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The Fetal Liver Volume Assessment by Three-Dimensional Ultrasound as a Parameter to Monitor Fetal Growth

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Abstract

Background: Measurement of fetal abdominal circumference is considered the mainstay of ultrasonographic determination of fetal growth and estimation of fetal weight. The fetal liver makes up most of the abdomen, as measured by means of abdominal circumference. Measurement of fetal liver volume to identify fetal growth restriction is of interest, since both the human and the rat have severely depleted hepatic glycogen stores associated with growth restriction.

Aim of Study: To assess the growth of the fetal liver in normal pregnancies and to evaluate the ability of fetal liver volume measurement for prediction of intra-uterine growth restriction.

Patients and Methods: Three-dimensional sonographic examinations were performed on 100 pregnant women. Those women were scanned twice during pregnancy, at 20-28 weeks and 34-40 weeks gestation. At each scan, HC, AC and FL were measured. In addition, 3D ultrasound was performed to obtain a volume of 3D data set of the fetal upper abdomen, and then, VOCAL software was used to calculate the fetal liver volume (LV). Women were then followed-up till delivery and had their babies weighed after birth.

Results: A statistically significant positive correlation was found between liver volume and both gestational age and birth weight. Liver volume measurement in the late 2 nd trimester was found to be superior to HC, AC and FL as a predictor for birth weight.

Conclusions: Our findings suggest that liver volume may be a useful measurement for early detection and diagnosing growth restricted fetuses.

Key Words: *Fetal growth restriction – Fetal liver volume – 3D ultrasound – 2D ultrasound – Three-dimensional sonography – Two-dimensional sonography.*

Introduction

THE small-for-gestational-age fetus is currently defined as having a birth weight below the 10 th percentile for gestational age. In fetuses at high risk for small-for-gestational-age, abdominal circumference below the 10th percentile had the greatest common sensitivity and estimated fetal weight below the 10th percentile had the greatest common odds ratio [1].

Han and Lean [2] reported that reduced liver size is currently thought to be the major factor contributing to the reduced abdominal circumference. The liver occupies most of the upper abdominal cavity, and itis the first organ to be affected by intra-uterine growth restriction (IUGR). Fetal liver weight is reduced in animal models of IUGR; therefore, direct measurements of fetal liver size may enhance early detection of the fetus at risk of IUGR [3].

Fetal liver volume (LV) measurements by echo planar magnetic resonance imaging have been reported [4]. It was suggested that the measurement of fetal liver volume has the potential to contribute to early assessment of fetal growth. However, examination of the fetus by magnetic resonance imaging is limited because of a relatively long acquisition time, artifacts caused by fetal movements, high cost, and limited acceptance by pregnant women [5].

Sonographic imaging techniques have been improved considerably and three-dimensional ultrasonography (3DUS) for imaging of the fetus is now available. Potential obstetric applications of three-dimensional ultrasonography for systematic examination of the developmental stages of the fetus [6], detection of fetal malformations [7], and birth weight prediction [8] have been reported. There have been also some reports on the growth of the fetal liver volume measured by three-dimensional ultrasonography in normal pregnancy [9] and growth-restricted fetuses [10].

It is well-documented that fetal growth restriction may have increased risks of perinatal morbidity

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and mortality. Early detection of fetal growth restriction is crucial in prenatal care and daily practice. Liver volume is very important in determining the status of fetal growth. However, to measure human fetal liver volume in utero precisely and noninvasively is not an easy task. With the recent advancement of three-dimensional ultrasound, the limitation in assessing fetal liver volume by two-dimensional ultrasound can be overcome. Fetal liver volume assessed by quantitative three-dimensional ultrasound can be used to predict fetuses with growth restriction antenatally [11].

Aim of the study was to assess the growth of the fetal liver in normal pregnancies and to evaluate the ability of fetal liver volume measurement for prediction of intra-uterine growth restriction.

Patients and Methods

This prospective study was conducted at the fetal medicine unit of El-Galaa Teaching Hospital over a period of two years and eight months commencing December 2011 till August 2014. We recruited 124 pregnant women. A hundred women had technically acceptable ultrasound liver recordings. An ultrasound liver recording qualified as acceptable if the entire contour of the liver could be manually outlined. If this parameter was not fulfilled, a new volume data set was obtained. Twenty-four women either had unacceptable liver recording or failed to attend for the 2 nd scan due to preterm delivery or failure of follow-up.

