Anxiety during pregnancy and low birth weight: An observational cohort study

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Abstract

Objective: To explore the effects of antenatal anxiety on fetal growth, and to investigate the effect of anxiety timing and the potentially different effect of trait anxiety and state anxiety on fetal growth. **Design:** Observational cohort study. **Setting:** Barcelona, Spain. **Population:** A cohort of 204 women with singleton pregnancies attending the antenatal clinic of a tertiary care setting during the strict lockdown of the COVID-19 pandemic in 2020. **Methods:** Psychosocial factors, maternal demographics, and obstetric outcomes were studied as potential predictors of low birth weight. The State-Trait Anxiety Inventory (STAIs, STAIt), the Edinburgh postpartum Depression Scale (EPDS) and the Medical Outcomes Study Social Support Survey (MOS-SSS) were used to assess symptoms of anxiety, symptoms of depression, and social support, respectively. **Main Outcome Measures:** Neonatal birth weight, head circumference and length. **Results:** There was a negative correlation between STAIt score (trait anxiety) and birth weight percentile (r=-0.228, p=0.047). In the univariate linear regression analysis, a lower maternal weight and BMI before pregnancy, parity, increased STAIt score and preterm birth below 37 weeks of gestation (p=0.008, p=0.015, p=0.028, p=0.047 and p=0.022, respectively) were identified as predictive risk factors for low birth weight. In the multivariate lineal regression analysis only a lower maternal weight before pregnancy and an increased STAIt score were independent predictors for low birth weight (p=0.020, p=0.049, respectively). **Conclusions:** Anxiety during pregnancy impacts birth weight, and specifically the trait anxiety, the one associated with the personality attributes, is a predictor for low birth weight.

INTRODUCTION

Fetal growth restriction is a common pregnancy complication, and is considered a leading cause of stillbirth, neonatal mortality, and short- and long-term neonatal morbidity. Low birth weight, typically defined as a birth weight below the 10^{th} percentile for gestational age, affects around 10% of births in Spain and up to 26-28% of births in underdeveloped regions of Africa and Asia.

Low birth weight is associated with increased morbidity in infants, children, and adults. Some morbidities associated with fetal growth restriction are increased risk of preterm birth, delayed child development, poor speech, and adolescence mental health disorders.

There are several maternal risk factors for low birth weight, such as advanced maternal age, ethnic origin, consanguinity, low body mass index, nulliparity, use of recreational drugs, alcohol, assisted reproductive techniques, congenital infections, and chronic medical disorders, such as chronic hypertension or diabetes mellitus. Another factor associated with low birth weight is maternal anxiety during pregnancy.

Anxiety is an emotion characterized by apprehension and somatic symptoms of tension in which an individual anticipates impending danger, catastrophe, or misfortune. The prevalence of anxiety disorder in the general population is 13.6%, but increases to 15.2% during pregnancy.

Researchers discriminate between state anxiety and trait anxiety. While state anxiety refers to a transient reaction to a stressful situation, trait anxiety is defined as a more persistent personality trait. Comparatively, less research has been conducted on the role of personality predisposition to anxiety.

There is conflicting data regarding the effect of maternal psychological distress on fetal growth. The fetoplacental-maternal unit may regulate fetal growth according to the type of psychological distress following a stressful event and even increase fetal growth in response to maternal stress in major areas of life. In addition, the effect of anxiety timing on birth weight is not well understood, and data shows opposing outcomes.

Briefly, while it is clear that anxiety during pregnancy is associated with a lower birth weight, it is not clear whether there are any differences on the effects of anxiety based on whether it is trait or state anxiety, or whether the impact of anxiety is different depending on the gestational age at which anxiety symptoms arise.

Therefore, the aim of this study was to study the effects of maternal anxiety on fetal growth. Secondary objectives were to investigate the effect of anxiety timing and the potentially different effects of trait anxiety and state anxiety on fetal growth.

METHODS

Study design

This was a prospective secondary analysis of a cohort with pregnant women recruited for the research study “Psychological impact and social support in pregnant women during the lockdown due to the SARS-CoV2 pandemic”. In the present analysis, we included pregnant women that attended Hospital de la Dona Vall d’Hebron during the COVID-19 lockdown in Barcelona, Spain, which lasted from 14^{th} March 2020 to 28^{th} Abril 2020. As expected during a strict pandemic lockdown, these women were exposed to an increased number of anxiety-triggering circumstances. Psychosocial factors, maternal demographics, and obstetric outcomes were analyzed as potential predictors of low birth weight.

