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ABSTRACT

Objective: Recent research has linked hypertensive diseases of pregnancy with adverse neurodevelopmental outcomes in childhood and adulthood. This study aimed to establish whether such effects are observed in infancy. **Method:** This was a prospective pregnancy cohort study of 2,785 pregnancies with complete data on hypertensive diseases of pregnancy. Mothers completed a validated Australian adaptation of the Toddler Temperament Scale (TTS) when the children were one year of age (N=2,384). Algorithms were used to classify children as difficult, slow to warm up, intermediate-high, intermediate-low or easy on the basis of their temperament scores. We then grouped difficult and intermediate-high infants together and compared them with easy, intermediate-low and slow to warm up infants. We used a multivariable logistic regression model and adjusted for known biomedical, sociodemographic and psychological factors from the pre- and postnatal period that may influence child behavioral development. **Results:** After adjusting for confounders, mothers who were diagnosed with gestational hypertension (OR=1.36, 95%CI= 1.06, 1.75) or preeclampsia (OR=2.23, 95%CI= 1.18, 4.23) were more likely to report that their infants were in the difficult or intermediate-high classifications in the first year of life compared to infants born to mothers without gestational hypertension or preeclampsia. **Conclusion:** These data suggest that the link between maternal hypertensive diseases of pregnancy and child behavioral development begins in the first year of life.

Abbreviations: OR (odds ratio), 95%CI (95% Confidence Intervals)

Keywords: hypertensive diseases of pregnancy; preeclampsia; behavior; temperament; gestational hypertension

INTRODUCTION

Hypertensive diseases of pregnancy, including gestational hypertension and preeclampsia, continue to pose a major risk for maternal and neonatal morbidity. In addition to the risks for the infant's physical health, such as intrauterine growth restriction, cerebral palsy and preterm birth, maternal hypertensive diseases of pregnancy have recently been linked to adverse neurobehavioral outcomes. Maternal gestational hypertension was found to predict mental health problems in offspring from age 8-14 years (1) and lower verbal ability in children at age ten,(2) while preeclampsia was associated with increased risk for depression in offspring at adulthood (3) and poorer intellectual ability in early adulthood.(4) Another recent study found that severe early-onset hypertensive complications of pregnancy, including preeclampsia and HELLP syndrome (hemolysis, elevated liver enzymes and low platelet count), were associated with abnormal developmental outcomes (e.g. cognition, motor development) at age 4.5 years, but that study found no link between gestational hypertension and child behavior.(5)

The mechanisms that underpin these relationships are as yet undetermined, but it has been suggested that changes in the intrauterine environment induced by hypertensive diseases of pregnancy may influence the developing fetal brain. This could be due to psychoneuroendocrine changes directly and indirectly associated with gestational hypertension and preeclampsia. Increases in circulating cortisol due to maternal stress and anxiety can impact fetal brain development,(6, 7) while other changes in the intrauterine environment induced by hypertensive diseases of pregnancy, such as oxidative stress, increase the risk for developmental problems in offspring.(8) Alternatively, it is possible that these findings may reflect side effects of the drugs used to treat maternal gestational hypertension and preeclampsia, such as methyldopa and labetalol. Intrauterine exposure to these medications has been found to increase the risk of child mental health problems such as sleep difficulties and Attention Deficit Hyperactivity Disorder (ADHD).(9) External factors common to both the development of hypertensive diseases of pregnancy and offspring mental health problems, such as parental relationship

instability and maternal overweight and obesity, may also influence child behavioral development.(10-12)

The idea that the relationship between hypertensive diseases of pregnancy and child mental health may be established in utero would be further supported if such a relationship was observed in infancy; however, the existing studies have not looked at outcomes so early in childhood. Temperament is understood to be an innate behavioral style, shaped by both biological predisposition and environmental influences.(13-15) The influences that have been found to shape temperament include those present in the intrauterine environment(13, 16) in addition to postnatal influences including maternal mood state,(17) interaction between mother and child (18) and marital conflict.(19) Temperament in turn is linked to the later development of psychopathology, with negative temperament states increasing vulnerability for the development of internalising and externalising problems in childhood.(20-22) Therefore it is possible that the observed relationship between hypertensive diseases of pregnancy and mental health problems through to adulthood may begin with changes in infant temperament induced at least in part by an intrauterine environment complicated by hypertensive diseases of pregnancy.

