Effects of Maternal Anxiety and Depression During Pregnancy in Chinese Women on Children's Heart Rate and Blood Pressure Response to Stress

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Running Title: Effect of Prepartum Stress on Children

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Sources of funding: The work was supported, in part, by the 2010 Primary Scientific Research Foundation of Xi'an Jiaotong University and National Nature Science Foundation of China (NSFC81170294).

Anthony M Dart is a Senior Principal Research Fellow of the National Health and Medical Research Council of Australia.

Abstract

Psychological disturbances, including anxiety and depression, are common during human pregnancy. Our objective was to determine if these maternal disturbances influence cardiovascular responses of the offspring.

The psychological status of 231 pregnant women was determined. Offspring (216) of these women were subsequently exposed to a video challenge stress when aged 7-9 years. Heart rate (HR) and blood pressure (BP) of the children were determined at rest, in response to video stress and during subsequent recovery.

Children's resting and stress induced increases in heart rate (HR, bpm), systolic (SBP, mmHg) and diastolic (DBP, mmHg) blood pressure were all greater in children whose mothers reported anxiety during pregnancy. Values (mean±sd) for resting HR, SBP and DBP were 75.15±5.87, 95.37±2.72 and 66.39±4.74 for children whose mothers reported no anxiety and an average of 81.62±6.71, 97.26±2.90 and 68.86±2.82 for children whose mothers reported anxiety at any level. Respective values for stress induced increments in HR, SBP and DBP were 14.83.±2.14, 16.41±1.97 and 12.72±2.69 for children whose mothers reported no anxiety and 17.95±3.46, 18.74±2.46 and 14.86±2.02 for children whose mothers reported any level of anxiety. Effects of maternal depression were less consistent. The effects of maternal anxiety remained in multivariate analyses which also included children's birth weight.

The results indicate a long term influence of maternal psychological status during pregnancy on the cardiovascular responses to stress amongst offspring. These effects may contribute to prenatal influences on subsequent health of the offspring.

Introduction

Cardiovascular disease (CVD) remains a major contributor to morbidity and mortality. A number of risk factors and behaviours in adult life contribute to the development of such disease including cigarette smoking, elevated cholesterol and elevated blood pressure. In addition to these well-established factors there is evidence that prenatal factors also influence the likelihood of CVD later in life. The original observations on the early origins of disease were related to the impact of low birth weight, and growth retardation, on adult cardiovascular risk[1-3].

In terms of cardiovascular risk a number of studies have specifically identified effects of prematurity and of low birth weight on subsequent blood pressure and on blood pressure variability[4-7]. It is also known that there is a strong tracking of blood pressure from childhood through to adult life[8-10] and that blood pressure variability and cardiovascular response to stress in children and young adults are predictive of later hypertension[10-13]. Hence assessment of both resting and stress induced increase in blood pressure in children is likely relevant to the later emergence of hypertension as a risk factor for cardiovascular disease.

Emotional lability is well recognised in human pregnancy. A study in a western population using the Prenatal Psychosocial Profile stress scale reported a prevalence of low-to-moderate psychosocial stress during pregnancy as high as 78% and of high levels of stress of 6%[14] whilst overall rates of 40-84% have been reported amongst pregnant Chinese women[15]. In a study from the UK using anxiety items from the Crown-Crisp experiential index and the Edinburgh Postnatal Depression Scale, anxiety was found in approximately 22% and depression in 19% of women during pregnancy[16]. Studies from Finland and South America using different evaluative instruments have reported rates of between 16 and 60% for anxiety and 20 and 30%

for depression[17, 18]. Variations in prevalence likely result from variation in operational definitions of stress, anxiety and depression as well as from differences in studied populations. The prevalence of clinically recognised anxiety states such as panic disorder is also higher during pregnancy[19].

A recent study has demonstrated an association between parental psychosocial stress, as determined by questionnaire, and subsequent blood pressure in children when aged 5 to 7(ref 20). Maternal stress was assessed at about 16 weeks of pregnancy. In the current study we have examined the effects of maternal anxiety and depression measured at various stages of pregnancy on children's resting blood pressure and in addition on the haemodynamic responses to video stress.

