Second Trimester Estimated Fetal Weight and Fetal Weight Gain Predict Childhood Obesity

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Objective To determine the extent to which fetal weight during mid-pregnancy and fetal weight gain from mid-pregnancy to birth predict adiposity and blood pressure (BP) at age 3 years.

Study design Among 438 children in the Project Viva cohort, we estimated fetal weight at 16-20 (median 18) weeks' gestation using ultrasound biometry measures. We analyzed fetal weight gain as change in quartile of weight from the second trimester until birth, and we measured height, weight, subscapular and triceps skinfold thicknesses, and BP at age 3.

Results Mean (SD) estimated weight at 16-20 weeks was 234 (30) g and birth weight was 3518 (420) g. In adjusted models, weight estimated during the second trimester and at birth were associated with higher body mass index (BMI) z-scores at age 3 years (0.32 unit [95% CI, 0.04-0.60 unit] and 0.53 unit [95% CI, 0.24-0.81 unit] for the highest vs lowest quartile of weight). Infants with more rapid fetal weight gain and those who remained large from mid-pregnancy to birth had higher BMI z-scores (0.85 unit [95% CI, 0.30-1.39 unit] and 0.63 unit [95% CI, 0.17-1.09 unit], respectively) at age 3 than did infants who remained small during fetal life. We did not find associations between our main predictors and sum or ratio of subscapular and triceps skinfold thicknesses or systolic BP.

Conclusion More rapid fetal weight gain and persistently high fetal weight during the second half of gestation predicted higher BMI z-score at age 3 years. The rate of fetal weight gain throughout pregnancy may be important for future risk of adiposity in childhood. *(J Pediatr 2012;161:864-70)*.

Human and animal studies suggest that developmental programming during critical periods of rapid growth, such as the prenatal period and infancy, influence the risk of cardiometabolic disease in later life.[1,2] Although many studies show that faster weight gain in early infancy predicts higher body mass index (BMI), higher blood pressure (BP), and increased risk for poor metabolic outcomes in childhood and adulthood,[3-6] there are few studies of the prenatal period.

Examining change in fetal weight is important because a single measure of weight at birth is inadequate to represent intrauterine weight gain patterns. For instance, an infant born at the 90th percentile at birth may represent a fetus who was large throughout gestation or one who gained weight rapidly only in the last trimester. Few studies have explored associations of fetal weight gain and childhood outcomes. In one study of Dutch children, no association was found between fetal weight gain during the third trimester and abdominal adiposity at age 2 years.[7] This study only measured change in fetal weight from the third trimester until birth. Measurements of fetal weight gain over both the second and third trimesters, reflecting a longer period of fetal growth may be more informative. No associations between static measures of fetal weight or change in fetal weight from the second trimester until birth and childhood systolic BP were found among children in the same cohort.[8]

A better understanding of the association of fetal weight gain and childhood outcomes may enable us to identify risk factors for obesity and high BP in the earliest stages of life. The purpose of this study was to evaluate the extent to which estimated fetal weight (EFW) in the second trimester and fetal weight gain from the second trimester until birth predict childhood obesity and BP. We hypothesized that more rapid fetal weight gain would be associated with higher BMI and BP in childhood as rapid weight gain in early infancy has similarly been associated with obesity and higher BP.[4,5]

AC	Abdominal circumference
AD	Abdominal diameter
BMI	Body mass index
BP	Blood pressure
BPD	Biparietal diameter
EFW	Estimated fetal weight
FL	Femur length
LMP	Last menstrual period

