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QUANTITATIVE CARDIOTOCOGRAPHY AND DOPPLER ULTRASOUND IN THE DETECTION OF HYPOXIA AMONG LATE-ONSET FGR

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Abstract

The aim of this paper was to evaluate the benefits of combining Doppler measurements of placental/fetal blood vessels with computerized cardiotocography (quantitative cardiotocogrpahy – qCTG) in the detection of fetal hypoxia (pH $<$ 7.20) among late-onset growth restricted (FGR) fetuses.

This is a retrospective observational study, including 356 singleton pregnancies diagnosed with late-onset fetal growth restriction (FGR). The trial was undertaken between 2018 and 2021 in Second Municipal Hospital for Obstetrics and Gynecology Sheynovo, which is a tertiary referral facility, located in Sofia, Bulgaria. Women participating in the study underwent serial cardiotocographic and Doppler examinations of umbilical artery (UA), middle cerebral artery (MCA), and ductus venosus (DV). The cerebro-placental ratio (CPR) was also calculated. Analysis of cardiotocographic findings was performed by standard CTG and the "quantitative cardiotocogrpahy" (qCTG) computer algorithm. Relationships between antenatal test results and cord artery pH $<$ 7.20 were analysed using logistic regression.

Three hundred and fourteen participants (88.2%) met the inclusion criteria. Logistic regression demonstrated that abnormalities in qCTG readings, CPR and DV Doppler velocimetry were independently correlated with the occurrence of fetal hypoxia (pH $<$ 7.20) in the newborn. The model obtained after elimination of variables that did not prove to be significantly correlated with the dependent variable (UA, P = 0.0882; MCA, P = 0.0592; Standard

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CTG, $P = 0.1738$) allowed the identification of neonatal hypoxia with 86.1% sensitivity and 79.5% specificity (AUC = 0.835, $P < 0.0001$). Furthermore, according to the equation derived from this final regression model, the probability of fetal hypoxia varies between a minimum of 6%, when none of the significant risk factors (DV, CPR and qCTG) are seen, to a maximum of 97% when all of them are being manifested.

This is the first study to incorporate qCTG in fetal assessment of late-onset growth restriction. It demonstrates that unlike standard cardiotocography, qCTG alone correlates strongly with hypoxia (pH < 7.20) at birth.

We are proposing a new diagnostic algorithm, called QDSP Protocol (Quantitative cardiotocography and Doppler Surveillance of Pregnancy), based on the combined use of qCTG, CPR and DV Doppler, which seems to be more accurate in the detection of hypoxia (pH < 7.20) in late-onset FGR, compared to listed Doppler modalities and standard CTG.

The implementation of QDSP Protocol in clinical practice has the potential to reduce the number of unnecessary operative deliveries and lower the morbidity/mortality rates in late-onset FGR fetuses, although further prospective studies are needed to support these assumptions.

Key words: quantitative cardiotocography, CTG, computerized CTG, Doppler, late-onset FGR, hypoxia, fetal monitoring

Introduction. In 2021, a consensus was formed around the notion that AC or EFW below or between the 3rd and 10th percentile for a population growth chart or customized standard defines the fetus as small for gestational age (SGA), whereas AC or EFW below the 3rd percentile can be used as an isolated characteristic of fetal growth restriction (FGR) [1].

Usually, the SGA fetus is small, but not at increased risk of adverse perinatal outcome, while FGR fetuses are more likely to be affected by adverse perinatal and long-term outcomes [2].

Two main forms of growth restriction have been identified – early (occuring $\leq$ 32nd week) and late-onset FGR (occuring $\geq$ 32nd week), differing significantly in terms of prevalence, gestational age at start, placental histopathological findings, Doppler velocimetry readings, maternal co-morbidities and perinatal outcomes [3–5].

Several contributory parameters, occuring after 32nd week of gestation, were recently introduced in the definition of late-onset FGR: AC $<$ 10th centile; EFW $<$ 10th centile; AC or EFW crossing centiles more than 2 quartiles; UA pulsatility index (PI) $>$ 95th centile or CPR $<$ 5th centile [1].

