Quantitative Assessment of Fetal Well-Being Through CTG Recordings: A New Parameter Based on Phase-Rectified Signal Average

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***Abstract*—Since the 1980s, cardiotocography (CTG) has been the most diffused technique to monitor fetal well-being during pregnancy. CTG consists of the simultaneous recording of fetal heart rate (FHR) signal and uterine contractions and its interpretation is usually performed through visual inspection by trained obstetric personnel. To reduce inter- and intraobserver variabilities and to improve the efficacy of prenatal diagnosis, new quantitative parameters, extracted from the CTG digitized signals, have been proposed as additional tools in the clinical diagnosis process. In this paper, a new parameter computed on FHR time series and based on the phase-rectified signal average curve (PRSA) is introduced. It is defined as acceleration phase-rectified slope (APRS) or deceleration phase-rectified slope (DPRS) depending on the slope sign of the PRSA curve. The new PRSA parameter was applied to FHR time series of 61 healthy and 61 intrauterine growth restricted (IUGR) fetuses during CTG nonstress tests. Performance of APRS and DPRS was compared with 1) the results provided by other parameters extracted from the PRSA curve itself but already existing in the literature, and 2) other clinical indices provided by computerized cardiotocographic systems. APRS and DPRS indices performed better than any other parameter in this study in the distinction between healthy and IUGR fetuses. Our results suggest this new index might reliably contribute to the quality of early fetal diagnosis.**

***Index Terms*—Cardiotocography (CTG), fetal monitoring, heart rate variability (HRV), phase-rectified signal average (PRSA).**

I. Introduction

THE activity of the fetal heart appears very early during pregnancy and depends on the progressive development of the nervous system of the embryo. During this process of maturation, the sympathetic and parasympathetic branches of the autonomic nervous system (ANS) play a fundamental role in controlling and modulating fetal heart rate (FHR).

Recording FHR and measuring its variability represent a noninvasive way to collect information about the fetal state and the proper development of the ANS [1]. Moreover, some FHR patterns can be directly connected to the level of fetal oxygenation that is essential for fetal well-being.

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For these reasons, FHR monitoring is considered crucial to identify risky conditions in the fetus. Their early detection contributes to the reduction of complications and fetal death episodes as well as diminishes the need for invasive interventions. FHR monitoring is also very important to minimize risks of fetal morbidity and mortality and to evaluate the optimal timing for delivery. Fetal pathological conditions such as intrauterine growth restriction (IUGR), diabetes, infections, and placental abruption can be diagnosed thanks to heart rate variability (HRV) analyses [2].

IUGR is one of the most severe causes of perinatal morbidity and mortality: it consists of a pathological inhibition of fetal growth, with a consequent failure of the fetus to attain its growth potential. It is strictly connected to fetal hypoxia and asphyxia. The incidence of IUGR is approximately 5% of all pregnancies [3]. Thus, fetal monitoring is extremely important to detect IUGR or other risky conditions in the fetus, supporting the decision process of clinicians.

The use of FHR monitoring strongly increased in the last decades, as statistical data about U.S. pregnancies show: 45% of laboring women in 1980, 62% in 1988, 74% in 1992, and 85% in 2002 were submitted to this screening procedure [4].

FHR can be measured using several technological approaches. The most diffused technique is cardiotocography (CTG), which combines the measure of FHR through a Doppler ultrasound probe with the detection of uterine contractions using a pressure sensor. Doppler ultrasound allows the detection of heart beat events by sensing fetal heart movements. The device generates a trace reporting the heart rate changes during the screening process [5].

An alternative approach to record FHR is fetal electrocardiography (FECG), made by external or internal electrodes, depending on the gestational age. External (or abdominal) FECG consists of placing the electrodes on the maternal abdomen, recording the electrical activity of both fetal and mother's heart and then separating the two signals, when possible, by means of dedicated algorithms [2]. Internal FECG can be recorded during labor only, after the rupture of the membranes, and consists of placing an electrode directly on the fetal scalp [6].

The CTG approach, although less accurate than internal FECG in the detection of FHR, is commonly employed in antepartum monitoring, because it is noninvasive and performs better than abdominal ECG in FHR detection.

In recent years, new ideas emerged in the field of fetal well-being assessment, with the goal of reducing invasiveness and allowing continuous and remote fetal monitoring. These

efforts have been mainly produced in the technological domain by designing and developing new monitors and devices based on different approaches (Echo4D, ST segment analysis (STAN) for intrapartum electronic fetal monitoring). Nonetheless reliable and quantitative indices, directly related to pathological events, are still the weak link in the fetal diagnostic chain.

In 2009, the American College of Obstetricians and Gynecologists (ACOG) tried to define the standards for nomenclature and interpretation of fetal monitoring [7]. The ACOG guidelines also summarize all statistics about the efficacy of fetal monitoring and underline the main problems in this field. As a matter of fact, most diagnostic conclusions derived from the analysis of CTG recordings rely on qualitative visual inspection of CTG traces and, thus, on the clinician's experience. This causes a diffused intraobserver and interobserver variabilities in CTG traces interpretation. An interesting paper [8] reports that when four obstetricians examined 50 cardiotocograms, they agreed in only 22% of cases. Two months later, the same clinicians interpreted 21% of the same tracings in a different way from what they did the first time. Moreover, eye inspection is unable to depict more complex events that can be extracted only by using quantitative approaches that investigate the information content of FHR variability signal. Thus, it is important to improve the reliability of FHR analysis by introducing new indicators related to the pathophysiological condition of the fetal heart.

