RELAIS : RCT on Evaluation of Late Iugr Screening

Single scan screening of fetal growth restriction versus Longitudinal Scan screening in the third trimester: a multicenter randomized protocol

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Background

In Italy, the universal sonographic pregnancy screening based on three examinations with the introduction of a third scan at 28-32 weeks of gestation failed its original aim to screen IUGR fetuses. Except for the very few early severe cases of IUGR that occur before 28 weeks of gestation (approximately 0.2%), the vast majority of fetal growth disorders occur later in gestation and are frequently missed by the early third trimester scan at 28-32 weeks of gestation.
As a result of clinical uncertainties many ultrasound examinations are then performed on the ground of "clinical indication" (M50 prescriptions). According to the CeDAP report for the year 2014, 41% of all pregnancies undergo four to six obstetrical sonographic examinations and 32% more than seven!
An even worse, unwanted result, of the Italian protocol is that "normal" scans at 30 weeks of gestation falsely reassure the clinician that might underestimate fetal growth restriction in late preterm or term pregnancies, with unexpected poor obstetrical outcomes in Labor and Delivery.

This failure puts the ground of the idea of uselessness of this early third trimester sonographic fetal growth checkpoint and the need of its cancellation.

In the meantime new scientific evidence showed the possible positive effects on neonatal outcome of a different protocol based on late third trimester screening.
Recent studies from UK, Sweden, Spain and France all agree that ultrasound on indication in the third trimester or screening in the early third trimester do not achieve any better sensitivity than 20% in detecting SGA, whereas late third trimester universal screening reaches and goes beyond 60% of SGA, especially when associated with uterine Doppler velocimetry.

Late and term IUGR fetuses, undergo major cardiovascular adaptation to cope with restricted nutritional supply from the placenta. These concepts emerged from evidences in experimental trials on animals, in the last decades were proved in severe IUGR human fetuses, and in the last five years had been confirmed in late and term IUGR, by means of Doppler investigation of fetal circulation and unquestionable evidence from flow volume studies in human fetuses by functional NMR. These studies all provide a solid ground for the epidemiological evidence put forward by JA Barker on the "fetal origin of coronary heart disease", a truly scientific breakthrough that opened the whole new era of "fetal programming".

This solid scientific background tells us clinicians that undetected problems of fetal growth restriction not only are an unfortunate condition for perinatal complication that should be tackled by wise and efficient clinical protocols with the aim to reduce immediate health threats to our newborns but also to flag these cases so that paediatricians and family doctors could threeimplement healthy lifestyles to prevent the forecasted metabolic and cardiovascular complication pending on these subjects.
In fact, this new focus on fetal growth is paralleled by a quest for a more dedicated attention to growth disorders in utero that, via altered fetal programming, might cause long term metabolic and cardiovascular problems. We quote this editorial published by The Lancet by the intramural director of the NIHCD, dr Roberto Romero: "*A general principle in developmental biology is that organisms are most susceptible to insults during periods of rapid growth. Therefore, it is somewhat paradoxical that even though the human growth rate is particularly rapid during fetal life, monitoring such growth in women with low-risk pregnancies is not part of standard obstetrical care.* ***This situation persists despite overwhelming evidence that fetal growth disorders are risk factors for adverse perinatal outcome and can predispose these infants to adult chronic diseases*.".**

These data lay down a possible revision of guidelines such as the NICE guideline on Antenatal Care published in 2008 and confirmed in January 2017 under the heading of "1.10 Fetal growth and well-being":

1.10.2 Ultrasound estimation of fetal size for suspected large-for-gestational-age unborn babies should not be undertaken in a low-risk population. [2008]
1.10.3 Routine Doppler ultrasound should not be used in low-risk pregnancies. [2008]
1.10.9 The evidence does not support the routine use of ultrasound scanning after 24 weeks of gestation and therefore it should not be offered**.**

The sum of biological and clinical evidence with the observation that more than 70% of pregnant women in Italy undergo more than 4 scans per pregnancy, and that even in well-organized regions such as Lombardy and Emilia Romagna more the 25% undergo more than 6 scans per pregnancy, makes a national based study mandatory on efficacy and efficiency of ultrasound screening of fetal growth restriction in order to comply with the criteria that international guidelines should be "tailored" according to local characteristics, clinical organization, cultural values, and, when possible, to local scientific evidence.

