Doppler velocimetry and non stress test in severe fetal growth restriction

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Summary

Objective: The aim of our study was to evaluate the efficacy of Doppler velocimetry and cardiotocography in surveillance of the fetus affected by severe fetal growth retardation (FGR) and hence their capacity in predicting adverse perinatal outcome. This could therefore permit the timing of delivery thus reducing perinatal morbidity and mortality.

Methods: 53 women with high risk pregnancies, all suffering from various pathologies such as gestational hypertension, pre-eclampsia, HELLP syndrome, Antithrombin III deficit, and in whom FGR (fetal abdominal circumference < 2.5th percentile for gestational age) diagnosed between the 24th and 35th week of gestational age, were retrospectively enrolled in the study. Doppler velocimetry was carried out on the main vascular districts - both arterial [umbilical artery (UA), middle cerebral artery (MCA), aorta (Ao) and uterine artery] and venous [umbilical vein (UV), ductus venosus (DV), inferior vena cava (IVC)]. Also evaluated was the amniotic fluid index (AFI). Daily non stress tests (NST) were conducted at least thrice a day for an overall period of not shorter than 60 min. Also considered were the methods of delivery and the perinatal outcome, e.g. gestational age at birth, perinatal mortality, incidence resuscitation, etc.

Results: The 53 patients studied were subdivided into three groups on the basis of the initial velocimetric exam of the umbilical and uterine arteries. Group A was comprised of those with altered waveforms of the UA, Group B those with altered waveforms on the uterine artery while Group C contained those with altered waveforms both of the UA and uterine artery. The period of study for group C was on average six days ($p < 0.05$) while for groups A and B they were on average 10 and 22 days, respectively. Group C also presented higher incidences of altered waveforms in the venous compartment, i.e. absent or reversed end diastole (ARDEF) was observed in 89% of the cases versus 0% and 7.6% observed in Group A and B, respectively. Altered waveforms in the DV and pulsations in the UV were both observed in Group C while the same was not observed in either group A or B. The NST did not show any substantial difference between the groups - only as the appearance of decelerations present in over half the cases in all groups at the end of the study.

Group C also presented higher incidences in adverse perinatal outcome as compared to groups A and B such as as low birth weight (868 g vs 1,324 g & 1,397 g, $p < 0.001$), neonatal resuscitation (52.6% vs 0% & 7.6% $p = 0.001$), longer periods of admission to neonatal intensive care unit (67 days vs 32 & 33 $p < 0.001$) and perinatal mortality (36% vs 0 & 0, $p < 0.05$).

The velocimetric indices which appear to better predict perinatal mortality are those related to the venous compartment giving a diagnostic accuracy of 92.8% (KI > 0.75) in case of pulsations in the UV, 86.6% (KI > 0.75) with alterations on the DV, and of 78.5% (KI > 0.40) for those on the IVC. Cardiotocography revealed to be less capable in predicting perinatal mortality giving a diagnostic accuracy of 66.6% (KI > 0.40) with a non reactive, non variable NST.

Conclusion: The data presented show that velocimetric modifications in the fetal venous compartment constitute a relevant prognostic sign in the prediction of perinatal mortality and neonatal resuscitation. The further the vessels compromised are from the heart, the higher is the relative risk for perinatal mortality, equal to 5.0 (95% C.I. = 0.61-40.9) with alterations on the IVC, of 8.2 (95% CI = 1.04-61.5) when they involve the DV, and of 18.0 (95% = 2.44-133) when pulsations are obtained on the UV.

Key words: Doppler Velocimetry; Non Stress Test; Severe Fetal Growth Restriction; Adverse perintal outcome.

Introduction

Since 1947, the first time the concept of the "small" newborn, a consequence of intrauterine deficiency and not solely of preterm birth, was introduced monitoring of complicated pregnancies due to intrauterine retardation has undergone enormous changes [1]. The aim of fetal and maternal surveillance in the case of fetal growth restriction (FGR) may in fact be summarised as the need to optimise timing of delivery before death of the fetus in the uterus or before it undergoes permanent damage. The incidence of serious neurological sequele in the "small for gestational age" newborns, often also premature, may in fact be over 35% [2]. Since timing of delivery is the only therapy available today, determination of gestational age becomes a fundamental variable that has to be evaluated before taking any irreversible decisions. It is therefore important, especially before the 34th week, that the biophysical methodologies (i.e. ultrasound, doppler velocimetry, cardiotocography) available to the obstetrician, help to determine the aetiology and the severity of the growth defect. The aim of these exams is to avoid unnecessary interventions on a "constitutionally small foetus that will not, in any way, benefit from premature birth and, particularly in the case of FGR, to not over prolong the time of delivery, leading to birth of a newborn who is already permanently compromised by asphyxia and acidosis.

