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ORIGINAL ARTICLE

# A modified prenatal growth assessment score for the evaluation of fetal growth in the third trimester using single and composite biometric parameters

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**Abstract**

*Objective*: To define modified Prenatal Growth Assessment Scores (mPGAS) for single and composite biometric parameters and determine their reference ranges in normal fetuses.
*Methods*: Nine anatomical parameters (ap) were measured and the weight estimated ($EWT_a$, $EWT_b$) in a longitudinal study of 119 fetuses with normal neonatal growth outcomes. Expected third trimester size trajectories, obtained from second trimester Rossavik size models, were used in calculating Percent Deviations (% Dev's) and their age-specific reference ranges in each fetus. The components of individual % Dev's values outside their reference ranges, designated +iapPGAS, -iapPGAS, were averaged to give +apPGAS and −apPGAS values for the 3rd trimester. The +iapPGAS and −iapPGAS values for different combinations of ap (c1a (HC, AC, FDL, ThC, $EWT_a$), c1b (HC, AC, FDL, ThC, $EWT_b$), c2 (ThC, ArmC, AVol, TVol), c3 (HC, AC, FDL, $EWT_a$)) were then averaged to give +icPGAS and −icPGAS values at different time points or at the end of the third trimester (+cPGAS, −cPGAS). Values for iapPGAS, ic1bPGAS, and ic2PGAS were compared to their respective apPGAS or cPGAS reference ranges.
*Results*: All mPGAS values had one 95% range boundary at 0.0%. Upper boundaries of 1D +apPGAS values ranged from 0.0% (HC) to +0.49% (ThC) and were +0.06%, +2.3% and +1.8% for EWT, AVol and TVol, respectively. Comparable values for −apPGAS were 0.0% (BPD, FDL, HDL), to −0.58% (ArmC), −0.13% (EWT), −0.8% (AVol), and 0.0% (TVol). The +cPGAS, 95% reference range upper boundaries varied from +0.36% (c1b) to +0.89% (c2). Comparable values for −cPGAS lower boundaries were −0.17% (c1b) to −0.43% (c2).
*Conclusions*: The original PGAS concept has now been extended to individual biometric parameters and their combinations. With the standards provided, mPGAS values can now be tested to see if detection of different types of third trimester growth problems is improved.

**Keywords**

Individualized growth assessment, pregnancy, Rossavik models, size standards

**History**

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## Introduction

In current clinical practice, fetal growth in the third trimester is most commonly evaluated by determining estimated fetal weight (EFW) [1–5]. Previous investigators have established weight estimation functions [6–18], developed EFW standards [19–43] and used EFW to predict neonatal outcomes [4,44–79]. However, several studies using Individualized Growth Assessment (IGA) have reported that in different fetuses and neonates, growth abnormalities affect anatomical parameters (ap) other than EFW [80–94].

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The Prenatal Growth Assessment Score (PGAS) was developed to solve this problem, utilizing a set of anatomical measurements (head circumference (HC), abdominal circumference (AC), femur diaphysis length (FDL), mid-thigh circumference (ThC) and estimated weight (EWT)) [95]. As originally defined, the PGAS was based on positive or negative pathological percent deviations (+% $Dev_p$, −% $Dev_p$ (Figure 1)) [95]. All % Dev values below the upper boundary (+% $Dev_p$ calculation), or above the lower boundary (−% Dev calculation), of a reference range were assigned a % $Dev_p$ value of zero. The average of all available +% $Dev_p$ or −% $Dev_p$ values (up to the time in pregnancy being evaluated) was defined as either the $+PGAS_{At}$ or $-PGAS_{At}$. The PGAS values for the entire third trimester were designated $+PGAS_{AT}$ or $-PGAS_{AT}$.

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Figure 1. Definition of pathological Percent Deviations. Positive and negative parts of the age-specific reference range for a given anatomical parameter were subtracted from the Percent Deviation value to give the +% $Dev_p$ and −% $Dev_p$ values.

