Group 2
Biostat 536

2nd Trimester Growth Measures and Poor Pregnancy Outcomes

Summary

Perinatal mortality is of serious concern in the developing world where access to prenatal care is limited. 755 women were followed prospectively from enrollment at a pre-natal clinic in South Africa until the live birth of their child to assess if measurements of *Symphysis-Fundal Height* (SFH) made between 20-30 weeks of estimated gestational age (EGA) were associated with adverse pregnancy outcomes, specifically low birth weight (≤2500 g). Those with a higher value of the minimal SFH/week measured between 20 and 30 weeks tended to have lower odds of giving birth to a low birth weight baby. A difference of 0.1 in minimal SFH(cm)/week was significantly associated with an odds ratio of 0.553 for low birth weight (95% CI: 0.355, 0.861; p=0.009) after adjustment for maternal age, height, smoking and parity, as well as infant sex and total number of pre-natal visits. A higher growth rate, measured by slope of change in SFH/week, was also associated with significantly reduced odds of low birth weight. (OR: 0.468, 95% CI: 0.274, 0.801; p=0.006) Using minimal SFH/week as the primary predictor, a predictive model performed reasonably well in discerning low birth weight outcomes. Area under the ROC curve was 0.713, suggesting that SFH may contribute to a reasonable prediction model for LWB but will need to be tested using new data.

- **Comment [a1]:** low income
- **Comment [a2]:** Why only low birth weight and not SGA or premature? (You explain your reasoning later, but this large of a departure from the question of interest should be noted in the summary as well)
- **Comment [a3]:** How many visits do you have in the interval of greatest interest?
- **Comment [a4]:** this is a bit problematic-see my later comments
- **Comment [a5]:** during 20-30 weeks?
- **Comment [a6]:** This would depend on the added predictive capability

Background

Perinatal mortality is a large problem in the developing world where access to prenatal care is limited. According to the WHO in 2005, 1 in 5 women in low-income countries lose a baby during her lifetime compared to only 1 in 125 women in high-income countries. Pregnancy outcomes such as low birth weight (birth weight ≤ 2500g), small for gestational age (below the 10th percentile for their gestational age), and pre-term delivery (<37 weeks of gestation) are associated with numerous complications including increase risk of neonatal death, pneumonia, and other infections.

During prenatal visits, women are often weighed to ensure they are properly nourished, the fetus is growing, and the mother's weight gain is not too large as to suggest she has pre-eclampsia, a dangerous condition for both the mother and fetus. In addition, symphysis-fundal height (SFH), an approximation of fetus size, measures the distance from the pelvic bones to top of the uterus. SFH, starting at 20 weeks, is expected to increases linearly with gestational age.

It is critical to identify those women with high-risk pregnancies early in their pregnancy so that they can be targeted for additional interventions and follow-up. This study was designed to follow pregnant women through their pregnancies to understand if weight and

SFH measurements taken during 20-30 weeks of pregnancy are associated with adverse birth outcomes.

Questions of Interest:

Questions posed by the project

1. 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?
2. Are measurements made between 20-30 weeks of estimated gestational age (EGA) associated with adverse pregnancy outcomes?
3. Is it possible to use measurements taken prior to 30 weeks of EGA to predict which women will have adverse pregnancy outcomes?

Questions to be answered by our analysis

1. Is there an association between *Symphysis-Fundal Height* (SFH) measured between 20-30 weeks of gestation and LBW after controlling for known or possible confounders (parity, smoking, maternal age, maternal height, infant sex, and number of ANC visits)?
2. Are measurements of covariates taken on or before 30 weeks of pregnancy predictive of LBW in the analyzed sample?

Because of concerns regarding the inaccuracy in the measurement of gestational age at birth, we are focusing our analysis on the primary outcome of LBW. We believe LBW will be the most precisely measured outcome. Furthermore, we have concerns that SGA is confounded by ethnicity. We would expect the size of babies to vary across populations relative to the average size of the population, but we do not have the ethnicity of the mother and therefore we are not examining this outcome.

Comment [a7]: I believe the measurement of GA at birth would for the most part be more reliable than EGA during pregnancy. Hence, I do not believe you should summarily discard the other outcomes. That is, it is okay to voice your concerns, but it would not be okay to not produce an analysis at all

We have chosen to use SFH as our primary predictor because in the case of normal development, there is a linear relationship between SFH and gestational age. Additionally, SFH is effectively zero at the start of pregnancy, so a single measurement of SFH can be informative of the overall growth trend. The relationship between maternal weight and gestational age, unlike that between SHF and gestational age, depends upon mother's weight before pregnancy. Thus, we chose to exclude maternal weight from consideration as a covariate because baseline values were unavailable in the current study. Spaghetti plots of weight and SFH measurements for a representative sample of subjects during the 20-30 weeks of gestation demonstrate these relationships (Figures 1-2).