For this reason, we have been working for many years, trying to quantify fetal well-being in an objective way and to overcome inter- and intraobserver variabilities [9], [10]. The purpose of this paper is to improve the quality of early diagnosis of fetal distress and disease conditions by introducing and applying a new index computed on the phase-rectified signal average (PRSA) curve [11]. The manuscript presents the results obtained after applying a set of parameters to a selected population of healthy and IUGR fetuses (61 + 61). Our objective is to combine and compare diagnostic performance of traditional parameters based on the time domain analysis, such as short time variability (STV) [12], Delta, long term irregularity (LTI) [12] and interval index [13], nonlinear parameters, such as approximate entropy (ApEn) [14], with this new proposed index. The performance of the new acceleration (or deceleration) phase-rectified slope [acceleration phase-rectified slope (APRS) or deceleration phase-rectified slope (DPRS)] parameter is also compared with other parameters computed on the PRSA curve by other research groups [15], [16].

The final goal of this study is to add the new proposed index to a set of parameters able to improve the early prenatal diagnosis. These indices are extremely important to reduce the inter- and intraobserver variabilities and, at the same time, to identify and diagnose risky conditions in the fetus, supporting clinicians in the decision process.

II. Materials and Methods

A. Data Collection

Our system consists of a HP-1350 CTG fetal monitor connected to a computer using a RS-232 serial port. However, our computerized system is compatible with any other CTG monitor using the HP data protocol (Agilent, Corometrics 170, Philips 50 A, etc.). The U.S. probe generates 998.4-kHz ultrasound bursts that repeat with a frequency of 3.2 kHz. The received echo is amplified thanks to a high-frequency amplifier with a gain of 120. Then, the signal is demodulated and band-pass filtered (100–500 Hz).

TABLE I
Pregnancy and Delivery Details

	Healthy	**IUGR**
N	61	61
Mother Age (years)	31.29±6.34	29.68±6.21
Gestational age at CTG recording (weeks)	34.78 ± 0.53	32.27±2.79
Gestational age at delivery (weeks)	39.74 ± 1.15	34.15 ± 2.99
Weight of the baby after delivery	3275 g± 518g	1479 g ± 608 g
Delivery mode	58% Spontaneous 42% Caesarean	14,8% Spontaneous 85,2% Caesarean

The CTG monitor is endowed with an autocorrelation control to compare every heart beat with the following one. The Doppler signal is sampled at 200 Hz (time sampling window: 5 ms). The autocorrelation function (ACF) is computed over a window of 1.2 s, corresponding to a minimum FHR of 50 bpm. A peak detection algorithm then detects the heart period from the ACF and a FHR value in bpm is produced. The CTG system updates the FHR value every 250 ms. In the commercially available system, the PC reads ten consecutive values of the buffer every 2.5 s and determines the actual FHR as the average of the ten values (corresponding to a sampling frequency of 0.4 Hz). In our previous works [9], [10], [17], [18] we decided to average two consecutive FHR values every 0.5 s in order to obtain FHR series of 2 Hz (1 sample every 0.5 s). The choice of taking a FHR value each 0.5 s represents a reasonable compromise to achieve an enough large bandwidth and an acceptable accuracy of the beat-to-beat intervals ($<$2 ms) [9].

B. Experimental Protocol

CTG recordings were collected at the Azienda Ospedaliera Universitaria Federico II, Napoli, Italy. Population was composed of 122 subjects (61 healthy and 61 IUGR). Both populations were defined "*a posteriori*," after delivery, on the basis of standard parameters (Apgar scores, weight, abdominal circumference): IUGR fetuses were selected by weight below the 10th percentile for their gestational age and abdominal circumference below the 10th percentile.

The healthy population was then selected from our database, consisting of more than 800 subjects, by trying to match as close as possible the gestational age of the IUGR recordings. Only CTG signals acquired during the 34th and 35th gestational week were included in the study, in order to have a population comparable to the IUGR one in terms of pregnancy period.

Table I summarizes population details. All recordings were acquired in a controlled clinical environment, with the pregnant woman lying on a bed. The average length of the recordings was 2730 $\pm$ 615 s for healthy subjects and 3418 $\pm$ 1033 s for IUGR fetuses.

C. Processing of FHR signals

The HP-1350 quantifies the quality of the acquired FHR signal with a color index: good (green), acceptable (yellow), and bad (red). This quality evaluation is based on the output of the autocorrelation procedure computed during data acquisition. Each FHR recording is then divided into windows of 360 data points (3 min). The red quality points are replaced by the average of the nearest five FHR points. If the trace contains more than five consecutive red-quality points or a subinterval includes more than 5% red quality values, that subinterval is left off the analysis. This approach allows correcting noisy segments or discarding them when the SNR ratio is too poor (insufficient) for further analysis. Acquisition and preprocessing procedure is fully described in [9].

D. Phase-Rectified Signal Average

PRSA is a technique introduced by Bauer *et al.* [11]. This approach allows the detection and the quantification of quasi-periodic oscillations in nonstationary signals affected by noise and artifacts, by synchronizing the phase of all periodic components.

