

## QT Dispersion and Electrocardiographic Changes in Women With Gestational Diabetes Mellitus

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### Summary

Gestational diabetes mellitus (GDM) represents additional risks to both mother and infant. Moreover it increases a woman's risk of cardiovascular disease in the postpartum. The aim of our study was therefore to detect changes of both the QT dispersion and the electrical heart field that could be typical for GDM. Body surface potential maps were obtained using the Cardiac 112.2 device from 26 young women with GDM and 54 young healthy pregnant women in the 36th week of pregnancy. The same recordings were obtained from 18 healthy women in the same age (19-36 years). The average QT dispersion ( $\pm$ SD) in women suffering from GDM was significantly higher ( $107\pm 25$  ms) both than in those with physiological pregnancy ( $73\pm 18$  ms) and than in the normal subjects ( $34\pm 12$  ms) ( $P<0.001$ ). Moreover we have found in GDM patients shorter QRS complex  $82.0\pm 6.8$  ms vs.  $89.5\pm 8.2$  ms in healthy pregnant women and  $90.8\pm 7.9$  ms in the control group ( $p=0.011$ ), more horizontal electrical heart axis [ $16.4\pm 20.1^\circ$  vs.  $42.4\pm 28.7^\circ$  and  $74.6\pm 39.2^\circ$  respectively ( $P<0.05$ )] and lower some depolarization and repolarization amplitudes on isopotential and isointegral maps. According to these results we suppose that described electrocardiographic changes reflect a deterioration of the complete process of ventricular depolarization and repolarization in GDM.

### Key words

QT dispersion • Electrocardiography • Gestational diabetes mellitus

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### Introduction

Gestational diabetes mellitus (GDM) is defined as a disorder of glucose tolerance occurring during pregnancy, which spontaneously improves after delivery or until the end of puerperium. The incidence is about 4 % of all pregnancies and it is the second most common endocrinological complication of pregnancy (following thyroid disorders). Its prevalence increases over last years and increasing numbers of women suffering from GDM correlate both with rising incidence of overweight and obesity in the population and increasing age of expectant mothers. Risk factors of GDM are overweight or obesity, expectant mother's age over 30 years, positive family history – GDM or type 2 diabetes (DM) in the history or currently in mothers or grandmothers, obstetric history with GDM, hypertension or preeclampsia in previous pregnancy, delivery of fetus with high birth weight, stillbirth or recurrent miscarriage (Riskin-Mashiah, 2009). Mothers with GDM have increasing risk of pregnancy complications, but also increased risk of some pathologies long after its termination. They have increased incidence of hypertension, preeclampsia, nephropathy, but they are also in the risk of both hypo- and hyperglycemia and if decompensated also ketosis and ketoacidosis. Further during the women's life increased incidence of hypertension and metabolic syndrome was found in up to 40 % up to 20 years following the occurrence of GDM (Retnakaran 2009). Risks for the fetus are not less serious. Higher glycaemia mainly in the third trimester leads to so called diabetic fetopathy –

increased birth weight and organ macrosomia. Following the birth, the children are at risk of hypoglycemia, hyperbilirubinemia, polycythemia plus spasms or breathing difficulties can result from hypocalcemia and hypomagnesemia. Children are more often obese, have higher proportion of body fat and the risk of the onset of type 2 DM and metabolic syndrome increases already during growing up.

The development of GDM occurs due to insulin resistance resulting from increasing amounts of “antiinsulin” hormones produced particularly by placenta, i.e. compounds decreasing the tissues’ sensitivity to insulin during pregnancy (Jovanovic-Peterson and Peterson 1996). Insulin resistance occurs in all pregnant women at the beginning of the second trimester and progresses during the third trimester. Decreased sensitivity of cells to insulin is compensated by appropriate increase of insulin production. However, women with GDM cannot raise insulin secretion sufficiently and hyperglycemia occurs. According to many international studies, e.g. HAPO study (2009), there is a direct relationship between glycaemia and the risks for the mother and fetus.

