects were divided into case and control groups according to the presence or absence of GDM with the OGTT findings between 24-28 weeks of pregnancy. OGTT test was carried out with 75 g oral glucose, those with fasting blood sugar [FBS]> 92, or 1-hour glucose greater than 180 or 2-hours glucose greater than 153, and glucose 3 hours more than 140.

Informed consent was obtained from all participants. Baseline information such as

maternal age, gravity, body mass index [BMI], family history of diabetes, personal past history of GDM, hypothyroidism, and PCO were checked. Hypothyroidism were defined as thyroid stimulating hormone [TSH]<2.5 in first trimester and on levothyroxine treatment. HRV parameters were obtained by analyzing the 24-hour heart rate Holter [Holter Recorder TELESMART from Medset, Germany]. The required parameters including SDNN, SDANN, Square rMSSD and the percentage of intervals >50 msec different from preceding interval [pNN50] were obtained through the Cardio smart 4.2.1.0 software.

Statistical analysis such as data standard deviation, the correlation between variables, relative frequency, and comparison between women with and without GDM was done by SPSS 17. Normality was checked by Kolmogorov Simonov test. Non parametric tests were done. We used Chi-Square, and Mann–Whitney U test. A P-value less than 0.05 were considered statistically significant.

## Results and Discussions

Among 101 subjects, 50 women were in GDM group and 51 women were in the control group. The total mean [±SD] age of studied population was 28.69 [±5.5] years old. The baseline characteristics of GDM and control groups are presented in Table 1. Totally, 70% of pregnant women with GDM had BMI over 25 and there was a significant relationship between BMI and GDM.

**Table 1:** The baseline characteristics of GDM (Gestational diabetes) and control group

| | GDM group[n=50] | Control group[n=51] | P-value |
|---|---|---|---|
| Age Mean [±SD] | 29.5 [± 5.8] | 27.7[ ± 5.2] | 0.11 |
| BMI<br>Mean [±SD] | 26.5 [± 3.9] | 24.7 [± 4.5] | 0.036 |
| Personal past history of GDM<br>Frequency [%] | 15[30%] | 0 | 0.0001 |
| Family history of GDM<br>Frequency [%] | 24[48%] | 16[31. %] | 0.033 |
| Hypothyroidism<br>Frequency [%] | 13[26%] | 8[15%] | 0.20 |
| PCO (Polycystic ovarian syndrome)<br>Frequency [%] | 4 [8%] | 5 [8%] | 1.00 |
| Pregnancy outcome [live birth]<br>Frequency [%] | 50 [100%] | 51 [100%] | 1.00 |

Table 2 shows the means of SDNN, SDANN and rMSSD were not statistically significant. The power analysis showed acceptable power of each of the studied HRV indices. The mean percentage of pNN50 was 5.7 [± 5.9] in the GDM group and 9.8 [± 8.5] in the control group. Statistical analysis showed a significant reduction in pNN50 among subjects with GDM [P-value < 0.0001]. After multivariate analysis, we found that reduction in HRV indices was significantly correlated with the presence of hypothyroidism [P-value: 0.001 for pNN50], PCO [P-value: 0.015 for SDANN and 0.004 for pNN50], past history of GDM [P-value: 0.03 for rMSSD], family history of diabetes [P-value: 0.012 for pNN50], insulin or metformin treatment compared with diet alone [P-value: 0.001 for SDANN and 0.0001 for SDNN].

In this study, HRV status was evaluated by analyzing the 24-hour heart rate Holter. The results showed a significant decrease in mean pNN50 in GDM group, compared with healthy pregnant women. Pöyhönen-Alho reported that in GDM, HRV parameters significantly reduced especially in the frequency domain of the high frequency [HF] parameter [14]. This parameter [HF] is closely related to the pNN50. Meanwhile, another study assessed the effect of GDM on hemodynamics and cardiovascular regulation. They concluded that the frequency-based parameters including high frequency [HF], low frequency [LF], and very low frequency [VLF] did not significantly change in pregnant women with GDM [15-17].

