Heart rate variability in fetuses of type 1 diabetes pregnancies

Introduction

Type 1 diabetes mellitus (T1D) is characterized by a lack of production of insulin, leading to high blood sugar levels. Its prevalence has doubled since 1980, and it affects up to 8.5% of the world's population.

T1D in pregnant women is associated with short- and long-term adverse effects for the fetus and neonate, such as cardiac structural and functional abnormalities [1]. The theory of fetal programming suggests that alterations of intrauterine life may predispose to certain disorders throughout later life [2]. Studies have shown significant cardiac structural changes in fetuses, including evidence of septal and right ventricular free wall hypertrophy, during the third trimester of pregestational diabetic pregnancy compared with normal controls [3].

One way to evaluate cardiovascular regulation is by analysis of heart rate variability (HRV). This is used to non-invasively measure regulation of the cardiovascular system by the autonomic nervous system (ANS). HRV is related to changes in the time interval between two heartbeats [two R waves on electrocardiography (ECG)], and reflects activity of the sympathetic and parasympathetic nervous systems at the sinus node. Spectral analysis is a tool for evaluating HRV. High frequency (HF) HRV ($>$ 0.15 Hz) is under the control of the parasympathetic system only, whereas low frequency (LF) HRV corresponds to the effect of both parasympathetic and sympathetic activity (0.04–0.15 Hz) [4].

The in-utero environment has lasting effects on fetal and neonatal HRV. Persistent autonomic dysfunction has been described in low-birth-weight babies over a 9-year follow-up. In diabetic mothers, Russell et al. [5] reported decreased HRV in neonates, with a shift towards sympathetic predominance.

Yet, no study has evaluated fetal HRV in diabetic mothers. Thus, the aim of the present study was to analyze HRV in fetuses of pregnant mothers with T1D and to compare them with the non-diabetic population. As our team has previously developed and tested, in women during labour, a Fetal Stress Index (FSI) specifically related to fetal parasympathetic activity [6], the present study also secondarily evaluated this index.

Materials and methods

This was a prospective observational study carried out at a tertiary level hospital and approved by the research ethics committee (CROG 2014-10-01). All patients signed a consent form.

Population

Women with T1D and singleton pregnancy were eligible for inclusion. Glycosylated haemoglobin (HbA_{1c}) was measured during the first, second and third trimesters. Data on preconception HbA_{1c} levels were retrieved from patients' medical files, and have been expressed in both traditional units and in mmol/mol, as recommended by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC).

For comparison, healthy (non-diabetic) controls were recruited at the emergency department. Women with uneventful singleton pregnancies were eligible for inclusion. Healthy controls were matched with the T1D group by gestational age. Exclusion criteria were gestational diabetes, type 2 diabetes, abnormal amniotic fluid index, fetal malformation, fetal growth restriction and macrosomia. Both groups were adjusted for gestational age.

To avoid confounding bias, patients with a pain and anxiety analogue visual scale score $>$ 5/10 were excluded. It is likely that pain and anxiety are confounding parameters when analyzing HRV, as both are associated with ANS dysfunction.

Description of the HRV analytical method

Cardiotocography (CTG) recordings of fetal heart rate (FHR) were made at study inclusion for every patient regardless of gestational age. Continuous FHR recordings were done with ultrasound probes and a Series 50 Fetal Monitor (Philips NV, Amsterdam, Netherlands) connected to a classic personal computer for data acquisition and storage. The analysis was done *a posteriori*. In contrast to the commonly used time–frequency transforms, wavelet transforms can analyze non-stationary signals, allowing assessment of transient and rapid changes in HRV. The R–R series HF spectral component was then measured from level 1 (mid-frequency of 2.667 Hz) to level 5 (mid-frequency of 0.167 Hz) by summing the squared wavelet coefficients on each level. LF power was estimated by summing the squared wavelet coefficients of levels 6 and 7 (mid-frequencies of 0.042 Hz and 0.083 Hz, respectively).

To reduce intersubject variability, HF and LF can also be measured as relative values. The relative HF (HFn.u.) was therefore computed as the value of the HF spectral component divided by total power minus the very low frequency (VLF) component: HFn.u. = HF/(HF + LF). The LF/HF ratio was also computed as an indicator of sympathovagal imbalance.

FSI was obtained through a specific algorithm, as previously described [6]. Briefly, the FSI uses spectral analysis to filter the signal to keep only HF oscillations and then computes oscillation magnitude in the time domain.

Statistical analysis

Two groups were compared in our study: fetuses of diabetic mothers; and fetuses of control mothers. All measurements were adjusted for gestational age. Statistical analyses were performed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Groups were compared by Mann–Whitney non-parametric test. Qualitative data were analyzed using a chi-squared test. Data are presented as medians (quartile 1–quartile 3) or as numbers (percentages). Significance was defined by a P value $<$ 0.05.

