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Gestational diabetes alters the fetal heart rate variability during an oral glucose tolerance test: a fetal magnetocardiography study

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Objective Gestational diabetes mellitus (GDM) potentially harms the child before birth. We previously found GDM to be associated with developmental changes in the central nervous system. We now hypothesise that GDM may also impact on the fetal autonomic nervous system under metabolic stress like an oral glucose tolerance test (OGTT).

Design We measured heart rate variability (HRV) of mothers and fetuses during a three-point OGTT using fetal magnetocardiography (fMCG).

Setting Measurements were performed in the fMEG Centre in Tübingen.

Population After exclusion of 23 participants, 13 pregnant women with GDM and 36 pregnant women with normal glucose tolerance were examined.

Methods All women underwent the same examination setting with OGTT during which fMCG was recorded three times.

Main outcome measure(s) Parameters of heart rate variability were measured.

Results Compared with mothers with normal glucose regulation, mothers with GDM showed increased heart rate but no significant differences of maternal HRV. In contrast, HRV in fetuses of mothers with GDM differed from those in the metabolically healthy group regarding standard deviation normal to normal beat (SDNN) ($P = 0.012$), low-frequency band ($P = 0.008$) and high-frequency band ($P = 0.031$). These HRV parameters exhibit a decrease only in GDM fetuses during the second hour of the OGTT.

Conclusions These results show an altered response of the fetal autonomic nervous system to metabolic stress in GDM-complicated pregnancies. Hence, disturbances in maternal glucose metabolism might not only impact on the central nervous system of the fetus but may also affect the fetal autonomic nervous system.

Keywords Autonomic nervous system, fetal development, fetal programming, gestational diabetes, heart rate variability, magnetocardiography, oral glucose tolerance test.

Tweetable abstract Metabolic stress reveals a different response of fetal autonomic nervous system in GDM-complicated pregnancies.

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Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance observed for the first time during pregnancy.[1] In Western countries the prevalence ranges from 1.7 to 11.6% in pregnant women,[2] and the incidence seems to be rising, not only because of lifestyle changes such as increasing maternal age and obesity, but also due to (epi-)genetic processes.[3]

GDM is associated with short-term and long-term adverse health effects for the offspring, commonly

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presenting as macrosomia, large-for-gestational-age and increased perinatal morbidity.[4] In later life these children have an elevated risk for overweight, diabetes and metabolic syndrome.[5–7]

This might be the consequence of the altered maternal metabolism, which impacts on the fetus, a mechanism called fetal programming.[8] Our group recently published that human fetuses of insulin-resistant mothers and mothers with GDM show alterations of the developing central nervous system.[9] When performing fetal magnetoencephalography (fMEG) during an oral glucose tolerance test (OGTT), latencies of evoked fetal brain responses increased in pregnancies complicated by GDM compared with pregnancies in mothers with normal glucose tolerance.[10] These results might indicate that maternal metabolism prenatally programmes central insulin resistance of the fetus with potential consequences in later life as described above.

The present study aims to provide further insights into mechanisms leading to the fetal phenotype associated with GDM. As changes in the central nervous system were detected, the autonomic nervous system (ANS) interlinking the brain and peripheral organs might also be affected. To determine the influence of GDM on the developing ANS, fetal magnetocardiography (fMCG) was applied.

Fetal magnetocardiography is a noninvasive method to detect the magnetic signals generated by the fetal heart and accurately record cardiac time intervals.[11] Heart rate and heart rate variability (HRV) are calculated from intervals in the time and frequency domain. HRV is an accepted diagnostic and prognostic tool to assess cardiac autonomic function. The ANS regulates HRV through sympathetic and parasympathetic (vagal) activities. It furthermore interacts with different brain areas, including brainstem, amygdala and cortical regions.[12] Hence, measurements of fetal HRV are a promising procedure to assess fetal well-being and, presumably, overall neurodevelopmental state.[13–15]

In the present study, we hypothesised that the maternal metabolism (e.g. gestational diabetes) impacts on the fetal ANS being revealed under metabolic stress conditions like an OGTT. We therefore measured HRV of mothers with and without GDM and their fetuses during an OGTT.