In early-onset FGR, deterioration of the fetal condition usually follows a more predictable progression pattern, compared to late-onset restriction of growth. It usually starts with abnormalities in umbilical and cerebral Doppler indices, followed by an increase of impedance in precordial venous flow and, ultimately, by abnormal biophysical parameters [3, 6, 7].

Late-onset FGR is more often than not characterized by normal umbilical

Doppler with mildly affected cerebral velocities. In case of further deterioration, a decrease in the cerebroplacental ratio (CPR) can be seen, followed by a decline in amniotic fluid volume and/or abnormal fetal heart rate parameters, preceding fetal demise [8,9]. However, in comparison to early-onset FGR, this progression pattern can be much quicker and unpredictable, which complicates decision making in regards to timing of delivery.

Currently, a consensus on surveillance/timing of birth in late-onset growth restricted fetuses is lacking, as several professional organizations have issued guidelines, which differ substantially from one another [10].

Despite existing differences, it is commonly acknowledged that Doppler velocimetry of the umbilical artery (UA), middle cerebral artery (MCA), cerebroplacental ratio (CPR), and ductus venosus (DV) is useful (although interpretations and regimens vary) and standard cardiotocography (CTG) should not be used as only form of surveillance [10]. The latter is mainly due to the fact that interpretation of standard CTG findings is subject to substantial inter- and intra-observer agreement inconsistencies, especially in relation to heart rate variability and presence of accelerations [11].

However, we hypothesize that the inconsistencies in CTG interpretation can be circumvented with the use of computerized CTG expert systems (ES) for fetal surveillance.

The ES used in this study was the "quantitative cardiotocography" (qCTG) method [12], which is a software solution for registration and visualization of cardiotocographic findings obtained by indirect cardiotocography. Currently, qCTG is available in the NEXUS/OBSTETRICS system, formerly known as the ARGUS system (Nexus GMT, Frankfurt, Germany), which is one of several recognized fetal monitoring systems [13, 14].

The aims of the study are to evaluate the benefits of combining Doppler measurements of placental/fetal blood vessels with computerized cardiotocography (qCTG ES) in the detection of fetal hypoxia (pH < 7.20) among late-onset fetal growth restriction (FGR) fetuses.

Methods. We performed a retrospective, observational study, including 314 singleton pregnancies, diagnosed with late-onset fetal growth restriction (FGR). The study was performed between 2018 and 2021 in Second Municipal Hospital for Obstetrics and Gynecology Sheynovo, which is a tertiary referral facility, located in Sofia, Bulgaria. This trial has been registered on Current Controlled Trials website (`http://www.clinicaltrials.gov/`; Trial registration identification number: NCT04447248; Registered 25/06/2020).

Late-onset FGR was defined either on the basis of one present solitary parameter or at least two of three contributory parameters, including an absolute biometric parameter (AC or EFW).

Solitary parameters (occurring after 32nd week of gestation, according to INTERGROWTH-21st fetal growth charts) [15]:

- AC or EFW < 3rd centile.

Contributory parameters (occurring after 32nd week of gestation, according to INTERGROWTH-21st fetal growth charts):

- AC < 10th centile;
- EFW < 10th centile;
- AC or EFW crossing centiles more than 2 quartiles;
- UA pulsatility index (PI) > 95th centile or CPR < 5th centile, occurring after 32nd week of gestation.

Inclusion criteria: presence of 1 solitary parameter or 2/3 contributory parameters, including AC or EFW; absence of sonographic and laboratory evidence of structural anomalies; absence of severe maternal complications; documented birth weight < 3rd centile; full follow-up documentation.

Exclusion criteria were absence of 1 solitary parameter or 2/3 contributory parameters, including AC or EFW; multiple pregnancies, congenital malformations and any chromosomal malformations known before labour and delivery, severe maternal complications, documented birth weight > 3rd centile, pregnancy loss, failure to obtain full follow-up documentation.

