The Application of First-Trimester Volumetry in Predicting Pregnancy Complications

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ABSTRACT
The application of first trimester volumetry in predicting pregnancy complications is a promising and interesting field in Obstetrics and Radiology. This was a descriptive review of first trimester volumetry in predicting pregnancy complications over a period of 6 months (January 1st, 2013 to June 30th, 2013). A search of literature on first trimester volumetry published in English was conducted. Relevant materials on first trimester volumetry were selected. Placenta volumes (PV) and embryo volume/fetal volume ratios in the first trimester are correlated with crown rump length (CRL) or gestational age (GA). Measurement of PV or placental quotient (PV/CRL ratio) is an early assessment to identify impaired trophoblast invasion and predict subsequent development of intrauterine growth restriction (IUGR) or pre‑eclampsia (PE). In early onset IUGR due to triploidy, or trisomy 13 or 18, a larger deficit in fetal volume is observed compared to CRL. In obstetric sonography, standardization of the 3D volumetric methodology is needed to improve reproducibility of measurement. The accuracy of these measurements is uncertain and current applicability to practice is not fully accepted, therefore, the current methods are yet to be standardized and general applicability is uncertain. Volumetry holds a good promise as an extra method for predicting IUGR, PE, aneuploidy, miscarriages, or stillbirth but lack of standardization currently limits its applicability.

KEY WORDS: 3D ultrasound, first trimester, pregnancy complications, volumetry

INTRODUCTION
Sonography is an excellent and a preferred modality for first trimester pregnancy evaluation.11 Ultrasonography has an essential role in determining the progress of pregnancy and predicting prognosis. The 3D volumetric methodology is more prone to irreproducibility of measurements and technically more demanding. However, it is not a substitute for conventional 2D ultrasound and both methods should be used together to get accurate and efficient ultrasound diagnosis.12 It is normally acceptable to do a trans-abdominal scan to evaluate an early pregnancy in majority of cases but a trans-vaginal scan would invariably provide a quick and more definitive answer.13 Trans-vaginal scan gives better resolution, exquisite view and is more accurate in first trimester pregnancy with profound benefits to patients and obstetricians.14,15

First trimester of pregnancy is defined as 12 weeks after the last menstrual period in a woman during her reproductive life. This period is fraught with a lot of complications associated with human formation, development and growth. First trimester ultrasonography therefore aims to establish viability, pregnancy dating, detect multiple pregnancy, observe uterine adnexal structures, measure nuchal translucency and evaluate limited fetal gross anomaly. However, first trimester ultrasound is now a means of predicting an abnormal fetal outcome not only in the presence of a live embryo but also before visualization of the embryo itself. There are findings which can be used to identify a subgroup of embryo at high risk of embryonic demise or subsequent diagnosis of fetal anomaly that requires close monitoring.4-6

It is feasible and reproducible with 3D ultrasound to measure the volumes of the embryo (EV),7,8 placenta (PV),9 fetus (FV),9 gestational sac (GSV),7,10 and yolk sac (YSV)7,11 accurately and reliably in the first trimester. An increase in FV or PV over gestation was greater than CRL9,12 First trimester prediction of intrauterine growth restriction (IUGR), preeclampsia, birth weight, aneuploidy,
miscarriage, complications in multiple pregnancies and homozygous thalassemia is a challenging and an emerging field in obstetrical sonography. Studies have been carried out to investigate the use of first trimester volumetry in the prediction of IUGR and pre-eclampsia (PE), birth weight, fetal sex, aneuploidy, miscarriage, complications in multiple pregnancies, and other adverse outcomes. The use of traditional prediction methods (maternal history, 2D ultrasonography and biochemical markers) have limitations and can only detect 77-88.9% of PE at 10% false positive rate. Sonographically, the use of 3D ultrasound to measure volumes of regularly or irregularly shaped objects is more accurate than 2D ultrasound and is more accurate and reliable for clinical evaluations.

The aim of this article is to review the use of first trimester ultrasound volumetry in predicting pregnancy complications.

**MATERIALS AND METHODS**

This was a 6-month descriptive review of the application of first trimester ultrasound volumetry in predicting pregnancy complications. Relevant literature search on this topic was from January 1st, 2013 to June 30th, 2013. A search of literature on first trimester volumetry published in English was conducted. Relevant materials on first trimester volumetry were selected. The keywords used are first trimester ultrasound volumetry, first trimester pregnancy complications and 3D ultrasound with selected references, conference papers, technical reports, journal articles, abstracts, relevant books, and internet articles using Medline, Google scholar, and PubMed databases were critically reviewed.

