Anxiety and Depressive symptoms in pregnancy predict low birth weight differentially in male and female infants - findings from an urban pregnancy cohort in India

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Abstract

Purpose

This study examined the contributions of antenatal anxiety, depression, and partner violence to low birth weight (LBW) in infants and to sex specific birth weight outcomes among mothers from a cohort in urban India.

Methods

Data from 700 mothers from the PRAMMS cohort (Prospective Assessment of Maternal Mental Health Study) was used. Pregnant women were assessed in each trimester - T1, T2 and T3, for symptoms of anxiety, and depression as well as partner violence. Multivariate analyses were performed for the whole sample and then for male and female infants separately. The final multivariable logistic regression models were each built using a backward selection procedure and controlling for confounders. To accommodate longitudinally measured data, change in scores (T2-T1 and T3-T2) of anxiety and depression were included in the model.

Results

Of the 583 women with a singleton live birth, birth weight was available for 514 women and LBW was recorded in 80 infants (15.6%). Of these, 23 infants were preterm. Overall, higher T1 Depression scores (OR: 1.11; 95%CI: 1.040, 1.187) and an increase in both Depression scores (OR: 1.12; 95%CI: 1.047, 1.195) from T1 to T2 and Anxiety scores (OR: 1.32; 95%CI: 1.079, 1.603) between T2 and T3 were predictors of LBW. Female infants had a higher chance of LBW with increase in maternal anxiety between T1 to T2 (OR: 1.69; 95%CI: 1.053, 2.708) and T2 to T3 (OR: 1.49; 95%CI: 1.058, 2.086). Partner violence during pregnancy just failed to reach conventional statistical significance (OR: 2.48; 95%CI: 0.810, 7.581) in girls. Male infants had a higher chance of LBW with higher baseline depression scores at T1 (OR: 1.23; 95%CI: 1.042, 1.452) and an increase in depression scores (OR: 1.25; 95%CI: 1.060, 1.472) from T1 to T2.

Conclusion

Increasing prenatal anxiety and depressive symptoms in different trimesters of pregnancy was associated with LBW with sex specific patterns of association in this sample from a Low and Middle Income Country.

KEY WORDS -PREGNANCY, DEPRESSION, ANXIETY, LOW BIRTH WEIGHT, DOMESTIC VIOLENCE , LOW AND MIDDLE INCOME COUNTRY

Introduction

Antenatal mental health problems are a significant global concern, with depression affecting 10% to 15% of pregnant women [1] and antenatal anxiety affecting 18.2% to 24.6 % across trimesters [2]. Systematic reviews have shown common mental disorders among pregnant women in Low- and Middle-income countries (LAMIC) to be higher than in high income settings [2,3]. Research has also focussed on the relationship of mental health in pregnancy with adverse pregnancy outcomes.

A meta-analysis which reviewed 29 studies, concluded that offspring of women with depression during pregnancy were at an increased risk for preterm birth (PTB), low birth weight (LBW) and intra-uterine growth restriction (IUGR) [4]. They also found risk of LBW infants amongst women with antenatal depression to be significantly higher for those from LAMIC (RR = 2.05; 95% CI 1.43-2.93) compared to those in United States (RR = 1.10; 95% CI 1.01-1.21) or European social democracies (RR = 1.16; 95% CI 0.92-1.47). However, a subsequent meta-analysis of 30 studies did not find a significant association between depression and LBW (OR = 1.21; 95% CI, 0.91 to 1.60; P = .195; [5].

More recently, a meta-analysis contrasting neonatal outcomes for pregnant women who did not receive treatment for depression compared to those without depression found significantly higher rates of PTB (OR = 1.56; 95% CI 1.25-1.94; 14 studies; I2, 39%) and LBW babies in the untreated depressed group (OR, 1.96; 95% CI 1.24-3.10; 8 studies; I2, 48%) [6].

Another systematic review and meta-analysis of studies done in LAMI countries included 64 studies (with 44,035 mothers) on antenatal depression and 9 studies (with 5,540 mothers) on adverse birth outcomes has shown that infants of depressed mothers are at higher risk for LBW (PRR = 1.66; 95% CI:1.06 – 2.61). The risk factors for antenatal depression included history of economic difficulties, poor marital relationships, common mental disorders, poor social support, bad obstetric history, and exposure to violence [7].

Finally, whilst maternal depression has been the most widely researched index of prenatal stress, antenatal anxiety has also been shown to affect perinatal outcomes. A meta-analysis which included 16 studies found that antenatal anxiety was significantly associated with

LBW in pooled data (OR = 1.80; 95% CI 1.48 to 2.18; P<0.00001) as it was with preterm birth (OR = 1.54; 95% CI 1.39 to 1.70) [8].

