

# MR Biomarkers of Gestational Age in the Human Fetus

Judy R. James<sup>1</sup>; Majid A. Khan<sup>1</sup>; David A. Joyner<sup>1</sup>; David P. Gordy<sup>1</sup>; Razvan Buciuc<sup>1</sup>; James A. Bofill<sup>2</sup>; Kenneth W. Liechty<sup>2</sup>; Manohar S. Roda<sup>1</sup>

<sup>1</sup>Department of Radiology, University of Mississippi Medical Center, Jackson, MS, USA

<sup>2</sup>University Center for Fetal Medicine, University of Mississippi Medical Center, Jackson, MS, USA

## Abstract

Fetal biometry measurements using ultrasound have been the standard for assessment of fetal development and gestational age, however, no similar standards exist for fetal\* MR imaging (MRI). Rapid high-resolution MRI evaluation of 110 fetuses with a gestational age =  $27 \pm 9$  weeks was performed and the bi-parietal-diameter (BPD), occipital-frontal-diameter (OFD), head-circumference

(HC), femur-length (FL), humerus-length (HL), and abdominal-circumference (AC) were determined and correlated with the ultrasound measurement. The results demonstrate an excellent correlation with ultrasound with insignificant differences between reported biometrics and gestational age. All of the MR biometric measurements correlated well with the ultrasound measurements

(slope =  $0.97 \pm 0.03$  and an  $R^2 = 0.91 \pm 0.03$ ). Gestational ages computed from the MR biometrics, also correlated well with the ultrasound ages (slope =  $0.97 \pm 0.04$ ;  $R^2 = 0.90 \pm 0.02$ ). There was no significant difference between the biometrics ( $p$ -value =  $0.13 \pm 0.07$ ) and the gestational ages ( $p$ -value =  $0.58 \pm 0.25$ ) obtained from either of the imaging modalities. The mean gestational age

**Table 1: Fetal MR imaging sequences and parameters:**

	T2 HASTE	TrueFISP	3D VIBE (In/Out phase)	FLASH	DWI
Sequence type	HASTE	TrueFISP	VIBE	GRE	EPI
Breath-hold	Yes	Yes	No	Yes	No
Concatenations	2	2	1	1	1
FOV (mm)	290	350	320	350	300
Slices (brain/body)	20/32	30/37	22/36	25/30	30/30
Slice thickness (mm)	5	4	5	7	5
Slice gap (mm)	0/0	0.6	0	1.4	1
TR (ms)	1200	4	8	113	5000
TE (ms)	85	2	4	4.6	85
Averages	1	1	1	1	2
PAT	Off	Off	2	Off	2
Flip angle	180	70	10	25	–
Fat suppression	No	No	Yes	No	Yes
Base resolution	256	256	256	256	156
Phase resolution	216	220	192	180	156
Receiver bandwidth	195	558	320	260	1282
Acquisition time (sec)	46	45	13	40	22

\*MR scanning has not been established as safe for imaging fetuses and infants under two years of age. The responsible physician must evaluate the benefit of the MRI examination in comparison to other imaging procedures.

obtained from MR was in excellent correlation with the ultrasound mean gestational age (slope = 0.99,  $R^2 = 0.92$ , p-value = 0.52). In addition, MRI was able to provide more anatomical and structural information regarding complex fetal anomalies. MR biometry can be used as an appropriate modality to accurately assess fetal gestational age, fetal development, and fetal growth proportions.

## Introduction

Assessment of fetal biometry is of vital importance in prenatal diagnosis and is an established way of assuring appropriate brain development. Ultrasound is considered to be a screening modality of choice for biometric assessment and is performed in great numbers everyday on very large populations of pregnant women and has established biometric reference standards in various cohorts of human fetuses. MRI, in contrast, is a complementary tool and is usually performed following detection of abnormalities with ultrasound, especially in cases where sonographic findings are equivocal. There have been significant advances in fetal MR imaging, with the advent of multiple new MR imaging techniques resulting in the increased utilization of MRI for fetal evaluation, especially in known cases of congenital fetal anomalies [1–3]. In addition, MR imag-

