Cardiac Electrical Alternans in Pregnancy: an Observational Study

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Abstract

In pregnancy, if the woman has a cardiovascular disease, her fetus has an increased risk of inherited cardiac genetic disorders. Aim of this study was to evaluate electrocardiographic alternans (ECGA, μV) of 23 pregnant women, comparing 12 mothers of fetuses with normal rhythm (Mum_NRF) and 11 mothers of arrhythmic fetuses (Mum_ArrF). ECGA is a noninvasive cardiac electrical risk marker able to reveal heart electrical instability. ECGA manifests in the ECG as P-wave alternans (PWA), QRS alternans (QRSA) and/or T-wave alternans (TWA). Analysis was performed by the enhanced adaptive matched filter method. ECGA distributions were expressed as: median (interquartile range). Comparisons were performed by the Wilcoxon rank-sum test. Although showing similar heart rate (Mum_NRF: 85 (19) bpm; Mum_ArrF: 90 (13) bpm), ECGA was higher in Mum_ArrF population than Mum_NRF one (PWA: 9 (7) μV vs. 14 (14) μV; QRSA: 9 (10) μV vs. 17 (16) μV; TWA: 12 (14) μV vs. 28 (17) μV), but only TWA distributions were statistically different. Moreover, TWA was higher than in a female healthy population (on average 18 μV) in 70% of Mum_ArrF, vs. 33% of Mum_NRF. Thus, higher TWA in our Mum_ArrF seems to reflect a more unstable heart electrical condition of arrhythmic fetuses' mothers than normal-rhythm fetuses' mothers.

1. Introduction

During pregnancy, the woman cardiovascular system undergoes physiologic adaptations to support the development of the fetus. These adaptations include incremented hemodynamic demands, hormonal changes, and alteration in the autonomic tone [1]. Therefore, cardiovascular risk can increase, and cardiac arrhythmias have a higher incidence [1]. The risk can become higher if the woman already has cardiovascular problems and may be significant also for fetuses.

The literature established a link between cardiovascular disease in the mother and the increased risk of inherited cardiac genetic disorders in the fetus [2-5]. In numerical terms, the risk of fetuses to inherit a congenital heart disease varies from 2% up to 50%, depending on the specific disease [2]. The possible correlation between maternal and fetal cardiac electrical conduction problems can be examined even from the point of view of the cardiac tissue. Indeed, cardiac tissue enables the cardiac mechanical activity through an electrical system of cellular polarization and depolarization. Thus, problems of cardiac tissue are related to cardiac electrical conduction issues and these problems may be inherited by fetuses [3-5]. Typical examples of cardiac electrical conduction problems are arrhythmias. Arrhythmias are present in 16.6% of fetuses in high-risk pregnancies after 21 weeks of gestation [4]. The debate on the etiology of fetal arrhythmogenicity of cardiac structures is still open. Possible causes are heart structural abnormalities, electrolyte problems of the cardiac tissue cells and even genetic origins [6]. In this contest genetic connection could be underlined in particular with regard to sinus bradycardia, familial atrial fibrillation and inherited arrhythmias that can have serious consequences for fetus life [4]. One of the inherited conduction problems that can lead to arrhythmias is long QT syndrome. This syndrome is a consequence of cardiac electrical conduction issue that affects 1 in 2,500 live births. Long QT syndrome can have genetic origins and can be hereditary [3].

In this context, maternal monitoring through cardiac risk indexes may be extremely important to discover or prevent cardiac disfunctions possibly inherited by fetuses. An important index of cardiovascular risk, particularly linked to the risk of developing arrhythmias, is cardiac alternans [7]. Cardiac alternans is an electrophysiological phenomenon that has multifactorial causes, possibly attributable to excessive inhomogeneity of the cardiac tissue [8]. Cardiac alternans can be observed in the electrocardiogram (ECG) as electrocardiographic alternans (ECGA). ECGA is beat-to-beat alteration of the amplitude, shape or polarity of P wave, QRS complex and/or T wave [7]. P-wave alternans (PWA) is associated to atrial electrical instabilities [7,9]. QRS complex alternans (QRSA) has been correlated to ventricular and supraventricular tachycardia [7,10-12]. Eventually, T wave alternans (TWA) was linked to the risk of developing ventricular arrhythmias, also malignant [7,13].