Methods

Ethics Statement

The study was approved by the Ethics Committee, the 1st Affiliated Hospital of Xi'an Jiaotong University. Written informed consent was obtained from mothers on behalf of their children, as approved by the Ethics Committee. Verbal consent was also obtained from children prior to their assessment.

Subjects

The cohort consisted of 216 mothers and children (from an initial cohort of 231 women as 15 were lost to follow up). 71 mothers were assessed for anxiety and depression during the first (≤16 weeks), 72 during the second (16-28 weeks) and 73 during the third (28-42 weeks) trimester. Children, who were all full term, were tested when aged between 7-9 years. Exclusion criteria amongst the children and mothers were a known history of psychiatric or cardiovascular disease. Sample size was based on previous estimates of the frequency of anxiety during pregnancy.

Assessment of Maternal Anxiety and Depression During Pregnancy

The Hamilton Anxiety Scale (HAMA) and Hamilton Rating Scale for Depression (HAMD, also known as HRSD) were used. HAMA is widely used as a scale to identify anxiety. A psychologist or trained physician asks 14 semi-structured questions, 7 related to psychological anxiety symptoms and 7 related to somatic anxiety symptoms, and then provides a score according to a 5-point scale for each item (0 - Not at all; 1 – Mild; 2 – Moderate; 3 – Severe; 4

- Very Severe). The total scores are used for assessment (Mild Anxiety: 18-25; Moderate Anxiety: 26-30; Severe Anxiety: >30). The HAMD is the most widely used outcome scale for depression studies. The 24-item HAMD questionnaire is the most common version used in mainland China scoring 5 points for each item as described for HAMA. The total scores are then used to quantify depression (Mild Depression: 10-19; Moderate Depression: 20-29; Severe Depression: >30). The two scales were translated and rigorously tested with different populations in mainland China. Their reliability and validity were assessed and approved by the responsible authority (Shanghai Mental Health Center).

Video stress test and measurement of haemodynamic indices

Measurement of children's cardiovascular response to a video game task was undertaken on a weekend at hospital-based offices. Clinic staff were not aware of results of mothers anxiety/depression questionnaires. All studies were performed under standardized conditions, in the fasting state between 9 am and 11 am and at least 30 min following collection of a venous blood sample. The task involved playing video games (Breakout; Atari, Sunnyvale, CA) lasting a total of approximately 10 minutes as previously described in detail[21]. Blood Pressure (BP) and heart rate (HR) were measured with an appropriately sized BP cuff connected to the children's non-dominant arm from a digital BP monitor (Omron HEM-907, Kyoto, Japan). BP and HR were measured before [rest BP (rBP) and rest HR (rHR)]; during and after video game plays. Three resting BP and HR measurements were obtained after the child had sat quietly for at least 2 minutes. The average of the last 2 measures was used in this analysis. HR and BP measurements were taken in duplicate starting 2 and 5 minutes after the onset of the video game and 5 minutes after its completion (recovery). The average of the 2 measurements was used on each occasion. Children continued playing during the measurements but without any

144 speech or extraneous other movement. The response to stress (Δ_{stress}HR and Δ_{stress}BP) was
145 taken as the maximum increase in HR and BP between the resting values and those obtained
146 during the video game. We also analysed recovery values (Δ_{recov}HR and Δ_{recov}BP) as the
147 recovery values minus the respective rest values.

148

149 **Statistical Analysis**

150 Statistical analysis was undertaken with SPSS v19. Results are given as mean±sd or N.
151 Between group comparisons were made by ANOVA followed, if significant, by Schéffe test
152 for multiple group comparison. Associations between variables were examined by Pearson's
153 correlation coefficient and r values are reported. Multivariate analyses were undertaken with
154 General Linear Model and with factors and covariates as indicated. Statistical significance was
155 defined as $p<0.05$.