It is already of common opinion that Doppler velocimetry constitutes one of the elective methods used to identify the cases of FGR directly linked to placental

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insufficiency and fetal hemodynamic compensation due to reduced intake of oxygen and other nutritional substances [3, 4]. Various experimental and clinical data sustain the hypothesis of redistribution of the blood circulation that benefits the brain, the heart, [5] the surrenal glands, [6] and the spleen [7] thus hindering the other organs and rest of the body [8]. Deterioration of the noxa patogena leads to progressive damage in cardiac function with consequent reduction in its out-put. In particular one notes a reduction in the after-load on the left side of the heart which is linked to vasodilatation in the cerebral vessels associated with increased after-load in the right segment of the heart which, on the other hand, is linked to a pathological increase in the impedance of the placenta and in the peripheral areas of the body [9]. Ulterior functional damage on the right side of the heart leads to increased pressure in the right atrium which is reflected by the appearance of velocimetric alterations in the inferior vena cava (IVC), in the ductus venosus (DV) and in the umbilical vein (UV).

The velocimetric abnormalities on the venous side, especially in the umbilical vein, lead to a high risk of prenatal death estimated to be about 63% by Arduini *et al.* [11]. In this phase of hemodynamic deterioration, cardiotocographic and biophysical alterations become evident in a period starting from two weeks following maximum cerebral vasodilatation and the appearance of the increasingly worsening alterations recorded on the venous side (ICV, DV, UV). However it is still debatable as to which cardiotocographic results are more frequently associated to the different moments of hemodynamic balance and subsequent imbalance that characterise FGR.

In this study, we carried out a retrospective study on pregnancies affected by severe FGR comparing the hemodynamic aspects recorded through color Doppler examination with the cardiotocographic results analysed through the non-stress test (NST).

Materials and Methods

Fifty-three pregnancies complicated by FGR diagnosed between the 24th and 35th week were retrospectively selected from January 1998 to January 1999.

Selection criteria consisted of:

- Ultrasonographic date of the pregnancy prior to the 20th week.
- Single foetus both cariotypically and antomically normal.
- Abdominal circumference less than the 2.5th percentile of the reference curves [12].
- Doppler recording carried out within two weeks from birth and a non stress test carried out within at least 24 hours from delivery.

The main clinical characteristics of the pregnancies chosen for the study are summarised in Table 1.

The velocimetric study was carried out using a commercially available Color Doppler-ultrasound machine (AU4 Esaote, Genoa-Italy), with a convex transducer (3.5-5 Mhz). The average intensity of the temporal/space peak never went over 100 mV/cm2 and the wall filter was fixed at 50 Hz with the sample volume between 2-4 mm. All the data used for the research were obtained in the absence of foetal respiratory and motor activity. The velocimetric recordings were carried out when at least five consecutive optimal waves of equal intensity were obtained by calculating an average of three values.

Table 1. — *Clinical characteristics of 53 pregnancies with fetal growth restriction (FGR)*

	No.	%
Gestational hypertension	18	33
Preeclampsia	16	30
HELLP Syndrome	5	9
AT III deficit	2	3
Idiopathic	12	24

The Doppler evaluation was carried out on the principal vascular districts of both the arterial and venous sides.

The umbilical artery (UA) was studied in its intermediate portion between the placental and fetal insertions. The middle cerebral artery (MCA) was studied in correspondence to the plane normally used for the measurement of the biparietal diameter immediately after its origin from the internal carotid artery. Aorta (Ao) peak velocity was studied in its outflow tract from the left ventricle. The inferior vena cava (IVC) was studied in its intermediate tract between the sovrahepatic veins and the renal veins; the ductus venosus (DV) at its umbilical origin and the umbilical vein (UV) itself at the level of the fetal insertion. The uterine arteries were identified with the help of color Doppler in the infero-lateral quadrant of the abdomen and the evaluation was carried out 1 cm above its crossing point with the external iliac artery. The angle between the direction of flow and that of the ultrasound neve went above 30° when studying the Ao outflow, the UA, the MCA, the DV and the UV; for the IVC and the uterine arteries angles up to 45° were retained as acceptable.

