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Fetal heart rate monitoring and neonatal outcome in a population of early- and late-onset intrauterine growth restriction

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Abstract

Aim: The early-onset intrauterine growth restriction (IUGR) is associated with severe placental insufficiency and Doppler abnormalities. The late-onset IUGR is associated with mild placental insufficiency and normal Doppler velocimetry. The computerized cardiotocographic (cCTG) monitoring is used to evaluate the fetal well-being in pregnancies complicated by IUGR. Our aim was to investigate the cardiotocographic characteristics of IUGR fetuses and to identify every cCTG difference between Healthy and IUGR fetuses.

Methods: Four hundred thirty pregnant women were enrolled starting from the 28th week of gestation until the time of delivery: 200 healthy and 230 IUGR fetuses. Fetal heart rate (FHR) baseline (FHR), short-term variability (STV), long-term irregularity (LTI), delta, interval index (II), approximate entropy (ApEn), high frequency (HF), low frequency (LF), movement frequency (MF), LF/(HF + MF) ratio (LF/(HF + MF)) and number of decelerations were examined. Newborn baby data were also collected.

Results: The parameters of short- and medium-term variability discriminate between IUGR and healthy fetuses before 36 weeks including FHR, STV, LTI and delta discriminate between each subgroup of IUGR were compared to each one of the other two ($P < 0.05$).

Conclusion: cCTG is a useful tool for the evaluation of chronic hypoxemia, which causes a delay in the maturation of all components of the autonomic and central nervous system. However, cCTG requires integration with fetal ultrasound and Doppler vessels evaluation to improve the ability to predict the neonatal outcome.

Key words: antepartum fetal monitoring, computerized cardiotocography, early-onset growth restriction, fetal heart rate, late-onset growth restriction.

Introduction

The term IUGR (intrauterine growth restriction) is used to define a fetus with estimated fetal weight <10th centile for the gestational age and it is not able to reach its genetically determined growth potential for many factors. To date, the definition of IUGR remains elusive and the best way to identify IUGR is yet to be determined.[1] IUGR complicated 3–9% of all pregnancies with 30% of stillborn infants cases.[2,3] In addition, IUGR is associated with a four- to eightfold higher perinatal mortality and a series of neonatal complications (persistent pulmonary hypertension, polycythemia, hypothermia, hypoglycemia, hyperglycemia, pulmonary hemorrhage, premature delivery, asphyxia intrapartum).[2–7]

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According to the time of onset of growth restriction we distinguished the early-onset from the late-onset IUGR. The early-onset (<32–34 weeks) represents 20–30% of all IUGRs and it is associated with severe placental insufficiency, Doppler abnormalities and preeclampsia (50% of cases).[7] According to some studies, the pathophysiology of early-onset is a reduction of more than 30% in the vascular area of the chorionic villi, resulting in severe placental insufficiency and chronic fetal hypoxia.[8–10]

The late-onset IUGR represent the 70–80% of IUGR cases, it is frequently associated with mild placental insufficiency and normal Doppler velocimetry. The pathophysiology of the late-onset is the insufficient maturation of the chorionic villi or the reduction of their area in the placenta.[9]

The electronic fetal heart rate (FHR) monitoring is one of the most widespread but not an invasive method to evaluate the fetal well-being during the antenatal period, especially in pregnancies complicated by IUGR.

Many efforts have been made to understand the mechanisms of regulation of FHR variability in Healthy and IUGR fetuses. Computerized cardiotocography (cCTG) provide a standardized method to evaluate conventional CTG parameters and introduced quantitative measures of linear and nonlinear indices related to FHR variability as a multiparametric analysis of fetal cardiovascular and nervous activity. The presence of significant beat to beat variation suggests intact baroreflex, sympathetic/parasympathetic tone and central control indicating normal central nervous system (CNS) responsiveness and normal local CNS metabolic environment reflecting fetal health.[10–12]

Our aim was to evaluate the trend of cCTG parameters in IUGR fetuses and to identify every cCTG difference between Healthy and IUGR fetuses.[13]

