The optimal control of blood glucose is associated with normal blood pressure 24 hours profile and prevention of the left ventricular remodeling in the patients with gestational diabetes mellitus

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Abstract

OBJECTIVE: The aim of this study was to evaluate the impact of the optimal diabetes control on the left ventricular parameters and ambulatory blood pressure in women with gestational diabetes mellitus (GDM).

METHODS: The patients with GDM were followed up according to predetermined protocol in order to optimize blood glucose and optimal weight gain. Ambulatory blood pressure monitoring (ABPM) and transthoracal and tissue echocardiography were examined in 36th week of pregnancy.

RESULTS: The age of 35 women with GDM was 33.1±3 and 30.5±4.4 years in 31 healthy control subjects (p=0.2). Fasting plasma glucose (FPG) in the patients with GDM was 5.0±0.5 mmol/L compared to 4.6±0.3 mmol/L in control subjects (p=0.002). Average weight gain during pregnancy was significantly lower in women with GDM; 10±7.6 kg vs. 13.1±3.7 kg in healthy pregnant women (p=0.05). No significant differences were recorded in 24 hours mean heart rate, systolic and diastolic blood pressure and number of nondippers between both groups. The significant correlation was detected between FPG and blood pressure dipping in subjects with GDM. Interventricular septal, posterior wall and relative wall thickness of the left ventricle were significantly higher in patients with GDM comparing to healthy pregnant women but no significant differences of the left ventricular functions were recorded.

CONCLUSION: The optimal control of diabetes in GDM is associated with normal 24 hours blood pressure profile and prevention of the left ventricular function changes in GDM patients. The differences in the left ventricular walls thicknesses may be explained by metabolic changes in GDM.

ORIGINAL ARTICLE

Abbreviations:

A	- late transmitral flow
A´	- late diastolic mitral annular motion
ABMP	- ambulatory blood pressure monitoring
aTPO	- anti-thyroid peroxidase
BMI	- body mass index
BP	- blood pressure
DT	- deceleration time
E	- early transmitral flow
E´	- early diastolic mitral annular motion
EF	- ejection fraction
FPG	- fasting plasma glukose
fT4	- free tyroxine
GDM	- gestational diabetes mellitus
HAPO	- Hyperglycemia and Adverse Pregnancy Outcomes (study)
HbA1C	- glycosylated hemoglobin
hCG	- human chorionic gonadotropin
HOMA IR	- Homeostasis Model Assessment of Insulin Resistance
IGF1	- insulin-like growth factor 1
IST	- interventricular septal thickness
oGTT	- oral glucose tolerance test
LVESD	- left ventricular end systolic dimension
LVEDD	- left ventricular end diastolic dimension
LVMI	- left ventricular mass index
MAP	- mean arterial pressure
PWT	- posterior wall thickness
RWT	- relative wall thickness
TDI	- tissue Doppler imaging
TSH	- thyroid - stimulating hormone

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy (Metzger & Coustan 1998). GDM is associated with a higher incidence of obstetric and postpartum complications both for mother and child. The typical mother complications are: increased risk of delivery by Caesarean section, maternal preeclampsia or an increased risk of developing type 2 diabetes mellitus and metabolic syndrome after delivery (Metzger *et al.* 2008; Feig *et al.* 2008). GDM is also associated with increased cardiovascular risk later in mother's life (Caballero 2003; Davis *et al.* 1999; Carpenter 2007). According to the recent research, in women with GDM when compared with healthy pregnant women, changes in the diurnal variation of blood pressure are observed, as well as increased index of the left ventricular mass and its diastolic function alternation (Freire *et al.* 2006; Soydinc *et al.* 2013). However, the intensity of blood glucose control during pregnancy was not precisely defined in these studies. Hence, the importance of optimal GDM compensation was not evaluated yet. It is possible that adequate compensation might have a major effect on the presence of the identified changes.