The last Doppler recordings before delivery were used for the statistical analysis. The values used for reference are printed elsewhere [13, 14]. The velocimetric measurements over the 95th percentile of the reference curves were considered abnormal for the pulsatility index (PI) of the UA, for the pre-load index (PLI) of the IVC, for the ratio S/A of the DV and for the resistance index (RI) of the uterine arteries. The MCA PI and the Ao Peak Velocity were considered to be abnormal when inferior to the 5th percentile. Furthermore, the presence of pulsations in the UV, defined as repetitive deflexions synchronised with atrial contractions at the end of diastole, were considered pathologic.

The quantity of amniotic fluid was established ultrasonographically using the amniotic fluid index (AFI) as proposed by Phelan [15].

All the pregnant women underwent a daily non-stress test (NST) thrice a day, for an overall period of not shorter than 60 minutes and was considered as reactive (NST-R: at least 2 accelerations in 20 mins of at least 15 beats per minute for a duration of 15 secs in correspondence to the fetal movements) or as non reactive (NST-NR: no response to the already mentioned criteria in 40 mins of observation) according to what was described by the American College of Obstetrics and Gynaecologists [16]. The reactivity could either have been spontaneous or triggered by external stimuli [17]. A long-term variable of at least 6 beats per minute was considered normal. Sporadic decelerations were considered normal, whilst periodic decelerations both variable and late were considered pathological.

Also taken into consideration were the methods of delivery and the prenatal results such as the gestational age and birthweight, caesarean sections for fetal distress, perinatal mortality, neonatal resuscitation, respiratory distress syndrome (RDS),

intra-periventricular brain haemorrhage (IVH) and the number of days spent in a neonatal intensive care unit (NICU).

Chi square and analysis of variance were used for the statistical analysis of the data. Results with $p > 0.05$ were considered to give statistically significant differences. We also calculated the sensitivity, the specificity and the predicted values, both positive and negative, for each Doppler parameter and for the NST in predicting perinatal death and neonatal resuscitation, also considered as unfavourable perinatal results. K. Cohen's index [18] was used to express a significant agreement between the test and the pathology (perinatal death and neonatal reanimation). K index (KI) ≥ -75 expresses an excellent association while values that range between 41 and 74 represent a fair to good agreement. Values of ≤ -40 indicate a poor association and therefore inefficiency of the test for the particular pathology considered [19].

For each Doppler parameter and NST, the relative risks (and confidence intervals at 95%) for perinatal mortality and neonatal resuscitation were calculated [20].

For the statistical calculations the SPSS program was used (statistical package for the social services program, version 8.0 adapted for windows).

Results

The 53 pregnancies studied were divided into three groups on the basis of an initial velocimetric examination carried out on the two different sides of the placenta: maternal (uterine artery) and fetal (umbilical artery). Group A grouped those with altered umbilical velocimetry but with normal uterine velocimetry, Group B those with abnormal uterine velocimetry and normal umbilical velocimetry, while Group C grouped those with abnormalities in both the vascular sides.

The study began on average in the 31st week of the gestational period for group A, at 30 weeks for those in group B and at 28 weeks for those in group C. The total period of study for group C was on average only six days which was significantly less than that obtained for group A (10 days) and group B (22 days) (Table 2).

Table 3 shows the results of the velocimetric control carried out before delivery. It clearly shows a high incidence of cases (89.4%) with absent diastole or reversed end-diastolic velocity (AREDF) that appeared in group C as compared to the other two groups (0% in group A and 7.6% in group B). No significant differences were observed among the three groups regarding the results referring to the MCA and the Ao, however higher incidences of abnormalities in the venous vessels were observed in group C. In fact in this group, the IVC was altered in 52.6% of the cases (vs 0% in group A and 34.6% in group B), while DV and UV alterations were observed in 36.8% of cases (vs 0% in the other two groups).

Reduction of amniotic fluid volume was observed in over half the cases without significant differences between the two groups (Table 4).