**Placental volumetry**

The components of placental volumetry include placental volume and placental quotient which is derived from placental volumetry. The placenta is defined by the basal and chorionic border with the uterine wall carefully excluded with 3D ultrasound. The measurement technique used is the VOCAL method with a 30A rotation angle or the multiplanar method as shown in Table 1. Placental quotient (PQ) is PV divided by the fetal CRL. This is the first trimester parameter to indicate whether a placenta is large or small for a given fetus. There are limitations in using placental volumetry for clinical application because of the physiological variations in placental shape, weight and volume at each stage of gestation, the heterogeneity of placental growth, and the increased placental thickness at the first trimester is a sonographic sign of homozygous thalassemia with a sensitivity of 72%.

**Embryo or fetal volumetry**

Embryo volume or fetal volume can be measured directly or by subtracting the amniotic fluid and yolk sac volumes from the gestational sac volume (GSV). Using a direct method, the fetus is measured by drawing a contour line along its head and trunk while excluding the limbs which often cross over each other or touch the face in the late first trimester. However, other clinicians suggested measurement of FV to include the limbs which represent a significant proportion (8-10%) of the size of the embryonic/fetal body. The head volume can be measured separately and then subtracted from the total head and trunk volume to obtain the volume of the fetal trunk.

VOCAL is a commonly used technique but it is more difficult and it is time consuming to measure embryonic limbs, which...
appear to be a separate and disconnected object from the trunk in certain planes unless a thin connecting stalk is drawn between the limbs and the trunk. VOCAL with 9A° rotation provides the best compromise among validity, reliability and time required for measurements when compared with 30A°, 15A° and 6A° rotation steps. Other methods used include the multiplanar technique and the XI VOCAL technique as shown in Table 1. 3D ultrasound (using a multi planar, VOCAL or XI VOCAL technique) is capable of providing a reproducible measurement of the fetal trunk and head volume at 11 + 0 to 13 + 6 weeks gestation. Semi-automated techniques, using both VOCAL and SonoAVC, facilitate the measurement of the embryo without the need to physically define its contour, which is the major limiting factor in the aforementioned techniques. However, there may be a significant difference in the volumetry between this semi-automated technique and the conventional VOCAL technique alone with 9A° rotations. There was a significant correlation between EV and GA or CRL with a linear association between 11 + 0 weeks and 13 + 6 weeks, or between a CRL of 45 and 84 mm. These findings are consistent with previous 2D sonographic studies on the S-shaped pattern of fetal growth with gestation, with the linear component at 10 and 13 weeks. A recent review by Ioannou et al. showed discrepancy in the reported normal volumes of first trimester embryos, ranging from 0.2-0.23 cm³ at 7 weeks to 3.91-5.12 cm³ at 10 weeks. The discrepancy is likely to be due to inconsistencies in 3D volumetric methodology, inadequate assessment of method repeatability and validity, and a diversity of mutually incompatible 3D imaging formats and software measuring tools. Standardization of the 3D volumetric methodology will help to improve quality assurance in fetal volumetry and then facilitate its clinical application.

### Gestational sac volumetry

Gestational sac is the amniotic cavity and the exoceolomic cavity in the first trimester. Gestational sac is the first definitive landmark of pregnancy which is consistently visible by 5 weeks of gestation. GSV is used for confirmation of an intrauterine pregnancy, calculation of GA before the fetus is viable and diagnosis of anembryonic pregnancy as shown in Table 1. GSV is measured using the VOCAL method with a 30A° rotation angle. In a study in 2009 by Rolo et al., intra-observer variability was small with an average difference between measurements of 0.5 cm³. There was a high correlation between GSV and GA or CRL, mean GSV increased from 8.50 cm³ at 10 weeks to 44.35 cm³ at 10 weeks and from 13 + 6 weeks. GSV increase from 5.00 to 50.28 cm³ for a CRL increased from 0.9 to 4 cm. GSV is closely related to amniotic fluid volume. GSV may reflect uteroplacental functions in the first trimester, and may predict adverse pregnancy outcome.

### Gestational sac fluid volumetry

Gestational sac fluid volume (GFSV) is obtained by taking measurements using VOCAL with a rotational step of 30A° rotation, and then subtracting the EV from the GSV. The components of placental volumetry include placental volume and placental volume which is derived from placentation. PV is used for confirmation of an intrauterine pregnancy, calculation of GA before fetal viability and subsequent development of IUGR. PV may be a better first trimester marker of IUGR than CRL. Abnormal amniotic fluid volumes may indicate pathology associated with adverse pregnancy outcomes.
GSFV can also be measured using the multiplanar method or VR as shown in Table 1.\textsuperscript{54} Sono AVC is automatic, but may significantly underestimate GSFV.\textsuperscript{50} There is significant correlation between GSFV and GA or CRL.\textsuperscript{42} Mean GSFV increased by approximately six to seven-folds from 7.81 to 50.28 cm\(^2\) for a CRL increase from 12 to 40 mm.\textsuperscript{42} The GSFV/EV ratio decreased with GA.\textsuperscript{24} In normal pregnancies, there was a progressive increase in amniotic fluid from 8 to 11 weeks of gestation.\textsuperscript{55} Abnormal amniotic fluid volumes may indicate pathology associated with adverse outcomes,\textsuperscript{56} and further studies are required.

