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A TEMPORAL MODEL OF DOPPLER DETERIORATION IN FETAL GROWTH RESTRICTION RELATED TO CARDIOTOCOGRAPHIC MONITORING

VREMENSKI MODEL DOPLERSKOG POGORŠANJA U ODNOSU NA KARDIOTOKOGRAFSKI NALAZ U FETUSA S USPORENIM RASTOM

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Original paper

Key words: fetal growth restriction; Doppler; cardiotocography; fetal surveillance

SUMMARY. ***Aims.*** To describe the time sequence of abnormal Doppler changes and its relationship with fetal heart rate (FHR) registrations in growth restricted fetuses. ***Methods.*** Fifteen singleton pregnancies with an ultrasound diagnosis of fetal growth restriction (abdominal circumference (AC) <2 SD) were prospectively and longitudinally evaluated. Fetal outcome included four perinatal deaths, seven emergency cesarean sections due to abnormal cardiotocographic (CTG) registers and four admissions in Neonatal Intensive Care Unit (NICU). ***Results.*** We observed »early« Doppler changes (15 to 10 days prior to delivery) in umbilical artery (UA), middle cerebral artery (MCA) and cerebral-placental ratio (CPR). »Late« Doppler changes included absent or reverse diastolic flow in umbilical artery, ductus venosus (DV) high resistance and umbilical venous blood flow decrease. These changes appear in a 10% of cases four to seven days prior to delivery and up to the 40% of cases on the same day of delivery. Although less frequently, umbilical vein pulsations, reverse »a« wave at DV and MCA increased flow resistance can also be observed closer to delivery. »Late« Doppler changes appear in 2/3 of cases with »early« Doppler changes and in a 40% of those with an abnormal CTG register. These changes precede one to 10 days the abnormal CTG patterns. All perinatal deaths took place in patients showing »late« Doppler changes (4/10), whereas an abnormal CTG without »late« Doppler changes lead to emergency cesarean delivery because a risk of loss of fetal well-being (7/10). ***Conclusions.*** Time sequence and the standard model of Doppler changes in fetal growth restriction were described. It is obviously not a rule for fetal deterioration to take place the same way in any individual affected fetus. Nevertheless, it is apparent that »late« Doppler changes usually precede an abnormal CTG pattern and are associated to a higher perinatal mortality.

Izvorni članak

Ključne riječi: usporeni fetalni rast, dopler, kardiotokografija, fetalni nadzor

SAŽETAK. ***Cilj istraživanja.*** Ustanoviti vremenski slijed abnormalnih doplerskih promjena i njihov odnos prema kucajevima srca (KČS) u fetusa s usporenim rastom (IUGR). ***Metode.*** Petanest jednoplodnih trudnoća s ultrazvučnom dijagnozom usporena fetalnog rasta (opseg abdomena <2 SD) su prospektivno praćene. Fetalni ishod je bio: četiri perinatalne smrti, sedam carskih rezova zbog abnormalnog CTG zapisa te četiri primitka djece u jedinicu intenzivne neonatalne terapije. ***Rezultati.*** Uočili smo »rane« doplerske promjene (15–10 dana prije poroda) u umbilikalnoj arteriji (UA), središnjoj cerebralnoj arteriji (MCA) i cerebralno/placentarnom omjeru. »Kasne« doplerske promjene su odsutni ili obrnuti dijastolički protok umbilikalne arterije, visoki otpor u duktus venosusu (DV) te smanjenje umbilikalnog venoznog protoka. Ove promjene nastupaju četiri do sedam dana prije poroda u 10% slučajeva, a na sam dan poroda u do 40% slučajeva. Premda manje često, pulsacije umbilikalne vene, obrnuti »a« val u DV i smanjeni otpor u MCA također mogu biti opažene uoči poroda. »Kasne« doplerske promjene nastupaju u 2/3 slučajeva »ranih« doplerskih promjena te u 40% fetusa s abnormalnim CTG zapisom. Ove doplerske promjene prethode jedan do 10 dana abnormalnim CTG zapisima. Sve perinatalne smrti su nastupile u pacijentica s »kasnim« doplerskim promjenama, a abnormalni CTG zapis bez »kasnih« doplerskih promjena je zbog rizika gubitka fetalnog dobrog stanja (7/10) indicirao hitni carski rez. ***Zaključak.*** Opisani su vremenski slijed i standardni model doplerskih promjena u fetusa s usporenim rastom. Očito je da u pojedinačnog fetusa nema pravila ni istoga načina za pogoršanje njegova stanja. Ipak, jasno je da »kasne« doplerske promjene obično prethode abnormalnom CTG zapisu te su povezane s povišenim perinatalnim mortalitetom.

