Summary

This analysis addressed three main questions: 1) Are there associations between maternal weight gain, symphysis-fundal height and the delivery of preterm, LBW, or small for gestational age babies 2)Are any other maternal or fetal characteristics associated with the delivery of preterm, LBW, or small for gestational age babies and 3) is it possible to develop a model that accurately predicts women at high risk for adverse pregnancy outcomes.

Of the variables in the original scientific question, minimum SFH normalized to EGA had significant associations with all outcomes of interest whereas weight, modeled as the maximum proportional maternal weight gain by week, was not. The ratio of SFH/week tended to be smaller in births with adverse outcomes (between 0.904 and 0.913). Regarding the creation of a prediction model, additional assessment of the identified predictors of interest would be necessary. Assumptions necessary for the description of associations have not been met in this observational analysis (large sample size, independent observations).

Comment [a1]: The analysis method leaves some things to be desired, but is generally acceptable.

The write-up is very poor. You have done no interpretation of the results in a way that would bridge the gap between the scientific question and the statistical analyses.

Comment [a2]: Lead off with overall goal. In this analysis in particular, failure to remember the goal can steer you wrong.

Comment [a3]: Tell us about the source of the data, the type of data, the sample size

Comment [a4]: The time of measurement of these predictors was all important to the question

Comment [a5]: define your terms

Comment [a6]: I'm not convinced. I think there was more than enough info in the data to suggest that these would not lead to good prediction.

Comment [a7]: Provide estimates, CI, P values

Comment [a8]: I think we are okay on both grounds.

Background

Adequate prenatal care is an important contributor to the delivery of a healthy infant. Lack of adequate prenatal care has been associated with adverse perinatal outcomes, such as preterm birth (prior to the 38th week of gestation), low birth weight (< 2500 grams), and small for gestational age (SGA) babies (below the 10th percentile of birth weight for the gestational age at which they are born). While improvements in prenatal care in developed nations have contributed to significant reductions in perinatal morbidity and mortality, adverse outcomes have not been so dramatically impacted in developing nations where scarce resources limit the availability and quality of adequate prenatal care for many women.

For providers in austere settings, the ability to identify women with a higher risk of delivering a preterm, low birth weight (LBW) or SGA infant using practical measurements made at routine prenatal visits might afford healthcare providers the opportunity to introduce more aggressive prenatal monitoring or direct women to care at specialized centers if needed. Examples of such routine measurements include maternal weight and the symphysis-fundal height (the distance from the pubic symphysis to the uterine fundus), both measurements that are typically obtained at each prenatal visit between 20-30 weeks estimated gestational age (EGA). This study was designed to examine associations between measurements of maternal weight and symphysis-fundal height (SFH) made between 20 – 30 weeks EGA and the three aforementioned adverse pregnancy outcomes with an overall goal of early identification of high-risk pregnancies.

Questions of Interest

<u>As stated in the consultant's proposal</u>:

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 which accurately distinguishes between women who will and will not have growth retarded babies?

As answered in this analysis:

1. For measurements made between 20-30 weeks EGA, are there associations between maximum proportional maternal weight gain by week or minimum SFH at any visit normalized to EGA and the delivery of preterm, LBW, or SGA babies or any combination thereof?

2. Are there associations between other maternal or fetal characteristics and the delivery of preterm, LBW, or SGA babies or any combination thereof?

3. Is it possible, using the information obtained by answering questions (1) and (2) above, to develop a model that accurately predicts women at high risk for adverse pregnancy outcomes?

Description of the Data

Data are provided from a prospective cohort study performed in a peri-urban setting in the Western Cape, South Africa. Information is available for 755 women with singleton pregnancies, all unable to afford private healthcare. Women were followed from the time of study enrollment (average EGA at the time of enrollment of 22 weeks) to delivery. Measurements obtained at enrollment and at each subsequent visit included maternal weight (in kilograms) as well as SFH (the distance from the pubic symphysis to the uterine fundus).

