RUSH: Seminars in Ultrasound CT and MRI article for proofing (# 249)
=====
Dear Author,

The proof of your article to be published by Elsevier in Seminars in Ultrasound CT and MRI is available as a PDF file at the following URL:
http://rapidproof.cadmus.com/RapidProof/retrieval/index.jsp

Also attached are instructions on the annotation of PDF files. You may also have a 'Query Form' as an attachment if we have any questions regarding your article.

Login: your e-mail address
Password: ----

Please note that proof corrections can now be annotated on-screen, which allows you to mark directly in the PDF file, and return the marked file as an e-mail attachment. To take advantage of this method, please download the free Adobe Reader version 7 (or higher; see the attached instructions).

Alternative methods of returning proof corrections:
If you do not wish to use the PDF annotations function, you may list the corrections (including replies to the Query Form) in an e-mail and return to us using the 'reply' button to this e-mail. Please list your corrections quoting line number.

If, for any reason, this is not possible, mark the corrections and any other comments (including replies to the Query Form) on a printout of your proof and fax this to the number given below, or scan the pages and e-mail, or mail to the address given below.

Please use this proof for checking the typesetting, editing, completeness and correctness of the text, tables and figures. Please ensure that you answer any questions (see the Query Form) that have arisen during the preparation of your proof. Significant changes to the article as accepted for publication will only be considered at this stage with permission from the Editor. We will do everything possible to get your article published quickly and accurately. Therefore, it is important to ensure that all of your corrections are sent back to us in one communication: please check carefully before replying, as inclusion of any subsequent corrections cannot be guaranteed.

If you submitted usable colour figures with your article they will appear in colour on the web, at no extra charge, as you can see in the attached PDF proof of your article. In the printed issue, colour reproduction depends on journal policy and whether or not you agree to bear any costs (not applicable to journals which appear only online). Any 'supplementary' material to your article (i.e., not appearing in print) will be accessible after your corrected article is placed online; such material is not part of the proofing procedure and is therefore not attached here.

Please respond promptly (even if you have no corrections): the sooner we hear from you, the sooner your corrected article will appear online. Note that we may proceed with publication of your article if no response is received.

Kind regards,

Marla Kipp
Issue Manager
Cadmus

300 West Chestnut Street
Ephrata, PA 17522
Ph: 717 738 9302, Fx: 717-738-9479 or 717-738-9478
E-mail: kippm@cadmus.com

INSTRUCTIONS ON THE ANNOTATION OF PDF FILES

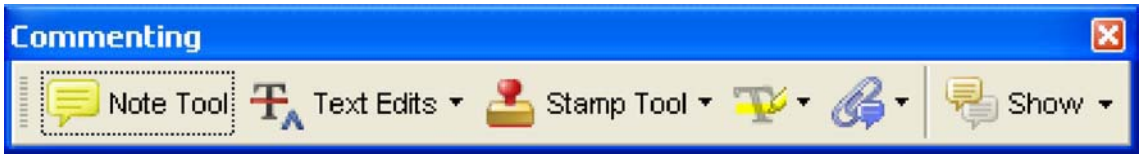
PDF files are self-contained documents for viewing on screen and for printing. They contain all appropriate formatting and all fonts, so that the correct result will be shown on screen and on the printout from your local printer.

To view, print and annotate your article you will need Adobe Reader version 7 (or higher). This program is freely available for a whole series of platforms that include PC, Mac, and UNIX and can be downloaded from http://www.adobe.com/products/acrobat/readstep2.html. The exact system requirements are given at the Adobe site: http://www.adobe.com/products/acrobat/acrrsystemreqs.html#70win.

PDF ANNOTATIONS (for this you will need Adobe Reader version 7 or higher)

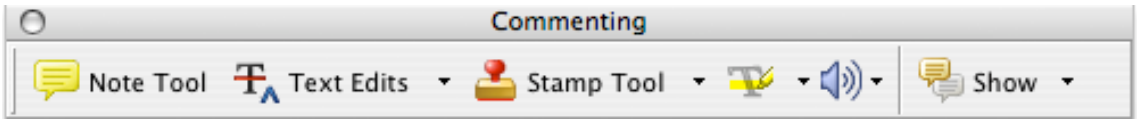
To make annotations in the PDF file, go to the main Adobe toolbar and change the cursor from a hand symbol to the normal cursor by clicking on the 'Select' button 

in the menu bar at the top. When you open the PDF file using Adobe Reader, the Commenting toolbar should be displayed automatically; if not, click on 'Tools', select 'Commenting' (or 'Comment & Markup'), then click on 'Commenting toolbar' (or Show Comment & Markup toolbar in Acrobat Reader 8, or Show Commenting Bar on the Mac). If these options are not available in your Adobe Reader menus then it is possible that your Adobe version is lower than version 7 or the PDF has not been prepared properly.



(PC, Acrobat 7)

(PC, Acrobat 8, right-click on title bar (Comment & Markup) to show additional icons)



(Mac)

RESPONDING TO THE AUTHOR QUERY FORM

Please check the Author Query Form and make any required responses in your annotations to the proof.

PLEASE DO NOT ATTEMPT TO EDIT THE TEXT ITSELF

TO INDICATE INSERT, REPLACE, OR REMOVE TEXT

- **Insert text**

  Click the 'Text Edits' button 

on the Commenting Toolbar. Click to set the cursor location in the text and simply start typing. The text will appear in a commenting box. You may also cut-and-paste text from another file into the commenting box. Close the box by clicking on 'x' in the top right-hand corner. It can be deleted by right clicking (for the PC, ctrl-click on the Mac) on it and selecting 'Delete'.

- **Replace text**

  Click the 'Text Edits' button 

on the Commenting Toolbar. To highlight the text to be replaced, click and drag the cursor over the text. Then simply type in the replacement text. The replacement text will appear in a commenting box. You may also cut-and-paste text from another file into this box. To replace formatted text (an equation for example) please Attach a file (see below).

- **Remove text**

  Click the 'Text Edits' button 

on the Commenting Toolbar. Click and drag over the text to be deleted. Then press the delete button on your keyboard. The text to be deleted will then be struck through.

HIGHLIGHT TEXT / MAKE A COMMENT

Click on the 'Highlight' button  on the Commenting Toolbar. Click and drag over the text. To make a comment, double click on the highlighted text and simply start typing.

ATTACH A FILE

Click on the 'Attach a File' button  on the Commenting Toolbar. Click on the figure, table or formatted text to be replaced. A window will automatically open allowing you to attach the file. To make a comment, go to 'General' and then 'Description' in the 'Properties' window. A graphic will appear indicating the insertion of a file.

LEAVE A NOTE / COMMENT

Click on the 'Note Tool' button 

on the Commenting Toolbar. Click to set the location of the note on the document and simply start typing. Do not use this feature to make text edits.

REVIEW

To review your changes, click on the 'Show' button 

on the Commenting Toolbar. Choose 'Show Comments List'. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.

UNDO / DELETE CHANGE

To undo any changes made, use the right click button on your mouse (for PCs, Ctrl-Click for the Mac). Alternatively click on 'Edit' in the main Adobe menu and then 'Undo'. You can also delete edits using the right click (Ctrl-click on the Mac) and selecting 'Delete'.

SEND YOUR ANNOTATED PDF FILE BACK TO ELSEVIER

Save the annotations to your file and return as an e-mail attachment using the 'reply' button to the original mail. Do NOT use the 'Send comments' feature of the Commenting Toolbar. Please ensure that all corrections are sent back to us in one communication (including responses to the Author Query Form), as subsequent corrections will not be possible.

Note: Comprehensive instructions are provided within your PDF file: to access these instructions please click on the Comments and Markup menu in the main tool bar, or click on Help.

FURTHER POINTS

- Any (grey) halftones (photographs, micrographs, etc.) are best viewed on screen, for which they are optimized, and your local printer may not be able to output the greys correctly.
- Colour artwork (if applicable): If you are unable to see any colour artwork, please check that the Display large images tick box under File-->Preferences--> General... (or the Mac menu Adobe Reader/Preferences…) is ticked.
- If the PDF files contain colour images, and if you do have a local colour printer available, then it will be likely that you will not be able to correctly reproduce the colours on it, as local variations can occur.
- If you print the PDF file attached, and notice some 'non-standard' output, please check if the problem is also present on screen. If the correct printer driver for your printer is not installed on your PC, the printed output will be distorted.

ELSEVIER

Seminars in ULTRASOUND CT *and* MRI

Evaluation of Fetal Growth and Fetal Well-Being

Irene Cetin, MD, Simona Boito, MD, PhD, and Tatjana Radaelli, MD

This article reviews the actual knowledge and future developments of ultrasound techniques for the evaluation of fetal growth and well-being. Sonography allows the visualization of the fetus in utero and is utilized worldwide for the evaluation of fetal growth and well-being. Fetal biometry assessment is performed in the second half of pregnancy when deviations of fetal growth can be best recognized through alterations of fetal abdominal circumference growth. Doppler velocimetry of utero-placental vessels identifies alterations of placental perfusion and is valuable in the assessment of fetal brain, heart, and liver perfusion, thus being utilized in the timing of delivery. Recently, three-dimensional ultrasound evaluation of fetal organs and placenta is being developed.