GDM significantly increases a woman's risk not only of type 2 diabetes mellitus but also of cardiovascular disease in the postpartum (Sullivan *et al.* 2012). In our previous work we have found differences in some parameters of the electrical heart field in patients with diabetes mellitus in comparison to controls (Zdarska *et al.* 2007). While the association of gestational diabetes mellitus and abnormal glucose tolerance is beyond doubt, its associations with other cardiovascular disease risk factors in the offspring are less clearly established. Women with gestational diabetes mellitus have an enhanced cardiovascular risk factor profile at 3-months postpartum and an elevated risk of future cardiovascular disease, as compared to their peers (Retnakaran 2009). As the dispersion of the QT interval (QTd) seems to be a useful parameter in detecting repolarization abnormalities that can be responsible for rhythm disorders (Mirvis 1985, van de Loo *et al.* 1994, Cowan *et al.* 1988, Day *et al.* 1990, Hii *et al.* 1992, Hohnloser *et al.* 1993, Barr *et al.* 1994, Somberg *et al.* 1985, Sporton *et al.* 1997, Kittnar *et al.* 2004), we have tried to measure QTd in addition to other changes of the electrical heart field in women with GDM.

**Table 1.** Basic characteristics of the examined groups (mean values  $\pm$  standard deviations).

|                      | Group 1 GDM      | Group 2 Pregnant | Group 3 Control |
|----------------------|------------------|------------------|-----------------|
| Number               | 26               | 54               | 18              |
| Age                  | 31.8 $\pm$ 3.9 * | 28.4 $\pm$ 4.7   | 26.4 $\pm$ 5.8  |
| BMI before pregnancy | 25.2 $\pm$ 3.6 * | 23.3 $\pm$ 3.3   | 21.7 $\pm$ 2.9  |

\* means significant difference against control group ( $p < 0.05$ ).

## Methods

### Patients

Electrocardiographic recordings were obtained from 3 groups (basic characteristics of the groups are in Table 1):

*Group 1 (GDM):* 26 pregnant women with GDM in 36<sup>th</sup> week of pregnancy on average, with mean age 32 years (27-40), and with BMI of 25.2 before pregnancy. Positive family or personal history was present in 19 women and further diseases in 8 (hypothyroidism 4, anemia 4). The group consisted of 18 women with a diet and 8 with insulin. Patients were followed and managed by the Diabetic Centre of Faculty Hospital in Motol. Results showing the degree of diabetes

compensation, such as glycohemoglobin, total cholesterol, lipids, CRP, cortisol, prolactin etc., and readings of blood pressure, were available.

*Group 2 (Pregnant):* 54 healthy non-obese women with physiologic pregnancy, examined in 36<sup>th</sup> week on average (35-37), mean age 28 years (19-36).

*Group 3 (Control):* Control group of 18 healthy, non-pregnant women with mean age of 26 years (20-35).

A healthy person was defined for the purposes of this project according to the following findings and data: negative cardiological family and personal history, normal arterial blood pressure, normal glycaemia, normal cholesterolaemia, normal ECG, non-smoker, normal body weight, negative neurological and endocrinological personal history, no cardioactive medication.

### Measurement

The examination was realized at standard conditions, in all cases by only one investigating person in order to assure full compatibility and reproducibility of obtained results in all examined groups. Data acquisition was performed in the morning and examined women relaxed for a few minutes before the recordings were made. While examined they were asked to be still to avoid muscle movements.

Electrocardiographic and vectorcardiographic recordings were obtained simultaneously using the Cardiac 112.2 device (Kittnar and Mlcek 2010). QT interval was measured from 80 unipolar chest leads used for body surface potential mapping. QT interval was measured from the start of the Q wave to the end of the T wave, each QT interval was corrected for the patient's heart rate (QTc) using Bazett's formula (van de Loo *et al.* 1994). QT dispersion was then defined as the difference between the maximal and minimal QT interval in any of the leads measured. Accordingly, QTc dispersion was defined as the difference between maximal and minimal heart rate-corrected QT interval QTc.

### Data analysis

For the processing of the electrocardiographic and vectorcardiographic data the computer program of the Cardiac 112.2 device was used. This program

determines common wave onsets, offsets and amplitudes for all 95 leads on one representative beat. The set of all leads comprised: 12 standard ECG leads, 3 orthogonal Frank's vectorcardiographic leads and 80 regularly placed unipolar body surface leads (Kittnar and Stovicek 1993).

QT intervals were measured manually by a single observer from curves on the device screen. He used the cursor to indicate the start of the Q wave and the end of the T wave. The curves were presented on the screen in a measure corresponding to a paper speed of 50 mm/s and a gain of 1 mV/cm. To check the reproducibility of measurement we have assessed both intraobserver and interobserver variability. Statistical evaluation of the assessed data was performed using the nonparametric Mann-Whitney test.