The varying findings across studies investigating the relationship between depression, anxiety and LBW are most likely related to methodological differences between studies [9]. Studies varied in design including differences in tools and methods used for assessment of depression and anxiety [10,11, 12,13, 14 15,16 20, 21 22].

The timing and the number of assessments during pregnancy has also varied across studies and may have influenced results. While most of the studies assessed the mothers only once during pregnancy, either in 3rd trimester or in 2nd trimester, only one study on birth outcomes assessed depressive symptoms in the 2nd and 3rd trimester [10]. Most studies did not assess depression or anxiety symptoms at multiple pregnancy time points, thus constraining the ability to assess the impact of timing of exposure to depression and anxiety across pregnancy.

A few studies have not accounted for confounders that might influence birth weight such as such as socioeconomic status (SES), antidepressant use during pregnancy, substance use, nutrition and presence of high risk obstetric conditions and the level of ante-natal health care utilisation [22,23].

Intimate partner violence (IPV) or Domestic Violence (DV) is another important factor that might influence LBW. While some studies assessed the influence of partner violence alone on birth weight [24–26], only three studies assessed partner violence when studying the association of depressive and anxiety symptoms with LBW [27–29]. IPV in pregnancy is a common problem in LAMIC as found in a meta-analysis of 92 independent studies worldwide [30]. Studies from several LAMI countries such as Ethiopia, Vietnam and Tanzania have also found an association between IPV in pregnancy and poor birth outcomes including LBW. However, there are fewer studies which have assessed the effect of both IPV and depressive symptoms[31].

Finally, little is known about whether the impact of prenatal mental health in pregnancy on LBW might be different for male and female infants especially in LAMIC settings. A growing body of evidence examining possible sex dependent effects on fetal growth in the broader western literature reports mixed findings to date [32–34].

Given that in pregnancy (i) IPV is known to be associated with maternal mental health problems such as depression and anxiety [35–37] (ii) comparatively high rates of maternal psychiatric disorders and IPV are separately reported in LAMICs [38–40], and (iii) to our knowledge few longitudinal studies have been conducted in LAMICs to examine the

contribution of these co-occurring risks to LBW, we sought to examine the independent and joint contributions of antenatal anxiety, depression, and IPV to infant birth weight in urban Bangalore. We also set out to examine whether these forms of prenatal stress exposure contribute to infant birth weight outcomes in a sex specific manner.

Methods

Data for these analyses comes from the Prospective Assessment of Maternal Mental Health Study (PRAMMS) cohort, which was established at the National Institute of Mental Health and Neurosciences, Bangalore in India, to study mental health and adverse psychosocial conditions of mothers during pregnancy and its impact on birth outcomes. A total of 700 women were recruited to the cohort in the first trimester of pregnancy from the antenatal clinics of three Urban Primary Health Centres (UPHCS) in the Southern area of Urban Bangalore district, India between August 2014 and November 2016.These UPHCs provided services to the neighbourhoods that covered 33 wards. All women who accessed the services at the antenatal clinics during this period and met inclusion criteria (pregnant women in their first trimester, residing in Bangalore and available for follow up after childbirth) were approached for participation in the study.

Exclusion criteria were women who had history of major mental illness such as psychosis or a bipolar disorder, who were identified to have major health complications (diabetes or hypertension) in the first trimester, were a high risk pregnancy, who currently used antidepressants or were using alcohol, nicotine or other psychoactive substances.

Participants were assessed for symptoms of depression and anxiety as well as partner violence at each trimester (T1, T2 and T3) following written informed consent. The study was approved by the Institutional Ethics Committee.

Measures

1. Depressive Symptoms

The Edinburgh Postnatal Depression Scale (EPDS),[41] a 10-item questionnaire, was used to screen for depressive symptoms. The total score on this scale ranges between 0 and 30 and gives a measure of depressive symptoms during pregnancy. The EPDS has been validated for use with women both during the pregnancy and the postpartum periods and a *Kannada* (predominant language spoken in Bangalore) version is available. Scores were used as a continuous measure for analysis.

2. ***Anxiety***

The subsection of the Patient Health Questionnaire (PHQ) on anxiety disorders [42] was used for screening anxiety symptoms. It consists of 7 items scored on a 3-point Likert-type scale. The total scores are in the range of 0 to 14 with higher scores indicating higher severity of Anxiety. This scale has been widely used in India and in the *Kannada* language as well. Scores were used as a continuous measure for analysis.