Therefore, in our research we analyzed whether the described changes in the left ventricular mass, functions alternation and ABPM are present also in situation, when GDM is adequately controlled according to a predetermined protocol.

METHODS

The local Ethic Committee of University Hospital in Prague Motol approved study that followed Helsinki protocol. Informed consent was obtained from each patient or healthy control woman before the study started. Duration of the pregnancy was determined by the last menstrual period and confirmed by ultrasound. All participants had oral glucose tolerance tests (oGTT), generating diagnostic indicators for GDM according to Czech National Diabetes Data Group criteria. GDM was diagnosed in the 24–28th week of gestation using oGTT with 75 g glucose load, when FBS in venous plasma was less than 7.0 mmol/L. Plasma glucose samples were collected at fasting, as well as one and two hours after glucose load. The diagnosis of gestational diabetes was established if either of test value was abnormal; if FPG exceeded 5.5 mmol /L, one hour plasma glucose exceeded 8.8 mmol/L or two hours oGTT plasma glucose exceeded 7.7 mmol/L.

Women with GDM received complex dietary counseling and insulin when necessary. Target glucose level in the treatment of GDM was a fasting blood glucose of less than 5.6 mmol/L, and less than 6.7 mmol/L for 2 hours after a meal.

Patients with a prior history of hypertension, preeclampsia, and chronic diseases were excluded from the study. All subjects were Caucasians, none smoked during pregnancy. All patients with GDM were followed and assessed at our outpatient center bi-weekly since establishing of diagnosis until delivery. In the meantime, they performed blood glucose self-monitoring, and glycosuria and ketonuria checks at home. Control subjects remained euglycemic throughout the whole pregnancy.

All other examinations were performed in the 36th week of gestation. The anthropometrics and biometric measurements – height (in meters) was taken using a stadiometer and the patients were required to stand upright, with the body and head touching the meter ruler (m). Weight (in kilograms) was taken using a standard weighing scale while the patient was wearing light clothes with shoes taken off. Body mass index (BMI) was calculated using the following formula: BMI= body weight (kg) / body height (m^2).

Basic laboratory tests including the determination of complete blood count, liver function tests, metabolic parameters (uric acid, total serum cholesterol, HDL, LDL cholesterol, triglycerides, FPG, glycosylated hemoglobin-HbA1c) were performed. Blood sample for the analyses of these parameters was collected after fasting between 6:30–7:30 a.m. into vacuum tube with ethylene diamine tetra acetic acid.

Serum insulin was measured by the electrochemiluminescence immunoassay method, enzymatic glucose determination was based on Slein method using hexokinase and glucose-6-phosphate dehydrogenase. All patients had calculated HOMA IR (Homeostasis

Model Assessment of Insulin Resistance) according to the formula: HOMA IR = glucose (mmol/L), insulin (mIU/L)/22.5 (Matthews *et al.* 1985). HbA1c was determined by high performance liquid chromatography, C-reactive protein by turbidimetric immunochemical assay method. Total cholesterol was measured by enzymatic, spectrophotometer method. Triacylglycerol was analyzed spectrophotometrically. Uric acid was determined using the uricase-f-methoxyaniline sodium salt (F-DAOS). The endocrine parameters that we examined in patients with GDM and controls included: serum levels of TSH, fT4, anti-thyroid peroxidase antibodies, progesterone, prolactin, hCG, and cortisol, where chemiluminescent immunoassay determination of the morning sample was used. Sandwich immunoradiometric method was used for determination of insulin-like growth factor 1.