Introduction

Severe fetal growth restriction (FGR), especially in preterm gestation, represents a major obstetric care problem. Timing delivery is a difficult choice between prematurity risks and ongoing pregnancy in an impaired ambient wich could induce multiorganic damage to fetal death.[1] Fetal heart rate (FHR) monitoring can detect hypoxemia[2,3] although it can be a too late sign of fetal compromise.[3,4] Biophysical profile score (BPS)[5] could also be applied but time sequence of Doppler changes identifies more precisely compensation and decompensation of fetal haemodynamic phases allowing the adequate timing of fetal delivery.[6]

Since cerebral blood flow centralization was established to precede in fifteen days late decelerations[7] a number of studies have tried to define the appropriate

sequence of pathological Doppler changes in fetal compromise.[8–12] The aim of the present work is to establish the time sequence of abnormal Doppler changes and its relationship with FHR tracings to obtain a model or nomogram of events making easier the obstetric surveillance and care in fetal growth restriction.

Patients and methods

Fifteen singleton pregnancies with an ultrasound diagnosis of fetal growth restriction have been prospectively and longitudinally evaluated. This group is part of a greater study including 272 normal gestations and 76 growth restricted fetuses carried out at the University General Hospital in Alicante (Spain). The study was approved by the hospital Ethics Committee and all patients gave their informed consent.

Fetal growth restriction was defined as a fetal abdominal circumference (AC) below 95% confidence limits of our normal reference curve (of normal gestations from the study). Gestational age was confirmed in each case by menstrual age and crown-rump length (CRL) at first trimester examination. All fetuses showed a weight below 10th percentile according to our Hospital reference curve.[13]

All ultrasound and Doppler examinations were performed by one of the authors (A.C.). Patients were included from 27 to 34 gestational weeks and follow-up was scheduled according to Doppler and FHR monitoring findings. Each case had at least two Doppler examinations. Doppler results were considered as strictly observational and not used for clinical management. Timing of delivery decision was made according to FHR (10 cases) and/or fetal-maternal associated conditions (5 cases).

All Doppler studies were done using a real time and color Doppler system (General Electric Logic 500; GE Medical Systems, Madrid, Spain) with a 2.5 – 4 MHz triplex transducer and a wall motion filter of 50 Hz. The spatial peak temporal average intensity (SPTA) was below 100 mW/cm^2. Each ultrasound examination included the flow velocity waveform (FVW) from the umbilical artery (UA), middle cerebral artery (MCA), ductus venosus (DV) and intrahepatic umbilical vein (UV). Umbilical artery signal was obtained as close as possible to its placental insertion.[14] Middle cerebral artery was located by color Doppler map over the sphenoid wing closest to transducer and sampled at its terminal portion.[15] Ductus venosus Doppler signal was recorded at the isthmus level, immediately after intrahepatic umbilical vein branching.[16] Umbilical vein FVW was obtained at intrahepatic level just before branching to portal vein and ductus venosus.[17]

