The Association between Routine Measurements Recorded during Antenatal Care Visits and Delivery of Growth-Retarded Infants

Submitted by Group 8

On December 16, 2013

Comment [A1]: This is a VERY nice report.

Summary

In resource limited settings, abbreviated gestation and fetal growth retardation are the second leading cause of infant mortality. Low technology metrics are needed to identify women at increased risk for adverse pregnancy outcomes to facilitate referrals to specialized prenatal services. During antenatal visits, the progression of the pregnancy is monitored through repeated measurements, including changes in maternal weight and symphysis-fundal height (SFH). Using cohort data from South Africa (n=755 pregnant women), we evaluated the association between changes in SFH and maternal weight measurements taken between 20-30 weeks gestation and delivery of an infant that was preterm, low birth weight, or small for gestational age. This association was evaluated using descriptive statistics and multivariate logistic regression analysis.

The multivariate results found that, when holding age, height, parity, and smoking status constant, a one-unit increase in the mean rate of change in SFH was associated with a *halving* of odds of giving birth to a growth retarded infant. The 95% confidence interval suggested that these observed data would not be unusual if the true odds ratio was between 0.29 and 0.86. With a corresponding p-value of .01, we conclude that a statistically significant association exists between mean change in SFH and delivering a growth retarded infant. However, no significant association was observed between mean change in maternal weight and delivering a growth retarded infant (aOR=0.75; 95% CI= 0.37, 1.5; p=.4112). These preliminary analyses suggest that SFH measurements, in conjunction with other maternal characteristics, might have potential in identifying women at risk for delivering growth-retarded infants.

Comment [A2]: of whom ??? have relevant data between 20-30 weeks EGA

Comment [A3]: this one unit is not very relevant scientifically when evaluating associations—while there are some subjects who might have measurements approaching this, they are almost certainly measurement error

Comment [A4]: Actually, I think we have enough data from a cursory assessment to be able to say that this association is not sufficient to serve as the basis of a useful predictive model.

Background:

The second leading cause of infant mortality in resource limited settings is abbreviated gestation and fetal growth retardation (low birth weight and small for gestational age). Low birth weight (< 2.5 kilograms) is associated with an increased susceptibility to disease and risk for failure to thrive. Infants born pre-term (prior to 37 weeks of gestation) frequently meet criteria for low birth weight (LBW) and often have underdeveloped organ systems, which can lead to long-term medical problems. An infant born below the tenth percentile for size given the estimated gestational age (small for gestational age, or SGA) is also at risk for adverse neonatal health outcomes, whether or not the infant is pre-term.

Regular prenatal care is essential in order to monitor signs and symptoms that may be indicators of different complications and inform on additional treatment or care services necessary for the woman during pregnancy. Clinic visits occur regularly throughout pregnancy and increase in frequency in the third trimester. Routine prenatal care includes screening for conditions that might affect the health of the mother and fetus and monitoring maternal blood pressure, maternal weight, and fetal size. The latter is measured by the distance from the symphysis of the pelvic bones to the top of the uterus (the symphysis-fundal height or SFH), and it tends to increase linearly over time starting at about 20 weeks of gestation. Since these measurements are low cost and routinely collected, it is hoped that they might be used to identify women at risk for delivering a growth retarded (GR) infant so that they can be referred to specialized prenatal services in a timely manner.

Questions of Interest:

The overarching goal of this study is to reduce perinatal morbidity through optimizing prenatal care for women in the Western Cape, South Africa (and potentially other resource limited settings). The initial question posed by the client was "Is there evidence that weight profiles and/or SFH profiles over pregnancy differ between women who do and do not deliver pre-term, LBW, and SGA babies?" With the dataset provided, this analysis attempts to determine whether an association exists between the average ratio of change in either maternal weight or symphysis-fundal height to change in estimated gestational age (EGA) between 20 and 30 weeks of gestation and delivering an infant that is either preterm, low birth weight, or small for gestational age among women of similar age, height, parity, and smoking status. This analysis pursued a more specific question, in terms of its definitions of exposure, outcome, and subject, than the question initially posed by the client. Exposure is modeled as the mean rate of change in each measurement (weight or SFH) between 20 and 30 weeks rather than as a single measurement so as to more accurately reflect intrauterine *growth* (as opposed to intrauterine *size* at a single point in time). Outcome is modeled as a composite of the three outcomes specified because higher risk of any of the three would presumably result in referral to specialized care. It was also important to compare women who were similar with respect to potential confounding factors, including age, height, parity, and smoking status.

Comment [A5]: nicely stated

The client also asked: "Is it possible, using measurements taken prior to week 30 of pregnancy, to develop a model which accurately distinguishes between women who will and will not have growth retarded babies?" We provided a qualitative answer to this question, informed by results from the first analysis, and described how our modeling approach would differ had we created predictive models rather than associative models.

