Statistical Analysis Plan: Association between maternal weight, fetal size and adverse pregnancy outcomes

Group 05

Summary

A cohort of 755 South African pregnant women were prospectively followed to determine if second-trimester maternal weight and symphysis fundal height were associated with 3 fetal outcomes (pre-term birth, low birth weight, and small for gestational age babies). We observed statistically significant associations between SFH and LBW (odds ratio [OR] 0.47; 95% CI: 0.28, 0.82; p=0.007), and with SFH and SGA (OR 0.48; 95% CI: 0.29, 0.80; p=0.005). These associations persisted after adjustment for maternal age, smoking status, parity category, and height (adjusted odds ratio [aOR] 0.46; 95% CI: 0.27, 0.80; p=0.006 for LBW, and aOR 0.49; 95% CI: 0.29, 0.83; p=0.008 for SGA, respectively). However, changes in maternal weight at 20 and 30 weeks of gestation were not associated with any of the fetal outcomes. These preliminary results suggest that smaller than average changes in SFH may be predictive of low birth weight and SGA in resource-limited settings.

Comment [A1]: Lead off with a statement about the overall goal.

Comment [A2]: lowi income

Comment [A3]: how often do we have relevant measurements?

Comment [A4]: 20-30 weeks EGA

Comment [A5]: pregnancy

Comment [A6]: Provide info on the availability of relevant data: there was not info from 20-30 weeks on all subjects

Comment [A7]: what are your units?

Comment [A8]: More interpretation than this is needed. Predictive capability does imply associations, but not vice-versa

Background

Gestational age and birth weight are important determinants of neonatal morbidity and mortality. Prematurity (birth before 37 weeks of gestation), low birth weight (LBW; <2500g), and small for gestational age babies (SGA; size and weight below 10th percentile for gestational age) are associated with increased risk of adverse health outcomes during the life course, particularly in resource-limited settings. In order to identify problems that may affect the health of the mother and/or fetus, pregnant women are advised to seek antenatal care, usually at primary health clinics. During antenatal screening, measurement of maternal and fetal anthropometric variables can help identify high-risk pregnancies. Maternal weight is monitored to assess maternal and fetal nutrition, and fetal growth is tracked using the symphysis-fundal height (SFH, the distance from the pubic symphysis to the uterine fundus). Mothers identified to have high-risk pregnancies are referred for specialist care.

We conducted a cohort study among pregnant women in the Western Cape, South Africa to determine whether maternal weight and fetal size predict high-risk pregnancies during the second trimester.

Comment [A9]: Probably strong words given the more "convenience" nature of the data. "Cohort" study would to me imply that there was a clear regimen of clinic visits followed, etc. But you are correct that this is more of a cohort study.

Specific Aims

1. To determine whether maternal weight and fetal size differ between women who have prematurity, LBW, and SGA babies and those who don't
2. To evaluate if maternal weight and fetal size, as measured between 20-30 weeks of gestation, predict risk of LBW, SGA and prematurity

Comment [A10]: maternal weight versus changes in maternal weight

Comment [A11]: fetal size versus fetal growth

Data Source

Data were obtained from a cohort study of 755 pregnant women who received public sector antenatal care in the Western Cape province of South Africa. Women were followed from approximately 22 weeks of gestation to delivery. The variables of interest collected at each antepartum visit were maternal weight and symphysis fundal height (SFH), along with smoking status, age, and parity. Outcome variables collected at delivery included the baby's birth weight, gestational age, and sex. A "Small for

Comment [A12]: how were visits determined, and how frequently did they come in?

Comment [A13]: these were at baseline

Gestational Age" (SGA) variable was created to identify babies whose size or weights were below the tenth percentile for their estimated gestational age (EGA).

Statistical Methods

Descriptive analysis was conducted to assess the distribution of variables of interest by preterm birth, low birthweight and SGA using Stata version 12. For continuous variables, the mean, standard deviation, minimum, maximum, median, 25% and 75% percentiles were assessed. There were few missing values (counted in Tables 1A-1C). Though we assumed that missing data were at random based on baseline characteristics, those with missing and non--missing outcomes were compared on maternal age, parity, smoking, and maternal weight to verify our assumptions. We created tables for each dichotomized pregnancy outcome, with summary statistics for each level of the covariates, in order to assess trends.

A total of six multivariate logistic regression models with robust standard error estimates were performed; one set of analyses were run using the predictor of maternal weight change per estimated gestational week (EGA, using measurements from between weeks 20 and 30) on each of the three dichotomous outcomes of interest (low birth weight, pre-term birth, and SGA). The other set of analyses used the predictor of change in SFH per EGA between 20 and 30 weeks on each of the same three outcomes. In the results that follow and in Tables 2A-C and 3A-C, we report the odds ratios, 95% confidence intervals, and p-values calculated in each of the six analyses.