A non-reactive NST was noted in 68% of the foetuses in group C, in 11% in group B while in all cases in group A a reactive NST was present at the beginning of the study. Furthermore, at the beginning of the study no decelerations were observed in either group A or B while they were observed in 42.1% of the cases in group C. The decelerations appeared on average after 17 days in the cases with altered umbilical velocimetry (group A), after 14 in the presence of velocimetric alterations only on the uterine side (group B) and after only two days in cases with both vascular districts altered (group C). However, at the end of the study, considered as the moment of delivery, the incidence of decelerations was uniform and dif-

Table 2. — *Duration of Doppler Study in 53 pregnancies complicated by severe FGR*

	Group A	Group B	Group C
Umbilical artery PI	> 95 th %tile	5-95 th %tile	> 95 th %tile
Uterine artery RI	5-95 th %tile	> 95 th %tile	> 95 th %tile
No. of Cases	8	26	19
Gestational age			
– *beginning of the study*	31+5	30+2	28+5
wks ± days (range)	(28+6/33+4)	(26+6/36+0)	(24+3/33+0)
– *end of the study*	33+1	33+3	29+4
wks ± days (range)	(31+2/37+0)	(28+6/39+4)	(26+6/33+0)
Duration of Doppler Study			
Days	10	22	6*
(range)	(0-22)	(0-70)	(0-18)

PI = pulsatility index; RI = resistance index; *p < 0.05.

Table 3. — *Final fetal hemodynamics in 53 pregnancies complicated by FGR, subdivided in relation to the first Doppler assessment of umbilical and uterine arteries (groups A, B, C).*

	Group A	Group B	Group C
Umbilical artery PI	> 95 th %tile	5-95 th %tile	> 95 th %tile
Uterine artery RI	5-95 th %tile	> 95 th %tile	> 95 th %tile
No. of Cases	8 (%)	26 (%)	19 (%)
AREDF UA	0	2 (7.6)	23 (89.4)**
MCA < 5th %tile	5 (62.5)	18 (69.2)	22 (84.2)
PV Aorta <5th %tile	4 (50)	4 (15.3)	9 (47.3)
PLI IVC > 95th %tile	0	9 (34.6)	10 (52.6)*
S/A DV > 95th %tile	0	0	7 (36.8)*
UV pulsation	0	0	7 (36.8)*

*p < 0.05; **p < 0.001; PI = pulsatility index; RI = resistance index; AREDF = absent or reverse end diastolic flow; MCA = middle cerebral artery; PV = peak velocity; PLI = pre-load index; IVC = inferior vena cava; UV = umbilical vein; UA = umbilical artery; DV = ductus venosus.

Table 4. — *Amniotic fluid index and cardiotocography in 53 pregnancies complicated by FGR, subdivided in relation to the first Doppler assessment of umbilical and uterine arteries (groups A, B, C).*

	Group A	Group B	Group C
Umbilical artery PI	> 95 th %tile	5-95 th %tile	> 95 th %tile
Uterine artery RI	5-95 th %tile	> 95 th %tile	> 95 th %tile
No. of Cases	8 (%)	26 (%)	19 (%)
AFI < 5 (last control)	5 (62.5)	12 (46.1)	12 (63.1)
Non reactive NST			
beginning of the study	0	3 (11.5)	13 (68.4)
end of the study	5 (62.5)	10 (38.4)*	16 (84.2)
Decelerations			
beginning of the study	0	0	8 (42.1)*
end of the study	5 (62.5)	12 (46.1)	12 (63.1)
– Appearance (wks ± days)	33+1	32+0	29+1
Range	(30+5/37+0)	(31+1/33+6)	(24+3/33+0)
– Time from the beginning of the study (days)	17	14	2*
Range	(5-27)	(0-55)	(0-8)

*p < 0.05; PI = pulsatility index; RI = resistance index; NST = non-stress test; AFI = amniotic fluid index

ferences among the three groups were insignificant. A non reactive NST was recorded in almost all the cases in group C (84.2%), in over half the cases in group A (62.5%), but in only a third in group B (38.4%) (Table 4).

The perinatal results, still considering the three groups separately, are summarised in Table 5. Differences in the gestational age at birth did not result statistically significant in the three groups compared, even though Group C showed an inferior gestational age at birth.

