BIOST 536 Project – Group 1

Summary

Two low–technology measurements are routinely taken when women come for pre-natal check-ups: symphysis-fundal height (SFH) and weight. The analysis had two objectives: first, to determine whether an association existed between either of these measurements early in the pregnancy (between 20-30 weeks) and the poor birth outcomes. The second objective was to determine if either of these measurements taken early in pregnancy could be predictive of poor birth outcomes. Data was collected on approximately 700 women in a prospective cohort study conducted in a prenatal clinic in a peri-urban area of Western Cape, South Africa. Logistic regression analysis did not find a statistically significant association between SFH/estimated gestational age and poor birth outcomes (OR 0.0310, 95% CI 0.0005, 1.8159 p=0.094). Nor was there a statistically significant association between weekly weight gain and poor birth outcomes (OR 0.6066, 95% CI 0.3495, 1.0527 p=0.076). One of the main problems with the study resulted from the observational nature of the study. There may be residual confounding or unmeasured confounding in our study.

Comment [a1]: I think you could have added the following facts without much increase in words, so I think you should

Comment [a2]: Note that these would be used in combination with some maternal factors

Comment [a3]: so we are interested in associations beyond the pre-pregnancy risk factors

Comment [a4]: Why not give the exact number, along with how many measurements you had over the period of interest

Comment [a5]: were these adjusted for anything? If so, say it

Comment [a6]: So lacking any association, it certainly seems that a predictive model will not be very good. State this.

Background

Neonatal mortality persists as a significant public health problem in sub-Saharan Africa, with rates about 6 times higher than in Europe and the United States. Medical problems associated with low birth weight and prematurity are responsible for about 30% of these deaths, according to the World Health Organization. Identification of pregnant women that are at risk for these outcomes is a priority, so that they can be referred for specialized care. In particular, mothers who are at risk for pre-term births (<38 weeks gestation), low birthweight (LBW) babies (<2500g) or small for gestational age (SGA) babies (below the 10th percentile of weight for gestational age at birth) may benefit from specialized care during pregnancy.

Maternal factors, including obesity, poor nutrition, smoking, genetics, and chronic medical conditions such diabetes, hypertension, and HIV are known to increase the risk for these outcomes and can be identified at the onset of pregnancy. In addition, pregnancy monitoring can identify conditions such as pre-eclampsia or gestational diabetes, which develop during pregnancy, and may identify fetuses with slow or restricted growth. Prenatal care visits present an opportunity to screen for these conditions and identify high-risk women for referral. In many African settings, however, this presents a challenge: women generally present late in pregnancy, ultrasound is rarely available to assess fetal growth, and human resources are limited, so that women only spend a few minutes with a health care provider at each visit. In this context, rapid, low technology methods are needed to screen for high-risk pregnancies. Symphysis-fundal height (SFH) is measured by the distance from the symphysis of the pubic bone to the top of the uterus and is a reliable measure of fetal size between 20-36 weeks gestation. Rapid gains in maternal weight may signify pre-eclampsia, while low weight gain may signify poor growth.

SFH and maternal weight are routinely monitored during prenatal care and may be useful indicators of pregnancy risk between 20 and 30 weeks of gestation, providing an opportunity to identify high-risk women and refer them to specialized care before delivery.

Questions of Interest

The overall goal is to identify high-risk pregnancies between 20-30 weeks gestation so that they can be referred for care to prevent poor neonatal health outcomes. Since we already know that certain baseline factors predict high-risk pregnancy, we now want to find out whether monitoring pregnant women during gestation can provide additional information to improve predictions. The questions posed to us were:

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? Of greatest interest would be the association between measurements made between 20 – 30 weeks EGA and the three adverse pregnancy outcomes, in order to be able to refer high-risk women to more intense prenatal care.
2) Is it possible, using measurements taken prior to week 30 of pregnancy, to develop a model that accurately distinguishes between women who will and will not have growth retarded babies?

We have refined these questions by defining weight profile and SFH profile and restricting the question to the time interval of greatest interest:

1. During the interval of 20-30 weeks gestational age, are either the weekly changes in maternal weight or the weekly changes in the ratio between SFH and estimated gestational age associated with risk for at least one of the following poor health outcomes: LWB, SGA or preterm birth?
2. Can either of these measurements two measurements taken at the clinic during the 20 to 30 week gestational age interval help to accurately identify women at risk of at least one of the poor health outcomes so they can be referred to specialty care?