To further understand this relationship, we proposed to study the relationship between hypertensive diseases of pregnancy and parent-reported infant temperament at 12 months of age. Using a large prospective pregnancy cohort we aimed to examine the specific contribution of hypertensive diseases of pregnancy on offspring temperament in infancy. We hypothesised that the offspring of women who had gestational hypertension or preeclampsia would be more likely to be classified as having a difficult temperament.

METHODS

Participants

This study was conducted using data from the Western Australian Pregnancy Cohort (Raine) Study, a prospective pregnancy cohort study of 2,868 live births with continuing follow-up at 21 years of age. Complete details of the initial cohort and recruitment procedures are published elsewhere.(23) The study mothers attended at least two antenatal appointments at the tertiary maternity hospital, King Edward Memorial Hospital (KEMH) where they were enrolled at 18 weeks' gestation, providing detailed sociodemographic, behavioral and clinical data at 18 and 34 weeks' gestation. The study families then completed a further follow-up when their child was 12 months of age. Informed consent was obtained at the time of enrollment in the study and at every subsequent follow-up and study protocols were approved by the Human Ethics Committees at KEMH and Princess Margaret Hospital for Children in Perth, Western Australia.

Toddler Temperament

Toddler temperament was assessed at one year of age using the Approved Australian Revision of the Toddler Temperament Scale.(24) This scale was based on the Carey Infant Temperament Questionnaire (CITQ) framework and was developed for use in the longitudinal Australian Temperament Project.(25, 26) The CITQ is a 97-item questionnaire that requires the primary caregiver to rate their child's behavior using a 6-point Likert scale. Algorithms were used to categorize children into one of five groups (Easy; Difficult: Slow to warm up (STWU); Intermediate high; and Intermediate low) based on their scores for the nine dimensions of the scale (activity level, rhythmicity, approach-withdrawal, adaptability, intensity, threshold of responsiveness, mood, distractibility, and persistence or attention span).(27) Children rated as intermediate were those who did not fit into one of the three basic profiles (Easy, Difficult STWU), with those closer to the Easy group categorized as

Intermediate-Low, and those closer to the Slow to warm up and Difficult groups as Intermediate-High.(24) Table 1 details the characteristics of the three basic temperament groups.

Due to the small sample size for some of the temperament profiles, the infants ranked in the intermediate-high category were grouped with the difficult infants.(28) The infants ranked as slow to warm up and intermediate-low were grouped with the easy infants.(28) Therefore we had two categories, difficult and easy.

Gestational Hypertension & Preeclampsia

Data regarding hypertensive diseases of pregnancy were available for 2,785 live births from the original cohort of 2,868 live born children. Full details of the collection of data on diagnoses of gestational hypertension and preeclampsia have been published elsewhere.(1) Gestational hypertension was defined according to international guidelines as a pregnancy-induced increase in systolic blood pressure of 140mmHg or more and/or a diastolic blood pressure of 90mmHg or more in women who were normotensive before the 24th week of pregnancy. We defined preeclampsia as gestational hypertension with the addition of proteinuria (≥ 0.3 g per 24 hours).(29) A three level predictor variable was created to represent women with: i) no gestational hypertension; ii) gestational hypertension only; and iii) preeclampsia. Just over 75% (n=2170) of our sample had normotensive pregnancies, while 537 (19%) had gestational hypertension without preeclampsia and 78 (3%) were diagnosed with preeclampsia.

Control Variables

We adjusted for numerous biological and psychosocial factors from pregnancy that may have been associated with our outcome or predictor variables. These factors were divided into two groups representing antenatal factors and peri- and postnatal factors. The antenatal factors included maternal

age, maternal education, parity, pre-pregnancy maternal body mass index (BMI), total family income, maternal smoking, the presence of the biological father in the family home, and the maternal experience of stressful events.(30) These data were all collected at 18 weeks gestation. We collected data on use of methyldopa (Aldomet) at any time during pregnancy, which were recorded from the contemporaneous medical records for each pregnancy. The peri- and postnatal factors included in our model were gestational age at birth, proportion of optimal birth weight (a measure of the appropriateness of fetal growth,(31)) breastfeeding duration and the length of admission to the special care nursery (SCN) following birth.