### Results

Reproducibility of the determination of QT dispersion was high in both intraobserver and interobserver comparisons. In absolute numbers, the difference between the first and second determination of QT dispersion in the same ECG tracing (intraobserver variability) ranged between 0 and 18 ms, with an average value of  $8 \pm 3$  ms. The values for interobserver variability varied between 0 and 21 ( $9 \pm 5$  ms).

**Table 2.** Electrocardiographic parameters of the examined groups (mean values  $\pm$  standard deviations).

|                                  | Group 1 GDM            | Group 2 Pregnant       | Group 3 Control   |
|----------------------------------|------------------------|------------------------|-------------------|
| Heart Rate ( $\text{min}^{-1}$ ) | $92.07 \pm 14.69^{**}$ | $93.24 \pm 17.41^{**}$ | $75.21 \pm 11.46$ |
| PQ interval (ms)                 | $124.7 \pm 19.5^*$     | $125.8 \pm 24.9^*$     | $149.5 \pm 19.3$  |
| QRS interval (ms)                | $82.0 \pm 6.8^{*+}$    | $89.5 \pm 8.2$         | $90.8 \pm 7.9$    |
| QT interval (ms)                 | $337.3 \pm 18.7^*$     | $337.5 \pm 19.6^*$     | $365.2 \pm 30.5$  |
| QTc interval (ms)                | $414.8 \pm 24.8$       | $417.1 \pm 28.9$       | $405.3 \pm 20.7$  |
| QT dispersion (ms)               | $107 \pm 25^{**++}$    | $73 \pm 18^{**}$       | $34 \pm 12$       |
| QTc dispersion (ms)              | $116 \pm 31^{**++}$    | $79 \pm 21^{**}$       | $36 \pm 13$       |
| Electrical heart axis (deg)      | $16.4 \pm 20.1^{*+}$   | $42.5 \pm 28.7$        | $74.6 \pm 39.2$   |
| QRS-T space angle (deg)          | $68.5 \pm 29.8^{*+}$   | $37.8 \pm 22.1$        | $25.6 \pm 19.9$   |

\* means significant difference against control group ( $p < 0.05$ ). \*\* means significant difference against control group ( $p < 0.01$ ). + means significant difference between GDM and Pregnant groups ( $p < 0.05$ ). ++ means significant difference between GDM and Pregnant groups ( $p < 0.01$ ).

The average QT dispersion ( $\pm$ SD) in the control group was significantly lower ( $34 \pm 12$  ms) than in women in the late period of pregnancy ( $73 \pm 18$  ms) ( $P < 0.001$ ) and also than in women with GDM ( $107 \pm 17$  ms). Significant

difference was proved between the pregnant group and GDM group as well ( $P < 0.01$ ). The results were very similar using rate corrected values with average QTc dispersion values. Significant differences were found also

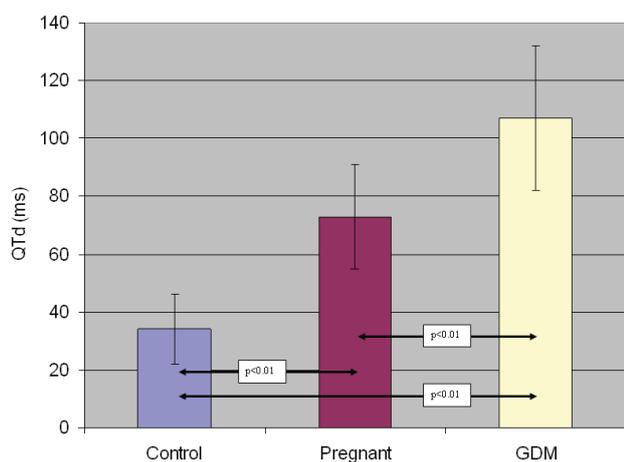
in the case of QRS complex duration, electrical heart axis and QRS-T space angle. All basic electrocardiographic parameters are summarized in the Table 2. Decreased amplitudes both in maximal and minimal depolarization

and maximal repolarization values in women with GDM were found as well as decreased activation time (Table 3). Important parameters with statistically significant differences are in Figures 1-4.