Aim of this study is to evaluate ECGA in a population of pregnant women, and to compare a group of mothers of fetuses with normal sinus rhythm against a group of mothers of arrhythmic fetuses.

2. Data and Methods

2.1. Clinical Data

Clinical data come from the "Non-Invasive Fetal ECG Arrhythmia Database" from Physionet [14-15]. This database contains non-invasive ECG records of 24 pregnant women acquired in a routine medical visit. Among them, 12 women were mothers of fetuses with normal cardiac rhythm (Mum_NRF) and 11 women were mothers of arrhythmic fetuses (Mum_ArrF). Mum_NRF had a gestational age of 23±5 weeks, while Mum_ArrF had a gestational age of 32±7 weeks (Table 1). The database includes 2 twin pregnancies. For one of the two pregnancies, fetuses are both with normal rhythm (Mum_NRF12), while for the other, one fetus had a normal rhythm, and one was arrhythmic, and this woman was not enrolled in the analysis. All ECG data were acquired by using the Cardiolab Babycard equipment. Two electrodes were positioned on the woman's chest for the acquisition of the maternal thoracic lead, five on the abdomen around the navel for the acquisition of the indirect fetal ECG leads and one on the pubic symphysis as reference. All the acquisitions of the cardiac signals lasted from 7 min to 32 min (Table 1). The sampling rate was 1000 Hz or 500 Hz and the resolution was 16 bits.

2.2. Automatic Electrocardiographic Alternans Detection and Statistics

Analysis of PWA, QRSA and TWA was performed by application of the enhanced adaptive matched filter (EAMF) method [7]. The method includes a pre-processing step and a consequent alternans estimation step.

During the pre-processing step, high-frequency and low-frequency interferences are removed by means of a 6th-order bidirectional Butterworth bandpass filter between 0.5 Hz and 35 Hz. The signal is also resampled to 200 Hz. Then, R peaks are identified, and baseline is subtracted from the signal. At this point, the landmarks of each section of the ECG are identified: the onset of P-wave (Pon), the onset of Q-wave (Qon), the end of the QRS complex (J) and the end of T-wave (Tend). Thus, P section (from Pon to Qon), QRS section (from Qon to J) and T section (form J to Toff) are estimated. RR intervals are computed and the ECGA analysis is performed only if the ECG trace meets two suitability conditions that test the stability of heart rate and the presence of a sinus rhythm. The first condition verifies that the standard deviation of the RR intervals does not exceed 10% of the mean RR interval. The second condition uses a correlation method: median QRS is computed over all the heartbeats present in the ECG trace and correlated against all QRS complexes of the ECG trace. If the correlation coefficient is lower than 0.85, heartbeat is replaced by the median heartbeat. The condition verifies that the number of replacements are no more than 10% of the total heartbeats of the ECG trace.
If both suitability conditions are met, the ECG undergoes the signal enhancement phase. This phase consists in setting to baseline all ECG sections but the one for which alternans has to be identified. Thus, from the preprocessed ECG trace three signals are generated: the P signal, the QRS signal and the T signal, where all sections are set to baseline but P section, QRS section, and T section, respectively. These three signals feed a very narrow band-pass filter. Particularly, after computing the alternans frequency (AF), equal to half heart rate, the filter is implemented as a 6th-order bidirectional Butterworth filter with cut-off frequencies of AF-0.06 Hz and AF+0.06 Hz. So, from P signal, QRS signal and T signal, all the frequency components are filtered out but the one pertaining the ECGA. For P-wave, if there is alternans, as output there is a pseudo-sinusoidal signal that represents PWA and has its maxima and minima in correspondence of the P-wave. Alternans amplitude (μV) is defined as twice the pseudo-sinusoid amplitude. If there is not alternans, the output is a constant signal, and the amplitude is 0 μV. Analogously, for QRS complex and T wave. The alternans area (μV×ms) is defined as the product of the alternans amplitude by the wave duration (ms) [7].