This method demonstrated its usefulness in FHR signal analysis, when episodes of increasing and/or decreasing FHR appear [15]. In fact, occurrence or absence of such periods can be related to the healthy status of the fetus [7]. Increases and decreases of FHR are controlled by the ANS, which modulates heartbeat intervals receiving inputs from heart, lungs, and blood vessels. In the Ob-Gyn literature, these increases and decreases of FHR are commonly referred as "accelerations" and "decelerations." These are not the terms we decided to adopt in this study as they do not necessary correspond to the definitions provided by the ACOG (American College of Obstetricians and Gynecologists) in 2009 [7]. Anyway, these modulation events could be studied by evaluating signal oscillations. For this reason, we introduced the PRSA method to quantify fetal well-being states and extract information on the ANS development and functioning from FHR modulation.

Computational procedure: Computing the PRSA curve requires a time series $i = 1, \ldots, N$, characterized by periodicities and correlations, as well as containing nonstationary and noise events. The first step is the computation of the so-called anchor points (APs). APs are fiducial points selected according to the average value of the signal before and after a certain instant *k*, within a selected time window.

In our analysis, we define as APs those x_i, belonging to the FHR time series, such as the following inequality stands, within a time window of length $2T$:

$$\frac{1}{T}\sum_{j=0}^{T-1} x_{i+j} > \frac{1}{T}\sum_{j=1}^{T} x_{i-j}. \tag{1}$$

The inequality (1) identifies APs that mark a signal increase. A similar inequality can be used to identify decreases by replacing the $>$ symbol with the $<$ symbol. According to this definition, around half of all points in the time series are identified as APs (see Fig 1, upper diagram). The T parameter can be used to control the upper frequency of the periodicities that are detected by PRSA. In our analyses, T values from $T = 5$ to $T = 100$, step 5, were tested.

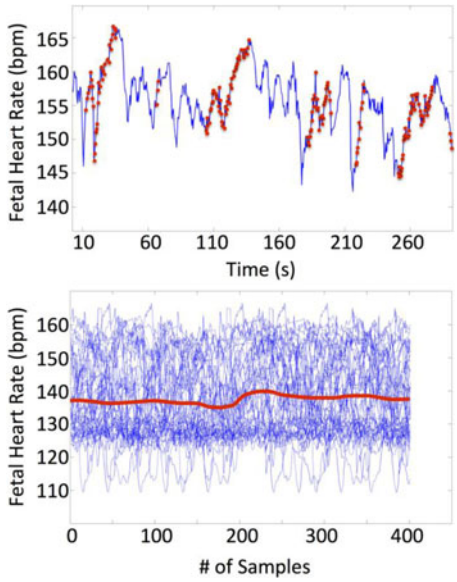

Fig. 1. Fetal heart rate series after the preprocessing steps (up): the APs are detected using disequality (1) and are highlighted as red points in the graph. Computation of PRSA curve (down): 400 samples windows around each AP are synchronized and averaged to obtain the PRSA curve, in red.

APs can be used to phase-rectify the signal [10], removing noise and preserving only periodic oscillations in the time series. After detecting the AP, windows of $2L$ samples are built around each AP. Since many of the APs are adjacent, many of the defined windows will overlap. The parameter L should be larger than the period of slowest oscillation that one wants to detect. We tested several values of L, ranging from 50 to 1000, step 20.

Fig. 1 (lower diagram) shows all $2L$ windows, obtained from the previous step, synchronized in their APs and averaged, in order to obtain a single PRSA curve per patient (red curve in the diagram). The averaging process filters out all nonperiodic components that are not synchronized, preserving the events with a fixed phase relationship with the APs only. For a more detailed description of the algorithm, please refer to [11].

After obtaining the PRSA curve, it is useful to summarize the information within a single parameter, which describes the dynamical characteristics of the curve. Bauer *et al.* [16] employed the acceleration (or deceleration) capacity parameter and applied it to identify a mortality predictor after myocardial infarction

$$\mathrm{AC(DC)} = [X(0) + X(1) - X(-1) - X(-2)]/4 \tag{2}$$

where $X(0)$ is the sample corresponding to the AP. This equation is a quantification of X by Haar wavelet analysis, where the scale of 2 is used. The same parameter was also employed by Kantelhardt *et al.* [19] to predict risk in heart attack survivals.

Huhn *et al.* [15] applied for the first time PRSA to FHR series. They employed a parameter very similar to the AC to identify and classify IUGR fetuses. They used the average acceleration (or deceleration) capacity (AAC), corresponding to the integral

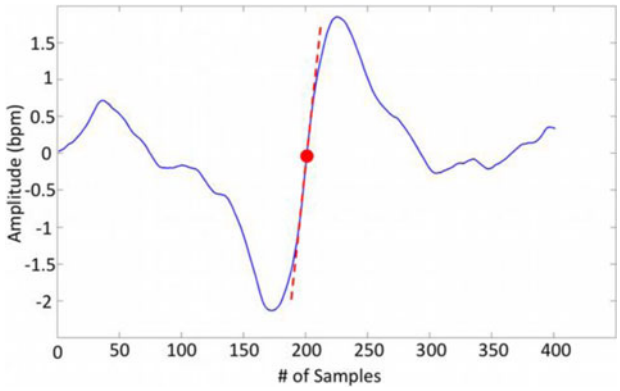

Fig. 2. Computation of the acceleration phase-rectified slope: the new parameter is defined as the slope of the PRSA curve in the AP.

measure of all periodic acceleration-related oscillations. The AAC was defined as follows:

$$\mathrm{AAC}(T) = \frac{1}{2T}\left[\sum_{i=0}^{T-1} X(i) - \sum_{i=-T}^{-1} X(i)\right]. \quad (3)$$