Analyses were adjusted for maternal age, smoking, and parity; maternal age, smoking status, and prior number of births are known to influence both maternal and fetal characteristics and so were considered confounders. Maternal height was also adjusted for; in some resource-poor populations, height can be a surrogate for maternal nutritional status, as well as a proxy for ethnicity, as the population under study is known to consist of multiple ethnicities that do vary considerably by height. Infant sex was also adjusted for as a precision variable, since male babies weigh more than female babies, on average. Maternal age was modeled with quadratic term (age squared) to relax the assumption of linearity. Parity was divided into clinically relevant categories of 0, 1-2, and 3 or more. The models were tested for normality of residuals, heteroscedasticity, outliers, and influence. We assessed whether maternal weight and SFH differed between mothers who had adverse pregnancy outcomes versus those who did not. Risk estimates are reported as odds ratios with 95% confidence intervals.

Missing values were a concern, as women who stopped coming to the clinic or refused measurements for any reason might have some characteristic that would predispose them to a different outcome than women who consistently came to the clinic and were measured. We decided to omit missing values. One factor in our decision was that we are most interested in early predictors of fetal outcomes in women who can be intervened on, i.e. women who consistently show up to the clinic. As this is our population of interest, trying to predict or impute missing values would not contribute much to our analyses.

Results

Tables 1A-1C present descriptive statistics of interest by the three adverse pregnancy outcomes examined. The study data followed 755 pregnant women not having private healthcare from enrollment to delivery. Overall, maternal age was slightly younger in

Comment [A14]: This makes it seem like you created this variable. I have grave concerns about this variable, so I would personally not be wanting to make it look like I created it. (Every single LBW was called SGA. This should not be the case: prematurity leads to LBW, but it is not always SGA.

Comment [A15]: You cannot do this. There is nothing in your data that can discriminate MAR from MNAR.

Comment [A16]: You did not tell us how you computed this

Comment [A17]: Nor did you tell us how you computed this. This makes a difference when it comes to using them in prediction.

Comment [A18]: The difference in weight is more pronounced in the tails of the distributions

Comment [A19]: Why? I would have just done it linearly.

Comment [A20]: Tested? You tested for these things? Why do we care about normality of residuals. You were doing logistic regression!!! I never expect the residuals to be normally distributed. In fact, if they were, you did logistic regression wrong. But even in linear regression I do not care about normality.

Comment [A21]: What was your response variable in these analyses? Were these t tests? Then why reporting OR. I am totally confused.

Comment [A22]: Not sure what you mean by missing data. Certainly we did not even have a record for some women at some weeks. Did you count that as missing?

Comment [A23]: "consistently" or "at the time they show up for clinic"

Comment [A24]: Were any excluded due to no data?

those having adverse birth outcomes compared to normal deliveries (24 vs. 25 years). Weekly average weight increase was similar among women with and without low birth weight and small for gestational age infants, and slightly lower for women experiencing preterm birth (0.86 vs. 0.91). Weekly average SFH increase of pregnant women with low-birth weight was approximately 6mm less than that of women without low-birth weight (Table 1A). Only 3% of women experienced pre-term birth (Table 1B) and weekly average SFH increase in pregnant women with pre-term birth was approximately 5mm lower than that of women without pre-term birth and approximately 7mm lower in women with SGA infants compared to those with infants of normal GA.

Comment [A25]: Give numbers in each category in the text

Comment [A26]: units

Comment [A27]: You are off by an order of magnitude

Results of multivariate logistic regressions evaluating the association between maternal weight increase during weeks 20 and 30 and adverse pregnancy outcomes after adjusting for age, parity, smoking, mother's height and infant sex are presented in Table 2A-2C. Overall, we did not find a statistically significant association between maternal weight and adverse pregnancy outcome, although there was a non-significant trend of higher odds pre-term birth with each kilogram increase in maternal weight over the average.

Comment [A28]: Give estimates, CI, p values. Even when not significant. In fact, it is sometimes most important to give these when it is not significant.

We also evaluated the association between changes in SFH per week of pregnancy and adverse pregnancy outcomes, adjusted for the previously mentioned variables (Tables 3A-3C). We found that, on average, the adjusted odds of a pregnant woman having a low-birth weight infant was 54% lower for each one-centimeter increase in SFH per week by week 30 (95% CI 20-73%) with higher odds of low-birth weight in the group with the lower increase in SFH per week, which was statistically significant. In addition, the adjusted odds of a pregnant woman having a SGA infant was 51% lower for a one-centimeter increase in SFH per week by week 30 (95% CI 17-71%) with higher odds of having a SGA in the group with the lower increase in SFH per week, which was statistically significantly different from 1. We found a similar trend in lower odds of 36% lower odds of pre-term birth for a one-centimeter increase in SFH per week, but this was not statistically significant.