ECGA analysis was performed on 32-heartbeat ECG

Table 1. Gestational age and recording duration specified for all the cases

Women	Gestational age (weeks)	Recording duration (min:s)
Mum_NRF1	20	10:05
Mum_NRF2	21	10:05
Mum_NRF3	32	10:07
Mum_NRF4	21	10:20
Mum_NRF5	23	10:05
Mum_NRF6	22	10:27
Mum_NRF7	21	10:00
Mum_NRF8	36	12:34
Mum_NRF9	20	10:00
Mum_NRF10	21	10:02
Mum_NRF11	24	07:20
Mum_NRF12	20	10:10
Mum_ArrF1	38	10:00
Mum_ArrF2	25	12:37
Mum_ArrF3	35	10:05
Mum_ArrF4	37	08:01
Mum_ArrF5	36	32:03
Mum_ArrF6	37	10:18
Mum_ArrF7	23	22:01
Mum_ArrF8	35	11:05
Mum_ArrF9	41	10:07
Mum_ArrF10	31	10:05
Mum_ArrF11	23	10:05

windows extracted every second. For each enrolled mother, if more than one ECG window was suitable, only the first one was considered. Prevalent alternans was defined as the ECGA form with the highest area.

Population distributions of heart rate, PWA/QRSA/TWA amplitudes and PWA/QRSA/TWA areas were expressed as median values and interquartile range (75^{th}-25^{th} percentiles) over the two groups of Mum_NRF and Mum_ArrF. Comparisons were performed by the Wilcoxon rank-sum test, with statistically significant level (p) set at 0.05 in all cases.

3. Results

Mum_NRF and Mum_ArrF showed similar heart rates; specifically, Mum_NRF group heart rate was 85 (19) bpm, while Mum_ArrF group was 90 (13) bpm. All signals met both the conditions testing the suitability for the ECGA analysis except for Mum_ArrF7 signal. For this reason, Mum_ArrF7 signal was excluded from subsequent elaborations. Thus, ECGA was measured in a total of 22 ECG signals (12 from women with normal cardiac rhythm fetuses and 10 from women with arrhythmic fetuses). Results about ECGA amplitude and area are showed on Table 2 and Table 3. ECGA was higher in Mum_ArrF group than Mum_NRF one and distributions were statistically different when considering PWA and TWA (Table 2 and Table 3; $p<0.08$ for QRSA). The prevalent alternans was TWA. Results about TWA amplitudes in function of RR are shown in Figure 1. Mum_NRF and Mum_ArrF are shown as blue and orange markers, respectively. Red dashed line borders the green area representing the physiological values [16].

Table 2. Alternans amplitudes and areas of mothers of normal rhythm fetuses (Mum_NRF); total values are expressed as median (IR).

	Alternans amplitude (μV); area (μV×ms)		
	PWA	**QRSA**	**TWA**
1	14; 1422	9; 736	9; 1770
2	0; 0	9; 685	13; 2528
3	6; 563	7; 557	7; 1471
4	8; 767	8; 616	9; 1817
5	9; 914	32; 2539	17; 3482
6	7; 738	15; 1217	41; 8117
7	15; 1520	24; 1948	33; 6653
8	17; 1705	19; 1505	25; 4922
9	9; 862	9; 741	6; 1104
10	0; 0	7; 579	6; 1282
11	13; 1265	0; 0	12; 2317
12	15; 1455	13; 1039	19; 3823
TOT	**9 (7); 888 (789)**	**9 (10); 738 (764)**	**12 (14); 2423 (2752)**

Table 3. Alternans amplitudes and areas of mothers of arrhythmic fetuses (Mum_ArrF); total values are expressed as median (IR). Values are compared against of mothers of normal rhythm fetuses (Mum_NRF).

