Outcome in early-onset Fetal Growth Restriction is best combining computerized fetal heart rate analysis with Ductus Venosus Doppler. Insights from the Trial of Umbilical and Fetal Flow in Europe

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Glossary

'a' wave	The point of the venous waveform denoting atrial contraction
AC	abdominal circumference
AED	absent end diastolic velocities (in relation to umbilical artery Doppler)
cCTG	computerized cardiotocography
DV	ductus venosus
EFW	estimated fetal weight
FGR	Fetal growth restriction
FHR	Fetal Heart Rate
MCA	Middle Cerebral Artery
RED	reversed end diastolic velocities (in relation to umbilical artery Doppler)
STV	short term variation (of the fetal heart rate)
TRUFFLE	**TR**ial of **U**mbilical and **F**etal **FL**ow in Europe
UA	umbilical artery

Abstract

Background Early onset fetal growth restriction represents a particular dilemma in clinical management balancing the risk of iatrogenic prematurity with waiting for the fetus to gain more maturity, while being exposed to the risk of intrauterine death or the sequelae of acidosis.

Objective The TRUFFLE (trial of umbilical and fetal flow in Europe) study was a European, multicenter, randomized trial whose purpose was to determine according to which criteria delivery should be triggered in early fetal growth restriction (FGR). We present the key findings of the primary and secondary analyses.

Study design Women with fetal abdominal circumference <10th percentile and umbilical pulsatility index >95th percentile between 26 and 32 weeks were randomized to one of three monitoring and delivery protocols. These were: fetal heart rate variability based on computerized cardiotography; "early" or "late" ductus venosus Doppler changes. A "safety net" based on fetal heart rate abnormalities or umbilical Doppler changes mandated delivery irrespective of randomized group. The primary outcome was normal neurodevelopmental outcome at 2 years.

Results Among 511 women randomized, 362/503 (72%) had associated hypertensive conditions. 463/503 (92%) of fetuses survived and cerebral palsy occurred in 6/443 (1%) with known outcome. Among all women there was no difference in outcome based on randomized group, however of survivors significantly more fetuses randomized to the late ductus venosus group had a normal outcome (133/144; 95%) than those randomized to computerized cardiotocography alone (111/131; 85%). In 118/310 (38%) of babies delivered before 32 weeks the indication was safety-net criteria: 55/106 (52%) in late ductus venosus, 37/99 (37%) in early ductus venosus and 26/105 (25%) in computerized cardiotocography groups. Higher middle cerebral artery impedance adjusted for gestation was associated with neonatal survival without severe morbidity (OR 1.24; 95%CI 1.02 to 1.52) and infant survival without neurodevelopmental impairment at 2 years (OR 1.33; 95%CI 1.03-1.72) though birthweight and gestational age were more important determinants.

Conclusion Perinatal and 2 year outcome was better than expected in all randomized groups. Amongst survivors, 2 year neurodevelopmental outcome was best in those randomized to delivery based on late ductus venosus changes. Given a high rate of delivery based on the safety net criteria, deciding delivery based on late ductus venosus changes and abnormal computerized fetal heart rate variability seems prudent. There is no rationale for delivery based on cerebral Doppler changes alone. Of note, most women with early onset fetal growth restriction develop hypertension.

Introduction

Advances in neonatal care over the last few decades have resulted in improved survival of preterm infants even at very early gestational ages.[1] However, morbidity, neurological impairment and decrements in intellectual and social performance is still prevalent and strongly associated with gestational age at birth.[2, 3] The situation becomes even more critical if prematurity is determined by the need to rescue the fetus from an unfavorable intra-uterine environment - as is the case in placental insufficiency. The outcome of these infants will not only depend on the degree of prematurity but also on the severity of fetal growth restriction (FGR).[4-6] Given that no targeted treatment exists for fetal growth restriction, delivery is the only intervention that can prevent severe hypoxemia and acidosis, and eventually intra-uterine death. Thus optimal monitoring and timing of delivery remains crucial in the management of early-onset FGR.[7]