Source of the Data

Seven hundred and fifty five (755) pregnant women were enrolled in a prospective cohort study conducted in a prenatal clinic in a peri-urban area of Western Cape, South Africa. Study enrollment occurred at an average gestational age of 22 weeks, though women may have been attending prenatal care from an earlier point. All women had singleton pregnancies and could not afford private healthcare (implying a similar socio-economic status). The dataset includes:

- Maternal characteristics at enrollment: age, height, parity, and smoking status. Very old and very young mothers are at increased risk for poor outcomes, as are women who smoke. Higher parity is associated with better birth outcomes and higher birth weights. Although height may not be associated with birth outcomes *per se*, it may be a surrogate for nutritional status or ethnic group, and these may predict birth weight or other outcomes. Estimated gestational age (EGA) was recorded at the first visit and each additional visit. The EGA at the first visit may be associated with poor health outcomes as mothers who believe they are having difficulty may make their initial visit to the clinic earlier in their pregnancy. Therefore we will consider all of these baseline factors as initial predictors of risk, which we will try to improve on by including minimum SFH/EGA ratio or maximum weekly maternal weight gain.

- Infant characteristics at delivery: sex, birthweight, gestational age, and an indicator of whether the infant was small for gestational age (SGA). Sex is associated with birthweight. Gestational age, birthweight and SGA are the birth outcomes of interest in this analysis.
- Data recorded during prenatal care visits between enrollment and delivery: gestational age, SFH and maternal weight. Our predictors of interest, the minimum SFH /EGA ratio or the maximum maternal weekly weight change, are derived from these measurements that are recorded over the course of pregnancy. EGA is measured from the last menstrual period (LMP) and can be imprecise. We will need to keep this in mind as we analyze the data.

Comment [a7]: define POI here, since you do not restate what the POIs are where you define it

The data on maternal characteristics at enrollment are fairly complete, with 6 missing values for height and 4 for smoking status. For birth outcomes, there are 4 missing values for sex, 4 for birthweight, and 5 for gestational age at birth. One individual had duplicate entries in the data set where the coding for SGA conflicted. The decision was made prior to conducting the analysis to code that individual as an occurrence of SGA. There were 3 women with missing birthweight and 4 women with missing gestational at birth. The number of prenatal care visits per woman between enrollment and delivery varied widely. All women had at least two consecutive weight measures to calculate weekly weight gain; there was only one woman who had no SFH measurements and for whom we could not calculate a minimum SFH/EGA ratio.

Statistical Methods

<u>Primary Outcomes and Predictors of Interest:</u> There are three birth outcomes used to generate our definition of at high risk: LBW is defined as <2500g at birth, preterm is defined as <38 weeks gestational age at birth, and SGA defined as below the 10^{th} percentile of weight for gestational age at birth. SGA is already dichotomous (yes or no) in the dataset. Birth weight and gestational age at birth are continuous, so we created dichotomous variables based on the definitions above. Since all three conditions are predictive of neonatal mortality, we considered a composite of the three as the primary outcome for our statistical analyses. Women were considered to have a poor birth outcome if the infant was LBW, SGA or preterm; otherwise she was considered to have a healthy outcome.

We considered two exposures, weight profiles over pregnancy and SFH profiles over pregnancy. We restricted our analyses to data collected between 20 and 30 weeks gestational age based on the question of interest. Since we expect women to differ with respect to gestational age at first visit, gestational age at last visit, and time between visits, the absolute change in SFH or weight between visits will differ. However, during the time period of interest, we know that SFH is expected be approximately equal to gestational age and we expect healthy weight gain to be approximately linear. Therefore, we decided to create the following variables for each visit: 1) ratio of SFH to EGA and 2) Average weight gain per week since the last visit. For each woman, our analyses will consider the minimum SFH/EGA ratio across all of her visits, since low SFH is indicative of poor fetal growth. Similarly, because increased weight gain may be indicative of pre-eclampsia, we will consider the maximum weekly weight gain in our analyses.

Descriptive Analyses: We calculated descriptive statistics for the participants at study enrollment, disposition of follow-up visits, including frequency and timing, and for the characteristics of infants at birth. We also calculated descriptive statistics at each visit between 20 and 30 weeks for the SFH/EGA ratio and average weekly weight gain since the last visit. All descriptive statistics are stratified by birth outcome (healthy vs. poor) to facilitate comparisons. For continuous variables we calculated the mean, standard deviation, and minimum and maximum values. For categorical variables we calculated the percentages (means).

