ARTICLE IN PRESS
EHD-03718; No of Pages 6
Early Human Development xxx (2012) xxx–xxx
Contents lists available at SciVerse ScienceDirect
Early Human Development
journal homepage: www.elsevier.com/locate/earlhumdev

The predictive value of first trimester fetal volume measurements, a prospective cohort study ☆,☆☆

Nicol A.C. Smeets [a,⁎], Bjorn Winkens [b], Marc Prudon [c], Joost van de Ven [d], Vera P.J. Gondrie [e], Frank van Deursen [f], S. Guid Oei [d,g]

[a] Department of Gynecology and Obstetrics, Atrium Medical Centre, Heerlen, The Netherlands
[b] Department of Methodology and Statistics, University of Maastricht, Maastricht, The Netherlands
[c] Department of General Practice, University of Maastricht, Maastricht, The Netherlands
[d] Department of Gynecology and Obstetrics, Máxima Medical Centre, Eindhoven-Veldhoven, The Netherlands
[e] Department of Surgery, Rijnstate Hospital, Arnhem, The Netherlands
[f] Department of Psychiatrics, Dijk & Duin, Purmerend, The Netherlands
[g] Department of Electrical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands

ARTICLE INFO

Article history:
Received 18 August 2012
Received in revised form 24 October 2012
Accepted 2 November 2012
Available online xxxx

Keywords:
Fetal
Volume
Three-dimensional
Ultrasound
Predictive value
Preterm birth
Low birth weight

ABSTRACT

Objectives: To determine if fetal volume (FV) measurements with three-dimensional ultrasound in the first trimester of pregnancy can detect the fetus at risk for preterm birth and/or low birth weight.
Methods: In this prospective cohort study, 538 participants were included during the routine first trimester ultrasound examination. Volume measurements were performed with VOCAL (9°). Firstly, the relation between FV and gestational age for a set of participants with normal pregnancies (training set), was assessed using multiple linear regression analysis, which was then used to determine the expected normal values. Secondly, for a new set of participants with normal pregnancies and a set of participants with complicated pregnancies (preterm birth and/or low birth weight), i.e. the validation set, the observed fetal volumes ($FV_{observed}$) were compared with their expected normal values ($FV_{expected}$) and expressed as a percentage of the expected normal value. The difference in mean percentage was then assessed with independent-samples t-test. Finally, logistic regression analysis was applied to the validation set to analyze the ability to predict the pregnancy outcome with FV calculation.
Results: Linear regression analysis of FV as a predictor of preterm birth and/or low birth weight did not result in significant ($p = 0.630$ and 0.290, respectively) or clinical relevant results (standardized effect sizes of 0.061 and 0.179, respectively). The predicting quality was also very low (AUC = 0.508 and 0.545 respectively).
Conclusions: Fetal volume measurements in the first trimester of pregnancy are not useful as a prognostic tool for predicting pregnancies of high risk for preterm birth or a low birth weight.

1. Introduction

Some have suggested that complications in pregnancy, such as preterm birth, low birth weight and birth weight that is small for gestational age (SGA), are the result of the intra-uterine conditions in the first trimester of pregnancy [1–4]. Preterm birth is a growing public health problem that has significant consequences for families. Preterm birth accounts for 12.5% of all births in the United States. The costs for society are at least $26 billion dollar a year [5]. Low birth weight (<2500 g) and birth weight that is SGA are associated with increased morbidity and mortality in the perinatal period and in later life [6].

The differences between normal and abnormal growth in early pregnancy are small if the fetal size is measured by the CRL [1,7,8]. Small first-trimester fetal size measured by the CRL, defined as the lowest 20%, was associated with an increased risk of being born preterm (7.2% vs 4.0%), a small size for gestational age (10.6% vs 4.0%), or with a low birth weight (7.5% vs 3.5%) [3]. The weakness of these findings is the low predictive value, therefore it is not a good screening test for selecting the high risk pregnancies.

Three-dimensional ultrasound (3DUS) volume measurements might give more information about fetal growth than 2DUS measurements by adding the third dimension in the analysis. Fetal volume (FV) measurements were the subject of earlier studies, showing that these volume measurements were reliable and reproducible [9,10],

☆ This study was performed at the outpatient ultrasound department of the Máxima Medical Centre, Veldhoven, The Netherlands.
☆☆ There was no financial support/funding received for this study.
⁎ Corresponding author at: Henri Dunantstraat 5, 6401 CX Heerlen, The Netherlands. Tel.: +31 45 57 66 515.
E-mail addresses: n.smeets@atriummc.nl (N.A.C. Smeets), bjorn.winkens@maastrichtuniversity.nl (B. Winkens), m.prudon@maastrichtuniversity.nl (M. Prudon), joost.vandeven@mmc.nl (J. de Ven), v.gondrie@gmail.com (V.P.J. Gondrie), f.vandeursen@alumni.maastrichtuniversity.nl (F. van Deursen), g.oei@mmc.nl (S.G. Oei).

0378-3782/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.earlhumdev.2012.11.001

even in twins [11,12]. A significant correlation between FV and the CRL was already confirmed, with an up to 35-fold increase of the FV and a 4.5-fold increase of the CRL in the first trimester of pregnancy [9–11,13,14]. As the FV rises 7 times faster than the CRL, it can be expected that slight abnormalities in the CRL will be more obvious in FV measurements. Falcon et al. reported that the chromosomal abnormal fetus has a significant smaller FV (10–15%) than the chromosomal normal fetus whereas the CRL was normal [10,14]. These findings suggest that it might be possible to detect early growth impairment with FV measurements, in cases with a normal CRL. Fajardo et al. reported recently that FV measurements performed significantly better than CRL in predicting inter-twin growth disturbances [15]. Antsaklis et al. reported in their pilot study that the FV correlates best with birth weight, compared to CRL and gestational sac volume [16]. These results are promising.