The issue of timing of delivery had first been addressed by the Growth Restriction Intervention Trial (GRIT) in which 587 babies were reported on.[8,9] This study randomized women with compromised small babies to immediate delivery or expectant management, based on equipoise of the clinician regarding optimal management. Early reports indicated that an expectant policy (time to delivery 4.9 days) seemed associated with a more favorable neurodevelopmental outcome that immediate delivery (0.9 days). At school age, however, no difference was found between immediate or delayed delivery.[10] From this or other studies there is no clear evidence to support delayed above early delivery.[11] A significant limitation of the GRIT was that neither gestational limits nor clinical criteria for monitoring and timing of delivery were defined. The only entry criterion for the study was the clinician's uncertainty on whether to deliver or continue the pregnancy.

Monitoring early fetal growth restriction and timing delivery has been undertaken in a variety of ways, including biophysical profile scoring [12] and umbilical artery Doppler[13], although there is little evidence underlying the use of either techniques. Different umbilical artery Doppler patterns identify different degrees of impaired placental function. Absent or reversed end diastolic velocities indicate impairment of the feto-placental circulation and presage fetal deterioration.[13] Longitudinal studies conducted on high-risk pregnancies have shown that the transition from AED to RED may be slow and gradual in early FGR, nevertheless, both AED and RED have been associated not only with increased fetal and neonatal mortality but also with a higher incidence of long-term neurological impairment when compared with FGR fetuses with positive end- diastolic velocities in the umbilical circulation.[14,15]

Since the early 2000s, attention has moved to assessment of the ductus venosus (DV; **Figure 1 & 2**) and computerized cardiotocograph (cCTG) analysis of fetal heart rate short term variation (STV) in order to guide timing of delivery in FGR (**Figure 3**).[16] A longitudinal observational study of FGR fetuses monitored by Doppler and computerized cardiotocography (cCTG), showed that before 32 weeks' gestation, ductus venosus (DV) Doppler abnormalities (**Figure 4**) in some cases preceded the onset of a low short term variability (STV), and that continuing pregnancy until the cCTG becomes abnormal in these cases was associated with a significantly higher perinatal mortality and worse composite perinatal outcome.[17] In particular, mortality was higher if both DV and CTG were abnormal than when only one was abnormal. Another multicenter study on a large cohort of FGR

pregnancies followed longitudinally also demonstrated that intact survival increased by 1-2% for every extra day spent in utero up to 32 weeks.[18] The balance in early-onset FGR is between on the one hand, prolonging pregnancy to reduce prematurity related complications, and in the other, timely intervention, to prevent mortality and limit morbidity.[19-21]

The issue of how to monitor and when to deliver in early onset FGR has until recently been informed by little evidence. Indeed, in a seminal Opinion fifteen year ago the inconsistencies in management of severe FGR with different monitoring strategies: biophysical profile, venous Doppler and fetal heart rate changes were highlighted. [7]

The TRUFFLE study (**TR**ial of **U**mbilical and **F**etal **FL**ow in **E**urope) was designed to answer the question of which methodologies should be used to monitor and according to which criteria deliver fetuses with early-onset FGR.[22] In doing so, the TRUFFLE study compared two techniques in the monitoring and timing of delivery in early onset (26-32 weeks) fetal growth restriction. These were ductus venosus Doppler (DV) and computerized CTG (cCTG) from which the fetal heart short term variability (cCTG-STV) can be ascertained. Both abnormalities of DV and cCTG-STV have been found to be closely associated with fetal hypoxia/acidaemia.[17, 23-25] Given expert uncertainty on the ideal trigger for intervention, the DV Doppler group was split into two arms: less severe ("early") abnormalities and more severe ("late") abnormalities. In the two Doppler DV groups, "safety net" criteria were used to trigger delivery based on the finding of very low cCTG-SVT. The presence of spontaneous, repetitive decelerations on CTG and/or deteriorating maternal condition prompted delivery in all three groups. After 32 weeks of pregnancy was managed according to local protocols.[26] In this review we will discuss the study design and results with relevance to their implementation in clinical practice.