The original PGAS was capable of detecting different types of fetal growth problems except those limited to only soft tissue abnormalities [82,95]. Moreover, it is limited by reference ranges determined from all 3rd trimester data without regard for age-specific differences [96] and it was initially proposed for only one combination of ap [95]. Equal weight is given to each component of this combination. In a recent IGA evaluation of fetal growth with normal neonatal growth outcomes, methods for calculating age-specific % Dev reference ranges were developed, allowing evaluation of % Dev values for an ap at individual third trimester time points [94]. This new capability makes it possible to follow the development of growth problems in specific anatomical structures [e.g. HC in hydrocephalus] on an individualized basis [use of % $Dev_p$]. With the addition of new soft tissue measurements [88–90] and a new weight estimation procedure [97] to our biometric measurements, it is now possible to explore how new combinations of size parameters can be used to evaluate growth abnormalities. Growth studies in both fetuses [86] and neonates [87,98], as well as the known biology of growth abnormalities [99–110], have shown that some ap are more frequently affected in different pathological states and therefore are more important in detecting either IUGR or Macrosomia [93,111–115]. A more suitable PGAS would be one that had a specific weighting factor for each ap, reflecting its importance in identifying different types of abnormal growth.

The main objective of this investigation was to re-define the PGAS so that a variety of single and composite size parameters could be utilized in evaluating fetal growth abnormalities. We also wanted to enable future use of different weighting factors for ap and provide new modified Prenatal Growth Assessment Scores (mPGAS) reference ranges for individual ap and their combinations.

## Methods

### Data

The data used for this investigation were obtained in a previous longitudinal study of size parameters in fetuses with normal neonatal growth outcomes, as determined from the modified Neonatal Growth Assessment Score (a composite neonatal size parameter [87,116]) and a sample-specific reference range [94]. The $m_3NGAS_{51}$ values were calculated from predicted and measured neonatal head circumference (HC), abdominal circumference (AC), mid-thigh circumference (ThC), crown-heel length (CHL) and weight (WT) values obtained as previously described [87]. As specified previously [87], the $m_3NGAS_{51}$ is the third mNGAS studied, contains five size variables and would be the first of a set of mNGAS's containing five variables if there were more than five variables.

Serial ultrasound examinations were carried out from approximately 18 weeks to 38 weeks, menstrual age (MA) (6–7 scans/fetus). Measurements of the HC, AC, FDL, ThC, biparietal diameter (BPD), humerus diaphysis length (HDL) mid-arm circumference (ArmC), fractional arm volume (AVol) and fractional thigh volume (TVol) were obtained at each scan using previously described methods [94]. Head cubes (Hcube) and abdominal cubes (Acube) were calculated from respective profile diameter measurements (see Appendix for calculations and profile diameter estimation procedures). EWT was calculated from Hcube and Acube values ($EWT_a$) [117] and from BPD, AC and TVol measurements ($EWT_b$) [97]. Fetal age was primarily determined from first trimester crown-rump length (CRL) measurements [94].

In the second trimester, Rossavik size models [$P = c(t)^{k+st}$] were specified by determining values for the coefficients c, k and s for each ap in every fetus using the methods described by Deter et al. [118]. The time variable $t$ was defined as the MA minus the start point [SP]: $t = MA - SP$ where the SP was calculated from the coefficients of the linear function fit the data obtained before 28.2 weeks, MA [$SP = -a_0/a_1$] [118]. These models were used to generate predicted 3rd trimester size trajectories for all ap in each fetus. Third trimester size measurements were compared to those predicted and % Dev's calculated using the following equation [86]:

$$\% \text{ Dev} = ((\text{measured value} - \text{predicted value}) / \text{predicted value}) \times 100$$

### Data analysis

*Generation of mPGAS values*

Percent deviation variance components, obtained using two-level random coefficient modeling [94], and the function of Royston [119] were used to generate age-specific variances ($Var_{Ti}$) (see additional details in Supplementary File S1).