All pregnancies were Egyptian women who attended El-Galaa Teaching Hospital antenatal clinic for follow-up and antenatal care services. Maternal age was 18-40 years (mean, 25.5 years). Women were recruited to participate in the study, which comprised of two ultrasound scans in the late second (20-28 weeks) and late third (34-40 weeks) trimesters, in addition to measuring the actual baby's weight after birth.

Fetal age determination was estimated from the first day of the last menstrual period or by the first trimester dating ultrasound scans. All deliveries were made in our teaching hospital and birth weights measured within the first 24 hours of delivery.

Inclusion criteria were primigravida, singleton intrauterine pregnancies and gestational age of 20 to 28 weeks and then between 34 and 40 weeks. Multiparas, multiple pregnancies, and women who were unsure of dates and had no early dating scans were excluded from our study.

Each patient was scanned twice during her pregnancy; the first scan was at the late second trimester, i.e., between 20-28 weeks, and the second follow-up scan was at the late third trimester i.e., between 34-40 weeks. This was performed using a GE Voluson 730 PRO ultrasound system provided with the Virtual Organ Computer-aided Analysis (VOCAL) software. A 5-MHz trans-abdominal 3D transducer was used.

In each scan, head circumference (HC), abdominal circumference (AC) and femur length (FL) were measured and recorded. VOCAL was used to calculate the fetal liver volume (LV) in the two scans for each pregnant woman. A cross section of the fetal liver was obtained in the same plane used to measure the abdominal circumference. Then, the 3D volume box was opened and adjusted to the cross section of the fetal abdomen (Regionof Interest) and the fetal abdomen scanned to obtain a 3D data set. The sweep angle was set at 90º. Volume acquisition lasted less than 1min. This produced a multiplanar image showing the fetal abdomen in three planes (transverse, longitudinal and coronal) (Fig. 1A,B,C). VOCAL software was then used with a thirty-degree rotational method obtaining a sequence of six sections of the fetal liver around a fixed axis. Then, the borders of the fetal liver were traced manually to complete its circumference. After finishing the six sections, the software automatically displays a 3D image of the fetal liver and calculates its volume (Fig. 2A,B). This was recorded and statistically analyzed.

Women who had all four measurements (HC, AC, FL, and LV) taken and recorded twice during their pregnancies, were followed-up until delivery and had their babies weighed within the first 24 hours and the actual birth weights recorded.

Statistical analysis:

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Data were statistically described in terms of mean ± standard deviation (±SD) and range, or frequencies (number of cases) and percentages when appropriate. Paired *t*-test was used to compare quantitative variables, whereas correlation coefficient test (*r*-value) was used to rank variables positively or inversely. *p*-values less than 0.01 were considered as highly significant, less than 0.05 were considered statistically significant, while *p*-values more than 0.05 were considered as statistically insignificant.