Methods

Participants

A total of 72 pregnant women were enrolled in this study. They took part in a trial examining fetal response latencies to auditory stimuli measured with fMEG before and during an OGTT.[9,10] During the fMEG measurement, fetal and maternal MCG were recorded simultaneously. The results of fetal brain activity of 40 women taking part in the present study measured with fMEG were reported in a previously published paper.[10]

Participants were recruited by medical employees of University Hospital Tübingen, Germany in cooperation with local gynaecologists. Inclusion criteria were singleton pregnancy and a gestational age of at least 27 weeks with either normal glucose tolerance (NGT group) or diagnosed gestational diabetes (GDM group). Exclusion criteria included pre-existing overt diabetes, fetal malformations or other developmental disorders. Women with previously diagnosed gestational diabetes were treated according to the guidelines for gestational diabetes of the German Diabetes Association and the German Society for Gynaecology and Obstetrics. All women with GDM performed blood glucose testing and received dietary counselling. None of the examined women with GDM was treated with insulin.

This study was approved by the Ethics Committee of the Medical Faculty of the Eberhard Karls University of Tübingen, Germany (reference number 339/2010BO1). Before data acquisition all participants gave written informed consent.

Examination setting

The examination followed a strict timetable (Figure 1) starting at 08.00 with a detailed interview and an abdominal ultrasound (Logiq 500MD; GE Healthcare, Chalfont St Giles, UK) to detect the position of the fetal head. This was followed by the first fMEG/fMCG measurement. All participants had to be fasting for at least 6 hours before withdrawal of the first blood sample (t = 0 minutes) and the subsequent OGTT.

Before the second and third blood withdrawals (t = 60 and t = 120 minutes) again fMEG/fMCG measurements were performed. The fMCG recordings were performed in the first 15 minutes without stimulation followed by the recording of auditory evoked fields. In the end, an abdominal ultrasound was performed to confirm the correct position of the fetal head.

Fetal magnetocardiography

The study was performed using a 156-channel system (VSM MedTech Ltd., Port Coquitlam, BC, Canada)

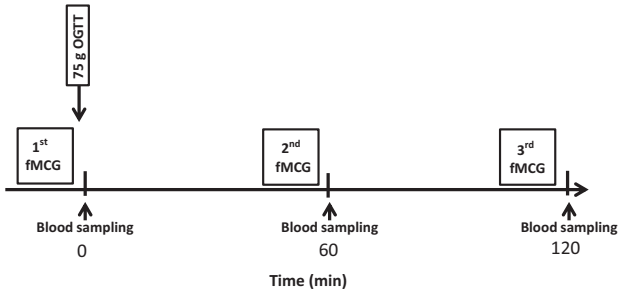

Figure 1. Examination settings.

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dedicated for fetal measurements at the fMEG Centre of the Eberhard Karls University of Tübingen, Germany. Biomagnetic signals were recorded from 156 primary sensors (superconducting quantum interference devices) arranged in a convex array able to cover the whole maternal abdomen. Three measurements of about 20 minutes each were made before, during and after OGTT. During examination, the pregnant women were sitting in an upright position leaning forward and laying their gravid abdomen in the convex shape. The sampling rate was set to 610.352 Hz.

The MCG signals were extracted in a two-step procedure. First a Hilbert transform was used to detect maternal QRS-complexes and eliminate extra beats (more than 20% deviation according to preceding and following intervals).[16,17] The marked QRS complexes were processed by a signal space projection technique to attenuate the maternal heart signal.[18] In the second step, fetal QRS complexes were marked by the same procedure as the maternal QRS complexes. The peak-to-peak time intervals for maternal and fetal heart were extracted and further analysed.

Analysis of HRV was performed with in-house software implemented using MATLAB (MATLAB Release 2014a; The Mathworks, Inc., Natic, MA, USA) and parameters for both maternal and fetal HRV were computed according to the definition reported in the Task Force Guidelines.[19]

The standard HRV time–domain parameters were obtained from ectopic-free RR interval segments: mean heart rate (meanHR), mean R-to-R interval (meanRR), standard deviation normal-to-normal interval (SDNN) and root mean square of successive differences (RMSSD). SDNN reflects the overall variability of heart beats during measurement time. RMSSD is an estimate of the short-term components of HRV.[19]

The estimation of spectral components in the low-frequency (LF) band (0.04–0.15 Hz) and the high-frequency (HF) band (0.15–0.40 Hz) were computed using Welch's method. Power spectra of the fetus were analysed at different frequency ranges as proposed by David et al.[20]—LF: 0.08–0.2 Hz and HF: 0.4–1.7 Hz. High frequency is consistently said to reflect parasympathetic outputs, whereas LF has been described as reflecting both sympathetic and vagal influences. The ratio of LF and HF bands is regarded as a measure of sympathovagal balance.[19]