Table 5. — *Perinatal outcome in 53 pregnancies complicated by FGR, subdivided in relation to the first Doppler assessment of umbilical and uterine arteries*

	Group A	Group B	Group C
Umbilical artery PI	> 95 th %tile	5-95 th %tile	> 95 th %tile
Uterine artery RI	5-95 th %tile	> 95 th %tile	> 95 th %tile
No. of Cases	8	26	19
Gestational age at delivery (wks ± days)	33+1	33+2	30+1
range	(31+2/37+0)	(28+6/39+4)	28+1/33+0)
Birthweight (g)	1324	1397	868**
range	(1000-1380)	(940-1710)	(700-1390)
Weight Deficit (%)	–29%	–26%	–32%
SGA (<10p)	8 (100%)	24 (96.1%)	19 (100%)
CS for foetal distress	3 (37.5%)	5 (19.2%)*	12 (63.1%)
Neonatal resuscitation	0	2 (7.6%)	10 (52.6%)**
Apgar < 7 at 5 min.	0	2 (7.6%)	7 (36.8%)
NEC	0	0	2 (10.5%)
IVH	0	0	0
RDS	4 (25%)	2 (7.6%)	7 (36.8%)
NICU (days)	32	33	67**
range	(10-65)	(7-55)	(44-93)
Perinatal mortality	0	0	7 (36.8%)*

*p < 0.05; **p < 0.001; NEC = necrotizing enterocolotis; RDS = respiratory distress syndrome; SGA = small for gestational age; IVH = intra-ventricular hemorrage; NICU = admission to the neonatal intensive care unit; Weight deficit (%) = weight deficit, in percentage, compared with the 50th percentile for the same gestational age.

The neonatal weight was on average lower in group C (868 g vs 1324 g and 1397 g) as compared to the other two groups; whereas the worst weight deficit, –32% for group C, did not reach statistical significance compared with the other two groups.

In the group with pathological velocimetry in both the maternal and fetal districts (group C) a higher incidence in neonatal resuscitation (52.6%) and perinatal mortality (31.5%) was observed. A longer period of admission in NICU (on average 67 days) as compared to the other two groups with vascular resistance augmented in only one of the vascular districts (Groups A and B). It is important to note that perinatal mortality did not occur in either of these two groups.

We further analysed perinatal data on the basis of the NST, taking into consideration three different groups on the basis of the presence of normal reactivity (NST-R), absence of reactivity but with normal variability (NST-NR-V) and on the absence of both reactivity and variability (NST-NR-NV). Table 6 clearly shows that the presence of normal reactivity highlights a population with better perinatal outcomes: higher gestational age at birth (34 weeks vs 30 weeks), weight at birth greater (1475 g vs 972 g and 1038 g) less incidence of decelerations (15% vs 73% and 84%) of caesarean sections due to fetal distress (7.6% vs 57% and 61.5%); a shorter period of admission in NICU (29 days vs 51 days and 55 days) and absence of perinatal deaths (0% vs 14.2% and 23%). The analysis of adverse perinatal predictive tests are summarised in Tables 7 and 8 for velocimetric parameters and Tables 9 and 10 for cardiotocographic parameters.

Table 6. — *Perinatal outcome in 53 pregnancies complicated by FGR, related to cardiotography*

No. of cases	NST-R 21	NST-NR-V 11	NST-NR-NV 21
Gestational age at delivery (wks ± days)	34**	30	30
range	(32-37)	(28-32)	(26-34)
Birthweight (g)	1475	972	1038
range	(1010-1850)	(700-1300)	(440-1550)
SGA (<10p)	21 (100%)	11 (100%)	19 (92.4%)
Decelerations	3 (15.2%)**	8 (73.5%)	17 (83%)
CS for foetal distress	2 (7.5%)*	6 (56.6%)	12 (60.3%)
Neonatal resuscitation	2 (7.5%)	3 (28.3%)	6 (30.1%)
Apgar < 7 at 5 min.	0	3 (28.3%)	6 (30.1%)
NEC	0	0	2 (7.5%)
IVH	0	0	0
RDS	2 (7.5%)	5 (43.3%)	3 (15.1%)
NICU (days)	29*	51	55
range	(7-70)	(20-66)	(28-93)
Perinatal mortality	0	2 (14.1%)	5 (23%)

*p < 0.05; **p < 0.001; NST = non stress test; R = reactive; NR = non reactive; V = normal variability; NV = absence of variability; CS = caesarean section; NEC = necrotizing enterocolotis; RDS = respiratory distress syndrome; SGA = small for gestational age; IVH = intra-ventricular hemorrage; NICU = admission to the neonatal intensive care unit.