A minimum of six FVW were recorded from each vessel with an insonation angle <60° in a fetal rest status without body or respiratory movements. Umbilical and middle cerebral artery Doppler recordings were evaluated through Resistance Index: RI=S–D/S.[18] At the ductus venosus the Resistance Index for veins was calculated (RIV=S–a/S, were a is maximum velocity in atrial contraction)[19] and maximum velocity was the parameter for the umbilical vein. Variance coefficient from three consecutive registers in ten normal pregnancies was 4.3% for umbilical artery RI, 3.4% for middle cerebral artery RI, 9.7% for ductus venosus RI and 6.8% for umbilical vein maximum velocity. An abnormal or pathologic Doppler result was considered when RI was over 95% confidence interval (2 SD) from our reference curve of normal gestations. Absent or reverse end diastolic umbilical artery flow was particularly considered. Cerebral-placental ratio (CPR) was also calculated from the relation MCA RI / umbilical artery RI.[20,21] Values below 2 SD of our reference curve of normal pregnancies were considered as abnormal. Umbilical venous velocity was taken as abnormal when below 95% confidence interval of our normal curve or pulsations present at its FVW.[22] Ultrasound examination included in all cases a complete fetal biometric study with biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL) and amniotic fluid index (AFI), as the sum of four uterine quadrants maximum height.[23] An AFI less than 5 was named as pathologic. Mean ultrasound and Doppler examination time was about twenty minutes.

Fetal heart rate was evaluated through cardiotocography registration (Hewlett Packard 8041-A, Hewlett Packard, Madrid) over a minimum period of thirty minutes and the mother resting on left lateral position. FHR-s were interpreted as abnormal or pathologic when not fulfilling Schifrin reactivity criteria (two FHR accelerations with a minimum amplitude of 15 b.p.m. and a 15 minutes minimum duration in association with fetal movements or uterine contractions over a period of ten minutes)[24] or tracings showed a diminished variability (less than 5 b.p.m.) or spontaneous decelerations or late decelerations regarding contractions were present. Sequence of CTG registrations was established according to results from once a week to several times a day.

Perinatal results were evaluated according to the following parameters: 1) emergency cesarean section due to risk of loss of fetal well-being; 2) preterm delivery; 3) intensive neonatal unit care admission; 4) Apgar <7 at five minutes and 5) perinatal death.

In each pregnancy, the number of days before delivery was determined according to a Doppler velocimetric parameter, AFI or FHR pattern persistently abnormal. Mean, SD and rank limits for days between abnormal or pathologic findings and delivery were calculated. The proportion of cases with abnormal Doppler and CTG during the 15 days prior to delivery was calculated and the cumulative percentage of abnormal variables with respect to delivery day has been graphically represented. Relationship between CTG and late Doppler changes has been individually evaluated to establish its concurrence or temporal connection.

Results

The age of pregnant women was 27.9±4.2 years, from 19 to 33 years. Nine patients presented with a pregnancy induced hypertension, one case of lupus erythematosus and pre-eclampsia and another one with HELLP syndrome. There were also a case with placental cysts, a placenta previa and a lymphoid leukemia case. In three cases there was no associated pregnancy alteration except fetal growth restriction. All newborns presented with some adverse perinatal result. There were four perinatal deaths, one of them intra-uterus. There were seven emergency cesarean deliveries for non-reassuring CTG patterns. Three newborns were admitted on NICU and one presented an Apgar <7 at five minutes requiring NICU admission too.

Table 1 shows Doppler longitudinal study characteristics. A total of 54 Doppler examinations over 15 pregnancies with a sonographic diagnosis of FGR from 27th to 35th gestational week have been performed. The surveillance time varied from 2 to 56 days and a mean of 4±1 data set per case were obtained. During the last 15 days the time interval between examinations varied from 1 to 9 days with a mean of 3.2±1.9 days.

