Influence of Gestational Diabetes on Fetal Heart Rate in Antepartum Cardiotocographic Recordings

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Abstract

In pregnancy, diabetes is known to increase the risk of adverse maternal and neonatal outcomes. It would be beneficial to find techniques that allow early investigation of the physio-pathological mechanisms involved to provide clinicians with tools for prevention and therapies. For that, cardiotocography (CTG) is a promising tool. However, the evidence is still scarce and the impact on clinical practice little. In this study, we aim at characterizing the changes induced by gestational diabetes (GDM) on the fetal heart rate series. To do so, we performed a retrospective cohort study on a CTG dataset containing more than 20000 recordings of which 852 belong to 301 GDM-diagnosed patients. We divided the recordings by gestational age (G.A.) into 4 groups (weeks: 31-35, 36, 37, 38 to delivery) and for each we identified a control population of equal size matched by comorbidities. We analyzed a comprehensive set of parameters from the time domain, frequency domain and non-linear analysis and assessed variations in median values on each feature. For all G.A. below the 38th week, we found a significant increase in the power in the movement frequency band ($p<0.01$) and an increase in the absolute value of Deceleration Reserve ($p<0.01$) in GDM vs control. Other significant values were also identified and are discussed in more detail in the paper.

1. Introduction

Gestational diabetes mellitus (GDM) is one of the most common medical conditions in pregnancy, and its prevalence is increasing. It has been proven to increase the risks for both the mother and the fetus, although they can be reduced by proper glycemic control [1]. Since it is considered a risk factor, women diagnosed with GDM are usually prescribed an antepartum cardiotocography (CTG) examination. CTG exam consists in the synchronous registration of the fetal heartbeat taken from a Doppler Ultrasound Probe in the mother abdomen and the Toco Signal, which measures uterine contractions [2].

The scientific literature concerning the impact of GDM on cardiotocographic traces is still scarce. In particular, there is a lack of studies including a large number of subjects and a comprehensive analysis of the signal. Indeed, the International Federation of Gynecology and Obstetrics marks the quality of evidence for the use of CTG in pregnancies complicated by GDM as very low, even though it gives a strong recommendation for its use [1]. In this study, we aim to address the aforementioned problem by comparing a comprehensive set of parameters between a large population of GDM-diagnosed patients and a matched control group at different gestational ages (G.A.) to investigate which parameters better quantify the effects of the maternal dysmetabolic condition on the fetal hear rate (fHR). We hypothesize that these parameters may be used for risk stratification and predictors of pregnancy outcome and aim at testing it in future studies. Furthermore, the physiological interpretability of the computed parameters should allow making hypotheses on the physio-pathological mechanisms involved.

2. Methods

2.1. Database description

The dataset used in this study is described in detail in [3]. It contains 21565 recordings obtained between 2013 and 2021 at Federico II University Hospital in Naples, Italy. The signal of interest in this study is the fetal heart rate (fHR) which is read by the tocograph with a sampling frequency of 2Hz. A quality index (good, acceptable, poor) is provided for every fHR sample. Each recording was annotated by specialized clinicians that were instructed to report every known maternal or fetal pathology. The diagnosis of GDM is made based on the results of the 1-step glucose tolerance test that is routinely performed in Italy even in the absence of risk factors (unless there is a pre-existing diagnosis of pre-gestational diabetes) [4].

From the complete dataset, we excluded the recordings annotated as twin pregnancies and/or fetal pathologies and selected only the recordings made after the 30th gestational week. All recordings are at least 20 minutes long. A total of 12369 recordings belonging to 5185 subjects survived the exclusion criteria. Among those, 852 recordings belonging to 301 subjects were annotated as GDM.

2.2. Data Balancing

The diabetic population has some differences compared with controls that may act as confounding factors in further analyses: GDM is associated with other conditions such as hypertension and obesity [1] and GDM-diagnosed women usually undergo cardiotocographic monitoring before non-diabetic women. To minimize this effect, we divided the dataset into 4 groups according to gestational age (weeks: 31 - 35, 36, 37, 38 to delivery). We then divided each group into "Diabetic" and "Non-diabetic" and downsampled the latter to obtain a control population of the same size balanced for conditions correlated and non-correlated with diabetes. The classification of maternal conditions as correlated or not with diabetes was done with the help of a Gynecologist. The most common comorbidities identified were obesity and hypertension. When the balancing was impossible to obtain only by downsampling the non-diabetic population the diabetic population was also down sampled. Repeated measurements on the same subject in the same group were excluded to ensure the independence of samples.

