How long does it take for an expectant management of early-onset intrauterine growth restriction with a persistent abnormal Doppler pattern before intrauterine death? 

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Abstract

Introduction
Early-onset intrauterine growth restriction (IUGR) remains one of the main challenges in maternity care. Doppler interrogation of foetal circulation can help to address the perinatal management, but in IUGR foetuses delivered below 26 weeks the high risk of stillbirth, independently of the Doppler evaluation has been described. Among all vascular districts, ductus venosus (DV) results the best predictor of intact survival.

Case report
We present a case of very early-onset IUGR foetus due to placental vascular insufficiency, describing the duration of persistent abnormal Doppler pattern in DV before foetal death when a compassionate care management is chosen.

Conclusion
In IUGR foetuses increased perinatal risks associate with progressive deterioration of arterial and venous Doppler parameters. In very early-onset IUGR, GA largely determines the risks of perinatal mortality, independently of the Doppler parameters. If a compassionate care management is chosen, the persistence of the Doppler abnormalities can persist 49 days before stillbirth. This finding could help the decision-making process by obstetricians and parents. Our report could add to previous and future studies to further refine the management guidelines for early-onset IUGR.

Introduction
Intrauterine growth restriction (IUGR) is associated with stillbirth, neonatal death, perinatal morbidity, and adult diseases. In most cases, IUGR is due to placental insufficiency, but may also be due to a number of other conditions, such as congenital anomalies, infections, or drug and substance misuse.

Generally, growth-restricted foetuses, once identified as such, benefit from an intensive antenatal surveillance by the systematic use of Doppler evaluation.

Several meta-analysis and cohort studies suggested that Doppler study could prevent adverse outcomes, even if controversy still exists about the optimal timing of delivery in order to reduce the prematurity-related morbidity and mortality.

In particular, early-onset IUGR (< 34 weeks of gestation) is associated with perinatal mortality rates as high as 46%, which warrant strict in utero monitoring to tailor planned delivery. A general agreement on gestational age (GA) as the strongest predictor of the probability of perinatal death in early-onset IUGR has been reported.

Therefore, the timing of delivery in early-onset IUGR foetuses is critically conditioned by the short-term risks of intrauterine or early postnatal death.

We report the duration of the compassionate management in the early-onset IUGR condition due to placental vascular insufficiency, characterized by the persistence of abnormal pattern in ductus venosus (DV).

Case report
A 40-years-old women, gravida 1, para 0, with chronic hypertensive disease in medical history, was admitted at the 24 weeks of gestation at our Perinatal Unit for suspected IUGR. Maternal hypertension was monitored and treated satisfactorily. All laboratory findings were normal. GA was confirmed by sonography in the first trimester.

A normal karyotype was obtained by amniocentesis. Longitudinal ultrasound examinations were performed with a 4-MHz pulsed vector transducer using a colour Doppler ultrasound with a high pass filter set at 100 Hz (Voluson E8, GE Healthcare Kretztechnik, Zipf, Austria). Standard biometric parameters (biparietal diameter, head circumference, abdominal circumference, and femur length) were taken using conventional ultrasounds scans and an estimated foetal weight (EFW) was calculated according to Hadlock’s formula.

Ultrasonography confirmed IUGR condition, as reported by EFW, resulting of 239g (1st percentile).

Anhydramnios condition was detected in absence of apparent structural abnormalities. All waveforms Doppler were performed in the absence of major foetal movements. A minimum of...
5-10 successive waveforms were recorded and evaluated for the
calculation of the pulsatility (PI) and resistance indices (RI) of the maternal
and foetal parameters. The detailed foetal Doppler included measurement
of the vascular resistance in umbilical artery (UA), middle cerebral artery
(MCA), ductus venosus (DV), umbilical vein (UV) and aortic isthmus (AoI). All
Doppler indices were abnormal, with absence and reverse of diastolic flow
in UA, decreased MAC-PI, reverse A wave in DV, pulsatility in UV and abnormal
impedance in AoI.

A decision-making process appeared very difficult, as well as the evaluation
of consequences on the foetal well-being and maternal health. In
consideration of the couple’s decision not to voluntary interrupt pregnancy,
the clinical dilemma was if to proceed with an immediate delivery, risking
high rate of neonatal death, respiratory diseases and neurosensory disability if survived, or
whether to delay delivery, with the possibility of stillbirth.

Ethics Committee approval was requested and neonatologists were consulted for discussing with the
couple both options of active management or delaying delivery as compassionate care.

The important psychological impact on the parents was also taken into
account and psychiatric support was offered. An observational
management with a follow up re-evaluation was chosen in agreement with the parents.

Doppler examination and maternal pathology were unchanged up to 30
weeks of gestation, confirming the previous evaluation.

An ultrasonographic scan was performed at 26 and 28 weeks of
gestation, with an EFW of 257g and 283g, respectively, in order to plan a
possible elective caesarean section, after antenatal treatment with
corticosteroids. The couple, informed

of the results of clinical investigations, confirmed their initial decision.