Methods

Source of data

Data was collected from a cohort study of 755 pregnant women with singleton pregnancies who could not afford private healthcare, just outside of an urban setting in the Western Cape, South Africa. The women were followed from enrollment (on average at 22 weeks gestation) until delivery. At enrollment, the participants' age, height, smoking status, and prior pregnancies was recorded. At enrollment and at each subsequent clinic visit, each woman's weight and symphysis fundal height (SFH) were recorded. A tape measure is used on a pregnant woman to determine the distance from the lowest to the highest part of their uterus, and this measurement is known as SFH. At delivery, the infant's birth weight, gestational age, sex, and SGA status were recorded.

Description of statistical methods (for manuscript)

Using descriptive statistics, the overall sample was characterized in terms of baseline maternal characteristics (maternal age, height, parity status, and smoking status), antenatal visits (gestational age at first visit, number of visits, number of visits between weeks 20 and 30, having at least 2 visits between weeks 20 and 30), and delivery outcomes (EGA at delivery, sex of infant, birth weight of infant, and percent of infants that were preterm, small for gestational age, and had a low birth weight). Continuous variables were summarized using the mean, standard deviation, minimum, and maximum values; categorical variables were summarized with a frequency and relative proportion. The number of missing values was reported for all variables. All subsequent analyses utilized a composite outcome variable that indicated whether the infant was pre-term, small for gestational age, or had a low birth weight. We repeated the descriptive analysis described above for mothers with and without a growth retarded infant.

To answer the primary question of whether changes in SFH and weight profiles are associated with having a GR infant, it was necessary to summarize longitudinal measurements of weight and SFH that were made during the 20th to 30th weeks of pregnancy. By definition, the mother must have had two or more antenatal visits during the 20^{th} to 30^{th} weeks in order to be assigned values for these derived parameters. We present descriptive statistics that compare mothers who did (87%) and did not (13%) have two or more antenatal visits between weeks 20 and 30, in terms of baseline and outcome characteristics. This comparison helps inform conclusions drawn from the subsequent analyses that excluded women who had <2 antenatal visits between weeks 20 and 30.

To answer the second question on the predictive value of the models, we qualitatively evaluated the goodness of fit of the model based on the Hosmer-Lemeshow[1] test of fit, which provides a table comparing the predicted and observed frequency for the data used to fit the model. Additionally, we interpreted the reduction in Akaike information criterion (AIC) of the full model compared with the base (intercept-only) model as an indication of the predictive value of the models. However, we deemed more precise quantitative evaluation of the predictive value of the models out of the scope of this project.

Comment [A6]: Just an editorial comment: While not incorrect to look at this, I personally find it not very useful. Like all such statistics, it gives false senses of security. Of course, you note this in your footnote

Comment [A7]: Similarly, I do not think this is particularly useful

The rate of change for each of the longitudinal measurements of SFH and weight was summarized in four slightly different ways, as described hereafter:

Comment [A8]: nicely explored and explained

- Minimum SFH/EGA: Minimum value that the ratio SFH/gestational age takes during the 20-30 weeks of pregnancy for each mother
- ΔSFH/ΔEGA: Change in SFH from the first to the last measurement during the 20-30 weeks divided by the number of weeks during which the measurements were taken
- LSE of SFH on EGA: The least square estimate of slope from linear regression of SFH on gestational age (in weeks) during the 20-30 weeks
- Minimum change rate SFH: Minimum of two rates of change in SFH: rate of change in SFH between the 1^{st} and 2^{nd} measurement and rate of change in SFH between 2^{nd} and 3^{rd} measurement during the 20-30 weeks of pregnancy. Each rate of change is defined as the ratio of change in SFH over the number of weeks during which the change occurred.

In parallel to the above four derived parameters, "Min. weight/EGA", "Δweight/ΔEGA", "LSE of weight on EGA" and "Minimum change rate weight" were derived to summarize the rate of change for the longitudinal series on mothers' weight. The crude association between each of these parameters and having a GR infant was then evaluated using descriptive statistics (mean, standard deviation, minimum, and maximum).

[1] For this qualitative analysis we solely relied on qualitative comparison of the expected and observed frequencies and did not factor in the test p-value which expectedly did not reject the hypothesis of a good fit.

Ultimately, the ΔSFH/ΔEGA and Δweight/ΔEGA was used as the predictor of interest based on which two multivariate logistic regression models were developed. Both models utilized the composite variable indicating having a growth retarded infant as the outcome. Maternal age (continuous), parity status (dichotomous 'no prior births, ≥ 1 birth), smoking status (dichotomous 'smoker/non-smoker'), and maternal height (continuous) were included in both models as potential confounders. No interaction terms were included in the models, because we did not, *a priori*, suspect that any of the available variables might modify the relationship between the predictors of interest and the outcome. Adjusted odds ratios and p-values were reported.