Yolk sac volumetry

Yolk sac volume is measured using VOCAL method with 30\(^\circ\) rotation\textsuperscript{11} or XI VOCAL.\textsuperscript{57} Yolk sac volume is not seen after 12 weeks.\textsuperscript{52} A persistently abnormal yolk sac shape is a predictor of abnormal outcome [Table 1].\textsuperscript{58} Large or abnormal yolk sacs are associated with a poor prognosis.\textsuperscript{53} In a study by Rolo et al.\textsuperscript{11} there was a poor correlation between YSV and GA or CRL. [Table 1]. The mean YSV increased from 0.063 cm\(^3\) at 7 weeks to 0.164 cm\(^3\) at 10 weeks.\textsuperscript{11} In another study,\textsuperscript{59} the mean YSV increased in a linear fashion up to 10 weeks, then maintained a plateau until 11 weeks and decreased thereafter.\textsuperscript{11} This can be explained by the yolk sac degeneration process secondary to vascular depletion.\textsuperscript{60} The absence or malformation of a yolk sac outside the normal growth pattern is associated with poor pregnancy outcomes.\textsuperscript{52,61} Variations in the yolk sac size, either too small (<2 mm) or too large (>6 mm) are associated with an increased risk of abnormal outcome Table 1).\textsuperscript{62}

Application of first trimester volumetry

The embryonic cardiac activity

In routine ultrasound scan, demonstration of embryonic cardiac activity indicates that the embryo is alive at the time of the examination. An abnormally slow heart rate or abnormally fast heart rate may predict impending demise. An embryonic heart rate consistently below 80 bpm is universally associated with subsequent embryonic demise. A heart rate of 100 bpm or higher is considered normal in embryos less than 5 mm in CRL. The presence of cardiac activity changes the prognosis in pregnant women presenting with threatened miscarriage from a 50% rate of pregnancy failure to a much more favorable conditions.\textsuperscript{58}

Birth weight prediction

A correlation between placental size and birth weight was demonstrated in an earlier study.\textsuperscript{18} In a recent study, PV multiples of the median were reduced in SGA neonate (0.88), but increased in large-for-gestational-age neonates (1.09) compared with appropriate-for-gestational-age neonates (1.0).\textsuperscript{18} A study of singleton low-risk pregnant women showed that EV during the first trimester of pregnancy correlates better with birth weight than CRL, GSV and PV [Table 1].\textsuperscript{19} A 10 mm\(^2\) increase in EV corresponds to a mean birth weight increase of 75 g, while a 1-mm increase in CRL corresponds to a birth weight increase of 113 g.\textsuperscript{19}

Intrauterine growth restriction

Pregnancies at risk of IUGR detected during antenatal period can reduce perinatal morbidity and mortality by four to five fold.\textsuperscript{62} Therefore, measurement of PV or PQ may be an efficient method for the early and simple identification of impaired first wave of trophoblast invasion, and subsequent development of IUGR [Table 1].\textsuperscript{14,15} In a recent prospective study of 1060 women, a small PV or PQ between 11 and 13 weeks was associated with high-resistance uterine perfusion in the second trimester.\textsuperscript{14} Unlike uterine artery Doppler, PV and PQ did not show any dependency on age, gravidity, BMI or smoking habits.\textsuperscript{14} In a study of singleton pregnancies, PQ at 12 weeks and uterine artery Doppler at 22 weeks had similar sensitivities (27.1 vs 28.1%) for predicting IUGR.\textsuperscript{24} A PQ of 10\(^{th}\) centile occurred in 10% of pregnancies and its sensitivity in predicting complications including IUGR, PE, or placental abruption was 22%.\textsuperscript{17}

Preeclampsia

Preeclampsia is a major cause of maternal and perinatal morbidity and mortality.\textsuperscript{57} It complicates 2-3% of pregnancies.\textsuperscript{57} In a prospective study of singleton pregnancies, logistic regression models for the detection of PE had a sensitivity of 38.5% (PQ at 12 weeks) versus 44.8% (uterine artery Doppler at 22 weeks).\textsuperscript{15} Taking a PQ that is at 10\(^{th}\) centile, the sensitivity for PE with and without SGA neonates was 30.8% and 20.0% respectively. It appears that PQ is less sensitive than uterine artery Doppler for the prediction of PE\textsuperscript{15} but similarly sensitive in approximately 50% in predicting the most severe complications in which delivery took place before 34 weeks.\textsuperscript{15}