The age-specific 95% reference range (95% $rr_i$) is then given by the following function:

$$95\% \ rr_i = \pm 2(Var_{Ti})^{0.5} \quad (1)$$

The positive and negative parts of the age-specific reference range for a given ap were subtracted from the percent deviation value to give the +% $Dev_p$ and −%$Dev_p$ values (Figure 1).

$$+\% \ Dev_{pi} = \%Dev_i - (+rr_i) \quad (2)$$

$$-\%Dev_{pi} = \%Dev_i - (-rr_i) \quad (3)$$

If the +% $Dev_{pi}$ had a negative value, it was set equal to zero, as were the positive −% $Dev_{pi}$ values. The +% $Dev_{pi}$ and −% $Dev_{pi}$ values of a specific ap for a given fetus (j) at individual time points [i] were designated $+\text{iapPGAS}_j$ and $-\text{iapPGAS}_j$ (definitions of all mPGAS's are given in Table 1). These two classes of $\text{iapPGAS}_j$ values were averaged to give the $+\text{apPGAS}_j$ and $-\text{apPGAS}_j$ values for the specified fetus over the entire 3rd trimester (Table 1).

To obtain $+\text{cPGAS}_j$ and $-\text{cPGAS}_j$ values for different combinations of anatomical parameters (Table 1: c1a, c1b, c2, c3), the $\text{apPGAS}_j$ values for the specified parameters were averaged. During pregnancy, +cPGAS and −cPGAS were calculated at each time point ($+\text{icPGAS}_j$, $-\text{icPGAS}_j$) using $\text{iapPGAS}_j$ values.

*Reference ranges*

The 95% reference ranges for positive and negative apPGAS's were determined for the 10 anatomical parameters studied. Since both types of apPGAS's have one limit at zero, the other limit was defined by sorting positive and negative values by size and then identifying the boundary that eliminated the largest 5% (in absolute value) (Figure 1). The 95% reference ranges for four composite PGAS values, c1aPGAS, c1bPGAS, c2PGAS and c3PGAS (see Table 1 for definitions), were determined in a similar manner.

The relationships of iapPGAS values to MA were evaluated with linear correlation. The use of reference ranges based on all 3rd trimester values (apPGAS) for evaluating iapPGAS's at different time points was tested by determining how many values were considered abnormal with these reference ranges. Similar assessments of ic1bPGAS's and ic2PGAS's calculated at different time points in the 3rd trimester were carried out as these cPGAS values were considered to be the most and least reliable representatives of the cPGAS's.

## Results

### Anatomical parameter prenatal growth assessment scores (apPGAS)

As shown in Table 2, the upper limits of the +apPGAS 95% reference ranges were between 0.0% [HC] and 0.49% [ThC] with the exceptions of AVol (2.30%) and TVol (1.76%). For

Table 1. Definitions of Modified Prenatal Growth Assessment Scores.

| PGAS Parameter | Abbreviation | Definition |
|---|---|---|
| Individual anatomical parameter | iapPGAS | Pathological Percent Deviation [% $\text{Dev}_p$] for a given anatomical parameter at a specified third trimester time point (can be positive or negative) |
| Anatomical parameter | apPGAS | Mean value of the % $\text{Dev}_p$ values obtained during the third trimester for a specific anatomical parameter (can be positive or negative) |
| Individual composite | icPGAS | Mean value of the % $\text{Dev}_p$ values obtained at a specified third trimester time point for a set of anatomical parameters (can be positive or negative) |
| Composite groups | cPGAS | Mean value of the % $\text{Dev}_p$ values obtained during the third trimester for a specified set of anatomical parameters (can be positive or negative)<br>c1aPGAS<br>HC, AC, ThC. FDL, $\text{EWT}_a$ (Hcube, Acube)<br>c1bPGAS<br>HC, AC, ThC. FDL, $\text{EWT}_b$ (BPD, AC, TVol)<br>c2PGAS<br>ArmC, AVol, ThC and TVol<br>c3PGAS<br>HC, AC, FDL, EWTa (Hcube, Acube) |

BPD = biparietal diameter, HC = head circumference, AC = abdominal circumference, FDL = femur diaphysis length; ThC = mid-thigh circumference; TVol = fractional thigh volume; EWT = estimated weight; Hcube = (head short axis × head long axis)$^{1.5}$; Acube = (abdominal short axis × abdominal long axis)$^{1.5}$; +% $\text{Dev}_p$ and −% $\text{Dev}_p$ : component of % Deviation outside upper and lower limits of age-specific % Deviation reference range, respectively.