Growth of the fetus in utero determines the good outcome of pregnancy, ie, the birth of a healthy and viable child. Normal fetal growth depends on genetic background, endocrine milieu, and the appropriate placental supply of oxygen and nutrients.[1]

Since its introduction into obstetrics in the late 1950s, ultrasound has played an increasingly important role in the characterization of normal fetal growth and the detection of fetal growth abnormalities. Fetal growth assessment is very important to clinicians as decrease or excess in fetal growth is associated with increased mortality and morbidity during the perinatal period[2] and may also be an important antecedent for childhood and adult disease.[3,4]

Improvements in image quality and scanning capability have progressively permitted visualization of greater anatomical detail, which, in turn, has led to more sophisticated analyses of the growth process.[5]

Fetal Growth and Fetal Well-Being

Changes that influence the supply of nutrients to the fetus might lead to alterations of the fetal growth trajectory. Intrauterine growth restriction (IUGR) is usually associated with placental insufficiency, while in gestational diabetes mellitus, it has always been hypothesized that excess fetal growth is deriving from the increased availability of maternal nutrients to the placenta.

Birth weight and gestational age at birth are the most important determinants of neonatal mortality[6] and numerous evidence suggests that low birth weight is associated with the development of the metabolic syndrome.[7]

A strong relationship has been observed between placental weight and birth weight[8] and data arising from large cohort studies have shown that the combination of a large placenta and low birth weight is a strong independent risk factor for cardiovascular disease in adulthood.[9]

The standard curves of birth weight that are commonly used are adjusted for gestational age as well as fetal gender. Other factors have been identified as important in determining birth weight and customized curves have been developed that take into account maternal characteristics such as height, weight, parity, as well as race and ethnic group.[10] Customized birth weight centiles try to assess weight against an individual calculated standard, which is based on the growth potential of each fetus.[11] Adjustments for differences in gestational age and maternal body mass index seem to better predict the SGA-associated risk of perinatal mortality.[12,13] AQ: 1

Fetal Biometry and Estimation of Fetal Weight

Most ultrasound measurements have been developed with the objective of assessing the size of the fetal trunk and thereby obtaining more accurate information concerning fetal growth.[14,15] Already in 1965 Thompson and coworkers obtained the earliest recorded attempts of fetal cross-sectional area of the trunk.[16] Moreover, trunk measurements have been further developed during the past years and many different techniques have been advocated. These include

Institute of Obstetrics and Gynecology, Foundation IRCCS Policlinico, Mangiagalli and Regina Elena, University of Milan, Milan, Italy.
Address reprint requests to: Irene Cetin, MD, Institute of Obstetrics and Gynecology, Foundation Policlinico, Mangiagalli and Regina Elena, via Commenda, 12, 20122 Milano, Italy. E-mail: Irene.Cetin@unimi.it

0887-2171/08/$-see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1053/j.sult.2008.01.002

measurements of the thoracic diameters and of the abdominal circumference.[17,18] Measurements of the abdominal circumference at the level of the fetal liver seems to hold the best accuracy and is currently considered an indicator of intrauterine fetal growth in the second half of pregnancy.[19] The rationale for this measurement is that it corresponds most closely with the size of the fetal liver. The work started by Evans and coworkers using an animal model[20] was subsequently confirmed by Gruenwald in the human fetus.[21]

Using ultrasound, other authors[22,23] indicated that the fetal liver is the earliest organ to be affected when intrauterine growth restriction occurs. The detection of fetal growth restriction by means of head circumference measurements in fact may be limited due to fetal brain sparing in the presence of chronic fetal hypoxemia.

An important condition in which we commonly see accelerated fetal growth is maternal insulin-dependent diabetes mellitus. In this clinical condition, fetal biparietal diameter and head circumference measurements conform to normal growth patterns, while growth of the abdominal circumference is abnormally accelerated.[24,25] So far, the ultrasound biometric parameters most commonly used for determining fetal growth are as follows:

- Fetal biparietal diameter and head circumference: these are obtained on a trans-axial section of fetal head that should appear as an oval shape. Landmarks for the right section are the thalamic nuclei and the cavum septi pellucidi (Fig. 1)
- Abdominal circumference: a transverse abdominal section should be obtained including fetal stomach, spine, and deep portion of the umbilical vein (U-shape) (Fig. 2).
- Femur length: measure of the bone diaphysis, excluding distal femoral epiphyses, present after 32 weeks (Fig. 3).

A deeper understanding of fetal growth patterns was reached through customizing the birth weight standard according to physiological variables such as maternal booking weight, maternal height, parity, fetal sex, and ethnic origin.[26]

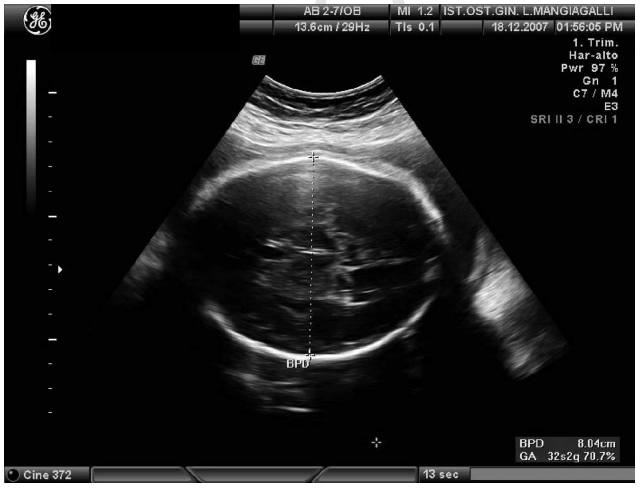


Figure 1 Transverse axial sonogram of the fetal head: measurement of biparietal diameter.

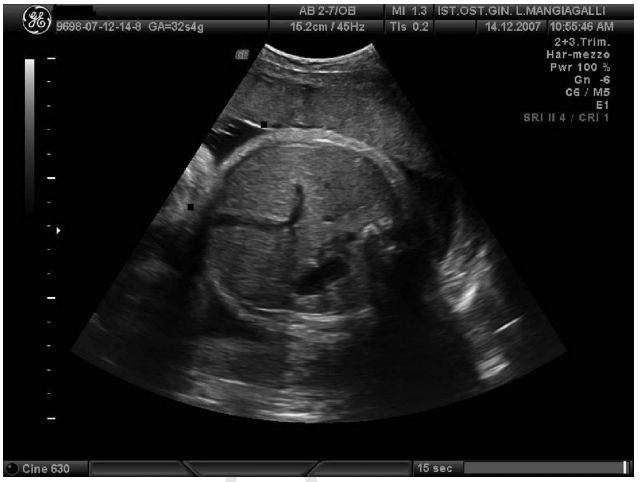


Figure 2 Transverse axial sonogram of the fetal abdomen.

Traditionally, charts of normal fetal biometry have been determined for local populations. As neonatal size was found to vary with the characteristics of the population,[27] these population-based fetal nomograms should be revised regularly, allowing their correct clinical application. In utero fetal growth studies suggested that certain maternal and pregnancy characteristics, such as maternal height and weight, smoking status, ethnic origin, parity, and maternal metabolism, may affect fetal growth.[28,29] Gardosi and coworkers, based on this concept, performed mathematical modeling in which the effects of pregnancy characteristics to produce a customized birth weight standard were taken into account.[11]

Since birth weight is regarded as an outcome measure of fetal growth, assessment of fetal growth in utero appears to be helpful in making clinical management decisions in very low birth weight or large babies. With modern sonographic technology, fetal weight can be estimated with reasonable accuracy.[30,31]

The most successful early approach to estimate fetal weight was a simple correlation between abdominal circumference and birth weight.[17] Numerous further attempts have com-

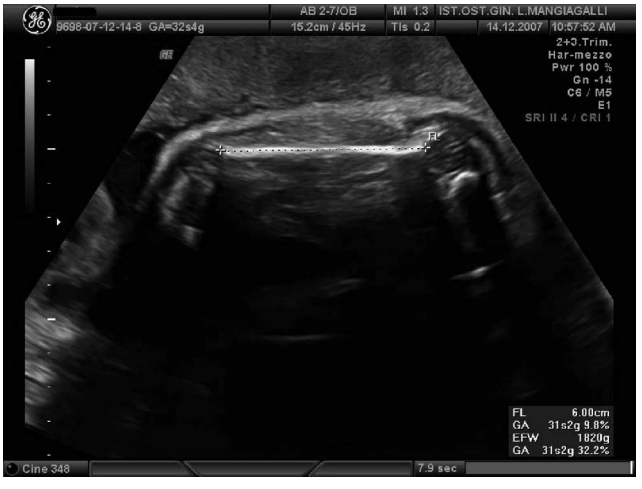


Figure 3 Longitudinal sonogram of the fetal femur length.

bined measurements in regression equations or volumetric formulae with different degrees of accuracy. Several of these methods have insignificant systematic errors, but random errors (ie, standard deviation of errors) of less than 7% are rarely reported. The accuracy of estimated fetal weight is also compromised by large intra- and interobserver variability.[32] Many regression formulae for sonographic fetal weight estimation have been published during the last 30 years, which, unfortunately, generally show poor rates of accuracy. Commonly used formulae in different birth weight groups were recently compared to assess whether any of the formulae are more or less favorable.[33] Over the whole weight range and in the subgroup of newborns with a birth weight less than 2500 g, two Hadlock regression formulae (including abdominal circumference, femur length, biparietal diameter with or without head circumference) showed the best levels of accuracy. Infants with a birth weight between 2500 and 3999 g and >4000 g were best estimated using the gender-specific Schild formula (different formulae for girls and boys)[34] and the Merz's regression formula, respectively.[35]

In summary, although ultrasound has been shown to be an invaluable tool for the assessment of fetal growth patterns, the measurements currently employed are less than ideal, since mathematic formulas are necessary to convert them into weight or volume.