3. Domestic Violence and Intimate Partner Violence

The questionnaire from the Indian Council of Medical Research task force study on Domestic and Partner Violence (on Health Consequences of Domestic Violence with special reference to Reproductive Health) was used for the assessment of domestic violence and intimate partner violence [43,44]. This measure has several culture specific items and has been used across the country. The instrument comprises of 18 abusive behaviours categorized under psychological abuse (e.g. using abusive language, threatening, neglecting), physical abuse (e.g. hitting, scalding, burning) and sexual abuse (coercion, denial, causing sexual injury). If the participants responded with a "yes" to any abusive behaviour in the three categories, it indicated the presence of violence. The total score ranges from 0 to 18 based on the number of abusive behaviours the women reportedly experienced. The measure was administered at each prenatal assessment time point. Violence is often under reported by women and any violence reported is known to be have a serious impact on mental health (including psychological violence) [45]. We therefore used presence or absence of violence of any partner violence reported at any point during pregnancy in the prediction model rather than scores.

4. ***Antenatal Healthcare Utilization Index***

Antenatal healthcare utilization was computed as a comprehensive score based on a woman's adequacy on the fulfilment of the following parameters outlined in the National Health and Family Survey 4 of India (NFHS-4) [46]. This includes the following items- registered for antenatal healthcare before the fourth month of pregnancy, completed a physical examination before the sixth month of pregnancy, taken more than three months of Iron and Folic acid

supplements and had more than three Antenatal health care visits during pregnancy. A score of 0 to 3 was assigned on each parameter based on the level of adherence, with 0 indicating that the parameter was not completed while a score of 3 indicated complete adherence. The responses were dichotomized as adequate (score of 2 and above) or inadequate (score of 1 or less) on each item. If all 4 items were adequate, the antenatal healthcare utilization were considered to be overall adequate, else it was inadequate. This final dichotomous variable which has also been used by the National Health and Family Survey 4 of India (NFHS-4) [46] to understand the level of antenatal health care utilisation among pregnant women was used for analysis.

5. Maternal Nutritional Status

This was measured using the maternal weight and height and calculating Body Mass Index (BMI) at the first assessment, which was considered as being closest to the pre pregnancy BMI.

6. Birth Outcomes

All mothers delivered in public health maternity facilities in Bangalore district. Birth outcomes were recorded based on medical records provided by these hospitals where all women in the study delivered. Birth weights following delivery are recorded reliably using an electronic weighing scale usually within an hour of birth in all public health facilities and they become part of the national database for maternal and infant health indices. Outcomes recorded included live births, Medical Termination of pregnancy (MTP), miscarriages, Intrauterine Deaths (IUD), neonatal deaths, and still births.

The criteria for Low birth weight (LBW) was used based on the World Health Organization (WHO) definition of birth weight of less than 2500 g (up to and including 2499 g) regardless of gestational age [47]. This definition of LBW has been in existence for many decades. Low birth weight maybe a result of preterm birth (PTB, short gestation <37 completed weeks), intrauterine growth restriction (IUGR, also known as fetal growth restriction), or both [48,49] .

Details of socio-demographic and obstetric data were also recorded and information on the gender of the infant, birth complications (if any), preterm births and mode of delivery was also collected.

The Study flow chart describes in detail the recruitment and follow up of the cohort. (Figure1)

Statistical Analysis

While 700 women were recruited at T1, 490 were available for assessments at T2 and 460 at T3. Data on birth weight was available for 514. The sample size for complete analysis hence varied from the 700 at intake. Missing data included women who did not keep their appointments for follow up assessments, those who refused consent to take part at that phase and poor birth outcomes. The poor outcomes included miscarriages, medical termination of pregnancy (MTP), Intra Uterine Deaths (IUDs), still births and neonatal deaths and twin pregnancies (Figure 1). Women for whom birth-outcomes were available did not differ from those whose records were not available on any of the socio demographic characteristics and scale measurements (EPDS and PHQ Anxiety scores, antenatal health care utilisation and domestic violence), except BMI. Women who gave any birth outcome information had higher BMI (21.01 ± 3.767) than those who did not (20.20 ± 3.609).

The effect of anxiety and depression on negative pregnancy outcome of LBW was assessed using a logistic regression model. The missingness in the longitudinal data at different time points was tested for Missing at Random (MAR) assumption and then imputation was performed. A linear interpolation by values immediately surrounding the missing value was carried out. Points were chosen on the bissectrices to provide an optimum solution for the imputation. The imputation was done for scores on EPDS, the anxiety subscale for PHQ and Partner Violence. In order to accommodate the longitudinally measured data while simultaneously avoiding the problem of multicollinearity, the change scores (T2-T1 and T3-T2) of the scales were calculated and included in the model. Baseline and change scores were considered in the model building in order to account for multicolinearily (due to repeated measurements) and to give a starting point for each individual.

