Original Article

Screening antenatal anxiety: Predicting its effect on fetal growth

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Abstract

Context: Maternal anxiety has an association with low birth weight. However, studies are scarce to determine any association between maternal anxiety and fetal growth. **Aims:** This study aims to determine the effect of maternal anxiety on fetal growth, measured by gestational age-dependent increase in fetal abdominal circumference (AC). The secondary objective is to determine the effect of maternal anxiety on other fetal parameters (biparietal diameter [BPD], head circumference [HC], femur length [FL]). **Settings and Design:** This cross-sectional study was conducted in a tertiary care hospital, Kolkata. **Materials and Methods:** Four hundred and ten pregnant mothers, between 14 and 40 weeks of gestation, were interviewed with socioeconomic and obstetric profile questionnaire and examined for anthropometric profile and presence and severity of pallor. Anxiety was assessed using Generalized Anxiety Disorder-7 (GAD) questionnaire. HC, AC, BPD, and FL were measured by ultrasound biometry. **Analysis Used:** A multivariable logistic regression analysis was done to determine the predictors of small-for-gestational-age (SGA). A robust mediation analysis was done to determine mediating effect of anxiety on gestational age-dependent increase in fetal AC. **Results:** Mild (odds ratio $[OR]_{Adjusted} = 6.23$, [2.41, 16.15]) and moderate ($OR_{Adjusted} = 22.42$, [5.00, 100.57]) anxiety was significantly associated with SGA fetus. Anxiety increased with the progression of gestation (β_{GAD}: 0.011 [0.007–0.015]) and it had a negative effect on fetal growth (standardized indirect effect of gestational age-mediated by anxiety on AC: −0.037 [−0.059, −0.022]). Anxiety also attenuated gestational age-dependent increment of HC. **Conclusion:** Mother's anxiety has a gestational age-dependent temporally incremental negative effect on fetal growth and brain development.

Keywords: Anxiety, fetal growth, maternal anxiety, small for gestational age, ultrasound biometry

Introduction

In recent years, a growing body of literatures on "foetal origins hypothesis" suggests that prenatal period is a critical time for fetal growth and thus a period of vulnerability; during which a range of exposures, including maternal psychological state, can have sustained effects across the lifespan, with implications for physical and psychiatric health through epigenetic pathways.[1,2]

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Evidence suggests that anxiety and stress during prenatal period has a severity and duration-dependent association with increased risk of preterm birth and low birth weight.[2,3] Furthermore, it has also been evidenced that disorders related to mother's mood are not more common or severe after childbirth than during pregnancy.[4] Therefore, it can be presumed that maternal stress and anxiety, had it had any biologically plausible association with preterm birth as well as low birth weight, such effect must have started "programming" the fetus toward low birth weight since antenatal period. However, most of the studies performed in this emerging field of research have mainly considered low birth

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weight as the outcome variable. This approach cannot establish the potential negative effect of antenatal anxiety on fetal growth and therefore there is a lack of conclusive evidence regarding the potential of preventive management of maternal anxiety through antenatal care on low birth weight, which is the ultimate outcome of growth retardation in utero.

Literature suggest that fetal growth can be estimated with considerable accuracy by measuring fetal abdominal circumference (AC), biparietal diameter (BPD), head circumference (HC), and femur length (FL) using ultrasound biometry, which is the gold standard for assessment of fetal size.[5,6] in utero growth is primarily estimated by AC and AC <10th percentile for gestational age is associated with poor perinatal outcome.[5] In this context, we conducted this study to determine the effect of maternal anxiety on fetal growth in utero, measured by gestational age-dependent increase in fetal AC. The secondary objective of the study is to determine the effect, if any, of maternal anxiety on other fetal parameters (BPD, HC, FL) measured by ultrasound biometry.

Subjects and Methods

This cross-sectional study was conducted in a tertiary care hospital in Kolkata. Data were collected from all eligible mothers, who had visited the ultrasonography clinic for fetoplacental profile (USG FPP clinic) of Radiology Department, 2 days per week, selected randomly, starting from December 2014 to February 2015.