Moreover, no significant differences were observed in a recent study when comparing clinical versus sonographic estimation of fetal weight in the normal weight range, except that, while the ultrasonographic method underestimated birth weight, the clinical method overestimated it. Moreover, ultrasound demonstrated more accurate compared to the clinical evaluation in detecting low-birth-weight babies.[36]

Evaluation of Fetal Body Composition

Fetal body composition changes throughout gestation. Specifically, a large and exponential deposition of fat tissue occurs during the second half of gestation, when most of fetal weight is gained.[37] Fetal fat mass growth seems to better correlate with the intrauterine environment, whereas fat-free mass shows stronger relationships with genetic factors. This is supported by evidence showing that the differences in weight at birth of babies born small or large for gestational age are due to the different percentage of fat at birth, representing up to 46% of the variance in neonatal weight.[38,39]

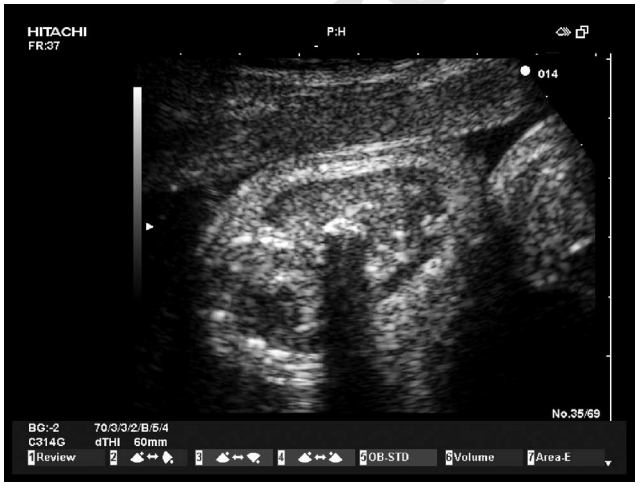


Figure 4 Fat mass measured at the level of middle arm: the measure was obtained as the difference between total arm area and lean mass area (muscle and bone).

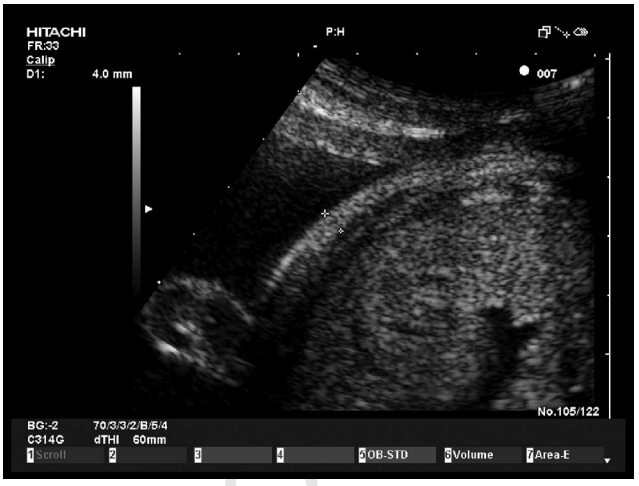


Figure 5 Abdominal fat thickness measured at the level of abdominal circumference.

Anthropometric ultrasound measurements of fetal body composition of normal fetuses have shown a unique exponential pattern of the growth profile during the second half of gestation both in lean mass and in fat mass.[40] Fat and lean mass can be measured at the level of the thigh and the arm (Fig. 4). Moreover, subcutaneous fat can be measured as F4 subcutaneous abdominal fat thickness (Fig. 5) and subscapular fat thickness. F5 Although alterations of fetal growth trajectory are associated with decreased abdominal circumference measurements, fetal biometry has limitations in differentiating the growth-restricted fetus from a fetus that is constitutionally small. Reduced subcutaneous fat mass has been shown in IUGR fetuses and the reduction is more significant when fat is normalized for body size.[41] On the other hand, in gestational diabetes mellitus the increased intrauterine growth is reflected in increased fetal fat mass deposition[42] and intrauterine ultrasound evaluation of fetal fat correlates with fetal leptin levels.[43]

Three-Dimensional Ultrasound in the Evaluation of Fetal Weight and Fetal Organ Volumes

With the introduction of three-dimensional (3D) sonography at the beginning of the 1990s, reproducible circumference and volumetric measurements have become feasible by simultaneous visualization of three orthogonal fetal sections and volume calculation has been considerably simplified.[44,45] Three-dimensional ultrasonography allows assessment of the shape and volume of fetal organs.[46-48]

3D Ultrasound Technique

The three-dimensional ultrasound technique uses computer processing for 3D reconstruction. A consecutive set of two-dimensional (2D) planes is acquired by movements of the ultrasound probe (free hand or mechanically) and constructed into a 3D data set by a computer. By using a position sensor or electromagnetic sensing device, the position of every pixel of 2D images within the volume is determined and 3D reconstruction can be built. The 3D ultrasound machine commonly used is equipped with an automatic volume scanning method. The ultrasound probe has a built-in mechanical device to move the transducer along with a position sensor. The patient setting of a 3D ultrasound examination is identical to that of a conventional 2D ultrasound examination. Orientation with real-time 2D ultrasound and optimization of the B-mode image (the normal 2D ultrasound mode) is necessary before 3D acquisition can take place. Acquisition is performed automatically after the examiner defines a region of interest (the so-called "volume box"). The digitized information of every section plane is loaded into a computer along with the information regarding its position. The 3D data set is thus composed of a set of voxels, each with a certain gray value and brightness. These values are interpolated to the voxels in-between two section planes.[47-49] After acquisition, three orthogonal planes in the direction of three orthogonal axes (x; y; z) are displayed on the monitor (multiplanar view) (Figs. 6 and 7). These planes can be moved and rotated freely with an automatic update of the perpendicular planes. 3D image reconstruction takes place after a box is set around the region of interest within the volume, thus extracting unwanted parts.

Liver Volume

As already discussed, numerous studies have shown that the most effective method of detecting impaired fetal growth is the sonographic measurement of the upper abdominal circumference.[50,51] However, this measurement is not completely satisfactory in that the positive-predicted value for detecting fetal growth restriction may be as low as 21%.[52] The fetal liver comprises most of the abdomen measured by the abdominal circumference, and changes in fetal liver weight are strongly associated with induced intrauterine growth restriction in animals.[1] Moreover, reduction in fetal liver weight is more pronounced than reduction in brain weight due to the brain-sparing effect, reflecting redistribution of fetal blood flow during chronic fetal hypoxemia.[53]

The reproducibility of fetal liver volume recordings and tracings has been shown to be quite accurate with a total coefficient of variation of less than 4%.[54] In uncomplicated pregnancy, fetal liver volume demonstrates a 10-fold increase with advancing gestational age (Fig. 8) and increasing fetal weight. The regression line, shown in Figure 9, demonstrates that the liver volume is proportional to estimated fetal weight during the second half of pregnancy. Fetal growth restriction is associated with reduced liver volume in every instance. When looking at the mean difference in liver volume between normal and reduced fetal growth, as expressed by the Z-score, a significant difference is confirmed when compared with the head circumference, confirming the brain-sparing effect during abnormal fetal development. It can be concluded that liver size is affected in fetal growth restriction, but fetal liver volume measurement is not a better discriminator than measurement of the upper abdominal circumference.