Statistical Analyses

Frequency data were compared for all predictor, outcome and control variables. We then entered our predictor variables into a binary logistic regression model with the outcome of difficult (including intermediate-high) temperament and reference category of easy temperament (including slow to warm up and intermediate-low infants). Univariate relationships were examined first (Model 1), followed by models including antenatal control variables (Model 2), and peri- and postnatal variables (Model 3). IBM SPSS Statistics 19.0 was used for the analyses.

RESULTS

We had complete toddler temperament data at age one for 2,384 children (204 deferred participation, 174 lost to follow-up, 21 withdrawn from study, 28 deceased, and 57 had temperament data missing at random).

When we examined temperament on an ordinal scale from easy to difficult (with slow to warm up infants in the middle), there was a significant linear by linear trend linking increasing severity of hypertensive diseases of pregnancy (with the assumption in our study that preeclampsia is more severe

than gestational hypertension) and increasingly difficult temperament in infancy (two-tailed $p=0.004$) (Table 1). We also observed a greater frequency of preeclampsia diagnoses for primiparous pregnancies ($p<0.001$), overweight and obese mothers ($p<0.001$), and mothers who reported a greater frequency of stressful event experiences during pregnancy ($p=0.043$). Smoking during pregnancy was associated with decreased risk for gestational hypertension or preeclampsia ($p=0.004$). Infants from pregnancies complicated by gestational hypertension and preeclampsia were significantly more likely to be admitted for longer stays in the special care nursery ($p<0.001$) and infants born to preeclamptic pregnancies were born significantly earlier than those whose mothers did not have diagnoses ($p<0.001$) and were breastfed for a shorter duration ($p=0.015$).

In our unadjusted analyses, gestational hypertension without preeclampsia (OR=1.27, 95%CI= 1.01, 1.60) and preeclampsia (OR=2.00, 95%CI= 1.19, 3.33) were both significantly associated with an increased risk for difficult temperament in infants at 12 months of age. The next model included antenatal variables in the analysis. The odds ratio for predicting difficult temperament following exposure to gestational hypertension increased and remained significant (OR=1.36, 95%CI= 1.06, 1.75, $p=0.016$) and there was a similar increase in the risk for difficult temperament following preeclamptic pregnancies (OR=2.17, 95%CI= 1.18, 4.01, $p=0.013$). Finally, we included the peri- and postnatal in the model and this last stage of adjustment had little effect on the odds ratios for gestational hypertension (OR=1.36, 95%CI= 1.06, 1.75, $p=0.017$) or preeclampsia (OR=2.23, 95%CI= 1.18, 4.23, $p=0.014$).

DISCUSSION

This is the first study of which we are aware to examine the relationship between offspring temperament in infancy and exposure to hypertensive diseases during pregnancy. We found that maternal gestational hypertension and preeclampsia were significantly associated with an increased risk

for difficult or intermediate-high temperament in babies during the first year of life by parent-report. Our results expand upon previous findings that maternal gestational hypertension was associated with an increase in behavioral problems in offspring,(1) poorer verbal ability at age 10,(2) and adverse developmental outcomes at 4.5 years (5) by demonstrating that effects are present in infancy. While not conclusive, this lends support to the hypothesis that an intrauterine mechanism may link maternal hypertensive disorders of pregnancy and child behavioral development.(32)