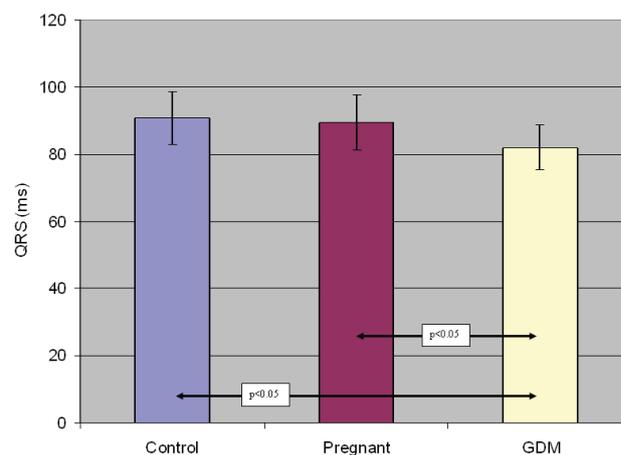
**Table 3.** Maximal and minimal depolarization values, maximal repolarization values, and activation times of the examined groups (mean values  $\pm$  standard deviations).

|                                | Group 1 GDM         | Group 2 Pregnant | Group 3 Control |
|--------------------------------|---------------------|------------------|-----------------|
| Max depolarization ( $\mu V$ ) | 904 $\pm$ 190 ** ++ | 1420 $\pm$ 240   | 1571 $\pm$ 257  |
| Min depolarization ( $\mu V$ ) | -1086 $\pm$ 227 * + | -1503 $\pm$ 327  | -1488 $\pm$ 259 |
| Max repolarization ( $\mu V$ ) | 320 $\pm$ 35 * +    | 389 $\pm$ 39     | 397 $\pm$ 36    |
| Activation time (ms)           | 64.4 $\pm$ 4.0 * +  | 71.3 $\pm$ 7.8   | 70.6 $\pm$ 5.6  |

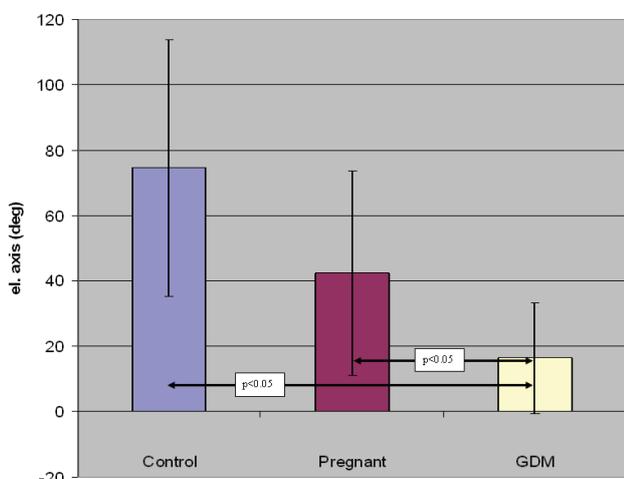
\* means significant difference against control group ( $p < 0.05$ ). \*\* means significant difference against control group ( $p < 0.01$ ). + means significant difference between GDM and Pregnant groups ( $p < 0.05$ ). ++ means significant difference between GDM and Pregnant groups ( $p < 0.01$ ).



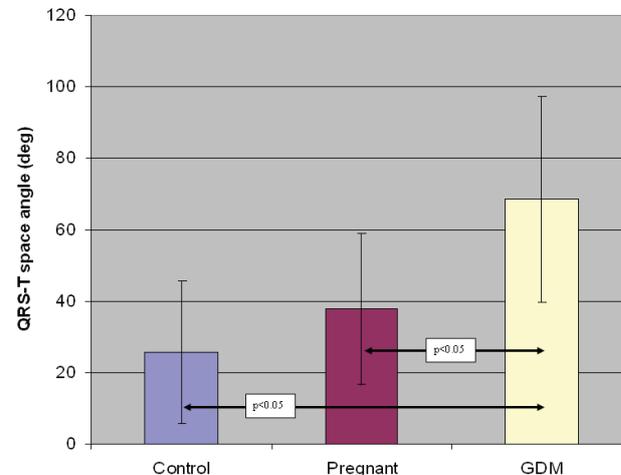
**Fig. 1.** Dispersion of the QT interval in examined groups (mean values  $\pm$  SD).