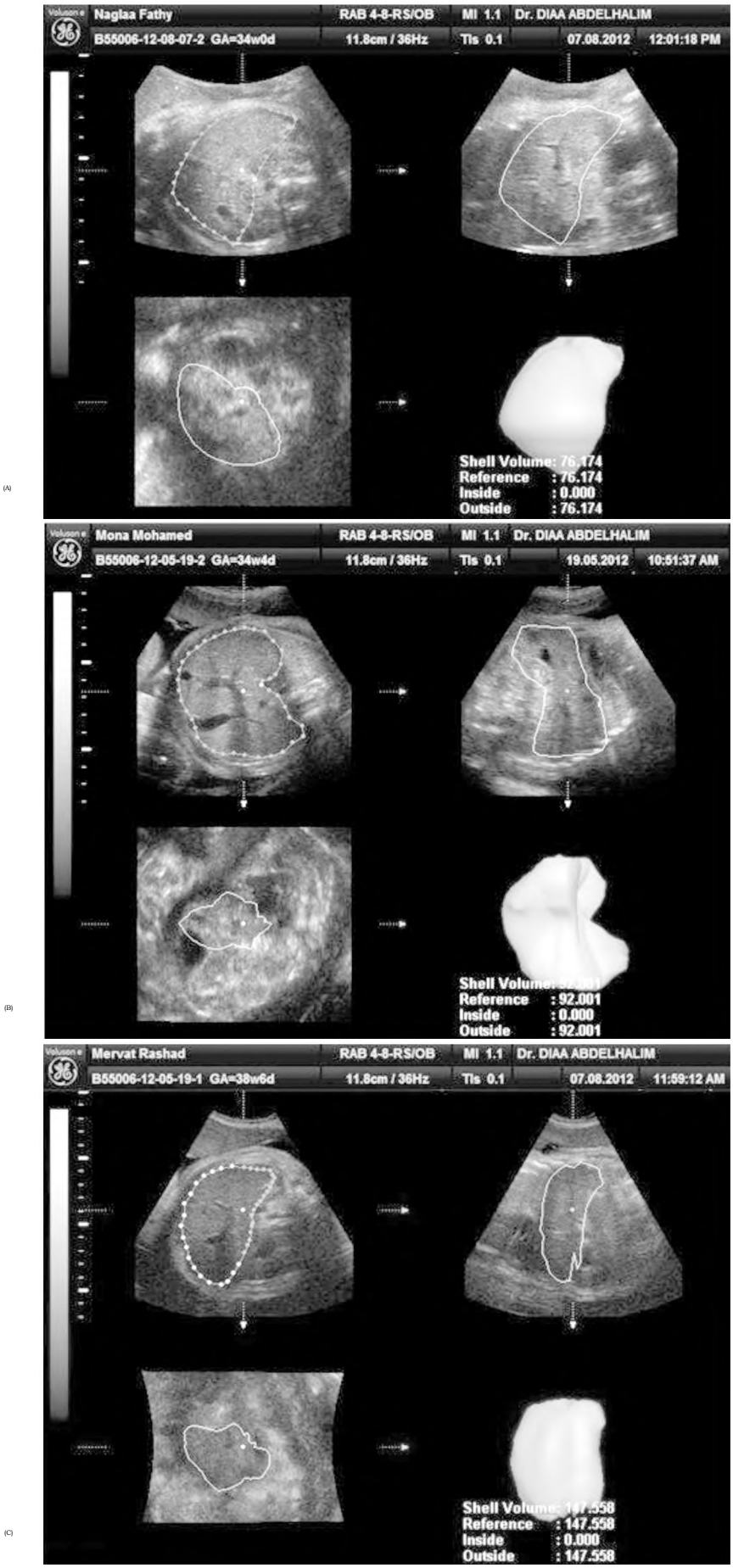
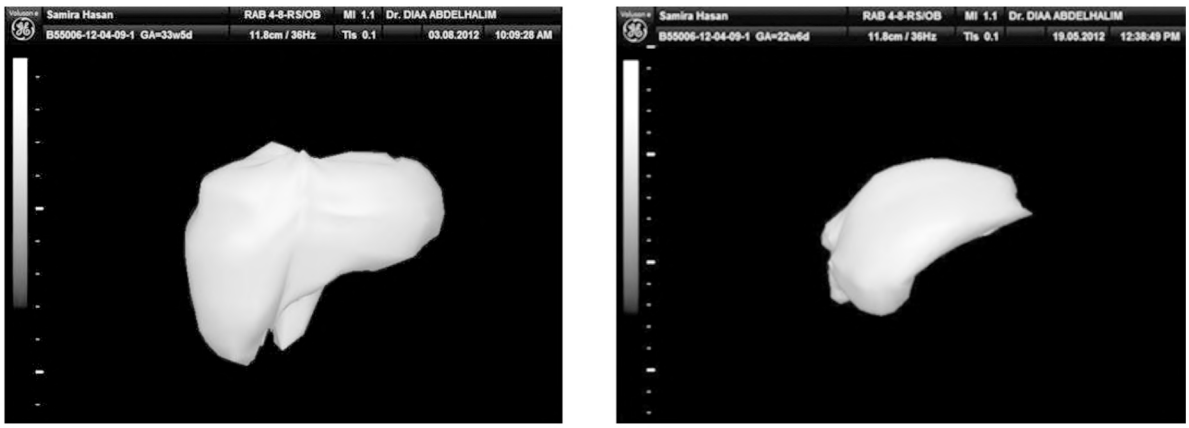


Fig. (1): Fetal liver volume by VOCAL (Multiplanar view) at (A) 34 weeks, (B) 35 weeks and (C) 39 weeks.