Inferential Analyses: We conducted separate logistic regression analyses with robust standard errors to determine whether an association existed between either the minimum SFA/EGA ratio or the maximum weekly weight gain and the composite of poor birth outcomes. Logistic regression is a form of regression analysis that is appropriate for binary outcomes and allows for both continuous and categorical covariates. Both predictors of interest were considered as continuous variables since we do not know what cutoff would be appropriate. However, some of the covariates in the adjusted analyses were categorical (e.g. smoking status). The parameter of interest in this logistic regression is the ratio of the odds of poor birth outcome in two groups of women who differ by 1 unit in the predictor of interest. Typically the odds ratio has a skewed distribution so the natural logarithm transformation of the odds ratio is used in logistic regression to perform inferential analysis on a more symmetric distribution. We use robust standard errors in case our data violates the assumptions about the expected mean-variance relationship for binary outcomes. This may happen if the model fits poorly and therefore does not describe the true relationship in the log-odds over groups, either because the log-odds are truly a linear function of the predictors, or because we have the wrong predictors (or transformations of the predictors) in our model. The robust method uses the sample variance rather than the mean-variance relationship to calculate the standard errors. Usually in large samples there is good agreement between the model-based variance estimate and the sample variance estimate, so the inference with robust standard errors may not differ substantially from the classical inference, but it is better to use the robust method in case the mean variance assumption is violated.

Univariate models were run to examine crude associations. However, it is known that other factors such as smoking behaviors influence pregnancy outcomes. The multivariate regression

Comment [a8]: Careful here. You are talking about a link function, not a transformation of the data. Hence, the “distribution” of the odds ratio that you would be talking about is a Bayesian prior distribution. I think a better motivation would be the instability of ratios as opposed to log ratios

Comment [a9]: well, yes, it is akin to the sample variance, though it is a little more complicated. So I might soften your wording here. Something like “essentially uses the sample variance”

Comment [a10]: This is not true in general, though to the extent that in large samples we will do a better job of modeling the mean relationships, it will be true.

model acknowledges and corrects for this possibility of confounding. In addition to correcting for confounding, the multivariate regression model can also adjust for precision variables. This type of variable is not as crucial to have in the model because the measure of association is not biased by their exclusion. However, the accuracy with which we make the estimate can be improved by including precision variables in a multivariate regression model. In the case of logistic regression, including precision variables allows us to better estimate the conditional, or individual level, effect of the predictors, rather than the marginal, or population level effect. Our multivariate model adjusted for smoking, age, height, parity, baseline BMI, and gestational age at first visit as known predictors of poor outcomes. Smoking is a dichotomous variable. Height, parity, BMI and gestational age were modeled linearly. Age was modeled as a quadratic term to allow flexibility in the model since we know that risk is higher at both younger and older ages.

After establishing an estimate of an association, it is important to determine if the result we got from our sample is typical if there was no true association between the predictor of interest and the response. A p-value is a quantification of how unlikely our results are when the truth is that there really is no difference in the odds ratio for the groups we are comparing. For this analysis we have determined that if the probability of our sample's result was less than 0.05 when the null hypothesis of no difference was true, this would be sufficient evidence that there is really a difference in the odds ratio of the two groups.

Comment [a11]: and if you wanted to slip into jargon and not irritate the Bayesians (who argue that you can not necessarily regard frequentist analyses as evidence), you could say "we could say with high confidence". This is of course a jargonistic use of the word "confidence"

A confidence interval is another way of quantifying the uncertainty in the estimation of association provided by the logistic regression. The confidence interval is the range of values that the true value of the association should be found in when our study results are typical. The measure of association in our analysis, the odds ratio, should be 1 if the null hypothesis is true and there is no difference in the odds ratio in the two groups we are comparing. Therefore confidence intervals that contain 1, indicate that our study results do not provide enough evidence to reject the null hypothesis of no association.

<u>Prediction:</u> Although neither predictor of interest was significantly associated with our composite for high risk pregnancy in the multivariate analysis, the point estimates were large for the effects of both minimum SFH/EGA ratio and maximum weekly weight gain, and the results were marginally significant ($p<0.1$). Therefore, we still thought it worthwhile to assess whether including either outcome in the logistic regression model improves the predictive ability. First we modeled only the scientifically relevant covariates for which we had data (smoking, height, parity, age, and BMI and gestational age at first visit). Then using receiver-operating curves (ROC), we compared those results to the results of two separate models with the minimum SFH/EGA and maximum weight gain added in as predictors. We compared the area under the curve (AUC) to assess whether the predictors of interest improved the models.

Comment [a12]: I would put this in Results, not Methods

Results

There are 755 women in the dataset, including one duplicate, which we excluded. Among those, 708 women had visits between weeks 20 to 30; 46 women who did not have any visits between weeks 20 and 30 were excluded from the analysis. 103 babies were born preterm, with a low birth weight, or were small for gestation age. 605 babies were born healthy. Baseline maternal characteristics, disposition of follow-up visits, and characteristics of infants at birth are summarized in Table 1, Table 2, and Table 3, respectively.