Every woman participating in the study underwent screening test for chromosomal anomalies at 11–13 weeks and fetal anatomy scan at 18–23 weeks of gestation. A fetal biometry scan was performed at 32nd week to rule out early-onset FGR. Doppler velocimetry of bloodflow in the umbilical artery (UA), middle cerebral artery (MCA), and ductus venosus (DV) was routinely performed. Cerebro-placental ratio (CPR) was also calculated. Standard and computerized CTG was performed in each patient. Doppler velocimetries were performed by a certified sonographer (PNI and MM), in the absence of fetal breathing and movements, using reference ranges described elsewhere [16, 17]. At least three even subsequent velocity waveforms were used.

Cardiotocographic recordings were obtained using standard, indirect CTG on Philips Viridia series 50A fetal monitors and the computerized qCTG ES. Interpretation of CTG findings was performed by a senior consultant, according to current FIGO consensus guidelines [11], and by the qCTG ES. It features a mathematical algorithm to quantify all major cardiotocographic findings (base fetal heart rate, short-term variability and decelerations). Based on that, a so-called CTG-score is being generated. The values of this score correlate with fetal pH, which allows for the generation of predictive pH values [12].

Doppler scans and CTG/qCTG testing intervals/interpretation were performed according to a unified protocol (Table 1):

Absent or reversed end diastolic (A/RED) flow in UA and/or CPR < 5th centile between 32nd and 34th week of gestation, indicated administration of corticosteroids for lungs maturation and shorter interval of fetal surveillance.

Indication for urgent delivery were:

Table 1

Testing intervals and interpretation of Doppler scans, CTG and qCTG

Diagnostic procedure	Criteria for abnormality	Recommendation
UA Doppler	A/RED flow	Once weekly if normal Every 3 days if abnormal
MCA Doppler	PI < 5th centile	Once weekly if normal Every 3 days if abnormal
CRP	< 5th centile	Once weekly if normal Every day if abnormal
DV Doppler	PIV > 95th centile; reversed or missing a-wave	Once weekly if normal Indication for delivery if abnormal
Standard CTG	FIGO classification	Once weekly if normal Every day if suspectful Indication for urgent delivery if abnormal
qCTG	pH < 7.20	Every time when standard CTG is performed

CTG related [11]

- presence of decreased (< 5 bpm) or increased (> 25 bpm) short-term variability (STV) of the fetal heart rate for more than 50 min;
- presence of repetitive late or prolonged decelerations for >30 min (20 min if combined with reduced variability) or one prolonged deceleration for > 5 min.

Doppler related

- DV PIV > 95th centile and/or reversed or missing a-wave.

In all cases, last Doppler measurements and CTG/qCTG recordings were performed within 2 hours of surgery/labour.

Immediately after delivery and before separation of the placenta, a segment of the umbilical cord was clamped and UA pH was measured in all cases.

Statistical methods. All Doppler measurements were converted to standard deviations from the expected mean (Z-scores). Prognostic pH-results calculated by the qCTG method and actual pH values measured directly from the UA, after delivery, were dichotomized. The relationship between all independent variables and the outcome measures was analyzed by multiple logistic regression. The chi-square test or Fisher's exact test were also used, as appropriate, to compare categorical variables.

Consequently, receiver-operator characteristic (ROC) curve was used as an additional method to evaluate the logistic regression model. The power of the model's predicted values to discriminate between positive and negative cases was quantified by the area under the curve (AUC).

The statistical analysis was performed using MedCalc v.12.2.1.0 and IBM SPSS v.19.0 statistical software.

Results. The inclusion criteria were met by 356 women, although 42 of them had to be withdrawn, due to reasons related to birth weight > 3th centile – 21 cases (5.89%), severe preeclampsia – 2 (0.56%), incomplete follow-up documentation – 17 (4.78%), and pregnancy loss – 2 (0.56%).