(A) (B)

Fig. (2): A 3D image of liver by VOCAL for the same fetus at (A) 23 weeks and (B) 34 weeks.

Results

Out of the 100 pregnancies, the number of confirmed normally developed fetuses was 91, the number of growth-restricted fetuses was 6 and the number of large-for-gestational-age fetuses was 3.

For all 100 cases, mean gestational age at delivery was 38.25 weeks ±1.7 (SD) and ranged from 34 to 42 weeks, while mean birth weight was 3081.5g±455 with a range of 1150 to 4600g. Regarding the growth-restricted fetuses, mean gestational age was 36.6 weeks ranging from 34 to 39 weeks, and mean birth weight was 1650g±95 and ranged from 1150 to 2100g. In large-for-gestational-age fetuses, mean gestational age was 38.3 weeks with a range from 38 to 39 weeks, and a mean birth weight of 4466g±505 with a range from 4300 to 4600g.

The study showed that mean fetal liver volume was 20.03mL±5.1 in the late 2 nd trimester (20-28 weeks) with a range from 11.8 to 39.8mL and 102 mL±19.6 in the late 3 rd trimester (34-40 weeks) which ranged from 53.6 to 161ml. Mean head circumference was 206.9mm±19 in the late 2 nd trimester (range from 169 to 253mm) and 316.6mm ±16 in the late 3 rd trimester (range from 275 to 368mm).

Mean abdominal circumference was 176mm± 19.8 in the late 2 nd trimester (range from 139 to 237mm) and 307mm±25 in the late 3 rd trimester (range from 228 to 384mm). Mean femur length was 39.4mm±4.5 in the late 2 nd trimester (range from 29.6 to 53.6mm) and 68mm±3.2 in the late 3 rd trimester (range from 56.7 to 78mm) (Table 1).

The following table and graph demonstrate the percentage of increase between the 2 nd and 3rd trimester measurements in each of the four parameters (LV, HC, AC and FL) (Table 2).

There was a statistically significant positive correlation between liver volume measured in the late 2 nd trimester and birth weight by using correlation coefficient test.

Based on this significantly positive correlation, birth weight can be predicted from the late 2 nd trimester liver volume measurement using the following equation:

$$W = mL + b$$

W = Birth Weight, m = 200 calculated by equation (slope), L = any value of liver volume b = intercept = –14

There was statistically significant positive correlation between gestational age versus different measures by using correlation coefficient test. There was no statistically significant correlation between maternal age and different measures by using correlation coefficient test (Table 3).

There was a statistically significant positive correlation between birth weight versus different 3rd trimester measures by using correlation coefficient test. There was a statistically significant positive correlation between gestational age versus different 3 rd trimester measures by using correlation coefficient test. There was no statistically significant correlation between maternal age versus different measures by using correlation coefficient test (Table 4).

This study showed that liver volume measurement in the 2 nd trimester is superior to AC and FL as a predictor for birth weight by stepwise linear regression (Table 5).

Table (1): Distribution of the studied cases as regard 2 nd and 3rd trimester measurements.

Variables	Mean ± SD	Range
2nd trimester:		
Gestational Age, GA (wks)	22.8±1.7	20-28
Liver Volume, LV (mL)	20.03±5.1	11.8-39.8
Head Circumference, HC (mm)	206.9±19	169-253
Abdominal Circumference, AC (mm)	176±19.8	139-237
Femur Length, FL (mm)	39.4±4.5	29.6-53.6
3rd trimester:		
GA (wks)	36.04±1.5	34-40
LV (mL)	102±19.6	53.6-161
HC (mm)	316.6±16	275-368
AC (mm)	307±25	228-384
FL (mm)	68±3.2	56.7-78

Table (2): Percentage of increase between the 2 nd and 3rd trimester measurements.