Table 2. Anatomical Parameter Prenatal Growth Assessment Scores (apPGAS).

| Parameter | *N* | 95% Range +apPGAS % | 95% Range −apPGAS % | No. Scans | Percent excluded +iapPGAS % | Percent excluded −iapPGAS % |
|---|---|---|---|---|---|---|
| BPD | 117 | 0.0 to +0.38 | 0.0 to −0.00 | 400 | 2.8 | 1.0 |
| HC | 117 | 0.0 to +0.00 | 0.0 to −0.11 | 400 | 1.1 | 2.5 |
| AC | 118 | 0.0 to +0.02 | 0.0 to −0.05 | 403 | 2.0 | 2.5 |
| FDL | 117 | 0.0 to +0.27 | 0.0 to −0.00 | 401 | 3.7 | 1.0 |
| ThC | 113 | 0.0 to +0.49 | 0.0 to −0.04 | 388 | 2.3 | 1.8 |
| HDL | 118 | 0.0 to +0.08 | 0.0 to −0.00 | 402 | 2.2 | 1.7 |
| ArmC | 118 | 0.0 to +0.17 | 0.0 to −0.58 | 402 | 2.5 | 3.0 |
| AVol | 118 | 0.0 to +2.30 | 0.0 to −0.80 | 402 | 3.7 | 1.7 |
| TVol | 118 | 0.0 to +1.76 | 0.0 to −0.00 | 403 | 3.5 | 1.2 |
| EWT | 117 | 0.0 to +0.06 | 0.0 to −0.13 | 399 | 2.0 | 2.3 |

BPD = biparietal diameter, HC = head circumference, AC = abdominal circumference, FDL = femur diaphysis length; ThC = mid-thigh circumference; TVol = fractional thigh volume; EWT = estimated weight; *N* = number of subjects scanned; −apPGAS and +apPGAS refers to mean values of % $\text{Dev}_p$ values for a specific anatomical parameter (positive or negative); +iapPGAS and −iapPGAS refer to pathological Percent Deviation [% $\text{Dev}_p$] for a given anatomical parameter at a specified third trimester time point [positive or negative]; 95% reference ranges were determined by sorting. Percent excluded: proportion of iapPGAS values excluded from the reference range using apPGAS reference range values.

the −apPGAS, the lower boundaries of the 95% reference ranges varied from 0.0% [BPD, FDL, HDL, TVol] to −0.58% [ArmC], with boundary values for the 3D parameters that were similar to those for the 1D parameters.

Linear correlations of +iapPGAS values against MA were not statistically significant except for ArmC [R: −0.11]. For −apPGAS, only those for HC [R: −0.11] and ArmC [R: −0.12] were statistically significant. Table 2 presents the proportion excluded if the apPGAS reference ranges were used as the boundaries between normal and abnormal values at all MAs. For +iapPGAS, the excluded proportion varied from 1.1% to 3.7%. Comparable values for −iapPGAS were from 1% to 3%. A smaller proportion of −iapPGAS values were excluded for 6/10 anatomical parameters but these differences between +iapPGAS and −iapPGAS were small.

## Composite prenatal growth assessment scores (cPGAS)

Table 3 presents the reference ranges for the four composite PGAS's [c1aPGAS, c1bPGAS, c2PGAS, c3PGAS]. The first combination [HC, AC, ThC, FDL, EWT (Hcube, Acube)] is essentially the same as the original PGAS [95] and had 95% reference ranges of 0.0% to +0.39% for +c1aPGAS and 0.0% to −0.18% for −c1aPGAS. The second combination (the same as c1aPGAS except that EWT (Hcube, Acube) was replaced by EWT (BPD, AC, TVol)) had 95% reference ranges of 0.0% to +0.36% and 0.0% to −0.17% for +c1bPGAS and −c1bPGAS, respectively. For the soft tissue combination [c2PGAS], composed of ArmC, AVol, ThC and TVol, the corresponding 95% reference ranges were 0.0% to +0.94% and 0.0% to −0.43%. Finally, the conventional biometry composite PGAS [c3PGAS] had 95% reference ranges for +c3PGAS and −c3PGAS of 0.0% to +0.45% and 0.0% to −0.19%. As can be seen, all reference range boundaries were less than 1.0%.