Non-invasive 24-hour ambulatory blood pressure monitoring (ABPM) was performed by oscilometry with a portable automated Cardiette bp one device (CardiLine, Milan, Italy) with calibration certification; simultaneous 24-hour heart rate monitoring was obtained. The unit was set to take reading every 30 minutes throughout 24 h. Patients were advised to maintain their usual daily activities. All ABPM evaluations were performed on a normal workday. The following parameters were evaluated: daytime, nighttime and 24-hour systolic, mean, and diastolic blood pressure and heart rate. Daytime and nighttime periods were based on the actual time of sleep reported by the patients. Nocturnal blood pressure (BP) dipping was calculated as follows: (awakeBP-sleepBP)×100/awakeBP). According to the criterion of Verdecchia, the patients with a nocturnal reduction in average daytime systolic BP and diastolic BP of less than 10% were classified as nondippers, whereas those with nighttime reduction of 10% or more were classified as dippers (Verdecchia *et al.* 1991).

Transthoracic echocardiography, including pulse Doppler and tissue Doppler imaging (TDI) were performed using a Philips Sonos® 7500 cardiac ultrasound unit (Philips Healthcare, Andover, MA, USA). Interventricular septal thickness (IST), posterior wall thickness (PWT), LV end diastolic diameter (LVEDD), LV end systolic diameter (LVESD), and left atrial diameter were determined. Relative wall thickness (RWT) was determined using 2× posterior wall thickness (PWT)/LVEDD. The LV ejection fraction was evaluated according to the Teicholz formula (Teichholz *et al.* 1976). Left ventricular mass (LVM) was calculated by the following equation following ASE (American Society of Echocardiography) convention (Lang *et al.* 2005; Devereux & Reichek 1977):

$$\text{LV Mass (g)} = 0.8\{1.04[([[\text{LVEDD}+\text{IST}+\text{PWT}]^3 - \text{LVEDD}^3)]\} + 0.6$$

Left ventricular mass index (LVMI) was determined as LVM/body surface area. Mitral inflow velocity was traced and the following variables of diastolic function were measured and evaluated: peak velocities of early (E) and late (A) transmitral flow, the ratio E/A, and deceleration time (DT). The peak velocities of early (E´) and late (A´) diastolic mitral annular motion (average of septal and lateral values) were determined from TDI recordings, and mitral E/E´ and E´/A´ ratios were calculated (Sohn *et al.* 1997).

Statistical analyses

Statistical analyses and database management were performed using SAS (SAS Institute, Cary, NC). Results are expressed as the mean ± standard deviation. The significance of differences in parameters was determined by Student's t-test for nonpaired samples and by chi-squared test on an appropriate basis. The correlation coefficient was obtained by the method of least squares, tests for normality by Kolmogorov-Smirnov tests. Relationships between parameters were tested by simple linear regression and correlation expressed by Pearson's correlation coefficient r. Linear regression analysis with partial correlation was used for relationships between FPG and systolic and diastolic nocturnal pressure, and BP night dipping. We tested the significance level alpha of 5% (α=0.05).

RESULTS

35 women with GDM and 31 healthy pregnant women were enrolled in the study. Clinical characteristics of the groups are shown in Table 1. There was no significant difference between the groups in terms of weight, height, BMI, age, weeks of parity. However, women with GDM had significantly lower weight gain during gestation than controls (p=0.05). The average age of 35 women with GDM was 32±4 years, compared to 30.3±4 years (NS) in 31 healthy women. 17 patients with GDM were primigravida, 18 women were in their second or third pregnancy. In the control group 21 were primigravida, and 10 controls in their second or third pregnancy. One patient with GDM and one healthy control were pregnant with twins, for other participants it was intrauterine pregnancy with a single fetus. 24 women with GDM were treated with diet modification, 4 with diet modification and conventional insulin regimen and 7 with diet modification and intensified insulin regimen. The average daily dose of insulin for patients with GDM treated with intensified insulin regimen at the time of examination was 15.7±5.2 units, in patients treated with conventional insulin regimen 7±2.9 units. FPG in women with GDM was 5.0±0.5 mmol/L compared to 4.6±0.3 mmol/L in healthy pregnant women (p=0.002). HOMA index in GDM patients was 2.6±2.0 compared to 1.7±1 in control group (p=0.049).