Comment [a13]: I would have given numbers for each of these categories. Also, did you verify that the classifications made sense with the data you had? For instance, in Table 2 you have a baby listed as 3781 g, and it is hard to imagine it was really pre-term, LBW, or SGA

Comment [a14]: I would have been more circumspect and said "had none of these characteristics". (We had no data on other possible problems.)

Baseline maternal characteristics

Baseline maternal characteristics are described in Table 1. Among women with healthy birth outcomes, the average weight at study enrollment is 63.23 kg (SD: 11.89) and the average height of the mother is 157.08 cm (SD: 6.59). The average BMI at study enrollment is 25.63 (SD: 4.60). The average age of the mothers is 25 years old (SD: 5.43) and the average number of previous deliveries is 1.14 (SD: 1.23). 29.40% of the mothers in this group are smokers. Mothers who later gave birth to a healthy baby were enrolled at an average of 21.87 weeks of gestation (SD: 3.21).

Among babies born preterm, with a low birth weight, or small for gestational age, the average weight at study enrollment is lower at 58.09 kg (SD: 10.92) and the average height of the mother is shorter at154.64 cm (SD: 5.84). The average BMI at study enrollment is also lower at 24.11 (SD: 4.32). Mothers with poor birth outcomes are younger (23.81 years, SD: 4.93) and have had fewer previous deliveries (0.89, SD: 1.12). A higher proportion (42.72%) of the mothers in this group are smokers. Mothers who later gave birth to a baby with poor birth outcomes were enrolled at an average of 21.65 weeks of gestation (SD: 2.79).

Table 1: Maternal Characteristics at Study Enrollment

		Healthy Birth Outcome (N=605)		**Poor Birth Outcome (N=103)**		**Total (N=708)**	
	Missing	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**
Age (years)	0	25.01 (5.43)	14 – 42	23.81 (4.93)	16 - 35	24.83 (5.38)	14 - 42
Parity	0	1.14 (1.23)	0 – 6	0.89 (1.12)	0 - 6	1.11 (1.22)	0 - 6
Smokers (%)	3	29.40%	-	42.72%	-	31.35%	-
Gest. Age (wks)	0	21.87 (3.21)	18 – 30	21.65 (2.79)	15 - 30	21.84 (3.16)	15 - 30
Weight (kg)	3	63.23 (11.89)	40.5 – 119.0	58.09 (10.92)	38.60 – 100.0	62.5 (11.89)	38.6 – 119.0
Height (cm)	5	157.08 (6.59)	106 – 176	154.64 (5.84)	142 - 172	156.74 (6.54)	106 - 176
BMI (kg/m^2)	8	25.63 (4.6)	16.86 - 49.13	24.11 (4.32)	15.86 - 39.56	25.42 (4.59)	15.86 - 49.13

Disposition of follow-up visits

Disposition of follow-up visits is described in Table 2. For mothers who gave birth to healthy babies, the average total number of visits from enrollment to delivery is 8.05 (SD: 2.09) and the average length of time between two successive is 2.12 weeks (SD: 0.55). The average number of visits between week 20 and 30 is 3.08 (SD: 1.04). The average SFH/EGA ratio at visits between weeks 20 and 30 is 0.97 (SD: 0.05), ranging from 0.75-1.17. The average weight gain per week is this group is 0.29kg (SD: 0.25), ranging from -0.62 – 1.72 kg.

For women who gave birth to infants with poor birth outcomes, the average total number of visits from enrollment to delivery is 7.19 (SD: 2.66) and the average length of time between two successive visits is 2.16 weeks (SD: 0.71). The average number of visits between week 20 and 30 is 3.12 (SD: 1.14). The average SFH/EGA ratio at visits between weeks 20 and 30 is 0.96 (SD: 0.07), ranging from 0.81 – 1.21. The average weight gain per week in this group is 0.25 kg (SD: 0.21), ranging from -0.75-0.74 kg.

Table 2: Disposition During Follow Up and Birth Outcomes

		Healthy Birth Outcome (N=605)		**Poor Birth Outcome (N=103)**		**Total (N=708)**	
	Missing	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**
Total Number of Visits	0	8.05 (2.09)	2 - 14	7.19 (2.66)	2 - 13	7.93 (2.2)	2 - 14
Weeks Between Visits	0	2.12 (0.55)	1.1 - 6	2.16 (0.71)	1.17 - 6.5	2.13 (0.57)	1.1 - 6.5
Number of Visits from 20-30 weeks	0	3.08 (1.04)	1 - 6	3.12 (1.14)	1 - 8	3.08 (1.06)	1 - 8
Weekly Weight Gain Between Visits (kg)	0	0.29 (0.25)	-0.62 - 1.72	0.25 (0.21)	-0.75 - 0.74	0.28 (0.25)	-0.75 - 1.72
SFH/EGA ratio	7	0.97 (0.05)	0.75 - 1.17	0.96 (0.07)	0.81 - 1.21	0.97 (0.05)	0.75 - 1.21
Birth Outcomes							
Gestational Age at Birth (weeks)	4	39.33 (1.22)	38 - 44	37.93 (2.22)	30 - 42	39.13 (1.49)	30 - 44
Birth Weight (kg)	3	3247.32 (403.98)	2510 - 4730	2230.15 (414.05)	1035 - 3780	3098.71 (541.68)	1035 - 4730
Small for Gestational Age (%)	0	0.00%	-	100.00%	-	15.00%	-
% Male	0	51.90%	-	41.75%	-	50.42%	-