There were 385 time points in 112 fetuses that had complete sets of measurements for calculating ic1bPGAS values. For +ic1bPGAS, the upper boundary of the 95% reference range was +0.38% while for −ic1bPGAS, the lower boundary of the 95% reference range was −0.14%. In Figure 2, the ic1bPGAS values are plotted against fetal age at the time of scan. The upper boundary of the +c1bPGAS and lower boundary of the −c1PGAS are shown as interrupted lines. Linear correlations were not significant for either +ic1bPGAS or −ic1bPGAS and the c1bPGAS boundaries excluded 5.0% of the +ic1bPGAS values and 3.1% of the −ic1bPGAS values, respectively (Table 3).

The ic2PGAS values could be calculated at 387 time points in 113 fetuses. For +ic2PGAS, the upper boundary of the 95% reference range was +1.3%. For −ic2PGAS, the lower boundary of the 95% reference range was −0.24%. In Figure 2, the ic2PGAS values are plotted as a function of fetal age at the time of scan. Linear correlations were not statistically significant for either +ic2PGAS or −ic2PGAS. Use of the upper boundary of the +c2PGAS excluded 6.7% of the +ic2PGAS values while use the lower boundary of −c2PGAS excluded 4.4% of the −ic2PGAS values (Table 3).

Table 4 gives examples of mPGAS values for fetuses with normal and abnormal 3rd trimester growth (* denotes the pathological values). The −iapPGAS values for different anatomical parameters are presented, together with the −ic1aPGAS values (far-right column) at specific third trimester time points. The last row of each table gives the −apPGAS values for different anatomical parameters at the end of the 3rd trimester. The average of all 3rd trimester −apPGAS values (−c1aPGAS) is presented in the lower, far-right corner. Differences between normal and abnormal growth are clearly illustrated, as is the evolution of growth abnormalities in different size measures.

## Discussion

### Principal findings of this study

This investigation defines different types of mPGAS for ten anatomical parameters and four combinations of these parameters. Using data from a previous study in fetuses with normal neonatal growth outcomes, reference ranges for the mPGAS at individual 3rd trimester time points [+iapPGAS, −iapPGAS], and at the end of the third trimester [+apPGAS, −apPGAS] were established for each anatomical parameter. Reference ranges for composite mPGAS's, both at individual 3rd trimester time points [+icPGAS, −icPGAS] and at the end of the third trimester [+cPGAS, −cPGAS] were also determined. This mPGAS system has been partially implemented as part of a freely available software download (iGAP) that can be accessed at http://igap.research.bcm.edu.

#### *Previous studies of PGAS*

Only two studies [82,95] have provided boundary values for a cPGAS and only lower limit values for −c1aPGAS were defined. Our 95% lower boundary of −0.18% was in

Table 3. Composite Prenatal Growth Assessment Scores (cPGAS).

| Parameter | N | 95% Range +cPGAS % | 95% Range −cPGAS % | No. Scans | Percent excluded +icPGAS % | Percent excluded −icPGAS % |
|---|---|---|---|---|---|---|
| c1a | 112 | 0.0 to +0.39 | 0.0 to −0.18 | – | – | – |
| c1b | 112 | 0.0 to +0.36 | 0.0 to −0.17 | 385 | 5.0 | 3.1 |
| c2 | 113 | 0.0 to +0.89 | 0.0 to −0.43 | 387 | 6.7 | 4.4 |
| c3 | 112 | 0.0 to +0.45 | 0.0 to −0.19 | – | – | – |

BPD = biparietal diameter, HC = head circumference, AC = abdominal circumference, FDL = femur diaphysis length; ThC = mid-thigh circumference; TVol = fractional thigh volume; EWT = estimated weight; $N$ = number of subjects scanned; c1a = HC, AC, ThC. FDL, $EWT_a$ (Hcube, Acube); c1b = HC, AC, ThC. FDL, $EWT_b$ (BPD, AC, TVol); c2 = ArmC, AVol, ThC and TVol; c3 = HC, AC, FDL, EWT (Hcube, Acube); Hcube = (head short axis × head long axis $)^{1.5}$; Acube = (abdominal short axis × abdominal long axis$)^{1.5}$; 95% reference ranges were determined by sorting.