Results

A total of 26 patients with T1D and 26 healthy controls were recruited. Computed CTG recordings were made from weeks 27 to 38.

There were no significant differences between groups for gestational age at inclusion, parity or body mass index (BMI). However, there was a significant difference in maternal age, with diabetic mothers being older [age 34 (31–37) years *vs.* 30 (25–33.5) years for controls; P = 0.006].

Maternal glycaemic control was satisfactory throughout pregnancy, with a median HbA_{1c} level of 6% (42 mmol/mol). The rate of fetal macrosomia was 42.3% in the diabetes group.

Spectral analysis showed that the fetuses of diabetic mothers had similar HF and LF components as the control group (Table 1). However, in the diabetes group, there was a significant increase in

Abbreviations: ANS, autonomic nervous system; AUC, area under the curve; BMI, Body Mass Index; CTG, cardiotocography; FECG, fetal electrocardiography; FHR, fetal heart rate; FSI, Fetal Stress Index; HF, high frequency; HRV, heart rate variability; LF, low frequency; NICU, neonatal intensive care unit; VLF, very low frequency.

Table 1
Heart rate variability in the control and type 1 diabetes mellitus (T1D) groups.

Parameters	Controls (n = 26)	T1D (n = 26)	P
LF	0.058 (0.046–0.101)	0.046 (0.030–0.097)	0.220
HF	0.013 (0.009–0.021)	0.011 (0.007–0.027)	0.728
HF/(HF + LF)	0.181 (0.160–0.201)	0.205 (0.178–0.231)	0.017
LF/HF ratio	5.03 (4.26–6.12)	4.16 (3.61–4.99)	0.012
Fetal Stress Index	50.6 (47.4–53.1)	51 (48–54)	0.400

Data are presented as medians (quartile 1–quartile 3). LF: low frequency; HF: high frequency.

HFn.u. [from 0.181 (0.160–0.201) to 0.205 (0.178–0.231); P = 0.017] and a decreased LF/HF ratio [from 5.03 (4.26–6.12) to 4.16 (3.61–4.99); P = 0.012]. No significant difference was found on FSI analysis between the control and diabetes groups [50.6 (47.4–53.1) and 51 (48–54), respectively].

Discussion

Altered maternal glucose metabolism has been shown to impact fetal brain and cardiac development, yet evaluation of its impact on fetal HRV and ANS has previously not been performed, whereas it is well documented in neonates and children [5,7]. In fact, our present study has found that the fetuses of diabetic mothers show evidence of altered HRV, with a decreased autonomic ratio suggestive of a shift towards parasympathetic predominance.

Fetal HRV is reported to be a reliable indicator of fetal well-being. HRV is a diagnostic and prognostic tool for assessing cardiac autonomic function, and the ANS regulates HRV through sympathetic and parasympathetic activity. The ratio of LF to HF band power provides a marker of sympathovagal balance [8]. HRV has also been shown to increase throughout the course of gestation, while the mean FHR decreases [8]. These changes reflect maturation of the fetal nervous system and an increase in vagal influence, a significant part of which takes place between 30 and 35 weeks of gestation. In normal fetuses, Van Laar et al. [8] demonstrated that the LF/HF ratio displayed a trend towards lower values as pregnancy progressed, indicating that the increase in HF band power was greater than in the LF band. In fact, the influence of sympathetic control becomes increasingly unbalanced beyond 30 weeks of gestation until term. However, in our study group, this gestational age correlation with ANS maturation was not observed, thereby leading to the assumption that fetal HRV might be an early indicator of altered cellular metabolic activity.

Several studies have analyzed HRV in diabetic populations of neonates, children and adults, but none were in antenatal settings [5,7]. In the neonatal period, Russell et al. [5] reported contradictory results, with decreased HRV in neonates of diabetic mothers and a significant shift towards sympathetic predominance compared with the normal cohort. Recordings were made between 1 and 6 days post-delivery, suggesting a possible adaptive mechanism for life *extra utero*. Kardelen et al. [7] found that overall HRV was markedly depressed in 47 children with insulin-dependent T1D compared with 46 healthy controls. According to our present results and those of the above-mentioned previous studies, a difference in autonomic balance can also be observed but with a shift towards parasympathetic predominance, in contrast to findings in children and adults. This could be due to the impaired neonatal transitional haemodynamics linked to cardiovascular and cerebrovascular immaturity, as suggested by Schierz et al. [9].

Our study also analyzed the FSI. In our previous work, it was revealed that, during labour, this index correlates well with the US National Institute of Child Health and Human Development FHR classification, and could be used to predict the onset of FHR abnormalities [6]. In the present study, there was no difference in FSI values between the control and diabetes groups.