Table 2 shows the mean time from detection of an abnormal parameter (Doppler, AFI or CTG register) and delivery day. *Figure 1* depicts the cumulative percentage of abnormal parameters during the 15 days prior to delivery. Two stages are clearly defined. A first stage of »early« Doppler changes affecting UA, MCA and CPR is detected from 15 to 10 days before delivery in almost the half of cases. The second stage presents with »late« Doppler changes including absent or reverse diastolic flow at umbilical artery and impaired venous flow. Absent diastolic umbilical artery flow, high resistance at ductus venosus *(Figure 2)* or a decreased umbilical vein velocity are detected in 10% of pregnancies 4 to 7 days prior to delivery and in as much as 40% on delivery day. Reverse flow at umbilical artery and venous pulsations appear at 3 days before delivery and to a 20% of pregnancies the day of delivery. An »a« wave inverted at the DV was observed in two cases, one of them finishing in neonatal death. In two perinatal death cases an increase in MCA resistance was the latest abnormal Doppler finding. AFI decreases from one stage to another in 30 to 50% of pregnancies along the last 5 days. CTG alterations appear on the last week from the beginning of the »late« Doppler changes reaching near a 70% of all cases on the day of delivery.

Figure 3 shows a diagram of Doppler changes in FGR over the last 15 days of pregnancy and its relationships with AFI decrease and abnormal CTG tests. In a 2/3 of

Table 1. Longitudinal Doppler study characteristics in 15 growth restricted pregnancies
Tablica 1. Karakteristike longitudinalne doplerske studije 15 trudnoća s usporenim rastom fetusa

Variable Varijabla	Mean±SD Prosjek±SD	Range Raspon
Gestational age at first exam (weeks) Dob trudnoće pri prvom pregledu (tjedni)	30,7±2,6	27,1–34
Gestational age at last exam (weeks) Dob trudnoće pri zadnjem pregledu (tjedni)	32,7±2,4	27,7–35,4
Monitoring period (days) Razdoblje nadziranja (dani)	15±15	2–56
N° exams / patient Broj pregleda po pacijentici	4±1	2–5
Interval among exams (days) Interval između pregleda (dani)	3,2±1,9	1–9

Table 2. Days between an abnormal Doppler parameter, AFI or CTG register and time of delivery in 15 growth restricted fetuses
Tablica 2. Dani između abnormalnog doplerskog zapisa, indeksa amnionske tekućine ili CTG zapisa i dana poroda u 15 fetusa s usporenim rastom

Parameter Parametar	n	Mean±SD Prosjek±SD	Range Raspon
AUARI	15	14,5±15,1	1–56
ICPR	15	12,7±10,5	0–27
AMCARI	14	9,7±8,6	0–27
AAFI	7	4,9±4,4	0–12
AEDVUA	7	2,9±3,8	0–10
ADVRI	4	2,5±5,0	0–10
AUVV	6	2,3±3,8	0–10
rin0ACTG	10	1,4±2,3	0–6
REDVUA	3	1,3±1,5	0–3
PUV	3	0,4±0,5	0–1

AUARI: abnormal umbilical resistance index – abnormalni indeks otpora a. umbilikalis; ACPR: abnormal middle cerebral/placental ratio – abnormalni cerebralno/placentarni omjer; AMCARI: abnormal middle cerebral artery resistance index – abnormalni indeks otpora a. cerebri medije; AAFI: abnormal amniotic fluid index – abnormalni indeks amnionske tekućine; AEDVUA: absent end-diastolic velocity in umbilical artery – nepostojeći dijastolični protok u a. umbilicalis; ADVRI: abnormal ductus venosus resistance index – abnormalni indeks otpora duktus venosusa; AUVV: abnormal umbilical vein velocity – abnormalni protok u v. umbilikalis; ACTG: abnormal cardiotocography pattern – abnormalni kardiotokografski zapis; REDVUA: reverse end-diastolic velocity in umbilical artery – povratni end-dijastolički protok u a. umbilikalis; PUV: pulsatile umbilical vein – pulsatilna v. umbilikalis.