For this analysis, maximum proportional maternal weight gain by week and minimum SFH at any visit normalized to EGA were assessed as predictors for the following outcomes of interest, all modeled as binary variables: preterm birth (prior to the 38^{th} week of gestation), low birth weight (< 2500 grams), small for gestational age (SGA) babies (below the 10^{th} percentile of birth weight for the gestational age at which they are born), and a composite outcome including any of these three. Additional variables assessed as predictors include mother's height (in centimeters), mother's age (in years), parity (number of deliveries, categorized as 1^{st}, 2^{nd}-5^{th}, or > 5^{th} pregnancy), smoking status (yes, no), and sex of the infant (male, female).

Comment [a9]: Does this mean divided by?

Comment [a10]: why categorized?

Data not included in this cohort:

1. Pre-pregnancy weight – potentially an important piece of information reflective of a woman's baseline nutritional status.
2. Maternal blood pressure measurements – an important element of perinatal screening, as elevated blood pressure during pregnancy may affect placental

Comment [a11]: do you have a surrogate that might work?

circulation and in uncontrolled or extreme circumstances (e.g. preeclampsia, eclampsia) lead to adverse fetal outcomes.

3. Information about chronic or acute infection during pregnancy – chronic infection with human immunodeficiency virus (HIV) or mycobacterium tuberculosis (TB) may affect fetal growth via numerous mechanisms and acute infections may be associated with adverse events such a preterm labor.
4. Women in the study population do not have a uniform number of visits. However, this information is reflective of a real-world setting in which women will have different levels of participation in outpatient clinic.

Statistical Methods

Potential associations between available maternal and pregnancy information and pregnancy outcomes were assessed in these analyses. The process used here represents a first step on the path to prediction modeling, as association between predictor and outcomes must first be established before meaningful prediction can occur.

The model building process was conducted as follows. Univariate analyses regressing each factor against each outcome were conducted. The univariate alpha criterion for inclusion in subsequent multivariate models was set at 0.20 *a priori* in order to improve the sensitivity of identifying potentially useful variables for use in future prediction modeling. Variables meeting the alpha criterion were then modeled multivariately. An alpha criterion for retention in the multivariate model was set *a priori* at the conventional 0.05 level. Models were reduced in a step-wise process where appropriate with any variables above the 0.05 removed from the model. This step-wise process was repeated until all covariates were significant. Note that no more than 2 steps were required for any outcome. Models reported are the final result of this model reduction process.

All models were log-linear regression using the Gaussian (Normal) distribution. Exponentiated parameter estimates (risk ratios) and 95% confidence intervals are reported as well as the p-values associated with the Wald chi-square testing the significance of the parameter estimate. Variances were computed using the Huber-White sandwich estimator.

The specification of the Gaussian distribution family was selected due its lack of a mean-variance relationship. While it is not known whether this assumed variance structure is completely correct for these data, this is not of primary concern for this type of analysis. Because we are seeking here to quantify the association by looking only a single parameter, the log(risk ratio), we need not be concerned that the specification of distribution family be exact. Rather we want to be confident that we are not mis-specifying the variance structure. Note that it will be more important that the model specification match the structure of the data for subsequent prediction modeling which will be concerned with the estimating the entire distribution for accurate prediction capability.

Comment [a12]: As discussed extensively in class, the use of the log link with the Gaussian family creates a weighting that is often undesirable.

Using Poisson regression is greatly to be preferred here. We handle the mean-variance by using the robust SE.

Analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC) and Stata SE 12 (Statacorp LP, College Station, TX).

Results

Table 1A presents baseline maternal factors by birth outcome. Of 755 total pregnancies, four were censored for the outcome low birthweight; five were censored for the outcome preterm, and none were censored for the outcome small-for-gestational-age. The mean maternal age for all births was 24.79 (SD 5.4) years, which differed only slightly in groups defined by adverse birth outcomes. 31.4% of all mothers smoked, and this prevalence decreased in groups defined by normal birth outcomes (between 29.4 and 30.8 percent) and increased in groups defined by adverse outcomes (between 38.5 to 43.2 percent).

Comment [a13]: I think you are misusing the term "censored" here. "Censored" is a very special kind of missing data.

38.8% of all births were to first-time mothers, while 59.3% of mothers had already experienced between one and four live births and 1.85% of births were to mothers with over 4 previous live births. In comparison, among births with any adverse outcome, 46.2% were to first-time mothers and 52.8% were to mothers having experienced 1-4 previous births.

Of the 755 total births, 39 pre-term, 79 low birth weight and 105 small-for-gestational-age outcomes were observed.