The analysis was based on a total of 1757 scans, performed on the remaining 314 pregnancies. Demographic and Doppler/qCTG characteristics are shown in Table 2.

T a b l e 2

Demographic, labour and CTG/qCTG/Doppler characteristics

Characteristics	Mean ± SD or n (%)
Maternal age	34 (21-44)
Maternal race	
Caucasian	314 (100)
Primipara	187 (59.6)
Multipara	127 (40.5)
Gestational age at admission (weeks)	33.1 ± 0.9
Gestational age at last CTG/qCTG/scan (weeks)	35.6 ± 2.1
Gestational age at delivery (weeks)	36.6 ± 2.3
Birth weight (g)	2240 ± 413
Antenatal corticosteroids	80 (25.4)
Standard CTG findings	
Normal	111 (35.4)
Suspicious	104 (33.1)
Abnormal	99 (31.5)
STV related	65 (20.7)
Decelerations related	34 (10.8)
qCTG	
Predicted pH > 7.20	239 (76.1)
Predicted pH < 7.20	75 (23.9)
Doppler	
MCA (PI < 5th centile)	56 (17.8)
UA (A/RED flow)	38 (12.1)
CPR (< 5th centile)	102 (32.5)
DV (PIV > 5th centile)	11 (3.5)
DV (absent or reversed a-wave)	8 (2.5)
Umbilical artery pH < 7.20 at delivery	64 (20.4)
Normal delivery	211 (67.2)
Cesarean section	103 (32.8)

Multiple logistic regression was used to determine the correlation of UA, MCA, DV Doppler and qCTG findings with hypoxia (pH < 7.20) in the UA at birth.

Table 3 demonstrates the variables which did not prove to be significantly correlated with the dependent variable (UA, $P = 0.0882$, MCA, $P = 0.0592$; Standard CTG, $P = 0.1738$).

T a b l e 3

Model Chi-square = 305.111; DF = 4; $P < 0.0001$; Goodness of Chi-square = 5.911; DF = 4; P = 1.0000

Independent variable	Coefficient	Standard error	P	Odds ratio	95% confidence interval
Standard CTG	0.66673	0.35519	0.1738	2.0881	5.4352–18.2344
UA	0.51134	0.35877	0.0882	1.9133	4.3154–19.4655
MCA	0.79431	0.31987	0.0592	1.8770	3.8995–20.1452
CPR	2.00016	0.32641	< 0.0001	8.1092	5.0099–19.8320
DV	2.42335	0.29872	< 0.0001	12.5551	3.4433–21.9112
qCTG	2.31006	0.34216	0.0002	10.8995	4.1123–20.5769
Constant	−2.76453				

On the other hand, CPR, DV and qCTG were found to correlate strongly with hypoxia (pH < 7.20) in the UA at birth. Consequently, according to the presented independent variables, the probability of UA pH < 7.20 can be described by the equation:

$$1/\{1 + \text{Exp}(-(-2.75182 + 1.71165 + 2.25987 + 2.11541))\}.$$

According to this logistic regression equation, the probability of fetal hypoxia varies between a minimum of 6%, when none of the above risk factors are seen, to a maximum of 97% when all of them are present (Table 4).

T a b l e 4

CPR – cerebro-placental ratio; PIV – pulsatility index for veins; qCTG – quantitative cardiotocography

CPR $<$ 5th centile	PIV $>$ 5th centile or reversed a-wave in Ductus Venosus	Abnormal qCTG (prognostic pH < 7.20)	Fetal hypoxia probability (%)
–	–	–	6
+	–	–	26
–	–	+	35
–	+	–	38
+	–	+	75
+	+	–	78
–	+	+	84
+	+	+	97

Discussion. Our results are in line with the existing evidence that UA velocimetry does not reliably predict neither placental insufficiency/hypoxia, nor adverse outcomes in late-onset FGR (where villous diffusion abnormalities are most often seen).