The birth outcome considered for the study was birth weight (normal birth weight: >= 2500 grams or low birth weight: < 2500 grams). The scores on depression, anxiety, violence, family income, and age of mother at recruitment were variables of interest, while baseline BMI, Parity, and AHUAT indicator were control variables. Based on the level of measurement, either a Mann Whitney-U Test (non-normal continuous variables) or Chi-Square Test (categorical variables) was performed to identify potential factors to be include in multivariable model. For multivariable analysis, logistic regression models for the outcome variables were fit. The statistically (significance of 0.1 at univariate analysis) and clinically

relevant variables were used for the model building. The final model was obtained using a backward selection procedure. After the final models were obtained, all multivariable models were re-estimated with the three control variables (Baseline BMI, Parity, and AHUAT indicator). The results were reported as odds ratio (OR) and 95% confidence intervals (95% CI). All the analyses were performed using SPSS (Version 22). The multivariable results are reported for the individual with all the available information (after imputation); these results were not found to be very much different from those obtained though listwise deletion.

Results

Sample characteristics:

The mean age of the women in this cohort was 23.02 years (SD=3.410). Just over half 367/686 (53.5%) were multiparous. While 13.8% (92/684) had primary education, 54.0% (369/684) had secondary level of education (≤ 10 years) and 86.6% (593/685) were homemakers. Half the sample (55.6%, 299/538) was from a lower socio-economic status and nearly half the sample (48.1%, 328/682) lived in joint families (a family where grandparents, the couple and other siblings live together and shared a kitchen). Alcohol use in partner was reported by 15.2% (104/685) of mothers.

Figure 1 gives details of the cohort and birth outcomes. Overall, 62 of 648 mothers had a poor pregnancy outcome (9.1%; 62/648). Among them 56.5% (35/62) had a miscarriage, 2 mothers had a medical termination of pregnancy; one mother was excluded because of high-risk pregnancy and another had an intrauterine death. Of the women who had a poor birth outcome, 29 % (18/62) were neonatal deaths and 8.1% (5/62) still births. A live birth was recorded for 583 mothers. Birth weight was available for 514 infants, of whom 80 had a low birth weight. Reliable data on birth weight and gender of the infant were available from 507 mothers (Females- 251; Males - 256). Amongst them, 43 female infants and 34 male infants had low birth weight.

Amongst the 80 infants who were classified as LBW according to the World Health Organisation classification [47,48], 23 were preterm (based on gestation age calculated from last menstrual period and date of birth). While the univariate analysis included data from mothers of the 80 infants with LBW, the multivariable analysis included complete information for 452 mothers from the cohort, of whom, 67 had LBW infants.

The following table shows the univariate comparisons between low birth weight and normal birth weight groups and the various independent variables of interest.

Table 1 about here (TABLE 1 : ***Univariate Analysis: Outcome Variable: Low Birth Weight)***

Whole sample Univariate Analysis

Among women who had an infant with LBW, the mean scores of depression were higher in all trimesters (T1: p-value = 0.001; T2: p-value = 0.001; T3: p-value =0.001) of pregnancy and the mean scores for anxiety were significantly higher in the third trimester (p-value = 0.009). More primiparous mothers had infants with low birth weight (p-value = 0.007). The remaining other variables including violence, antenatal healthcare utilisation score, baseline BMI, education, socio-economic status and age of mother were not found to be associated with birth weight (Table 1).

Table 2 about here (TABLE 2: Multivariable Analysis - Outcome Variable: Low Birth Weight)

Whole sample Multivariable Analysis

Longitudinal data was available from 452 mothers who had completed at least two assessments in the antenatal period. Analysis using multiple logistic regression was performed for these 452 individuals who had provided information on all variables included in the model. Women who contributed information in the multiple logistic regression model had higher baseline anxiety, lower education level and better antenatal healthcare utilization, compared to those who were not included for it. The odds of low birth weight increased by 11% for baseline (OR: 1.11; 95% CI: 1.040, 1.187) and by 12% for each subsequent unit increase in depression level (from baseline) in the second trimester (OR: 1.12; 95% CI: 1.047, 1.195). Increase in anxiety scores between the 2nd and 3rd trimester increased the chances of LBW by 32% (OR: 1.32; 95% CI: 1.079, 1.603). Multipara women were 43% less likely to have an infant with LBW (OR: 0.57; 95% CI: 0.331, 0.980).