To our knowledge, this was the first study to document antenatal fetal HRV in T1D pregnant mothers using spectral analysis. Nevertheless, this work has some limitations. First, all recordings were made at a single time point and not repeated during the pregnancy. Second, analysis of HRV was obtained with the use of CTG and not fetal electrocardiography (FECG). Spectral analysis of fetal HRV can be used to monitor fetal ANS, particularly during labour, as proposed by various teams [8]. Analysis of fetal HRV as a clinical routine procedure differs substantially from analysis of postnatal HRV. Fetal heart activity is generally monitored by CTG, which estimates the fetal cardiogram based on evaluation of ultrasound pulses reflected from the fetal heart. CTG delivers the momentary heart rate with limited accuracy, and our low sampling rate could have further reduced the statistical significance of the results. FECG, registered during birth using a scalp electrode, delivers a signal of high temporal resolution, allowing accurate beat-to-beat HRV analysis. At present, there is no FECG device routinely used in antenatal clinics.

The final study limitation was that maternal glycaemic control was monitored through the HbA_{1c}, which is a retrospective parameter of glycaemia. A maternal HbA_{1c} level $\leq$ 6% (42 mmol/mol) was considered adequate for glycometabolic control. Continuous glucose monitoring appears to be a promising tool for improving metabolic control, and several teams using such devices have shown that HRV is related to glucose blood concentrations [10]. Further studies are now needed to confirm whether fetal HRV is indeed related to variations of maternal blood glucose concentration.

Conclusion

Our present study has found evidence of a significant shift towards parasympathetic predominance in the fetuses of T1D mothers. It would be of interest to correlate exposure of the developing heart to fluctuations in maternal glycaemia with subsequent alterations in fetal HRV.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgments

M. Flocteil collected data. J. de Jonckheere did the statistics, contributed to discussion and reviewed the manuscript. C. Garabedian and Y. Hamoud researched the data and wrote the manuscript. L. Storme, P. Deruelle, A. Vambergue and V. Houfflin-Debarge contributed to the discussion and reviewed the manuscript.

Dr Charles Garabedian is the guarantor of this work and, as such, had full access to all the data in the study and takes full responsibility for the integrity and accuracy of the data analysis.

References

[1] Vambergue A, Fajardy I. Consequences of gestational and pregestational diabetes on placental function and birth weight. World J Diabetes 2011;2:196–203.
[2] Plagemann A. Maternal diabetes and perinatal programming. Early Hum Dev 2011;87:743–7.
[3] Pauliks LB. The effect of pregestational diabetes on fetal heart function. Expert Rev Cardiovasc Ther 2015;13:67–74.
[4] Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J 1996;17:354–81.
[5] Russell NE, Higgins MF, Kinsley BF, Foley ME, McAuliffe FM. Heart rate variability in neonates of type 1 diabetic pregnancy. Early Hum Dev 2016;92:51–5.
[6] Garabedian C, Butruille L, Servan-Schreiber E, Ficheur G, Storme L, Deruelle P, et al. Fetal heart-rate variability: validation of a new continuous, noninvasive

computerized analysis. Gynecol Obstet Invest 2016. http://dx.doi.org/10.1159/000452668 [Epub ahead of print].
[7] Kardelen F, Akçurin G, Ertuğ H, Akcurin S, Bircan I. Heart rate variability and circadian variations in type 1 diabetes mellitus. Pediatr Diabetes 2006;7:45–50.
[8] Van Laar JOEH, Porath MM, Peters CHL, Oei SG. Spectral analysis of fetal heart rate variability for fetal surveillance: review of the literature. Acta Obstet Gynecol Scand 2008;87:300–6.
[9] Schierz IAM, Pinello G, Piro E, Giuffrè M, La Placa S, Corsello G. Transitional hemodynamics in infants of diabetic mothers by targeted neonatal echocardiography, electrocardiography and peripheral flow study. J Matern Fetal Neonatal Med 2017;1–8.
[10] Iwasaki S, Kozawa J, Fukui K, Iwahashi H, Imagawa A, Shimomura I. Coefficient of variation of R-R interval closely correlates with glycemic variability assessed by continuous glucose monitoring in insulin-depleted patients with type 1 diabetes. Diabetes Res Clin Pract 2015;109:397–403.