Participants

A total of 217 pregnant women attending Hospital de la Dona Vall d’Hebron during the lockdown period were offered to participate in the study. Of those, 204 (94%) accepted to participate and were included in the study. Of those, 164 (80.4%) completed the depression questionnaire (Edinburgh Postpartum Depression Scale, EPDS) and 109 (53.4%) completed the anxiety questionnaire (State-Trait Anxiety Inventory, STAI). Two participants were excluded due to twin pregnancies, which have different growth patterns as compared to singleton pregnancies. Finally, 107 women were included in the analysis.

Variables

Outcome Variables:

Neonatal birth weight (BW), head circumference (HC) and length (Lt) were the main outcome variables. Gestational age at delivery and the need for admission to the special care baby unit were also recorded.

Demographics and pregnancy variables:

In order to describe the study population, we focused on psychosocial and demographic factors impacting birth weight: maternal age, infant gender, ethnic origin, maternal height, maternal weight before pregnancy, maternal weight gain during pregnancy, parity, pregnancy-induced hypertensive disorder, gestational diabetes, preterm birth <37 weeks of gestation, smoking status and high-risk pregnancy.

Gestational age and trimester based on gestational age at the beginning of the COVID-19 lockdown in Spain (14 March 2020) were calculated for each participant so as to identify the time when anxiety symptoms due to the COVID-19 lockdown may have appeared.

Maternal body mass index (BMI) at the beginning of the pregnancy was calculated based on weight before pregnancy (kg)/height (m^2).

The local protocol of the antenatal clinic was used to identify participants with high-risk pregnancies.

Psychosocial questionnaires:

During visits to the antenatal clinic, several questionnaires were prospectively administered to detect anxiety and depression symptoms, as well as the absence of social support.

The EPDS is a 10-item self-reported scale designed to specifically detect postpartum depression. Each item is rated on a 4-point scale ranging from 0 to 3, with higher scores indicating a greater severity of the depression. The Spanish validation of the EPDS gave an optimal cut-off value of 10/11 for combined major and minor depression, sensitivity was 79%, and specificity was 95.5%, with a positive predictive value of 63.2% and a negative predictive value of 97.7%. In addition, a cut-off value of 13 has a sensitivity of 62%, and a specificity of 98.1%, with a positive predictive value of 76.5% and a negative predictive value of 96.4%. The gold standard for the diagnosis of postpartum depression is an assessment during a clinical interview with a mental health professional.

The STAI is a 40-item self-reported scale designed to detect state anxiety (STAIs) and trait anxiety (STAIt). The STAI is the most used rating scale for measuring anxiety symptoms. Its validity and reliability have been carefully evaluated. Each item is rated on a 4-point scale ranging from 0 to 3, with higher scores indicating a greater severity of the anxiety. For comparison to international studies, the 0-3 range in the 4-point scale has been changed to 1-4, as in those studies. The STAI scale has also been validated to use it in pregnant women. Range of scores for each subtest is 20–80, with higher scores indicating a greater severity of the anxiety. A cut-off value of 39–40 has been suggested as a value able to detect clinically significant symptoms of anxiety scale.

Finally, the Medical Outcomes Study Social Support Survey (MOS-SSS) is a 20-item self-reported questionnaire developed by the Rand and Medical Outcomes Study teams to measure the level of social support. This scale measures positive social interactions, as well as tangible, affectionate and emotional/informational support. The MOS-SSS has shown good reliability and validity. The Spanish version of the MOS-SSS has also been validated, showing satisfactory psychometric properties.

Data sources and measurements

Study data were prospectively collected from electronic medical records (SAP® software) and managed using REDCap electronic data capture tools hosted at [VHIR- VALL DE HEBRON HOSPITAL]

Regarding biometric variables, birth weight was measured in kg, and HC and Lt were measured in cm. For birth weight percentiles, the curves were adapted to Spanish populations by adjusting for sex and gestational age. For HC and Lt percentiles, the Spanish curves were used.

Tobacco use was considered if the patient had smoked during the first trimester of pregnancy according to the patient medical records. EPDS variables were transformed to categorical, setting a cut-off value of 10.

Statistical analysis

Regarding descriptive statistics, continuous variables were reported as the mean and standard deviation, while categorical variables were reported as frequency and percentage.

A univariate regression analysis was performed to identify the psychosocial and demographic factors impacting birth weight. A Pearson's coefficient correlation was performed for quantitative variables and birth weight. A multivariable analysis clustered all significant variables from the previous univariate test and measured their combined effect on birth weight.

Statistical significance was set at an α error <0.05. All reported probability values were two-tailed. The SPSS software, IBM SPSS Statistics for Windows, version 23 (IBM Corp.) was used for statistical purposes.