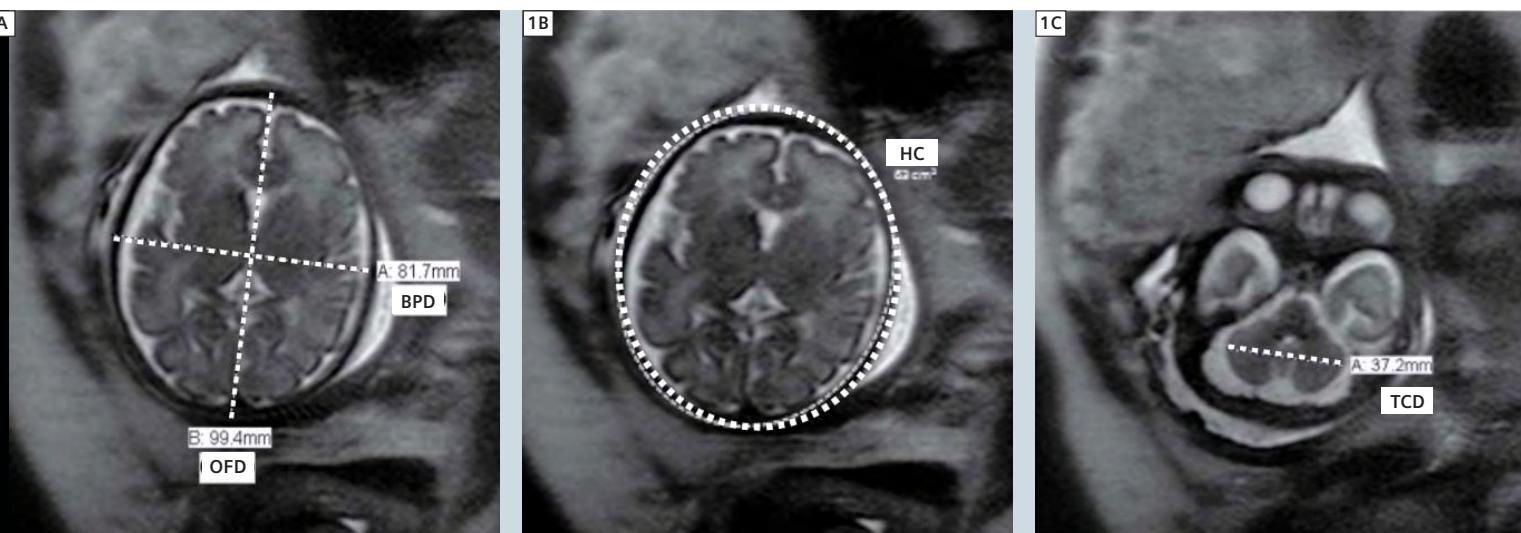
ing provides greater detail, improved spatial resolution and soft-tissue contrast than routine ultrasound imaging. Hence, it is now more feasible to determine normal biometric data for fetuses from just a few MRI sequences. The use of MRI as an adjunct to ultrasound in fetal imaging is becoming widespread in clinical practice and in the literature. Fast MR imaging sequences have been helpful in eliminating fetal motion artifacts while providing superior resolution and anatomic detail of the fetal brain [4–9]. A potential advantage of the improved high contrast resolution is to accurately acquire and measure fetal biometric values, which can be used as a screening tool to identify fetuses that fall outside the normal range of measurements and thus are at increased risk of morphologic abnormalities. Comparisons of MRI and ultrasound in the measurement of fetal biometric values and organ size have been shown in some reports with limited number of fetuses [10–11]. As expected, a good agreement between the two methods exists with a slight advantage to MRI in certain cases, such as fetal weight estimation and measurement of the posterior fossa [12]. Since we already obtain ultrasound and MR whole-body images of high-risk fetuses, a decision was made to analyze MR fetal biometry mea-

surements of fetal head, abdomen, and extremities from a large cohort of MR fetal images and compare to ultrasound values. Our aim was to perform multi-parameter assessment of bi-parietal diameter (BPD), occipital frontal diameter (OFD), head circumference (HC), femur length (FL), humerus length (HL) and abdominal circumference (AC) and the gestational ages determined from these measurements and correlate these findings with ultrasound. We hope that the findings from this study could add a crucial dimension to fast imaging MRI for reliable normal fetal biometric evaluation.

## Methods

### a) Study population

A retrospective review of the MRI database for fetal MRI examinations was performed. Once the study protocol was reviewed and approved by the institutional review board (*University of Mississippi Medical Center, Jackson, MS, USA*), a retrospective measurement analysis for fetal biometrics of high-risk fetal MR images ( $n = 110$ , gestational age =  $27 \pm 9$  weeks) was done with images acquired using conventional MR techniques. Pregnant women with high-risk fetuses were referred for an MRI scan by the ultrasound, obstetric, maternal fetal medicine or pediatric surgery departments. An ultrasound report was avail-



**1** MR images showing multi-parameter assessment of gestational age with fetal head measurements: **(1A)** bi-parietal diameter (BPD) and occipital frontal diameter (OFD), **(1B)** trans-cerebellar diameter (TCD) and **(1C)** head circumference (HC).

able for each fetus with the respective reported fetal biometrics and corresponding gestational ages.