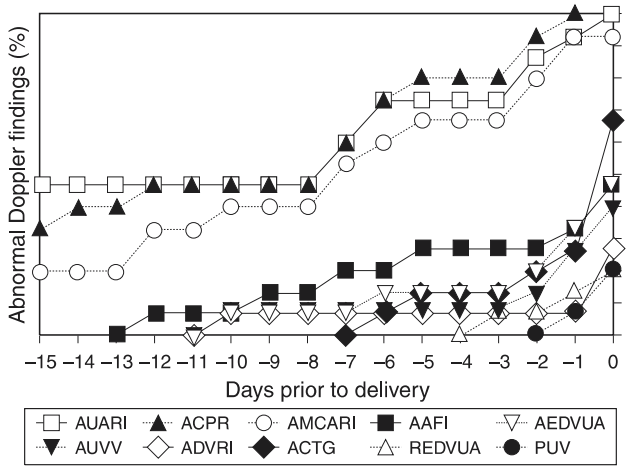

Figure 1. The cumulative percentage of abnormal Doppler variables, amniotic fluid index and cardiotocography in relation to day before delivery. (abbrevations like in Table 2)
Slika 1. Kumulativni postotak abnormalnih doplerskih nalaza, indeksa amnionske tekućine i kardiotokografskog zapisa u odnosu na dan prije poroda. (kratice kao u tablici 2.)

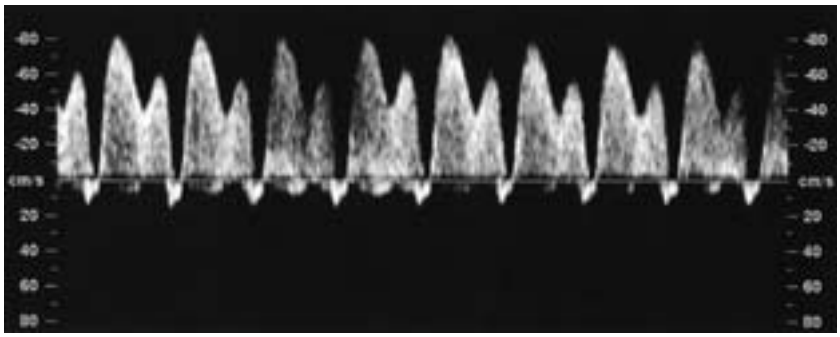

Figure 2. Doppler signal showing an extreme resistance increase at ductus venosus: a reverse »a« wave

Slika 2. Doplerski zapis koji pokazuje krajnji porast otpora u duktus venosusu: obrnuti val »a«

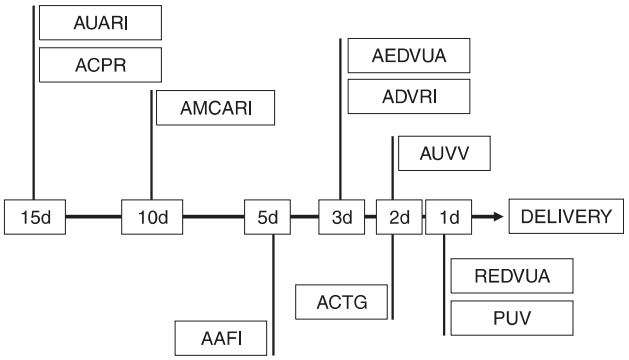

Figure 3. Standard Doppler changes diagram in fetal growth restriction during the last 15 days and its relationship with abnormal amniotic fluid index and abnormal CTG (abbreviations like in Table 2)

Slika 3. Standardne doplerske promjene kod usporenja fetalnog rasta tijekom posljednjih 15 dana trudnoće i njihov odnos s abnormalnim indeksom amnionske tekućine i abnormalnim CTG-om (kratice kao u slici 2.)

cases »early« Doppler changes are followed by »late« Doppler changes. In only one case the unique abnormal finding was an altered RI at umbilical and middle cerebral arteries. The fetus was delivered by cesarean at 33 weeks after a failed induction of labour indicated for FGR and maternal hypertension. NICU admission was due to prematurity without any other complications. In a 27% of cases (4/15) an abnormal CTG without »late« Doppler changes was present. On the contrary, another 27% of cases showed normal CTG along with abnormal »late« Doppler changes. Finally, CTG and Doppler were both altered in the 40% of cases (6/15), in 1/3 simultaneously. FHR was abnormal in only one case (17%) whereas in the 50% of cases »late« Doppler changes preceded in one to ten days the abnormal CTG. All perinatal deaths appeared in pregnancies showing »late« Doppler changes (4/10) while an abnormal CTG without »late« Doppler changes led to an emergency cesarean due to risk of loss of fetal well being (7/10).