Multivariate Analyses for males and females separately

When Logistic analyses were conducted separately by infant sex we found an increase in anxiety scores from baseline to T2 and from T2 to T3 significantly increased the chances of LBW by 69% (OR: 1.69; 95% CI: 1.053, 2.708) and 49% (OR: 1.49; 95% CI: 1.058, 2.086) respectively for female infants. Exposure to partner and domestic violence more than doubled the OR for chances of LBW in females however the contribution to the model was non-significant (OR: 2.48; 95% CI: 0.810, 7.581), which may reflect the small cell sizes available. Parity did not contribute to the model significantly for female infants.

For male infants a higher baseline depression score and change in depression score from T1 to T2 significantly increased the odds of LBW by 23% (OR: 1.23; 95% CI: 1.042, 1.452) and 25% (OR: 1.25; 95% CI: 1.060, 1.472) respectively. Exposure to partner violence did not contribute to the model. (Table 2).

Discussion

Our longitudinal study sought to examine the independent and joint contributions of antenatal anxiety, depression, and IPV to infant birth weight in urban Bangalore, in South India. We also set out to examine whether these forms of prenatal stress exposure contribute to infant birth weight outcomes in a sex specific manner. Our findings add to the literature supporting a relationship between anxiety and depression in pregnancy and low birth weight. They also suggests there may be important sex-specific effects of anxiety, depression and IPV on birth weight outcomes.

Our finding of an association between antepartum depression and LBW is consistent with prior research investigating these associations [6]. Our study also supports previous research on the association of antepartum anxiety with birth outcomes. A meta-analysis of twelve studies found that antepartum anxiety was associated with increased risk of LBW (pooled RR: 1.76; 95% CI: 1.32, 2.33) [50]. Similarly, in our population, women who reported increasing anxiety symptoms from the second to third trimester of pregnancy (OR: 1.32) had 1.32-fold higher odds of LBW (95% CI: 1.079, 1.603).

A previous study from Malaysia found higher Relative Risks for the association of LBW with antenatal depression and antenatal anxiety. However, they had used categorical measures for anxiety and depression and also had only one assessment during pregnancy, unlike our study

which used continuous scores and repeat measures [28]. Similarly a Turkish study among 1119 mothers, found co-morbidity of major depression and anxiety disorders in pregnant women to be associated with greater negative effects on birth weight compared to either major depression or anxiety disorders alone [51]. However, here the assessment of anxiety and depression was done within 24 hours of childbirth and may not be comparable to our study.

In the current study, depression in early pregnancy seemed to be a risk factor for low birth weight and increased anxiety later in pregnancy presented an additional risk in our whole sample analysis. These findings compare with a study done in Iran, which assessed pregnant mothers admitted to the hospital during their 2nd or 3rd trimester and found that there was a negative correlation between general and pregnancy specific stress, anxiety and depression during pregnancy and infant birth weight [52]

There are very few studies that have assessed both depression and anxiety in a longitudinal manner [53]. The advantage of longitudinal analysis is that it helps us understand how changes in mental health between trimesters may contribute to risk for poor birth outcomes.

We chose to use anxiety and depression measures as continuous variables to overcome problems of different cut offs in different populations of perinatal women using the EPDS, especially since there are relatively low cut-offs required in some LAMIC settings [2,3]. A previous meta-analytic study has shown that categorical measures showed higher relative risk for LBW compared to continuous measures. i.e. when depression was used as a categorical variable RR: 1.49; 95% CI: 1.25, 1.77, whilst when depression was used as a continuous variable the relative risk was lower RR: 1.04; 95% CI: 0.99, 1.09 [4]. In our study, the relatively low scores on EPDS and PHQ Anxiety, and a change from one trimester to another, still contributed meaningfully and significantly to the prediction of low birth weight when they were endorsed. This low rate of endorsement might reflect lower psychological distress in this community sample or under reporting of emotional symptoms for cultural reasons. Future work is required to examine the relationship between scores on such screening tools and diagnostic interview data so we are better placed to understand cross-cultural variation in levels of symptom endorsement in different settings.

The rates of partner violence reported by mothers of babies within the normal birth weight and the low birth weight groups were 14.6% and 20.3% respectively. These rates are in line with

previous surveys conducted in pregnancy in India which have indicated average prevalence rates for IPV of 24% [30]. Previous studies from LAMI countries like Ethiopia, Vietnam and Tanzania have shown that women exposed to physical violence during pregnancy were three to five times more likely to report LBW compared to those who did not [54] [55,25].

To our knowledge there is only one previous cross sectional study from China [56], which has examined the role of IPV on birth outcomes in the context of depression (but not anxiety), whilst another study from Brazil found that exposure to physical violence during pregnancy was associated with a 2.2-fold increased risk of LBW [31] and that this risk was not significantly attenuated when depression symptoms were adjusted for in analyses. The differences in how depression was analysed in association with IPV precludes direct comparison of our findings with these studies.