The inclusion criteria were:

- Fetal ultrasound reports with all fetal biometrics (BPD, OFD, HC, FL, HL and AC), except TCD, should be included in the chart.
- Fetal ultrasound report must have estimated gestational ages from each biometrics (except OFD) reported in the chart.
- Fetal ultrasound report must have the average composite gestational age reported.
- Ultrasound and MRI scans of the fetus must have been done on the same day or within  $\pm 3$  days for correlation purposes.
- Absence of movement artifacts which would render the measurements inaccurate.
- Absence of significant intracranial abnormalities and/or absence of significant body abnormalities which may affect head or abdominal size and measurements.
- Absence of skeletal dysplasia.

MRI examinations for these high-risk fetuses were performed because of increased risk and/or positive family history of cranial pathology (including suspicion of infectious fetopathy, suspicion of cerebral abnormality, absent septum pellucidum, giant cisterna magna, Dandy Walker variants, cerebral biometry at the lower limit of the normal on ultrasound), cleft lip and/or palate, spina bifida, club foot, polyhydramnios, suspected esophageal or duodenal atresia, lung lesions like sequestration, CCAM, maternal disease (with possible consequences for fetal cerebral development), congenital heart defects, incidental mass lesions detected on ultrasound like lymphangioma, teratoma and placental abnormalities. The cases with intracranial abnormalities causing hydrocephalus from aqueductal stenosis, Arnold Chiari malformation, intracranial hemorrhage, obstructive mass lesions and microcephaly, which may and/or would affect head size and measurements, were excluded. The cases with signifi-

cant body wall and diaphragmatic abnormalities like gastroschisis, omphalocele, diaphragmatic hernias, ectopia vesicae, which may affect abdominal size and measurements were also excluded. The cases with severe oligohydramnios were excluded, due to difficulty in obtaining the measurements.

#### **b) Non-contrast image acquisition on MR scanner**

Fetal MRI was performed on 1.5T MR scanners (MAGNETOM Espree and MAGNETOM Symphony a Tim System, Siemens Healthcare, Erlangen, Germany) with optimized fetal MR protocols to image fetuses and pregnant women in an effective and timely manner. The subjects were positioned supine with the coil placed on their torso. The coil was positioned in such a way that the liver was in the centre of the coil. No respiratory or cardiac gating was used. Proton images were acquired with the 6-channel Body Matrix coil anterior coupled with 6 channels of the Spine Matrix coil posterior for a total of a 12-channel array.

Fast imaging MR sequences such as Half-fourier-Acquisition-Single-shot-Turbo-spin-Echo (HASTE), True-Fast-Imaging-with-Steady-state-Precession (TrueFISP), Fast-Low-Angle-Shot (FLASH), Volumetric-Interpolated-Breath-hold-Examination (VIBE), T1 Gradient-Recalled-Echo (GRE) and Diffusion-Weighted (DW) images were included in the fetal MR scans. Imaging parameters used for these sequences are reported in Table 1. These sequences were used to acquire high-resolution whole-body images of the fetus in different orientations (sagittal, coronal and axial planes). The fetal images were then sent to a reporting database for review by radiologists.

#### **c) Fetal biometric measurements**

Two expert radiologists (M.K. and M.R.) in neuro imaging and body imaging reviewed all the fetal MR images and performed the biometric measurements independently. The appropriate and specific planes and slices for reporting the fetal head, abdomen, and extremity measurements were chosen from the MR images presented to them.

#### **■ Head measurements**

BPD, HC, OFD and TCD were measured as part of the head measurements, shown in Figure 1. The BPD and OFD were measured on a transverse axial section of the fetal head which included the falx cerebri anteriorly and posteriorly, the cavum septum pellucidum anteriorly in the midline and the thalamus. The BPD was measured from the outer edge of the nearer parietal bone to the inner edge of the more distant parietal bone in relation to the anterior abdominal wall so as to match with the ultrasound technique. The OFD was measured perpendicular to the BPD from the outer edge to the outer edge of the bones. The longest transverse width of the cerebellum, either on axial or coronal plane, was measured in the posterior fossa views to obtain TCD measurement.

#### **■ Abdomen measurements**

The abdominal circumference was measured at the level of the liver and stomach of the fetus, including the left portal vein at the umbilical region, shown in Figure 2A. This measurement was used in the assessment of gestational age and fetal growth, particularly in the second half of the pregnancy to demonstrate normal fetal proportions.