Variables	2nd trimester	3rd trimester	% of change	*t*	*p*
LV	20.03±5.1	102±19.6	435±145	42	0.000HS
HC	206.9±19	316.6±16	54.5±14.6	49	0.000HS
AC	176±19.8	307±25	75.9±22	12	0.000HS
FL	39.4±4.5	68±3.2	74.9±21	13	0.000HS

Table (3): Correlation between 2 nd trimester measures versus birth weight, gestational age and maternal age.

Variables	*r*	*p*
Birth weight:		
LV	0.21	0.02S
HC	0.009	0.93
AC	0.03	0.76
FL	0.008	0.94
Gestational age:		
LV	0.69	0.000HS
HC	0.56	0.000HS
AC	0.66	0.000HS
FL	0.78	0.000HS
Maternal age:		
LV	0.12	0.33
HC	0.06	0.55
AC	0.15	0.38
FL	0.08	0.60

Table (4): Correlation between 3 rd trimester measures versus birth weight, gestational age and maternal age.

Variables	*r*	*p*
Birth weight:		
LV	0.57	0.000HS
HC	0.81	0.000H5
AC	0.75	0.000HS
FL	0.68	0.000HS
Gestational age:		
LV	0.47	0.000HS
HC	0.70	0.000H5
AC	0.45	0.000HS
FL	0.55	0.000HS
Maternal age:		
LV	0.05	0.76
HC	0.03	0.66
AC	0.11	0.40
FL	0.02	0.81

Table (5): Correlation between birth weight versus all predictor measures by linear regression.

Variables	Beta error	*p*	95% CI
LV	2.7	0.000HS	10-23
AC	3.6	0.000HS	18.7-29
FL	24	0.02S	7.4-105

Discussion

In this study, 100 pregnant women were recruited. Ninety-one out of them proved to have normal for gestational-age fetuses, six small for gestational age fetuses and three large for gestational age fetuses. The results showed that fetal growth restriction was associated with reduced liver volume in every instance. There was a statistically significant positive correlation between liver volume and both gestational age and birth weight by using correlation coefficient test.

The present study demonstrated a five-fold increase in liver volumefrom 20.03±5.1mL in the late 2nd trimester (20-28 weeks) to 102±19.6mL in the late 3rd trimester (34-40 weeks). Whereas the increase was 1.5, 1.7 and 1.7 for HC, AC and FL respectively between the two scans. In other terms, the percentage of change was 435% for LV, 54.5% for HC, 75.9% for AC and 74.9% for FL.

In a study conducted on 135 pregnant women, Suzui et al., **[12]** found that normal fetal hepatic volume is tenfold larger at the end of gestation, as compared with that at the beginning of the second half of pregnancy (i.e. at 20 weeks), a finding which can be considered consistent with the results of our study if we put into account that the mean gestational age of our first scan was nearly 23 weeks and for the second one was 36 weeks.

The higher percentage of change of liver volume in the second half of pregnancy, compared with the other parameters, is supposed to make it a more sensitive tool in detecting growth-restricted fetuses. However, the technical difficulty in measuring liver volume, the unavailability of 3D ultrasound in all maternity units and the lack of enough trained sonographers prevent liver volume measurement from taking its proposed position in this context. Needless to say, that not all 3D ultrasound systems are provided with the VOCAL software which accurately measures volumes of bizarre-shaped organs such as liver [13].

Our study also revealed a statistically significant positive correlation between liver volume measured in the late 2nd, as well as the late 3rd trimester and birth weight by using correlation coefficient test. Moreover, in the 2nd trimester, liver volume was the only parameter to show a significantpositive correlation with birth weight. While in the 3rd trimester, all 4 parameters (LV, HC, AC and FL) showed this significantly positive correlation.

By stepwise linear regression, the study showed that liver volume measurement in the 2nd trimester is superior to AC and FL as a predictor for birth weight. While HC in the 2nd trimester proved not to be significant.