Inclusion criteria

Pregnant mothers having singleton live fetus of gestational age of ≥14 weeks (to avoid the possible confounding effect of beta human chorionic gonadotropin level during early pregnancy).[7,8]

Exclusion criteria

- Gestation >40 weeks
- Elderly primi
- Known illness (e.g., diabetes, hypertension, obesity, obstructive airway disease, thrombotic disease, heart disease, chronic renal disease, and collagen vascular disease)
- Acute illness in the preceding 3 months
- Mothers who ever smoked
- History of intake of psychiatric medication (s), alcohol during current pregnancy.

Sample size

Considering the prevalence of small-for-gestational-age (SGA) in India as 46.9%, the sample size was calculated to be 385.[9] Among 478 pregnant women, with gestational age ≥14 weeks, who attended the department during the study, 419 were eligible, and among them, 410 consented to participate.

Data collection

Mothers were interviewed to obtain information regarding demographic characteristics (age, education, occupation, family type, per capita income) and obstetric history (parity, history of intrauterine growth restriction, previous miscarriage or abortion) using a predesigned pretested structured questionnaire and screened for anxiety using Generalised Anxiety Disorder (GAD) 7 questionnaire.[10] The height of pregnant woman was measured using standardized procedure and weight was obtained from the antenatal card and body mass index was calculated. Mothers were clinically examined to detect pallor over conjunctivae, tongue, and palms or nail beds and pallor was defined as present if found in at least two sites (one site being palm). Pallor was graded according to severity of palmar pallor.

Data regarding fetal HC, AC, BPD, and FL were obtained from USG FPP.

Observed HC, AC, BPD, and FL were compared with expected 10th percentile score of HC, AC, BPD, and FL for gestational age.[11] SGA fetus was defined as AC less than the 10th percentile for the corresponding gestational age.

Statistical analysis

Bivariate analysis and multivariable backward stepwise logistic regression analyses were done including all the explanatory variables to determine their association with SGA. For logistic regression, maternal anxiety was transformed into three-level ordinal variable: No (GAD ≤5), mild (GAD ≤10), moderate (GAD ≤15), and severe (GAD >15) anxiety. Sobel test was performed to determine any mediating effect of anxiety on the relationship between gestational age and AC. Based on the result of Sobel test, a robust mediation analysis was done including gestational age as the independent variable, anxiety as the mediating variable, AC as the outcome variable and taking all other explanatory variables as covariates. Secondary outcome analyses were carried in a similar manner for all other fetal parameters. All analyses were done using IBM SPSS version 20 (IBM Corp. Released 2011. Armonk, NY: IBM Corp.) and Hayes' Process Tool.

Ethical consideration

PNDT act was strictly followed while performing USG. Ethical permission was obtained from the Institute Ethics Committee.

Results

Table 1 shows the baseline characteristics of the study participants. About 60% of the mothers had no anxiety, 36% had mild and 3% had moderate anxiety. None of the participants had severe anxiety.

13.41% of the fetuses were SGA. While the proportion of not anxious mothers having SGA fetus was only 3.21%, the proportion was 26.35% and 61.35% for mothers with mild and moderate anxiety, respectively [Table 2].

Lower maternal age, heavy work, higher parity, joint family, pallor, and anxiety (both mild and moderate) were found

to be associated with SGA on bivariate analysis. In the adjusted model, only mild (odds ratio [OR] $_{Adjusted}$ = 1.16, [0.42, 3.19]) and moderate pallor ($OR_{Adjusted}$ = 4.74 [1.52, 14.79]) and mild ($OR_{Adjusted}$ = 6.23, [2.41, 16.15]) and moderate ($OR_{Adjusted}$ = 22.42, [5.00, 100.57]) anxiety were significantly associated with SGA [Table 3].

Maternal anxiety had a significant mediating effect on the relationship between gestational age and AC in Sobel test (effect − 0.054 ± 0.013; $P < 0.000$). In mediation analyses, maternal anxiety was found to be increased with the progression of gestation (β_{GAD}: 0.011 [0.007–0.015]) and anxiety had a negative effect on fetal growth (standardized indirect effect of gestational age-mediated by anxiety on AC: −0.037 [−0.059, −0.022]) with a small effect size (ratio of indirect to direct effect: −0.037 [−0.058, −0.022]). Increased maternal age, higher per capita income and increased level of mother's education was associated with less anxiety; while heavy work during pregnancy and presence of pallor predicted higher anxiety [Table 4 and Figure 1].