Oral glucose tolerance test

In all participants, an OGTT was performed at ≥27 weeks of gestation. After a fasting time of at least 6 hours, a first venous blood sample (t = 0 minutes) was obtained followed by the ingestion of a 75-g glucose solution (Dextro O.G.T.®; Roche Diagnostics, Mannheim, Germany). Another two venous blood samples were obtained after 60 and 120 minutes (t = 60, t = 120 minutes).

Diagnosis of GDM was according to the criteria of the International Association of Diabetes and Pregnancy Study Groups with at least one out of three values exceeding the defined limits of 92 mg/dl of fasting glucose, 180 mg/dl 1 hour after glucose ingestion and 153 mg/dl 2 hours after glucose ingestion.[21]

Blood samples

Blood glucose concentrations were determined photometrically (ADVIA 1800; Siemens Healthcare Diagnostics, Eschborn, Germany). Plasma insulin concentrations were measured with the immunoassay system ADVIA Centaur Insulin Test (Siemens Healthcare Diagnostics).

Statistics

The statistical analysis of data was performed with SPSS Statistics for Windows version 22.0 (IBM SPSS Statistics, Amonk, NY, USA). Results were regarded as statistically significant with $P < 0.05$. Missing values were excluded pairwise. Normal distribution was computed using Shapiro–Wilk test.

Parametric data were analysed by a two-way analysis of variance including the factor time (the three time-points) and group (NGT, GDM) and non-parametric data were analysed using Friedman test. Statistically significant and normally distributed results were additionally analysed by means of t-test for independent samples to reveal differences between the groups (healthy versus GDM) or t-test for paired samples to identify differences in one group during the course of time. As results were statistically significant, but not normally distributed, Mann–Whitney U-test or Wilcoxon signed-rank test was performed.

In the calculations, logarithmic values were used. Data are provided in the text and tables as mean ± standard deviation, whereas in Figures 2 and 3 and in Figure S1, means and standard error of the means are illustrated.

Results

Data sets

Twenty-three women were excluded because they did not complete all three measurements during the OGTT. Reasons for drop-out were discontinuation according to dizziness (nine women; two GDM) or insufficient detection of signals (ten women; two GDM) during fMEG-/fMCG-measurement, missing blood samples (two women), present insulin therapy (one woman) and fetal heart defect detected after birth (one woman). Hence, the analysed study cohort included 49 pregnant women in at least the 27th week of gestation. Thirty-six were healthy women (NGT group) and 13 were diagnosed with gestational diabetes (GDM group). Further clinical characteristics are shown in Table 1.

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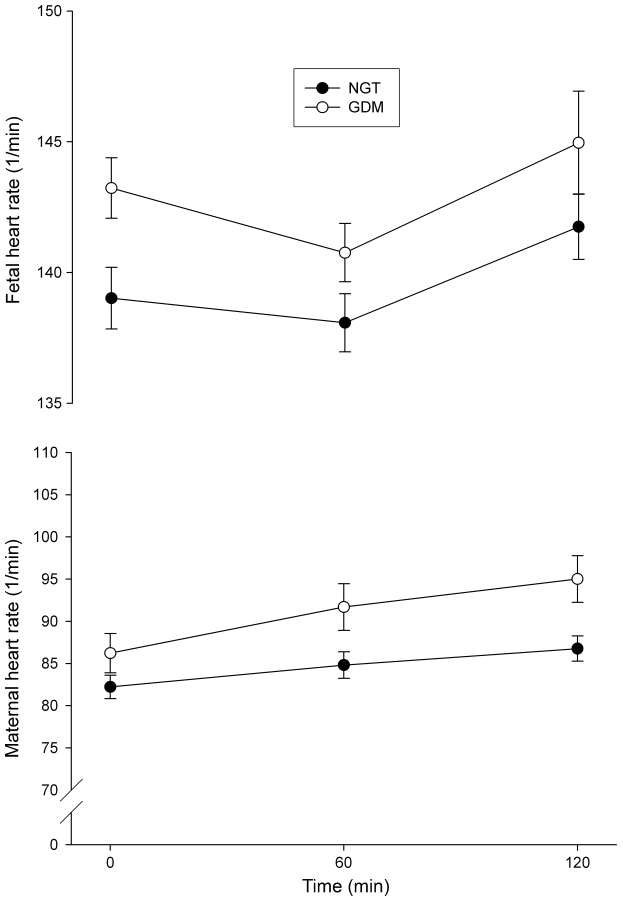

Figure 2. Mean maternal heart rate ± standard error of the mean versus mean fetal heart rate ± standard error of the mean within the three measurements.