In our analysis, we introduced a new parameter computed on the PRSA curve. Indeed, since in FHR signals the diagnostic information is contained in the number and the temporal characteristics of increases and decreases in heart rate, we define the acceleration (or deceleration) phase-rectified slope (APRS or DPRS), as the slope of the PRSA curve computed in the AP (see Fig. 2)

$$\mathrm{APRS} = \left.\frac{\partial X(i)}{\partial i}\right|_{i_{AP}}. \quad (4)$$

This parameter is a descriptor of both the average increase (and decrease) in FHR amplitude (absolute change of heart frequency) and the time length of the increase (or decrease) event. According to [7], these two measures are the most used in clinical practice to quantify fetal well-being.

E. Time-Domain Parameters

In order to provide a precise and complete picture of fetal well-being, we also considered a set of time domain parameters that are commonly and traditionally used to quantify fetal well-being. These parameters describe the temporal properties of the FHR series. Parameters were computed by the commercial version of the CTG system, on FHR series obtained by averaging ten FHR values over 2.5 s windows (ten samples). Thus, every minute of signal contains 24 points, 2.5 s spaced. This signal is expressed in ms and we will refer to it as T_{24}.

1) *Short time variability (STV).* The STV is a parameter that quantifies FHR variability over a short time scale. The index was computed using the definition provided by Arduini *et al.* [20]

$$\mathrm{STV} = \mathrm{mean}[|T_{24}(i+1) - T_{24}(i)|]_i = \frac{\sum_{i=1}^{23} |T_{24}(i+1) - T_{24}(i)|}{23}, i = 1, \ldots, 23. \quad (5)$$

The STV is computed over windows 1 min long. After that, the values of STV obtained from different windows are averaged. Using this approach each patient is described by a unique value of STV.

2) *Long-Term Irregularity (LTI).* The LTI is used to quantify the variability over longer time scales. For the analyses, we employed the LTI index proposed by Haan *et al.* [21], which shows less correlation with the STV index. LTI is computed over 3 min windows of the T_{24} signal. It is defined as the interquartile range [1/4; 3/4] of the distribution of the modal $m_{24}(j)$, where

$$m_{24}(j) = \sqrt{T_{24}^2(j+1) + T_{24}^2(j)}, j = 1, \ldots, 71. \quad (6)$$

The values of LTI obtained from different windows are averaged to obtain a unique value per patient.

3) *Interval Index (II).* The II is another parameter that describes the variability of FHR over a short period. The definition proposed by Arduini *et al.* [20] was used for the analysis

$$\mathrm{II} = \frac{\mathrm{std}\left[|T_{24}(i+1) - T_{24}(i)|\right]}{\mathrm{STV}}, i = 1, \ldots, 23 \quad (7)$$

where $\mathrm{T}_{24}(i)$ is 1 min of RR signal. As we did with the previous parameters, the II values computed over different windows are averaged to obtain a single II value per patient.

4) *Delta.* Delta is the simplest parameter we used in the analysis. It simply describes the range of the signal in a given interval of time. Delta was computed over windows 1 min long using the following equation:

$$\mathrm{Delta} = \max_i\left[T_{24}(i)\right] - \min_i\left[T_{24}(i)\right], i = 1, \ldots, 23. \quad (8)$$

The Delta values computed over different windows are averaged in order to describe each patient with a unique Delta value.

F. Approximate Entropy

In the analysis, the ApEn was used to quantify the nonlinear dynamics of FHR series and to verify if nonlinear characteristics of the signal are able to distinguish healthy fetuses from IUGR ones. ApEn is a descriptor of the regularity of the system under study. ApEn was defined by Pincus [14]: given N points $u(i)$, the algorithm constructs sequences $x_m(i)$ obtained by taking $x_m(i) = [u(i), \ldots, u(i+m-1)]$, and it computes, for each $i \leq N - m + 1$, the quantity

$$C_i^m(r) = \frac{1}{N}\left\{\#j \leq n - m + 1 | d\left[x_m(i), x_m(j)\right] \leq r\right\}. \quad (9)$$

C_i^m measures, with a tolerance r, the regularity of patterns comparing them to a given pattern of length m (m and r are fixed values: m is the detail level at which the signal is analyzed and r is a threshold, which filters out irregularities). The ApEn is then defined as

$$\mathrm{ApEn}(m, r) = \Phi^{m+1} - \Phi^m$$

TABLE II
RESULTS FROM THE ANALYSIS OF HRV SIGNALS IN FETUS POPULATIONS

Parameter	Healthy (mean ± std)	IUGR (mean ± std)
Subject Number	**61**	**61**
Time Parameters		
Delta (ms)	42.9 ± 11.97	29.67 ± 9.25
STV (ms)	6.7 ± 2.24	4.29 ± 1.62
Interval Index	0.87 ± 0.07	0.86 ± 0.06
Long Term Irregularity (ms)	21.46 ± 6.53	17.17 ± 5.37
Non Linear Parameter		
Approximate Entropy	1.33 ± 0.2	1.27 ± 0.19
PRSA parameters		
Acceleration Capacity (bpm)	-0.045 ± 0.56	0.012 ± 0.126
Average Acceleration Capacity (bpm)	1.49 ± 1.89	1.873 ± 1.27
Acceleration Phase Rectified Slope (bpm)	0.17 ± 0.04	0.119 ± 0.043
Deceleration Capacity (bpm)	-0.16 ± 0.52	-0.0146 ± 0.129
Average Deceleration Capacity (bpm)	-1.36 ± 1.25	-1.802 ± 1.365
Deceleration Phase Rectified Slope (bpm)	-0.17 ± 0.04	-0.117 ± 0.042