Materials and Methods

This retrospective study was carried out at the Department of Obstetrical-Gynecological and Urological Science and Reproductive Medicine of the Federico II University (Italy) in a period of 3 years (2015–2017). All pregnant women gave their written informed consent. Starting from a population of 5400 pregnant women 430 pregnant women composed of 200 Healthy and 230 IUGR fetuses fulfilled the criteria of the study. Inclusion criteria were Caucasian ethnicity; singleton pregnancy; certain pregnancy dating; cCTGs with a signal loss of less than 15% over the whole record. cCTG monitoring was recorded once a week for IUGR and Healthy fetuses but only the last cCTG record within 24 h of delivery was considered and the delivery indication was only for fetal condition in IUGR group. We considered as 'Healthy' a fetus whose growth is appropriate for gestational age without any chromosomal and major congenital anomalies. Healthy fetuses were subjected to cCTG monitoring at the same gestational weeks of IUGR ones as admission test in hospital for preterm contractions without preterm premature rapture of membranes or vaginal swab positive for infections before labor. Newborn baby data (sex, weight, Apgar score, access to neonatal intensive care, umbilical artery pH and gas values) were collected.

We excluded preexisting maternal disease, drug abuse, fetuses with chromosomal and major congenital anomalies, and inadequate umbilical cord samples at birth.

The pregnant women were enrolled starting from the 28th week of gestation until the time of delivery. Gestational age was accurately calculated from the first day of the last menstrual period and confirmed by ultrasound measurement of the embryo or fetus in the first trimester, according to the population nomograms.[14] The diagnosis of IUGR was based on the evaluation of estimated weight and estimated abdominal circumference below the 10th centile, according to the gestational age. In the early-onset IUGR the diagnosis was also based on the Doppler criteria (pulsatility index [PI] of UA >95th centile for the gestational age irrespective of the presence or absent of reversed end-diastolic flow).[8]

To discriminate between early- and late-onset IUGR, the study population was divided into three subgroups according to the gestational age at delivery (<32th weeks of gestation; from 32th to 36th weeks of gestation; >36th weeks of gestation).

The tests were made with the same frequency in all cases.

Among 28 + 0 to 32 + 0 weeks of gestation, elective cesarean section was performed in case of absent end-diastolic flow in the UA or DV PI >95th centile and/or cCTG abnormalities (low short-term variability or recurrent deceleration). After 32 + 1 weeks of gestation elective cesarean section was performed in the case of PI >95th centile in the UA or PI <5th centile in the middle cerebral artery and/or cCTG abnormalities (e.g. low short-term variability).

For most patients, the delivery occurred after at least 24 h the administration of maternal steroids before 34 weeks.

Signal acquisition

The antepartum cCTG monitoring was performed in a controlled clinical environment with the patient lying on an armchair. cCTG records were obtained using Corometrics 170, General Electrics. The cardiotocograph is equipped with two transducers: the first one is an ultrasound transducer to detect the FHR, posted next to the focus of maximum auscultation of fetal heart; the second one is a pressure transducer for uterine contractile activity located next to the uterine fundus.

The cardiotocograph is connected to a smartphone that, via general packet radio service, sends traces to the operation center, interfaced to 2CTG2 system (SEA) for computerized analysis on segments 3 min long of recording.

The FHR records were performed according to the American College of Obstetrician and Gynecologists guidelines and the FHR analysis was carried out using segments of 3 min (360 data points) without missing data, in order to prevent influences of incorrect heart rates and to obtain the same length of analysis segment for all parameters investigated, irrespective of the traces length. The initial, the middle and the final 3 min of each trace were averaged, in order to obtain a single analysis segment for each trace.

The hewlett packard (HP) fetal monitors use an autocorrelation technique to compare the demodulated Doppler signal of a heartbeat with the next one. Each Doppler signal is sampled at 200 Hz (5 ms). The time window over which the autocorrelation function is computed is 1.2 s, corresponding to an FHR lower bound of 50 bpm. A peak detection software then determines the heart period (the equivalent of RR period) from the autocorrelation function. With a peak position interpolation algorithm, the effective resolution is better than 2 ms.