The definition of early onset Fetal Growth Restriction

As smallness of the fetus can be constitutional, due to fetal malformations, chromosomal abnormalities and infections,[19,20] the population in the TRUFFLE study was restricted to impaired fetal growth considered to be of utero-placental origin. The inclusion criteria were singleton pregnancies with fetal Abdominal Circumference (AC) below the 10^{th} percentile, gestational age between 26^{+0} and 31^{+6} weeks and an umbilical artery Doppler pulsatility index >95^{th} centile.[22,26] The ACOG and RCOG definition of growth restriction is based only on AC or estimated fetal weight (EFW) below the 10^{th} percentile.**Error! Bookmark not defined.**, [27] This definition includes patients with failure of growth not dependent on utero-placental function and thus includes also fetuses whose smallness is not directly related to placental insufficiency.[19, 20] In the TRUFFLEstudy, the definition of abdominal circumference <10^{th} percentile and umbilical impedance >95^{th} percentile was arrived at through expert consensus of the investigator group in 2002. This has stood the test of time and with minor variation represents the combination of parameters that are closely related to perinatal morbidity (PORTO)[28] and a recent Delphi consensus (Delphi refers to the process by which expert opinion is focused towards a conclusion in a stepwise, iterative way).[29]

The 26^{+0} and 31^{+6} weeks range was chosen as representing where maximum uncertainty existed, given uncertainty of outcomes at gestational ages below 26 weeks and with a fetal

weight below 500g and the low incidence of severe neonatal complications at or after 32 weeks of gestation.[30]

Monitoring techniques and criteria for delivery

The standard of care in Maternal Fetal Medicine Units in Europe formed the basis of management for the study. Given the lack of a universally accepted protocol for monitoring these pregnancies and criteria for timing delivery, the aim of TRUFFLE was to compare the outcome in the survivors of FGR pregnancies at two years of age when the timing of delivery was based on different monitoring techniques, namely cCTG-STV or DV Doppler.

Computerized cCTG (Fig 1) reflect changes in fetal sympathetic, parasympathetic activity and chemoreceptors occurring during the process of hypoxic deterioration in placental FGR. [23,24] The increase in DV pulsatility index with progression to absent and reverse flow velocities of the a-wave (atrial contraction) (Fig 2 a, b and 3 a, b) is typically seen only in severe and early gestational age FGR fetuses.[16, 18, 31, 32] After 32 weeks, abnormal cardiotocography (late decelerations, reduced variability) will almost invariably precede DV abnormalities.[16] Hypoxemia and acidemia result in altered sympathetic and parasympathetic activity, hence in decreased fetal heart rate variation, reflected by a lower cCTG-STV.[23,24] Late (shallow) decelerations are indicative of a chemoreceptor-mediated response to fetal acidemia and of a direct depression effect of acidemia on myocardial tissue.[25]

Randomization arms

Patients were randomized into three arms for the decision to deliver:

1. abnormal cCTG-STV (<3.5 msec at 26^{+0}-28^{+6} weeks and <4msec at 29^{+0}-31^{+6} weeks)
2. "Early" DV Doppler abnormalities: PI>95th percentile
3. "Late" DV Doppler abnormalities: absent or reversed a-wave

***Safety-net criteria for delivery*.** In cases randomized to DV changes, the trigger for delivery was a cCTG-STV <2.6 msec at 26^{+0}-28^{+6} weeks and <3 msec at 29^{+0}-31^{+6} weeks. Spontaneous repeated persistent decelerations on CTG represented a safety net criterion in all three trial arms. At gestations beyond 32 weeks, the policy for delivery was based on local protocols. Reversed end-diastolic velocities in the UA was recommended as a reason to deliver the fetus after 32 weeks but was permissible after 30 weeks, absent end diastolic velocities after 34 weeks but permissible after 32 weeks.