	Alternans amplitude (μV); area (μV×ms)		
	PWA	**QRSA**	**TWA**
1	9; 859	9; 710	24; 4847
2	22; 2224	19; 1524	33; 6650
3	7; 653	25; 1987	22; 4349
4	13; 1261	16; 1278	13; 2652
5	36; 3610	72; 5748	42; 8418
6	24; 2450	77; 6173	57; 11492
7	-	-	-
8	13; 1307	9; 755	31; 6255
9	10; 965	0; 0	17; 3356
10	28; 2802	18; 1463	34; 6711
11	15; 1531	11; 852	17; 3302
TOT	**14* (14); 1419* (1485)**	**17 (16); 1371 (1232)**	**28* (17); 5551* (3355)**

*: $p<0.05$

4. Discussion

This study aimed to evaluate ECGA in a population of pregnant women comparing mothers of fetuses with normal rhythm and mothers of arrhythmic fetuses. ECGA is a noninvasive cardiac electrical risk marker able to reveal electrical instability affecting the atria [9] or/and the ventricles [13]. The method used to quantify ECGA was the EAMF method, able to reliably identify and quantify ECGA in all its possible forms [7]. EAMF reveals PWA, QRSA and TWA in both groups, but values of amplitude

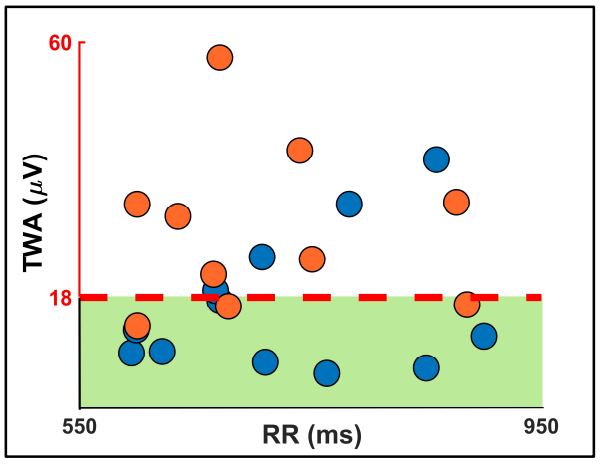

Figure 1. TWA amplitude values for mothers of normal rhythm fetuses (Mum_NRF, blue markers) and mothers of arrhythmic fetuses (Mum_ArrF, orange markers). Green area indicates normal range of values [16].

and area are in general lower in Mum_NRF then in Mum_ArrF.

ECGA is a heart-rate dependent phenomenon [17], but in this case the ECG acquisitions were performed in the same condition for all women, and this is confirmed by the similar heart rates, so higher ECGA values in Mum_ArrF group cannot be interpreted as being heart rate driven.

To the best of our knowledge, in the literature, there are no similar studies considering ECGA in pregnancy, so the obtained values were compared with previously analyzed healthy female population. The only ECGA form studied on a healthy population is TWA (previously quantified in terms of amplitude and not of area) and TWA is prevalent in our pregnant women groups. Thus, focusing on TWA, 70% of Mum_ArrF shows higher values than the range of physiological ones (on average, 0-18 μV), vs only 33% of Mum_NRF (Figure 1). Physiological values were estimated considering TWA amplitude computed on a healthy female population analyzed with a similar method in a previous work [16]. Higher values of TWA in Mum_ArrF group may represent a not completely stable condition for the electrical heart functioning. This situation may occur for several reasons, and also for a pathological state, possibly inherited by the fetus, who in turn manifests arrhythmia. The lack of information on the women health status and age allows us to do quite speculative hypothesis and do not permit sure deductions but opens the way to the possible use of ECGA as a mean to monitor women during pregnancy. Studies on wider populations of pregnant women with known age and health status (also of the fetus) may provide more consistent results and possibly confirm our observations and validate our results.

5. Conclusion

This preliminary observational study shows higher TWA in Mum_ArrF, possibly reflecting a more unstable heart electrical condition of arrhythmic fetuses' mothers than normal-rhythm fetuses' mothers.

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