#### **■ Extremities measurements**

The long bones were measured along their true longest axis. The visualization of femoral or humeral shaft and the visualization of both cartilaginous ends indicated that the image plane was on the longest axis and is the optimal measurement plane, shown in Figures 2B and C. The calipers were placed along the diaphyseal shaft excluding the epiphysis.

Both the radiologists were completely blinded to the ultrasound measurements and gestational ages reported from the ultrasound scan for each of these fetuses. Once the MRI measurements were reported, corresponding gestational ages were tabulated from the same reference charts as used in ultrasound.

#### **d) Statistical correlation**

MR fetal biometrics reported by the radiologists was correlated using linear squares regression (slope,  $R^2$ ) analysis and Pearson's bivariate parametric corre-

lations coefficients, R, (*p*-value ( $P_{\text{Pearson}}$ )  $\leq 0.05$  level) with the ultrasound measurements. Student's *t*-test was performed to determine any significant differences between the biometric measurements and gestational ages obtained from the two imaging modalities (*p*-value ( $P_{\text{t-test}}$ )  $< 0.05$ ). All statistical analyses were done in Microsoft Excel® or IBM SPSS Statistics 19.

## Results

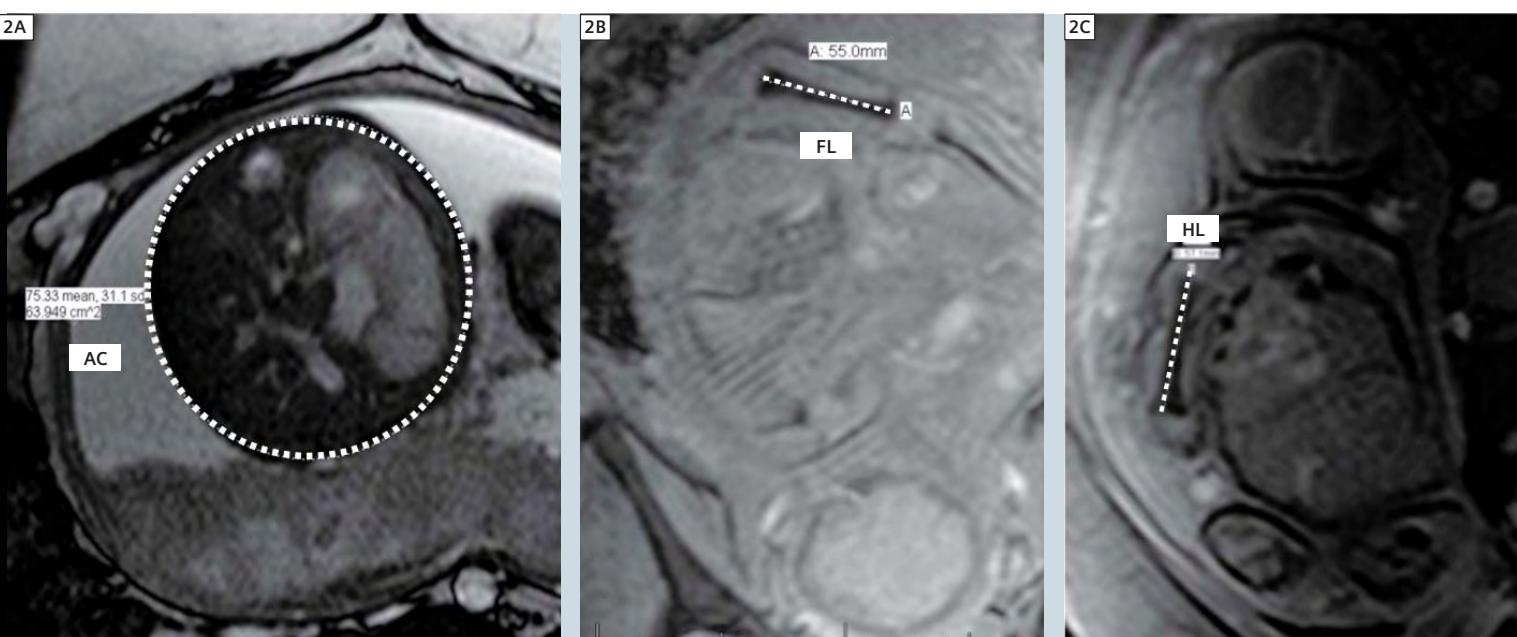
Results showed an excellent correlation with insignificant differences between ultrasound and MRI reported biometrics and gestational ages. All the MR biometric measurements correlated well with the ultrasound measurements (slope =  $0.97 \pm 0.03$  and an  $R^2 = 0.91 \pm 0.03$ ) as shown in Figure 3. Gestational ages computed from the MR biometrics, also correlated well with the ultrasound ages (slope =  $0.97 \pm 0.04$ ;  $R^2 = 0.91 \pm 0.02$ ) as shown in Figure 4. There was no significant difference between the biometrics ( $P_{\text{t-test}} = 0.13 \pm 0.07$ ) and the gestational ages ( $P_{\text{t-test}} = 0.58 \pm 0.25$ ) obtained from both the imaging modalities. Mean gestational age from MR was in excellent correlation with ultrasound mean

gestational age (slope = 0.99,  $R = 0.96$ ,  $P_{\text{Pearson}} < 0.01$ ,  $P_{\text{t-test}} = 0.52$ ) as shown in Figure 5.