For our models which were built to study associations, we assumed independent observations. Additionally, we used robust estimates of variance for our inference to avoid the assumption of homoscedasticity. Lastly, we deemed our sample size large enough with sufficiently large number of cases observed. Given the stated assumptions and beliefs about our models, we consider them appropriate for studying the association question posed by the client.

Comment [A9]: in logistic, it is an assumption of model fit, because this relaxes the mean-variance based estimates of SE.

Three statistical software packages were used in this analysis. Summarization of longitudinal measurements was done in R, version 3.0.2. Statistical analyses were performed using Statistical Analysis Software (SAS), version 9.2 (SAS Institute, Cary, NC) and STATA, version 13.1 (StataCorp, College Station, Texas)

Philosophy behind analytic decisions

The analysis was based upon a composite outcome variable that summarized whether the infant born was pre-term, small for gestational age, or had low birth weight. We decided to use a composite variable rather than evaluating each of these three outcomes, because being at-risk for any one of the adverse birth outcomes should presumably result in referral to specialized care. Additionally, having one model that assessed the relationship between the predictors of interest and an adverse event would be more straightforward than three separate models that assessed three different, but closely related, adverse events.

Comment [A10]: yes

Of the five women who were missing data on pre-term delivery, two had SGA infants. We coded these women as having a growth retarded baby; the remaining three women who were either missing information for SGA or had null values for SGA were not assigned an outcome value and were excluded from all bivariate and multivariate analyses.

The decision to utilize ΔSFH/ΔEGA and Δweight /ΔEGA was made as this measure was expected to be a good approximation for the rate of change in SFH. At the same time this ratio is intuitive, easy to compute and record even onsite by the care providers.

Interpretation of parameter estimates, p-values, and confidence intervals

Inference on the association between predictors of interest (weight and SFH profiles) and having a growth retarded infant will be based largely upon results from the multivariate logistic regression models. Determination of whether the adjusted odds ratio is statistically significant will be made using a 2-sided 0.05 level test. A significant odds ratio (OR) for the ratio of the ΔSFH/ΔEGA and Δweight/ΔEGA will be interpreted as data not being inconsistent with the existence of an association between the ratio of change and the odds of having growth retarded infants. The magnitude of the estimate will be viewed as the expected factor by which the odds of having a growth retarded infant scales when comparing any two groups of mothers who are only differing in their value of ΔSFH/ΔEGA or Δweight /ΔEGA by 1 unit. The precision of the parameter estimates will be represented with a 95% confidence intervals.

Results

<u>Association between weight or SFH profiles over pregnancy and delivery of growth-retarded infants</u>

Sample Description

The cohort consisted of 755 pregnant women receiving prenatal care in a peri-urban public health setting. Descriptive statistics for the entire cohort are presented in Table 1. Women were enrolled from 15 weeks of gestation to 39 weeks of gestation (mean 22.5±4.0) and were followed until they gave birth. The women ranged in age from 14 to 43 years old with a mean age of 24.8 (±5.4) years. Two hundred thirty one (31%) women were smokers; drinking and illicit drug use status was unknown. All were pregnant with a single fetus at the time of enrollment. Four hundred sixty two (61%) had given birth previously; 240 (32%) had one, 133 (17%) had two, and 89 (12%) had three or more previous pregnancies. Total previous pregnancies ranged from 0-6 with a mean of 1(±1). No information was available on complications or outcome of previous pregnancies.

Women were seen in the clinic for an average of 7.7 (± 2.3) visits (range: 2-14). In order to address the question posed, we focused on data obtained during visits occurring between 20 and 30 weeks of gestation. Specifically, in order to model proxies for intrauterine growth, we required measurements taken from at least two visits during this period. The cohort as a whole had an average of 2.9 (±1.3) visits during this period (range: 0-8), while 658 (87.2%) women had two or more visits between 20 and 30 weeks. The primary analysis focused on this subset. Women excluded from further analysis for having less than 2 visits during the weeks 20-30, had similar mean values for age, height, and parity to their counterparts. However, slight difference was observed with respect to smoking history and birth outcomes between the groups with the excluded mothers having slightly lower smoking rate (22.7% vs. 32.0%) and also lower rate of GR infants (9.3 vs. 14.7)

The cohort gave birth at a mean gestational age of 39.2 (±1.5) weeks. The earliest delivery occurred at 30 weeks, whereas the latest occurred at 44 weeks. Twenty four (3.2%) were born pre-term (prior to 38 weeks). Three hundred sixty eight (49.1) of the babies born were female. Mean birth weight of the infants was 3.1 kg (± 0.5, range 1.0-4.7). Seventy five infants (10%) met criteria for low birth weight (< 2.5 kg), while a slightly higher number (n=105, 13.9%) were small for gestational age. The infants that were small for gestational age were inclusive of those who were pre-term and met criteria for low birth weight, therefore there were 105 total women who gave birth to growth retarded infants.