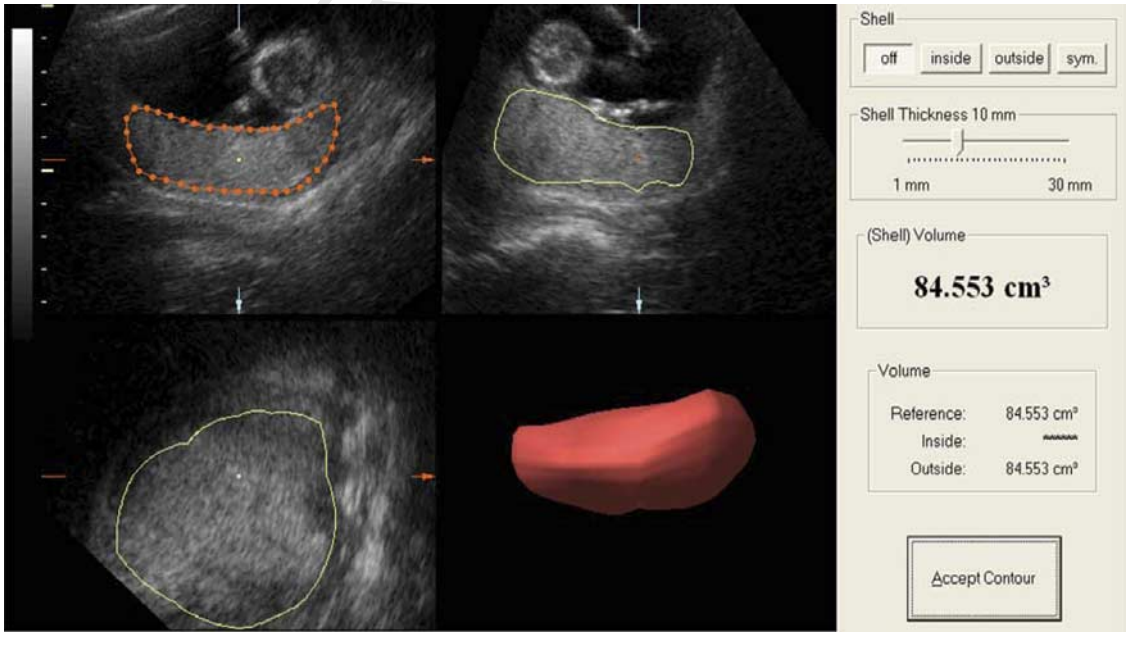


Figure 6 Placental volume calculations and the final three-dimensional image of the placenta. (Color version of figure is available online.)

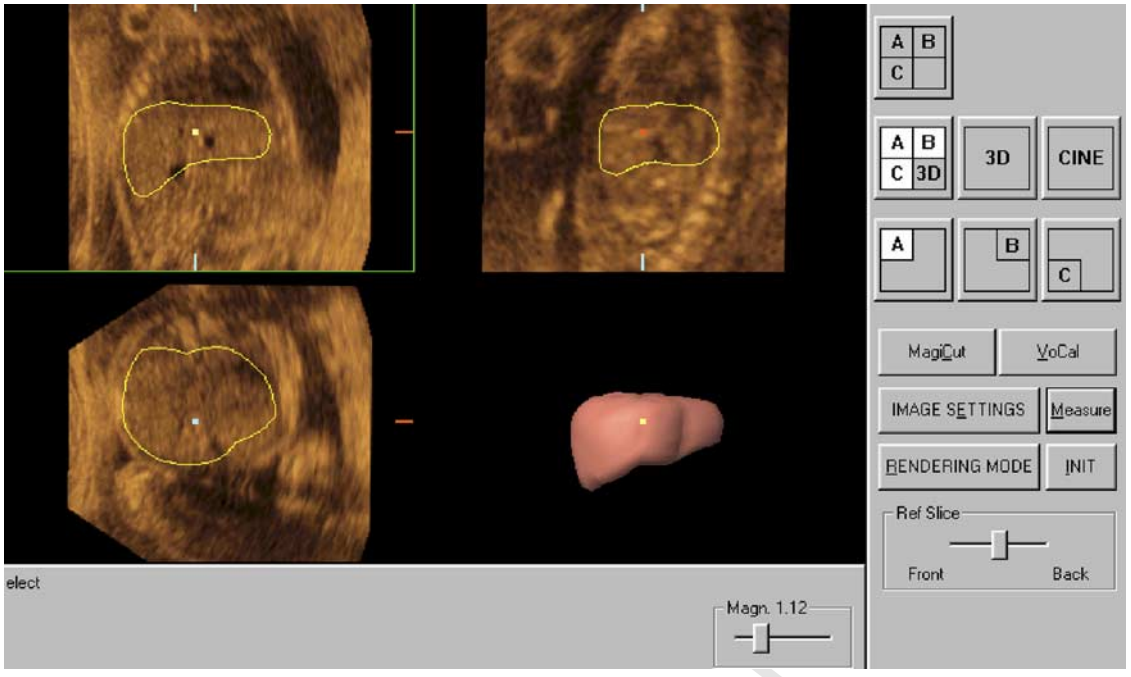


Figure 7 Liver volume calculations and the final three-dimensional image of the fetal liver. (Color version of figure is available online.)

Brain Volume

Both fetal biparietal diameter and fetal head circumference are standard parameters in establishing normal and abnormal fetal biometry.[14] With the use of a 3D sonographic method, it is now possible to measure fetal brain volume with an acceptable intraobserver variability. A nearly 10-fold increase in fetal brain volume takes place during the second half of gestation. At the same time brain growth demonstrates a marked slow down as expressed by a weekly increment in brain volume at 34 weeks of only one-third of the weekly increment at 19 weeks of gestation. When fetal brain weight derived from brain volume is examined, this represents 14 to 17% of total estimated fetal weight. Fetal brain volume measurement in conjunction with fetal liver volume determination could provide insight into the nature of abnormal fetal growth.

Brain Liver Volume Ratio

Post-mortem studies have established that fetal growth restriction is associated with an increased brain/liver volume ratio. During fetal hypoxemia, reduction in fetal brain weight is less pronounced than fetal liver weight and this phenomenon is caused by fetal circulatory centralization and fetal

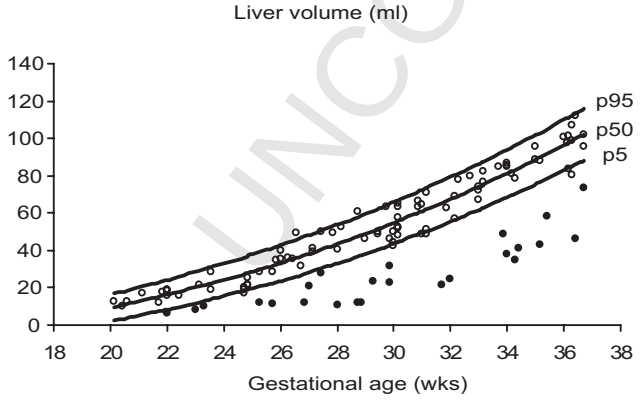


Figure 8 Liver volume (milliliters) relative to gestational age (weeks). The figure shows that all liver volumes of the growth-restricted fetuses are situated below the P5 reference level. Open circles (○) represent individual normal values; solid line (—): P5, P50, and P95 reference lines. Closed circles (●) represent fetal growth restriction. GA = gestational age. P50: cubic fit = $0.0012 \times GA^3 + 0.0443 \times GA^2 - 18.268$. P5-P95 = P50 ± 1.64 ($-0.2408 \times GA - 0.4560$).

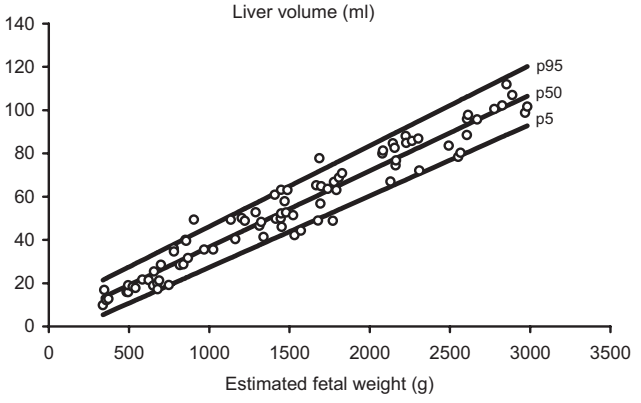


Figure 9 Liver volume (milliliters) relative to estimated fetal weight (grams). The regression line demonstrates that the liver volume is proportional to estimated fetal weight during the second half of pregnancy. Open circles (○) represent individual normal values; solid line (—): P5, P50, and P95 reference lines. Estimated fetal weight. P50: linear fit = 35.190623 × EFW + 1.560381. P5-P95 = P50 ± 1.64 (1.300713 × EFW + 4.447085).

brain sparing, resulting in asymmetrical growth restriction. Using 3D ultrasound scanning a mean brain/liver volume ratio of 3 was found in normal developing pregnancies and a maximum value of 10 has been reported in IUGR fetuses.[55] These measurements indicate the possibility of calculating fetal brain/liver volume ratio as a tool to monitor fetal growth restriction, and to indirectly indicate fetal hypoxemia. It thus becomes of interest to evaluate how this ratio relates to umbilical venous volume flow, responsible for oxygen transfer to the fetus. An inverse relation has been found in the growth-restricted fetus between fetal brain/liver volume ratio and fetal weight-related umbilical venous blood flow. Raised fetal brain/liver volume ratios were first found at reduced fetal weight-related umbilical venous volume flows of 70 ml/min/kg, and an average gestational age of 30 weeks.[55]

Placental Volume

Ultrasound is the most sensitive and less invasive method to evaluate placental size and morphology. The three-dimensional approach allows the calculation of placental volume in the first and second trimester of pregnancy. Intra- and inter-observer reproducibility of placental volume measurements was tested showing a good reproducibility.[56] Reference values for placental volume in normally developing fetuses have been established during the first half of pregnancy according to a cross-sectional study design (Fig. 10).[56] Mean placental volume (P50) ranged between 15.8 ml at 10 weeks and 198.4 ml at 23 weeks. A positive correlation existed between placental volume and fetal biparietal diameter ($r = 0.81$). Normal placental volume is 12-fold larger at midgestation compared with the beginning of pregnancy, confirming that placental growth occurs mainly in the first half of pregnancy.