A strong correlation was also observed for each of the fetal head and body biometric measurements and gestational ages between MRI with ultrasound. This was also confirmed to be significant by Pearson's parametric correlations done at 0.01 levels. For HC, measurement and age correlation between the two imaging modalities was with a slope = 0.99 and 0.99,  $R = 0.97$  and 0.96  $P_{\text{Pearson}} < 0.01$  for both and  $P_{\text{t-test}} = 0.34$  and 0.32. For BPD, measurement and age correlation was with a slope = 0.95 and 0.96,  $R = 0.95$  and 0.98  $P_{\text{Pearson}} < 0.01$  for both, and  $P_{\text{t-test}} = 0.38$  and 0.34. For OFD, the measurement correlation was with a slope = 0.95,  $R = 0.9$ ,  $P_{\text{Pearson}} < 0.01$  and  $P_{\text{t-test}} = 0.34$ . Gestational age estimated from OFD was not reported in the ultrasound report for comparison purposes with MRI. For AC, measurement and age correlation was with a slope = 1.02 and 0.98,  $R = 0.96$  and 0.96,  $P_{\text{Pearson}} < 0.01$  and  $P_{\text{t-test}} = 0.51$  and 0.46. For FL, measurement and age correlation was with a slope = 0.95 and 1.00,  $R = 0.91$  and 0.91,  $P_{\text{Pearson}} < 0.01$  for both and  $P_{\text{t-test}} =$

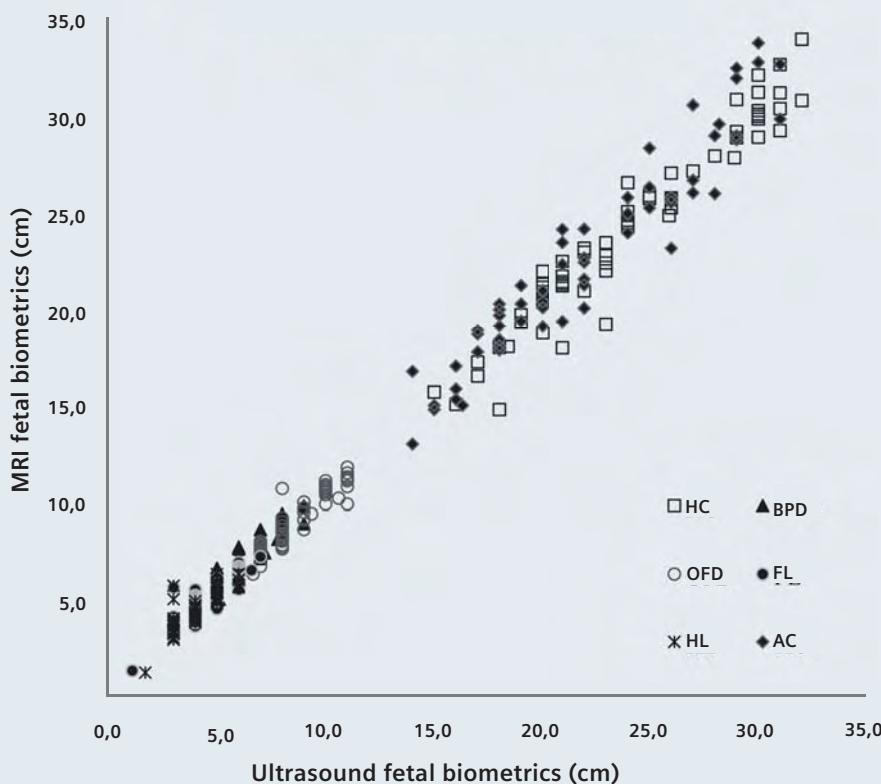
0.50 and 0.44. For HL, measurement and age correlation was with a slope = 0.99 and 1.0,  $R = 0.86$  and 0.88,  $P_{\text{Pearson}} < 0.01$  for both and  $P_{\text{t-test}} = 0.43$  and 0.40.