Comparison of Mothers with and without Growth Retarded Infants

The 105 mothers of growth retarded infants were compared to the 647 women who gave birth to term, normal-weight infants (Table 3). Women in the former group were, on average, slightly younger (23.8 ±4.9 years vs. 24.9 ±5.4 years), slightly shorter (154.6 ±5.9 cm vs. 157.0 ±6.5 cm), and were more likely to smoke (43% vs. 29%). Women in both groups had, on average, one previous pregnancy, and each group contained women with the full range of previous pregnancies (0-6). The women who did not give birth to a growth retarded infant had, on average, a higher number of total clinic visits (7.8 ±2.2 vs. 7.1 ±2.6) but a slightly lower number of average visits between 20 and 30 weeks (2.9 ±1.3 vs. 3.1 ±1.2). A slightly higher proportion of mothers without a growth retarded infant than with were excluded from the analysis due to missing visits (14.7% vs. 9.3%). Women who had a growth retarded infant gave birth between 30 and 42 weeks at a mean gestational age of 37.9 ±2.2 weeks. Women who did not have a growth retarded infant gave birth at term or later (38-44 weeks, mean 39.4 ±1.2 weeks). There was a higher percentage of female infants in the growth retarded group (59% vs. 48%).

Comparison of Derived Parameters that Summarize Changes in SFH and Maternal Weight Profiles

Various methods for calculating rate of change in SFH and maternal weight in women who did and did not give birth to a growth retarded infant and who had at least 2 clinic visits between 20 and 30 weeks of gestation are displayed in Table 4. Women who had a growth retarded infant demonstrated lower rates of both SFH increase and weight gain regardless of the method of calculation. Thinking ahead to the potential for clinical utility, the mean overall rate of change in SFH and weight between 20 and 30 weeks was chosen for subsequent analyses due to its simplicity and ease of calculation.

Crude and Adjusted Measures of Association between Mean Rate of Change in Symphysis-Fundal Height and Bearing a Growth Retarded Infant

Both groups had positive mean rates of change in fundal height (Table 4). Mothers who did not have a growth retarded infant had a ΔSFH/ΔEGA of 1.04±0.4, which was 0.14 units higher than those who did (0.91±0.4, Table 4). The results of a multivariate logistic regression analysis of the association between giving birth to a growth retarded infant and mean rate of change in fundal height between weeks 20 and 30, controlling for maternal age and height, multiparity (previous pregnancy vs. first pregnancy) and smoking status are shown in Table 5. A one-unit increase in the ΔSFH/ΔEGA was associated with 0.50 the odds of giving birth to a growth retarded infant, holding age, height, parity, and smoking status constant. From a 95% confidence interval calculated using robust standard errors, the data observed would not be unusual if the true odds ratio was between 0.29 and 0.86. This association was significant with a p value of 0.01, therefore we reject the null hypothesis of no association between ΔSFH/ΔEGA and birth outcome in women of the same age, height, parity and smoking status. Increased age and height were both significantly associated with slightly decreased odds of poor birth weight outcome, whereas smoking was significantly associated with nearly twice the odds of having a growth retarded infant. Having had a previous child appeared to be associated with reduced odds of poor outcome, but this result was not significant.

Crude and Adjusted Measures of Association between Mean Rate of Change in Maternal Weight and Bearing a Growth Retarded Infant

Similar to fundal height, both groups had mean positive Δweight/ΔEGA. However, the difference between the two groups was small. Mothers who had growth retarded infants had an overall mean Δweight/ΔEGA of 0.21±0.4, while mothers who did not have a growth retarded infant had a Δweight/ΔEGA of 0.23±0.4) - a difference of 0.02 units. The results of a multivariate logistic regression analysis of the association between giving birth to a growth retarded infant and Δweight/ΔEGA, controlling for maternal age and height, parity, and smoking status, are shown in Table 6. A one-unit increase in the Δweight/ΔEGA was associated with an odds ratio of giving birth to a growth retarded infant of 0.75, among mothers of similar age, height parity, and smoking status. From a 95% confidence interval calculated using robust standard errors, the data observed would not be unusual if the true odds ratio was between 0.37 and 1.50. With a p-value of 0.41, this association did not reach significance at a $p<0.05$ level. We therefore fail to reject the null hypothesis that there is not an association between Δweight/ΔEGA measured during 20 to 30 weeks and birth outcome in women of the same age, height, parity and smoking status. .