Maternal indications for delivery were considered as independent of fetal condition, randomization arm and gestational age.[22,26]

Primary outcome. Given the high rate of perinatal survival even in early preterm infants, the primary outcome was not based on perinatal mortality and morbidity. Instead the study was powered on a primary outcome of survival without cerebral palsy or neurosensory impairment, or with a Bayley III developmental score [33] of more than 85, at 2 years of age.[26]

Secondary Outcomes were perinatal mortality, neonatal and infant morbidity and mortality.

Patient characteristics:

The TRUFFLE study cohort consisted of 511 women recruited of 542 eligible for study inclusion. The mean maternal age was 31 years, 63% were nulliparous, 84% were Caucasian with a mean BMI of 25 kg/m^2. No differences in demographic features were reported in the three trial arms. Hypertensive disorders of pregnancy were either already present at recruitment or developed during the observational period in 50% of cases with no difference between the three-randomization arms[26] and complicated 73% of the pregnancies by the time of delivery. Comparing these data with the incidence of pregnancy hypertension, chronic hypertension and preeclampsia in the general population,[34] it was apparent that the population entering the TRUFFLE study was destined for uteroplacental impairment from an early gestational age. Hypertensive disease, preeclampsia and severe FGR is strongly associated with abnormal uterine artery Doppler velocimetry, although this parameter was not required for study inclusion.[35]

Results: Fetal and neonatal risks of early Fetal Growth Restriction

Mortality: The mean gestational age at delivery was 30.7 weeks and neonatal weight 1019 grams.[22] Antenatal death occurred in 12 cases (2.4%), including 5 cases where parents declined consent to delivery. In spite of the severity of FGR, 92% babies survived to discharge. These results are more favorable than those previously reported from observational studies.[4, 18]

Morbidity: Severe morbidity among live births was present in 24% of infants and 5% of neonates died in the perinatal period. Overall, 71% of survivors were discharged from the neonatal wards without severe morbidity. The most common causes of early neonatal morbidity were sepsis (18%) and bronchopulmonary dysplasia (10%). Relatively infrequent were germinal matrix hemorrhage (2%) and cystic periventricular leukomalacia (1%).[26]

2year survival and neurodisability*:* Of all women recruited to the study, there were non-significant differences in survival without infant neurodisability at 2 years: 77% for the cCTG group, 84% for the "early" DV group and 85% for the "late" DV group, p 0.09; this analysis included all deaths. However, among the survivors in a predefined primary analysis, the percentage of infants without neurodevelopmental impairment at 2 years of age, corrected for prematurity, was significantly higher (95%) in the "late" DV group compared to the cCTG arm (85%). In the same arm (late DV changes, i.e. zero or reversed "a" wave) the better neurological outcome was associated with a small and non-significant excess of antenatal deaths.[26]

Middle cerebral artery Doppler and outcome: Normalized for gestation using z-scores, middle cerebral artery pulsatility index and umbilico-cerebral ratio at inclusion were associated with 2-year survival with normal neurodevelopmental outcome (odds ratio 1.33; 95% confidence interval 1.03-1.72 and odds ratio 0.88; 95% confidence interval 0.78-0.99,

respectively) as were gestation at delivery and birthweight p50 ratio (odds ratio 1.41; 95% confidence interval 1.20-1.66, and odds ratio 1.86; 95% confidence interval 1.33-2.60, respectively).[36]

"Safety Net" deliveries before 32 weeks: the TRUFFLE protocol applied up to 32 weeks. In those delivered before 32 weeks, the safety-net criteria triggered delivery in 38% of cases: 52% of 106 cases in the late DV group, 37% of 99 cases in the early DV and 25% of 105 cases in the cCTG-SVT group. Other fetal or maternal indications accounted for 30% of all deliveries below 32 weeks.[37]