AIM

Given the evidence that the universal sonographic screening is far much better than selective screening in detecting fetal growth disorders (1) ,the aim of this trial is to assess the efficacy and efficiency of two universal sonographic screening protocols for fetal growth disorders:

- the "single scan" **screening** according to the local LEA, based on evaluation of fetal biometry at 28-32 weeks of gestation (in the Regions were the "early screening" is recommended) as it is in the Italian NHS protocol, after ultrasound dating at 10-13 weeks of gestation and anatomy screening and fetal biometry at 19-22 weeks of gestation.
- the **longitudinal screening**, similarly providing a scan at 10-13 weeks of gestation for dating, and a second scan at 19-22 weeks of gestation based on biometric and Uterine artery Doppler velocimetry procedure, and subsequently both one scan at 28-32 weeks and another one at 35-37 weeks of gestation .

STUDY DESIGN

Type of study:

multicentre diagnostic, open randomised trial.

Inclusion criteria:

Eligible cases are **nulliparous pregnant women,** with first trimester ultrasound assessment of gestational age, **who conceived singleton fetuses.** If the crown-rump-length (CRL) differs of more than ± 3-5 days from the last menstrual period, gestational age is calculated on the CRL. Women who agree to participate are randomized to the Single scan protocol or Longitudinal scan protocol. In practical terms this mean that in each participating centre the randomization will be on two arms but the time of the single scan assessment will be dependent on the Regional Health Authority regulation (LEA: Livelli Essenziali di Assistenza)

Exclusion criteria:

- major medical disease
- pregnancy conceived by IVF/ICSI
- known immune disorders or clinical thrombophilic conditions;
- twin pregnancies;
- high risk for preeclampsia detected in those centres that perform pre-eclampsia screening at first trimester
- Papp-A at Combined-Test<0.2

Study protocol:

Eligibility check, information on this trial, offer to be recruited will be performed by the local investigator at the 19-21 weeks of gestation scan.

Women who agree to take part into the trial and sign an informed consent, will be randomized **to the Single Scan Protocol (28-32 weeks scan) or to the Longitudinal Scan Protocol (scan both at 28-32 AND 35-37 weeks).** Demographic characteristics and medical history of recruited women are recorded on the CRF. The same demographic and clinical data of eligible women who refuses to be recruited will be recorded for analysis between trial cohort and eligible non recruited women. To define fetal growth disorders we will adopt the Delphi criteria for the diagnosis of IUGR.

Women randomized to the **Single scan Protocol** will receive the standard package of sonographic anatomy and biometric screening offered by the Regional Health Service at 19-21 weeks of gestation and biometric screening at 28-32.

- **Single Scan protocol at 19-21 weeks**: if **AC biometry and/or fetal weight are normal** a biometric scan is scheduled basing on the regional LEA at 28-32 weeks of gestation .If **AC biometry and/or fetal weight are abnormal the case is excluded** from further analysis for third trimester screening, and the patient is then monitored according to local protocol.

- **Single Scan at 28-32 weeks**: if **AC biometry and/or fetal weight is abnormal <10th, or crossed 50th centile from mid-trimester (screen positive)** further management will be performed according to local protocols**.**

All suspected fetal anomalies will be excluded from further analysis.

Women randomized to the **Longitudinal Scan Protocol,** besides the fetal anatomy screening**,** will receive a package of anatomy and biometric screening and Doppler interrogation of the Uterine arteries at 19-21 weeks of gestation and at 28-32 and 35-37 according to the following criteria:

- **Longitudinal Scan Protocol at 19-21 weeks**: if both **AC biometry and/or fetal weight** a biometric scan is scheduled at 28-32 weeks of gestation *regardless the result of the Uterine Artery Doppler investigation*. If **AC biometry and/or fetal weight are abnormal the case is excluded** from further analysis for third trimester screening, and the patient is then monitored according to local protocol

- **Longitudinal Scan Protocol at 28-32 weeks**: a standard package of fetal biometry, Amniotic Fluid index and Doppler interrogation of the Uterine arteries, Umbilical artery and Middle cerebral artery will be performed. If the **AC biometry and/or fetal weight** are normal, another biometric scan will be scheduled at 35-37 weeks of gestation and monitored until delivery according to local protocols **(screen negative).**

- **Longitudinal Scan Protocol at 35-37 weeks**: a standard package of fetal biometry, Amniotic Fluid index and Doppler interrogation of the Uterine arteries, Umbilical artery and Middle cerebral artery will be performed. If **AC biometry and/or fetal weight is abnormal <10th, or crossed 50th centile from mid-trimester (screen positive)** further management will be performed according to local protocols.