Comment [A29]: Isn't this way outside the range of plausibility? I recognize that vagaries of measurement may lead to some differences, but a woman truly averaging 0.5 cm/week or 1.5 cm/week over the interval of 20-30 EGA seems too much of a difference.

Of course, when it comes to prediction, you will have to decide what to do with such measurement error. But when reporting the associations, it is probably better to stick with differences that are closer to 1 or 2 SD.

Because I do not know how you computed your average weekly change, I cannot assess how bad this might be.

There were 97 women who were missing data on SFH per week and maternal weight gain. They were omitted from the analysis (Table 2-3).

Comment [A30]: This needs to be near the top of the Results section.

Discussion

In this observational cohort of approximately 750 women attending an antenatal clinic from their second trimester through birth, we found that changes in maternal weight at 20 and 30 weeks were not associated with any of the three fetal outcomes assessed, though there was a non-significant trend for a greater than 2-fold risk of pre-term birth with each one kilogram increase in maternal weight over the average by week 30. When we analyzed SFH as a predictor of interest for adverse fetal outcomes, we found statistically significant associations with both low birth weight and SGA indicating that for each cm increase in SFH, we observed greater than 50% reduced risk of these outcomes for women of similar age, smoking status, parity, and height. It does appear that we can conclude that smaller than average changes in SFH may be predictive of low birth weight and SGA. This result is hardly surprising, since SFH is a proxy for infant size; infants that are smaller at 20 and 30 weeks will have an SFH reflective of this, and will also generally continue to be smaller than average at birth. Determining an effective intervention for women with SFH measurements that are increasing slower than average will form the basis for future predictive studies with an interventional component.

Comment [A31]: Actually, I find that SGA and non-SGA infants have very similar average measurements up to about 27 weeks, and then it starts diverging. So it is of key importance when the differences might show up.

However, while it may be possible to form a predictive model using a threshold SFH increase per week in the clinic as a basis for an intervention in observational studies such as these, we should be cautious in over-interpreting the results until they can be replicated in another population. Also, the number of pre-term births was quite small in this population (n=24), so we may not have been able to capture that relationship accurately, as reflected by the larger confidence intervals for this outcome. We also did not correct for multiple comparisons at this time. For this first-pass association analysis, we are more interested in uncovering potential associations for future studies, and do not want to over-correct and potentially lose interesting results. Future studies should evaluate these questions in separate cohorts or correct p-values for multiple comparisons.

Comment [A32]: You were to comment on the likelihood that a good predictive model could be found. I argue that there is more than enough info in the data to tell you it will not be of real practical use.

Additionally, though we attempted to include appropriate confounders in our model, we may still be missing some important additional data. The variables available for analysis were limited to what was collected in the clinic, and we would be better served with more precise measurements of health, such as blood pressure and/or blood sugar readings. Missing data on the outcome is a limitation of this analysis, as a large number of individuals (almost 100) had to be omitted from the regressions because of missing information. We assumed the data was missing at random, which is unlikely given that higher risk women may be more likely to be lost to follow-up. Future research should attempt to characterize the reasons for loss to follow-up.

Table 1A. Characteristics of women attending antenatal clinics by birth weight

	Low birth weight (<2500 grams) n=75			Normal birth weight (>=2500 grams) n=680		
	Number missing	**Mean (SD) or N (%)**	**Range**	**Number missing**	**Mean (SD) or N (%)**	**Range**
Maternal characteristics						
Age at enrollment (years)	0	24 (4.79)	16 - 34	0	25 (5.44)	14 - 43
Parity						
0		36(48%)			257(38%)	
1-2		32(43%)			341(50%)	
3 or more		7(9%)			82(12%)	
Smoking (%)	0	33(44%)		5	198(29%)	
Weekly Average Weight increase (Kg)	1	0.45(0.24)	0 - 1.5	1	0.44(0.19)	0.06 - 1.3
Infant characteristics						
Weekly Average Symphysis fundal height increase (cm)	1	0.86(0.22)	0 - 1.61	1	0.92(0.17)	0 - 1.76
Birth weight (g)	0	2071.20 (351.08)	1035 - 2490	4	3220.4 (414.5)	2510-4730

Comment [A33]: I probably would have presented the % nulliparous, along with the average parity. I do not see why you categorized