The K index (KI) highlighted an optimal association between the flussimetric parameter and neonatal resuscitation only for AREDF of the UA (diagnostic accuracy: 78.7% K.I. > 0.75), and a satisfactory association for an increased PLI in the IVC (diagnostic accuracy: 76.9% K. I. > 0.40) and in the presence of umbilical venous pulsations (diagnostic accuracy: 80% K.I. > 0.40).

Perinatal deaths appear to be associated to the presence of ARDEF of the UA (diagnostic accuracy: 75.7% KI > 0.75) and to the presence of IVC Preload Index > 95% (diagnostic accuracy: 78.5% K.I. > 0.40), of DV S/A > 95% (diagnostic accuracy: 86.6% K.I. > 0.75) and pulsatility in UV (diagnostic accuracy: 92.8% K.I. > 0.75).

As regards cardiotocography, (Table 9), none of the parameters taken into consideration (NST-NR-V, NST-NR-NV, decelerations) appear to be optimally associated to either neonatal resuscitation or perinatal mortality. Only the NST-NR-NV present a satisfactory predictability both for neonatal resuscitation (diagnostic accuracy: 67.7% K.I. > 0.40) and perinatal mortality (diagnostic accuracy: 66% K.I. > 0.40).

Further analysis of the perinatal data in relation to the presence or lack (Table 10) of velocimetric abnormalities on the venous side independent of their location (IVC, DV, UV) show significant differences between the two groups.

Almost all the cases with venous alterations presented contemporary hemodynamic alterations at the MCA and the UA levels; in addition AREDF in the UA in 87.5% of

Table 7. — *Overall diagnostic accuracy of Doppler parameters in prediction of neonatal resuscitation*

Velocimetric parameters	Abnormal %	Sensitivity %	Specificity %	PPV %	NPV %	Diagnostic accuracy %	False positives %
UA > 95th %	42.8	50	42.1	11.1	91.6	57.1	38
AREDF UA	30.3	71.4	80.7	50	91.3	78.7	15.1**
PI MCA < 5th %	64.5	85.7	41.6	30	90.9	51.6	45.1
PV Aorta < 5th %	31.5	33.3	80.0	50	66.6	62.5	12.5
PLI IVC > 95th %	23	50	88.8	66.6	80	76.9	7.6*
S/A DV > 95th %	6.2	20	100	100	73.3	75	0
UV pulsations	10	28.5	95.6	66.6	81.4	80	3.3*

*KI Kappa Index > 0.40; **KI > 0.75; PPV = positive predictive value; NPV = negative predictive value; PI = pulsalitity index; AREDF = absent or reverse end diastolic flow; MCA = middle cerebral artery; PV = peak velocity; PLI = pre-load index; IVC = inferior vena cava; UV = umbilical vein; UA = umbilical artery; DU = ductus venosus.

Table 8. — *Overall diagnostic accuracy of Doppler parameters in prediction of perintal mortality*

Velocimetric parameters	Abnormal %	Sensitivity %	Specificity %	PPV %	NPV %	Diagnostic accuracy %	False positives %
UA > 95th %tile	66.6	100	48.2	21.5	100	54.5	45.4
AREDF UA	39.3	100	72.4	33.3	100	75.7	24.2**
PI MCA < 5th %tile	71.8	100	31.0	9.0	100	48.1	51.8
PV Aorta < 5th %tile	35.2	33.3	69.2	20	81.8	62.5	25.0
PLI IVC > 95th %tile	44.4	66.6	81.8	50.0	90.0	78.5	14.2*
S/A DV > 95th %tile	20.0	66.6	91.6	66.6	91.6	86.6	6.6**
UV pulsations	13.7	75	95.8	75	95.8	92.8	3.5**

*KI > 0.40; **KI > 0.75; PPV = positive predictive value; NPV = negative predictive value; PI = pulsalitity index; AREDF = absent or reverse end diastolic flow; MCA = middle cerebral artery; PV = peak velocity; PLI = pre-load index; IVC = inferior vena cava; UV = umbilical vein; UA = umbilical artery; DU = ductus venosus.