2.3. Parameters computation

We computed the set of parameters listed in Table 1, which also include relevant references for their definition and computation. Regarding PRSA-related parameters, the PRSA signal was calculated from the fHR series expressed in bpm in agreement with [5,6]. When comparing results, it should be noted that [7] and other authors used the RR series expressed in ms instead. The hyperparameters used are: L = 200, T = 40 and s = 1 for APRS and DPRS; L = 40, T = 1 and s = 2 for DR; L = 25, T = 2 and s = 1 for AAC e ADC. The samples with poor quality index were prevented from being anchor points.

The Multi Scale Entropy curve was computed as the Sample Entropy (m=2, r=0.15*std) at different scales. The slope was evaluated between scales 5 and 1. In the computation of the Approximate Entropy, r was set to 0.1 * std and m to 1. The Lempel Ziv complexity was computed with the coding procedure presented in [8]. We set p to 0.02 for the binary coding and to 0.01 for the ternary.

The sympathovagal balance was computed as the ratio of LF over HF, thus excluding MF.

Features from the frequency domain and LTI were computed on non-overlapping windows of 3 minutes; DELTA, STV and II on windows of 1 minute, while non-linear features were computed on windows of 20 minutes. Segments with more than 5% of interpolated points (i.e., poor quality index) were excluded from the computation of parameters.

For every recording, the mean of the values obtained in each window for each feature has been computed in order to extract a single value for each of them.

Table 1. List of the computed parameters and relevant references. t.d. stands for "time domain", f.d. for "frequency domain and n.l. for "non-linear".

Parameter		Ref.
DELTA [ms]	t.d.	[9]
Interval Index [ms] (II)	t.d.	[9]
Short Term Variability [ms] (STV)	t.d.	[9]
Long Term Irregularity [ms] (LTI)	t.d.	[9]
Mean Frequency [bpm] (meanF)	t.d.	
#big accelerations per hour (#AAC)	t.d.	[10]
#small accelerations per hour (#aac)	t.d.	[10]
Total Power [ms^2] (PTot)	t.d.	[2]
Low Frequency Power [ms^2] (LF)	f.d.	[2]
Movement Frequency Power [ms^2] (MF)	f.d.	[2]
High Frequency Power [ms^2] (HF)	f.d.	[2]
Sympathovagal balance (LF/HF)	f.d.	
Acceleration Phase Rectified Slope [bpm] (APRS)	n.l.	[5]
Deceleration Phase Rectified Slope [bpm] (DPRS)	n.l.	[5]
Average Acceleration Capacity [bpm] (AAC)	n.l.	[6]
Average Deceleration Capacity [bpm] (ADC)	n.l.	[6]
Deceleration Reserve [bpm] (DR)	n.l.	[7]
Binary Lempel Ziv Complexity (LZ2)	n.l.	[8]
Ternary Lempel Ziv Complexity (LZ3)	n.l.	[8]
Sample Entropy (SampEn)	n.l.	[8]
Approximate Entropy (ApEn)	n.l.	[8]
Multiscale Entropy Slope (MSE)	n.l.	[8]

3. Results

The numerosity and the incidence of comorbidities in the groups tested are reported in Table 2. All the discussed parameters were tested for differences between the two populations. Since most of the analysed features do not follow a normal distribution, differences in median values between diabetics and controls were evaluated using the Mann-Whitney U test. Results are considered significant if $p<0.05$. The median values and the p-values of the statistical tests are summarized in Table 3.

Table 2 - Tested Population. N is the sum of Diabetic and Non-Diabetics, which are represented in equal numbers. C and NC are the percentages of conditions correlated and non-correlated with diabetes, which are equal in the two populations.

G.A.	N	C	NC
31-35	228	29%	9%
36	254	21.3%	9.5%
37	274	23%	13%
38+	242	15%	10%

Table 3 -Results of the Mann –Whitney U test: ° p <0.1, *p<0.05, **p<0.01, ***p<0.001