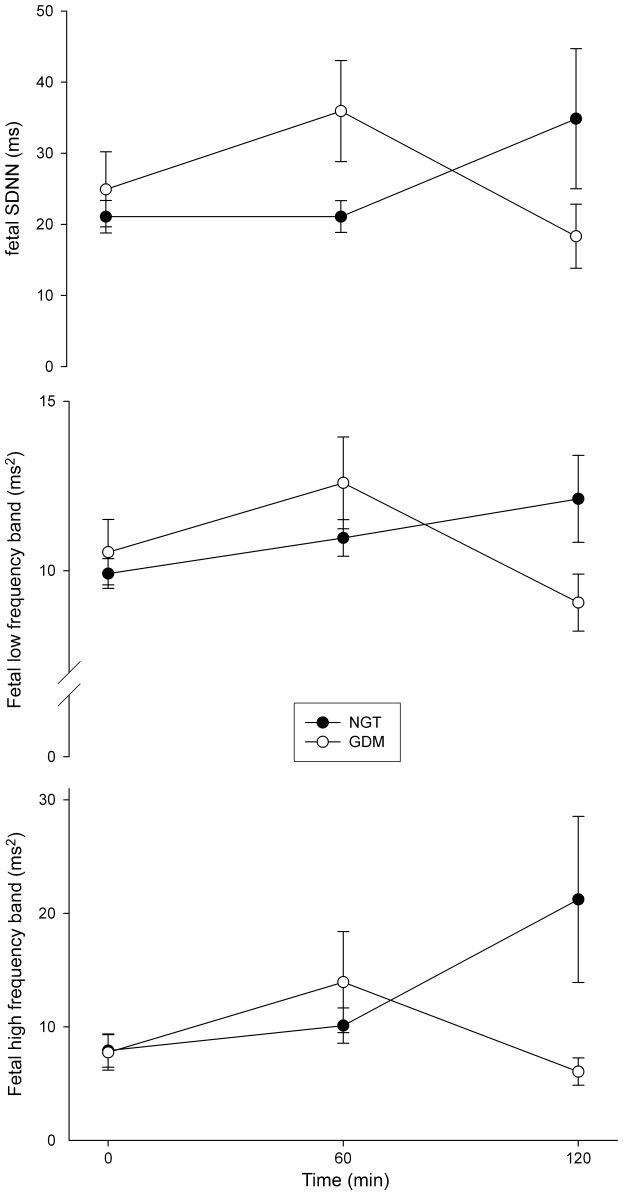

Figure 3. Mean values of fetal heart rate patterns ± standard error of the mean in the three measurements.

Glucose metabolism

Blood values are summarised in the Supplementary material (Table S1, Figure S1). Glucose and insulin levels significantly increased over time in both groups ($P < 0.001$). By definition, glucose ($P < 0.001$) and insulin levels ($P = 0.039$) were higher in women with GDM. Regarding time and group interaction, the increase in blood glucose and insulin levels after oral glucose intake was higher in the GDM group compared with the NGT group ($P < 0.001$ and $P = 0.043$, respectively).

Maternal HRV

After glucose intake the mean heart rate tended to accelerate in both groups of women. However, no significant main effect for time was observed regarding mean heart rate or any other heart rate pattern over time. A significant main effect for group was observed as GDM compared with those with NGT showed a higher heart rate ($P = 0.023$, see Figure 2 and Table S2).

Spectral analysis revealed neither a significant difference in maternal HRV between women with GDM and NGT at baseline nor a significant effect of oral glucose load on maternal HRV (Table S2). For LF/HF, a significant time × group interaction was observed ($P = 0.041$). However, this was mainly driven by a difference in basal LF/HF.