Doppler Velocimetry: Profiles and Estimation of Flows

Uterine and Umbilical Blood Flow Profiles

Uterine blood flow provides oxygen and nutrient supply to the placenta and to the fetal circulation. During normal pregnancy, deep anatomic and functional changes occur in the utero-placental circulation. Between 10 and 24 weeks of gestation, two subsequent trophoblast migration waves into spiral arteries wall lead to a larger lumen diameter and a total lack of wall arterial elasticity. Spiral arteries progressively become low wall resistance vessels, allowing the physiological increase of blood flow into the intervillous space. Adequate placentation is essential to guarantee a normal obstetric outcome. Doppler studies show vessel remodeling is rapid, with the loss of proto-diastolic notching by 12 weeks and low resistance indices by 20 weeks or sooner.[57,58] On the contrary, when placentation is deficient (incomplete/absent trophoblast migration into arteries wall), notching remains, and high resistance may persist even after 24 to 26 weeks; pregnancy is associated with a significantly higher risk of both maternal (gestational hypertension, preeclampsia) and fetal diseases (intrauterine growth restriction). Uterine artery Doppler velocimetry represents the gold standard to screen and to diagnose placental defects in at-risk pregnancies. In these pregnancies the utero-placental circulation remains in a state of high resistance, which may cause generalized endothelial cell injury, compromising vascular integrity and an atherosis-like process with consequent small-vessel occlusion, local ischemia, and necrosis.[59] This condition can be noninvasively evaluated by Doppler ultrasound[60]: uterine artery Doppler measurements show that impedance to flow in the uterine arteries (ie, Resistance Index or S/D ratio) decreases with gestational age in normal pregnancies (Fig. 11A). On the contrary, impedance to flow is increased in established preeclampsia and IUGR[61] (Fig. 11B). A correlation between qualitative and semi-quantitative Doppler indices and histological placental lesions has been consistently reported.[62-65] There have been a number of studies that have examined the ability of uterine artery Doppler velocimetry to predict complications of impaired placentation.[66] Most studies have used uterine artery Doppler in the second trimester showing detection rates of 80 to 90% for early onset preeclampsia (requiring delivery before 34 weeks), but only of 41 to 45% for preeclampsia at any gestational age, with false-positive rates between 5 and 7%.[67] Using first-trimester screening shows a similar trend, although overall detection rates are lower than screening in the second trimester.[68,69]

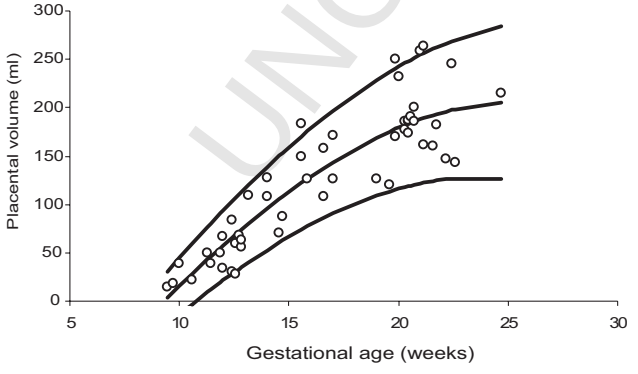


Figure 10 Placenta volume (milliliters) relative to gestational age (weeks). Open circles (○) represent individual normal values; solid line (—): P5, P50, and P95 reference lines. P50: cubic fit = $-228.75 + 25.8124 - 0.0135 \times$ (gestational age).[3] P5-P95 = P50 $\pm$ 1.645 $\times$ 1.25 $\times$ ($-1.9685 + 1.6315$) $\times$ (gestational age).

Fetal Circulation

Umbilical artery is the first and most studied vessel in obstetrics. Doppler study of umbilical artery is not time consuming and can be done with any Doppler system, with or without the support of B-mode real-time ultrasound image. In the assessment of blood flow characteristics of the umbilical artery, any index (S/D ratio, Pulsatility Index, or Resistance Index) has been found to be accurate.[60] Pulsed Doppler assessment of the umbilical artery blood flow in ongoing pregnancy is characterized by low-resistance blood flow pattern with high velocities in both systolic and diastolic phase of the cardiac cycle, but this varies with gestation. End-diastolic velocity in the umbilical artery is the result of the placental resistance. In early normal pregnancy, when the placenta is

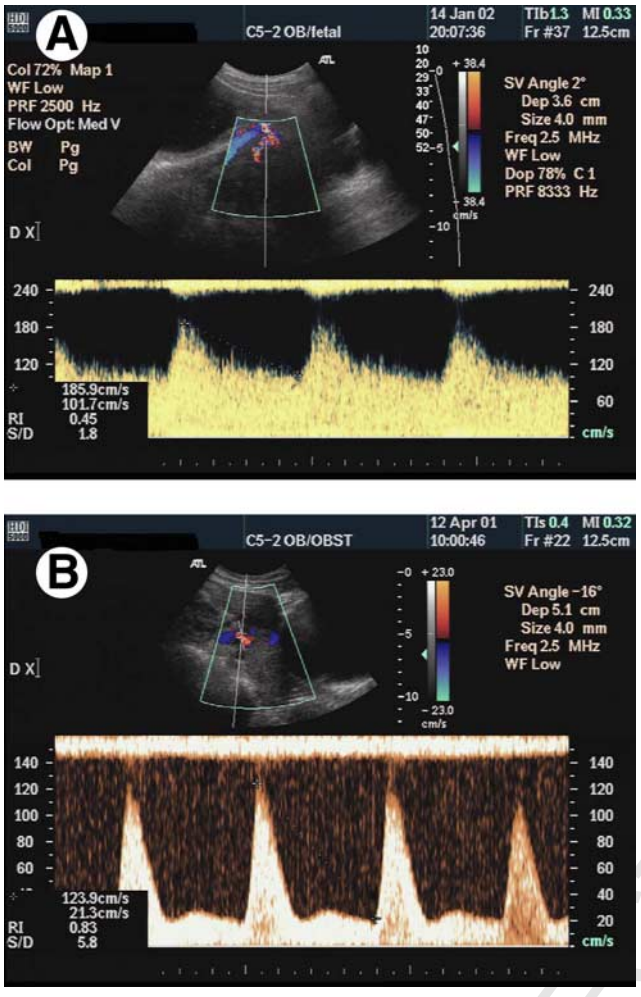


Figure 11 Uterine artery Doppler measurements showing in (A) normal waveform with Resistance Index and S/D ratio within normal ranges. (B) A blood flow profile typically present in pregnancies complicated by preeclampsia or IUGR: RI and S/D ratio are increased and a proto-diastolic notch is well documented. (Color version of figure is available online.)

still a high resistance unit, decreased or absent end-diastolic velocity are probably normal, but successful placental invasion leads to falling resistance and continuous diastolic flow in the umbilical artery Doppler by 14 to 18 weeks at the latest[70] (Fig. 12). A continuous decline in umbilical artery resistance over gestation closely correlates with normal birth weight, low risk of fetal distress, neonatal complications, and longer term manifestations of placental deficiency.[71] Conversely, rising resistance and severity of changes in Doppler velocimetry, with progression to the loss and eventually the reversal of end-diastolic flow, significantly correlates with worse perinatal outcome[72] (Fig. 13). Despite this evidence, current fetal surveillance and timing of delivery are primarily based on changes observed in the fetal heart recording (FHR). However, when FHR tracing has become abnormal, up to 77% of IUGR fetuses are already hypoxic and acidemic.[73]

Recent technological advances in ultrasound and Doppler imaging have permitted detailed examination of fetal vessels in the peripheral and central circulations. Fetal hypoxia and acidemia have been found to be associated with abnormal velocimetry of the middle cerebral artery, the aorta, the inferior vena cava, and the ductus venosus, demonstrating preferential blood flow to the brain and myocardium, and reduced perfusion to the splanchnic organs.[74] The increased frequency of intraventricular hemorrhage in decreased or absent end-diastolic velocity/REDV IUGR babies offers specific evidence of the role of the brain-sparing effect.[75] Worsening flow in the umbilical artery and persistent dilatation of the middle cerebral artery can be defined as early stage modifications, being present 2 to 3 weeks prior to any changes in the FHR tracing in more than 50% of IUGR fetuses.[74]