Patients with GDM were divided into two subgroups: group treated with lifestyle changes and insulin-treated group. Comparison of these two groups showed no statistically significant difference. Anthropometrics and biometric parameters as shown in Table 2. Analyses

Tab. 1. Baseline characteristics and laboratory values of study groups.

	GDM (n=35)	Controls (n=31)	*p*-value
Age (years)	32±4	30.3±4.2	0.1
Week of pregnancy during examinations	36.2±1.1	35.75±1.1	0.08
Height (cm)	166±5.9	168.3±7.4	0.11
Weight (kg)	77.2±13.3	77.1±13.5	0.97
Weight gain (kg)	10±7.6	13.1±3.7	0.05
BMI (kg/m^2)	28.2±3.8	27.1±4.1	0.3
Total cholesterol (mmol/l)	7±1	7.1±0.8	0.66
LDL cholesterol (mmol/l)	4±0.9	4.4±0.7	0.04
HDL cholesterol (mmol/l)	1.86±0.4	1.8±0.3	0.5
Triglyceride (mmol/l)	2.75±1	2.67±0.76	0.7
hsCRP (mg/l)	4.2±3.6	3.8±3.5	0.6
Fibrinogen	4.5±0.6	4.58±0.52	0.5
Leucocytes	8.8±2.7	9.7±2.3	0.14
HbA1c (mmol/mol)	40±3.8	34±3	<0.01
HbA1c (%, DCCT)	5.8±0.6	5.3±0.5	<0.01
Fasting blood glucose (mmol/l)	5±0.67	4.6±0.36	<0.01
Serum insulin value (mU/l)	16.92±17	13.2±8.1	0.25
HOMA index	2.63±2.6	1.7±1.0	0.049

BMI - body mass index

Tab. 2. Comparison of baseline characteristics of the patients with GDM treated with insulin and on diet only.

	Insulin (n=11)	Diet (n=24)	*p*-value
Age (years)	33.1±3	30.5±4.4	0.2
Height (cm)	167±6.7	165.1±5.5	0.4
Weight (kg)	80.8±13.8	75.7±12.8	0.3
Weight gain (kg)	9±9.2	10.6±6.6	0.6
BMI (kg/m^2)	28.8±3.9	27.9±3.8	0.5
Fasting blood glucose (mmol/l)	5.3±0.7	4.9±0.6	0.17
Serum insulin value (mU/l)	15.6±7.6	17.6±20	0.7
HbA1C (%, DCCT)	5.7±0.4	5.6±0.4	0.45
HbA1C (mmol/mol)	39±4	38±4	0.32
Total cholesterol (mmol/l)	7±0.9	7±1	0.91
LDL cholesterol (mmol/l)	4.2±0.8	3.9±0.9	0.4
HDL cholesterol (mmol/l)	1.7±0.3	1.9±0.4	0.05
Triglyceride (mmol/l)	2.9±0.8	2.7±1.2	0.5
hsCRP (mg/l)	3.8±4.1	4.4±3.3	0.7
Serum uric acid (umol/l)	273±43	234±47	0.02
Fibrinogen	4.7±0.5	4.4±0.6	0.1
Leucocytes	8.4±2.2	9±3	0.5
Erythrocytes	3.9±0.3	4±0.4	0.5
Hemoglobin (g/dl)	11.5±1.3	11.8±1.4	0.5
HOMA index	2±1	2.9±5	0.32