The HP monitor produces an FHR value in bpm every 250 ms. In the commercially available system, the PC reads 10 consecutive values from the monitor every 2.5 s and determines the actual FHR as the average of the 10 values (corresponding to an equivalent sampling frequency of 0.4 Hz). We used a modified 2CTG2 software, which averages two consecutive values in order to read the FHR values each 0.5 s (2 Hz). The choice of reading the FHR values each 0.5 s represents a reasonable compromise to achieve an enough large bandwidth (Nyquist frequency of 1 Hz) and an acceptable accuracy of the FHR signal.

The following cCTG parameters were examined: fetal heart rate baseline (FHR), short-term variability (STV), long-term irregularity (LTI), delta, interval index (II), approximate entropy (ApEn), high frequency (HF), low frequency (LF), movement frequency (MF), LF/ (HF + MF) ratio (LF/(HF + MF)) and number of decelerations.

Baseline. It is a running average of the heart rate where accelerations and decelerations are defined as deviations of the FHR from the baseline lasting a sufficient amount of time. In an automated system for the evaluation of the CTG recordings, a reproducible determination of the baseline is fundamental. We used a real-time version of Mantel's algorithm.[15]

Short-term variability: STV quantifies FHR variability over a very short time scale on a beat-to-beat basis. Considering 1 min of interbeat sequence, T_{24}(i) in ms, i = 1, …, 24, we defined STV as:

$$\mathrm{STV} = \mathrm{mean}[|T_{24}(i+1) - T_{24}(i)|]_i = \frac{\Sigma_{i=1}^{23}|T_{24}(i+1) - T_{24}(i)|}{23}$$

where T_{24}(i) is the value of the signal ?(i) taken each 2.5 s. The differences in these 24 values per minute are calculated and their absolute values were averaged.[16]

Long-term irregularity: LTI is computed on a 3-min segment of interbeat sequence in milliseconds. Given a signal? 24(i) with i ∈ [1; 72], LTI is defined as the interquartile range (1/4; 3/4) of the distribution of the modal $m_{24}(j)$ with i ∈ [1; 71][16]:

$$m_{24}(j) = \sqrt{{T_{24}}^2(j) + {T_{24}}^2(j+1)}$$

Approximate entropy: ApEn is a collection of statistical indexes. It measures the regularity and, indirectly, the correlation and the persistence of a signal: small values indicate reduced signal irregularity. We use the original definition by Pincus[17]:

$$\mathrm{ApEn\_(m,r)} = \frac{\Sigma_{i=1}^{N-m+1}\log \mathrm{C}_i(m,r)}{N-m+1} - \frac{\Sigma_{i=1}^{N-m}\log \mathrm{C}_i(m+1,r)}{N-m}$$

where m is a natural number, r is a positive real and N = 720. The parameter m determines the lengths of the vectors that are compared. By increasing m it increases the degree of detail for the signal analysis. The r parameter represents the filtering level or, in other words, the tolerance level with respect to signal outliers: differences between two vectors smaller than r, in absolute value, are considered not relevant.[18]

Delta: Given a minute of signal in millisecond $T24(i)$ with $i \in [1; 24]$, Delta is defined as the difference between the maximum and minimum FHR values and represents medium term variability:

$$\text{Delta} = \max T_{24}(i) - \min T_{24}(i)$$

Arduini *et al*.[16] excluded big accelerations and decelerations from the calculation.

Interval index: II is calculated as the coefficient of variation between the differences of all FHR values in 1 min of interbeat sequence, taken each 2.5 s. It was proposed by Yeh *et al*.[19] as a long-term variability statistic. We adopted the formulation used by Arduini *et al*.[16]:

$$\text{II} = \frac{\text{std}[T_{24}(i+1) - T_{24}(i)]}{\text{STV}}, \quad i = 1, \ldots, 23$$