**Table 2:** HRV (heart rate variability) indices between two studied groups

| | GDM Mean [±SD] | Control Mean [±SD] | P-value | Power |
|---|---|---|---|---|
| SDNN (standard deviation of all normal to normal R-R intervals) | 95.62 [± 24] | 100.18 [±21.4] | 0.21 | 0.77 |
| SDANN (standard deviation of five minutes' averages normal to normal R-R intervals) | 79.94 [± 20.6] | 86.26 [± 18.6] | 0.11 | 0.87 |
| rMSSD (root of the mean of the squares of successive normal to normal R-R interval differences) | 33.1 [± 23.2] | 33.0 [± 18.8] | 0.97 | 0.11 |
| pNN50 (The percentage of intervals >50 msec) | 5.7 [± 5.9] | 9.8 [± 8.5] | 0.0001 | 1.00 |

Other HRV parameters including SDNN, SDANN, and rMSSD decreased in GDM women but did not have a significant difference with the healthy group. The absence of a significant difference in other HRV parameters between the two groups was accounted for by the fact that each index reflected a part of autonomic nervous system activity and there was precedence in changing these parameters [18-20]. According to Umentani et al., the fastest and earliest change in autonomic neuropathy is a decrease in the pNN50 index. Also, it should be noted that SDNN and SDANN reductions are gradual [16, 21-23].

According to the results of the current inquiry, in obese women [BMI> 25] with gestational diabetes, a further decrease in mean pNN50 was observed. In Yadav's study, the effect of body fat mass on the function of the autonomic system and its effect on HRV was evaluated. The results showed that SDNN, rMSSD, and pNN50 parameters in subjects with BMI> 30 significantly reduced [17, 24-26]. It is probably because obesity increases sympathetic activity and suppresses parasympathetic function so it can lead to poor cardiac autonomic control, which can be further impaired by conditions such as diabetes and insulin resistance.

We found that the presence of hypothyroidism with GDM results in further reduction of HRV parameters. Another study performed by Xing *et al*., showed that hypothyroidism may lead to autonomic dysfunction especially in time-axis parameters [18, 27-29].

The results of our study showed that the mean pNN50 and SDANN significantly reduced among individuals with a history of PCO. And the mean of these indices significantly decreased in the GDM group with a history of PCO. Gui found that in women with PCO, SDNN and pNN50 are significantly lower than the those of control group [19, 30-33]. Women with polycystic ovaries suffer from autonomic neuropathy due to decreased parasympathetic function and increased sympathetic tone. Besides, PCO is associated with obesity and insulin resistance.

Our analysis revealed a significant difference in HRV parameter [SDNN and SDANN] between subjects treated with insulin or metformin compare with those treated with diet alone. In general, metformin-treated patients had a greater reduction in these indices. HRV parameters did not differ significantly between insulin-treated individuals and those treated with metformin. In an RCT on animal models performed by Apaijai, it was concluded that despite previous evidence of cardio protective effects of metformin, this drug has a very limited effect on HRV indices [20, 34-36]. Paolisso's study reflected that insulin treatment in a patient with insulin resistance cannot improve autonomic system function [21, 37-39]. In another study in the United States, it was found that the blood level of insulin was inversely proportional to HF and LF parameters, and in fact, people with high levels of insulin in their blood have a lower HRV.

## Conclusions

It seems that there is a correlation between cardiovascular autonomic system imbalance and gestational diabetes, especially in the pNN50 index. This parameter is strongly indicative of parasympathetic activity. In addition, in cases of hypothyroidism, history of PCO, and previous history of GDM, there is further impairment of

autonomic system function measured by HRV indices. In women with insulin or metformin therapy, despite proper glycemic control, cardiovascular regulation has not been balanced. It is like because pregnant women who only received diet, have better glycemic status at the time of diagnosis and during pregnancy, which could result in a better autonomic system function.