Results

The study group comprised 216 children with an average age of 7.96 ±1.12 years, birth weight of 3.34± 0.40 Kg and of whom 111 were boys. All children were full term and free of significant disease at the time of the study. 66 of the mothers had neither anxiety nor depression at their prenatal assessment. 58 of the mothers had both anxiety and depression (of any level) whilst 42 had isolated anxiety and 50 isolated depression. None of the mothers smoked cigarettes during the pregnancy (and only 4 reported smoking at other times). None of the mothers had a history of, or treatment for, psychiatric illness prior to their pregnancy.

Effect of Maternal Anxiety on Children's Resting, Stress and Recovery Haemodynamic Responses

Table 1 shows the baseline demographic and haemodynamic values for the children according to the results of the mothers anxiety questionnaire. Birth weight was lower in children whose mothers reported moderate or severe anxiety than in those whose mothers did not. Children's baseline HR, SBP and DBP were all higher in those whose mothers reported anxiety with greater effects seen in those with moderate or severe, rather than mild, anxiety.

Table 2 shows the maximum video stress induced increase in HR, SBP and DBP according to mother's anxiety questionnaire responses. Δ_{stress}HR, Δ_{stress}SBP and Δ_{stress}DBP were all greater in children whose mother's questionnaire responses indicated the presence of anxiety. Similar findings (not shown) were present if analyses were conducted separately for each trimester with the exception that there were no significant differences in ΔDBP related to maternal anxiety for mothers assessed in trimester 3.

Recovery of HR and BP to baseline values were also impaired in children whose mothers reported anxiety during pregnancy (Table 2).

Effect of Maternal Depression on Children's Resting, Stress and Recovery Haemodynamic Responses

In contrast to maternal anxiety there were no significant differences in birth weight when analysed by maternal depression questionnaire responses. In addition an effect of maternal depression on resting haemodynamic parameters was limited to HR (Table 3). Video stress induced increases in SBP were related to mothers depression questionnaire responses, whilst Δ_{stress}HR and Δ_{stress}DBP were not (Table 4).

Recovery of heart rate (Δ_{recov}HR) was not affected by maternal depression. However maternal depression was associated with delayed recovery in SBP and DBP (table 4).

Effects of Birth Weight on Children's Haemodynamics

Birth weight was inversely related to children's resting haemodynamic parameters with r vales of -0.293 for HR ($p<0.001$), -0.203 for SBP ($p<0.01$) and -0.180 for DBP ($p<0.01$). Birth weight was also inversely related to children's video stress responses for all parameters with r vales of -0.18 for Δ_{stress}HR ($p=0.08$), -0.242 for Δ_{stress}SBP ($p<0.001$) and -0.196 for Δ_{stress}DBP ($p<0.01$). Respective values for recovery variables (Δ_{recov}) were -0.048 ($p=0.485$), -0.264 ($p<0.001$) and -0.231 ($p<0.01$).

Combined Effects of Maternal Anxiety, Maternal Depression and Children's Birth Weight.

As noted, children's birth weight was inversely related to maternal anxiety score and also to children's resting HR and BP as well as to their video stress induced increments and recoveries. In addition, 57 of the mothers had questionnaire responses positive for both anxiety and depression. We therefore undertook multivariate analyses with the haemodynamic measure as the dependent variable, maternal anxiety and maternal depression scores as factors (4 levels for each, ie absent, mild, moderate, severe) and with birth weight as a covariate. Results from these analyses are shown in Table 5. For stress induced increments (Δ_{stress}) the significance of anxiety score results remained for all HR and BP measures. The significance of depression score results was limited to rHR, Δ_{stress}SBP, Δ_{recov}SBP, Δ_{recov} DBP.

Significant interaction between the effects of maternal anxiety and depression were limited to recovery BP values. Recovery values for SBP (mmHg) were 5.83±4.54 for children whose mothers reported any level of anxiety but no depression, 4.62±5.31 for children whose mothers reported any level of depression but no anxiety and 10.17±5.55 for children whose mothers reported both anxiety and depression. Respective values for DBP were 6.88±3.16, 4.82±5.31 and 10.27±3.012. There were no significant independent effect of birth weight.