Yamaleyeva et al., [14] have found similar results. Their study showed that, when expressed as a percentage of the normal P50, the decrease in hepatic volume is more pronounced than is the reduction in head circumference or upper abdominal circumference. When looking at the mean difference in hepatic volume between normal and reduced fetal growth, as expressed with the z score, they found a significant difference only when comparing these values with head circumference, which confirms the brain-sparing effect during abnormal fetal development. They concluded that acceptable reproducibility exists for hepatic volume determinations and that in fetal growth restriction, reduction is more pronounced for hepatic volume than for head or upper abdominal circumference. They also added that hepatic volume is a better discriminator than head circumference but not upper abdominal circumference.

Acuña et al., [15] showed that 3D sonography was superior to 2D sonography in a reproducibility test of fetal LV assessment. Moreover, the LV assessed with the traditional 2D sonographic method was significantly less than that measured with 3D sonography. These authors recommended that 3D sonography instead of 2D sonography should be used for reaching an accurate assessment of fetal LV. Cooper et al., [16] reported that fetal LVcalculated with 3D sonography correlated linearly with menstrual age.

There are a few reports on the growth of liver length (LL) in SGA fetuses measured by 2D sonography, and the results were conflicting. Teo et al., [17] concluded that the LL in SGA fetuses was smaller than in AGA fetuses and that LL measurement may be useful in the detection of SGA. In their study, however, SGA was defined as an infant with a birth weight at or below the 25th percentile, and descriptive statistics were not obtained.

Despite the ease of measurement, it may be apparent that the LL is a rathercrude measure for characterizing the growth of an object with a complex shape such as the fetal liver. Therefore, the LL may not be the most appropriate parameter for evaluation of liver growth [18].

Two-dimensional sonography (for estimated fetal weight) was used to identify all 10 SGA infants in the study of Mazurek et al., [19]. Therefore, 2D and 3D sonography were probably similar in their ability to correctly classify SGA infants, as opposed to LL, a sonographic parameter that appears to be a relatively insensitive marker.

Gaccioli, et al., [20] undertook a prospective and cross-sectional study using quantitative 3D ultrasound to assess the efficacy of fetal liver volume in predicting FGR. During the study period, 42 fetuses with FGR and 375 fetuses without FGR were included for the LV assessment in utero by 3D ultrasound. All the fetuses were singletons and had follow-up to delivery to ensure whether they were complicated with FGR or not. Their results revealed that fetal LV assessed by 3D ultrasound can differentiate well fetuses with FGR from those without FGR. The sensitivity of fetal LV inpredicting FGR was 97.6%, with specificity 93.6%, predictive value ofpositive test 63%, predictive value of negative test 99.7% and accuracy 94%. They concluded that fetal LV assessed by quantitative 3D ultrasound can be used to predict fetuses with FGR antenatally. Their data support that fetal LV assessment by 3D ultrasound would be a useful test in detecting fetuses with FGR.

Fetal growth restriction (FGR) remains a leading contributor to perinatal mortality and morbidity and metabolic syndrome in later life. Fetal growth restriction (FGR) is not synonymous with SGA. Some, but not all, growth restricted fetuses/infants are SGA while 50-70% of SGA fetuses are constitutionally small, with fetal growth appropriate for

maternal size and ethnicity. The likelihood of FGR is higher in severe SGA infants **[21]**.

A prerequisite for a judicious diagnosis of FGR is accurate dating of the pregnancy. The last menstrual period, when certain, reliably dates the pregnancy. Alternatively, dating is performed with sonography. Abnormal fetal growth is detected with the clinical suspicion of a subnormal uterine size, followed by abdominal palpation and direct measurement of the symphyseal-fundal distance. Abdominal palpation has a sensitivity of 30% for detecting SGA fetuses. The symphysis-fundal distance has a sensitivity of 27-86% and specificity of 80-93% for detecting SGA. The use of customized symphysial-fundal distance charts which consider anthropometric characteristics and ethnicity reportedly improve detection **[22]**.

Ultrasound is the benchmark for accurate pregnancy dating and diagnosis of FGR. However, there is room for error and FGR is undetected in about 30% of routinely scanned cases and incorrectly detected in 50% of cases. Estimated fetal weight is calculated using polynomial equations combing BPD, femur length, and the abdominal circumference. The mostcommon formulas are those reported by Gaccioli et al., **[20]** and Lai, et al., **[22]**. Using these formulas, FGR is typically defined as estimated fetal weight less than the 10 th, 5th, or 3rd percentile for the gestational age or below 2 standard deviations of the mean for the gestational age.