agreement with previous boundary values [−0.24%, −0.4%]. The 95% lower boundary of −c1bPGAS [−0.17%] observed in this investigation was also consistent with the −c1aPGAS lower boundary values. The upper boundaries of both +c1aPGA and +c1bPGAS [+0.39%,+0.36%] were similar. The 95% lower boundary of −c2PGAS [−0.38%] was close to those for −c1aPGAS but the 95% upper boundary for +c2PGAS [+0.74%] was somewhat higher. c3PGAS upper

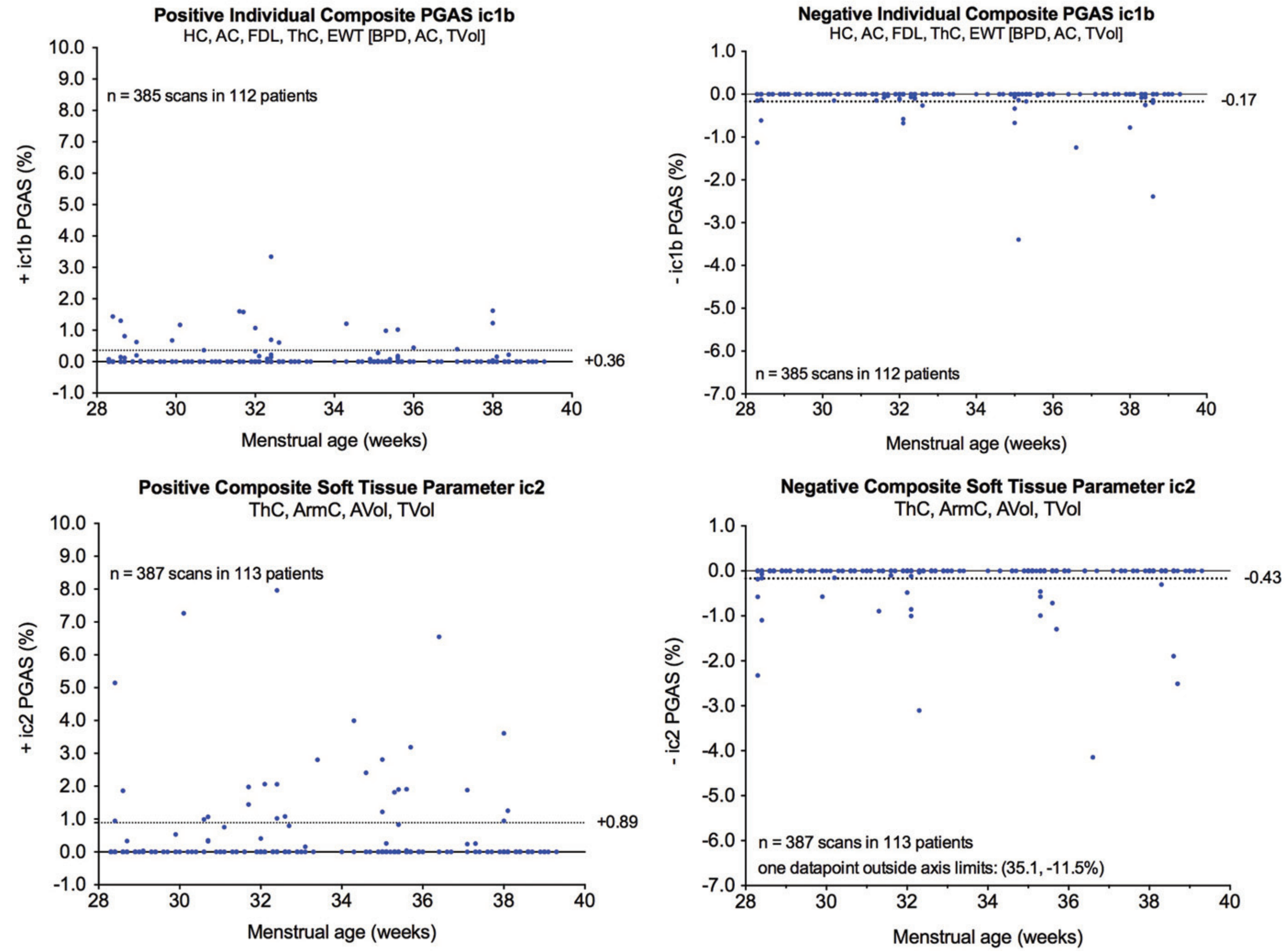


Figure 2. Evaluation of individual composite PGAS values for ic1bPGAS and ic2PGAS. These specific examples demonstrate composite parameters that include at least one soft tissue component such as fractional arm volume (AVol), fractional thigh volume (TVol), mid-arm circumference (ArmC), and mid-thigh circumference (ThC).