Comment [a8]: Well, no, but during the period of linearity, it is such that SFH is approximately EGA

Comment [a9]: Okay, but don't you think that the first wt measurement you have would be better than nothing?

Comment [a10]: This is a result. It is okay ot mention in methods that you chose this because of your results, but delay the presentation and reference to the results

Data Source

We received data on 755 pregnant women with singleton pregnancies receiving pre-natal care in in a peri-urban setting in the Western Cape, South Africa. These women were enrolled on average during the 22nd week of pregnancy and followed till birth. Upon enrollment the woman's age, smoking status, height, and parity were recorded. During each clinic visit the woman's weight and SFH were measured. At birth, the infant sex, weight, and gestational age were recorded and the infants were determined to be SGA and/or preterm. These 755 women represent 5849 prenatal visits over the course of their pregnancy.

We are missing some pertinent data

1. We do not have pre-pregnancy (baseline) weights for any women.
2. We are missing blood pressure measurements for women. We therefore cannot evaluate the presence of pre-eclampsia, or eclampsia in the patients, nor control for its presence in the association between weight gain and adverse outcomes.
3. Some women, (N=46) were enrolled after the critical window of 20-30 weeks. Therefore these women cannot be used in the analysis of the association between measurements taken at 20-30 weeks and pregnancy outcomes. The primary analysis is therefore restricted to only women who were enrolled at or before 30 weeks of gestation.
4. We are missing outcomes on infants (LBW n=4). For those women missing outcomes have been excluded from the analysis
5. We are missing some covariate data on the women

Methods

Subjects

The initial sample consisted of 755 pregnant women with a total of 5849 clinic visits. Given the purpose of this study, subjects who had no SFH measurements between 20-30 weeks of gestation were dropped from the analysis (n=47) as well as those who had missing birth weight outcomes (an additional n=4), leaving a final sample of 704 subjects.

Exposure variables

Because the number of visits during 20-30 weeks varied among subjects, we decided to use two derived measures of SFH/week to summarize trends in the repeated SFH measurements for each subject.

First, we were interested in a variable that would indicate whether the subject fell behind what would be the expected growth trend for pregnant women (an increase in 1 cm SFH/week from zero at the start of pregnancy). Taking this dependence into account, SFH measurements taken between 20 and 30 weeks were divided by gestational week of the visits when the corresponding measurements were taken. We then reported the minimum value of this ratio for each subject to produce the minimal SFH/week. All women with at least one SFH measurement between 20 and 30 weeks would thus have a valid value for this predictor.

Second, we wished to quantify an overall growth rate for SFH during the 20 to 30 week period. To do this, we fit the least-squares linear trend of SFH vs. gestational age using all observations in the 20 to 30 week period, and reported the estimated slope coefficient for each woman. All women with only one SFH measurement between 20 and 30 weeks would thus have a valid minimal SFH/week measurement, but not a valid slope measurement.

Comment [a11]: for each woman separately, or as part of a composite model with random slopes? (I bet you did the former, but there are multiple ways it could have been done.)

Using these two SFH variables together, we felt we were able to address questions of whether a small fetus during 20-30 gestation weeks measured by SFH is related to low birth weight, and whether a low growth rate of the fetus measured by SFH change during this time period is related to low birth weight.

Outcome variable
Birth weight was categorized into low birth weight (below 2500 grams) and normal (2500 grams or greater). Although birth weight was given as a continuous variable, the widely used cutoff point 2500g was used so that the interpretation of the results would be of greater clinical relevance.

Covariates
Information were available on mothers' height (in cm), age (in years), number of prior deliveries (parity; categorized into 0 vs. 1 or more), smoking (yes vs. no), and sex of the infants. All of these were thought to be causally associated with birth weight of the infants. Therefore, they would be included in the multivariate models as confounders or precision variables.

Descriptive analysis
The descriptive statistics (frequencies and percentages for categorical variables and mean/standard deviations for continuous variables) of covariates as well as birth outcomes were stratified by the medium value of the minimal SFH between 20-30 weeks. Evidence for confounding was then evaluated. Missingness was noted.