Fetal HRV

Throughout the OGTT, fetal heart rate significantly changed (main effect time, $P = 0.005$). After oral glucose load, fetal heart rate tended to decrease from baseline fMCG measurement (NGT 139.0 ± 7.1/minute versus GDM 143.2 ± 4.2/minute) to second fMCG measurement (NGT 138.1 ± 6.7/minute versus GDM 140.8 ± 4.0/minute) and

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increased in the third fMCG measurement 95–110 minutes after oral glucose load (NGT 141.8 ± 7.5/minute versus GDM 145.0 ± 7.1/minute) (Figure 2).

Mean fetal heart rate was higher in fetuses of mothers with GDM compared with fetuses of mothers with NGT in all three measurements ($P = 0.005$, Table 2). No significance was detected when testing for the effect of time × group interaction.

Concerning time and frequency domains of HRV, no significant main effect for group or time was observed. However, regarding time × group interaction, a significant difference between fetuses of mothers with GDM and NGT in SDNN ($P = 0.012$), LF ($P = 0.008$) and HF ($P = 0.031$) was observed (Figure 3 and Table 2).

The SDNN was rising in the NGT group after glucose intake (first fMCG 9.9 ± 2.6 ms; second fMCG 11.0 ± 3.2 ms; third fMCG 12.1 ± 7.7 ms) whereas in the GDM group it was initially rising and then dropped in the third measurement beneath baseline level (first fMCG 10.5 ± 3.5 ms; second fMCG 12.6 ± 4.9 ms; third fMCG 9.1 ± 3.0 ms; Figure 3).

In the frequency domain analysis similar differences were observed. At baseline, absolute values of LF and HF were in a similar range in all participants. After maternal glucose intake, absolute values of both frequency bands were increasing from baseline to final measurement in the fetuses of NGT group (LF: first fMCG 21.1 ± 13.7 ms^2, second fMCG 21.1 ± 13.4 ms^2, third fMCG 34.9 ± 59.0 ms^2; HF: first fMCG 7.9 ± 8.7 ms^2, second fMCG 10.1 ± 9.3 ms^2, third fMCG 21.2 ± 43.9 ms^2). In contrast, in the fetuses of mothers with GDM both LF and HF bands were similarly increasing in the first hour after glucose intake but decreased in the second hour of the OGTT (LF: first fMCG 24.9 ± 19.1 ms^2, second fMCG 35.9 ± 25.6 ms^2, third fMCG 18.3 ± 16.3 ms^2; HF: first fMCG 7.8 ± 5.6 ms^2, second fMCG 14.0 ± 16.0 ms^2, third fMCG 6.1 ± 4.3 ms^2). Results of the endpoint measurement of GDM group were even below baseline values in both groups (Figure 3).

Table 1. Clinical characteristics of the study group

	NGT (mean ± SD)	GDM (mean ± SD)	Range	*P*-value
Maternal age (years)	32.44 ± 4.68	34.54 ± 4.63	24–44	0.172
Previous pregnancies	1.58 ± 0.69	2.62 ± 1.71	1–5	**0.006**
Previous childbirth	0.31 ± 0.47	0.85 ± 0.80	0–2	**0.007**
Gestational age (weeks)	30.78 ± 2.73	30.38 ± 2.75	28–36	0.659
Maternal height (cm)	167.31 ± 6.31	164.23 ± 6.31	152–184	0.139
Maternal BMI before pregnancy (kg/m^2)	23.78 ± 4.24	27.96 ± 6.37	17.63–41.74	**0.012**
Maternal BMI during measurement (kg/m^2)	26.90 ± 3.87	31.78 ± 6.28	19.56–45.54	**0.002**
Relative maternal BMI gain per week (kg/m^2/week)	0.10 ± 0.04	0.12 ± 0.05	0.01–0.21	0.115
Fetal length (cm)	50.64 ± 3.33	51.46 ± 2.26	40–56	0.568
Fetal weight (g)	3384.44 ± 518.70	3547.69 ± 471.49	1690–4410	0.347

BMI, body mass index; SD, standard deviation. Significant *P*-values are printed in bold font.