Our study makes an important novel contribution to the literature in analysing how IPV is associated with birth outcomes in girls and boys separately. In our whole sample analysis, IPV did not contribute significantly to the multivariate model predicting low birth weight, however, it is worthwhile noting that the stratified analyses did show IPV to be a potential risk factor for LBW in girls but not boys, with an OR that just failed to meet conventional statistical significance (OR: 2.48; 95% CI: 0.810, 7.581). The rate of violence reported by mothers of LBW girls was nearly double that reported for normal weight infants (27.8% vs 14.8%). However, these findings should be viewed with caution, given the broad confidence intervals which undoubtedly reflect the small numbers experiencing violence and LBW, and the role of IPV requires replication in future studies.

The second study objective was to conduct stratified analyses by infant sex. An increase in anxiety scores from first to second and then from second to third trimester significantly increased the chances of LBW by 69% and 49% respectively for female infants. In contrast, for male infants a higher baseline depression score in the first trimester of pregnancy and change in depression score from the first to the second trimester significantly increased the odds of LBW by 23% and 25% respectively. Paradoxically, mothers of male infants with increasing PHQ Anxiety during the course of pregnancy (at T1 and change from T1 to T2) seem to have a reduction in their risk of LBW (OR: 0.63; 95% CI: 0.287, 1.388 and OR: 0.62; 95% CI: 0.298, 1.301) however this result did not achieve statistical significance. Since this marginal result is counterintuitive it does serve to highlight, alongside the marginal results

reported above for IPV as a risk for LBW in female infants, the need for an even larger scale study which can replicate and extend the findings of the current study with the aim of informing the focus of future early intervention targets and uncovering possible mechanisms for any such sex specific effects identified.

A number of mechanisms have been proposed by which antepartum mental disorders may contribute to increased risk of LBW. Anxiety has been shown to be associated with hypothalamic-pituitary-adrenal (HPA) axis hyperactivity[57–59]. When triggered by stressors, the HPA axis stimulates the secretion of cortisol throughout the body. Mood disorders may cause an increase in the release of CRH from the placenta via the actions of catecholamines and cortisol [60]. Additional evidence implicates pro-inflammatory cytokines in the pathogenesis of psychiatric disorders, particularly major depression[61].

There is evidence that female fetuses adapt to poor intrauterine conditions by decreasing growth rate, while fetal male response may be less adaptive, and may be expressed as IUGR, stillbirth or early pregnancy loss [62,63]. The differential effects associated with fetal sex may suggest different placental function such as placental gene expression, immune functions and response to cortisol [63,64]. Females may have increased HPA axis reactivity and female placentas may increase permeability to glucocorticoids following maternal stress, as compared to males [65].

Sex-specific effects of maternal prenatal stress on birth outcomes have been reported in previous studies. A study in Israel of chronic maternal stress found that female fetuses were at increased risk for preterm birth and low birth weight [66]. Similarly, in Chile, maternal prenatal exposure to a negative life event was associated with a reduction in gestational age and increased risk of preterm birth, especially in girls [67]. Ae-Ngibise et al studying the effect of prenatal stress on birth outcomes in Ghana, had similar findings with increased exposure response relationship between prenatal maternal stress and reduced birth weight and head circumference in girls [68]. In our study, we found evidence that prenatal stress (as measured by anxiety and depressive symptoms) was associated with LBW in both males and females but it appeared that females were vulnerable to increases in anxiety across trimesters and throughout pregnancy whereas males appeared vulnerable to depression in early pregnancy and to increases in depression from first to second trimester. The risk associated with these forms of prenatal stress for LBW also appeared to be proportionately higher for LBW in females. More research that elucidates the mechanisms underlying associations between maternal

psychopathology and risk of LBW in LAMIC settings is clearly warranted, including those related to possible differential effects based on the sex of the foetus.

Our present study has several strengths. First, depression and anxiety were assessed longitudinally rather than at a single time point which helped in understanding the role of these symptoms in each trimester and change across the pregnancy. Independent and joint effects of prenatal stress including IPV were examined. Second being a prospective study, reporting was not conditional on infant outcomes. Well-trained interviewers administered structured questionnaires previously validated among pregnant women. We examined the role of several potential confounders which were mentioned in earlier studies as influencing results [9]. Multivariate analyses controlled for, any confounding variables that were found to be significantly associated with LBW at a bivariate level. A data imputation procedure was employed to account for the attrition at each phase followed by appropriate analysis for inference. Additionally, we also examined whether or not there was evidence of sex-specific effects.