TABLE III
RESULTS OF THE T-TEST COMPARISON BETWEEN HEALTHY AND IUGR PATIENTS

Parameter	t-test	p-value
Time Parameters		
Delta	1	1.45e-9*
Short Time Variability	1	1,22e-9*
Interval Index	0	0,37
Long Term Irregularity	1	2.08e-4*
Non Linear Parameter		
Approximate Entropy	0	0.06
PRSA parameters		
Acceleration Capacity	0	0.44
Average Acceleration Capacity	0	0.20
Acceleration Phase Rectified Slope †	1	1.12e-9*†
Deceleration Capacity	0	0.07
Average Deceleration Capacity	0	0.06
Deceleration Phase Rectified Slope	1	9.57e-12*†

* Statistical significance < 0.05.
†Parameter introduced in this study.

where

$$\Phi^m(r) = \frac{1}{(N-m+1)} \sum_{i=1}^{N-m+1} \ln C_i^m(r). \qquad (10)$$

The ApEn was computed over 3 min windows using $r = 0.2$ and $m = 1$. Then, ApEn values computed over different windows were averaged in order to get a unique parameter per patient.

III. RESULTS

All parameters were computed on the cardiotocographic recordings of 61 healthy and 61 IUGR fetuses. For each parameter, we obtained a single value per subject. Table II summarizes all parameters for the two populations. We have reported only the results obtained using $T = 40$ samples (20 s) for AP identification, and $L = 200$ (200 s window) for PRSA construction. Those values showed the best performance in classifying IUGR and healthy subjects.

Before direct comparison, we verified that the two populations showed Gaussian distributions for all parameters using the Kolmogorov–Smirnov test.

We tested the performance of the parameters in discriminating healthy from IUGR patients using the t-test. Table III summarizes the results. Between the time parameters, Delta and STV show the best performance in the discrimination task (Delta: p-value of 1.45e–9; STV: p-value of 1.22e–9). LTI is also efficient in the discrimination (p-value: 2.08e–4). II is the only time parameter which fails to reject the null hypothesis of the t-test. The nonlinear parameter we employed in the analysis, ApEn, does not allow the rejection of the null hypothesis at 5% significance level.

The parameter we introduced in this paper shows overall the best performance. Indeed the APRS allows the rejection of the null hypothesis with a p-value of 1.12e–9. The DPRS behaves even better, with a p-value of 9.57e–12. The DPRS is the parameter in the analyses which exhibits the smallest p-value in the discrimination between healthy and IUGR patients. On the contrary, with our data, AC and AAC are not efficient in the discrimination. Fig. 3 shows the boxplots, which summarize the results for the two populations. The boxplots confirm the statistics described above, since Delta, STV, APRS, and DPRS are the parameters that behave most efficiently in discriminating healthy and IUGR patients.

In order to determine the optimal discrimination threshold, we computed the ROC curves for the most efficient parameters. Fig. 4 shows the ROC curves computed for the APRS, DPRS, and STV. For APRS, we obtained a cut-off point of 0.1327, which guarantees a sensitivity of 0.7413 and specificity of 0.8033. The corresponding AUC is 0.8235. For DPRS, we obtained a cut-off value of -0.1426, corresponding to a sensitivity of 0.7705 and specificity of 0.7541 (AUC = 0.8371). For STV, we obtained a cut-off point of 5.4658, corresponding to a sensitivity of 0.7636 and specificity of 0.75. The AUC for the STV parameter was 0.8160.

Finally, we also quantified the correlation between the new parameter introduced in the analysis, APRS, and the two parameters that are traditionally and most commonly used in the clinical practice, STV and Delta. APRS shows significant correlation with both the parameters. As Fig. 5 displays, the healthy and IUGR population are clearly recognizable as two very separate clouds of points in the graphs. This result confirms how efficient the new parameter is. Comparable results were obtained using the DPRS in place of APRS (results are not shown but are summarized in Table IV).

IV. DISCUSSION

The aim of this paper was to find more reliable indices for the evaluation of fetal states thus preventing possible disease conditions. We introduced a new parameter able to reliably discriminate IUGR fetuses from normal ones. APRS and DPRS indices were defined as the slope of the phase-rectified signal average curve computed on FHR recordings. The parameter is quantitatively linked to the increase and decrease events (accelerations and decelerations) of the HRV signal. The strength of this index was verified by comparing its performance with