Detection of the fetus with a small FV might result in earlier detection of high risk pregnancies, with the possibility to customize healthcare in these cases. A longitudinal follow up study is necessary in order to obtain this knowledge.

The objective of the present prospective cohort study is to determine if it is possible to detect whether the fetus is at risk for preterm birth and/or low birth weight for gestational age by measuring the fetal volume with three-dimensional ultrasound in the first trimester of pregnancy.

2. Materials and methods

This is a longitudinal prospective cohort study, performed at a teaching hospital in The Netherlands. Participants were included during the routine first trimester ultrasound examination for three years. Fetal volume measurements and data collection were completed afterwards.

2.1. Recruitment

All 538 consecutive participants with an appointment for the routine first trimester ultrasound scan with nuchal translucency (NT) measurement were asked to participate in this study. The inclusion criteria were: a singleton pregnancy, maternal age > 18 years, gestational age between 11^{+0} and 13^{+6} weeks. Exclusion criteria were: a multiple pregnancy and an uncertain gestational age. An uncertain gestational age is defined as an unknown date of the first day of the last menstrual period or no knowledge of the length of the menstrual cycle. Participants were included after signing an informed consent form. Each participant filled out two questionnaires, one about their general and obstetric history and another one after the delivery about the pregnancy, delivery and neonatal outcome. The participants were referred from other surrounding hospitals and midwives for the first trimester ultrasound scan and the nuchal translucency measurement, which indicates that this is a low risk population.

2.2. Fetal imaging

The Kretz Voluson 730 3D ultrasound scanner (General Electrics Kretz, Zipf, Austria) was used in combination with the RAB4-8P wide band convex volume probe, a real time 4D-broadband electronic curved-array transducer with a frequency range of 4–8 MHz. The angle sweep was 75°. The three-dimensional volumes were acquired during the standard abdominal first trimester scan by an investigator certified for NT measurements. The gestational age was established by menstrual dates and confirmed by routine fetal biometry. For volume acquisition the fetus had to be motionless during scanning.

2.3. Data acquisition

The routine first trimester (abdominal) ultrasound scan and NT-measurement were performed according to international guidelines [17,18]. 3D View™ (General Electronics, Sonoview II) was used to receive, store digitally and measure the fetal volumes from the 3DUS-datasets. After obtaining the ideal (midsagittal) plane for NT-measurement, an automatic 3DUS sweep was performed, which consists of multi-planar and surface reconstruction modes. All the ultrasound scans were performed by one sonographer. The acquired datasets were collected and stored on a hard disk for offline processing and volume calculation. The volume measurements were performed by one of the four investigators who were blinded for the results of the first trimester scan. Each dataset was measured once.

The VOCAL imaging software (an extension of 3D View™) was used for the FV measurements. As the human embryo has an irregular shape, the manual mode was used to outline the Region Of Interest (ROI), the fetal head and rump, in all cross sections. It was not possible to include the fetal extremities in these measurements, because the software does not allow one to define separate structures in one cross section. Therefore the ROI had to consist of one continuous object in every cross section. This method has also been used by others [10–12,14,16].

The fetal volumes were calculated with a rotational step of 9° in the A(axial)-plane, which is a longitudinal plane. This 9° rotation is to be preferred in irregular objects, as it is as reliable as the 6° rotation, but significantly faster to perform [19].

The 9° rotational step results in a sequence of 20 longitudinal sections of the fetus around a fixed axis. In each of these planes the two-dimensional (2D) contour of the fetus was defined manually, as described by others [10–12,14,16]. The VOCAL program then calculated the volume of the defined contour. After calculation the computed reconstruction of the fetus was displayed together with the fetal volume. Fig. 1 shows the image of a calculated volume. There can be an undulating surface of the 3D image, which is caused by the rotational steps and represents the ROIs in each measured plane. We have previously reported that the inter- and intraobserver agreement of fetal volume measurements by 3DUS is very high [20].

The four investigators also completed the data files concerning the pregnancy outcome. When no questionnaire was received, a reminder was sent to the participants. Non-responders were contacted by phone and the hospital database was searched for information about the pregnancy outcome.

2.4. Statistical analysis

2.4.1. Primary analysis

Pregnancies complicated by preterm birth and a low birth weight were extracted from the cohort. The remaining cohort was defined as 'normal'. Firstly, for a random sample of these 'normal' pregnancies (defined as the training set), the relation between FV and gestational age (GA) at time of the ultrasound scan was assessed using multiple linear regression analysis, accounting for fetal gender and parity. This model was then used to determine the expected values of fetal volume for a normal pregnancy, which are referred to as expected normal values. Secondly, for a new set of participants with normal pregnancies and a set of participants with complicated pregnancies (together defined as the validation set), the observed fetal volumes ($FV_{observed}$) were compared with their expected normal values ($FV_{expected}$) and expressed as a percentage of the expected normal value, i.e. percentage error $= 100\% * (FV_{observed} - FV_{expected}) / FV_{expected}$. The mean difference in percentage error between the set of normal versus complicated pregnancies was then compared using the independent-samples t-test. Finally, logistic regression analysis was applied to the validation set in order to analyze the possibility of predicting the pregnancy outcome after fetal volume calculation in the first trimester, using this percentage error. The prediction quality is presented by the area under the ROC curve (AUC). Complicated pregnancies were defined by preterm birth and/or low birth weight for gestational age, or only by low birth weight for gestational age.

Please cite this article as: Smeets NAC, et al, The predictive value of first trimester fetal volume measurements, a prospective cohort study, Early Hum Dev (2012), http://dx.doi.org/10.1016/j.earlhumdev.2012.11.001