While arterial waveforms describe downstream resistance in critical vascular beds, venous Doppler provides important data about cardiac function. Among the studied veins, the inferior vena cava has a wide variation within normal fetuses,[76,77] and the umbilical vein has an irrelevant sensitivity despite a very specific indication of stillbirth risk, resulting in a very low predictive value for asphyxia, or even stillbirth.[78]

The ductus venosus provides a unique combination of advantages, being a primary regulator of venous return in both normal and abnormal fetuses, and being responsive to changes in oxygenation, independent of cardiac function. Moreover, although all studied venous vessels provide a valuable correlation with fetal and neonatal morbidities, the retrograde ductus venosus atrial-wave is the simplest to recognize and is the best predictor of perinatal mortality, neonatal circulatory collapse, and other critical morbidities.[79]

Sequence of Doppler Velocimetry Profile Changes in IUGR

The pathophysiology of intrauterine growth restriction has been investigated in numerous studies that have led to the characterization of a specific placental phenotype leading to reduced nutrient transfer followed by placental respiratory

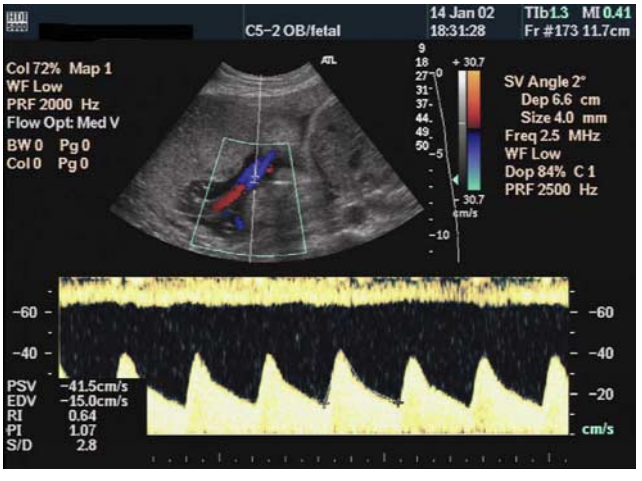


Figure 12 Umbilical artery Doppler waveform: presence of continuous diastolic flow in the umbilical artery of a normal fetus. All impedance indices (PI, RI, and S/D ratio) decrease with gestation, representing a decrease in placental vascular resistance. (Color version of figure is available online.)

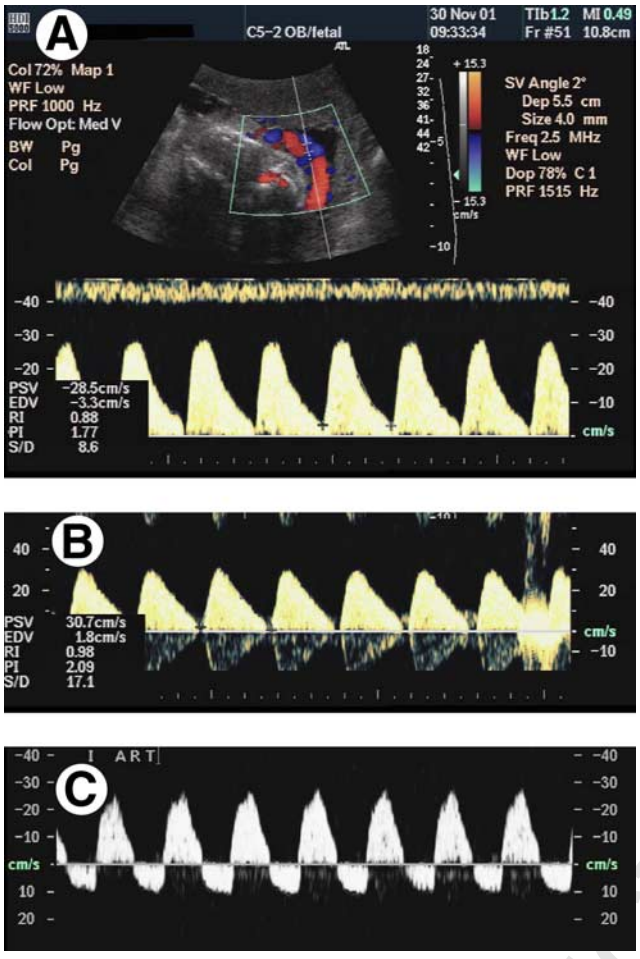


Figure 13 Increased placental vascular resistance correlates with worst perinatal outcome. IUGR fetuses show progressive worsening of the waveform with a reduction (A) and the loss of end-diastolic flow (B) until the reversal of end-diastolic flow (REDF) (C). (Color version of figure is available online.)

failure and fetal hypoxemia.[80,81] A temporal sequence of events has been described in the fetus indicating (1) reduction of growth under normoxic conditions, followed (2) by an adaptation phase with compensatory hemodynamic changes, which include blood flow redistribution towards essential organs such as the brain, heart and adrenal gland at the expenses of other organ systems (liver, lungs, kidneys, bowel).[74] This phenomenon is the so-called "centralization" of the fetal circulation. This compensatory phase of the disease can be recognized clinically by typical Doppler ultrasound findings, including a decrease in the pulsatility index of the middle cerebral artery, a decrease in the amniotic fluid, and by increased echogenicity of the bowel. The duration of this compensatory phase is variable, sometimes lasting weeks, and appears not to have deleterious short-term consequences, although it is likely to be associated with changes in fetal programming potentially associated with increased likelihood of long-term consequences.[82] When the adaptation phase with these compensatory mechanisms reach their limit, (3) myocardial dysfunction occurs.

At this time, hemodynamic decompensation is clinically recognized by abnormal venous Doppler waveforms, which are considered to reflect increased pressure in right atrium and/or dilatation of the DV and are often associated with metabolic acidemia.[83] Hypoxemia and acidemia have been well described to occur significantly only in this phase and are associated to abnormal fetal heart rate tracings.[73] Once the disease enters this decompensatory phase, the fetus is at high risk of dying and of developing multisystem organ failure.[84]

Estimation of Umbilical Venous Volume Inflow

Until recently, evaluation of the umbilical venous circulation has evoked only limited interest in favor of the umbilical artery circulation. Few data have appeared on volume flow due to the lack of precision of components measurements, notably cross-sectional vessel size. By means of a method that allows accurate determination of umbilical venous cross-sectional area, it has become possible to obtain a full picture of the clinical significance of subsequent volume flow calculations in the human fetus. Umbilical venous volume flow demonstrates no differences at the fetal, placental, or free loop site of the umbilical cord.[85] Normal mean umbilical venous blood flow ranges between 33 ml/min at 20 weeks and 220 ml/min at 36 weeks, which is a sevenfold increase.[54] When calculated per kilogram fetus as shown in Fig. 14, there is a significant decrease in normal volume blood flow from 117.5 ± 33.6 ml/min at 20 weeks to 78.3 ± 12.4 ml/min at 36 weeks of gestation. F14

The sevenfold increase between 20 and 36 weeks in umbilical venous volume flow has been established under physiological circumstances and is mainly determined by an increase in cross-sectional vessel size, with a significant

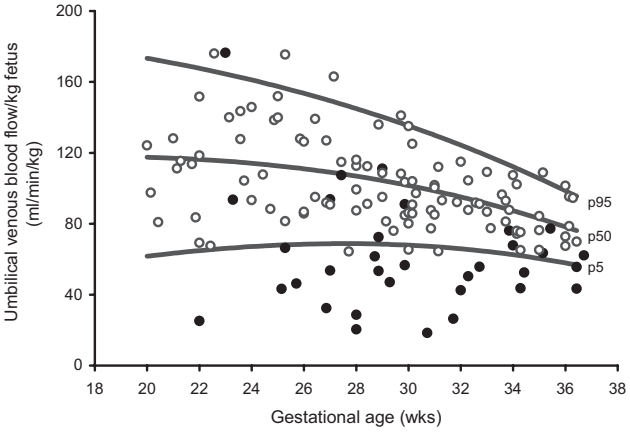


Figure 14 Umbilical venous volume flow/kg estimated fetal weight (ml/min/kg) relative to gestational age (GA). Open circles (○) represent individual normal values; solid line (—): P5, P50, and P95 reference lines. Closed circles (●) represent fetal growth restriction. GA = gestational age. P50: cubic fit = $-0.001670 \times GA^3 + 1.579665 \times GA + 99.293341$. P5-P95 = P50 ± 1.64 ($1.076244 \times GA + 48.623154$).

reduction in fetal weight-related umbilical venous volume flow.

Fetal growth restriction is associated with significantly lower umbilical venous volume flows, which again is mainly determined by a reduction in cross-sectional vessel size.[54] In this condition, umbilical artery Pulsatility Index reflecting feto-placental downstream impedance is significantly raised when fetal weight-related umbilical venous volume flow is below the lower limit (5th centile) of the normal range compared with normal values.