Power spectral analysis of FHR variability: The Power Spectrum of FHR variability can be quantified during the period of activity and fetal sleep by the use of mathematical algorithms in the following frequency ranges: low frequency (LF: 0.03–0.15 Hz), movement frequency (MF: 0.15–0.50 Hz, not present in adult human subjects) and high frequency (HF: 0.50–1.00 Hz) ranges, generally. LF and HF bands are associated with the autonomic nervous system (ANS) activity (mainly sympathetic and parasympathetic branches, respectively) while the MF band is connected to fetal movements and maternal respiratory frequency. The LF/(HF + MF) ratio was also estimated as well and it quantifies the autonomic balance between neural control mechanisms from different origin (in accordance with the LF/HF ratio normally calculated in adults). For a detailed description of how these parameters are computed, please refer to Reference [13]

Statistical analyses

Data statistical analysis was performed using statistical package for social science (SPSS) version 19.0 software for windows statistical package. The Kolmogorov–Smirnov test showed a Gaussian distribution in both populations for all parameters investigated. Analysis of variance (ANOVA) test investigated the existence of a statistical significant difference between Healthy and IUGR fetuses and among the three subgroups of IUGR.

Results

In a period of 3 years we evaluated 430 singleton pregnancies, composed of 200 Healthy and 230 IUGR fetuses. IUGR group was composed of 72 fetuses below the 32th week of gestation, 112 fetuses between the 32th and 36th week of gestation, and 46 fetuses over the 36th week of gestation.

The 20.5% of the IUGR fetuses were transferred to neonatal intensive care (TIN) at birth and neonatal mortality occurred in 8.4% of cases before 32th weeks. Fetal pH at birth was in the range of normality for all subgroups (Table 1), we excluded 26 IUGR and

Table 1 Maternal and perinatal characteristics

	Healthy			IUGR		
	<32 weeks	32–36 weeks	>36 weeks	<32 weeks	32–36 weeks	>36 weeks
Demographic data						
Patients (*n*)	20	80	100	72	112	46
Maternal age (years)†	34 ± 3.9	33 ± 5.8	32.09 ± 4.9	32.8 ± 5.4	32.2 ± 5.7	32.6 ± 6.6
Week of delivery†	30.7 ± 0.9	35.5 ± 2.5	39.3 ± 1.1	29.5 ± 1.7	34.8 ± 1.4	37.5 ± 3.9
Cesarean section (%)	25	50	39	98.5	94.3	47.8
Vaginal delivery (%)	75	50	61	1.5	5.6	52.2
Neonatal data						
Birth weight (g)†	1646 ± 158	2651 ± 669	3311 ± 372	939 ± 311	1698 ± 365	2186 ± 423
Female (%)	40	50	45	25	49.1	56.4
Apgar <7 at 1 min (%)	10	2.5	1	61.1	9.8	10.8
Apgar <7 at 5 min (%)	0	0	0	12.5	3.6	0
pH†	7.31 ± 0.03	7.30 ± 0.04	7.28 ± 0.08	7.25 ± 0.1	7.31 ± 0.5	7.30 ± 0.07
pCO_2†	38 ± 2.9	44.67 ± 4.94	45.8 ± 9.7	47.22 ± 14.1	48.44 ± 8.8	48.8 ± 10.5
pO_2†	18 ± 4.08	21.11 ± 16.2	19.7 ± 8.3	7.77 ± 9.2	7.11 ± 5.4	16.5 ± 13.2
Base Excess†	−2 ± 2.9	−2 ± 3.23	−4.4 ± 3.3	−1.6 ± 4.6	−1.5 ± 3.1	−1.9 ± 3.6
Neonatal mortality (%)	0	0	0	8.4	0	0

†Values above are expressed as mean ± standard deviation.

39 Healthy for inadequate umbilical cord samples at birth for both pH and gas values (insufficient blood sampling and/or errors in pH and gas analysis by the pH meter).

The ANOVA test revealed a significant difference for birth weight, week of delivery, Apgar Score at 1 min, pO_2 and pCO_2 between each subgroup of study compared to each one of the other group ($P < 0.05$), as they were preselected for the differences. In the 32–36th weeks subgroup, the ANOVA test also showed a statistically significant difference for Apgar at 5 min, while no difference was observed between '<32 weeks versus 32–36 weeks' in IUGR for pO_2. ($P < 0.05$).