Characteristics of infants at birth

Characteristics of infants at birth are also shown in Table 2. Among babies born healthy, 51.90% are boys. The average gestational age is 39.33 weeks (SD: 1.22) and the average birth weight is 3247.32 g (SD: 403.98). Among babies born with any of the poor birth outcomes, 41.75% are boys. The average gestational age is 37.93 weeks (SD: 2.22) and the average birth weight is 2230.15 g (SD: 414.05). 100% of babies with poor birth outcomes were considered small for gestational age.

Weekly Weight Gain and SFH/EGA Ratio At Visits From Weeks 20-30

Table 3 shows weekly weight gain and SFH/EGA ratios during follow-up visits. At most gestational ages, women with healthy birth outcomes had higher average weekly weight gain than women with poor birth outcomes, with exception at weeks 28 and 29. The maximum weekly weight gains were larger at each visit, but the minimums were generally smaller as well.

This is because there were more women with healthy birth outcomes, and thus more visits among these women at each gestational age, so we expect a wider range of values. The average of SFH/EGA ratios at each visit had a narrow range, from 0.93-0.98. From weeks 27-30, women with poor outcomes had slightly lower SFH/EGA ratios than women with healthy birth outcomes, but there is no discernable trend before week 27.

Table 3: Weekly Weight Gain and SFH/EGA per Visit from Weeks 20-30

Weekly Weight Gain Between Visits

	Healthy Birth Outcomes (N=605)			**Poor Birth Outcomes (N=103)**			**Total (N=708)**		
Gest Age	# Visits	Mean (SD)	Range	# Visits	Mean (SD)	Range	# Visits	Mean (SD)	Range
20	144	0.10 (0.34)	-0.5 - 2.15	16	0.03 (0.10)	0.0 - 0.0	160	0.10 (0.32)	-0.5 - 2.15
21	76	0.29 (0.65)	-2.2 - 2.2	16	0.09 (0.33)	-0.5- 0.85	92	0.25 (0.61)	-2.2 - 2.2
22	154	0.28 (0.49)	-1.3 - 2.6	26	0.21 (0.35)	-0.15 – 1.0	180	0.27 (0.47)	-1.3 - 2.6
23	104	0.36 (0.55)	-1.0 - 3.2	21	0.26 (0.34)	-0.10 – 1.0	125	0.35 (0.52)	-1.0 - 3.2
24	165	0.31 (0.46)	-1.45 - 1.5	37	0.23 (0.28)	-0.3 - 0.83	202	0.29 (0.44)	-1.45 - 1.5
25	126	0.41 (0.71)	-0.35 – 6.0	24	0.26 (0.61)	-1.5 – 2.0	150	0.39 (0.69)	-1.5 – 6.0
26	193	0.36 (0.57)	-0.65 – 5.8	24	0.25 (0.31)	-0.27 – 1.2	217	0.35 (0.55)	-0.65 – 5.8
27	123	0.48 (0.74)	-2.5 – 6.0	26	0.38 (0.36)	-0.1 – 1.5	149	0.46 (0.69)	-2.5 – 6.0
28	307	0.34 (0.41)	-1.9 - 2.0	50	0.39 (0.48)	-0.95 - 1.8	357	0.35 (0.42)	-1.9 – 2.0
29	122	0.36 (0.54)	-1.2 - 2.5	26	0.54 (0.46)	-0.2 - 1.73	148	0.39 (0.53)	-1.2 - 2.5
30	348	0.40 (0.48)	-1.6 – 3.0	50	0.37 (0.52)	-1.7 - 1.4	398	0.39 (0.48)	-1.7 – 3.0
Total	1862	0.34 (0.53)	-2.5 – 6.0	316	0.30 (0.43)	-1.7 – 2.0	2178	0.34 (0.52)	-2.5 – 6.0