Discussion

There are several major findings from this study. Children born to mothers who respond positively to an anxiety questionnaire during their pregnancy have higher resting, stress and recovery heart rates and blood pressures than those whose mothers respond negatively. These effects are greater with increasing levels of anxiety. In contrast children born to mothers who respond positively to a depression questionnaire show effects limited to resting heart rate, stress induced increase in SBP and recovery BP. Birth weight is lower in mothers who respond positively to the anxiety questionnaire and is inversely related to the resting and stress HR and blood pressure. However in multivariate analyses the effects of anxiety score remain significant whereas those of birth weight do not. Such analyses also indicate a significant delay in recovery of BP in children whose mothers reported both anxiety and depression compared with those reporting anxiety or depression in isolation. However there was no evidence for any such interaction in relation to rest or stress HR and BP.

Anxiety and depression are both common causes of psychologic distress in pregnant women[14, 15]. Estimates of prevalence vary amongst different studies most likely due to differences in the operational definitions used. In our study although anxiety and depression were common during pregnancy moderate or severe levels of anxiety and depression were only present in 17% and 11% respectively, with the majority of these being moderate. None of the women were being treated for psychiatric disorders prior to their participation.

The concept of a prepartum contribution to the determination of future CVD has widespread though not universal support. The original evidence was provided by the link between low

birth weight and future cardiovascular events and foetal growth retardation is one postulated mechanism to account for influences on events later in life[1, 2]. Low birth weight can arise from a number of causes including cigarette smoking, impaired nutrition and anxiety[22-24]. Cigarette smoking was not a factor in the current study where overall prevalence of cigarette smoking was very low and no women reported smoking during pregnancy. The low overall prevalence is in keeping with recent epidemiological data from China where smoking rates in 2010 were 52.9% for men but only 2.4% for women[25]. In agreement with previous studies, we also noted that birth weight was lower in children born to mothers who had experienced anxiety during pregnancy. Furthermore we found an inverse relationship between birth weight and the children's haemodynamic responses when these were examined by correlation analysis. However when analysed by multivariate analysis including the levels of anxiety and depression experienced by the mothers during pregnancy, the effects of birth weight on childrens haemodynamic and cardiovascular responses were no longer significant. It is thus possible that some of the effects attributed to low birth weight on future cardiovascular health could be due to the effects of anxiety or depression during pregnancy, rather than to effects of birth weight per se. However, it is important to note that only 5% of the children (all of whom were full term) in the current study were of low birth weight (ie <2.5 Kg). This is in general consistent with the overall prevalence of low birth weight reported for China[26].

A number of animal studies, principally but not exclusively in rodents, have supported the hypothesis that exposure of pregnant animals to various sorts of stress can influence the cardiovascular responses of their offspring[3, 27-29]. In contrast to the animal literature the number of human studies examining the effects of psychological distress during pregnancy on cardiovascular responses and the HPA axis function amongst offspring are limited[3]. In a recent

study of a large cohort from the Netherlands it was shown that psychosocial stress assessed at around 16 weeks of pregnancy was associated with blood pressure of the offspring when the children were aged 5-7[20]. Our findings concur with this observation but extend it to the assessment of stress (measured as anxiety and depression) at other times of the pregnancy and to the assessment of children blood pressure response to a video game challenge. We find that maternal anxiety affects childrens haemodynamic measures whether assessed during the first, second or third trimester. In addition the haemodynamic responses to video stress are also dependent on maternal anxiety, and to a lesser extent depression.

This study does not explain the mechanism by which maternal psychological factors exert their effects. Elevation in mothers cortisol as a result of psychological distress is one potential mechanism. Administration of dexamethasone during pregnancy has been shown to alter the pattern of cardiovascular responses in offspring[30]. Some studies have also reported effects beyond the first generation[27]. Exogenous dexamethasone has the advantage of being less metabolised by placental 11β hydroxysteroid dehydrogenase type 2 than is the native hormone but studies would suggest that sufficient maternal corticosteroid is able to access the foetal circulation to produce similar effects[27, 30]. Foetal exposure to increased cortisol, as well as possibly other factors, may then exert antenatal effects on future health through alterations in the Hypothalmo-Pituitary Axis (HPA) axis[27, 28, 31, 32]. Given the widespread distribution of gluco- and mineralo- corticoid receptors and the existence of both genomic and non-genomic effects, alterations in the HPA axis could be expected to exert a wide variety of effects including on central and peripheral systems relevant to BP and HR control[27, 33].