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Methods

We studied participants in Project Viva, a prospective, observational, cohort study of gestational diet, pregnancy outcomes, and offspring health.[9] The details of recruitment and retention procedures are available elsewhere.[9] All mothers provided written informed consent. The human subjects committees of Harvard Pilgrim Health Care, Brigham and Women's Hospital, and Beth Israel Deaconess Medical Center approved the study protocols. Of the 2128 women who delivered a live infant, we excluded 45 infants born < 34 weeks' gestation. Of the 2083 remaining women, 1653 (79%) had at least one fetal ultrasound at 16 to 20 weeks' gestation. To avoid using the ultrasound data for dating as well as growth, we excluded 203 women whose ultrasound indicated a gestational age that was ≥10 days of the predicted due date based on last menstrual period (LMP). Of those, we further excluded 678 whose ultrasound was missing one or more measures of fetal abdominal diameter (AD), biparietal diameter (BPD), or femur length (FL), which are measures needed to calculate EFW. Because these ultrasounds were clinical studies intended for a fetal survey to detect structural anomalies, most of the missing biometric data were due to missing AD (673 of 678). The BPD and FL for the 772 participants with all 3 measures were similar to those among the 678 participants we excluded (41.0 vs 39.9 mm and 26.8 vs 26.9 mm, respectively), suggesting no systematic bias by availability of biometric measures. Finally, 334 participants were missing measurements of BMI (kg/m^2) or BP (mm Hg) at age 3, yielding a final cohort of 438 mother-fetus-child subjects for analysis (**Figure 1**; available at www.jpeds.com). Compared with the participants missing age 3 outcome measures, the mothers in the final cohort were older (mean age 31.1 vs 30.1 years) and more likely to be married (92% vs 86%), to be college graduates (67% vs 51%), and to have household incomes >$70 000 (66% vs 53%). Children were more likely to be of white race (61% vs 51%). Other maternal and child characteristics, including maternal BMI, did not differ among included and excluded groups.

We abstracted measurements of AD, BPD, and FL from fetal ultrasounds obtained at 16-20 weeks' gestation and birth weight from the hospital medical record. We converted AD to abdominal circumference (AC) using the geometric formula: Circumference = πr^2. We calculated EFW using the formula by Hadlock et al: Log10 EFW = 1.335 − 0.0034(AC)(FL) + 0.0316(BPD) + 0.0457(AC) + 0.1623(FL).[10] We used this formula because it has previously been found to have the least bias and best precision in predicting measured weight at birth compared with 13 other formulas.[11]

During an in-person visit at age 3 years, trained research assistants weighed children with a digital scale (model 881; Seca, Hamburg, Germany) and obtained height and subscapular (SS) and triceps (TR) skinfold measurements using standardized techniques.[12] They used a standardized protocol to measure child BP with a Dinamap Pro100 (Critikon, Inc, Tampa, Florida) automated oscillometric recorder, taking up to 5 measurements 1 minute apart in each child. The child's position, activity level, the extremity used, cuff size, and measurement sequence number at the time of BP measurement were recorded. Research staff participated in biannual in-service training to ensure measurement validity (I.J. Shorr, MPS personal oral communication, 2004-2007). Interrater and intrarater measurement errors were within published reference ranges.[13]

Our main outcomes were adiposity and BP at age 3 years. We calculated age- and sex-specific BMI z-score using US national reference data[14] and used this measure as a continuous variable as well as examined obesity (age- and sex-specific BMI ≥95th percentile). We used the sum and ratio of SS and TR skinfold thicknesses to represent adiposity and central adiposity, respectively.[15] We used systolic BP at age 3 years as our main BP outcome because it predicts later BP better than diastolic BP and is measured with more validity in children.[16]

Mothers reported information about their age, education, household income, marital status, parity, duration of breastfeeding at 1 year, smoking status, and child sex and race/ethnicity in structured interviews and questionnaires. We calculated prepregnancy BMI (kg/m^2) from maternal self-report of height and prepregnancy weight. We calculated total gestational weight gain as the difference between the last recorded clinical weight before delivery and the self-reported prepregnancy weight. We previously reported the validity of self-reported prepregnancy weight in our cohort.[17] We categorized women as having gained inadequate, adequate, or excessive weight according to 2009 Institute of Medicine guidelines for weight gain during pregnancy.[18] We obtained glucose tolerance status based on glycemic screening from the medical record. Definitions of glucose tolerance status are described elsewhere.[19] We abstracted the first 3 maternal systolic BP levels after 28 weeks' gestation from the medical record and calculated the mean.

Statistical Analysis

Because weight is highly correlated with gestational age, we first adjusted EFW and birth weight for gestational age at each measurement time point. We then ranked EFW and birth weight into sex-specific quartiles, coded 1-4. To represent fetal weight gain, we created a 16-category variable according to quartile of second trimester EFW and birth weight, with participants in the lowest quartile of both EFW and birth weight as the reference group.

We examined bivariate relationships among our main exposures, other covariates, and our outcomes. For trend *P* values, we used Mantel-Haenszel χ^2 for categorical characteristics and linear regression for continuous outcomes. After testing model assumptions, we used multivariable linear and logistic regression models to examine independent associations of second trimester EFW, birth weight, and, separately, the change in fetal weight quartile from the second trimester until birth with our main outcomes. To estimate the associations with systolic BP at age 3 years, we used mixed-effects