**Fig. 2.** QRS complex duration in examined groups (mean values  $\pm$  SD).



**Fig. 3.** Electrical heart axis in examined groups (mean values  $\pm$  SD).



**Fig. 4.** Space angle QRS-T in examined groups (mean values  $\pm$  SD).

## Discussion

The present study aimed to determine the eventual changes in the dispersion of QT interval in the patients with GDM from ECG curves used the body surface potential mapping. Consideration of greater number of leads for determination of QT dispersion appears to determine QT dispersion more accurately than assessment in only 12 or even 6 precordial leads. The use of low number of leads was undoubtedly the main cause of repeatedly suggested poor reproducibility (Kautzner *et al.* 1994, Day *et al.* 1990). Enhanced accuracy for QT dispersion assessment from 12-lead ECG in comparison with only 6 precordial leads was reported as well (van de Loo *et al.* 1994, Higham and Campbell 1994). Moreover, the reproducibility could be influenced by the measure of the ECG curve (a paper speed and a gain) and especially lower time resolution (25 mm/s) was suggested to be an important reason for poor reproducibility (Glancy *et al.* 1996). Both the intra- and interobserver variability of QT and QTc dispersion assessed in this study permits use of this method to determine changes in QT dispersion as the detected changes lie well above the errors encountered in this study.

Our previous results have suggested that the QT interval and QTd are changed both in the physiological late pregnancy (Lechmanova *et al.* 2002) and in the diabetes mellitus (Palova *et al.* 2010, Zdarska *et al.* 2007). We have concluded therefore that QT dispersion can reflect not only increased risk of serious tachyarrhythmias especially due to myocardial ischaemia but it must be interpreted simply just as “an unspecific sign of changed course of repolarization”. The present study proved that QTd in the control group is significantly shorter than in physiological pregnancy and GDM. Moreover QTd was significantly prolonged in patients with GDM in comparison to the healthy pregnant women (the pregnant group). It can be interpreted that factors responsible for prolongation of QTd are added together.

Higher age and BMI in group with GDM in comparison to the control group were found. Nevertheless these differences cannot explain electrocardiographic changes: in one of our previous studies only a lower heart rate and a longer QT interval were found in older persons (Slavicek *et al.* 2001). In the present study the results were quite opposite in the GDM group (that is older than the control group). In a study focused on QT dispersion in obese patients increased QT

dispersion was observed in patients with severe obesity with BMI higher than 35 (Mshui *et al.* 1999) what was not our case.

Shortened QRS interval in group with GDM in comparison to the other two groups corresponds to the shortening of the activation time in GDM patients. These findings are consistent with our previous results in type 1 diabetic patients (Palova *et al.* 2010). QT interval was prolonged both in GDM patients and healthy pregnant women but this was evidently due to increased heart rate as there were no significant differences of QTc among studied groups. Increased intraventricular conductance can be explained by activation of the sympatho-adrenergic axis due to increased production of placental prolactin in the gestational diabetes mellitus (Newbern and Freemark 2011).

Horizontal electrical heart axis was found in all pregnant women and its direction differs significantly from the control group. Significantly more horizontal direction of the axis in women with GDM can be explained by increased size of fetus but we cannot exclude also remodeling of myocardium. This hypothesis is partially supported by increased QRS-T space angle in the group of GDM women. The opening of spatial angle between integral vectors of the QRS complex and T wave depends on the different depolarization and repolarization pattern (Pisvejcova *et al.* 2002) and can be related to a left ventricular overload or hypertrophy (Ruttkay-Nedecky 1983). Moreover it is an indicator of adrenergic tonization of the working myocardium (Andrasyova *et al.* 1998) what can contribute to the increased intraventricular conductance.

Decreased depolarization and repolarization amplitudes are most probably caused by the geometrical changes of the chest organs in the late pregnancy particularly by the increased content of lipid tissue between the heart and measuring electrodes.

One of the main limitations of this study is that the group of GDM patients is not fully consistent particularly as for their treatment: 8 of them were treated by insulin, 18 were just on a diet. On the other hand all of them were well compensated both as for glycaemia ( $5.11 \pm 0.66$  mmol/l) and HbA1c ( $28.6 \pm 0.31$  mmol/mol). Moreover 4 women from the GDM group were treated because of hypothyreosis but also these patients were fully compensated by pharmacological treatment.

The electrocardiographic parameters were not so far systematically studied in spite of fact that GDM represents increased cardiovascular risk in the

postpartum. Based on our results it can be concluded that there are at least functional changes in the electrical heart field in GDM patients that can contribute to the risk. Because of significant differences in comparison to the physiological pregnancy described affection of the electrical heart field cannot be explained just by the geometrical changes of the chest organs in the late pregnancy or by hormonal influence of gestational hormones but most probably other hormonal disturbances

related to a deteriorated metabolic control in GDM women are responsible for these changes.

### Conflict of Interest

There is no conflict of interest.

### Acknowledgements

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