Review Article

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.[1] 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.[2] 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.[1] Trans-vaginal scan gives better resolution, exquisite view and is more accurate in first trimester pregnancy with profound benefits to patients and obstetricians.[1,3]

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 CRL.[9,12] First trimester prediction of intrauterine growth restriction (IUGR), preeclampsia, birth weight, aneuploidy,

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miscarriage, complications in multiple pregnancies and homozygous thalassemia is a challenging and an emerging field in obstetrical sonography.[13] Studies have been carried out to investigate the use of first trimester volumetry in the prediction of IUGR and pre-eclampsia (PE),[14-17] birth weight,[18,19] aneuploidy,[20-23] miscarriage,[24-26] complications in multiple pregnancies,[27,28] homozygous thalassemia[29] and other adverse outcomes. The use of traditional prediction methods (maternal history, 2D ultrasonography and biochemical markers) have limitations[30-32] and can only detect 77-88.9% of PE at 10% false positive rate.[30,31] 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.[33,34]

The accuracy of volumetry depends on the measurement technique, the object being measured and the observer.[35] A wide discrepancy in reported normal volumes of first trimester embryo[36] and other structures was probably a result of inconsistencies in the measurement technique used, poor auditing,[35,36] inadequate assessment of technique repeatability and validity, and a diversity of mutually incompatible 3D imaging formats and software measuring tools.[13] Measurement of the gestational sac diameter and crown rump length has been used to determine GA and for the evaluation of miscarriage. Practically, measurement of CRL has limitations and less reliable before 7 weeks and after 10 weeks gestation because of undefined embryonic contour and fetal movements.[37] Furthermore, placenta is an irregular structure, the influence of measurement error is larger than it is for the fetus which is relatively regular and symmetrical.[35,38] The clinical use of placental volumetry is further limited by physiological variations in placental shape, weight and volume[39] at each stage of gestation[40] and the heterogeneity of placental growth.[34] The increased placental thickness at the first trimester is a sonographic sign of homozygous thalassemia with a sensitivity of 72%.[41]

Volume calculations are often performed using the multiplanar method (which is time consuming) or a rotational method with virtual organ computer-aided analysis (VOCAL) software.[7,9,10,42] Newly introduced volumetric tools include a semiautomated virtual reality (VR) system, ISpace VR which allows the creation of a 'hologram' of the ultrasound image, depth perception and interaction with the rendered objects,[43] an automated tool for fluid filled spaces, sonography-based automated volume count[44] and extended imaging (XI) VOCAL.[14,35] 3D volumetry should be measured using a standardized method to give reproducible results. This is not possible because different clinicians applied different techniques for 3D volumetry of different structures and presented different reference data.

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.[45] The measurement technique used is the VOCAL method with a 30A° rotation angle[24] or the multiplanar method as shown in Table 1.[29] Placental quotient (PQ) is PV divided by the fetal CRL.[15] This is the first trimester parameter to indicate whether a placenta is large or small for a given fetus.[13] There are limitations in using placental volumetry for clinical application because of the physiological variations in placental shape, weight and volume[39] at each stage of gestation,[40,46] the heterogenous nature of placental growth[16] and the reproducibility and accuracy of measuring the volume of the placenta, an irregular structure as shown in Table 1.[34]

Embryo or fetal volumetry

Embryo volume or fetal volume can be measured directly[8] or by subtracting the amniotic fluid and yolk sac volumes from the gestational sac volume (GSV).[47] 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.[48] 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.[49] 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.[22]

VOCAL is a commonly used technique[8] 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.[34] Other methods used include the multiplanar technique and the XI VOCAL technique as shown in Table 1.[35] 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.[35] Semi-automated techniques, using both VOCAL and SonoAVC,[8] 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° relations.[50] There was a significant correlation between EV and GA or CRL,[8,19] with a linear association between 11 + 0 weeks and 13 + 6 weeks,[10] or between a CRL of 45 and 84 mm.[10] 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.[51]

A recent review by Ioannou *et al*.[36] showed discrepancy in the reported normal volumes of first trimester embryos, ranging from 0.2-0.23 cm^3 at 7 weeks to 3.91-5.12 cm^3 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.[36]