Table 2 Results of comparison between Healthy and IUGR fetuses

	Healthy (mean ± SD)	IUGR (mean ± SD)	*P*-value*
FHR (bpm)			
<32th	143.06 ± 8.63	143.49 ± 7.52	0.91
32th–36th	135.6 ± 10.34	138.8 ± 9.64	0.22
>36th	137.19 ± 8.11	134.38 ± 10.2	**<0.05****
STV (ms)			
<32th	5.34 ± 1.88	3.11 ± 1.31	**<0.01**
32th–36th	6.67 ± 1.89	5.11 ± 2.30	**<0.05**
>36th	6.39 ± 1.87	6.13 ± 1.88	0.36
LTI (ms)			
<32th	19.70 ± 4.07	14.51 ± 5.77	0.08
32th–36th	21.51 ± 6.29	18.49 ± 6.03	0.06
>36th	21.70 ± 5.94	21.33 ± 5.53	0.68
ApEn			
<32th	1.22 ± 0.17	1.24 ± 0.23	0.08
32th–36th	1.28 ± 0.16	1.33 ± 0.18	0.06
>36th	1.31 ± 0.16	1.28 ± 0.19	0.68
Delta (ms)			
<32th	35.85 ± 9.54	24.82 ± 10.13	**<0.05**
32th–36th	41.8 ± 9.43	33.22 ± 11.65	**<0.05**
>36th	41.12 ± 10.04	39.25 ± 8.75	0.21
II			
<32th	0.83 ± 0.01	0.87 ± 0.06	0.19
32th–36th	0.85 ± 0.08	0.84 ± 0.06	0.44
>36th	0.85 ± 0.05	0.83 ± 0.05	**<0.05**
LF (ms^2)			
<32th	84.63 ± 4.85	79.74 ± 6.83	0.16
32th–36th	82.33 ± 5.20	81.10 ± 5.84	0.43
>36th	81.66 ± 5.41	80.98 ± 12.13	0.56
MF (ms^2)			
<32th	9.35 ± 1.62	12.20 ± 3.45	0.10
32th–36th	11.91 ± 3.55	13.15 ± 9.09	0.59
>36th	12.93 ± 3.42	11.18 ± 3.44	**0.001**
HF (ms^2)			
<32th	6.02 ± 4.54	8.01 ± 4.70	0.41
32th–36th	8.00 ± 9.27	6.86 ± 4.72	0.43
>36th	5.41 ± 3.17	6.06 ± 3.68	0.20
LF/(HF + MF)			
<32th	5.17 ± 3.24	3.99 ± 2.47	0.36
32th–36th	3.51 ± 1.95	4.20 ± 1.99	0.19
>36th	4.13 ± 2.07	3.91 ± 2.38	0.5
Deceleration (*n*)			
<32th	0.00 ± 0.00	0.78 ± 1.55	0.32
32th–36th	0.00 ± 0.00	0.43 ± 0.87	**0.05**
>36th	0.07 ± 0.26	0.35 ± 0.75	**<0.001**

**P*-value for comparison between Healthy and IUGR; **Values in bold are statistically significant. ApEn, approximate entropy; FHR, fetal heart rate; HF, high frequency; II, interval index; IUGR, intrauterine growth restriction; LF, low frequency; LF/(HF + MF), the LF/(HF + MF) ratio; LTI, long-term irregularity; MF, movement frequency; SD, standard deviation; STV, short-term variability.

Finally, in the subgroup >36th week, a statistically significant difference was also observed for the Base Excess ($P < 0.05$). No differences were found with respect to the gender of newborns.

The aim of the study was to identify which parameter or parameters set is most efficient in the discrimination between Healthy and IUGR fetuses. The ANOVA test showed statistically significant differences between Healthy and IUGR in the <32th week subgroup for STV and Delta. In the comparison between Healthy and IUGR in the 32–36th subgroup a statistically significant difference is observed for STV, Delta and the number of decelerations, while in the >36th subgroup, the ANOVA test showed statistically significant differences for FHR, II, MF and the number of decelerations (Table 2).