RESULTS

Demographics, obstetric outcomes, neonatal outcomes, and scores in psychosocial questionnaires

The STAI questionnaire was completed during the lockdown period by 107 women who had agreed to participate in the study and had available data. Figure 1 shows the flow diagram of participants. Table 1 shows descriptive demographics, obstetric outcomes and neonatal outcomes, and scores of the psychosocial questionnaires completed by the participants included in the study.

Analysis of a potential correlation between anxiety and birth weight percentile

There was a negative correlation between STAIt score and birth weight percentile (r=-0.228, p=0.047) (Figure 2). There was also a negative correlation between STAIs score and birth weight percentile, but it was not statistically significant (r=-0.183, p=0.060). Other neonatal biometric parameters (HC and Lt) did not show a correlation with STAIt or STAIs.

There was a negative correlation between STAIs score and gestational age at the beginning of the lockdown period (r=-0.223, p=0.022), which means that the lower the gestational age when lockdown started, the higher the state anxiety during pregnancy. However, gestational age at the beginning of the lockdown did not show any correlation with birth weight (r=0.115, p=0.242). On the other hand, there was a certain correlation between gestational age at the beginning of the lockdown period and birth weight percentile (r=0.170, p=0.082).

Regression analysis of birth weight predictors

A univariate linear regression analysis was performed to identify demographic, obstetric and psychosocial variables as potential risk factors of low birth weight. A lower maternal weight and BMI before pregnancy, higher parity, an increased STAIt score and preterm birth below 37 weeks of gestation (p=0.008, p=0.015, p=0.028, p=0.047, and p=0.022, respectively), were identified as predictive risk factors for low birth weight percentiles.

In addition, an increased STAIs score, tobacco use, and a lower gestational age at the beginning of the lockdown period showed a trend for prediction of lower birth weight percentiles, as shown in Table 2.

A multivariate lineal regression analysis (Table 3) was performed with those variables identified as risk factors for low birth weight percentiles in the univariate linear regression analysis. When combining maternal weight before pregnancy, parity, STAIt score and smoking status, only a lower maternal weight before pregnancy and an increased STAIt score were independent predictors for low birth weight percentile (p=0.020, p=0.049, respectively).

Discussion

Main results

The present study shows, firstly, that anxiety symptoms during pregnancy are associated with lower birth weight percentiles. Secondly, trait anxiety (STAIt) shows a higher association with lower birth weight percentiles than state anxiety (STAIs). Thirdly, regarding the effect of anxiety timing on fetal growth, although there was a certain trend, it is not clear whether the appearance of anxiety symptoms at an earlier gestational age is associated with lower birth weight percentiles. In addition, there was a negative correlation between state anxiety and gestational age at the time when anxiety symptoms first appear, suggesting that women experienced higher state anxiety when exposed to the stressful event at a lower gestational age.

Strengths and limitations

The main limitation of this study is the small sample size; it is likely that higher sample sizes may have led to the conclusion that both trait anxiety and state anxiety are associated with lower birth weight percentiles. Nevertheless, this study was designed around specific stressful circumstances, during the COVID-19 pandemic lockdown, which represented an ideal scenario for investigating the effects of anxiety on birth weight, despite the reduced sample size. Another limitation of this study may be the selection bias due to including different anxiety symptoms according to the trimester of pregnancy. However, in a previous study conducted by our group, no statistically significant differences were found when analyzing STAIs and STAIt scores according to trimester of pregnancy. Finally, anxiety cannot be induced in an experimental research setting for ethical reasons. Therefore, the fact that this study included patients that were exposed to stressful circumstances in real life is the major strength of the present study.

Interpretation

Meta-analyses have identified an association between antenatal anxiety and low birth weight (OR=1.80). The mechanism underlying this effect is known as "fetal programming". Several studies using animal models have proved that maternal distress negatively influences infant outcomes in childhood and adulthood. Evidence suggests that this occurs via effects on the development of the fetal nervous system, and maternal mood disorders have also been shown to activate the maternal hypothalamic-pituitary-adrenal (HPA) axis and program the HPA axis and physiology of the fetus in an adverse way. Maternal anxiety during pregnancy may increase fetal exposure to maternal glucocorticoids, leading to low birth weight and higher glucocorticoid levels in the neonate. Cortisol levels in cord blood are increased in intrauterine growth retardation, implicating endogenous cortisol in fetal growth. Glucocorticoid levels normally rise over pregnancy, and glucocorticoid receptors are highly expressed in the placenta, mediating metabolic and anti-inflammatory effects. While lipophilic steroids easily cross the placenta, fetal glucocorticoid levels are much lower than levels in maternal circulation because of placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD-2), which converts active glucocorticoids (cortisol and corticosterone) to inert 11-keto forms (cortisone, 11-dehydrocorticosterone) . Studies of 11β-HSD-2 null mice provide evidence for a causal association between 11β-HSD-2, reduced birth weight, and anxiety-like behavior in adulthood . This finding is consistent with findings that antenatal maternal stress affects neurodevelopment .