Exploratory Analyses

The model parameters included as covariates were chosen *a priori* based on the possibility that each may confound the association between rates of change in growth measurement and birth outcome. *A priori*, we did not have reason to believe that any of the available variables (maternal age, height, parity, and smoking status) modified the association between ΔSFH/ΔEGA profiles and having a growth retarded infant; therefore, interaction terms were not included in the models. However, the potential for effect modification was explored through comparing mean ratio of change measures by outcome status, stratified by age, height, smoking status, and parity (see Figure 1). No strong evidence of effect modification was seen for any of the covariates but we decided to examine the covariate that showed the largest change in the effect: age.

To examine effect modification by age, it was broken down into categories of <19 (10th percentile), 19-32 (11th to 89th percentiles) and >32 (90th percentile) years. In the largest age category (19-32 year old mothers), mothers with a non-growth retarded baby had greater ΔSFH/ΔEGA measures than mothers with a growth-retarded baby. The opposite relationship was observed for women 18 years and younger. Mothers ages 32 and older had similar changes in SFH profiles, regardless of their outcome status. When this same stratified analysis was repeated for changes in weight profiles, no association between Δweight/ΔEGA and outcome status was observed in the youngest age strata; in the middle age group, weight change was greater among women without a growth retarded infant compared to women with a growth retarded baby; the opposite was observed among women in the oldest age category. On an exploratory basis, we fit the models with interaction terms for age which was not significant, further confirming the decision to exclude it from the models.

Potential of ΔSFH/ΔEGA and Δweight/ΔEGA of pregnancy in prediction of birth outcomes

To assess the fit of the models described above, we calculated observed and expected outcome frequencies (tables not included), which agreed fairly well. Also, we noted the substantial reduction in the value of the AIC of the full model relative to the base model. These observations strengthened our faith that the models above fit the data fairly well. However, we cannot quantify the accuracy of these models as predictive tools on newly collected data based on these crude evaluations.

The models constructed in the above analysis were built to evaluate the association between changes in SFH or weight during 20th to 30th weeks of pregnancy and bearing a growth-retarded infant. Given the multivariate results that showed a statistically significant association between ΔSFH/ΔEGA and bearing a growth retarded infant, we expect our SFH model to have some predictive value in identifying the at-risk pregnancies. The non-significant aOR corresponding to Δweight/ΔEGA suggest that changes in weight profile has less potential to accurately discriminate between women who will and will not delivery growth retarded infants. However, the above models were not built for prediction purposes; they were based upon *a priori* assumptions to evaluate hypotheses about the causal relationships between the predictors of interest, and the outcome (e.g. bearing a growth retarded infant).

Comment [A11]: Actually, a very quick assessment of the overlap between the two groups says that this association is unlikely to prove useful for a prediction model.

If you choose a cutoff that provides 50% sensitivity, it only provides 75% specificity or so. Because there is about a 6:1 ratio of low risk to high risk, this yields a very low PPV.

Hence, I would argue that not much time needs to be spent on the analyses you nicely describe below.

If the primary goal had been to create prediction models, we would have allowed for data to take precedence over prior knowledge and beliefs in dictating the structure of the models. For such models, estimation of the prediction error requires validation of the model, for which one can partition the available data into a so-called "training" and "validation" subsets. The former is used for estimating the parameters of the model and the latter for estimation of the error rate of the model. When minimization of the prediction error is the first priority, the training and validation can be cyclically repeated with different models until the estimated training error is minimized. Such models can have optimal predictive values, although they can often be complex and lack the interpretability needed when our scientific question requires studying associations.

Discussion

Our explanatory model suggests that higher rates of increase in symphysis-fundal height between 20 and 30 weeks are associated with reduced odds of giving birth to a growth retarded infant, controlling for potential confounding factors including maternal age, height, parity and smoking status. Increased age and height were both significantly associated with slightly decreased odds of having a growth retarded infant. Not surprisingly, smoking was significantly associated with nearly twice the odds of having a growth retarded infant. Having had a previous child appeared to be associated with reduced odds of poor outcome, but this result was not statistically significant when the model included age as well[2]. In contrast to fundal height, we did not find a statistically significant association between Δweight/ΔEGA and adverse birth outcome.

Of the two measures we tested (SFH and maternal weight), it appears that SFH is a better proxy for fetal growth in utero than maternal weight. This is not entirely surprising as many factors can influence maternal weight gain that may not greatly impact the infant's birth weight. Fluctuations in water retention, for example, contribute to increases in maternal weight but would not be expected to impact fetal growth.

We chose to model the weight and fundal height variables similarly, as the mean rates of change in the measures across the timespan between the first and last visits occurring between 20 and 30 weeks estimated gestational age. This was chosen after examining the crude associations between poor birth weight outcome and SFH and weight modeled in various ways. We concluded from this first pass examination that the methods seemed largely comparable and that modeling the measurement variable as a change between two points in time would be of the greatest interest given the overall clinical goal of the study (i.e. identifying a straightforward calculation that clinicians could use).