	31-35			**36**			**37**			**38+**		
	Median		p.	Median		p.	Median		p.	Median		p.
	Diab.	Cont.		Diab.	Cont.		Diab.	Cont.		Diab.	Cont.	
DELTA	38.8	38.8	n.s.	39.7	38.5	n.s.	39.4	39.8	n.s.	40.3	39.3	n.s.
II	0.840	0.851	n.s.	0.838	0.837	n.s.	0.832	0.841	n.s.	0.829	0.834	n.s.
STV	5.95	5.77	n.s.	6.25	5.85	n.s.	6.24	6.36	n.s.	6.27	6.27	n.s.
LTI	63.5	83.4	n.s.	97.0	80.0	n.s.	94.6	96.0	n.s.	96.8	84.0	n.s.
meanF	139.6	139.4	n.s.	138.9	139.4	n.s.	138.8	137.3	n.s.	137.7	135.7	n.s.
#ACC	9.24	8.79	n.s.	10.92	9.78	n.s.	10.27	11.75	n.s.	11.2	10.89	n.s.
#acc	4.04	4.36	n.s.	4.09	4.06	n.s.	3.77	3.89	n.s.	4.21	5.03	n.s.
PTot	186.9	187.5	n.s.	200.6	179.33	n.s.	200.9	178.3	°	211.5	189.9	°
LF	82.6	78.5	n.s.	**89.8**	**78.0**	**	89.0	82.6	n.s	**89.2**	**80.58**	*
MF	**2.31**	**2.14**	**	**2.36**	**2.19**	**	**2.42**	**2.30**	***	2.43	2.32	°
HF	**1.01**	**1.16**	**	1.08	1.16	°	1.09	1.16	°	1.17	1.18	n.s
LF/HF	31.4	30.53	°	**34.0**	**28.54**	***	**32.6**	**29.43**	**	**31.2**	**28.76**	*
DPRS	-0.208	-0.198	n.s.	**-0.223**	**-0.204**	*	-0.213	-0.22	n.s.	-0.218	-0.21	n.s.
APRS	0.196	0.195	n.s.	0.205	0.1844	°	0.197	0.201	n.s.	0.196	0.197	n.s.
ADC	-2.11	-2.16	n.s	-2.19	-2.12	n.s	-2.15	-2.15	n.s	-2.10	-2.15	n.s
AAC	1.68	1.77	n.s.	1.76	1.73	n.s.	1.77	1.78	n.s.	1.73	1.76	n.s
DR	**- .094**	**- .069**	***	**- .110**	**- .068**	***	**- .107**	**- .082**	**	- .100	- .095	n.s.
LZ2	0.982	0.985	n.s.	0.983	0.988	n.s	**0.980**	**0.993**	*	**0.980**	**0.992**	*
LZ3	**0.920**	**0.903**	**	0.916	0.903	n.s.	**0.914**	**0.900**	*	**0.911**	**0.903**	*
SampEn	0.67	0.67	n.s.	0.64	0.64	n.s.	**0.62**	**0.67**	*	**0.65**	**0.71**	*
ApEn	1.24	1.26	n.s	1.19	1.22	n.s	**1.15**	**1.22**	*	**1.21**	**1.30**	*
MSE	0.154	0.141	n.s	**0.157**	**0.144**	*	0.159	0.149	n.s	0.155	0.150	n.s

3. Discussion

None of the classical time-domain parameters (i.e., STV, DELTA, LTI, II, mean frequency) showed significant differences, confirming the unsuitability of the indices most used in clinic for the management of diabetes in pregnancy. Similar results were also obtained in [5] and [10]. Several significant differences were instead identified in the spectral and non-linear analyses. We observed an increase in the LF and MF bands, that have been associated with the activity of the sympathetic nervous system and fetal movements respectively [2]. In addition, we noticed a decrease in HF, which is an indicator of parasympathetic activity. These results suggest that gestational diabetes causes a state of fetal hyperactivation. Interestingly, despite our findings are inconsistent with the ones by Lobmaier et al. [5] who observed a significant increase in AAC and ADC, frequency domain parameters allow us to reach similar conclusions regarding the hyperactivation of the sympathetic nervous system in GDMs, which may

explain the increased risk of developing hypertension later in life.