Table 4. Fetal growth evaluation using mPGAS.

| MA weeks | −ihcPGAS§ % | −iacPGAS % | −ifdlPGAS % | −ithcPGAS % | −iewtPGAS % | | −ic1aPGAS† % |
|---|---|---|---|---|---|---|---|
| Fetus 1: Normal growth in the third trimester | | | | | | | |
| 28.3 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | | 0.00 |
| 32.3 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | | 0.00 |
| 35.3 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | | 0.00 |
| 38.1 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | | 0.00 |
| −apPGAS‡ | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | −c1aPGAS¶ | 0.00 |
| Fetus 2: IUGR in the third trimester | | | | | | | |
| 27.7 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | | 0.00 |
| 30.7 | −1.40* | −4.76* | 0.00 | −0.63* | −1.30* | | −1.62* |
| 32.7 | 0.00 | 0.00 | 0.00 | −5.27* | 0.00 | | −1.05* |
| −apPGAS | −0.47* | −1.59* | 0.00 | −1.97* | −0.33* | −c1aPGAS | −0.87* |

*Abnormal values.
†–ic1aPGAS: average of the five −iapPGAS values at specific time points
‡–apPGAS: average of all −iapPGAS values for specified anatomical parameter.
¶–c1aPGAS: average of the five −apPGAS values.
§–iapPGAS: negative individual Prenatal Growth Assessment Score for different anatomical parameters (ap).

and lower boundaries were similar to those for c1aPGAS and c1bPGAS. All boundary values were less than 1%. These results suggest that cPGAS values will be sensitive indicators of growth abnormalities.

### *Modified PGAS for individual anatomical parameters (apPGAS)*

Originally, PGAS was designed for size assessments involving a combination of anatomical parameters [95]. Results from our current investigation demonstrate that the concept underlying PGAS [evaluation of pathological % Dev's [95] can now be extended to individual anatomical parameters. The use of apPGAS boundaries (more reliable since they based on means of iapPGAS values obtained during the 3rd trimester) excluded less than 5% of the iapPGAS values, indicating that they represent conservative criteria for detecting abnormal iapPGAS values. A quantitative, overall assessment of 3rd trimester growth is now provided for individual anatomical parameters by the apPGAS's. Sequential calculation of +apPGAS and −apPGAS values after each time point studied provides a running summary of individual parameter growth processes during the third trimester.

### *Modified PGAS for specified sets of anatomical parameters (cPGAS)*

Given the heterogeneity of growth abnormalities [86], using sets of anatomical parameters may be more effective in evaluating such problems since different anatomical parameters are sensitive to different types of growth abnormalities [86,87,99–101,120–127] (Table 1). The original, global PGAS [c1aPGAS] was effective in identifying twins with IUGR unless only soft tissue was affected [82,95]. This latter type of growth problem may now be detected using our new soft tissue PGAS [c2PGAS]. Detection of early changes in soft tissue occurring in IUGR and Macrosomia [98,99,128–130] could be important in the prediction of subsequent metabolic and cognitive abnormalities in children and adults. A recent study has shown that term SGA neonates with normal umbilical Doppler findings have increased risks for axonal loss and cognitive deficits at 6 years of age [131].

### *Modified PGAS for individual sets of anatomical parameters (icPGAS)*

The icPGAS provides a means for quantitatively assessing size at a specific time point using any set of anatomical parameters. By averaging the icPGAS values obtained at all-time points up to the current scan, one obtains a running summary of how the type of growth represented by the set of anatomical parameters is progressing. The use of icPGAS during the 3rd trimester requires definition of a boundary between normal and abnormal values. The use of the boundaries for the cPGAS reference ranges at the end of the 3rd trimester provide conservative criteria for detecting abnormal fetal growth based on individual composite PGAS values at different third trimester time points.