Inference
Logistic regressions were used to assess the association between SFH and risk of low birth weight because the outcome was binary. Using a logistic model, we estimated the odds ratio of having a low birth weight comparing women differing in one unit in the predictor. Because SFH/week is expected to center around 1.0, we rescaled the minimal SFH/week by multiplying it by 10. This results in a more reasonable interpretation for the estimated coefficient (odds ratio corresponding to a difference of 0.1 cm/week). A multivariate logistic model with robust standard error estimates was used to assess the association between the primary predictor of interest, minimal SFH/week, and risk of low birth weight, adjusting for parity, maternal age, height and smoking as well as the post-pregnancy outcomes including infant sex and total number of ANC visits. This means we are making comparisons between women differing in one unit in the predictor (again, by 0.1 in minimal SFH/week) but same in all other risk factors. Five subjects with missing values for the adjustment variables were dropped from this analysis, resulting in a final analytic sample of n=699.

Comment [a12]: This is quite problematic. You are definitely conditioning on the future here. That is, if a woman was seen more often because of late pregnancy complications this could be high. Furthermore, the possibility that the SFH measurements in weeks 20-30 led to more visits, you are diminishing the predictive capability of those measurements.

A second model, with slope of change in SFH/week instead of minimal SFH/week, was fit on a reduced sample including only women with at least two SFH measurements between 20 and 30 weeks (n=649). Odds ratios, p values and 95% confidence intervals were reported for all inferential models

Prediction

To evaluate the possibility of constructing a predictive model for low birth weight using measurements taken prior to 30 weeks of pregnancy, we refit the inferential models using only covariates that can be measured during 20 to 30 weeks of pregnancy. We then evaluated the predicted odds of low birth weight in discerning actual birth outcomes using varying cutoffs and plotting an ROC curve. Because of the small number of events (n=75 LBW), we did not feel we had an adequate sample to perform cross-validation; thus, these results are strictly exploratory.

Comment [a13]: what is an ROC curve?

Covariates in the predictive model included the adjustment covariates of parity, maternal age, height and smoking status. As for the predictors of interest, fitting a predictive model using only the minimal SFH/week and not any kind of change-over-time measurement would allow for predictions to be made on women who only visited once during 20 to 30 weeks of pregnancy. In our current sample, this increases the sample size, and this decision might be relevant for actual practice as well. Accordingly, we decided to only include minimal SFH/week in the predictive models unless the inferential model suggested that slope was much more strongly associated with low birth weight outcomes.

Results

Descriptive analysis

The primary analysis was performed on 704 subjects with an average of 8.0 total ANC visits and an average of 3.1 visits between 20 and 30 weeks. To assess potential confounding, we examined differences in the distributions of measured covariates between subjects above and below the median value of our primary predictor, minimal SFH/week between 20 and 30 weeks (Table 1). Subjects with minimal SFH/week above the median value (0.9259) tended to have higher age and lower height on average, though these differences were small compared to the spread of the data. They also had a slightly lower proportion of male babies and fewer ANC visits. Variables that appeared to be more strongly associated with low minimal SFH/week were maternal smoking and first-time deliveries.

Comment [a14]: Tell us about the cases you excluded.

Inference

Among women included in the primary inferential model (n=699), those with a higher value of the primary predictor, minimal SFH/week measured between 20 and 30 weeks, tended to have lower odds of giving birth to a low birth weight baby (≤2500 g). Specifically, a difference of 0.1 in minimal SFH/week was significantly associated with an odds ratio of 0.553 for low birth weight (95% CI: 0.355, 0.861; p=0.009) after adjustment for maternal age, height, smoking and parity as well as infant sex and total number of ANC visits (Table 2).

Among women included in the secondary inferential model (n=649), those with a higher value of the primary predictor, slope of change in SFH/week between 20 and 30 weeks, also tended to have lower odds of giving birth to a low birth weight baby. Specifically, a difference of 1.0 in the slope of SFH during 20 to 30 weeks was significantly associated with an odds ratio of 0.468 for low birth weight (95% CI: 0.274, 0.801; p=0.006) after adjustment for maternal age, height, smoking and parity as well as infant sex and total number of ANC visits (Table 3).

Prediction

The predictive model is presented in Table 4. Compared to the primary inferential model, which differs by including the post-30 week variables infant sex and total ANC visits (Table 2), the magnitude and precision of the predicted covariates are similar. The model performed reasonably well in discerning low birth weight outcomes, with an area under the ROC curve of 0.713 and a fairly symmetrical balance of false positive and false negative rates (Figure 3).

Comment [a15]: How did you decide "reasonably well". What was the contribution from the SFH variables? How many women would you be sending to the high risk clinic? How many of those would be truly high risk? Provide some interpretation of what your ROC curve means.