The analysis from various biometric measurements from MRI vs. the respective MR gestational ages yielded very interesting results. It was observed that some head and body measurements increased in a linear fashion with gestational age but some of the fetal biometric measurements increased more rapidly than others as gestational age increased as exposed by the slope of the correlation charts. HC and AC measurements had an almost perfect linear increase with age (slope = 1.02 and 0.91,  $R^2 = 0.97$  and 0.93 respectively) where as BPD had a slope = 3.61 ( $R^2 = 0.98$ ), OFD had a slope = 2.91 ( $R^2 = 0.91$ ), FL had a slope = 4.07 ( $R^2 = 0.97$ ) and HL had a slope = 4.71 ( $R^2 = 0.95$ ). Results also showed that HL and FL developed at a much faster rate than other measurements with gestational age. This was in concordance with the ultrasound measurement correlations with their respective gestational ages. In addition to using MRI for deriving accu-



**2** MR images showing multi-parameter assessment of gestational age with fetal body measurements: (2A) abdominal circumference (AC), (2B) femur length (FL) and (2C) humerus length (HL).

## Biometrics correlation chart



**3** Biometric correlation chart showing strong correlation (slope =  $0.98 \pm 0.03$  and  $R^2 = 0.91 \pm 0.03$ ) between measurements obtained from MRI and ultrasound.

rate fetal biometrics, MRI was also able to provide additional information regarding the fetal anomalies.

### Discussion

In this study, non-invasive MRI has been used to perform fetal biometry measurements and to determine gestational ages based on the measurements from a reasonably large cohort of patients with a large gestational age range ( $n = 110$ , gestational age =  $27 \pm 9$  weeks) with high accuracy and good correlation with ultrasound measurements throughout the gestational age range. In this project, various biometric measurements were performed in the fetal images and compared to ultrasound to establish the reliability and accuracy of MRI in providing biometric values as well as gestational ages. Biometric measurements were derived from MRI and ultrasound for BPD, OFD, HC, FL, HL and AC and additional values such as TCD obtained from MR images. TCD is not routinely

reported on ultrasound in our institution. Biometrics was done on high-risk fetuses without any significant intracranial abnormalities which could affect the head measurements and/or without any significant body abnormalities which could affect the body measurements. Fetal biometry and gestational age determination using ultrasound is considered the gold standard and is appropriate for screening purposes. This has resulted in various accurate fetal growth charts [13] that are used for age determination and validation of MRI measurements since there have been no charts developed yet based on MRI measurements. But, MRI of the fetuses is gaining widespread acceptance due to its improved spatial resolution and soft-tissue contrast as compared to ultrasound [14–15]. But in current clinical practice, MRI is still not the foremost choice of modality for screening fetuses for normality or abnormalities. Ultrasound is definitely the primary

choice for fetal imaging. Ultrasound being widely available, easy to use and less expensive than other imaging modalities makes it a convenient modality of choice for fetal imaging. Ultrasound imaging does give a clear image of the soft tissues but is not capable of identifying all fetal anomalies as on an MRI scan due to the lack of spatial resolution and visual clarity. Ultrasound images are highly dependent on the operator and are interpreter dependent, too. The ultrasound images are also highly influenced by fetal positioning, for instance if the fetal head is low in the pelvis, it is highly challenging to acquire clear ultrasound images. Additionally, fetal ultrasound can often be suboptimal due to beam limitations enforced by maternal body habitus. However, the peripheral skeletal evaluation is better on ultrasound due to real time cine imaging.

MRI is normally a complementary technique to ultrasound for evaluation of fetus and fetal anomalies. MRI visualization of the fetus is not limited by fetal position and provides a superior soft-tissue contrast, spatial resolution and has superior abilities to distinguish internal structures such as gray and white matter in the brain, neck, spine, lungs, mediastinum, liver, kidneys and wall of the abdomen. Multiple views obtained using MRI with an adjustable FOV allows for visualization of the whole fetus in relation to the gravid uterus. MRI also makes it possible to acquire true cerebral and abdomen biometric measurements rather than measurements of the skull vault [16]. One of the limitations MRI faces is its relatively high motion sensitivity. Fetal motion causes artifacts that deteriorate image quality and can render the scan non-diagnostic for measurement purposes. Due to the selection of fast imaging sequences, we were nevertheless able to produce images with high quality and high signal-to-noise ratio (SNR) within 15–20 s. The fast imaging sequences used for the study included breath-hold T2 HASTE, steady-state – free-precession TrueFISP, 3D VIBE, and DW images in all 3 planes – axial, coro-