In secondary outcome analysis mild ($OR_{Adjusted}$ = 4.90, [2.30, 10.41]) and moderate ($OR_{Adjusted}$ = 9.92, [3.93, 25.04]) pallor and mild anxiety ($OR_{Adjusted}$ = 4.36, [2.18, 8.73]) had significant association with small fetal BPD for gestational age. No association was found between maternal anxiety and small FL for gestational age [Supplementary Table 1].

Anxiety was statistically significant mediator of the relationship between gestational age and HC (Sobel test: Effect: −0.041 ± 0.01; P = 0.0000) (standardized indirect effect: −0.032 [−0.05, −0.02]; ratio of indirect to direct effect: −0.033 [−0.049, −0.020]) [Supplementary Table 2].

Table 1: Background characteristics of the study population (*n*=410)

Characteristics	Categories	Frequency (%)
Age*		26.15 (3.81)
Education (completed)	Below primary	39 (9.51)
	Primary	136 (33.17)
	Middle	166 (40.49)
	Secondary and above	69 (16.83)
Occupation	Sedentary	289 (70.49)
	Moderate	38 (9.27)
	Heavy	83 (20.24)
Per capita income (Rs./month)	<842 (Prasad's social Class V**)	1 (0.24)
	842-1684 (Prasad's social Class IV)	22 (5.37)
	1685-2807 (Prasad's social Class III)	100 (24.39)
	2808-5614 (Prasad's social Class II)	268 (65.37)
	>5614 (Prasad's social Class I)	19 (4.63)
Family type	Nuclear	254 (61.95)
	Joint	156 (38.05)
Gestational age (weeks)	14-28	244 (59.51)
	28-40	166 (40.49)
Parity	0	190 (46.34)
	1	91 (22.20)
	2	110 (26.83)
	3 or more	19 (4.63)
Height*		154.67 (4.50)
Pallor	Absent	166 (40.49)
	Mild	192 (46.83)
	Moderate	52 (12.68)

*For continuous variables mean±SD has been mentioned, **Modified BG Prasad scale 2014 has been used for determination of social class. SD: Standard deviation

Table 2: Distribution of small-for-gestational age foetus with respect to maternal anxiety in the study population (*n*=410)

	SGA absent, *n* (%)	SGA present, *n* (%)	Total, *n* (%)
Maternal anxiety			
Absent	241 (96.79)	8 (3.21)	249 (60.73)
Present			
Mild	109 (73.65)	39 (26.35)	148 (36.10)
Moderate	5 (38.46)	8 (61.54)	13 (3.17)
Total	355 (86.59)	55 (13.41)	410

SGA: Small-for-gestational age

Discussion

We found that anxiety and pallor were significant predictors of growth restriction in fetus. In addition, the explained variability in the risk factor model was largely improved on modeling the gestational age-dependent confounding effect of anxiety on fetal growth. In this model, we found that antenatal anxiety increased with the advancement of pregnancy and had a negative effect on fetal AC. This implied that anxiety had a time-dependent incremental negative effect on fetal growth. A similar effect of anxiety was found on fetal HC. This finding was also in line with the finding that fetal BPD was significantly less in the presence of prenatal anxiety. In addition, we found that antenatal anxiety was significantly less among mothers with higher age, higher per capita monthly income, and higher level of education, while mothers having pallor and mothers involved in heavier work had higher anxiety.

The findings of our study support the evidence laid down by previous researchers that prenatal anxiety and fetal growth restriction were correlated.[12-14] However, our study extended the available knowledge by implying that maternal anxiety was not an attribute with fixed level and that its negative effect on fetal growth was incremental with respect to gestational age.