Discussion

The TRUFFLE findings in context

Overall, outcomes for very preterm fetuses with FGR were much better than previously assumed: 82% of children with known outcome survived without neurological impairment. With the exception of cerebral ultrasound abnormalities, commonly used neonatal morbidity criteria are poor markers of later neurodevelopmental outcome. Indeed, 2-year neurodevelopmental impairment was not preceded by any component of composite neonatal morbidity in 56% of cases.[38] Gestational age at both study entry and delivery were strongly related to morbidity and mortality. Thus, specific morbidity/mortality tables in relation to gestational age at entry in the study and GA at delivery can be used for accurate parental counseling. The most important independent determinants of the composite adverse outcome (death or severe morbidity) were the presence of maternal hypertensive disease, low gestational age and a low estimated fetal weight at study inclusion.

Implications for clinical practice

Optimal timing of delivery of the early FGR fetus is achieved by monitoring with both DV and cCTG-STV. In those randomized to the late DV group there was better neurological outcome in surviving children, with non-significantly higher antenatal mortality. The latter was unlikely to be due to the lower cCTG -STV safety-net criteria in the DV randomization arm compared to those of the cCTG arm, as in 6 of the 7 cases fetal death would have been inevitable even had they been allocated to another randomization arm Hence delivery should be undertaken when the a-wave in the DV reaches the zero line (absent a wave) or when there is a pathologically low STV. This lower cCTG-STV cut-off was chosen assuming that an STV of 2.6 msec is the lowest cut-off that was clinically appropriate given the high chance of hypoxemia/acidemia below this level. [24, 39] The presence of spontaneous, repetitive fetal heart rate decelerations or maternal indications should trigger delivery independently of DV and cCTG- STV evaluation. Monitoring frequency of DV Doppler evaluation and cCTG was not established by the study, however it is reasonable to suggest frequent monitoring of cCTG and DV Doppler with a 'sliding scale' from at least every 2 - 3 days to daily, based on the severity of FGR and UA Doppler abnormalities.
A sub-analysis of babies delivered before 32 weeks' gestation, in other words those whose management was strictly defined by the protocol, showed that more than one third was delivered based on safety-net criteria, and another one third for other feto-maternal reasons.[38] Hence in clinical practice, a significant proportion of fetuses will be delivered because of cCTG-STV abnormalities, even before DV changes occur. However, overall data from the TRUFFLE trial [22, 26] and sub-analyses,[37] show a better outcome by the integrated use of both DV and cCTG-STV.

Variability of measurements

There is considerable biological variation in Doppler measurements and we did not formally assess this in the TRUFFLE study. Our recommendation is that Doppler measurements should be performed by experienced clinicians and the pulsatility index should be repeated at least three times at each assessment to verify uniformity of findings. It is still a subject of a debate

as to whether maternal steroids administration to promote fetal lung maturation affects umbilical artery Doppler (pseudo-normalization of absent flow in the UA)[41] and fetal heart rate. The day-to-day risk of an abnormally low cCTG-STV prompting delivery was 5%, and not predictable by the previous cCTG-STV [40]. TRUFFLE used two different cut-offs: in the cCTG arm (STV <3.5msec and 4 msec at below 29 weeks and between 29-32 weeks, respectively) and as a 'safety-net' in the DV arm (<2.6 and 3.0 msec, at below 29 weeks and between 29-32 weeks, respectively).[26] Though not mandated by the protocol, the majority of participating centers undertook daily CTG monitoring. In the case of maternal hypertension and/or HELLP syndrome we advise repeating assessments more frequently, since fetal deterioration may occur very rapidly.