Discussion

In this study the longitudinal evolution of the circulatory changes in the growth restricted fetus was assessed. There are a very small number of studies about this topic[8–12] and to the best of our knowledge this is the first one in our country. Our results, in general, are similar to those of Ferrazzi et al.[12] A time sequence in Doppler changes is confirmed according to severity of fetal compromise. The first alterations to take place are »early« Doppler changes affecting umbilical artery, cerebral-placental ratio and middle cerebral artery. Umbilical flow resistance may be altered even more than a month before delivery, whereas flow redistribution and cerebral vascular resistance decline appear some ten days prior to delivery. »Late« Doppler changes affect the venous circulation mainly. During the week preceding delivery a significant increase in ductus venosus resistance and a decrease in umbilical vein flow velocity take place. These »late« changes include also an absent or reversed diastolic flow at the umbilical artery and umbilical vein pulsatility. Ferrazzi et al.[12] consider an absent diastolic flow at the umbilical artery as an »early« change, appearing even 15 days prior to the end of pregnancy. This finding could be explained by the fact that the population under study presented with very early and severe FGR cases. Finally, according to our results, the »a« wave inversion at the ductus venosus and the increase in middle cerebral artery resistance appear exceptionally on the same day of delivery and usually associated to perinatal death. The probability of occurrence and severity of this changes declines with advancing gestation. That is probably related to an earlier delivery indication before deterioration as prematurity is a minor risk.[10]

Fetal heart rate monitoring is a validated technique to assess fetal compromise although it has important interpretation problems.[6] The interobserver agreement is very poor when interpreting reactivity and decelerations, both acting as main diagnostic clues.[25] If computerised analysis precludes subjectivity it must be taken into account that although a »reactive« pattern correlates with fetal well-being, a non-reactive register has a low positive predictive value.[26] FHR variability reduction and decelerations have been related to hypoxia[2] but when registers turn into abnormal ones, more than a 77% of fetuses present with hypoxia and acidemia.[3,4]

A negative correlation between venous flow pulsatility and FHR variability has been demonstrated.[9] Before 32 weeks ductus venosus resistance increase and variability decrease become abnormal some few days before delivery. Variability reduction appears before ductus alteration in 50% of cases,[10] while a 60% of non-reactive CTG fetuses does not show »late« Doppler

changes.[12] Our results demonstrate that only a 60% of fetuses with abnormal CTG pattern showed »late« Doppler changes. These changes precede in a half of cases the abnormalities in CTG and only in 17% of cases the CTG pattern was altered prior to »late« Doppler changes. »Late« Doppler changes are significantly associated to a bad perinatal outcome,[9–12,27] specially an increase of perinatal mortality.[10,12,27] All perinatal deaths in our study group showed »late« Doppler changes and none took place when there were no »late« Doppler changes. In contrast, one only abnormal CTG register leads to an emergency cesarean section. Recently, it has been demonstrated also the low value of an oxytocine challenge test when the venous Doppler is altered.[28] Nevertheless, some authors believe the more advisable in cases of fetal growth restriction is a combination of Doppler, CTG and biophysical profile to predict intrauterine compromise and fetal outcome in the face of timing delivery.[29]

In conclusion, Doppler changes appearing in deteriorating growth restricted fetuses have been longitudinally evaluated. This has allowed us to describe a temporal sequence of events and propose a standard model as a useful clinical management guide even if not all fetuses follow the expected sequence. Nevertheless, it is clear that when present, »late« Doppler changes usually precede an abnormal CTG register and are associated to a higher perinatal mortality. The possibility to improve the management of these cases using a combination of multiple surveillance tests demands randomised prospective clinical trials to evaluate different diagnostic and surveillance protocols.

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