Table 9. — *Overall diagnostic accuracy of cardiotocographic parameters in prediction of neonatal resuscitation and perinatal mortality*

	Neonatal Resuscitation			Perinatal Mortality		
CTG	NST-NR-V	NST-NR-NV*	DECELER.	NST-NR-V	NST-NR-NV*	DECELER.
Abnormal %	71	81.8	54.4	71	81.8	54.4
Sensitivity %	28.5	57.1	75	25	75	57.1
Specificity %	79.1	70.8	53.8	84.6	65.3	50.0
VPP %	28.5	36.3	20	20	25	25
VPN %	79.1	85	93.3	88	94.4	80
Diagnostic Accuracy%	67.7	67.7	56.6	76	66.6	51.6
False Positive%	16.1	22.5	40.0	13.3	30	38.7

*KI > 0.40; PPV = positive predictive value; NPV = negative predictive value; NST = non stress test: R = reactive; NR = non reactive; V = normal variability; NV = absence of variability.

the cases was present as opposed to 20% of the cases without modifications of the venous flussimetric parameters. In none of the cases with a compromised venous situation was a NST-R present, whilst in 75% of the cases non reactive and non variable traces were noted. In the cases with compromised venous districts, it was necessary to intervene through caesarean section at a precocious gestational age as compared to the other group (29 weeks vs 32 weeks); within the same group, we observed a perinatal mortality of up to 50% while in the group without venous abnormalities, all the newborns survived. An analogous behaviour was noted regarding neonatal resuscitation, which was necessary in 50% of the cases versus 10% of the newborns in the group without venous velocity waveforms abnormalities.

The relative risk (RR) estimated for neonatal resuscitation and perinatal death for each Doppler and cardiotocographic parameter can be observed in Table 11.

In cases with umbilical vein pulsations, the RR for neonatal resuscitation was 6.5 times higher and perinatal mortality was 18 times higher than in the cases without pulsations. No other parameters examined presented such RR.

General analysis of Table 11 allows us to confirm that the velocimetric abnormalities on the venous districts are associated with a RR for perinatal deaths greater than that correlated to the alterations in the arterial compartment or to the deterioration of the fetal heart rate patterns.

Discussion and conclusion

The data obtained from our study clearly highlights that, in the presence of velocimetric modifications of the fetal venous system, the risk of perinatal death is extremely high.

Table 10. — *Doppler velocimetry, cardiotocographic parameters and perinatal outcome related to Doppler abnormalities in the venous system*

	ABNORMAL DOPPLER VENOUS VELOCIMETRY	
No. of Cases	*Absent* 39 (73.6%)	*Present* 14 (26.4%)
UA > 95th %	80%	100%
MCA < 5th %	56%	100%
AREDF UA	20%	85.7%*
NST-R	56%	0*
NST-NR-V	16%	28%
NST-NR-NV	28%	78.5%*
Decelerations	52%	64.2%
Perinatal mortality	0%	50%*
Resuscitation	10%	50%*
Apgar < 7 at 5 min	12%	35.7%
NEC	0%	14.2%
RDS	20%	14.2%
Weight deficit %	–30%	–29%
CS for foetal distress	32%	64.2%
GA at delivery (wks)	32	29**

*p < 0.05; **p < 0.001; NST = non stress test: R = reactive; NR = non reactive; V = normal variability; NV = absence of variability; AREDF = absent or reverse end diastolic flow; MCA = middle cerebral artery
UA = umbilical artery; CS = caesarean section; NEC = necrotizing distress syndrome; GA = gestational age.

It is very interesting to note that the further the distance of the venous vessels compromised are from the heart, the higher is the risk and this is five times greater than normal when the alterations are present at the IVC level and eight times greater at the DV level. The risk is 18 times greater when pulsations are recorded at the umbilical vein level.