All scans after the dating scan in the first trimester are performed with mid-high quality ultrasound units. All ultrasound measurements follow the same protocols as those used in the clinical service, i.e. measurement of fetal head circumference, abdominal circumference, and femur length, using standard techniques.

Images produced to obtain recorded measurements are stored on digital media.

Attending clinicians are informed of the results obtained both by the Single Scan and by the Longitudinal Scan Protocols and will act according to local protocols when a diagnosis of IUGR is the result of the scan.

Measurements of outcome

This study is designed to generate level 1 evidence of diagnostic effectiveness
For both protocols, screen positive and screen negative results are based on the antenatal detection of a small for gestational age (SGA) neonate namely a newborn with a birth weight <10th centile.

MAIN OUTCOME

The main outcome of the two protocols in screening late preterm and term SGA fetuses at term is measured based Intergrowth21th newborn weight charts centiles <the 10th according to gender.

SECONDARY OUTCOME

1. Mode of delivery
2. Caesarean section rate
3. Composite mild adverse neonatal outcome (Apgar score at 5 minutes <7, pH < 7.10, or BD >8mmol/L, admission at NICU)
4. Composite severe adverse perinatal (stillbirth or term live birth associated with neonatal death, hypoxic ischaemic encephalopathy, use of inotropes, need for mechanical ventilation, or severe metabolic acidosis (defined as a cord blood pH <7·0 and base deficit >12 mmol/L).

TERTIARY OUTCOME

1. Econometrics of the two protocols, and of the estimated sanitary costs of outcomes

EXPECTED RESULTS

We hypothesize that the Longitudinal Scan Protocol with a 28-32 AND a 35-37 weeks universal screening will outperform the Single scan Protocol for the primary outcome regarding the detection Rate of IUGR. On the other hand, as this Protocol will be the more expensive one, we hypothesize that the most cost effective protocol will be the universal single late scan at 35-37 weeks of gestation so underlying the clinical utility of a late single scan for the low risk population.
The secondary outcomes are subjected to local protocols and we should expect a reduction of the composite neonatal adverse outcome in the late single scan protocol and in the longitudinal one.
Last but not least, we hypothesize that the inferred Econometrics of the two protocols will provide evidence of the reduced health care costs of the universal screening when properly based on biological and clinical data obtained by this branch of medicine in recent years (R.P.) versus old tenets of the early years of the introduction of ultrasound in obstetrics (I.P.).

STATISTICS

Sample size is based on sensitivity in detecting SGA below 10th centile weight at birth. For the 28-32 group, sensitivity is based on results by Roma et al. (22.5%). The results published by Sovio et al. are instead taken for the "longitudinal" group (57% sensitivity).
The sample size calculations have been carried out for the comparison between the 28-32 only group vs. the "longitudinal". Calculations considered a confidence level of 95% (1-alpha) and an 80% power (1-beta), and a one to one ratio between the 28-32 only groups and the "longitudinal". According to Fleiss (Fleiss JL. Statistical methods for rates and proportions, II Ed. John Wiley & Sons, New York, 1981. page 45, formulas 3.18 & 3.19), for the 28-32 group vs. the "longitudinal", each arm should comprise 32 subjects, which implies 64 for two arms. The sample size needed considering both AGA and SGA, will then be 64x10=640. Considering 10% of drop-out and incomplete data the final sample size should be increased of such percentage, reaching 704 subjects.
The sample should be recruited according to the number of deliveries per year of each institute involved in the multicenter study. Analysis will be based on intention to treat. Demographic and maternal characteristics variables will be collected in order to describe the population of women recruited in the study and reassure about the result of randomization
A Kolmogorov-Smirnov or Shapiro-Wilk test and visual plot inspection will be used to assess normality of arithmetic data distributions. Parametric or non-parametric tests will be used to compare variables between the groups, and comparison of proportions will be performed using Chi-square or Fisher's exact test, as appropriate.
Logistic regression models will be used to determine the magnitude of the association between ultrasound variables and newborn's weight <10° centile and neonatal outcome.
Performance of Single Scan and Longitudinal Scan screening policy in identifying late preterm and term SGA will be calculated and compared between arms. The area under the receiver operating characteristic (ROC) curve will be estimated with 95% confidence intervals. Next, the screening performance will be then summarized in terms of sensitivity, specificity, positive and negative predictive values and likelihood ratios.
A p value <0.05 will be considered statistically significant.

Figure 1 : Flow chart of the randomized trial