BMI - body mass index; GDM - gestational diabetes mellitus

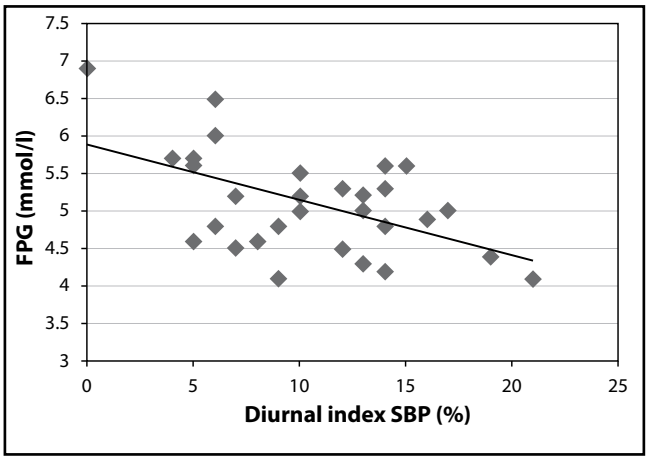

Fig. 1. Linear correlation of FPG with SBP dipping in patients with GDM. r=–0.53; *p*<0.01; FPG - fasting plasma glucose; SBP - systolic blood pressure; GDM - gestational diabetes mellitus

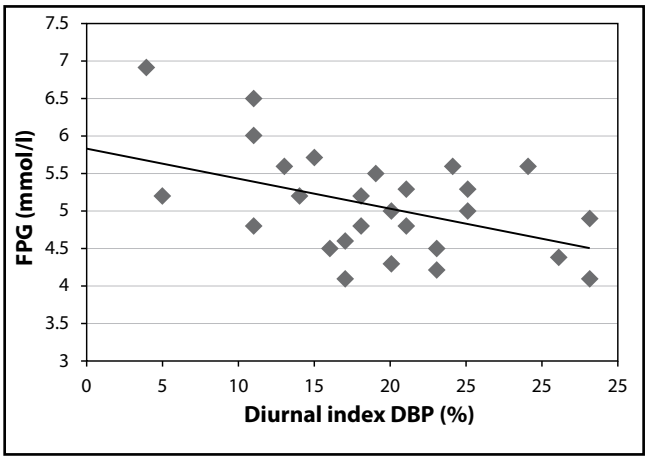

Fig. 2. Linear correlation of FPG with DBP dipping in patients with GDM. r=–0.503; *p*<0.01; FPG - fasting plasma glucose; DBP - diastolic blood pressure; GDM - gestational diabetes mellitus

of laboratory parameters between subgroups women with GDM showed statistically significant higher level of uric acid and lower level of HDL cholesterol in the insulin treated group.

In both groups, GDM and control women, heart rate, systolic BP, diastolic BP and mean BP were of similar values. The day and night variation BP are presented in Table 3. The higher presence of nondippers has not been found in any of examined groups. According to the correlation analyses, there was a significant negative correlation between FPG and nocturnal systolic and diastolic blood pressure dipping in women with

GDM group (Figures 1 and 2) whereas this correlation in healthy controls was not significant. A positive correlation between FPG and nocturnal BP (systolic, diastolic and mean BP) in-group women with GDM (*p*-value=0.04, 0.01 and 0.02 respectively, r=0.38, 0.45 and 0.42 respectively) was also detected.

Patients with GDM did not have detectable changes in term of diastolic dysfunction comparing to controls (peak velocities of early (E) and late (A), the ratio E/A, deceleration time (DT), the peak velocities of early (E´) and late (A´) diastolic mitral annular motion, mitral E/E´ and E´/A´ ratios). However the patients with GDM had significantly larger interventricular septum diameter, posterior wall thickness and relative wall thickness (*p*-value=0.04, <0.01 and 0.01, respectively). Echocardiography results are presented in Table 4. In order to eliminate effect of the insulin therapy, patients in GDM group were divided to two subgroups: patients treated by lifestyle changes only and patients who required insulin treatment. No significant differences in echocardiography values and ABMP results were present between these two subgroups.

Tab. 3. ABPM results in patients with GDM and healthy control subjects.