This analysis has several limitations. With regard to the derived parameter, rate of change in weight and SFH profiles, we did not analyze the impact of the variability in length of observation on the model. It is

[2]Simultaneously testing age and parity (as defined here) was indeed significant at the 0.05 level

possible that the association may vary between women with differing durations between first and last measurements. Furthermore, the decision to model rate of change in growth parameters resulted in the exclusion of women with fewer than two visits between twenty and thirty weeks. Although the women excluded were similar to the women who attended two or more appointments on the demographic measures that we had available, there are unmeasured factors with a potential to impact pregnancy outcome that were not measured and very well could have differed between the two groups (e.g. drug and alcohol use, marital status, education level, etc) that could also impact pregnancy outcome. Thus, we are concerned that our analytic approach might have limited the generalizability of our results and might not have controlled for all possible confounders.

Nonetheless, this analysis provides evidence that changes in SFH, but not maternal weight, are associated with having a growth retarded infant. Future evaluations should (1) assess whether the observed relationship varies by maternal age group, (2) better control for confounders, (3) be more inclusive of all pregnant women, and (4) determine the predictive utility of SFH measurements delivery growth to distinguish between mothers who will and will not deliver growth retarded infants.

Table 1: Sample Description

	N Missing	Overall Sample (n=755) Frequency (%)	Mean (SD)	Min, Max
Baseline Maternal Characteristics				
Maternal Age	1		24.8 (5.4)	14, 43
Maternal Height	7		156.7 (6.5)	106, 176
Parity	1		1.1 (1.2)	0, 6
Smoker, %	5	231 (30.8)	--	--
Antenatal Visits				
Gestational Age at 1st Visit	0		22.5 (4.0)	15, 39
Number of Visits	0		7.7 (2.3)	(2, 14)
Number of Visits between 20 and 30 EGA	0		2.9 (1.3)	(0, 8)
Had ≥2 visits between weeks 20 and 30	0	658 (87.2)		
Delivery Outcomes				
Gestational Age at Delivery	6		39.2 (1.5)	30, 44
Sex of infant, % female	5	368 (49.1)	--	--
Birth weight of Infant (Kg)	5		3.10 (0.5)	1.04, 4.73
Low birth weight infant	4	75 (10.0)	--	--
Small for gestational age	0	105 (13.9)	--	--
Preterm	5	24 (3.2)	--	--

Table 2: Description of Mothers with and without ≥2 visits between weeks 20 and 30

	Mothers with ≥2 visits (n=658)				**Mothers with <2 visits (n=97)**			
	N Missing	Frequency (%)	Mean (SD)	Min, Max	N Missing	Frequency (%)	Mean (SD)	Min, Max
Baseline Maternal Characteristics								
Maternal Age	0		24.8 (5.4)	14, 42	0		24.4 (5.4)	14, 43
Maternal Height	5		156.8 (6.6)	106, 176	1		156.1 (5.6)	138, 171
Parity	0		1.1 (1.2)	0, 6	0		1.2 (1.2)	0, 5
Smoker, %	4	209 (32.0)			0	22 (22.7)		
Delivery Outcome								
Growth retarded infant	3	209 (14.7)			0	9 (9.3)		

Comment [A12]: Good to examine

Table 3: Description of Mothers with and without a Growth Retarded Infant

	Mothers with a Growth Retarded Infant (n=105)				**Mothers without a Growth Retarded Infant (n=559)**			
	N Missing	Frequency (%)	Mean (SD)	Min, Max	N Missing	Frequency (%)	Mean (SD)	Min, Max
Baseline Maternal Characteristics								
Maternal Age	1		23.8 (4.9)	16, 35	0		24.9 (5.4)	14, 43
Maternal Height	6		154.6 (5.9)	142, 172	0		157.0 (6.5)	106, 176
Parity	1		0.9 (1.1)	0, 6	0		1.1 (1.2)	0, 6
Smoker, %	1	45 (43.3)			0	186 (28.8)		
Antenatal Visits								
Gestational Age at 1st Visit	0		21.9 (3.3)	15, 36	0		22.6 (4.1)	18, 39
Number of Visits	0		7.1 (2.6)	2, 13	0		7.8 (2.2)	2, 14
Number of Visits, 20 and 30 EGA wks	0		3.1 (1.2)	0, 8	0		2.9 (1.3)	0, 6
Had ≥2 visits between weeks 20 and 30	0	96 (91.4)			0	559 (86.4)		
Delivery Outcomes								
Gestational Age at Delivery	2		37.9 (2.2)	30, 42	0		39.4 (1.2)	38, 44
Sex of infant, % female	1	59 (56.7)			0	308 (47.6)		
Birth weight of Infant (Kg)	1		2.2 (0.4)	1.0, 3.8	0		3.2 (0.4)	2.5, 4.7
Low birth weight infant	1	75 (72.1)			0	0 (0)		
Small for gestational age	0	105 (100.0)			0	0 (0)		
Preterm	2	24 (23.3)			0	0 (0)		