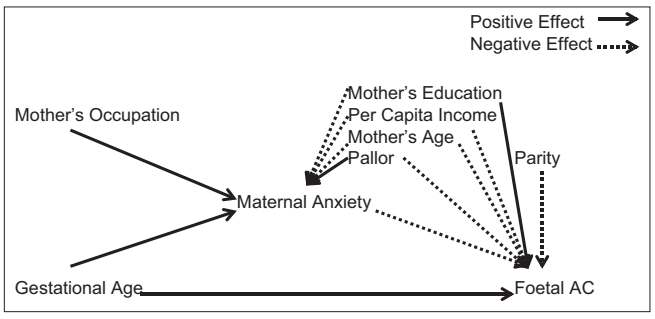

Figure. 1: Relationship between gestational age, maternal anxiety, and fetal abdominal circumference in the presence of different cofactors (*n* = 410)

Moreover, the negative effect of anxiety on fetal HC and BPD implied a poor neurodevelopmental outcome including low IQ among children of anxious mothers, which corroborated with past evidence.[15,16] Our study additionally extended the knowledge that more prolonged was the prenatal anxiety, the more grievous impact it would have on the brain development of the fetus.

Table 3: Association of small-for-gestational age with explanatory variables: Bivariate and multivariate analyses (*n*=410)

Explanatory variables (reference category*)	Categories	OR**	CI	AOR***	95% CI
Age	Per year increase	0.80	0.73-0.88		
Education (secondary and above)	Below primary	2.62	0.97-7.04		
	Primary	1.08	0.46-2.54		
	Middle	0.71	0.30-1.70		
Occupation (sedentary)	Moderate	0.53	0.06-4.94		
	Heavy	4.13	1.45-11.80		
Per capita income	Per rupee increase	1.00	1.00-1.00		
Family type (nuclear)	Joint	2.97	1.66-5.31		
Parity	Per unit increase	0.43	0.29-0.65		
Height	Per centimeter increase	0.97	0.91-1.04		
Pallor (no pallor)	Mild pallor	2.94	1.22-7.07	1.16	0.42-3.19
	Moderate pallor	22.71	8.95-57.68	4.74	1.52-14.79
Anxiety (no anxiety)	Mild anxiety	10.78	4.87-23.84	6.23	2.41-16.15
	Moderate anxiety	48.20	12.86-180.58	22.42	5.00-100.57

*Reference categories of the categorical variables have been shown in the parenthesis. **ORs for bivariate analyses have been shown in the OR column. ***AOR at the final step of multiple LR (backward LR) has been shown in the AOR column. Hosmer Lemeshow test: $\chi 2$ (df), P - 0.459 (3), 0.93; Nagelkarke R^2: 0.32. ORs: Odds ratios; CI: Confidence interval; AOR: Adjusted odds ratio; LR: Logistic regression

The biologically plausible explanation of the negative effect of maternal anxiety on fetal growth can be implied by the role of increased cortisol level during anxiety and stress in altering fetoplacental circulation.[12,17]

The findings also implied that improvement in educational and financial status of women, delayed age of pregnancy, and less heavy work during pregnancy and reduction of anemia would reduce the mother's anxiety during antenatal period and improve fetal outcome. This implication supported the available evidence that provision for social support among pregnant mothers to reduce life stress were necessary for better birth outcome.[18]

The design being cross-sectional the establishment of a causal effect of maternal anxiety on fetal growth is subject to further investigation. In addition, we described anemia during pregnancy with the presence of pallor only. Hemoglobin estimation was not possible due to limited resources. Assessment of maternal anxiety was limited to assessment by GAD 7 only. The implication that anxiety increases temporally with advancing gestation is subject to further confirmation by longitudinal studies serially estimating anxiety of the same mother at different ages of gestation.

On balance, our study informs the policy that the existing programs on maternal and child health should integrate with mental health programs to prevent anxiety during pregnancy and to provide early diagnosis and adequate treatment to anxious mothers to improve fetal growth, and brain development and prevent low birth weight. The role of the frontline workers in improving the family climate by counseling the family members and thereby reducing the stress among pregnant mothers may be investigated for a cost-effective solution.