However, there are some limitations that need to be considered when interpreting the results of our study. Firstly, mental health outcomes were based on validated screening questionnaires with good psychometric properties rather than through a clinical interview. Secondly, we used depression and anxiety symptom scores as a continuous variable rather than as clinical conditions. Thirdly, while we controlled for several potential confounders such as BMI, parity and antenatal health care utilisation, there remains the possibility that we may have missed a few factors which may have influenced our results. Maternal nutrition may influence infant birth weight. We had baseline BMI for all other mothers as an indicator of nutrition. However, better measures of nutrition including haemoglobin may be needed. Fourthly, we used the World Health Organisation definition of LBW as an outcome measure rather than using the small for gestational age criteria. Also, women who contributed information in the multiple logistic regression model had higher baseline anxiety and lower education levels compared to those who were not included for it which meant that the final analysis included women who had higher risk. Lastly, this cohort consists of women from low income urban settings and results from this longitudinal study may not be generalizable to the entire population of South Asian pregnant women.

The finding that anxiety and depressive symptoms are associated with higher odds of LBW emphasize the need for assessment of mental health as a routine part of antenatal care alongside

physical evaluation like weight and blood pressure. Our findings like those from other LAMICS [69–71], support increased public health efforts to identify and provide services for mental health problems and partner violence among pregnant women as a method of preventing poor birth outcomes. The use of simple screening tools that are culturally relevant and can be administered easily by community health workers will help in identifying women who need psychosocial interventions. Using a stepped care approach treatment algorithms can be planned for women presenting to obstetric clinics who are found to have psychosocial risk factors to ensure better birth outcomes.

Conflict of Interest Statement –

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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TABLE 1: Univariate Analysis: Outcome Variable: Low Birth Weight

Outcome Variable(Infant)		**Normal Birth Weight (N)**		**Low Birth Weight (N)**		**P-Value**
		N	**Mean ± SD; [Median (IQR)]**	**N**	**Mean ± SD; [Median (IQR)]**	
Socio economic status	***Lower/Below Poverty Line***		192 (57%)		33 (54.1%)	0.677
	Middle/Higher		145 (43%)		28 (45.9%)	
Education	***Up to secondary***		308 (71 %)		51 (63.8%)	0.196
	Above secondary		126 (29%)		29 (36.3%)	
Antenatal Health Care Utilization	***Inadequate***		212 (53%)		33 (49.3%)	0.570
	Adequate		188 (47%)		34 (50.7%)	
Violence at any time during pregnancy	**Absent**		362 (85.4%)		63 (79.7%)	0.204
	Present		62 (14.6%)		16 (20.3%)	
Parity	**Primi**		189 (43.5%)		48 (60%)	0.007
	Multi		245 (56.5%)		32 (40%)	
Age (years)		434	23.02 ± 3.426 ; [22 (21, 25)]	80	22.71 ± 3.074 ; [22 (20.25, 25)]	0.612
T1 Body Mass Index (kg/m^2)		429	20.92 ± 3.686; [20.30 (18.12, 23.23)]	79	21.18 ± 4.316 ; [20.34 (18.41, 23.11)]	0.928
T1 EPDS scores		434	2.15 ± 4.873 ; [0 (0, 2)]	80	3.26 ± 5.787 ; [0 (0, 4)]	0.003
T2 EPDS scores		390	1.28 ± 3.496 ; [0 (0, 0.63)]	67	2.81 ± 4.969 ; [0 (0, 3)]	0.001
T3 EPDS scores		390	1.41 ± 3.70 ; [0 (0, 0)]	67	3.03 ± 5.410 ; [0 (0, 3)]	0.001
T1 PHQ Anxiety scores		434	0.29 ± 1.158 ; [0 (0, 0)]	80	0.25 ± 1.061 ; [0 (0, 0)]	0.448

T2 PHQ Anxiety scores	390	0.25 ± 1.03 ; [0 (0, 0)]	67	0.42 ± 1.350 ; [0 (0, 0)]	0.672
T3 PHQ Anxiety scores	390	0.20 ± 0.92 ; [0 (0, 0)]	67	0.73 ± 2.079 ; [0 (0, 0)]	0.009