A comparison study between early- and late-onset IUGR was made to highlight any difference among cCTG parameters. The ANOVA test showed a statistically significant difference between the three IUGR subgroups for the following parameters: FHR, STV, LTI, II, Delta, ApEn, HF and number of decelerations (Table 3).

Among the IUGR subgroups, the ANOVA test with Bonferroni correction evidenced a statistically significant difference between each subgroup of the study compared to each one of the other two ('<32th week' vs '32–36th week'; '<32th week' vs '>36th week'; and '32–36th week' vs '>36th week' groups) for FHR, STV, LTI, Delta ($P < 0.05$). A statistically significant difference was found between '<32th week' and '32–36th week', '<32th week' and '>36th week' for II and between '<32th week' versus '32–36th week' for ApEn in IUGR subgroups. No statistically significant differences were found for spectral analysis parameters.

We evaluated the correlation between fetal pH values at birth and STV values in Healthy and IUGR fetuses delivered by cesarean section, in order to avoid the effect of labor on fetal pH at birth. Receiver operating characteristic (ROC) curves have not shown a correlation between STV and pH values in IUGR (area = 0.371; $P = 0.076$) and in Healthy group (area = 0.516; $P = 0.084$) (Fig. 1).

Discussion

Aim of this study was to investigate the cardiotocographic characteristics of IUGR fetuses and to identify every cCTG differences between Healthy and IUGR fetuses. In order to improve clinical management, we decided to separate IUGR fetuses into three subgroups, according to different pathophysiology between early- and late-onset IUGR. In fact, the early onset is associated with severe placental insufficiency and Doppler abnormalities, while the late onset is frequently associated with mild placental insufficiency and normal Doppler velocimetry.[8,20]

The STV is the most significant indicator of fetal homeostasis, especially when it is compared to long and medium term variability. In fact, STV is the most extensively studied parameter of cCTG, because it is able to assess the baroreflex and the integrity of the ANS and its connections with the CNS[11,12]: normal

Table 3 Results of comparison among IUGR subgroups

	IUGR			
	<32 weeks (media ± SD)	32–36 weeks (media ± SD)	>36 weeks (media ± SD)	*P*-value
FHR (bpm)	143.49 ± 7.52	138.8 ± 9.64	134.38 ± 10.26	**<0.0001***;***; **0.003**$^{\mathbf{A-B}}$**; **<0.0001**$^{\mathbf{A-C}}$; **0.013**$^{\mathbf{B-C}}$
STV (ms)	3.11 ± 1.31	5.11 ± 2.30	6.13 ± 1.88	**<0.0001**; **<0.0001**$^{\mathbf{A-B}}$; **<0.0001**$^{\mathbf{A-C}}$; **0.006**$^{\mathbf{B-C}}$
LTI (ms)	14.51 ± 5.77	18.49 ± 6.03	21.33 ± 5.53	**<0.0001**; **<0.0001**$^{\mathbf{A-B}}$; **<0.0001**$^{\mathbf{A-C}}$; **0.011**$^{\mathbf{B-C}}$
ApEn	1.24 ± 0.23	1.33 ± 0.18	1.28 ± 0.19	**<0.05**; **0.016**$^{\mathbf{A-B}}$; 0.968^{A-C}; 0.375^{B-C}
Delta (ms)	24.82 ± 10.13	33.22 ± 11.65	39.25 ± 8.75	**<0.0001**; **<0.0001**$^{\mathbf{A-B}}$; **<0.0001**$^{\mathbf{A-C}}$; **0.002**$^{\mathbf{B-C}}$
II	0.87 ± 0.06	0.84 ± 0.06	0.83 ± 0.05	**<0.0001**; **0.001**$^{\mathbf{A-B}}$; **<0.0001**$^{\mathbf{A-C}}$; 0.825^{B-C}
LF (ms^2)	79.74 ± 6.83	81.10 ± 5.84	80.98 ± 12.13	0.52; 0.824^{A-B}; 1.000^{A-C}; 1.000^{B-C}
MF (ms^2)	12.20 ± 3.45	13.15 ± 9.09	11.18 ± 3.44	0.20; 1.000^{A-B}; 1.000^{A-C}; 0.230^{B-C}
HF (ms^2)	8.01 ± 4.70	6.86 ± 4.72	6.06 ± 3.68	**0.05**; 0.297^{A-B}; **0.051**$^{\mathbf{A-C}}$; 0.859^{B-C}
LF/(HF + MF)	3.99 ± 2.47	4.20 ± 1.99	3.91 ± 2.38	0.70; 1.000^{A-B}; 1.000^{A-C}; 1.000^{B-C}
Deceleration (*n*)	0.78 ± 1.55	0.43 ± 0.87	0.35 ± 0.75	**0.05**; 0.124^{A-B}; 0.086^{A-C}; 1.000^{B-C}