Comment [A34]: This cannot be correct, because we had many women with no visit in weeks 20-30. Or maybe it is the sample sizes in the column heading that are wrong

Table 1B. Characteristics of women attending antenatal clinics by fetal gestational age at delivery

	Pre-term birth (<37 weeks) n=24			Full-term birth (>=37 weeks) n=731		
	Number missing	**Mean (SD) or N (%)**	**Range**	**Number missing**	**Mean (SD) or N (%)**	**Range**
Maternal characteristics						
Age at enrollment (years)		24 (4.78)	18 - 33		25 (5.40)	14 - 43
Parity (range)						
0		10(42%)			283(39%)	
1-2		11(46%)			362(50%)	
3 or more		3(13%)			86(12%)	
Smoking (%)	7	7(29%)		5	224(31%)	
Weekly Average Weight increase (Kg)	0	0.49(0.34)	0 - 1.5	2	0.44(0.19)	0.06 - 1.3
Infant characteristics						
Weekly Average Symphysis fundal height increase (cm)	0	0.86(0.33)	0 - 1.61	2	0.91(0.17)	0 - 1.76
Birth weight (g)	0	1787.2 (326.2)	1035 - 2188	4	3149.2 (482.0)	107 - 4730

Table 1C. Characteristics of women attending antenatal clinics by fetus size at birth

	Small for gestational age n=105			Normal for gestational age n=650		
Variable	**Number missing**	**Mean (SD) or N (%)**	**Range**	**Number missing**	**Mean (SD) or N (%)**	**Range**
Maternal characteristics						
Age at enrollment (years)	0	24(4.90)	16 - 35	1	25(5.45)	14 - 43
Parity (range)						
0		49(47%)			244(38%)	
1-2		46(44%)			327(50%)	
3 or more		10(10%)			79(12%)	
Smoking (%)	1	45(43%)		3	186(27%)	
Weekly Average Weight increase (Kg)	1	0.43(0.23)	0 - 1.5	1	0.45(0.19)	0.06 - 1.3
Infant characteristics						
Weekly Average Symphysis fundal height increase (cm)	1	0.85 (0.22)	0 - 1.67	1	0.92 (0.17)	0 - 1.76
Birth weight (g)	1	2231.1 (411.6)	1035 - 3780	3	3246.2 (402.1)	2510-4730

Table 2A. Association between low birth weight and average maternal weight increase per week during weeks 20-30

	Unadjusted (N=656)			Adjusted*(N=641)		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Average maternal weight increase (kg) per EGA during weeks 20-30	0.94	0.49, 1.81	0.858	1.36	0.65, 2.86	0.416

*Estimate adjusted for smoking, maternal age, height, parity, and infant sex.

Comment [A35]: Before this table, I would have presented descriptive statistics on SFH and weight by EGA. I think you would have found it extremely informative when trying to interpret your difference in the SFH change per EGA

Table 2B. Association between pre-term birth and average maternal weight increase per week during weeks 20-30

	Unadjusted (N=656)			Adjusted*(N=616)		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Average maternal weight increase (kg) per EGA during weeks 20-30	1.92	0.87, 4.23	0.104	2.11	0.90, 4.97	0.087

*Estimate adjusted for smoking, maternal age, height, parity, and infant sex.

Table 2C. Association between SGA and average maternal weight increase per week during weeks 20-30

	Unadjusted (N=656)			Adjusted* (N=641)		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Average maternal weight increase (kg) per EGA during weeks 20-30	0.79	0.42, 1.49	0.462	0.94	0.46, 1.91	0.86

*Estimate adjusted for smoking, maternal age, height, parity, and infant sex.

Table 3A. Association between low birth weight and change in SFH per change in week during weeks 20-30*

	Unadjusted (N=658)			Adjusted* (N=649)		
Outcome variable	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
SFH per wk	0.47	0.28, 0.82	0.007	0.46	0.27, 0.80	0.006

*Estimate adjusted for smoking, maternal age, height, parity, and infant sex.

Table 3B. Association between pre-term birth and change in SFH per change in week during weeks 20-30 (N=658)

	Unadjusted (N=658)			Adjusted* (N=649)		
Outcome variable	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
SFH per wk	0.63	0.24, 1.66	0.346	0.64	0.22, 1.84	0.406

*Estimate adjusted for smoking, maternal age, height, parity, and infant sex.

Table 3C. Association between SGA and change in SFH per change in week during weeks 20-30 (N=657)

	Unadjusted			Adjusted*		
Outcome variable	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
SFH per wk	0.48	0.29, 0.80	0.005	0.49	0.29, 0.83	0.008

*Estimate adjusted for smoking, maternal age, height, parity, and infant sex.