Delivery after 32 weeks

Although the TRUFFLE study stopped recruiting at 32 weeks, many of the pregnancies continued beyond that gestation, if the criteria for delivery were not yet met. TRUFFLE did not investigate which Doppler criteria should be used for delivering these fetuses. However, Doppler evaluation of the umbilical artery (UA) becomes increasingly more important with advancing gestation. RED flow may always prompt delivery beyond 32 weeks and AED beyond 34 weeks. Beyond 34 weeks it is unusual to observe an AED pattern and delivery is often then triggered by other fetal criteria. From these gestational age decisions as to the timing of delivery will take into account the maternal condition, fetal growth, estimated fetal weight and should be left to the clinical judgment of the managing team. Given the current interest in the fetal adaptive response to chronic hypoxemia assessed by Doppler of the middle cerebral artery (MCA) pulsatility index and its ratio with the umbilical artery (cerebro-placental ratio)[42], we undertook a secondary analysis of MCA Doppler in the TRUFFLE cohort. MCA Doppler did not add useful information for clinical management of these pregnancies.[36]

Conclusion

The optimal management of early FGR fetuses should integrate clinical, Doppler and cCTG parameters in order to ensure safe deferral of delivery for the fetus and the mother, or a timely intervention.[43] Centers formerly acting upon cCTG-STV alone should be aware that severe anomalies in the DV, when they precede cCTG abnormalities, are an indication for undertaking delivery. Alternatively, when the DV is still normal, they can confidently defer delivery, provided the cCTG-STV remains above the safety net 'cut-off' level. Non computerized CTG assessment does not allow an objective assessment of fetal heart rate variability and, though its utility was not tested in this study, is not recommended for this reason. Although TRUFFLE did not specifically investigate monitoring frequency, cCTG-STV and Doppler of UA and DV should be undertaken with increasing frequency after the onset of AED in the UA, with more intensive monitoring in case of rapid deterioration. In summary, a predefined and agreed protocol, based on or similar that of TRUFFLE [22] is likely to lead to optimal perinatal and infant outcome.

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Figure legends

Figure 1. Schematic representation of the fetal central venous circulation: highly oxygenated blood coming from the placenta reaches the liver trough the the umbilical ven (Umb vein). About 40% is shunted directly to the heart through the ductus venosus (DV) and the rest is directed to the right liver lobe. The DV and the left and right hepatic veins (LHV, RHV) drain into the inferior vena cava. The highly oxygenated blood in the DV forms a jet streaming preferentially from the right to the left atrium, (through the foramen ovale =FO), and through the left ventricle and the ascending aorta (Ao Asc) to the fetal brain.

Figure 2. 2D and color Doppler imaging of ductus venosus (a); example of normal second trimester DV waveform. The "S" wave indicates systole, "D" wave diastole and the "a" wave that denotes late diastole (atrial contraction). The vertical arrow shows positive flow

Figure 3. One hour recording of computerized fetal heart rate analysis according to the Dawes and Redman criteria. The criterion no. 8 shows the short-term variation (STV) used in the TRUFFLE study as CTG criterion for deciding upon delivery in severe FGR.

Figure 4. Examples of DV velocimetry with progression (from top to bottom) from increased pulsatility index (PI), to absent and reversed flow during the "a" wave. Positive (forward) and negative (reversed) flow are denoted.