This is the earliest report of behavioral difficulties following pregnancy complicated by gestational hypertension and/or preeclampsia. Although the pathways that may be implicated in this effect cannot be definitively determined from this study, given the strong evidence that infant temperament is to a degree innate, the findings suggest that the mechanisms underlying this relationship may be at least in part a result of intrauterine biological and environmental influences rather than stemming exclusively from environmental influences in the child's growth and development. One possible pathway may be that of psychoneuroendocrine changes that underlie hypertensive diseases of pregnancy and difficult temperament.(6) Maternal anxiety, resulting in increased circulating cortisol during pregnancy, has been associated with a greater risk for developing preeclampsia,(7) and although the placenta partially protects the fetus from the effects of maternal cortisol, around 10-20% of active maternal cortisol passes through the placenta and may affect the development of the fetal stress response system, potentially influencing child temperament.(33) Hypertensive disorders of pregnancy may also expose the fetus to oxidative stress which is related to an increased risk for neonatal morbidity, although little is known about fetal neurodevelopmental effects.(8) While a controlled trial of antihypertensive medications (methyldopa and labetalol) did not show adverse effects for the fetus,(34) such medications have since been implicated in later mental health problems for children.(9) We adjusted for use of methyldopa in our analyses; however we did not have sufficient sample size for methyldopa use to draw conclusions as to the impact of this medication. It may also be that a cardiovascular or

metabolic pathway can explain these results. A pattern of physiological hyperreactivity (elevated heart rates, sympathetic adrenomedullary activation, rises in plasma cortisol) has been observed in behaviorally inhibited children, and it may be that hypertensive disorders in the mother transmit this cardiovascular profile to the child, resulting in difficult temperament.(35) We considered maternal overweight and obesity to be a distal risk factor in this analysis and adjusted for maternal BMI in our adjusted models. As mentioned in the introduction, there are likely to be other psychosocial factors that impact upon both hypertensive diseases of pregnancy and toddler temperament, such as relationship instability.(10, 11) We also acknowledge that our reliance on maternal report of infant temperament means that these reports may be compromised by a range of factors that can influence the way the mother sees her child.(36) Many of the existing studies have relied on maternal self-report for child mental health (1, 5) and the validity of maternal self-report could be compromised by a difficult pregnancy complicated by hypertensive diseases of pregnancy. Women who experience a high risk pregnancy or birth have been shown to be more protective in their parenting and more sensitive to their child's behavior which in turn may influence their reports of their child's behavioral adjustment.(37)

Difficult temperament in infancy is linked to an increased risk for the later presentation of almost all Axis 1 Psychiatric Disorders, including major depressive disorder, anxiety disorders, and eating disorders,(38-40) though it is important to note that this relationship may not follow a linear trajectory.(41) Regardless we suggest that the children of women who are diagnosed with hypertensive diseases of pregnancy should be routinely followed-up as part of postnatal care and mothers of children with difficult temperaments could be offered support where needed in order to reduce the likelihood that these children will go on to develop later behavioral or emotional problems.

The strength of this study was the prospectively collected data from pregnancy prior to the measurement of temperament at age 12 months. We also had high rate of participant retention in the

study with over 80% (n=2384) of eligible participants completing the toddler temperament scale at age one. We had available extensive data regarding potential confounding and mediating factors and were thus able to examine the impact of gestational hypertension and preeclampsia following adjustment for these other factors. One limitation is the reliance on maternal report for toddler temperament data and women who are experiencing mental distress may provide less reliable data.(42) However, recent study found relatively consistent results between maternal report and laboratory temperament assessments. (17) We did not have data available to account for maternal psychopathology. A further limitation is that there may have been other unmeasured environmental influences in the first year of life that have contributed to the findings of this study.

Our results suggest that maternal gestational hypertension and preeclampsia predict difficult infant temperament at one year of age, adding considerably to the limited existing research in this emerging area of enquiry. Our findings lend support to the hypothesis that child behavior may be biologically programmed by a hypertensive environment within the womb and demand further investigation of potential biological mechanisms that may explain this relationship in future investigations.

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Table1: Temperament dimensions as categorized by the Approved Australian Revision of the Toddler Temperament Scale (25)

Temperament Classification	Behavioral Profile		
	High	Low	Variable
Easy	Approach, Adaptability, Rhythmicity	Intensity, Negative mood	-
Slow to warm up (14)	Negative mood	Approach, Adaptability, Intensity	Rhythmicity
Difficult	Intensity, Negative mood,	Approach, Adaptability, Rhythmicity	-