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.[52] GSV is measured using the VOCAL method with a 30A° rotation angle.[12,42] In a study in 2009 by Rolo *et al*.,[12] intra-observer variability was small with an average difference between measurements of 0.5 cm^3. There was a high correlation between GSV and GA or CRL[7,12,19] mean GSV increased from 8.50 cm^3 at 7 weeks to 44.35 cm^3 at 10 weeks[18] and 69 ml at 11 weeks to 144 ml at 13 + 6 weeks.[23] GSV increase from 5.00 to 50.28 cm^3 for a CRL increased from 0.9 to 4 cm.[12] GSV is closely related to amniotic fluid volume. GSV may reflect uteroplacental functions in the first trimester,[53] and may predict adverse pregnancy outcome.[26]

Gestational sac fluid volumetry

Gestational sac fluid volume (GSFV)) is obtained by taking measurements using VOCAL with a rotational step of 30A° rotation,[42] and then subtracting the EV from the GSV.[42]

Table 1: Volumetry methods and pregnancy outcome

Volumetry	Measurement technique	Relationships	Correlations	Pregnancy outcome
Placental volume (PV)	Vocal method with a 30A° rotation angle or multiplanar method	The components of placental volumetry include placental volume and placental quotient which is derived from placental volumetry. PV is reduced in small-for-gestational age neonates but increased in large for-gestational age	Strong correlation occurred between PV and CRL or GA from 7 weeks to 13+6 weeks	Measurement of PV may be an efficient method for identification of impaired wave of trophoblast invasion and subsequent development of IUGR
Embryo or fetal volume (EV or FV)	Directly measured by subtracting the amniotic fluid and yolk sac volumes from the gestational sac volume (GSV). (Vocal with 9A° is a better method of measurement). Others are multiplanar technique, XI VOCAL technique	It is common to encounter discrepancy in the reported normal volumes of first trimester embryos 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	Significant correlation between EV and GA or CRL from 11 weeks to 13 + 6 weeks or between CRL + 45 mm to 84 mm. EV correlates better with birth weight than CRL, GSV and PV	PV may be a better first trimester marker of IUGR than CRL
Gestational Sac Volume (GSV)	Measured using VOCAL method with a 30A° rotation angle	Closely related to amniotic fluid volume. May reflect uteroplacental functions in first trimester. May predict adverse pregnancy outcome	High correlation between GSV and GA or CRL from 7 weeks to 10 weeks and from 11 weeks to 13+6 weeks	GSV is used for confirmation of an intrauterine pregnancy, calculation of GA before fetal viability and diagnosis of anembryonic pregnancy (slighted ovum)
Gestational sac fluid volume (GSFV)	Measured using VOCAL with 30A° rotation, mulitplanar method or virtual reality system (VR)	In normal pregnancies, there was a progressive increase in amniotic fluid from 8 to 11 weeks of gestation	Significant correlation exists between GSFV and GA or CRL. GSFV/EV ratio is decreased with GA	Abnormal amniotic fluid volumes may indicate pathology associated with adverse pregnancy outcomes
Yolk sac volume (YSV)	Measured using VOCAL method with 30A° rotation or XI VOCAL technique	YSV is not seen after 12 weeks. Persistently abnormal yolk sac shape is a predictor of abnormal pregnancy outcome	YSV correlates poorly with GA or CRL from 7 weeks to 10 weeks	Too large or too small or abnormal yolk sac is associated with a poor prognosis or an increased risk of abnormal pregnancy outcome

GSFV can also be measured using the multiplanar method or VR as shown in Table 1.[54] Sono AVC is automatic, but may significantly underestimate GSFV.[50] There is significant correlation between GSFV and GA or CRL.[42] Mean GSFV increased by approximately six to seven-folds from 7.81 to 50.28 cm^3 for a CRL increase from 12 to 40 mm.[42] The GSFV/EV ratio decreased with GA.[54] In normal pregnancies, there was a progressive increase in amniotic fluid from 8 to 11 weeks of gestation.[55] Abnormal amniotic fluid volumes may indicate pathology associated with adverse outcomes,[56] and further studies are required.