Table 4: Description of Changes in SFH and Weight Measurements between Weeks 20 and 30, among Women with at Least 2 visits during this Period (n=658)

	Mothers with a Growth Retarded Infant (n=96)				Mothers without a Growth Retarded Infant (n=559)			
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum
Min. SFH/week	0.91	0.1	0.8	1.1	0.93	0.1	0.6	1.1
ΔSFH/ΔEGA	0.90	0.4	-1.5	2.0	1.04	0.4	-1.4	3.6
LSE of SFH on weeks	0.91	0.4	-1.5	2.0	1.03	0.4	-1.4	3.6
Min. change rate SFH	0.58	0.7	-4.0	2.0	0.72	0.5	-3.2	3.6
Min. weight/week	2.12	0.4	1.4	3.5	2.28	0.4	1.5	4.3
Δ weight /ΔEGA	0.38	0.3	-1.5	1.1	0.42	0.4	-1.0	3.0
LSE of weight on weeks	0.38	0.3	-1.5	1.1	0.42	0.4	-1.0	3.0
Min. change rate weight	0.22	0.4	-1.5	1.0	0.23	0.4	-2.2	3.0

Comment [A13]: I think you would have found it informative to look at descriptive statistics for SFH and weight by EGA for these two groups. There are only 11 weeks to consider, and that would have presented info re sparsity of data and trends in the measures.

You would have found little difference in the means for the weight variables, and hints at separating curves for SFH only at the later weeks in the period of interest.

Table 5: The association between minimum ratio of SFH to EGAand having a growth-retarded infant, adjusted for maternal age, parity, smoking status, and height, among women with ≥2 visits between weeks 20 and 30.

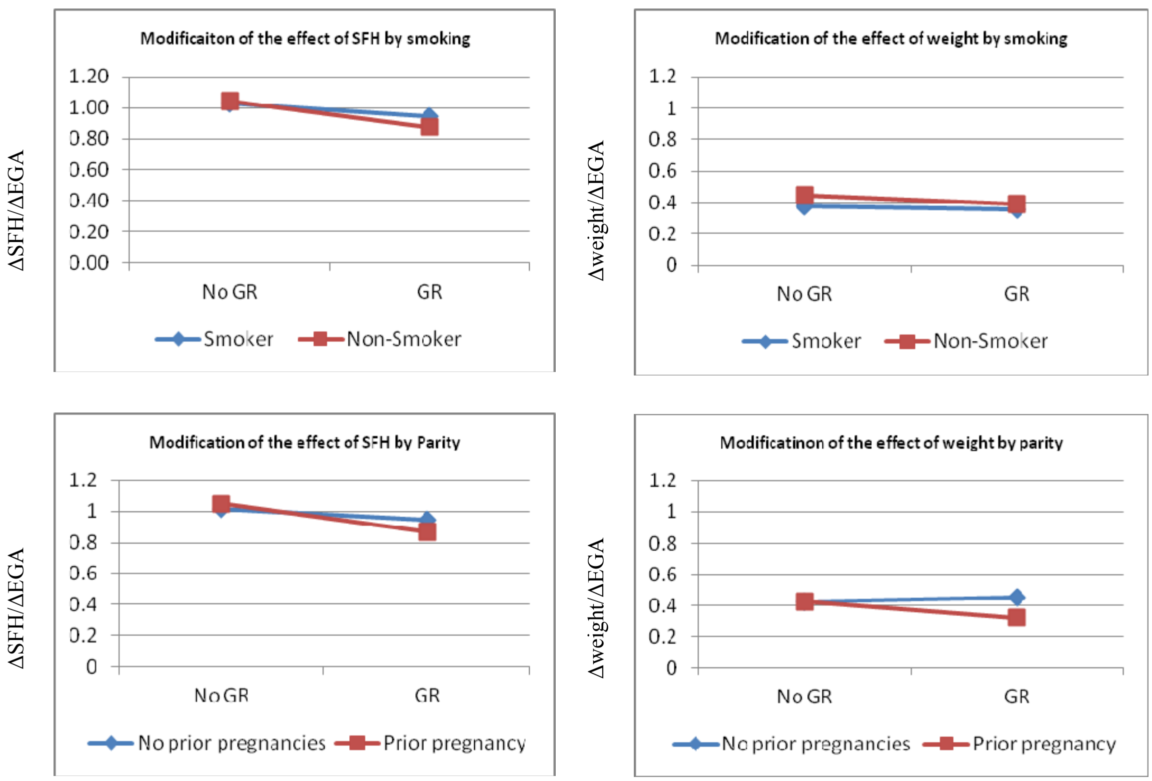
	aOR(95% CI)	P-value
ΔSFH/ΔEGA	0.50 (0.29, 0.86)	0.0117
Mother's Age	0.96 (0.91, 0.98)	0.2022
Parous (vs. nulliparous)	0.74 (0.41, 1.33)	0.3108
Smoker	1.96 (1.23, 3.12)	0.0048
Maternal Height	0.94 (0.91, 0.98)	0.0007