Figure 1

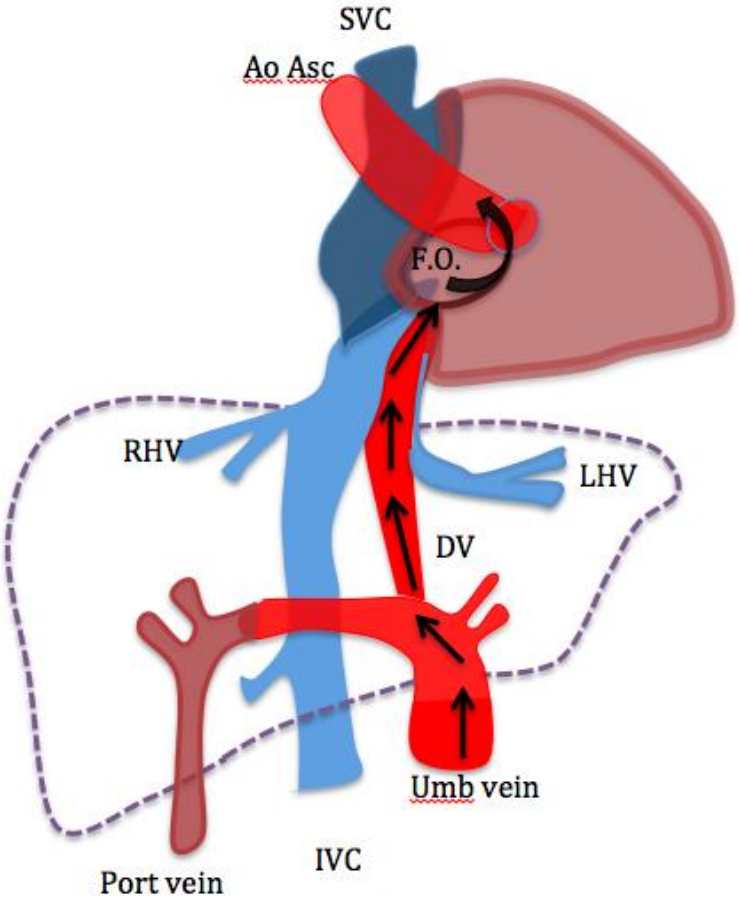
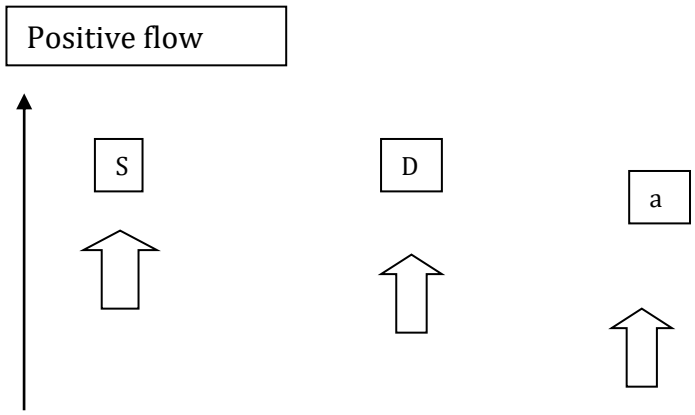
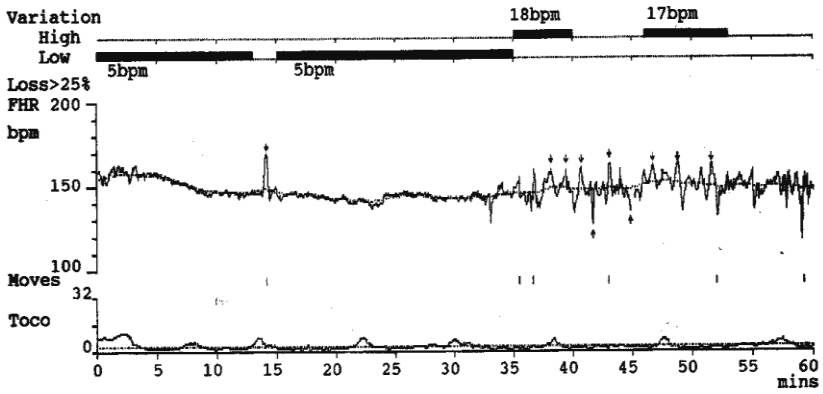


Figure 2



1 **Figure 3**



STOP at 60 mins.
ANALYSIS at 60 mins.