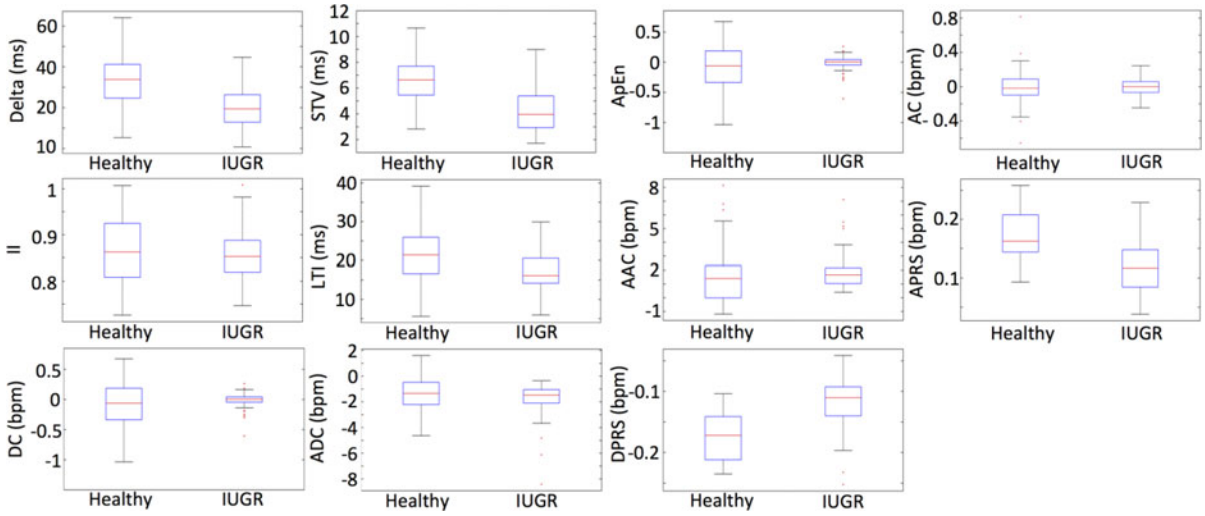

Fig. 3. Boxplots summarize the performances of the computed parameters in the discrimination between healthy and IUGR patients.

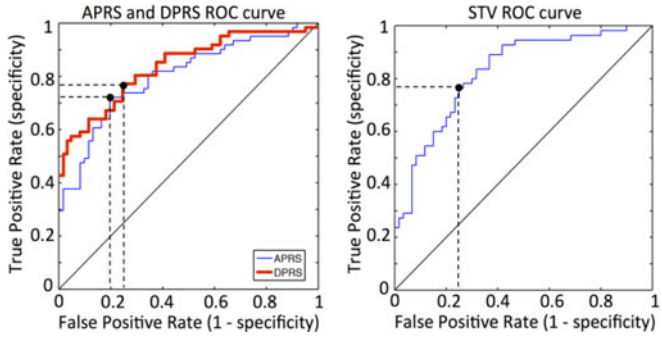

Fig. 4. (Left) ROC curves of APRS (blue thin line) and DPRS (red thick line) computed using 150 intervals. Cut-off value is 0.1327 for APRS and –0.1426 for DPRS. (Right) ROC curve for STV computed using 150 intervals. Cut-off value = 5.4658.

TABLE IV
CORRELATION VALUES BETWEEN STANDARD PARAMETERS AND THE INDICES INTRODUCED IN THE ANALYSIS

Correlation between APRS and:	**Correlation value**	**P-value**
STV	0.6563	1.68e-15
Delta	0.6590	1.18e-15
Correlation between DPRS and:	**Correlation value**	**P-value**
STV	-0.6714	1.17e-16
Delta	-0.6807	5.8e-17

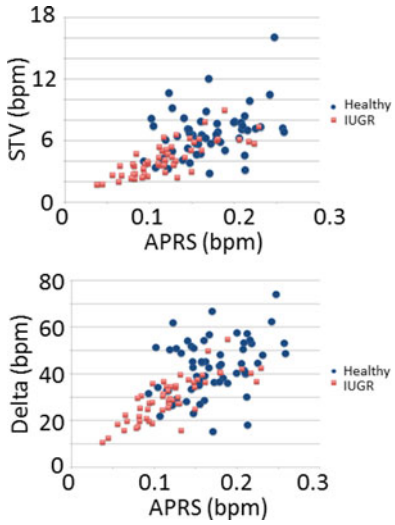

Fig. 5. Correlation between APRS and STV (up) and between APRS and Delta (down). Blue circles represent healthy subjects and red squares mark IUGR fetuses. The two populations are clearly recognizable as two distinct clouds of points.

three different sets of parameters that are employed in fetal heart rate analysis: 1) time domain parameters, 2) nonlinear parameters (ApEn), and 3) other parameters computed on the PRSA curve. The results on a population of 122 subjects (61 normal and 61 IUGRs, carefully selected) show that the parameter we are proposing performs better than any other considered in the comparison. This is confirmed both by the t-tests on the two populations and by the ROC curves shown in Fig. 4.

According to [14], the PRSA curve describes the main increase and decrease episodes (or patterns) in the FHR time series under analysis. Although these events do not correspond exactly to the definitions, usually employed in the clinical routine, of "acceleration" and "deceleration" of FHR signal, they provide almost the same information about the FHR time course.

As a matter of fact accelerations and decelerations are the FHR increase and decrease patterns mostly used by clinicians to quantify fetal well-being. The practice bulletin guideline by the ACOG [7] defined the standards for the interpretation of FHR series: risky conditions are often associated with changes in the entity of accelerations and, mainly, decelerations, in terms of amplitude, duration, and shape. For this reason, we worked to define a global index descriptive of the entity of FHR increases and decreases. The slope of the PRSA curve depends both from the amplitude and duration of such events and that is the reason why it has been proposed to distinguish healthy and IUGR patients.