Comment [a14]: there is overlap

Table 1B presents pregnancy measurements, the main predictors of interest (SFH and mother's weight), and length of observation by birth outcome. The average number of clinical visits from enrollment to birth was 7.74 (SD2.3), and was slightly lower among those births with adverse outcomes (7.14). The average length of observation in the total population was 15.59 weeks and tended to be shorter among births resulting in adverse outcomes. The minimum ratio of SFH/week among all births was 0.927. This ratio tended to be smaller in births with adverse outcomes (between 0.904 and 0.913). Average maximum proportional maternal weight gain by week among the entire population was 0.00272, compared to 0.00225 among births with any adverse outcome.

Comment [a15]: Is this an average?

Table 3 presents the results of initial univariate analyses of predictors of interest. SFH by week of gestation, maternal age, parity, smoking status, maternal height, and infant sex were significantly associated with any adverse outcomes. Maximum proportional maternal weight gain by week was not found to be statistically significant in any of the outcomes. Results were inconclusive for several models of pre-term as the model was unable to converge on a likely estimate.

Comment [a16]: What are your measures of association

Table 4 presents the results of the multivariate regression run on coefficients that proved to be predictive in univariate analysis. After adjusting for smoking status, infant sex, maternal height, and parity, minimum SFH at any visit normalized to EGA remained significantly associated with all adverse outcomes.

Discussion

We have identified several potential predictors of adverse fetal outcomes among women evaluated within a specific obstetrics clinic in South Africa. Of the variables most pertinent to the original scientific question (weight profiles and/or SFH profiles over pregnancy), minimum SFH normalized to EGA was found to have significant associations with all pre-specified outcomes of interest whereas weight, modeled as the maximum proportional maternal weight gain by week, was not. Importantly, the manner in which predictors of interest were defined should be taken into consideration as alternate choices may result in different estimates of association. That is, definition of weight as the maximum proportional maternal weight gain by week may provide different estimates as compared to an assessment of maximum weight by EGA.

Of the assessed outcomes, SGA had the largest number of significantly associated covariates, including SFH conditioned on measurement date, maternal height, parity, smoking and infant sex. Notably, the estimates for predictors of SGA and our composite outcome including any of our three adverse events are quite similar, suggesting that a composite outcome may not provide a significant advantage in terms of encompassing more information than is already available with the individual outcomes.

In this dataset, missing observations may impact the precision of the estimates or potentially produce biased estimates if the missingness is associated with our outcomes of interest. However, it should be noted that the evaluation of pregnant women in under-developed nations is likely to continue to produce such missing data, making the available observations potentially reflective of a real-world scenario. Finally, baseline characteristics, including evidence of prior adverse event and infections, and blood pressure measurements may be other important predictors that cannot be considered in this dataset.

Regarding the creation of a prediction model, additional assessment of the identified predictors of interest would be necessary. Assumptions necessary for the description of associations have been met in this observational analysis (large sample size, independent observations). However, a linear relationship between the predictors modeled as continuous variables and the outcomes of interest is necessary for accurate prediction in individual women. These relationships might be further assessed to document such and explore the most apt definition of maternal weight and SFH profiles. In addition, threshold values for the non-binary predictors would need to be identified and evaluated via a mechanism such as receiver operating characteristic curves. A desire for sensitivity would likely prevail over a the need for specificity given the goal of identifying high-risk pregnancies, though the usefulness of such a predictive model might be impacted by the prevalence of adverse outcomes in other settings.

Table 1A. Baseline maternal factors, by birth outcome

	Any adverse outcome	Normal delivery	Pre-term[1] (Yes)	Pre-term[1] (No)	LBW (Yes)	LBW (No)	SGA (yes)	SGA (no)	All births
Mean maternal age, years (SD)	24.05 (5.1)	24.91 (5.4)	24.23 (4.7)	24.79 (5.4)	24.09 (5.1)	24.87 (5.4)	23.85 (4.9)	24.94 (5.4)	24.79 (5.4)
Mean maternal height, cm (SD)	154.7 (6.04)	157.0 (6.52)	154.6 (5.80)	156.8 (6.51)	153.7 (6.04)	157.0 (6.47)	154.6 (5.87)	157.0 (6.54)	156.7 (6.50)
Prevalence of smoking among mothers[2] (%)	43.1	29.4	38.5	30.8	43.2	30.0	43.1	29.4	31.4
Prior live births (n)									
0	50	243	18	273	38	255	49	244	293
1-4	57	391	21	424	40	408	55	393	448
>4	1	13	0	14	1	13	1	13	14
Total Pregnancies	108	647	39	711	79	676	105	650	755

[1] Term status was missing for five women. Total for pre-term outcome was 750.
[2] Smoking status was missing for four women. Total for smoking exposure was 751.