Y. Hamoud[a,b,*], J. de Jonckheere[a,c], A. Vambergue[a,d], V. Houfflin-Debarge[a,b], L. Storme[a,e], M. Flocteil[c], P. Deruelle[a,b], C. Garabedian[a,b]

[a]*Univerisy of Lille, EA 4489, Perinatal Environment and Health, 59000 Lille, France*
[b]*CHU Lille, Department of Obstetrics, 59000 Lille, France*
[c]*CHU Lille, CIC-IT 1403, 59000 Lille, France*
[d]*CHU Lille, Department of endocrinology and diabetes, 59000 Lille, France*
[e]*CHU Lille, Department of Neonatology, 59000 Lille, France*

*Corresponding author. CHU Lille, Department of Obstetrics, Avenue Eugène-Avinée, 59037 Lille cedex, France
E-mail address: hamoud.yasmine@gmail.com (Y. Hamoud)

Received 25 June 2017
Accepted 2 July 2017
Available online 31 July 2017

http://dx.doi.org/10.1016/j.diabet.2017.07.002

Diabetes-related distress is reduced in people with type 1, but not type 2 diabetes after participating in a diabetes treatment and teaching programme

Abbreviations

DM1	diabetes mellitus type 1
DM2	diabetes mellitus type 2
DTTP	diabetes treatment and teaching programme
HbA1c	glycated haemoglobin
PAID	Problem Area in Diabetes Scale

Introduction

The importance of participating in a structured diabetes treatment and teaching programme (DTTP) on metabolic control and quality of life in patients with diabetes was raised as early as 1985 by Assal et al. [1]. In addition, the German guidelines for psychosocial well being in diabetes recommend offering all patients with diabetes and a heavy diabetes-related psychological burden the opportunity to participate in a specific DTTP to reduce distress [2]. In particular, a DTTP should be provided if there are worries about the development of complications (such as blindness, amputation) and the patient feels overwhelmed.

The aim of this prospective, longitudinal study was to assess diabetes-related distress in patients with diabetes mellitus type 1 (DM1) or type 2 (DM2) at baseline and to evaluate whether their burden and distress were reduced after participation in a DTTP. Furthermore, metabolic control as a secondary outcome was compared before and after the DTTP.

Research design and methods

All individuals who participated in a DTTP at a university department of endocrinology and metabolic diseases outpatients' clinic during the investigation period (1 January to 31 December 2014) were interviewed before (T0), immediately after (T1) and 6 months after (T2) participation in the DTTP. Inclusion criteria were age $\geq$ 18 years and a diagnosis of either DM1 or DM2. Those with intermediate hyperglycaemia, pregnant women and people who did not understand the German language were excluded. All included patients gave their informed consent to participate.

All participants attended a structured, problem-orientated DTTP (devised by Grüßer and Jörgens). The DTTPs were conceived as group sessions and aimed to support the self-management skills of diabetes patients in everyday life, but also included lessons concerning self-measurement of urine/blood glucose, nutrition, physical activity and diabetes complications. Insulin injection and dose adjustment were further elements for those on insulin therapy.

Diabetes-related burden was assessed with the Problem Area in Diabetes (PAID) scale, a 20-item questionnaire wherein each question is scored from 0 to 4, with 0 = no problem and 4 = a serious problem, and a possible range of 0–100 points. Higher scores indicate more diabetes-related distress, and a PAID score $\geq$ 40 is considered to reflect high diabetes-related distress.

Diabetes-related quality of life was assessed using the evaluated Audit of Diabetes-Dependent Quality of Life (ADDQoL) questionnaire, with scores ranging from -9 to +3. Lower scores are associated with poorer diabetes-related quality of life.

The World Health Organization (Five) Well-Being Index (WHO-5) consists of five questions and assesses current well-being as well as mental health. Each item can be scored from 0 to 5 points, resulting in a total score of 0 to 25. Higher scores are associated with greater well-being.

Satisfaction with diabetes treatment was evaluated by the Diabetes Treatment Satisfaction Questionnaire (DTSQ) for status (score range: 0–36), with higher scores indicating greater treatment satisfaction. In addition, changes in diabetes treatment satisfaction (DTSQc) were assessed immediately after participating in the DTTP at visit T1 (range: -18 to +18), with higher scores indicating greater treatment satisfaction after the intervention.

Clinical and laboratory data were collected from the patients' electronic records on the day of each visit (T0, T1 and T2) by each individual patient. Three to six months prior to the study, participants were instructed to document all episodes of hypoglycaemia. Non-severe hypoglycaemia was defined as the presence of typical symptoms (sweating, poor concentration, feeling shaky) that disappeared quickly after carbohydrate intake, or a plasma glucose $\leq$ 3.9 mmol/L with no symptoms. Severe hypoglycaemia was defined as a need for glucagon or intravenous glucose injection. HbA1c was adjusted to the mean normal value of healthy people (5.05%, 32 mmol/mol) from the Diabetes Control and Complications Trial.

Statistical analyses

All analyses were performed using IBM SPSS Statistics 21.0 software (IBM Corp., Armonk, NY, USA). All continuous data