The velocimetric abnormalities present in the central venous system are all characterised by an increase in pulsation synchronised with the atrial contractions at the diastolic end. These pulsations are caused by lack of compensatory mechanisms due to hypoxia, an event which coincides with the beginning of progressive cardiac insufficiency [10]. The worse the degree of cardiac insufficiency, the further from the heart will the anomalies, in the venous waveforms, appear. In fact alterations in the IVC (Table 11), present in 44.4% of our cases, were associated to a RR for perinatal mortality of more than five times greater (95% CI 0.61-40.9) than in their absence; abnormalities in DV (S/D < 95th %tile) of our growth restricted fetuses, were correlated to a RR of eight times greater (95% CI 1.04-61.5); UV pulsations were recorded in only 13.7% of our cases but were associated with a RR 18 times greater (95% CI 2.44-133).

Rizzo *et al.* [21] have shown that the velocimetric alterations more frequently correlated with acidemia and foetal hypercapnia, studied using funicolocentesis, are those present at the IVC level whilst hypoxia, which induces a centralisation of the circle with redistribution of hematic flow at the cerebral level, is perfectly foreseen and monitored by the velocimetry of the MCA. The persistence and protraction of hypoxia lead to damage of cardiac functions (consequently of the venous velocimetry) and conseguently to the onset of hypercapnia and foetal acidosis.

The results of the cardiotocography studied, instead, do not present the same clinical performance; only the NST-NR-NV is associated with a risk of perinatal death 2.1 times greater (95% CI 0.99-4.7). The NST-NR-NV is present in 75% of the cases with venous velocimetric alterations compared to 28% in the cases with alterations present only on the arterial side.

The decelerations were recorded in an overlapping way in the groups with and without venous compromise: 64.2% and 52%, respectively.

The CTG tracing characterised by an absence of reactivity and variability (NST-NV-NR) could be a peculiarity of a foetus affected by FGR in a decompensation phase. However, some authors speculate [22] that such a CTG result is present in 60.6% of SGA newborns, independent of any possible associations with acidemia at birth.

However, being faced with a population of premature babies affected by FGR, there are reasonable doubts as to the reliability of CTG in predicting neonatal death. No random trials exist which demonstrate the benefit of using CTG in monitoring a foetus with FGR.

In an article by Black and Campbell [23], CTG is compared to Doppler and the same authors conclude that, in cases of FGR characterised by significant prematurity, the study of arterial and venous blood flow is not only the

Table 11. — *Perinatal mortality and neonatal resuscitation: relative risk*

BIOPHYSICAL PARAMETERS	Perinatal Mortality RR	95% CI	Neonatal Resuscitation RR	95% CI
PI UA	3.16	(0.371-37.6)	1.19	(0.270-5.23)
PI MCA	0.909	(0.829-8.90)	1.47	(0.934-2.31)
PV Aortic	1.10	(0.127-9.49)	1.67	(0.311-8.93)
AREDF UA	7.33	(0.920-58.4)	3.71	(1.49-9.29)
PLI IVC	5.0	(0.611-40.9)	4.5	(0.556-36.4)
S/A DV	8.25	(1.04-61.5)	4.0	(0.447-35.8)
UV pulsation	18.0	(2.44-133)	6.57	(0.695-62.1)
Decelerations	1.14	(0.53-2.43)	1.62	(0.806-3.28)
NST-NR-V	1.67	(0.238-11.1)	1.37	(0.336-5.6)
NST-NR-NV	2.17	(0.99-4.7)	1.96	(0.901-4.79)

95% CI = 95% confidence intervals; RR = relative risk; NST = non stress test; R = reactive; NR = non reactive; V = normal variability; NV = absence of variability; AREDF = absent or reverse end diastolic flow; MCA = middle cerebral artery; UA = umbilical artery; PI = pulsatility index; PV = peak velocity; PLI = pre-load index; IVC = inferior vena cava; UV = umbilical vein; DV = ductus venosus.

most logical approach but also unquestionably more reliable than CTG, both computerised and traditional. Though our study sustains this hypothesis, other studies are required before considering these traditional methods as unuseful.

In the final analysis, the presence of alterations on the venous side could constitute a sufficient reason for the programming of delivery without having to wait for alterations at the umbilical artery level (ARDEF) or on the biophysical side or of the CTG. This clinical protocol was recently suggested by Mari *et al.* [24] and seems to be confirmed by our results. Nevertheless it remains evident that further studies are required before suggesting this as the line of management.

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