Decreased impedance in MCA was found to be a sign of poorer perinatal outcome and neurodevelopment, but not of hypoxia [18], (Table 3). However, unlike its individual components – MCA and UA pulsatility indices, CPR seems to be a sensitive parameter for hypoxia. CPR's practicality is further displayed in cases with normal borderline measurements of MCA and UA, where the ratio can become abnormal and thus indicate mild fetal hypoxia [15]. Data from our regression model supports these observations (Table 3).

Higher pulsatility index for veins (PIV) and/or missing/negative a-wave in DV also correlates well with hypoxia ($P < 0.0001$, Table 3).

In the course of this study, we found that a substantial number of newborns that were urgently delivered due to CTG indications alone, were not suffering from hypoxia at birth, which demonstrated that the correlation between standard CTG and fetal hypoxia was weak ($P = 0.1738$, Table 3). The high incidence of these inaccurate readings can be explained by the fact that STV (seen in about 60% of abnormal CTG readings) is difficult to interpret without electronic assistance, therefore promoting higher levels of observer variability.

On the other hand, qCTG is based on a mathematical algorithm, which quantifies four STV parameters simultaneously: the number of high and low points per minute, mean beat-to-beat variability per minute and oscillation amplitudes. The computation of all listed variables is called "microfluctuation" [12], which seems to eliminate the aforementioned subjectivity and thus enhances the qCTG algorithm, making it a good predictor of hypoxia at birth ($P = 0.0002$, Table 3).

Data from the presented regression model allows for hypoxia risks estimations in the investigated group of late-onset FGR fetuses. The equation, derived from this model estimates a 6% probability of fetal hypoxia, whenever qCTG is normal and there are no pathologic changes in CPR and DV Doppler measurements.

Our study suggests that in the presence of qCTG or DV Doppler changes, the probability of fetal hypoxia raises to about 35/38% (Table 4).

Whenever simultaneous alterations in qCTG/CPR or qCTG/DV Doppler occur, hypoxia can be seen in 75% and 84%, respectively. And finally, if abnormal Doppler DV, CPR and qCTG coexist, the risk of fetal hypoxia is estimated at 97% (Table 4).

Our mathematical model allowed the identification of neonatal hypoxia with 86.1% sensitivity and 79.5% specificity (AUC=0.835, $P < 0.0001$) and is an important prerequisite for the already ongoing prospective, multicentred, randomized study aiming to determine whether the new QDSP Protocol (qCTG and Doppler Surveillance of Pregnancy) ES could improve the management strategies and lower the morbidity/mortality rates in late-onset FGR fetuses.

A possible limitation of this trial is its nature. Being an observational study, it cannot fully assess the clinical implications of qCTG in regard to fetal hypoxia prevention at birth and especially longterm outcomes (at the first and second year of life), related to oxygen deficiency.

Also, it is important to acknowledge that this trial was retrospectively registered, which is often viewed as a potential source of reporting bias. This work was originally carried out to improve obstetric outcomes in Bulgaria and, given the target audience, trial registration was not originally sought. However, our research has already led to changes in local obstetric practice and in light of the All Trials campaign, which promotes the registration and publication of all performed trials (www.alltrials.net), this trial was registered to increase the transparency and accessibility of computed data.

Conclusion. This is the first study to incorporate qCTG (quantitative cardiotocography) in fetal assessment of late-onset growth restriction. It demonstrates that unlike standard cardiotocography, qCTG alone correlates strongly with hypoxia (pH < 7.20) at birth.

We are proposing a new diagnostic algorithm, called QDSP Protocol (Quantitative cardiotocography and Doppler Surveillance of Pregnancy), based on the combined use of qCTG, CPR and DV Doppler, which seems to be more accurate in the detection of hypoxia (pH < 7.20) in late-onset FGR, compared to listed Doppler modalities and standard CTG.

The implementation of QDSP Protocol in clinical practice has the potential to reduce the number of unnecessary operative deliveries and lower the morbidity/mortality rates in late-onset FGR fetuses, although further prospective studies are needed to support these assumptions.

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