Estimation of Uterine Artery Volume Flow

Quantitative information of the utero-placental blood volume flow can widely improve our knowledge on utero-placental vascularization throughout gestation. However, up to now, despite extensive clinical use of uterine Doppler waveform analysis, only few studies have proposed methods to quantify the blood volume flow through uterine arteries and a correlation between flow and resistance Doppler indices in these vessels has never been described. Our group recently reported preliminary data of a mean uterine blood flow volume of 237.8 ml/min (range, 94 to 654.5 ml/min) at mid gestation.[86] These values indicate that, in normal pregnancy at mid gestation, there is a great variability in the amount of blood flow volume that supplies placental tissue. This uterine flow volume redundancy seems to remain stable up to term, since the uterine flow volume in the third trimester is 528.9 ml/min (range, 201.9 to 1471.4 ml/min) and does not seem related to side of placental insertion.

Conclusions

Ultrasound has become an invaluable tool in obstetrics that has made possible to both clinicians and parents knowledge of the fetus while in the mother's womb. Fetal growth and well-being can be evaluated by traditional fetal biometry assessment performed in the second half of pregnancy. Moreover, when deviations of fetal growth are recognized, Doppler velocimetry of utero-placental and fetal vessels is utilized in the timing of delivery. New technologies are now being studied to better describe fetal body composition and development of fetal organs.

Acknowledgment

This work was supported in part by the Association for the Study of Malformations (ASM).

References

AQ: 3

1. Cetin I, Sparks JW Determinants of Intrauterine Growth: Neonatal Nutrition and Metabolism (ed 2). Hay WW, Thureen P, 2005
2. Bernstein IM, Horbar JD, Badger GJ, et al: Morbidity and mortality among very-low-birth-weight neonates with intrauterine growth restriction. The Vermont Oxford Network. Am J Obstet Gynecol 182: 198-206, 2000
3. Barker DJ: Fetal and Infant Origins of Adult Disease. London, BMJ Press, 1992
4. Pettitt DJ, Baird HR, Aleck KA, et al: Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. N Engl J Med 5:446-451, 1983
5. Deter RL, Harrist RB, Hadlock FP, et al: The use of ultrasound in the assessment of normal fetal growth: a review. J Clin Ultrasound 9:481-493, 1981
6. Alexander GR, Kogan M, Bader D, et al: US birth weight/gestational age-specific neonatal mortality: 1995-1997 rates for whites, Hispanic and blacks. Pediatrics 111:61-66, 2003
7. De Rooij SR, Painter RC, Holleman F, et al: The metabolic syndrome in adults prenatally exposed to the Dutch famine. Am J Clin Nutr 86: 1219-1224, 2007
8. Heinonen S, Taipale P, Saarikoski S: Weights of placentae from small-for-gestational age infants revisited. Placenta 22:399-404, 2001
9. Barker DJP, Bull AR, Osmond C, et al: Fetal and placental size and risk of hypertension in adult life. BMJ 301:259-262, 1990
10. Gardosi J, Chang A, Kalyan B, et al: Customized antenatal growth charts. Lancet 339:283-287, 1992
11. Gardosi J, Mongelli M, Wilcox M, et al: An adjustable fetal weight standard. Ultrasound Obstet Gynecol 6:168-174, 1995
12. Clausson B, Gardosi J, Francis A, et al: Perinatal outcome in SGA births defined by customised versus population-based birthweight standards. BJOG 108:830-834, 2001
13. Zhang X, Platt RW, Cnattingius S, et al: The use of customized versus population-based birthweight standards in predicting perinatal mortality. BJOG 114:474-477, 2007
14. Campbell S, Thoms A: Ultrasound measurement of the fetal head to abdomen circumference ratio in the assessment of growth retardation. Br J Obstet Gynaecol 84:165-174, 1977
15. Campbell S, Warsof S, Little L, et al: Routine ultrasound screening for the prediction of gestational age. Obstet Gynecol 65:613-620, 1985
16. Thompson HE, Holmes JH, Gottesfeld KR, et al: Fetal development as determined pulse echo techniques. Am J Obstet Gynecol 92:44-52, 1965
17. Campbell S, Wilkin D: Ultrasonic measurement of fetal abdomen circumference in the estimation of fetal weight. Br J Obstet Gynaecol 82:689-697, 1975
18. Wladimiroff JW, Bloesma CA, Wallenburg HC: Ultrasonic diagnosis of the large-for-dates infant. Obstet Gynecol 52:285-288, 1978
19. Meire HB: Ultrasound assessment of fetal growth patterns. Br Med Bull 37:253-258, 1981
20. Evans MI, Mukherjee AB, Schulman JD: Animal models of intrauterine growth retardation. Obstet Gynecol Surv 38:183-192, 1983
21. Gruenwald P: Fetal deprivation and placental pathology: concepts and relationships. Perspect Pediatr Pathol 2:101-149, 1975
22. Murao F, Takamiya O, Yamamoto K, et al: Detection of intrauterine growth retardation based on measurements of size of the liver. Gynecol Obstet Invest 29:26-31, 1990
23. Roberts A, Nava S, Bocconi L, et al: Liver function tests and glucose and lipid metabolism in growth-restricted fetuses. Obstet Gynecol 94:290-294, 1999
24. Ogata ES, Sabbagha R, Metzger BE, et al: Serial ultrasonography to assess evolving fetal macrosomia. Studies in 23 pregnant diabetic women. JAMA 243:2405-2408, 1980
25. Roberts A, Mitchell J, Murphy C, et al: Fetal liver length in diabetic pregnancy. Am J Obstet Gynecol 170:1308-1312, 1994
26. De Jong CL, Gardosi J, Dekker GA, et al: Application of a customised birthweight standard in the assessment of perinatal outcome in a high risk population. Br J Obstet Gynaecol 105:531-535, 1998
27. Wohlfahrt J, Melbye M, Christens P, et al: Secular and seasonal variation of length and weight at birth. Lancet 352:1990, 1998
28. Love EJ, Kinch RAH: Factors influencing the birth weight in normal pregnancy. Am J Obstet Gynecol 91:342-349, 1965
29. Catalano PM, Drago NM, Amini SB: Maternal carbohydrate metabolism and its relationship to fetal growth and body composition. Am J Obstet Gynecol 172:1464-1470, 1995
30. Hadlock FP, Deter RL, Harrist RB: Sonographic detection of abnormal fetal growth patterns. Clin Obstet Gynecol 27:342-351, 1984
31. Hadlock FP, Harrist RB, Sharman RS, et al: Estimation of fetal weight with the use of head, body, and femur measurements—a prospective study. Am J Obstet Gynecol 151:333-337, 1985