A second area of knowledge concerns the effects of anxiety on infant birth weight. These studies can be classified according to the type of psychological stressor investigated. Some evidence suggests that major life events consistently predicted lower fetal growth or birth weight, whereas measures of perceived stress had small or negligible effects. However, chronic stressors, such as racial disparities, have been even more reliable predictors of low birth weight. Recent experimental evidence suggests that the nature of stressful life events, as well as the timing of exposure to such events, are important determinants of these type of psychological stressors effects. In the present study, the COVID-19 pandemic lockdown was considered as an important stressful event, where anxiety symptoms were increased in pregnant women. In addition, women with higher rates of trait anxiety were more likely to give birth to babies with a lower birth weight. Our findings are consistent with those of a study that explored the potential association between trait anxiety and low birth weight. However, that study did not assess state anxiety, and for trait anxiety, they used the State-Trait Personality Inventory (STPI) instead of the STAI questionnaire. In our study, although only trait anxiety showed a statistically significant correlation with birth weight percentile, state anxiety showed a certain trend for predicting low birth weight percentile.

The effect of trait anxiety on birth weight may be explained by the fact that trait anxiety is related to more prolonged and widespread symptoms, that may impact various aspects of wellbeing, and therefore can increase levels of glucocorticoids on maternal blood for longer periods, activating the fetal HPA axis for a longer period. However, this hypothesis needs further research to be confirmed.

On the other hand, exposure to psychological stressors can be a predictor of increased birth weight when controlling for gestational age. There is data suggesting that the fetoplacental-maternal unit may regulate fetal growth according to the type of stressful event and even increase fetal growth in response to maternal stress due to major stressful events.

Regarding the effect of anxiety timing on birth weight, our study shows a certain correlation between the timing of anxiety symptoms (gestational age at the beginning of the lockdown) and birth weight percentile, indicating that the earlier the stressful event occurs during pregnancy, the lower the birth weight percentile. However, when analyzing the effect of prenatal anxiety timing in other studies, data were inconsistent. Some studies suggest that psychosocial distress (anxiety and depression symptoms) during late pregnancy (30th week of gestation) is a predictor of low birth weight. On the other hand, gestation lengths and predicted birth weight was lower for participants exposed to a stressful event, such as an ice storm, at an earlier gestational age (during early to mid-pregnancy), as compared to the third trimester. Therefore, it is likely that, in a stressful event, such as a natural disaster or a lockdown due to a pandemic, the earlier the gestational age at which the mother is exposed to such stressful event, the lower the birth weight percentile.

In this sense, we have included in the analyses birth weight percentiles adjusted for gestational age and gender, since the effect on birth weight for preterm neonates may have led to bias in many of the studies already published, and our aim was to focus exclusively on low birth weight.

Antenatal anxiety and depression symptoms may place a greater financial burden on healthcare systems. Consequently, an early identification of pregnant women with anxiety or depression symptoms and access to perinatal mental health services are crucial for reducing the impact of perinatal mental disorders. There are already several screening strategies for depression and anxiety during pregnancy, and there is evidence suggesting that an appropriate and timely intervention may minimize symptoms during pregnancy and the postpartum period. Although improvement of anxiety symptoms also improves neonatal outcomes is not yet clear, some mindfulness-based interventions for stress management have shown a reduction in the percentage of neonates with a birth weight below the 10th percentile.

Since the conditions in this study were very specific, as it was conducted during a lockdown due to a global pandemic, the external validity of our results may be limited. Nevertheless, the results of this study may be extrapolated to a population living with chronic stress and showing a higher prevalence of anxiety.

In conclusion, our results show that anxiety during pregnancy impacts birth weight. More specifically, trait anxiety, which is associated with personality traits, is a predictor for low birth weight. A deeper understanding of the mechanisms underlying a stressful event that may impact neonatal outcomes may help to promote the development of interventions that may reduce the effect of psychosocial stressors during pregnancy, thus improving maternal and neonatal outcomes. Regarding the effect of anxiety timing on birth weight, our data seems to suggest that the earlier the anxiety symptoms appear, the lower the birth weight. However, this hypothesis requires further research to be confirmed.

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Ethics

This study was approved by the Institutional Review Board of Vall d'Hebron Research Institute PR(AMI)186/2020 on 27 March 2020. Informed consent was obtained from all participants.