Table 2. Results of fetal heart rate patterns during OGTT

	First fMCG (mean ± SD)		Second fMCG (mean ± SD)		Third fMCG (mean ± SD)		*P*-value		
	NGT	GDM	NGT	GDM	NGT	GDM	Time	Group	Time × Group
MeanHR (1/min)	139.0 ± 7.1	143.2 ± 4.2	138.1 ± 6.7	140.8 ± 4.0	141.8 ± 7.5	145.0 ± 7.1	**0.005**	0.060	0.734
MeanRR (ms)	433.6 ± 22.0	420.6 ± 12.4	436.5 ± 21.2	427.9 ± 12.2	426.1 ± 24.2	415.6 ± 19.4	**0.006**	0.052	0.745
SDNN (ms)	9.9 ± 2.6	10.5 ± 3.5	11.0 ± 3.2	12.6 ± 4.9	12.1 ± 7.7	9.1 ± 3.0	0.657	0.845	**0.012**
RMSSD (ms)	6.1 ± 2.6	5.9 ± 1.8	7.3 ± 2.9	8.1 ± 4.1	8.6 ± 6.8	5.7 ± 1.7	0.841	0.624	0.072
LF (ms^2)	21.1 ± 13.7	24.9 ± 19.1	21.1 ± 13.4	35.9 ± 25.6	34.9 ± 59.0	18.3 ± 16.3	0.426	0.590	**0.008**
HF (m^2)	7.9 ± 8.7	7.8 ± 5.6	10.1 ± 9.3	14.0 ± 16.0	21.2 ± 43.9	6.1 ± 4.3	0.666	0.693	**0.031**
LF/HF	4.0 ± 2.5	3.8 ± 1.7	2.9 ± 1.7	4.2 ± 2.8	2.5 ± 1.5	3.4 ± 1.9	0.149	0.184	0.162

P-values of SDNN, RMSSD, LF, HF and LF/HF are shown for calculations with logarithmic values. Significant *P*-values are printed in bold font.

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Discussion

Main findings

Maternal glucose metabolism is shown to impact on the fetal central nervous system as alterations in auditory evoked fetal brain responses were detected in pregnancies involving GDM during oral glucose load.[9,10] In that context, the present study was designed to yield further evidence regarding influences of maternal blood glucose levels and insulin sensitivity on fetal parameters with a specific focus on the ANS. During an OGTT, we assessed the activation state of the ANS by monitoring maternal and fetal heart rate patterns using fMCG recording. We observed HRV in the fetuses of mothers with GDM to be differently affected postprandially compared with fetuses of mothers with NGT. We found evidence that the autonomic nervous function is already influenced in the fetal state by the maternal metabolism being revealed by oral glucose load.

Strengths and limitations

One strength of the present study is that we were able to monitor simultaneously fetal and maternal parameters of HRV in metabolically precisely characterised women using a five-point OGTT. To adequately detect HRV signals, women have to place the abdomen in the convex sensor shape during the measurements in advanced pregnancy. Discontinuation of participants due to dizziness during the procedure or inadequate detection of signals were the main reasons for drop-out. This has led to a relatively high drop-out rate of 32%.

Little is known about alterations of HRV in the fetal period in general. In fetuses, HRV has consistently been shown to increase throughout gestation.[13,22] Mean fetal heart rate significantly decreases with progress of pregnancy.[22,23] These observations are thought to reflect a gain of vagal influence, maturation of the fetal nervous system, and hence overall fetal development.[13,14] Furthermore, fetal HRV as such depends on multiple influences including maternal blood pressure, thermoregulation and respiration as well as fetal behavioural, activation and sleeping states.[15,24] However, no significant differences in HRV were observed for time of day and fetal gender.[25]

Interpretation

In mothers with GDM, we observed a higher heart rate before and during the OGTT compared with mothers with NGT. Previous research in adults showed a positive correlation of glucose intake, plasma insulin levels and functional changes in the ANS. As blood levels of glucose and insulin rose, mean heart rate increased.[26,27] This is thought to be related to a concomitant sympathetic activation.[28]

Patients with overt diabetes as well as those with subclinical glucose intolerance were shown to have a generally higher resting heart rate compared with healthy individuals.[29] A higher heart rate has also been detected in women with GDM compared with control women.[30] As women with GDM had higher levels of blood glucose and plasma insulin compared with the NGT group in the present study, our findings corroborate the presumed interactions of hyperglycaemia and/or hyperinsulinaemia and sympathetic activation.