Among the PRSA-related features, the one that better differentiated between the two populations is the Deceleration Reserve. As shown in Figure 1, nearly all the recordings show a negative value, indicating a predominance in decreasing trends in the fHR series. Indeed, the theoretical value of DR for a stochastic stationary Gaussian process is 0 [7] and departures from this value are originated by asymmetries in the signal. This effect is more pronounced in GDMs, that show a significantly lower median value. The relation between DR and the activity of the ANS must be further investigated. The measures of entropy (i.e., SampEn and ApEn) showed a better ability to differentiate the populations at an advanced gestational age, with slightly lower values for the diabetic one. The observed reduction in complexity is a result similar to that obtained in the analysis of other pathologies (e.g., [7]). The Lempel Ziv Complexity is a measure of the regularity of the variations in the series and is strongly dependent on the coding procedure [8]. Its interpretation is not trivial, but results suggest it may be useful in differentiating GDMs from controls, especially when the ternary coding is used. As shown for example in Figure 1, even significantly different parameters do not allow to completely separate GDMs and controls. However, classification of GDM condition only is not the main goal of our study. In fact, suitable techniques for clinical diagnosis of GDM already exist (i.e, glucose tolerance test). Our approach aims at using CTGs biomarkers to quantify the risk in pregnancies complicated by diabetes. We hypothesize that the parameters that vary between the two populations may be predictors of pregnancy outcomes and provide clinicians with additional information to determine the best course of action. A different protocol was written to test this hypothesis and the study is currently in progress.

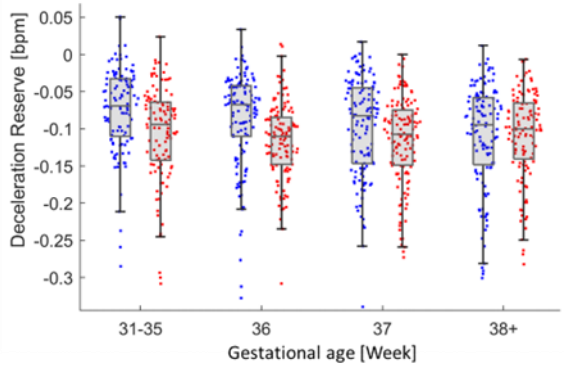

Figure 1 Values of DR in the GDM population (red) vs control (blue).

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References

[1] International Federation of Gynecology and Obstetric (FIGO), "Initiative on gestational diabetes mellitus: a pragmatic guide for diagnosis, management, and care," 2015. doi: 10.1016/j.solidstatesciences.2005.08.010.

[2] M. G. Signorini, G. Magenes, S. Cerutti, and D. Arduini, "Linear and nonlinear parameters for the analysis of fetal heart rate signal from cardiotocographic recordings," IEEE Transactions on Biomedical Engineering, vol. 50, no. 3, pp. 365–374, 2003, doi: 10.1109/TBME.2003.808824.

[3] E. Spairani, B. Daniele, G. Magenes, and M. G. Signorini, "A novel large structured cardiotocographic database," 2022 44th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC), 2022, pp. 1375-1378, doi: 10.1109/EMBC48229.2022.9871340.

[4] Fondazione Confalonieri Ragonese, "Raccomandazioni sulla cardiotocografia ante partum," 2021.

[5] A. Fanelli, G. Magenes, M. Campanile, and M. G. Signorini, "Quantitative assessment of fetal well-being through ctg recordings: a new parameter based on phase-rectified signal average," IEEE Journal of Biomedical and Health Informatics, vol. 17, no. 5, pp. 959–966, 2013, doi: 10.1109/JBHI.2013.2268423.

[6] S. M. Lobmaier et al., "Influence of gestational diabetes on fetal autonomic nervous system: a study using phase-rectified signal-averaging analysis," Ultrasound in Obstetrics and Gynecology, vol. 52, no. 3, pp. 347–351, 2018, doi: 10.1002/uog.18823.

[7] M. W. Rivolta, T. Stampalija, M. G. Frasch, and R. Sassi, "Theoretical value of deceleration capacity points to deceleration reserve of fetal heart rate," IEEE Transactions on Biomedical Engineering, vol. 67, no. 4, pp. 1176–1185, 2020, doi: 10.1109/TBME.2019.2932808.

[8] M. Ferrario, M. G. Signorini, and G. Magenes, "Complexity analysis of the fetal heart rate variability: early identification of severe intrauterine growth-restricted fetuses," Medical & Biological Engineering & Computing, vol. 47, pp. 911–919, 2009, doi: 10.1007/s11517-009-0502-8.

[9] M. G. Signorini, N. Pini, A. Malovini, R. Bellazzi, and G. Magenes, "Dataset on linear and non-linear indices for discriminating healthy and IUGR fetuses," Data in Brief, vol. 29, 2020, doi: 10.1016/j.dib.2020.105164.

[10] D. Arduini, G. Rizzo, and C. Romanini, "Computerized analysis of fetal heart rate," Journal of Perinatal Medicine, vol. 22, no. Suppl.1, pp. 22–27, 1994, doi: 10.1515/jpme.1994.22.s1.22.

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