Table 1: Frequency data for predictor and control variables (N=2785)^a

Hypertensive diseases of pregnancy

	n	None n=2170 %	Gestational Hypertension n=537 %	Preeclampsia n=78 %	p-value
Toddler Temperament					0.004
Easy	1066	45.4	42.8	37.9	
Intermediate-Low	634	27.3	24.6	21.2	
Slow to Warm Up	123	5.0	5.9	4.5	
Intermediate-High	296	11.8	13.8	21.2	
Difficult	265	10.5	12.9	15.2	
Maternal Age					0.667
<20 years	273	8.9	12.9	15.5	
20-29.9 years	1431	52.4	49.1	49.4	
30+ years	1064	38.7	38.1	35.1	
Maternal Education					0.088
<High school completion	1691	60.3	62.4	70.1	
High school completion	1082	39.7	37.6	29.9	
Parity					<0.001
First born	1347	45.7	57.5	60.3	
Older siblings	1438	54.3	42.5	39.7	
Gender					0.112
Female	1365	49.9	45.6	47.4	
Male	1420	50.1	54.4	52.6	
Biological father with family					0.049
Yes	2427	87.9	85.7	81.8	
No	354	12.1	14.3	18.2	
Low Family Income					0.783
≤ \$24,000 per annum	1142	43.4	44.2	43.7	
>\$24,000 per annum	1478	56.6	55.8	56.3	
Maternal BMI					<0.001
Underweight	320	12.8	6.3	13.0	
Healthy weight	1946	71.8	67.0	54.5	
Overweight	319	9.9	17.5	15.6	
Obese	180	5.5	9.1	16.9	
Smoking in pregnancy					0.004
None	2035	71.8	76.7	82.1	
1+ daily	750	28.2	23.3	17.9	
Stress Events in Pregnancy					0.043
None	550	22.7	20.4	15.4	
1-2 events	1019	41.1	39.4	43.1	
3+ events	929	36.3	40.2	41.5	
Length of stay in SCN					<0.001
No stay	2473	91.0	85.7	50.0	
≤1 week	202	5.8	10.8	23.1	
1-4 weeks	67	2.0	2.4	14.1	
>4 weeks	43	1.2	1.1	12.8	
Use of methyldopa (Aldomet)					<0.001
No	2728	100.0	93.9	69.2	
Yes	57	0.0	6.1	30.8	

	n	None	Gestational Hypertension	Preeclampsia	p-value
		Mean (SD)	Mean (SD)	Mean (SD)	
Breastfeeding duration	2366				<i>0.015</i>
(months)		7.74 (7.05)	7.13 (7.30)	5.50 (5.58)	
Percentage of Optimal	2779				<i>0.068</i>
Birthweight (POBW)		97.58 (13.72)	97.78 (13.33)	94.00 (16.22)	
Gestational age	2764				<i><0.001</i>
(weeks)		39.39 (2.08)	39.25 (1.89)	36.36 (3.64)	

^aMissing data not shown, row percentages for each variable presented

Table 2: Adjusted logistic regression analysis showing effect of maternal gestational hypertension and preeclampsia on difficult or intermediate-high infant temperament in comparison with easy temperament

	Model 1 ^a OR (95% CI) [†] <i>p</i> N=2384	Model 2 ^b OR (95% CI) [†] <i>p</i> N=2076	Model 3 ^c OR (95% CI) [†] <i>p</i> N=2048
Difficult or Intermediate-High temperament			
Gestational hypertension	1.27* (1.01, 1.60) <i>0.042</i>	1.36* (1.06, 1.75) <i>0.016</i>	1.36* (1.06, 1.75) <i>0.017</i>
Preeclampsia	2.00* (1.19, 3.33) <i>0.008</i>	2.17* (1.18, 4.02) <i>0.013</i>	2.23* (1.18, 4.23) <i>0.014</i>

* significant at $p < 0.05$ ** significant at $p < 0.005$ [†] odds ratio and 95% confidence intervals

^a Unadjusted results; ^b Adjusted for pre-pregnancy factors (maternal age, maternal education, parity, pre-pregnancy maternal body mass index (BMI), total family income, maternal smoking, the presence of the biological father in the family home, the maternal experience of stressful events and any use of methyldopa (Aldomet)); ^c Adjusted for pre-pregnancy factors, prenatal factors, and perinatal factors (proportion of optimal birth weight, breastfeeding duration, length of stay in SCN and gestational age at birth).