TABLE 2: Multivariable Analysis - Outcome Variable: Low Birth Weight				
Variable	**Mean ± SD; [Median (IQR)] Normal Birth Weight: 385 (85.18 %)**	**Mean ± SD; [Median (IQR)] Low Birth Weight: 67 (14.82%)**	**Odds Ratio (95% CI) Total: 452 (100%)**	**P value**
T1 EPDS scores	2.25± 5.063; [0 (0,2)]	3.01 ± 5.468; [0 (0,4)]	1.11 (1.040, 1.187)	0.002
EPDS scores (T1 to T2) Change	-0.98 ± 4.881; [0 (-0.6 , 0)]	-0.20 ± 5.718; [0 (-2,0)]	1.12 (1.047, 1.195)	0.001
PHQ Anxiety scores (T2 to T3) Change	-0.05 ± 1.053; [0 (0,0)]	0.31 ± 1.932; [0 (0,0)]	1.32 (1.079, 1.603)	0.007
Parity (Multipara)	221 (57.4 %)	29 (43.3%)	0.57 (0.331, 0.980)	0.042
T1 Body Mass Index	21.03 ± 3.728; [20.35 (18.177, 23.344)]	21.16 ± 4.470; [20.36 (18.372, 22.449)]	1.02 (0.948, 1.089)	0.657
Antenatal Healthcare Utilisation (Adequate)	186 (48.3%)	34 (50.7%)	0.96 (0.559, 1.659)	0.893
Low birth weight (Female)	**Normal Birth Weight: 183 (83.56%)**	**Low Birth Weight: 36 (16.44%)**	**Total: 219 (100%)**	**P value**
T1 EPDS scores	2.20 ± 4.843; [0 (0,2)]	2.94 ± 5.918; [0 (0,3.75)]	0.97 (0.831, 1.134)	0.709
T1 PHQ Anxiety scores	0.31 ± 1.132; [0 (0,0)]	0.19 ± 1.004; [0 (0,0)]	1.06 (0.627, 1.789)	0.830
EPDS scores (T1 to T2) Change	-0.85 ± 5.293; [0 (0,0)]	-0.32 ± 5.942; [0 (-1.75,0)]	0.96 (0.849, 1.088)	0.531
PHQ Anxiety scores (T1 to T2) Change	-0.02 ± 1.389; [0 (0,0)]	0.50 ± 1.715; [0 (0,0)]	1.69 (1.053, 2.708)	0.030
PHQ Anxiety scores (T2 to T3) Change	-0.13 ± 1.048; [0 (0,0)]	0.28 ± 2.212; [0 (0,0)]	1.49 (1.058, 2.086)	0.022
Violence (any time during pregnancy) -Present	27 (14.8%)	10 (27.8%)	2.48 (0.810, 7.581)	0.112
Parity (Multipara)	101 (55.2%)	17 (47.2%)	0.66 (0.305, 1.448)	0.304
T1 Body Mass Index	20.68 ± 3.781; [20.07 (18.032, 22.748)]	22.13 ± 5.014; [20.64 (18.819, 25.062)]	1.09 (0.998, 1.189)	0.057
Antenatal Healthcare Utilisation (Adequate)	95 (51.9%)	18 (50%)	0.95 (0.442, 2.056)	0.904
Low birth weight (Male)	**Normal Birth Weight: 201 (87.01 %)**	**Low Birth Weight: 30 (12.99 %)**	**Total: 231 (100%)**	**P value**
T1 EPDS scores	2.32 ± 5.276; [0 (0,2)]	3.17 ± 5.059; [1 (0,5)]	1.23 (1.042, 1.452)	0.014

T1 PHQ Anxiety scores	0.33 ± 1.294; [0 (0,0)]	0.43 ± 1.331; [0 (0,0)]	0.63 (0.287, 1.388)	0.252
EPDS scores (T1 to T2) Change	-1.10 ± 4.496; [0 (-1,0)]	-0.27 ± 5.519; [0 (-2,0)]	1.25 (1.060, 1.472)	0.008
PHQ Anxiety scores (T1 to T2) Change	-0.12 ± 1.324; [0 (0,0)]	-0.33 ± 1.470; [0 (0,0)]	0.62 (0.298, 1.301)	0.208
PHQ Anxiety scores (T2 to T3) Change	0.103 ± 1.057; [0 (0,0)]	0.33 ± 1.605; [0 (0,0)]	1.35 (0.924, 1.98)	0.120
Violence (any time during pregnancy) -Present	32 (15.9%)	5 (16.7%)	0.45 (0.108, 1.898)	0.279
Parity (Multipara)	119 (59.2%)	11 (36.7%)	0.48 (0.207, 1.133)	0.094
T1 Body Mass Index	21.35 ± 3.664; [20.93 (18.389, 23.820)]	19.68 ± 2.91; [20.25 (17.486, 21.444)]	0.88 (0.769, 1.018)	0.086
Antenatal Healthcare Utilisation (Adequate)	91 (45.3%)	15 (50%)	1.28 (0.538, 3.052)	0.575