Yolk sac volumetry

Yolk sac volume is measured using VOCAL method with 30A° rotation[11] or XI VOCAL.[57] Yolk sac volume is not seen after 12 weeks.[52] A persistently abnormal yolk sac shape is a predictor of abnormal outcome [Table 1].[58] Large or abnormal yolk sacs are associated with a poor prognosis.[52] In a study by Rolo *et al*.,[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.[11] In another study,[59] the mean YSV increased in a linear fashion up to 10 weeks, then maintained a plateau until 11 weeks and decreased thereafter.[11] This can be explained by the yolk sac degeneration process secondary to vascular depletion.[60] The absence or malformation of a yolk sac outside the normal growth pattern is associated with poor pregnancy outcomes.[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).[52]

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.[58]

Birth weight prediction

A correlation between placental size and birth weight was demonstrated in an earlier study.[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).[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].[19] A 10 mm^3 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.[19]

Intrauterine growth restriction

Pregnancies at risk of IUGR detected during antenatal period can reduce perinatal morbidity and mortality by four to five fold.[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].[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.[14] Unlike uterine artery Doppler, PV and PQ did not show any dependency on age, gravidity, BMI or smoking habits.[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.[24] A PQ of 10th centile occurred in 10% of pregnancies and its sensitivity in predicting complications including IUGR, PE, or placental abruption was 22%.[17]

Preeclampsia

Preeclampsia is a major cause of maternal and perinatal morbidity and mortality.[57] It complicates 2-3% of pregnancies.[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).[15] Taking a PQ that is at 10th 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[15] but similarly sensitive in approximately 50% in predicting the most severe complications in which delivery took place before 34 weeks.[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),[20] and that the inclusion of PV measurements as an additional marker to nuchal translucency may improve the sensitivity of first trimester screening.[20] In another study in 2005, the mean PV for GA was smaller in conjunction with trisomies 13 and 18 than in normal pregnancies.[21] However, no difference was observed between normal pregnancies and those with trisomy 21 or Turner syndrome.[21]

In a study reported by Leung *et al*.,[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.[12] FV may be a better

first-trimester marker of IUGR than CRL. Compared with chromosomally normal fetuses, the fetal head volume for CRL was significantly smaller in conjunction with trisomy 21, trisomy 13 and Turner syndrome, but similar in association with trisomy 18 and triploidy.[22] The fetal trunk volume for CRL was significantly smaller in all chromosomal abnormalities except Turner syndrome.[22] The IUGR was symmetrical with the head and trunk being equally affected in fetuses with trisomy 21 and Turner syndrome, but asymmetrical, with trunk being more severely compromised than the head, in those with triploidy and trisomies 18 and 13.[22]

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.[23]

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%.[41] Early onset IUGR and placentomegaly were probably caused by fetal anemia and hypoxia association with homozygous thalassemia. Consistent with result of another study,[12] 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,[27] median twin and triplet PVs were 1.66 and 2.28 multiples of the median for singletons, respectively.[13] 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.[27]

In a dichorionic twin pregnancy, discordance in growth with a distinctly small PV was associated with an abnormal twin with triploidy of maternal phenotype.[28] 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.[24] The GSV: EV ratio in missed miscarriage was significantly higher than those in ongoing pregnancies.[53] However, in another study, a logistic regression analysis showed no significant correlation between GSV and the outcome of missed miscarriage managed expectantly.[25] 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.[26] It appears that 3D volumetric assessment does not improve the diagnosis of miscarriage over conventional 2D sonographic measurements.[24-26]

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.[7-11,42] The traditional prediction method focuses on clinical history, 2D sonographic parameters and biochemical markers.[30-32] First-trimester volumetry represents an important tool for the prediction of birth weight and pregnancy complications.[14-29] 3D ultrasound showed a strong correlation between PV and EV, and CRL or GA in the first trimester.[9,12] 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%.[15] 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.[35] The wide discrepancy in reported volumes of first trimester embryo[36] and other structures was as a result of inconsistencies in the measurement technique used, poor auditing,[33,36] 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[39] at each stage of gestation,[40,46] and the heterogeneity of placental growth.[34]

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.[36] 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.[63]

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