Discussion

Like all observational studies, the results of this analysis should be interpreted with caution. These results show that there is strong association between SFH measurements during 20-30 weeks of gestation and a low birth weight baby. The inferential models showed that both a single low measurement of SFH (taking into account the expected dependence on gestational age), as well as a low slope of change in SFH during 20 to 30 weeks, were associated with higher risk of LBW. These associations are still significant after adjustment for known confounders of number of ANC visits, maternal age, infant sex, parity, maternal smoking, and maternal height. This conclusion is supported by both the magnitude of the point estimates and the p values. Of note, more frequent ANC visits also appeared to be strongly associated with reduced risk of LBW. Although number of ANC visits was associated with the outcome, it would be a poor predictor of LBW and other adverse pregnancy outcomes as the majority of ANC visits occur after the window for intervention between 20-30 weeks.

Our predictive model does not directly address the question of whether measurements of SFH during 20-30 weeks of pregnancy are predictive of LBW. Because all available data was used to build the model, the ROC curve presented may over estimate the predictive potential of SFH measurements. That said, the ROC curve suggests that a single measure of SFH between 20-30 weeks may have predictive potential. We did not consider the slope of SFH as a predictor, because we had specified previously that we would not use it unless it demonstrated a much stronger association than minimal SFH/week in the inferential models. Using the slope as a predictor would require two measurements of SFH for each woman, which would reduce the amount of subjects we could calculate predictions for. In any case, the predictive models will need to be validated using new data. If an additional sample of the same population could be obtained, we could utilize a model-building algorithm including the minimal SFH as a possible predictor, and use cross-validation methods to find the best model.

Finally, it is implicit that all models in this study are conditional on a live singleton birth. Because of this, the inferential models must be interpreted with this condition in mind.

Arguably, from a prediction standpoint, it is just as important to target care to women who are likely to miscarry or have a stillborn child, and these women might have a similar risk profile for low birth weight outcomes. However, our predictive model would be built conditionally on set of subjects who we know did not have these outcomes. This might result in biases that are impossible to eliminate without information on women who did not give birth do a live infant. If there were additional patients from the cohort, it would be beneficial to use their data to test the predictive model.

Comment [a16]: I agree

Tables and Figures:

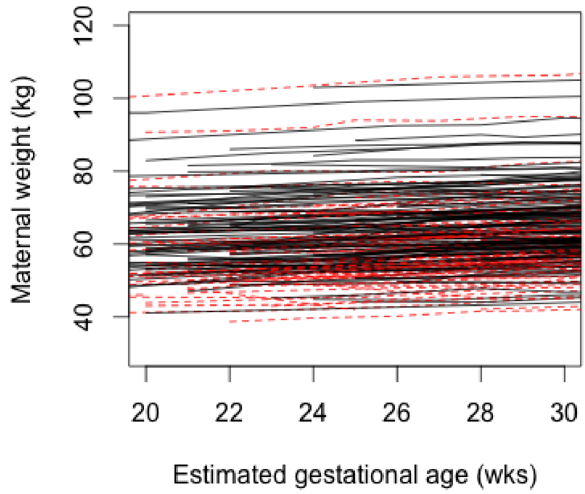

Figure 1. Spaghetti plot of maternal weight (kg) by estimated gestational age between 20 and 30 weeks of pregnancy. Shown is a representative sample (n=340) of subjects who did not give birth to a low birth weight baby (—) and all subjects (n=75) who did give birth to a low birth weight baby (---)**.**

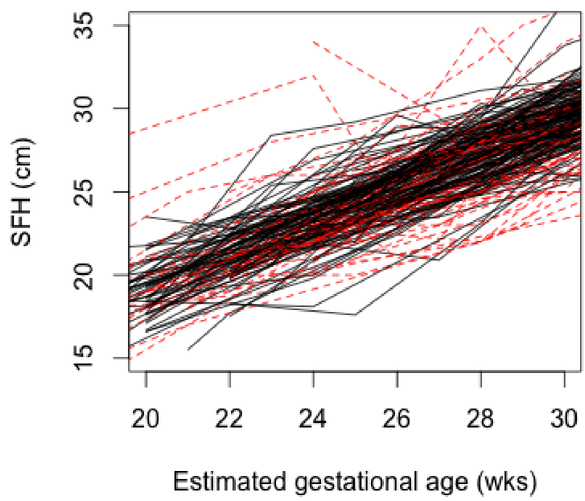

Figure 2. Spaghetti plot of SFH (cm) by estimated gestational age between 20 and 30 weeks of pregnancy. Shown is a representative sample (n=340) of subjects who did not give birth to a low birth weight baby (—) and all subjects (n=75) who did give birth to a low birth weight baby (---)**.**