	GDM (n=35)	Controls (n=31)	*p*-value
24 hours mean heart rate	84.3±10.4	85.3±9.7	0.7
24 hours systolic blood pressure (mmHg)	111±7.1	113±6.7	0.19
24 hours diastolic blood pressure (mmHg)	71±6.8	72±6	0.9
24 hours mean arterial pressure (mmHg)	84±6,5	85.5±6.5	0.4
Day-phase mean arterial pressure (mmHg)	86.7±6.4	87.76±6	0.19
Night-phase mean arterial pressure (mmHg)	73.1±6.8	77.8±7.4	0.01
MAP dipping (mmHg)	12.5±5.6	9.9±5.9	0.1
Day-phase systolic BP (mean, mmHg)	112.1±6.5	114.8±6.7	0.19
Night-phase systolic BP (mean, mmHg)	100.4±7.6	106.8±7.9	0.19
Systolic blood pressure dipping (mmHg)	12±5.7	8.1±5.3	<0.01
Day-phase diastolic BP (mean, mmHg)	72.1±5.5	74±6.3	0.21
Night-phase diastolic BP (mean, mmHg)	59±5.9	63.5±7.4	<0.01
Diastolic blood pressure dipping (mHg)	13.5±6.4	10.6±6.3	0.07
Day-phase heart rate	86.1±7.4	87.9±9.7	0.4
Night-phase heart rate	73.4±10	75.9±9,8	0.3
Heart rate dipping	12.4±6	12±5	0.9

ABPM - ambulatory blood pressure monitoring; BP - blood pressure; GDM - gestational diabetes mellitus

DISCUSSION

Results of the recent studies suggested significant abnormalities of cardiovascular system in the patients with GDM (Freire *et al.* 2006; Soydinc *et al.* 2013). According to their results, there is a significant increase of mass of left ventricle, impaired diastolic function of left ventricle, and a change in ABPM profile in terms of growth in nondipper pregnant women with GDM in comparison with the control healthy women. Nondipping of nocturnal blood pressure seems to be a determinant of cardiac hypertrophy and remodeling, and was found to be a cardiovascular risk factor independent of ambulatory blood pressure levels even in normotensive subjects (Hoshide *et al.* 2003; Ohkubo *et al.* 2002). However, in the cited studies, algorithm of GDM treatment has not been defined, though its determination may be very important. One recent Finnish study (Heiskanen *et al.* 2010) showed that, with proper metabolic control of women with GDM during pregnancy when compared with healthy pregnant control subjects, significant changes in autonomic vegetative system are not present, as it was previously assumed (Poyhonen-

Tab. 4. Echocardiography examination in patients with GDM and healthy control subjects.

	GDM (n=35)	Controls (n=31)	*p*-value
E/A	1.52±0.4	1.4±0.4	0.26
E(m/s)	0.76±0.17	0.72±0.1	0.3
A (m/s)	0.51±0.1	0.54±0.12	0.4
E´ (cm/s)	10±1.7	10.11±1.7	0.8
A´(cm/s)	9.6±1.6	8.85±1.9	0.1
E/E´	0.078±0.02	0.071±0.01	0.17
LVEDd (mm)	46.8±4.3	47.6±4	0.4
LVESd.(mm)	25±4	22.7±8.8	0.2
IST (mm)	9.6±1	9.1±0.8	0.04
PWT (mm)	9.6±0.8	9±1	<0.01
LV mass (g)	155.6±29	147.3±27	0.2
LV mass index (g/m2)	82±13	78.5±11	0.3
RWT	0.4±0.05	0.38±0.03	0.01
EF	65±4.9	63.2±4.8	0.16

E - early peak of mitral blood flow velocity; A - late peak of mitral blood flow velocity; E´ - early diastolic mitral annular motion; A´ - late diastolic mitral annular motion; LVEDd - left ventricular end diastolic diameter; LVESd - left ventricular end systolic diameter; IST - intraventricular septal thickeness; PWT - posterior wall thickness; LV - left ventricle; RWT - relative wall thickness; EF - ejection fraction of left ventricle

Alho *et al.* 2010). In our study, all patients with GDM were adequately controlled in accordance with a predetermined protocol.