ADVICE ONLY. THIS IS NOT INTENDED AS A DIAGNOSIS

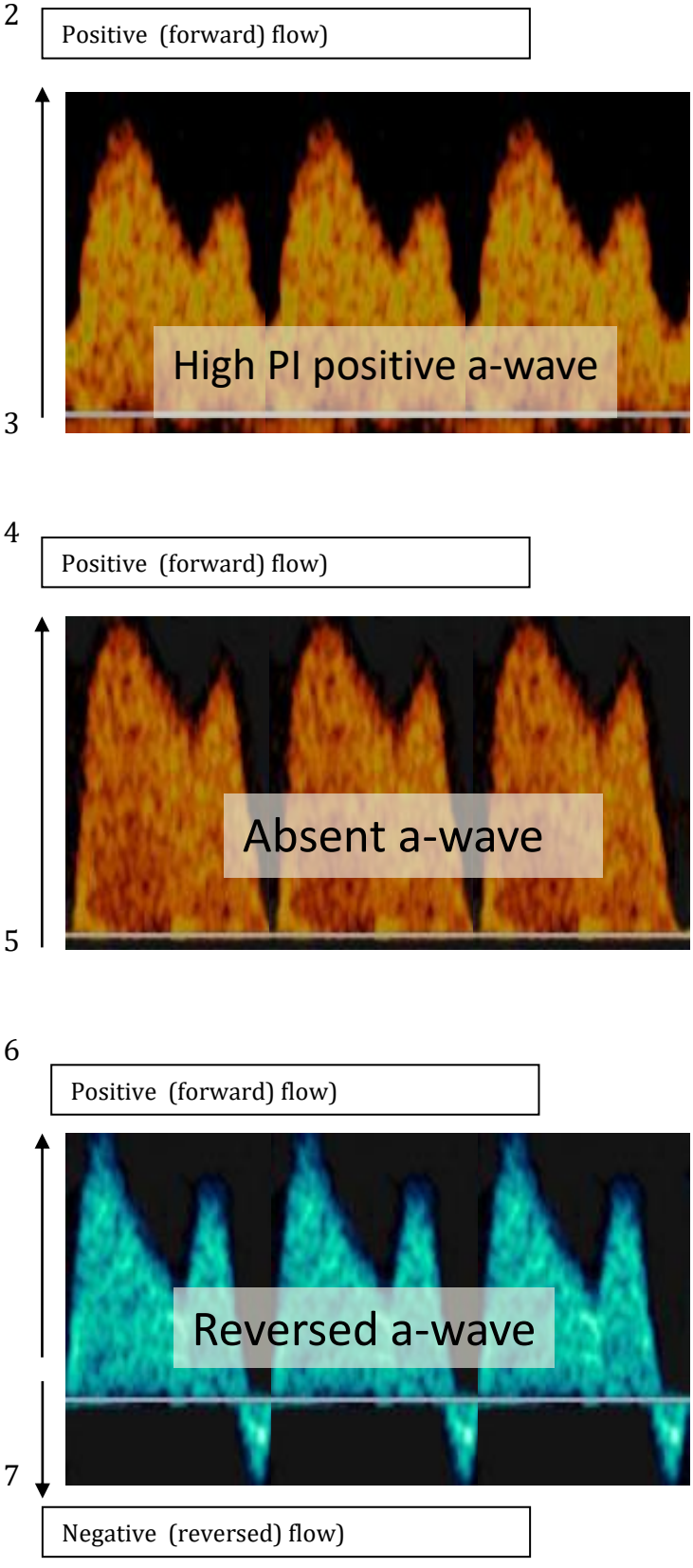
1. SIGNAL LOSS (%)	0.6		
2. CONTRACTION PEAKS	7		
3. FETAL MOVEMENTS (per hour)	6	*	
per min in High 0.25 in Low 0.00			
4. BASAL HEART RATE (bpm)	147		
5. ACCELERATIONS > 10 bpm & 15 sec	8		
> 15 bpm & 15 sec	2		
6. DECELERATIONS > 20 lost beats	0		
7. HIGH EPISODES (min)	12	(17.44 bpm)	
at 39 wks 24.8% of normal fetuses have less variation			
LOW EPISODES (min)	33	(4.80 bpm)	*
8. VARIATION OVERALL SHORT-TERM (ms)	4.5	(1.63 bpm)	

HOWEVER - note High episodes of 12 minutes with 0.25 moves/minute.

2

3

Figure 4


Positive (forward) flow)
High PI positive a-wave
Positive (forward) flow)
Absent a-wave
Positive (forward) flow)
Reversed a-wave
Negative (reversed) flow)