Information was only available in this study on the psychological status in mothers during pregnancy. It is therefore possible that the effects attributed here to anxiety and depression during pregnancy could at least in part be due to persistent changes in mothers mood. However levels of emotional distress are much higher during pregnancy than reported for non-pregnant women[14, 15] and in women assessed 8 months after delivery[16] suggesting that pregnancy specific factors are also involved. In fact, the time of highest risk for women to develop psychological disorders is during pregnancy but these often go unrecognised and untreated[31, 34]. It is also possible that genetic transmission of susceptibility to heightened stress plays a role.

In conclusion, our findings contribute to the body of evidence supporting an effect of prenatal influences on subsequent development, in particular in relation to the cardiovascular system. These may contribute to the development of subsequent cardiovascular disease. It remains to be determined if measures to reduce maternal anxiety during pregnancy will be effective in reducing haemodynamic stress responses in the offspring.

Acknowledgements

We greatly thank all the participants and their families for their participation in this study.

Conflict of Interest

None.

Summary Table

What is known about this topic?

- Low birth weight is associated with subsequent increased blood pressure and cardiac risk.

- Although animal studies show marked effects of stress during pregnancy on cardiovascular parameters in the offspring, there is only limited data on this in humans.

What this study adds.

- Maternal anxiety during human pregnancy is positively associated with resting and stress related blood pressure and heart rate in offspring. This is evident for anxiety levels assessed at each trimester.

- Birth weight is inversely related to maternal anxiety and to children's resting and stress related increase in blood pressure and heart rate.

- In multivariate analyses including maternal anxiety and birth weight, the effects of anxiety but not birth weight on childrens heart rate and blood pressure remained significant.

- Effects of maternal depression on children's blood pressure and heart rate were less consistent but did affect recovery.

Table 1: Childrens Demographics and Resting Haemodynamics by Maternal Anxiety Score

Maternal Anxiety Score	None (<18)	Mild (18-25)	Moderate (26-30)	Severe (>30)
Trimester (1/2/3)	24/48/44	22/16/24	21/6/5	4/2/0
Gender (M/F)	55/61	35/27	17/15	4/2
Age (y)	8.06±0.43	7.85±1.74	783±1.41	8.21±0.53
BMI	23.21±2.92	22.70±2.92	22.72±3.25	19.26±1.23*
Fasting Glucose (mmol/l)	4.70±0.73	4.69±0.44	4.70±0.36	4.65±0.56
Birth Weight (Kg)	3.46±0.33	3.40±0.29	3.01±0.43$^{***\#\#\#}$	2.38±0.13$^{***\#\#\#\wedge\wedge}$
HR (bpm)	75.15±5.87	78.58±5.93**	85.94±4.74$^{***\#\#\#}$	90.00±2.19$^{***\#\#\#}$
SBP (mmHg)	95.37±2.72	96.35±2.77	98.31±2.34***	101.00±2.36$^{**\#}$
DBP (mmHg)	66.39±4.74	66.84±3.96	70.06±2.92**	73.00±1.09$^{**\#}$

Results are n or mean±sd.

$^{*, **, ***}$ p< 0.05, 0.01, 0.001 compared with None.

$^{\#, \#\#\#}$ p< 0.05, 0.001 compared with Mild.

$^{\wedge\wedge}$ p< 0.01 compared with Moderate.

Table 2: Childrens Blood Pressure and Heart Rate Response to Stress by Maternal Anxiety Score

Maternal Anxiety Score	**None (<18)**	**Mild (18-25)**	**Moderate (26-30)**	**Severe (>30)**
Δ_{stress}HR (bpm)	14.83±2.14	17.98±3.40***	17.66±3.76***	19.17±2.56**
Δ_{stress}SBP (mmHg)	16.41±1.97	18.00±2.42***	19.94±2.06$^{***\#\#}$	20.00±2.09**
Δ_{stress}DBP (mmHg)	12.72±2.69	14.29±1.86**	15.69±2.03***	16.33±1.21**
Δ_{recov}HR (bpm)	2.00±7.08	7.09±10.59**	8.25±6.56**	6.50±6.86
Δ_{recov}SBP (mmHg)	2.73±4.48	7.17±5.84***	9.84±4.69***	12.50±2.58***
Δ_{recov}DBP (mmHg)	3.05±3.10	8.20±3.44***	9.40±3.42***	12.50±1.51$^{***\#}$

Results are mean±sd.