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**Authors' contributions**
All authors contributed toward data analysis, drafting and revising the paper and agreed to responsible for all the aspects of this work.

**Conflict of Interest**
The authors declare that there is no conflict of interest in the publication of this paper.

**Ethical issues**
In this study, except for maintaining the secrets of the patient in accordance with the Helsinki Treaty, the patients were assured that their information would be confidential and used only for the purpose of the research. In addition, no additional costs were imposed on patients. The proposal was approved by ethics committee of Yazd Shahid Sadoughi University of Medical Sciences.

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**References**

[1]. Lakshmi K., *Asian J. Nurs. Educ. Res.*, 2020, **10**:286 [Crossref], [Google Scholar], [Publisher]
[2]. Maheshwari P., Shanmugarajan T.S., *Res. J. Pharm. Technol.*, 2017, **10**:1589 [Crossref], [Google Scholar], [Publisher]
[3]. Smitha K.R., D'Almeida S., *Int. J. Adv. Nur. Management*, 2015, **3**:42 [Google Scholar], [Publisher]
[4]. Maheshwari P., Guna B., Kumar R.M., Renugadevi S., *Res. J. Pharm. Technol.*, 2017, **10**:4206 [Crossref], [Google Scholar], [Publisher]
[5]. Arul Mozhi D., Vijaya Manickam R., Gowri M., *Int. J. Adv. Nur. Management*, 2014, **2**:177 [Crossref], [Google Scholar], [Publisher]
[6]. Somwanshi S.B., Bairagi P.D., Kotade K.B., *Asian J. Pharm. Res.*, 2017, **7**:118 [Crossref], [Google Scholar], [Publisher]
[7]. Chihani B., Djaballah C., Derouiche S., *Asian J. Pharm. Res.*, 2020, **10**:177 [Google Scholar], [Publisher]
[8]. Meenakshi K., Maragatham G., *Res. J. Pharm. Technol.*, 2019, **12**:3891 [Google Scholar], [Publisher]
[9]. Žákovičová E., Kittnar O., Slavíček J., Medová E., Šváb P., Charvát J., *Physiol. Res.*, 2014, **63**:S479 [Crossref], [Google Scholar], [Publisher]
[10]. Burger A.J., Aronson D., *Pacing Clin. Electrophysiol.*, 2001, **24**:53 [Crossref], [Google Scholar], [Publisher]
[11]. Weissman A., Lowenstein L., Peleg A., Thaler I., Zimmer E.Z., *Diabetes Care*, 2006, **29**:571 [Crossref], [Google Scholar], [Publisher]
[12]. Sugunakar M.B.S., Maruthy K.N., Johnson P., *Res. J. Pharm. Technol.*, 2021, **14**:921 [Crossref], [Google Scholar], [Publisher]