**P*-value for comparison of the three groups using the ANOVA test; ***P*-value for comparison of the three groups using the ANOVA test with the Bonferroni correction A–B (<32 weeks vs 32–36 weeks), A–C (<32 weeks vs >36 weeks), B–C (32–36 weeks vs >36 weeks) groups; ***Values in bold are statistically significant. ApEn, approximate entropy; FHR, fetal heart rate; HF, high frequency; II, interval index; IUGR, intrauterine growth restriction; LF, low frequency; LF/(HF + MF), the LF/(HF + MF) ratio; LTI, long-term irregularity; MF, movement frequency; SD, standard deviation; STV, short-term variability.

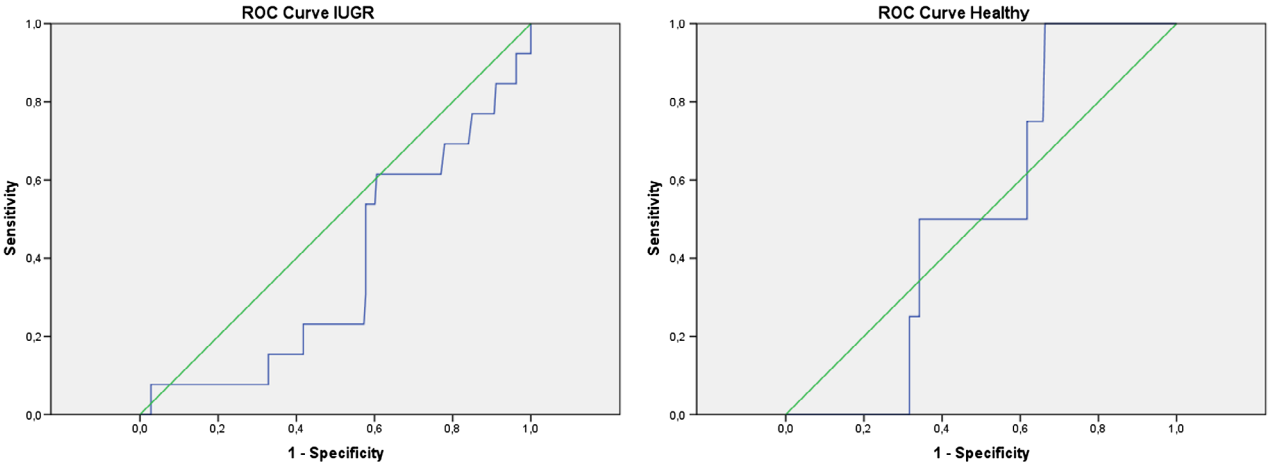

Figure 1 ROC curves between STV and pH values at birth in IUGR and Healthy fetuses, respectively. ROC, receiver operating characteristic; IUGR, intrauterine growth restriction; STV, short-term variability.

STV values reflect an healthy ANS, normal activity of chemoreceptors, baroreceptors and cardiac responsiveness, while low STV values are associated with impending deterioration of fetal oxygen supply and therefore fetal distress.[21,22]

In the clinical practice, abnormal low STV values reflect acute changes in the fetal condition and they are associated with an increased risk of motor and neurological delay in preterm IUGR and damage in specific brain areas with cognitive effects as gestation advances.[23]

It is reported that in IUGR fetuses there is a delay in the stages of biophysical development, which may be related to chronic hypoxia.[24] This delay affects the ANS maturation.