References:

Figure legends:

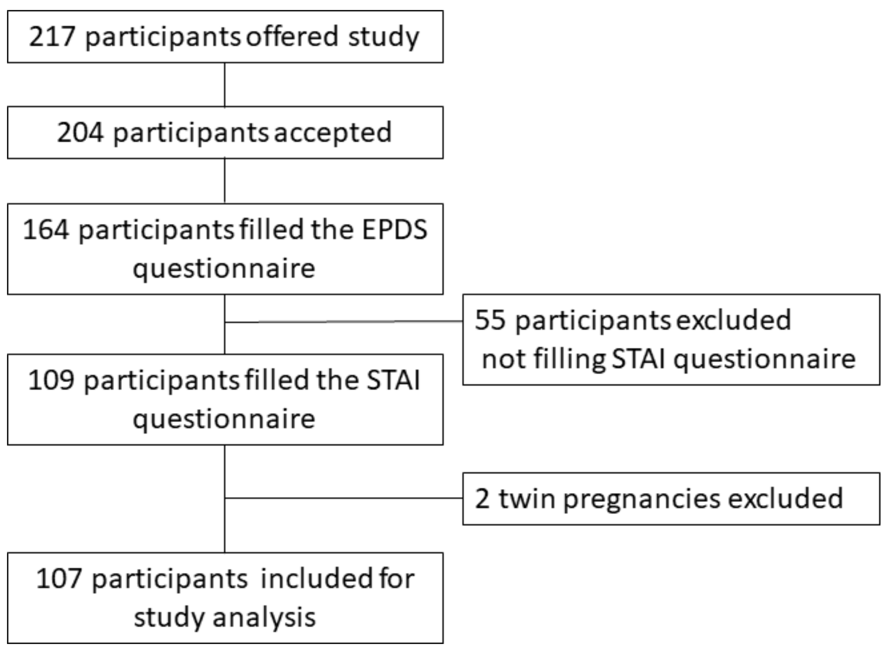
Figure 1. Flow diagram.

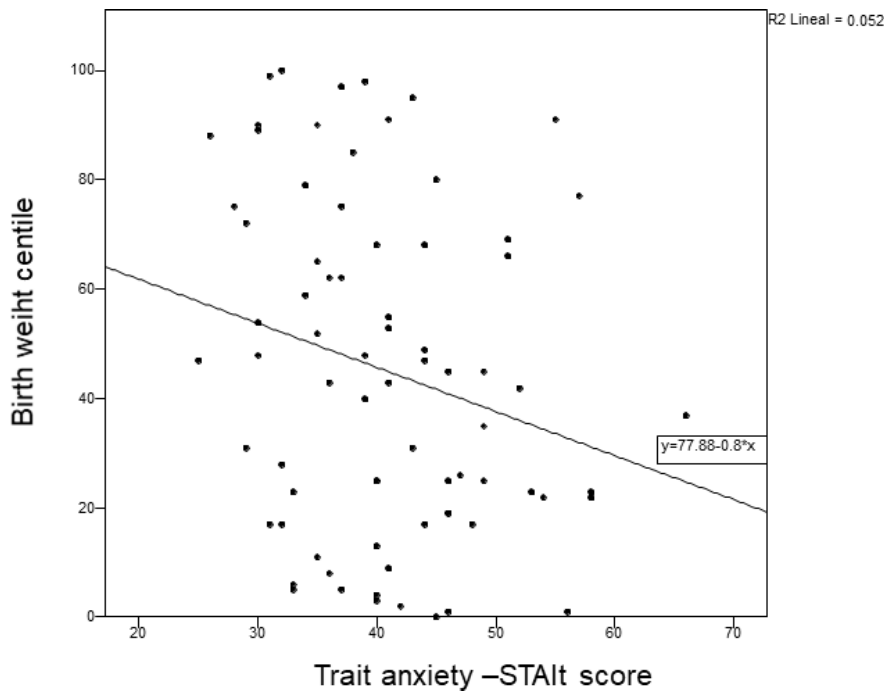
Figure 2. Graphical representation of the correlation between STAIt score and birth weight percentile.

Table 1. Maternal demographics, obstetric outcomes, neonatal outcomes, and data from psychosocial questionnaires (n=107).

Table 2. Univariate linear regression analysis to explore a potential correlation between birth weight percentile (adjusted for gestational age at delivery and neonate gender) and risk factors.

Table 3. Multivariate lineal regression analysis to explore a potential correlation between birth weight percentile (adjusted for gestational age at delivery and neonate gender) and risk factors.





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