Table 1. Descriptive statistics of the sample by minimal SFH/week, n=704

	Minimum SFH/WK between 20-30 weeks	
	Below the Median(<=0.9259) n=350	Above the Median (>0.9259) n=354
Age (mean, SE)	24.4 (5.4)	25.3 (5.3)
Maternal height (mean, SE)	156.9 (6.9)	156.5 (6.1)
Missing	3	2
Prior deliveries (n, %)		
0	141 (40.3)	130 (36.7)
1+	209 (59.7)	224 (63.3)
Maternal smoking (n, %)		
Yes	121 (34.6)	100 (28.2)
No	229 (65.4)	254 (71.8)
Infant sex (n, %)		
Male	180 (51.4)	177 (50.0)
Female	170 (48.6)	177 (50.0)
Total ANC visits (mean, SE)	8.1 (2.28)	7.8 (2.2)
Preterm delivery (n, %)		
Yes	122 (35.0)	138 (39.0)
No	227 (65.0)	216 (61.0)
Missing	1	0
SGA (n, %)		
Yes	286 (81.7)	317 (89.5)
No	64 (18.3)	37 (10.5)
Birth weight (n, %)		
<2500 g	301 (86.0)	330 (93.2)
>= 2500 g	49 (14.0)	24 (6.8)

Comment [a17]: I probably would not have used the median, because I do not expect that half the subjects would fall into the high risk group. Granted it is hard to guess what cutoff to use, but using something more to the extreme (but not too extreme) might be better.

Table 2. The minimal SFH per week during 20-30 weeks of gestation and risk of having a low birth weight baby, n=699

Predictors	OR	95%CI	P value
Min. SFH/WK during 20-30 weeks *10	0.553	0.355, 0.861	0.009
Maternal age	0.995	0.937, 1.056	0.858
Maternal height	0.927	0.882, 0.975	0.003
Maternal smoking	0.622	0.363, 1.064	0.083
Baby Female	1.383	0.818, 2.337	0.226
Parity 1+	0.575	0.295, 1.120	0.104
ANC visits	0.786	0.688, 0.899	<0.001

R^2=0.1126

Comment [a18]: It would have been very informative to give a table of average SFH by EGA for women who did or did not have LBW baby.

Table 3. The slope of SFH during 20-30 weeks of gestation and risk of having a low birth weight baby, n=649

Predictors	OR	95%CI	P value
Slope of SFH during 20-30 weeks	0.468	0.274, 0.801	0.006
Mother's age	0.989	0.932, 1.049	0.711
Mother's height	0.925	0.882, 0.970	0.001
Mother's smoking	0.668	0.383, 1.162	0.153
Baby Female	1.530	0.888, 2.634	0.125
Having 1+ prior deliveries	0.607	0.309, 1.190	0.147
ANC visits	0.791	0.688, 0.910	0.001

R^2=0.1097

Table 4. Predictive model for LBW, using the minimal SFH per week during 20-30 weeks of gestation and other covariates measured prior to 30 weeks, n=699

Predictors	OR	95%CI	P value
Min. SFH/WK during 20-30 weeks *10	0.573	0.374, 0.878	0.010
Maternal age	0.981	0.924, 1.040	0.519
Maternal height	0.926	0.882, 0.972	0.002
Maternal smoking	0.557	0.330, 0.940	0.028
Parity 1+	0.699	0.373, 1.310	0.264

R^2= 0.0733

Comment [a19]: What does R squared mean?

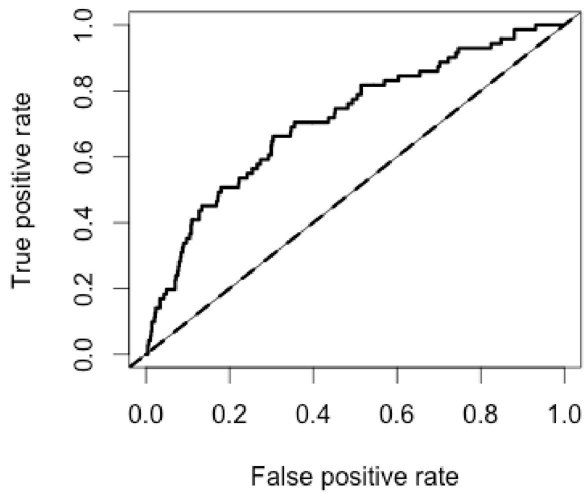

Figure 3. ROC curve for predictive model using measurements collected on or prior to 30 weeks of pregnancy: minimal SFH/week, maternal age, smoking status and parity (n=699). Area under the curve = 0.713.

Comment [a20]: How much does this add over the other variables?