[13]. Rawal K., Sethi G., Saini B.S., Saini I., *Res. J. Pharm. Technol.*, 2019, **12**:3854 [Crossref], [Google Scholar], [Publisher]
[14]. Pöyhönen-Alho M., 2011 [Google Scholar], [Publisher]
[15]. Heiskanen N., Saarelainen H., Valtonen P., Lyyra-Laitinen T., Laitinen T., Vanninen E., Heinonen S., *Clin. Physiol. Funct. Imaging*., 2008, **28**:384 [Crossref], [Google Scholar], [Publisher]
[16]. Umetani K., Singer D.H., McCraty R., Atkinson M., *J. Am. Coll. Cardiol.*, 1998, **31**:593 [Google Scholar], [Publisher].
[17]. Yadav R.L., Yadav P.K., Yadav L.K., Agrawal K., Sah S.K., Islam M.N., *Diabetes, Metab. Syndr. Obes. Targets Ther.*, 2017, **10**:57 [Crossref], [Google Scholar], [Publisher].
[18]. Xing H., Shen Y., Chen H., Wang Y., Shen W., *Chin. Med. J.,* 2001, **114**:906 [Crossref], [Google Scholar], [Publisher].
[19]. Gui J., Wang R.H., *Reprod. Biomed. Online*, 2017, **35**:113 [Crossref], [Google Scholar], [Publisher]
[20]. Apaijai N., Pintana H., Chattipakorn S.C., Chattipakorn N., *Endocrinology*, 2012, **153**:3878 [Crossref], [Google Scholar], [Publisher]
[21]. Mehrpisheh S., Memarian A., Mahyar A., Valiahdi NS. BMC Pediatr, 2018, **18**:178 [Crossref], [Google Scholar], [Publisher]
[22]. Jahandideh H., Yarahmadi A., Rajaieh S., Ostvar Shirazi A., Fard M.M., Yarahmadi A., *J. Pharm. Ree. Int.*, 2019, **31**:1 [Crossref], [Google Scholar], [Publisher]
[23]. Etemadi S., Mahmoodiyeh B., Rajabi S., Kamali A., Milanifard M., *Ann. Romanian Soc. Cell Biol*., 2021, **25**:2417 [Google Scholar], [Publisher]
[24]. Fard A.M.M., Fard M.M., *Eurasian J. Sci. Technol.*, 2021, **1**:284 [Crossref], [Google Scholar], [Publisher]
[25]. Danesh H.A., *Focus Med. Sci. J*., 2018, **4** [Google Scholar], [Publisher]
[26]. Danesh H.A., Saboury M., Sabzi A., Saboury M., Jafary M., Saboury S., *Med. J. Islam. Repub. Iran*, 2015, **29**:172 [Google Scholar], [Publisher]
[27]. Alimoradzadeh R., Mokhtare M., Agah S., *Iran. J. Age*., 2017, **12**:78 [Crossref], [Google Scholar], [Publisher]
[28]. Mehrpisheh S., Memarian A., Mahyar A., Valiahdi NS. *BMC Pediatr*, 2018, **18:**178
[29]. [Crossref], [Google Scholar], [Publisher]
[30]. Memarian A., Ameri E., Aghakhani K., Mehrp-Isheh S., Ameri M., *Iranian Journal of Public Health,* 2021, **45**: 960 [Crossref], [Google Scholar], [Publisher]
[31]. Memarian A, Mehrpisheh S., *Acta Med Iran.* 2015, **53**:663 [Google Scholar], [Publisher]
[32]. Aghakhani K, Heidari M, Ameri M, Mehrpisheh S, Memarian A., *Acta Med Iran.* 2015, **53**:652 [Crossref], [Google Scholar], [Publisher]
[33]. Aghakhani K, Kordrostami R, Memarian A, Asl ND, Zavareh FN., *J Forensic Leg Med.* 2018, **56**:80 [Crossref], [Google Scholar], [Publisher]
[34]. Memarian, A., Farhidnia, N., Fallahi, F., *Anesthesiology and Pain Medicine,* 2018, 8: e64707 [Crossref], [Google Scholar], [Publisher]
[35]. Nazari B., Amani L., Ghaderi L., Khanbabayi gol M., *Trauma Monthly*, 2020, **25**:262 [Crossref], [Google Scholar], [Publisher]
[36]. Hashemzadeh K., Dehdilani M., Gol M.K., *Int. J. Womens Health Reprod. Sci*., 2021, **9**:69 [Crossref], [Google Scholar], [Publisher]
[37]. Hashemzadeh K., Dehdilani M., Khanbabayi gol M., *Int. J. Women's Health Reprod. Sci*., 2020, **8**:406 [Google Scholar], [Publisher]
[38]. Shahidi N., Mahdavi F., Gol M.K., *J. Educ. Health Promot.*, 2020, **9**:153 [Crossref], [Google Scholar], [Publisher]
[39]. Eghdam-Zamiri R., Khanbabayi Gol M., *Iran. J. Obstet. Gynecol. Infertil.*, 2020, **22**:15 [Crossref], [Google Scholar], [Publisher]

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