Results we obtained are coherent with the existing literature on fetal monitoring. Indeed, according to [7], FHR decelerations

are more significant than accelerations to quantify fetal risky conditions because their time courses are strictly related to the physiological recovery from possible hypoxic states. The results obtained applying DPRS and APRS confirm this observation. DPRS performed better than APRS in the discrimination task. We obtained a lower p-value in the t-test and, at the same time, we also obtained a larger AUC in the ROC curve.

APRS and DPRS proved to be correlated with short term variability (STV) and delta, two time domain indices that are generally considered as fundamental to assess fetal well-being in the clinical practice. Interestingly, correlation values between these time domain indices and our APRS and DPRS are statistically significant, even if the computational process to obtain them is extremely different. As a matter of fact, the parameters are computed on two totally different version of the original time series: Delta and STV are computed on the FHR signal, by excluding accelerations and decelerations (as suggested by Arduini *et al*. [20]), while APRS and DPRS are computed on the PRSA curve, a 400 samples time series obtained after an averaging process. This confirms that APRS and DPRS can be used as additional parameters to help clinicians in the difficult task of identifying IUGR fetuses during pregnancy.

As a further outcome, by applying the approach proposed by Huhn [15] to our sample population, we obtained significantly different results in the discrimination of IUGR from normal fetuses. Indeed in our analysis both the indices proposed by Huhn (AAC and ADC) [15] failed in the discrimination between healthy and IUGR patients, while those parameters were highly discriminating in their paper. We believe this difference could be partially explained by the great difference in the gestational age of the two groups in the paper of Huhn *et al*. (33th gestational week for IUGR fetuses versus 37th for healthy ones), by the different sampling frequency and by the preprocessing steps we introduced in our paper. As a matter of fact, we preventively removed artifacts and bad quality FHR segments before computing time parameters, nonlinear parameters and PRSA curve, in order to standardize the temporal series that were used in the analysis. In this way, a more efficient and unbiased comparison can be obtained.

However, even our study presents few critical issues that should be discussed.

Although the two populations of fetuses we selected for the analysis (Healthy and IUGRs) had comparable and partially overlapping gestational ages at the moment of the cardiotocographic monitoring (healthy $= 34.78 \pm 0.53$ weeks and IUGR $= 32.27 \pm 2.79$ weeks), their average values and distribution are not exactly the same. Gestational age might affect the value of the computed parameters, which are subject to changes during the development of the fetus in the evolution of the pregnancy. In order to minimize this problem, we selected for the healthy population only CTG recordings performed during the 34th and 35th gestational week. Recording CTG data before the 34th week was unfeasible, because healthy pregnant women usually are not submitted to fetal monitoring before this week of gestation. IUGR fetuses are delivered (usually by a cesarean section) well in advance the normal end of the pregnancy, while healthy patients are usually monitored only during the final part of the gestational period.

Second, in our population sample, the CTG recordings of healthy patients are shorter than the recordings of IUGR patients and the length of time series in the two groups differs by 1000 s on average. This difference might bias the results: longer recordings are associated with a larger number of APs and, so, more windows are included in the averaging process to build the PRSA curve. Anyway, in order to use all the available information, we decided to proceed with the analysis of the complete time series without cutting the longer ones. Additional tests confirmed that the difference in signal length does not involve significant changes in the computed DPRS or APRS parameters. This happens because the number of windows that are averaged in the process, over a certain threshold, does not affect the slope value of the curve.

Third, as other research groups, we have proposed other indices to assess fetal well-being that have not been included in this comparative analysis [17]. They are parameters based on the frequency content of FHR signals [18], other nonlinear parameters (sample entropy or Lempel Ziv Complexity [10], [18]), and parameters based on the energy content of FHR [20]. We tried to focus our comparison on few significant and popular indexes, currently used in the clinical practice. They represent a limited set but provide an accurate picture of the state of the art in this field. This allows a one to one comparison of the different indices and avoids an excessive dispersion of the analysis.

The most important remark about the new APRS (DPRS) parameter, is that this index integrates in one figure of merit, the complex physiological mechanisms that affect the number, amplitude, and time course of the increases (or decreases) of the FHR signal related to fetal well-being. Its computation allows an immediate evaluation of the fetal condition, which can be automatically extracted by a computer procedure, without the identification of each acceleration (or deceleration) episode as it is usually done in the clinical practice.

V. Conclusion

The final goal of our research is to define a set of indices that could help the clinicians in the critical task of detecting fetal pathological conditions. A new index APRS (DPRS) has been proposed, able to discriminate IUGR from healthy fetuses. It is computed as the slope of the PRSA curve at the anchor point. It shows very good performance when compared with a set of indices that are usually considered to quantify fetal well-being in the clinical practice. APRS and DPRS show the best performance in the discrimination task, behaving better than other parameters computed from the PRSA curve as well as than standard time parameters such as short time variability, long-term irregularity, and Delta. Moreover the two slopes of the PRSA curve do not represent only statistically significant indices, but they are strictly related to physiological events affecting FHR. In some way they summarize the average time course of accelerations and decelerations throughout the whole recording session. This means that the information about the capabilities of fetal cardiovascular control is partially condensed in only two numbers.

APRS and DPRS turned to be simple and reliable indicators of the correct behavior of the ANS in the fetus. They are easily

computed in "one shot" analysis of the whole tracing, without any need to segment the recording in 1 min chunks as it happens for STV and Delta indices, and to identify, separate, and analyze individually each acceleration and deceleration.