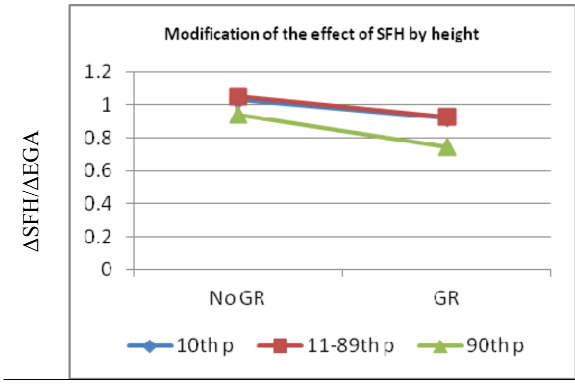
Table 6: The association between minimum ratio of weight to EGAand having a growth-retarded infant, adjusted for maternal age, parity, smoking status, and height, among women with ≥2 visits between weeks 20 and 30.

	aOR(95% CI)	P-value
Δweight/ΔEGA	0.75 (0.37, 1.5)	0.4112
Mother's Age	0.96 (0.9, 1.02)	0.1404
Parous (vs. nulliparous)	0.75 (0.42, 1.35)	0.3408
Smoker	1.93 (1.21, 3.07)	0.0056
Maternal Height	0.95 (0.91, 0.98)	0.0011

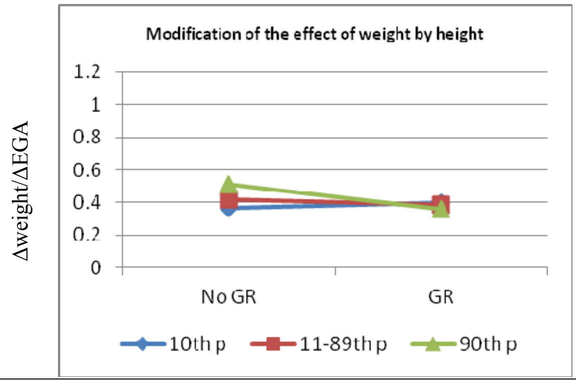
Figure 1: Assessment of Effect Modification by Smoking Status, Parity, and Height

Ratio of SFH Measures	Ratio of Weight Measures





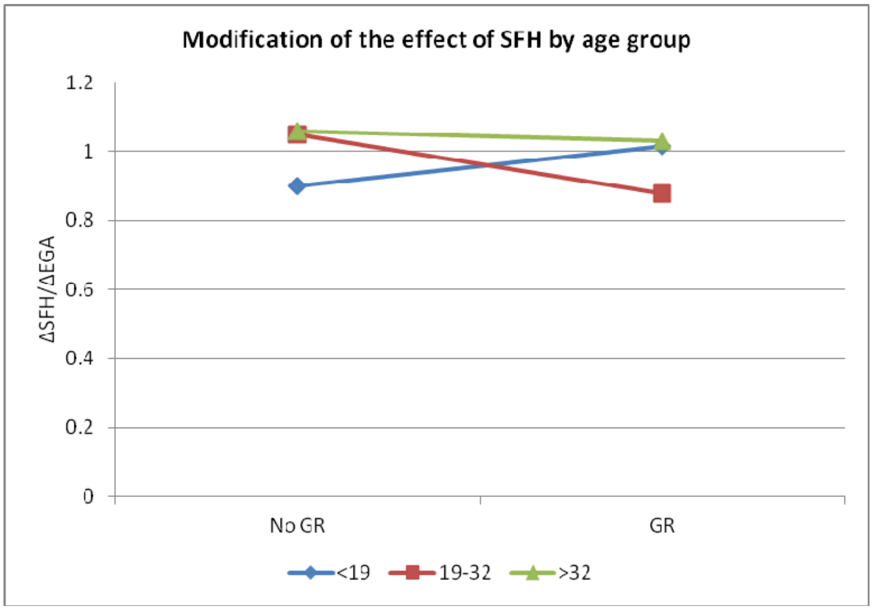
Modification of the effect of SFH by height
ΔSFH/ΔEGA
1.2
1
0.8
0.6
0.4
0.2
0
No GR
GR
10th p
11-89th p
90th p



Modification of the effect of weight by height
Δweight/ΔEGA
1.2
1
0.8
0.6
0.4
0.2
0
No GR
GR
10th p
11-89th p
90th p

Figure 2: Assessment of Effect Modification by Age

SFH



Weigh
t