AQ: 4

32. Dudley NJ: A systematic review of the ultrasound estimation of fetal weight. Ultrasound Obstet Gynecol 25:80-89, 2005
33. Siemer J, Egger N, Hart N, et al: Fetal weight estimation by ultrasound: comparison of 11 different formulae and examiners with differing skill levels. Ultraschall Med 2008 (in press)
34. Schild RL, Sachs C, Fimmers R, et al: Sex-specific fetal weight prediction by ultrasound. Ultrasound Obstet Gynecol 23:30-35, 2004
35. Merz E, Lieser H, Schicketanz KH, et al: Intrauterine fetal weight assessment using ultrasound. A comparison of several weight assessment methods and development of a new formula for the determination of fetal weight. Ultraschall Med 9:15-24, 1988
36. Shittu AS, Kuti O, Orji EO, et al: Clinical versus sonographic estimation of foetal weight in Southwest Nigeria. J Health Popul Nutr 25:14-23, 2007
37. Enzi G, Zanardo V, Caretta F, et al: Intrauterine growth and adipose tissue development. Am J Clin Nutr 34:1785-1790, 1981
38. Catalano PM, Tyzbir ED, Allen SR, et al: Evaluation of fetal growth by estimation of neonatal body composition. Obstet Gynecol 79:46-50, 1992
39. Catalano PM, Thomas A, Huston-Presley L, et al: Increased fetal adiposity: a very sensitive marker of abnormal in utero development. Am J Obstet Gynecol 189:1698-1704, 2003
40. Bernstein IM, Goran MI, Amini SB, et al: Differential growth of fetal tissues during the second half of pregnancy. Am J Obstet Gynecol 176:28-32, 1997
41. Padoan A, Rigano S, Ferrazzi E, et al: Differences in fat and lean mass proportions in normal and growth-restricted fetuses. Am J Obstet Gynecol 191:1459-1464, 2004
42. Larciprete G, Valensise H, Vasapollo B, et al: Fetal subcutaneous tissue thickness (SCTT) in healthy and gestational diabetic pregnancies. Ultrasound Obstet Gynecol 22:591-597, 2003
43. Cetin I, Morpurgo PS, Radaelli T, et al: Fetal plasma leptin concentrations: relationship with different intrauterine growth patterns from 19 weeks to term. Pediatr Res 48:646-651, 2000
44. Schild RL, Fimmers R, Hansmann M: Fetal weight estimation by three-dimensional ultrasound. Ultrasound Obstet Gynecol 16:445-452, 2000
45. Hafner E, Schuchter K, Van Leeuwen M, et al: Three-dimensional sonographic volumetry of the placenta and the fetus between weeks 15 and 17 of gestation. Ultrasound Obstet Gynecol 18:116-120, 2001
46. Kuo HC, Chang FM, Wu CH, et al: The primary application of three-dimensional ultrasonography in obstetrics. Am J Obstet Gynecol 166: 880-886, 1992
47. Baba K: Development of three-dimensional ultrasound in obstetrics and gynecology: technical aspects and possibilities, in 3-D Ultrasound in Obstetrics and Gynecology. Merz E. Lippincott Williams and Wilkins, Philadelphia, 1998
48. Nelson TR, Pretorius DH: Three-dimensional ultrasound imaging. Ultrasound Med Biol 24:1243-1270, 1998
49. Merz E, Benoit B, Blaas HG, et al (ISUOG 3D Focus Group): Standardization of three-dimensional images in obstetrics and gynecology: consensus statement. Ultrasound Obstet Gynecol 29:697-703, 2007
50. Seeds JW: Impaired fetal growth: ultrasonic evaluation and clinical management. Obstet Gynecol 64:577-584, 1984
51. Warsof SL, Cooper DJ, Little D, et al: Routine ultrasound screening for antenatal detection of intrauterine growth retardation. Obstet Gynecol 67:33-39, 1986
52. Baker PN, Johnson IR, Gowland PA, et al: Measurement of fetal liver, brain and placental volumes with echo-planar magnetic resonance imaging. Br J Obstet Gynaecol 102:35-39, 1995
53. Groenenberg IA, Wladimiroff JW, Hop WC: Fetal cardiac and peripheral arterial flow velocity waveforms in intrauterine growth retardation. Circulation 80:1711-1717, 1989
54. Boito SM, Laudy JA, Struijk PC, et al: Three-dimensional US assessment of hepatic volume, head circumference, and abdominal circumference in healthy and growth-restricted fetuses. Radiology 223:661-665, 2002
55. Boito S, Struijk PC, Ursem NT, et al: Fetal brain/liver volume ratio and umbilical volume flow parameters relative to normal and abnormal human development. Ultrasound Obstet Gynecol 21:256-261, 2003
56. Boito S, Moschetta M, Mandia L, et al: Three-dimensional assessment of placenta volume during the first half of pregnancy. J Soc Gynecol Investig 12:327, 2005
57. Kurjak A, Zalud I, Predanic M, et al: Transvaginal color and pulsed Doppler study of uterine blood flow in the first and early second trimesters of pregnancy: normal versus abnormal. J Ultrasound Med 13: 43-47, 1994
58. Kurdi W, Campbell S, Aquilina J, et al: The role of color Doppler imaging of the uterine arteries at 20 weeks' gestation in stratifying antenatal care. Ultrasound Obstet Gynecol 12:339-345, 1998
59. Pijnenborg R, Vercruysse L, Hanssens M. The uterine spiral arteries in human pregnancy: facts and controversies. Placenta 27:939-958, 2006
60. Campbell S, Diaz-Recasens J, Griffin DR, et al: New Doppler technique for assessing uteroplacental blood flow. Lancet 26:675-677, 1983
61. Trudinger BJ, Giles WB, Cook CM: Uteroplacental blood flow velocity—time waveforms in normal and complicated pregnancy. Br J Obstet Gynaecol 92:39-45, 1985
62. Khong TY, De Wolf F, Robertson WB, et al: Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for-gestational age infants. Br J Obstet Gynaecol 93:1049-1059, 1986
63. Meekins JW, Pijnenborg R, Hanssens M, et al: A study of placental bed spiral arteries and trophoblast invasion in normal and severe pre-eclamptic pregnancies. Br J Obstet Gynaecol 101:669-674, 1994
64. Ferrazzi E, Bulfamante G, Mezzopane R, et al: Uterine Doppler velocimetry and placental hypoxic-ischemic lesion in pregnancies with fetal intrauterine growth restriction. Placenta 20:389-394, 1999
65. Madazli R, Budak E, Calay Z, et al: Correlation between placental bed biopsy findings, vascular cell adhesion molecule and fibronectin levels in pre-eclampsia. BJOG 107:514-518, 2000
66. Papageorghiou AT, Yu CK, Nicolaides KH: The role of uterine artery Doppler in predicting adverse pregnancy outcome. Best Pract Res Clin Obstet Gynaecol 18:383-396, 2004
67. Papageorghiou AT, Yu CK, Bindra R, et al: Fetal Medicine Foundation Second Trimester Screening Group. Multicenter screening for pre-eclampsia and fetal growth restriction by transvaginal uterine artery Doppler at 23 weeks of gestation. Ultrasound Obstet Gynecol 18:441-449, 2001
68. Martin AM, Bindra R, Curcio P, et al. Screening for growth restriction by uterine artery Doppler at 11-14 weeks of gestation. Ultrasound Obstet Gynecol 18:583-586, 2001
69. Detti L, Johnson SC, Diamond MP, et al: First-trimester Doppler investigation of the uterine circulation. Am J Obstet Gynecol 195:1210-1218, 2006
70. Goldkrand JW, Moore DH, Lentz SU, et al: Volumetric flow in the umbilical artery: normative data. J Matern Fetal Med 9:224-228, 2000
71. Valcamonico A, Danti L, Frusca T, et al: Absent end-diastolic velocity in umbilical artery: risk of neonatal morbidity and brain damage. Am J Obstet Gynecol 170:796-801, 1994
72. Karlsdorp VHM, Van Vugt JMG, Van Geijn HP, et al: Clinical significance of absent or reversed end diastolic velocity waveforms in umbilical artery. Lancet 344:1664-1668, 1994
73. Pardi G, Cetin I, Marconi AM, et al: Diagnostic value of blood sampling in fetuses with growth retardation. N Engl J Med 328:692-696, 1993
74. Ferrazzi E, Bozzo M, Rigano S, et al: Temporal sequence of abnormal Doppler changes in the peripheral and central circulatory systems of the severely growth-restricted fetus. Ultrasound Obstet Gynecol 19: 118-121, 2002
75. Baschat AA, Gembruch U, Viscardi RM, et al: Antenatal prediction of intraventricular hemorrhage in fetal growth restriction: what is the role of Doppler? Ultrasound Obstet Gynecol 19:334-339, 2002
76. Huisman TWA, Stewart PA, Wladimiroff JW: Flow velocity waveforms in the fetal inferior vena cava during the second half of normal pregnancy. Ultrasound Med Biol 17:679-682, 1991
77. Rizzo G, Arduini D, Romanini C: Inferior vena cava flow velocity waveforms in appropriate—small-for-gestational-age fetuses. Am J Obstet Gynecol 166:1271-1280, 1992
78. Baschat AA, Gembruch U, Weiner CP, et al: Qualitative venous Doppler waveform analysis improves prediction of critical perinatal out-

comes in premature growth-restricted fetuses. Ultrasound Obstet Gynecol 22:240-245, 2003
79. Kiserud T: The ductus venosus. Semin Perinatol 25:11-20, 2001
80. Pardi G, Marconi AM, Cetin I: Placental-fetal interrelationship in IUGR fetuses—a review. Placenta 23:S136-S141, 2002
81. Sibley CP, Turner MA, Cetin I, et al: Placental phenotypes of intrauterine growth. Pediatr Res 58:827-32, 2005
82. Barker DJ: Adult consequences of fetal growth restriction. Clin Obstet Gynecol 49:270-283, 2006
83. Bellotti M, Pennati G, De Gasperi C, et al: Simultaneous measurements of umbilical venous, fetal hepatic, and ductus venosus blood flow in growth-restricted human fetuses. Am J Obstet Gynecol 190:1347-1358, 2004
84. Baschat AA, Cosmi E, Bilardo CM, et al: Predictors of neonatal outcome in early-onset placental dysfunction. Obstet Gynecol 109:253-261, 2007
85. Pennati G, Bellotti M, De Gasperi C, et al: Spatial velocity profile changes along the cord in normal human fetuses: can these affect Doppler measurements of venous umbilical blood flow? Ultrasound Obstet Gynecol 23:131-137, 2004
86. Rigano S, Boito S, Padoan A, et al: Reduction of uterine artery blood flow volume is correlated to reduced fetal mass in pregnancies with abnormal uterine resistance index. Ultrasound Obstet Gynecol 30:457, 2007

AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES 1

AQ1— Please spell out SGA.

AQ2— Please spell out REDV.

AQ3— Please supply publisher and location for ref. 1. Please identify Hay WW and Thureen P.

AQ4— Please spell out BJOG throughout references. Br J Obstet Gynaecol?

AQ6— Update available?

AQ5— Please verify page range is correct for ref. 43.