Table 1B. Pregnancy measurements, by birth outcome

	Any adverse outcome	Normal delivery	Pre-term[1] (Yes)	Pre-term[1] (No)	LBW (Yes)	LBW (No)	SGA (yes)	SGA (no)	Total
Mean EGA at enrollment, weeks[2] (SD)	22.64 (2.00)	22.91 (2.66)	22.51 (1.89)	22.89 (2.61)	22.47 (1.91)	22.92 (2.64)	22.66 (2.01)	22.90 (2.66)	22.86 (2.58)
Mean EGA at last measurement, weeks (SD)	36.28 (3.25)	38.39 (1.93)	33.50 (3.05)	38.25 (2.10)	35.65 (3.26)	38.37 (1.96)	36.26 (3.29)	38.38 (1.93)	38.09 (2.29)
Mean length of observation, weeks[3] (SD)	14.39 (4.71)	15.79 (4.30)	12.13 (4.99)	15.71 (4.32)	14.06 (4.77)	15.77 (4.31)	14.34 (4.74)	15.79 (4.30)	15.59 (4.38)
Mean clinical visits during from enrollment to birth (SD)	7.14 (2.6)	7.85 (2.2)	5.25 (2.4)	7.83 (2.2)	6.83 (2.6)	7.85 (2.2)	7.11 (2.7)	7.85 (2.2)	7.74 (2.3)
Mean clinical visits between 20 and 30 weeks (SD)	3.08 (1.2)	2.86 (1.3)	3.08 (1.3)	2.88 (1.3)	3.10 (1.2)	2.87 (1.3)	3.06 (1.2)	2.87 (1.3)	2.90 (1.3)
Maximum proportional maternal weight gain by week, mean (SD)[4]	0.0107 (0.0079)	0.0116 (0.010)	0.0105 (0.0099)	0.0114 (0.010)	0.0110 (0.0086)	0.0115 (0.010)	0.0106 (0.0080)	0.0116 (0.010)	0.0114 (0.010)
Min SFH/week[5]	0.913 (0.066)	0.929 (0.050)	0.904 (0.070)	0.928 (0.060)	0.910 (0.063)	0.929 (0.060)	0.913 (0.067)	0.929 (0.060)	0.927 (0.061)
Sex of infant, % female[6]	57.7	47.6	59.0	48.4	58.7	47.9	57.7	47.6	49.0

Total number of women was 755.
[1] Term status was missing for five women. Total for pre-term outcome was 750.
[2] EGA at enrollment was missing for 46 women. Total was 709.
[3] Length of observation was missing for 2 women. Total was 753.
[4] Proportional maternal weight gain was missing for 97 women. Total was 658.
[5] Ratio of SFH to week was missing for 47 women. Total was 708.
[6] Sex of infant was missing for four women. Total for pre-term outcome was 751.

Table 2. Available Data

	Any adverse outcome	Pre-Term	LBW	SGA	Total
Number women with visits at					
20	16	7	13	16	160
21	18	6	16	16	92
22	26	10	17	26	180
23	21	5	16	21	125
24	38	18	27	37	202
25	26	11	20	26	152
26	28	8	18	25	219
27	27	10	22	26	149
28	52	19	36	50	357
29	27	9	25	26	149
30	54	17	35	52	401
Total visits	333	120	245	321	2186
Number women with *x* visits between 20 and 30 weeks					
0	2	0	1	2	46
1	7	3	4	7	51
2	20	10	16	20	143
3	42	13	33	42	266
4	30	11	19	27	207
5	4	0	4	4	31
6	2	1	1	2	10
7	0	0	0	0	0
8	1	1	1	1	1
Total	108	39	79	105	755

Comment [a17]: This was good to examine.