The results of this study showed that fetal growth restriction was associated with reduced liver volume in every instance. There was a statistically significant positive correlation between liver volume and both gestational age and birth weight by using correlation coefficient test.

The study also demonstrated a five-fold increase in liver volume compared to a 1.5, 1.7 and 1.7 for HC, AC and FL respectively between the late 2 nd and late 3rd trimesters and that the percentage of change was 435% for LV, 54.5% for HC, 75.9% for AC and 74.9% for FL.

Moreover, in the 2nd trimester, liver volume was the only parameter to show a significant positive correlation with birth weight. While in the 3rd trimester, all 4 parameters (LV, HC, AC and FL) showed this significantly positive correlation. By stepwise linear regression, the study showed that liver volume measurement in the 2 nd trimester is superior to AC and FL as a predictor for birth weight. While HC in the 2nd trimester proved not to be significant.

Conclusion:

Measurement of fetal liver volume may contribute to the early detection of fetal growth restriction. The liver occupies most of the upper abdominal cavity, and it is the first organ to be affected by fetal growth restriction, since it is associated with severely depleted hepatic glycogen stores.

The results of this study demonstrated that fetal growth restriction was associated with reduced liver volume in every instance. There was a statistically significant positive correlation between liver volume and both gestational age and birth weight. Moreover, liver volume measurement in the late 2nd trimester was found to be superior to HC, AC and FL as a predictor for birth weight.

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حجم كبد الجنين باستخدام الموجات فوق الصوتية ثلاثية الأبعاد كمقياس لمتابعة نمو الجنين

خلفية البحث: يعتبر قياس محيط بطن الجنين الدعامة الأساسية لتحديد نمو الجنين وتقدير وزنه بالموجات فوق الصوتية. يتكون كبد الجنين من معظم أجزاء البطن مقاساً بمحيط البطن. يعد قياس حجم كبد الجنين لتحديد تقييد نمو الجنين أمراً مهماً، حيث أن كلاً من الإنسان والجرذ قد استنفد بشدة مخازن الجليكوجين لكبدية المرتبطة بتقييد النمو.

الهدف من البحث: هو دراسة نمو كبد الجنين أثناء الحمل وكذلك تقييم قدرة قياس حجم الكبد للجنين على التنبؤ والتشخيص المبكر لحالات (نقص النمو الجنينى).

المريضات وطرق البحث: قمنا بهذه الدراسة فى وحدة طب الجنين بمستشفى الجلاء التعليمى وشملت ١٠٠ سيدة حامل بطفلها الأول حيث تم فحصهن مرتين أثناء الحمل باستخدام الموجات فوق الصوتية ثلاثية الأبعاد مرة ما بين ٢٠–٢٨ أسبوعاً والأخرى بين ٣٤–٤٠ أسبوعاً من عمر الحمل. فى كل مرة كان يتم أخذ مقاسات محيط الرأس ومحيط البطن وطول عظمة الفخذ، كما أنه كان يتم قياس حجم كبد الجنين باستخدام الموجات فوق الصوتية ثلاثية الأبعاد، ثم بعد ذلك يتم متابعتهن حتى نهاية حملهن وقياس وزن الطفل بعد الولادة.

نتائج البحث: أوضحت هذه الدراسة أن حجم كبد الجنين كان أقل من كل حالات (نقص النمو الجنينى) بدون استثناء، كما أنه كانت هناك علاقة طردية بين حجم كبد الجنين وكل من عمر الحمل ووزن الجنين بعد الولادة. كما بينت نتائج الدراسة زيادة حجم كبد الجنين فى القياس الثانى بمعدل ٥ أضعاف عن القياس الأول، فى حين كانت الزيادة بمعدل ١٠٥ فقط لمحيط الرأس و ١٠٧ لمحيط البطن و ١٠٧ لعظمة الفخذ.

الاستنتاج: تشير النتائج التى توصلنا إليها إلى أن حجم الكبد قد يكون مقياساً مفيداً للكشف المبكر وتشخيص الأجنة المقيدة النمو.