A real benefit of antihypertensive treatment in the chronic hypertension
patient were observed during the pregnancy and other complications
were not detected.

At 30 weeks of gestation, absent
cardiac activity was recorded and the labour induction was planned. A 305g
stillbirth was delivered. Post-mortem
examination was performed.

Histological examination of the
placenta revealed abnormalities in
terms of maldevelopment, such as
massive perivillous fibrin deposition and distal villous hypoplasia, and
obstruction, such as complete villous infarction. An autopic evaluation
excluded any structurales anomalies.

Discussion

In pregnancies complicated by IUGR
due to placental dysfunction, the
foetus is at risk for intrauterine
deterioration and irreversible
compromise in terms of long-term cardiovascular
and neurodevelopmental adverse outcomes.

Consequently, the obstetric
management is faced with the task of
determining the best surveillance
approach to allow safe pregnancy
prolongation and to identify the
threshold that favours intervention.

To support this practice, the clinical
characteristics of foetal deterioration
and its relationship with foetal and
neonatal outcomes should ideally be
known, especially for early IUGR,
where ongoing surveillance and delayed delivery carry the risks of
unanticipated stillbirth, while
immediate delivery increases the risk
of prematurity-related morbidity and
mortality.

In foetuses with early IUGR a typical
pattern of clinical progression has
been described. In this type,
early signs of placental dysfunction
are arterial Doppler abnormalities, such as elevated UA and decreased MCA
blood-flow resistance, while late
responses are marked by progression
to reversed UA and-diastolic velocity
and venous Doppler abnormalities.

Doppler evaluation of foetal venous
flow-velocity waveforms is of clinical
relevance in these conditions that are
associated with cardiovascular
manifestations. In contrast to arterial
flow, velocity waveform characteristics
of the venous-flow profile relate to
atrial pressure and volume changes
throughout the entire cardiac cycle,
producing a multiphasic flow pattern.

Among the foetal venous vessels, DV
has a special role because its flow is
under active regulation and its anatomy
results in a flow velocity profile that is
typically antegrade throughout the
entire cardiac cycle and, therefore,
leads itself to qualitative assessment,
suggesting the DV atrial flow as the
strongest Doppler predictor for
perinatal mortality in preterm
IUGR.

Unfortunately, its predictive value
notwithstanding, it has been suggested
that the DV provides limited
information below 26 weeks because the
mortality rate is very high in these
cases, and in the group of IUGR
foetuses between 26 and 28 weeks of
gestation, it may provide useful
information and allow stratification
between high and low risks of perinatal
mortality, helping in the decision-
making process in this subgroup of
foetuses.

Previous data suggest that, when used
in combination with venous Dopplers,
UA and MCA do not provide clinically
useful information for the prediction
of mortality, while AoI is essentially a surrogate marker of the
degree of brain sparing. Consequently,
and similarly to MCA Doppler, it
becomes elevated very early in the
sequence of foetal haemodynamic
adaptation to placental
insufficiency.
In addition, progressive changes in AoI Doppler values are strongly correlated with those occurring in the DV.\textsuperscript{5,9,10}

Among the several publications investigating the relationships between persistent abnormal Doppler pattern and perinatal outcome in IUGR there are only few longitudinal analyses. Actually, only the studies by Turan and Bilardo provide an indirect suggestion that the progressive deterioration of DV Doppler abnormalities independently worsens neonatal outcome,\textsuperscript{4,10,11} testing the duration of persistent Doppler abnormalities has an impact on stillbirth.\textsuperscript{4} In recognition of this fact, longitudinal studies are very complex to conduct for the adverse outcome, although it is essential to characterize the expected clinical pattern of progression in pregnancies complicated by IUGR.\textsuperscript{10,11}

Normally, in IUGR foetuses Doppler changes play an important role in the diagnosis and management of these foetuses, and the dilemma of optimal antenatal management is to identify the time point at which the risks of chronic hypoxia outweighs the risks of iatrogenic prematurity.\textsuperscript{4}

Moreover, when IUGR complicated by a very serious Doppler pattern is detected in early GA, a delayed clinical management is recommended.\textsuperscript{1,2,3,4,9,10,11} An average wait of about six days before stillbirth has been described.\textsuperscript{2,3}

Recently, Turan et al. identified a persistence of absent or reversed flow in DV ranging from 1 to 45 days.\textsuperscript{5} In the current report, the expectant management of an early IUGR complicated by very serious Doppler pattern has been prolonged until to 49 days.

**Conclusion**

In IUGR foetuses the increased perinatal risks associate with progressive deterioration of arterial and venous Doppler parameters. In very early-onset IUGR, GA largely determines the risks of perinatal mortality, independently of the Doppler parameters.

If a compassionate care management is chosen, the persistence of the Doppler abnormalities can persist 49 days before stillbirth. This finding could help the decision-making process by obstetricians and parents.

Our report could add to previous and future studies to further refine the management guidelines for early-onset IUGR.

**References**