## Novel aspects of this investigation

This evaluation of fetal growth is based on IGA (each fetus is its own control) that accounts for differences in growth potential and minimizes variability between fetuses. The primary measure, pathological % Dev's, takes into account the normal variation associated with each measurement of a % Dev. As reference ranges are now provided for both single and combinations of ten anatomical parameters, at specific time points and at the end of the 3rd trimester, the mPGAS system gives new options for analyzing fetal growth patterns.

## Study limitations

This investigation was limited by the unavailability of pathological cases. These cases are needed to determine weighting factors for the components of composite mPGAS's. Accordingly, the optimal mPGAS values for separating normally growing fetuses from those with growth abnormalities cannot be established.

## Implications for research and clinical care

By adjusting for differences in growth potential and minimizing variability at individual 3rd trimester time points, the mPGAS provides a versatile tool for evaluating fetal growth abnormalities. The characterization of fetal growth abnormalities made possible by this approach could result in more specific links between growth abnormalities and perinatal complications. With such information, the clinician would have a better assessment of risk for fetuses with specific types of growth abnormalities. This should enhance clinical decision-making in these complicated pregnancies.

## Conclusions

A mPGAS has been used to evaluate third trimester pathological % Dev's values and the concept is now been extended to individual anatomical parameters and new combination of these parameters. This novel procedure permits the generation of scores for different sets of anatomical parameters at both specified time points and at the end of the third trimester. Third trimester reference ranges are also specified for both individual anatomical parameters and for four different sets of combined parameters. We hypothesize that the mPGAS will improve detection and monitoring of abnormal third trimester growth that is expressed differently in individual fetuses.

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## Declaration of interest

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## Appendix

### Estimation of head and abdominal profile diameters from conventional fetal ultrasound measurements

The application of IGA to EWT requires special weight estimation procedures. At present, only the two methods described by Deter et al. [117] and Lee et al. [97] have been used in IGA analyses. The former is based on measurements of Head Cube and Abdominal Cube parameters. This requires Head and Abdominal Profile Diameter measurements as the cubes are calculated in the following manner [132]:

$$\text{Hcube [before 26 wks, MA]} = (\text{HSA} \times \text{HLA})^{1.5};$$

$$\text{Hcube [after 26 wks., MA]} = (\text{BPD} \times \text{FOD})^{1.5}$$

$$\text{Acube} = (\text{ASA} \times \text{ALA})^{1.5}$$

where HSA and ASA are the head and abdominal short axes, HLA and ALA are the head and abdominal long axes, and FOD is the fronto-occipital diameter. The method of Lee et al estimates fetal weight from measurements of the BPD, AC and TVol [97]. Both of these weight estimation procedures have similar reference ranges.

The Deter method is limited because profile diameters are usually not recorded, although available, when HC and AC measurements are made using an elliptical measurement tool. In the Lee method, a 3D ultrasound system must be used to measure TVol. To facilitate the use of IGA with EWT, a procedure for estimating profile diameters from conventional BPD, HC and AC measurements has been developed.

A study was carried out using 123 fetuses studied longitudinally (17–41 weeks, MA) as described previously [94]. The majority (68.3%) had normal neonatal growth outcomes and 993–994 measurements of BPD, HSA, HLA, FOD, HC, ASA, ALA, and AC (HC and AC measured using the elliptical tool) were available for analysis. Algebraic rearrangement and regression analysis, as described previously [133], were used to obtain the following equations for generating estimates of the needed diameters:

$$\text{estimated HSA} = 0.09071 + (1.03216 \times \text{BPD}) \quad R^2 = 99.5\%$$

$$\text{estimated HLA} = 0.79884((\text{HC}^2/4.9298) - \text{estimated HSA})^{1/2}$$

$$\text{estimated FOD} = 0.29737 + (0.91567 \times \text{estimated HLA}) \quad R^2 = 98.3\%$$

$$\text{estimated abdominal mean diameter (AMD)} = \text{AC}/3.14$$

$$\text{estimated ASA} = 0.13993 + (0.920513 \times \text{estimated AMD}) \quad R^2 = 96.5\%$$

$$\text{estimated ALA} = 0.02208 + (1.01794 \times \text{estimated AMD}) \quad R^2 = 97.7\%$$

These head and abdominal diameter estimates are used to calculate Hcube and Acube parameters, which can then be used to estimate weight when direct diameter measurements are not available for this purpose.