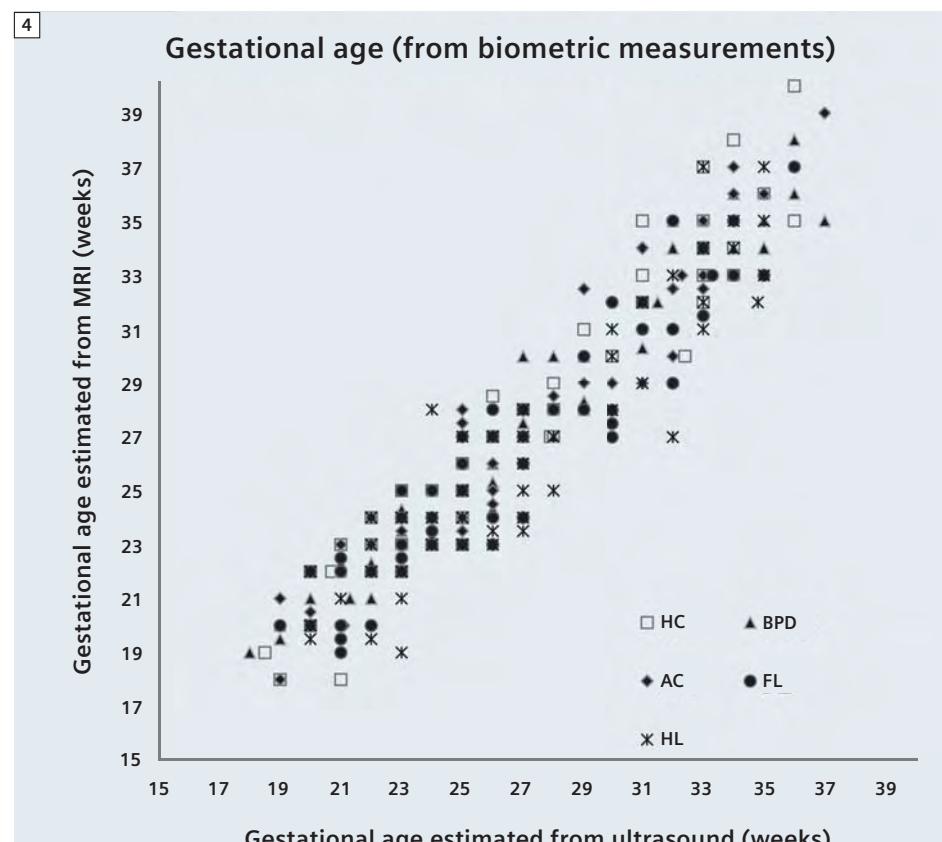
nal and sagittal. All sequences had relatively low SAR characteristics. To enhance SNR and the speed of the scans, an iPAT factor of 2 (GRAPPA 2) was enabled. The FOV was adjusted to the body part of interest. For example, FOV was reduced in the case of the fetal brain such that reading would be similar to that in adults. Sufficient phase oversampling was provided to avoid phase wrap artifacts from the mother's body. Breath-hold times were carefully calibrated to avoid any breathing artifacts while maintaining a scan time of ~ 20 s per breath-hold.

The radiologists chose the appropriate sequence for evaluation and measurement of the head and various body parts. It was noted that most of the head measurements were done by drawing appropriate regions-of-interest (ROI) on the axial or coronal T2 HASTE images where as the head and the abdominal circumferences were done on the axial TrueFISP images due to high SNR and high T1/T2 contrast enabling visualization of the structures more clearly. FL and HL measurements were mostly done on sagittal T1-weighted GRE sequences such as 3D FLASH or VIBE due to enhanced contrast of bones versus surrounding tissues. DWI and apparent diffusion coefficient computed maps also helped visualize the bones very clearly due to hypointense signal.

Correlation charts between head and body MRI and ultrasound biometric measurements and gestational ages (starting from 18 weeks) showed that there was a strong correlation between the two modalities for the biometrics examined, though HL and FL showed a slightly lower correlation ( $R^2 = 0.86$ ) compared to others. Reports exist that document no measure of the HL and FL from fetal MRI due to signal void of the bony cortex on MRI [7, 17]. The orientation of the femur is much less predictable than those of the head and abdomen. This leads to time consuming post-processing technique and less accurate results. Despite these challenges, our results correlated well. The ultrasound surely has the added advantage in evaluating peripheral skeletal evalua-