Therefore the present trial is in line with earlier studies showing that maternal acute hyperglycaemia and hyperinsulinaemia induce a shift of sympathovagal balance toward sympathetic activation. As no significant inter-group differences in HRV were detected, chronic hyperglycaemia, as seen in overt diabetes, might be needed to cause detectable differences in HRV. Of note, in a previous study a decreased HRV was seen in women with GDM years after pregnancy, suggesting that this parameter is predictive for pre-type 2 diabetes.[31]

Regarding the results of fMCG recordings in the current trial, we found fetal heart rate to be increased after maternal glucose ingestion. This is consistent with most previous investigations in healthy women and women with diabetes.[32–34] Recently, accelerations of fetal heart rate have been shown to correlate with high glucose levels of mothers with diabetes.[35] Basal fetal heart rate was higher in pregnancies complicated by GDM compared with the control group of this study, but only as a trend. However, the fact that not all studies detected an interaction of fetal heart rate patterns and blood glucose levels might be due to differences in glucose supply and study design.[36]

Remarkably, the present study demonstrated significant differences in the course of fetal HRV during OGTT between fetuses of mothers with GDM and fetuses of mothers with normal glucose metabolism (control group). SDNN, LF and HF were almost continuously rising postprandially during the OGTT in the control group. In contrast, in the fetuses of the GDM group SDNN, LF and HF were initially rising in the first hour of the OGTT and then decreasing in the third measurement 120 minutes after glucose intake beneath baseline level (Figure 3). These findings indicate altered fetal HRV being revealed under conditions of metabolic stress, as hyperglycaemia, in pregnancies complicated by GDM. Specifically, a reduced SDNN as well as reduced HF and LF bands indicate alternations of the ANS of the fetus during postprandial hyperglycaemia and hyperinsulinaemia.

Reduced fetal HRV is associated with deteriorated fetal outcome and disturbed fetal neurodevelopment.[13] These results are of high relevance indicating that fetuses of

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pregnancies involving GDM might have a lower capacity for compensation of adverse influences.

Moreover, peripheral insulin sensitisation has been associated with alterations of HRV in adults. Remarkably, insulin sensitivity has been found to correlate with an increase of the HF band in adults,[37] suggesting that the observed decrease of the fetal HF band could reflect reduced insulin sensitivity in fetuses of pregnancies involving GDM. Importantly, it has also been demonstrated that individual fetal heart rate and fetal HRV are associated with mental, psychomotor and language abilities in the first years after birth, suggesting prognostic factors at least for early childhood.[38] Recently, a study has been published showing changes in HRV in neonates of women with type 1 diabetes,[39] supporting our thesis of a causal role of *in utero* exposure to higher glucose levels and presenting evidence regarding persistent changes in HRV.

Because we found changes during OGTT between brain and ANS responses in fetuses of mothers with and without gestational diabetes,[40] we performed an exploratory correlation analysis of the changes in fetal brain responses and fetal ANS. We did not find any significant correlations in the postprandial state. This is in line with the current knowledge of the interaction of early evoked brain responses and ANS changes. Lyytinen et al.[41] showed that auditory evoked mismatch responses are not associated with changes in the ANS.

Conclusions

In conclusion, the current investigation revealed alterations in HRV in fetuses of mothers affected by GDM after glucose load. In fetuses of the GDM group, the ANS responded differently when exposed to metabolic stress than in fetuses of mothers with NGT. This is in line with previous results of our group showing that in fetuses of mothers with GDM the central nervous system responded differently to oral glucose load compared with healthy pregnancies. Our findings, in context with previously described interactions, emphasise the importance of good glycaemic control and frequent clinical surveillance of mother and child. Current observations encourage strict diagnostic criteria for GDM and overt diabetes during pregnancy to avoid potential functional alterations of the fetal central and autonomic systems. To determine whether these findings reflect acute changes or if they result in long-term clinical complications, further investigations are needed.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

EF and KW contributed equally to this work, they were involved in the design of the study, data acquisition and analysis and interpretation of data. EF drafted the article. LF, KL, HMH, FS and MW were involved in data acquisition. HUH contributed to interpretation of the data and revised the article. ISK, SB, HP and AF contributed to the conception and design of the study and to the analysis and interpretation of data and revised the article. All authors approved the current version of the article. AF is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Details of ethics approval

This study was approved on 26 August 2010 by the Ethics Committee of the Medical Faculty of the Eberhard Karls University of Tübingen, Germany (reference number 339/2010BO1).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Mean maternal glucose and insulin levels ± standard error of the mean within the three measurements.

Table S1. Results of the blood withdrawals during OGTT.

Table S2. Results of maternal heart rate patterns during OGTT. ■

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