**, *** $p< 0.01, 0.001$ compared with None.

$^{\#}$, $^{\#\#}$ $p< 0.05, 0.001$ compared with Mild.

345 **Table 3: Childrens Demographics and Resting haemodynamics by Maternal**
346 **Depression Score**

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Maternal Depression Score	**None (<10)**	**Mild (10-19)**	**Moderate (20-29)**	**Severe (>30)**
Trimester (I/2/3)	37/33/38	25/31/29	7/8/6	2/0/0
Gender (M/F)	53/55	45/40	13/8	0/2
Age (y)	8.09±0.86	7.78±1.48	8.15±0.43	7.5±0.42
BMI	22.88±2.93	22.99±3.22	22.56±2.26	21.67±5.96
Fasting Glucose (mmol/l)	4.63±0.72	4.70±0.49	4.86±0.40	5.05±0.63
Birth Weight (Kg)	3.31±.41	3.34±0.39	3.48±0.27	4.00±0.84
HR (bpm)	76.67±7.31	78.66±6.58	83.00±4.75**	85.0±4.24
SBP (mmHg)	96.13±2.94	96.28±3.11	96.62±2.50	97.00±1.41
DBP (mmHg)	67.31±4.67	67.66±4.54	67.90±3.70	70±

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349 Results are mean±sd.

350 **$p < 0.01$ compared with None.

Table 4: Childrens Blood Pressure and Heart Rate Response to Stress by Maternal Depression Score

Maternal Depression Score	None (<10)	Mild (10-19)	Moderate (20-29)	Severe (>30)
Δ_{stress}HR (bpm)	15.77±3.13	16.80±3.29	16.76±3.31	16.00±
Δ_{stress}SBP (mmHg)	16.84±2.46	18.02±2.42*	18.57±2.22*	18.50±2.49
Δ_{stress}DBP (mmHg)	13.19±3.00	14.18±2.16	14.43±1.77	15.00±1.41
Δ_{recov}HR (bpm)	3.86±6.37	3.87±10.15	9.61±9.61	14.00±11.3
Δ_{recov}SBP (mmHg)	3.06±4.30	6.67±6.35***	11.04±3.36$^{***\#\#}$	11.50±0
Δ_{recov}DBP (mmHg)	3.72±3.63	7.54±4.19***	8.47±3.73***	9.00±1.41

Results are mean±sd.

$^{*, ***}$ $p< 0.05, 0.001$ compared with None.

$^{\#\#}$ $p<0.01$ compared with Mild.

Table 5: Table shows significance levels from multivariate analyses with Anxiety and Depression scores as factors and birth weight as a covariate.

	Anxiety Score	Depression Score	Interaction	Birth Weight
rHR (bpm)	**0.000**	**0.000**	0.478	0.749
rSBP (mmHg)	**0.000**	0.553	0.341	0.634
rDBP (mmHg)	**0.005**	0.502	0.839	0.811
Δ_{stress}HR (bpm)	**0.000**	0.345	0.174	0.761
Δ_{stress}SBP (mmHg)	**0.000**	**0.001**	0.155	0.828
Δ_{stress}DBP (mmHg)	**0.000**	0.239	0.686	0.997
Δ_{recov}HR (bpm)	**0.000**	0.067	**0.007**	0.631
Δ_{recov}SBP (mmHg)	**0.000**	**0.000**	**0.030**	0.171
Δ_{recov}DBP (mmHg)	**0.000**	**0.000**	**0.001**	0.311

The table shows the *p* value for the factors, anxiety score, depression score, their interaction and birth weight.

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