SFH/EGA Ratio at Each Visit

	Healthy Birth Outcomes (N=605)			**Poor Birth Outcomes (N=102)**			**Total (N=707)**		
Gest Age	# Visits	Mean (SD)	Range	# Visits	Mean (SD)	Range	# Visits	Mean (SD)	Range
20	144	0.96 (0.09)	0.60 - 1.45	15	0.96 (0.05)	0.90 - 1.05	159	0.96 (0.09)	0.60 - 1.45
21	76	0.96 (0.07)	0.74 - 1.15	16	0.93 (0.09)	0.81 - 1.19	92	0.96 (0.08)	0.74 - 1.19
22	154	0.96 (0.08)	0.76 - 1.21	26	0.97 (0.07)	0.86 - 1.14	180	0.96 (0.08)	0.76 - 1.21
23	104	0.96 (0.07)	0.74 - 1.23	21	0.98 (0.10)	0.83 - 1.22	125	0.96 (0.08)	0.74 - 1.23
24	165	0.97 (0.08)	0.75 - 1.25	36	0.97 (0.12)	0.79 - 1.42	201	0.97 (0.08)	0.75 - 1.42
25	126	0.97 (0.07)	0.70 - 1.19	25	0.95 (0.07)	0.80 - 1.12	151	0.97 (0.07)	0.70 - 1.19
26	193	0.97 (0.06)	0.79 - 1.17	25	0.97 (0.06)	0.81 - 1.12	218	0.97 (0.06)	0.79 - 1.17
27	123	0.97 (0.06)	0.77 - 1.20	26	0.95 (0.08)	0.81 - 1.11	149	0.97 (0.07)	0.77 - 1.20
28	307	0.98 (0.06)	0.76 - 1.15	50	0.95 (0.09)	0.79 - 1.25	357	0.97 (0.06)	0.76 - 1.25
29	122	0.98 (0.06)	0.82 - 1.15	26	0.96 (0.09)	0.76 - 1.21	148	0.97 (0.07)	0.76 - 1.21
30	348	0.98 (0.06)	0.79 - 1.22	50	0.94 (0.06)	0.83 - 1.13	398	0.97 (0.06)	0.79 - 1.22
Total	1862	0.97 (0.07)	0.60 - 1.45	316	0.96 (0.08)	0.76 - 1.42	2178	0.97 (0.07)	0.60 - 1.45

Comment [a15]: I probably would have given the SFH instead of the ratio in this table. Note that falling off the rate of growth will have lesser impact on the ratio toward the end of the interval due to the larger denominator. So for descriptive purposes giving the SFH measurements might allow us to see things better

Regression Analyses

Table 4 shows the results of univariate and multivariate regression analyses. In the univariate logistic regression with minimum SFH/EGA ratio as the independent variable and poor birth outcome as the dependent variable, the odds ratio for a one unit difference in the minimum SFH/EGA between weeks 20 and 30 is 0.0143 (95% confidence interval [CI]: 0.0003 - 0.5634, p=0.023). Since the range of SFH/EGA ratios in our data are from 0.75 to 1.21 (table 2), a 1-unit change would be a large difference. The unexponentiated coefficient in the regression model is -4.2453 for a 1 unit difference in the minimum SFH/EGA ratio. Therefore, the coefficient would be -0.0424 for a .01 unit difference in the minimum SFH/EGA ratio, and the odds ratio for this size difference would be $e^{-0.0424}$ or 0.958. This means that a 0.01 unit higher minimum SFH/EGA ratio is associated with a 4.16% lower odds of having a poor birth outcome in this population. Similarly, a 0.1 unit higher SFH/EGA ratio is associated with a 34.6% lower odds of a poor birth outcome.

Comment [a16]: I would only give comparisons that were relevant. in the sense that they were within the range of your data.

After adjusting for age, parity, height, smoking status, BMI at enrollment, and gestational age at enrollment, the association between minimum SFH/EGA ratio and poor birth outcomes was attenuated. The adjusted odds ratio is 0.0310 (95% CI: 0.0005-1.8159, P=0.094). The adjusted odds ratio for a 0.01 unit higher minimum SFH/EGA between weeks 20 and 30 is 0.9658, meaning that women with a 0.01 unit higher minimum SFH/EGA ratio have a 3.4% lower odds of poor birth outcomes in this population. However, this difference is not statistically significant from zero so we cannot reject the null hypothesis of no association between minimum SFH/EGA ratio and poor birth outcome.

In the univariate analysis with maximum weekly weight gain during weeks 20 to 30 as the independent variable and poor birth outcomes as the dependent variable, the odds ratio for weekly weight gain is 0.6930 (95% CI: 0.4761-1.0087, p=0.056). This means that a 1-kilogram higher maximum weekly weight gain during week 20 and 30 is associated with a 30.7% *lower* odds of having poor birth outcomes. This is in the opposite direction from our hypothesized relationship. Since the range of average weekly weight gain in our sample is -0.75-1.72, 1kg would be a large difference. It might be more useful to think about the effect of a 0.1 kg difference in maximum weekly weight gain. The odds ratio for this change would be 0.964, meaning that a 0.1kg higher maximum weekly weight gain is associated with a 3.6% lower odds of a poor birth outcome in this population.