Obviously they do not represent the "panacea" for reliably assessing fetal well-being, but they can simplify the automatic analysis of FHR recordings and can be included in a set of quantitative parameters helping the clinicians in the hard task of the prenatal diagnosis.

REFERENCES

[1] M. V. Kamath and E. L. Fallen, "Power spectral analysis of heart rate variability: A noninvasive signature of cardiac autonomic function," *Crit. Rev. Biomed. Eng.*, vol. 21, no. 3, pp. 245–311, 1993.

[2] M. A. Hasan *et al.*, "Detection and processing techniques of FECG signal for fetal monitoring," *Biol. Proced. Online*, vol. 11, no. 1, pp. 263–295, 2009.

[3] D. Peleg, C. M. Kennedy, and S. K. Hunter, "Intrauterine growth restriction: Identification and management," *Amer. Family Physician*, vol. 58, no. 2, pp. 453–460, 1998.

[4] J. A. Martin, B. E. Hamilton, P. D. Sutton, S. J. Ventura, F. Menacker, and M. L. Munson, "Births: Final data for 2002," *Nat. Vital Stat. Rep.*, vol. 52, no. 1, pp. 1–102, 2003.

[5] M. J. Stout and A. G. Cahill, "Electronic fetal monitoring: Past, present and future," *Clin. Perinatol.*, vol. 38, no. 1, pp. 127–142, 2011.

[6] C. Peters, R. Vullings, J. Bergmans, G. Oei, and P. Wijn, "Heart rate detection in low amplitude non-invasive fetal ECG recordings," in *Proc. IEEE Eng. Med. Biol. Soc.*, 2006, pp. 6092–6094.

[7] "Intrapartum fetal heart rate monitoring: Nomenclature, interpretation, and general management principles," *Clin. Manage. Guidelines Obstet.—Gynecol.*, vol. 106, pp. 192–202, 2002.

[8] P. V. Nielsen, B. Stigsby, C. Nickelsen, and J. Nim, "Intra- and inter-observer variability in the assessment of intrapartum cardiotocograms," *Acta Obstet. Gynecol.*, vol. 66, pp. 421–4, 1987.

[9] 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 Trans. Biomed. Eng.*, vol. 50, no. 3, pp. 365–374, Mar. 2003.

[10] M. Ferrario, M. G. Signorini, and G. Magenes, "Complexity analysis of the fetal heart rate variability: Early identification of severe intrauterine growth-restricted fetuses," *Med. Biol. Eng. Comput.*, vol. 47, no. 9, pp. 911–919, 2009.

[11] A. Bauer, A. Bunde, P. Barthel, R. Schneider, M. Malik, and G. Schmidt, "Phase rectified signal averaging detects quasi-periodicities in non-stationary data," *J. Phys. A*, vol. 364, pp. 423–434, 2006.

[12] R. K. Laros, W. S. Wong, D. C. Heilbron, J. T. Parer, S. M. Shnider, H. Naylor, H. , and J. Butler, "A comparison of methods for quantitating fetal heart rate variability," *Amer. J. Obstet. Gynecol.*, vol. 128, no. 4, pp. 381–392, 1977.

[13] S. Y. Yeh, A. Forsythe, and E. H. Hon, "Quantification of fetal heartbeat-to-beat interval differences," *Obstet. Gynecol.*, vol. 41, no. 3, pp. 355–363, 1973.

[14] S. M. Pincus, "Approximate entropy (ApEn) as a complexity measure," *Chaos*, vol. 5, pp. 110–117, 1995.

[15] E. A. Huhn, S. Lobmaier, T. Fischer, R. Schneider, A. Bauer, K. T. Schneider, and G. Schmidt, "New computerized fetal heart rate analysis for surveillance of intrauterine growth restriction," *Prenat. Diagn.*, vol. 31, no. 5, pp. 509–514, 2011.

[16] A. Bauer, P. Barthel, and R. Schneider, "Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: Cohort study," *Lancet*, vol. 367, pp. 1674–1681, 2006.

[17] G. Magenes, M. G. Signorini, D. Arduini, and S. Cerutti, "Fetal heart rate variability due to vibroacoustic stimulation: Linear and nonlinear contribution," *Methods Inf. Med.*, vol. 43, pp. 47–51, 2004.

[18] M. Ferrario, M. G. Signorini, G. Magenes, and S. Cerutti, "Comparison of entropy-based regularity estimators: application to the fetal heart rate signal for the identification of fetal distress," *IEEE Trans. Biomed. Eng.*, vol. 53, no. 1, pp. 119–125, Jan. 2006.

[19] J. W. Kantelhardt, A. Bauer, A. Y. Schumann, P. Barthel, and R. Schneider, "Phase-rectified signal averaging for the detection of quasi-periodicities and the prediction of cardiovascular risk," *Chaos*, vol. 17, no. 1, pp. 015112-1–015112-9, 2007.

[20] D. Arduini, Rizzo, G. Piana, A. Bonalumi, P. Brambilla, and C. Romanini, "Computerized analysis of fetal heart rate—Part I: description of the system (2CTG)," *J. Matern. Fetal Invest.*, vol. 3, pp. 159–164, 1993.

[21] J. D. Haan, J. V. Bemmel, B. Versteeg, A. Veth, L. Stolte, J. Janssens, and J. Eskes, "Quantitative evaluation of fetal heart rate patterns—Part I: Processing methods," *Eur. J. Obstet. Gynecol.*, vol. 3, pp. 95–102, 1971.

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