Aneuploidy

A study in 2002 showed that the median PQ in a group of mixed chromosomal abnormalities (0.67) was significantly lower than that in normal fetuses (0.98),\textsuperscript{20} and that the inclusion of PV measurements as an additional marker to nuchal translucency may improve the sensitivity of first trimester screening.\textsuperscript{20} In another study in 2005, the mean PV for GA was smaller in conjunction with trisomies 13 and 18 than in normal pregnancies.\textsuperscript{21} However, no difference was observed between normal pregnancies and those with trisomy 21 or Turner syndrome.\textsuperscript{21}

In a study reported by Leung et al.,\textsuperscript{13} an early-onset IUGR due to aneuploidy, a larger deficit in FV than CRL was observed. This observation in discrepancy is due to a larger growth rate of FV than CRL (five to six fold vs two fold) in normal fetuses at between 11 + 0 and 13 + 6 weeks.\textsuperscript{12} FV may be a better
An early method to identify impaired placental growth was by assessment of the technique of 3D ultrasound showed a strong correlation between PV and EV, and CRL or GA in the first trimester. However, this method alone probably cannot predict all cases of at-risk pregnancies.

The mean GSV for GA was smaller in pregnancies with triploidy and trisomy 13 than in normal pregnancies, probably due to a reduced amniotic fluid volume.

**Thalassemia**

Fetal homozygous thalassemia is the most common cause of hydrops fetalis in Southeast Asia. Using placental thickness, the sensitivity to predict an affected pregnancy before 12 weeks of gestation was 72% with a specificity of 97%. Early onset IUGR and placental hypoxia were probably caused by fetal anemia and pulmonary hypoxia association with homozygous thalassemia. Consistent with results of other studies, it appears that 3D volumetry is more sensitive than CRL in detecting IUGR in early pregnancy.

**Multiple pregnancies**

In a prospective study on twin and triplet pregnancies at 11 + 0 to 13 + 6 weeks of gestation, median twin and triplet PVs were 1.66 and 2.28 multiples of the median for singletons, respectively. It is likely that PV in multiple pregnancies does not depend on chorionicity. There was no difference in the rate of placental growth between 11 and 13 + 6 weeks among singletons, twins and triplets.

In a dichorionic twin pregnancy, discordance in growth with a distinctly small PV was associated with an abnormal twin with triploidy of maternal phenotype. With assisted reproductive technology, early volumetry has an important role in the early diagnosis, growth and wellbeing.

**Miscarriage**

In earlier study, the correlation between the GSV and CRL or GA was weaker in cases of missed miscarriage than ongoing pregnancies. The GSV: EV ratio in missed miscarriage was significantly higher than those in ongoing pregnancies. However, in another study, a logistic regression analysis showed no significant correlation between GSV and the outcome of missed miscarriage managed expectantly. In asymptomatic pregnant women, YSV outside the 5th to 95th percentile or GSV less than the 5th percentile were associated with spontaneous miscarriage in univariate but not in regression analysis. It appears that 3D volumetric assessment does not improve the diagnosis of miscarriage over conventional 2D sonographic measurements.

**CONCLUSIONS**

It is possible and reproducible to undertake volumetry of the placenta, fetus, gestational sac, gestational sac fluid and yolk sac in the first trimester using 3D ultrasound. The traditional prediction method focuses on clinical history, 2D sonographic parameters and biochemical markers. First-trimester volumetry represents an important tool for the prediction of birth weight and pregnancy complications. 3D ultrasound showed a strong correlation between PV and EV, and CRL or GA in the first trimester. An early method to identify impaired trophoblast invasion is by measurement of PV/PQ. This is used to predict the subsequent development of IUGR at a sensitivity of 27.1% or PE at 38.5%. However, this method alone probably cannot predict all cases of at-risk pregnancies.

The accuracy of volumetry depends on the measurement technique, the object being measured and the observer. The wide discrepancy in reported volumes of first trimester embryos and other structures was as a result of inconsistencies in the measurement technique used, poor auditing, inadequate assessment of technique repeatability and validity, and a diversity of mutually incompatible 3D imaging formats and software measuring tools. Clinical application of placental volumetry is limited by the physiological variations in placental shape, weight and volume at each stage of gestation, and the heterogeneity of placental growth.

**Prospects of 3D volumetry**

Application of 3D volumetry in the first trimester is feasible and reproducible in the prediction of IUGR, PE, birth weight, homozygous thalassemia and other adverse pregnancy outcome. In future, 3D volumetry will be easier, simpler and more accurate with reduced measurement interval.

Standardization of 3D volumetric methodology and further exposure in ultrasonography will improve the quality assurance in first-trimester volumetry, and facilitation in clinical evaluations. Further advancement of 3D technology may allow a semiautomated or automated measurement of 3D volumetry in a reliable and accurate approach. It may be feasible to perform assessments of the vascularization and blood flow of the placenta when 3D power Doppler ultrasound and histogram analysis are used.

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