In comparison with previous studies that reported the higher systemic blood pressure with impaired diurnal rhythm and the higher left ventricular mass with worsening of its diastolic function in women with GDM (Freire *et al.* 2006; Soydinc *et al.* 2013), FPG was reduced in our study for more than 15%.

Significant negative correlation between FPG and diurnal variability of the measured BP explains relatively low incidence of nondipper women with GDM detected in our study. The graph showing the correlation of BP decline at night and FPG clearly demonstrate the difference of BP dipping for FPG 5.6 mmol/L – mean value in the previous study (Soydinc *et al.* 2013) and 5 mmol/L reached by our patients. The correlation of BP decline was discovered with FPG and not HbA1c probably because both ABPM and FPG depend on the current condition while HbA1c expresses diabetes compensation for last few weeks. Most studies found a low correlation between glycosylated hemoglobin and mean, fasting, postprandial blood glucose in patients with gestational diabetes mellitus (Brustman *et al.* 1987; Hod & Yogev 2007). Furthermore, the association between glycosylated hemoglobin and the incidence of complications including macrosomia in GDM is low (Loke *et al.* 1994; Wyse *et al.* 1994; Mazze 2002; Weissmann-Brenner *et al.* 2004).

The nocturnal blood pressure in the group of women with gestational diabetes mellitus was lower compared to the control group. The cause of this change is not entirely clear. Given the relatively large part of women treated with insulin, it would be possible that nocturnal blood pressure decline might have been associated with induced night hypoglycemia. Therefore the relevant clinical and laboratory parameters of women with GDM who were taking insulin, with those who were treated with dietary modification alone were compared. Women treated with insulin had significantly lower HDL-cholesterol and higher levels of uric acid, suggesting a higher cardiovascular risk compared to women with GDM who were treated only with diet (Assmann *et al.* 1996; Weverling-Rijnsburger *et al.* 2003; Fang & Alderman 2000; Holme *et al.* 2009). However, the changes between systolic and diastolic blood pressure during the day and night and diurnal variability were not statistically significant between this two subgroups, which indirectly argues against the hypothesis that cause for a drop in blood pressure in the population of our GDM patients was hypoglycemia.

We believe, that following comprehensive care, weight gain in women with GDM during pregnancy was significantly lower than in the control group. According to one of outcomes in the HAPO study, risk of developing preeclampsia was higher with greater maternal BMI. Thus, maternal obesity is a strong risk factor for gestational hypertension (Yogev *et al.* 2010; Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study: associations with maternal body mass index 2010). Overweight and insulin-resistant women are more prone to developing hypertensive complications and preeclampsia than their normal-weight normoglycemic counterparts (Kayemba-Kay's *et al.* 2013). Following a good comprehensive care in our group plasmatic insulin level was not statistically significantly increased and HOMA-IR showed just borderline increased insulin resistance. The comprehensive care can participate in reducing the risk of developing gestational hypertension and incidence of nondippers in the patients with GDM.

The reduction of pressure load in women with GDM was associated with decrease of the left ventricular cavity size as well as prevention of the left ventricular diastolic dysfunction in comparison with healthy pregnant women.

On the other hand, mild but significant thickening of the interventricular septum diameter and posterior wall of the left ventricle in women with GDM was recorded in comparison with control group. These changes are not consistent with ABPM results. However, despite of keeping strict protocol fasting plasma glucose and HbA1c were still significantly higher in GDM patients for whole period of pregnancy than in healthy control subjects. This may induce some morphological changes in myocardium (Nunoda *et al.* 1985; van Hoeven & Factor 1990; Regan *et al.* 1977).

CONCLUSION

The optimal control of blood glucose and comprehensive care in GDM is associated with normal blood pressure 24 hours profile and prevention of the left ventricular function changes in GDM patients. The difference in the left ventricular walls thicknesses may be explained by metabolic changes related to GDM.

Competing interests

The authors declare that they have no competing interests.

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