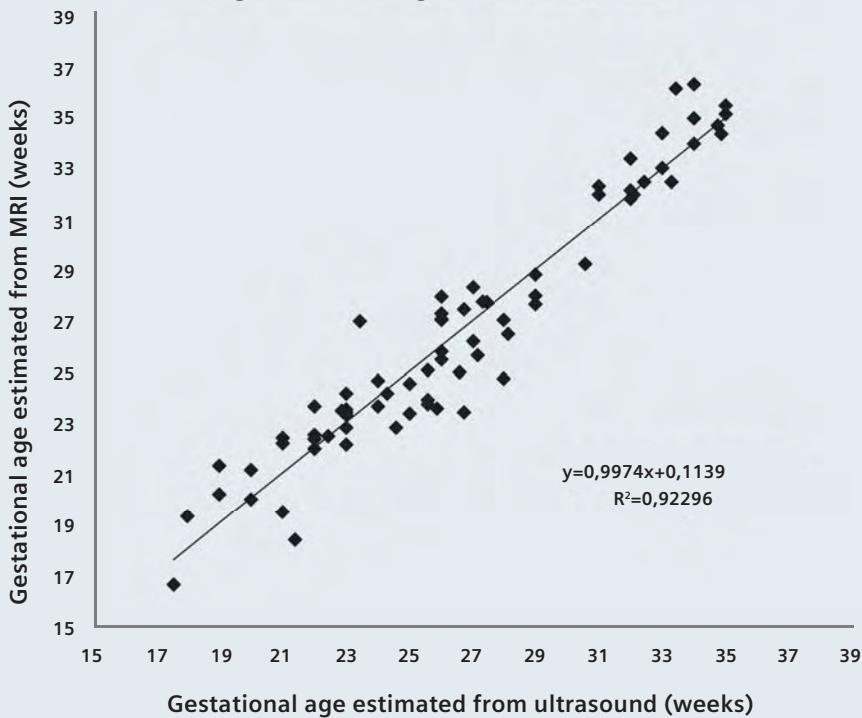
tion due to real time cine imaging. TCD is a stable gestational age independent parameter for early detection of fetal growth abnormalities. TCD measurements from MRI could not be compared since the ultrasound reports did not specify the respective measurements. Similarly, the gestational age based on OFD was not reported in the ultrasound for comparison with MRI. It was also very interesting to note that not all the head and body biometric measurements developed in a linear pattern with increasing GA. Some of the structures increased in size more rapidly than others as gestational age went up, as observed from the slopes of the correlation charts. HC and AC measurements had a near perfect linear increase with GA whereas BPD, OFD and FL and HL measurements increased at much faster rate than HC and AC. Among all

the parameters, HL and FL had the maximum rate of growth than other measurements. One of our major limitations in this study was the lack of follow-up of the new borns to ascertain that they were normal. This would be of particular interest if there was no abnormality detected during pregnancy on ultrasound or with MRI. The sample size was also relatively small with only 110 subjects. Intra-rater reliability of the measurements and inter-observer error were not quantified. However, both the ultrasound maternal-fetal medicine physicians/technologists and the MRI operators/radiologist were highly experienced in obtaining fetal scans/ biometric values and most likely provided accurate and reliable data.



**4** Correlation chart showing strong relation between the gestational ages obtained from various biometric measurements on MRI and ultrasound (slope =  $0.97 \pm 0.04$  and  $R^2 = 0.91 \pm 0.02$ ).

## Mean gestational age correlation chart



**5** Average fetal gestational age obtained from ultrasound and MRI shows a strong correlation as indicated by the slope.

## Conclusion

Fetal\* MRI is a very useful diagnostic tool to evaluate fetal anomalies and could be a great adjunct to ultrasound for determining the fetal biometrics and gestational ages. A multi-parameter assessment of fetal gestational ages was possible with rapid high-resolution MRI techniques. An excellent correlation was observed with insignificant differences between ultrasound and MRI reported biometrics. In addition, MRI was able to provide more information regarding determination of other biometric measurements, such as trans-cerebellar diameter, and can also be very useful as a problem solving tool in assessing complex congenital anomalies. Our future goal is to include new MR biomarkers to demonstrate normal fetal growth proportions and to be able to predict fetal anomalies from biometric deviations at various gestational ages. Developments in MRI technology such as DWI and tensor imaging will further expand the role of fetal MRI to functionally map the developing brain and make it an indispensable tool in prenatal medicine.

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### Contact

Manohar S. Roda, M.D.  
Radiology  
University of Mississippi Medical Center  
2500 North State Street  
Jackson, MS 39216  
USA  
Phone: +1 (601) 815-5615  
Fax: +1 (601) 984-4986  
mroda@umc.edu

### Judy Rose James, Ph.D.

Radiology  
University of Mississippi Medical Center  
2500 North State Street  
Jackson, MS 39216  
USA  
Phone: +1 (601) 984-2585  
Fax: +1 (601) 984-4986  
jjames2@umc.edu

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