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Table 4: Time-varying (gestational age-dependent) confounding effect of mother's anxiety on fetal abdominal circumference: Result of mediation analysis (*n*=410)

Models		Variables	β_{GAD}	β_{AC}	
				Not adjusted for GAD	Adjusted for GAD
Model 2 (outcome: Fetal AC)	Model 1 (outcome: Mother's GAD score)	Gestational age (days)	0.011 (0.007-0.015)	1.39 (1.34-1.43)	1.44 (1.40-1.48)
		Mother's age (years)	−0.22 (−0.27-−0.17)	0.57 (0.08-1.05)	
		Per capita monthly income (in 1000 Rupees)	−0.5 (−0.7-−0.4)		−1.4 (−2.7-−0.2)
		Mother's education (years of schooling)	−0.15 (−0.27-−0.02)	2.82 (1.31-4.33)	2.10 (0.66-3.54)
		Mother's occupation (each level increase from sedentary work)	0.24 (0.12-0.37)	−2.20 (−3.61-−0.79)	
		Parity		1.2 (0.2-2.2)	−1.79 (−3.54-−0.03)
		Pallor	0.65 (0.39-0.91)	−8.02 (−10.89-−5.15)	−4.85 (−7.52-−2.18)
		Mother's anxiety (GAD score)			−4.88 (−6.24-−3.51)

β_{GAD}: Coefficient in model with mother's GAD score as outcome; β_{AC}: Coefficient in model with fetal AC as outcome. Only statistically significant coefficients have been displayed in the table. Variables included: Gestational age, mother's age, maternal education, maternal occupational severity, per capita monthly income, family type, parity, grade of pallor. GAD: Generalised anxiety disorder; AC: Abdominal circumference

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Association of dichotomized fetal biometric outcomes with explanatory variables: Multivariate analyses (*n*=410)

Explanatory variables (reference category*)	Categories	Biparietal diameter[a]		Femur length[b]	
		AOR	95% CI	AOR	95% CI
Parity	One unit increase	0.65	0.50-0.86	-	-
Occupation (heavy)	Moderate	-	-	0.00	0.00
	Sedentary	-	-	0.31	0.11-0.89
Pallor (no)	Mild	4.90	2.30-10.41	-	-
	Moderate	9.92	3.93-25.04	-	-
Anxiety (no)	Mild	4.36	2.18-8.73	-	-
	Moderate	4.29	0.94-19.55	-	-

*Reference categories of the categorical variables have been shown in the parenthesis. Goodness-of-fit of final model: [a]Hosmer Lemeshow test: χ^2 (df), P - 14.658 (8), 0.07, Nagelkarke R^2: 0.19; [b]Hosmer Lemeshow test: χ^2 (df), P - 11.356 (8), 0.18, Nagelkarke R^2: 0.11. Variables entered at step 1 for all the backward LR were - mother's age, maternal education, maternal occupational severity, per capita monthly income, family type, parity of the mothers, grade of pallor, maternal height, and maternal anxiety. AOR: Adjusted odds ratio; CI: Confidence interval; LR: Logistic regression

Supplementary Table 2: Time-varying (gestational age-dependent) confounding effect of mother's anxiety on fetal head circumference: Result of mediation analysis (*n*=410)

Models		Variables	β_{GAD}	β_{HC}	
				Not adjusted for GAD	Adjusted for GAD
Model 2 (outcome: fetal HC)	Model 1 (outcome: GAD score)	Gestational age (days)	0.011 (0.007-0.015)	1.23 (1.19-1.27)	1.27 (1.23-1.31)
		Mother's age (years)	−0.22 (−0.27-−0.17)		−0.49 (−0.90-−0.08)
		Per capita monthly income (1000 Rs.)	−0.5 (−0.7-−0.4)	1.4 (0.6-2.3)	
		Mother's education (years of schooling)	−0.15 (−0.27-−0.02)	2.11 (0.86-3.37)	1.56 (0.36-2.76)
		Mother's occupation (each level increase from sedentary work)	0.24 (0.12-0.37)	−2.20 (−3.61-−0.79)	−1.61 (−2.72-−0.50)
		Pallor	0.65 (0.39-0.91)	−4.73 (−7.03-−2.44)	−2.30 (−4.42-−0.18)
		Mother's anxiety (GAD score)			−3.74 (−4.68-−2.81)

β_{GAD}: Coefficient in model with mother's GAD score as outcome; β_{HC}: Coefficient in model with fetal HC as outcome. Only statistically significant coefficients have been displayed in the table. Variables included: Gestational age, mother's age, maternal education, maternal occupational severity, per capita monthly income, family type, parity, grade of pallor. HC: Head circumference; GAD: Generalised anxiety disorder