Comment [a17]: But we would hypothesize that either higher or lower weight gain would be associated with problems: High weight gain perhaps indicative of pre-eclampsia, and lower weight gain associated with poor fetal growth. (I would expect the latter to predominate, owing to the relative rarity of pre-eclampsia)

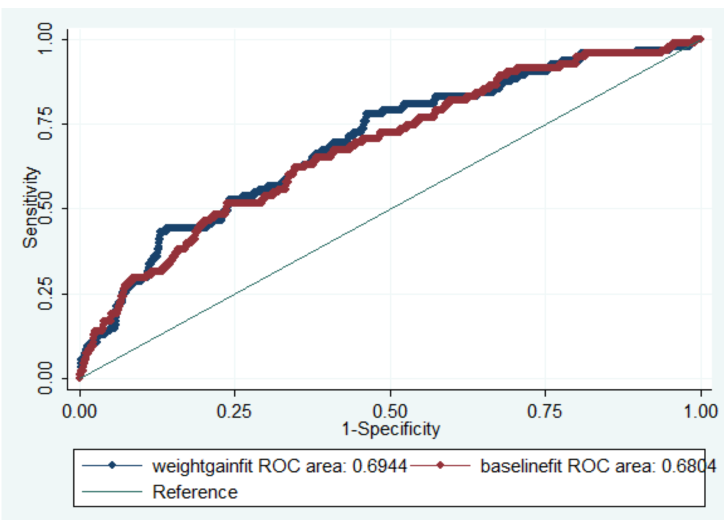
After adjusting for age, parity, height, smoking status, BMI at enrollment, and gestational age at enrollment, the association between maximum weekly weight gain before week 30 and poor birth outcomes was also attenuated. The odds ratio is 0.6066 (95% CI: 0.3496-1.0527, p=0.076). A one kilogram higher maximum weekly weight gain during weeks 20-30 is associated with a 39.34% lower odds of having poor birth outcomes. A 0.1 kg higher maximum weekly weight gain is associated with a 4.88% lower odds of having a poor birth outcome.

	Univariate Analysis				Multivariate Analysis			
	OR	95% CI		p-value	OR	95% CI		p-value
Min SFH/EGA Ratio	0.0143	0.0003	0.5634	0.023	0.0310	0.0005	1.8159	0.094
Max Weekly Weight Gain	0.6930	0.4761	1.0087	0.056	0.6066	0.3496	1.0527	0.076

Prediction

Although the results of the regression analyses did not show statistically significant associations between the odds of a poor outcome and minimum SFH/EGA ratio or maximum weekly weight gain, the point estimates indicated a protective effect, and the p-values were both marginally significant ($p<0.10$). Therefore, we still felt it worthwhile to investigate the predictive value of these variables. We created a prediction model from risk factors that could be identified at enrollment into prenatal care, including age, parity, height, baseline BMI, smoking status, and gestational age at enrollment. The area under the ROC curve (AUC) for this model was 0.6804. Adding maximum weekly weight gain to this model (Figure 1) increases the AUC very slightly, 0.6944. This difference is not statistically significant (P=0.1540) and is not large enough to be meaningful. Adding minimum SFH/EGA ratio to the baseline prediction model (Figure 2) also slightly improves the AUC, from 0.6836 to 0.6925. The slight difference in the baseline AUC in this comparison is due to 1 observation being omitted due to missing data for the minimum SFH/EGA ratio). This difference is also small and not statistically significant (P=0.4024).

Figure 1: ROC curves for model with baseline predictors and with weight gain added



Comment [a18]: Even in a report like this, it is probably good to list everything in the multiple regression model her. Of major interest to me would be whether both POIs are in this model. Your prior paragraph suggest no, but your later discussion seems to suggest yes. (I think no is the answer, any your discussion is not relevant to your models)