Our results are expression of different etiopathogenesis between early- and late-onset IUGR; in fact, in early-moderate IUGR, a statistically significant difference is evident in the parameters of short- and medium-term variability (STV and Delta) compared to healthy ones of the same gestational age. This difference could be a manifestation of the effect of chronic hypoxia on the development and functioning of the autonomous fetal nervous system (SNA). In the late-onset IUGRs, this difference is not meaningful, probably because of mild-moderate uteroplacental insufficiency which determines a minor impact on neurodevelopment; in our study only FHR and MF are statistically different between late-onset IUGR and Healthy subgroups.

Movement frequency quantifies fetal movements, basically of the trunk. It also depends on maternal breathing, as an high correlation between the fetal MF component and the maternal respiratory frequency was found. Lower MF values in IUGR fetuses reflect a minor reactivity and responsiveness to external and internal stimuli, expression of lower energy and/or oxygen reserves of these fetuses than the healthy fetuses.[25]

In our study, the FHR values were found to be lower in late-onset IUGR subgroup than in Healthy ones; this result is in disagreement with the evidence that IUGR causes a delay in the maturation of the parasympathetic branch of the ANS with a compensatory activity of the sympathetic branch. However, some studies, showed lower FHR in late-onset IUGR than in Healthy at the same gestational age, and higher FHR in early-onset IUGR than Healthy at the same gestational age. It has been suggested that the sympathetic nervous system is more affected than parasympathetic tone in IUGR. Therefore, the prevalence of the parasympathetic tone could justify the finding of a lower baseline at certain gestational ages.[24,26,27]

According to Baschat,[21] the longitudinal progression of abnormal Doppler waveforms in the early IUGR deterioration of uteroplacental function is the following: elevated umbilical artery blood flow resistance and reduced umbilical vein flow volume precede the onset of a growth delay, followed by decreased middle cerebral artery impedance and increased brain venous blood flow velocities which characterize the 'brain sparing effect'. These early responses are physiologically followed by late-onset Doppler abnormalities such as absent/reversed umbilical artery end-diastolic velocity, absent/reversed ductus venosus waves. Instead in late-onset IUGR there is not always evidence of this

progression because the umbilical artery and the ductus venosus are almost always regular, while the middle cerebral artery can occasionally shows a reduced PI.

In the context of IUGR fetuses, statistically significant differences were found on the basis of gestational age. FHR baseline shows a progressive reduction as the gestational age increases, it could be the consequence of the progressive maturation of the parasympathetic branch of the ANS.

Short-, medium- and long-term variability values were different for all pairwise comparisons between IUGR subgroups, showing lower values in the early-onset IUGR with respect to the late-onset ones.

These results could be related to progressive maturation of the ANS but they also could be influenced by different degree of involvement of the SNA at the hypoxic insult: as soon as the insult occurs, the damage and the onset of an alteration of the biophysical parameters will be more serious.

According to our previous study,[28] chronic hypoxemia is responsible for a delay in the maturation of all the components of the ANS and their integration with the CNS. This delay causes lower values of short- and long-term variability.

In addition, chronic hypoxemia is associated with normal pH values at birth, while low pH values mainly correlate with progression to metabolic and respiratory acidosis. According to literature, our study shows a weak no correlation between STV values and pH at birth in IUGR and Healthy groups. This correlation is probably caused by three outliers with low STV and pH values. In fact, Kapaya *et al*. showed moderate accuracy of STV in predicting fetal acidemia; also Pels *et al*. did not support an association of STV and short- or long-term outcome.[29,30]

Studies evaluating the monitoring of pregnancies complicated by IUGR are very heterogeneous and its pathophysiology is constantly evolving. As a result, to date no shared global guidelines on IUGR monitoring are available and the timing of delivery a preterm IUGR fetus remains one of the major challenges in obstetrics. Cardiotocography is a useful tool for the evaluation of these fetuses, but requires integration with fetal ultrasound and Doppler vessels evaluation to improve the ability to predict the neonatal outcome.

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