It would have been extremely useful for you to provide descriptive for SFH and maternal weight in this table

Table 3. Univariate regression models

	Any adverse outcome	Pre-Term	LBW	SGA
Maximum proportional maternal weight gain by week	0.011 (0.00, 321144) p=0.4938	☙	0.044(0.00, 111470000) p=0.7767	0.0003 (0.00, 342052) p=0.4428
SFH by week of gestation	0.0363 (0.0025, 0.518) **p=0.0145**	0.0095 (0.0002, 0.42) **p=0.0158**	0.0268 (0.0014, 0.51) **p=0.0159**	0.0339 (0.0022, 0.51) **p=0.0146**
Maternal age	0.974 (0.94, 1.01) **p=0.1332**	0.984 (0.93, 1.04) p=0.5612	0.976 (0.94, 1.02) p=0.2397	0.968 (0.94, 1.00) **p=0.0717**
Parity, categories				
0 prior live births	1.0	☙	1.0	1.0
1-4 prior live births	0.746 (0.53, 1.06) p=0.1002		0.688 (0.45, 1.05) p=0.0807	0.734 (0.51, 1.05) p=0.0886
>4 prior live births	0.419 (0.062, 2.81) p=0.3703		0.551 (0.081, 3.73) p=0.5409	0.427 (0.064, 2.87) p=0.3817
Overall (2df)	**p=0.1728**		p=0.2166	**p=0.1661**
Parity, continuous	--	0.919 (0.70, 1.21) p=0.5492	--	--
Smoking status	0.582 (0.41, 0.83) **p=0.0029**	0.708 (0.38, 1.32) p=0.2791	0.565 (0.37, 0.87) **p=0.0091**	0.582 (0.41, 0.83) **p=0.0029**
Maternal height	0.974 (0.95, 0.99) **p=0.0330**	0.973 (0.94, 1.00) **p=0.0841**	0.968 (0.94, 1.00) **p=0.0243**	0.973 (0.95, 1.00) **p=0.0318**
Infant sex	1.42 (0.99, 2.04) **p=0.0578**	1.50 (0.81, 2.79) p=0.2011	1.48 (0.95, 2.29) **p=0.0800**	1.42 (0.99, 2.04) **p=0.0578**

Comment [a18]: What do any of these numbers mean?

Values are estimated risk ratio (95% confidence interval), p-value for the Wald chi-square computed using the Huber-White sandwich estimator of variance. **Boldface indicates statistical significance at $\alpha = 0.20$.**

ↄз Model could not be fit reliably.

Table 4. Multivariate regression models

	Any adverse outcome	Pre-Term	LBW	SGA
Maximum proportional maternal weight gain by week	--	--	--	--
SFH conditional on measurement date	0.0470 (0.0023,0.96) **p=0.0466**	0.0047 (0.0001, 0.25) **p=0.0083**	0.0171 (0.0008, 0.36) **p=0.0090**	0.0470 (0.0023,0.96) **p=0.0466**
Maternal Age	--	--	--	--
Maternal Height	0.971 (0.95, 0.99) **p=0.0138**	0.975 (0.95, 1.00) **p=0.0822**	0.967 (0.94, 1.00) **p=0.0228**	0.991 (0.94, 1.0) **p=0.0138**
Parity, categories		--	--	
0 prior live births	1.0			1.0
1-4 prior live births	0.623 (0.43, 0.92) p=0.0166			0.623 (0.43, 0.92) p=0.0166
>4 prior live births	0.184 (0.024, 1.4) p=0.1030			0.184 (0.024, 1.4) p=0.1030
Overall (2df)	**p=0.0124**			**p=0.0124**
Parity, continuous	--	--	--	--
Smoking status	0.595 (0.41,0.87) **p=0.0077**	--	0.713 (0.45, 1.14) p=0.1569	0.595 (0.41,0.87) **p=0.0077**
Infant Sex	1.567 (1.04, 2.35) **p=0.0300**	--	1.564 (0.95, 2.57) p=0.0780	1.567 (1.04, 2.35) **p=0.0300**

Values are estimated risk ratio (95% confidence interval), p-value for the score chi-square computed using the Huber-White sandwich estimator of variance. **Boldface indicates statistical significance at $\alpha = 0.05$.**