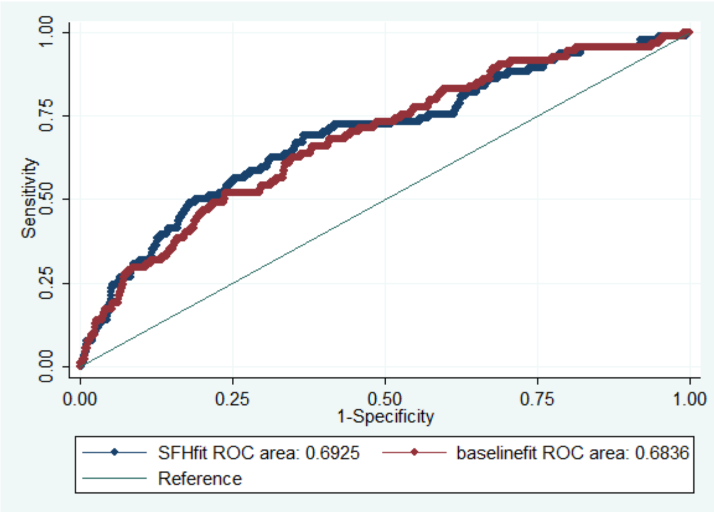
Comment [a19]: I will venture to state that if you cannot demonstrate an association, there will never be a good predictive rule. However, I still would have done the analysis you did in order to drive that point home.

Comment [a20]: My personal bias is that AUC is overused as a criterion.

That having been said, this was a very nice analysis that showed that there was basically no improvement over using just the baseline variables.

You could have made a comment about how bad the predictive model was for the baseline variables: To identify 50% of the poor outcome pregnancies, you would have identified about 25% of the others. With about a 1:6 ratio, in order to identify about 50 of the 100 hundred poor outcome pregnancies, you would identify 150 of the 600 other pregnancies. That means the PPV of such a rule was only about 25% or less. And you are missing half the high risk population. (I am doing these calculation in my head, so it is not very accurate. But you get the idea.)

Figure 2: ROC curves for model with baseline predictors and with SFH/EGA ratio added



Discussion

The first goal of the analysis was to determine for measurements taken between 20 and 30 weeks of pregnancy whether an association existed between either SFH/EGA and odds of poor birth outcomes or weekly weight gain and the odds of poor birth outcomes. The univariate logistic regression analysis indicated that the SFH/EGA had a statistically significant association. However, the descriptive statistics of our sample indicate that the gender distribution of the babies in the two groups defined by healthy/unhealthy outcomes was remarkably different. It is known that gender of baby is associated with SFH during pregnancy, so gender of the baby could confound the relationship between SFH/EGA and poor birth outcome. Mother's smoking status is another known confounder, which is also distributed unevenly in the two groups.

Neither of the adjusted logistic regression models for maximum weekly weight gain nor minimum SFH/EGA during weeks 20 and 30 had a statistically significant association with poor birth outcomes, including LBW, SGA, and pre-term delivery. The p-values did not reach the 0.05 significance level. The non-significant associations between the predictors of interest (POI) with poor birth outcomes may be due to the relatively small sample size and a lack of statistical power. Analyzing the information in Table 3 we see that there are many fewer measurements earlier on in the pregnancy (weeks 20-25). The maximum weekly weight gain and minimum SFH/EGA during weeks 20 and 30 measured in our study may not accurately reflect the true maximum and minimum values had those women come in for visit each week during that period of the pregnancy. Confirming prior research we note that some maternal characteristics, including height, BMI at enrollment and smoking status were significantly associated with poor

Comment [a21]: This is some jargon that is OK, but you need to explicitly state that SFH/EGA ratio and weight change are your POIs birth outcomes. The associations were likely to remain significant after adjusting for multiple comparisons.

Although the reductions in odds ratios associated with the POIs were not significant, the magnitudes were big so we decided to further investigate whether including either of these measurements would improve predictions of poor birth outcomes. The prediction model that included only age, parity, height, baseline, smoking status, and gestational age was fair. Adding either of the predictors that we were interested in was not able to further improve the AUROC by a significant amount.

A limitation of our analysis is that the POIs in our analysis may be correlated since they are both an indirect measure of fetus growth, and there might be a multiple comparison issue in our analysis. The p-values may be inflated and the amount inflated depends on the strength of the correlation. In this dataset, mother's pre-pregnancy BMI, a proxy to mother's nutritional status, is not available. Therefore, we used BMI at enrollment as a proxy to pre-pregnancy BMI. BMI at enrollment is a function of BMI at enrollment, height, and weight gain during pregnancy prior to enrollment. Mother's weight gain prior to enrollment is also a measure of fetus growth and is likely to be correlated with our POIs. Data are also not available on maternal health conditions at pregnancy onset or during gestation (including weight or obesity, HIV, diabetes, & hypertension), previous birth outcomes, and blood pressure during prenatal care visits, or maternal ethnicity. All are important predictors of pregnancy risk. There is a risk of confounding by these unmeasured factors.

Comment [a22]: This would only matter if you had both of them in the same model when assessing associations. This would not matter at all in your predictive models.

Comment [a23]: Given the goal of prediction, I would not talk as much about the possibility of confounding, and I would talk more about the greater prediction that we might be able to attain if we had this data.