Cardiology in the Young

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Maternal mental distress and cortisol levels in pregnancies with congenital heart disease

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Abstract

Objectives: Prenatal maternal stress is associated with adverse offspring outcomes, which may be mediated by maternal stress hormones. However, evidence supporting the association between maternal stress and cortisol levels in high-risk pregnancies is limited. This study aims to determine the relationship between self-reported maternal mental distress and maternal salivary cortisol levels in pregnancies complicated by foetal CHD compared with healthy pregnancies. *Methods:* We recruited women with pregnancies complicated by foetal CHD and healthy pregnancies. Maternal saliva was collected between 22 and 40 gestational weeks. Standardized questionnaires measuring stress, depression, and anxiety were completed by patients. Generalized estimating equation was used to evaluate associations between maternal mental distress scales and cortisol levels. *Results:* We studied 165 women (55 CHD, 110 controls) and collected 504 cortisol samples (160 CHD, 344 controls). Women carrying CHD foetuses had higher stress, anxiety, and depression scores compared to women carrying healthy foetuses. However, maternal cortisol levels did not significantly differ in CHD and controls. Cortisol levels were higher in women carrying foetuses with functionally single-ventricle versus two-ventricle CHD. In both CHD and controls, there was no significant association between maternal stress, depression or anxiety scores and cortisol levels. *Conclusion:* Our data suggest that self-reported maternal stress, anxiety, and depression are not associated with maternal salivary cortisol levels in CHD and healthy pregnancies. The impact of maternal mental distress on foetal health may be through other mediating pathways other than maternal cortisol concentrations.

Cortisol is a stress-responsive hormone that is the product of the hypothalamic–pituitary–adrenocortical axis.[1] Cortisol modulates blood sugar levels, regulates metabolism, reduces inflammation, and promotes memory formulation. During pregnancy, excessive foetal exposure to maternal cortisol has been linked to impaired foetal growth and increased risks of cardiovascular and metabolic diseases in adulthood.[2–4] Similarly, animal studies suggest elevated maternal cortisol levels affect foetal growth, cardiovascular function, metabolism, and endocrine status.[4] In humans, elevated prenatal cortisol exposure has been associated with larger amygdala and smaller hippocampus size, as well as subsequent cognitive and affective problems in infants and children offspring.[5,6] Studies in healthy non-pregnant humans suggested that cortisol levels are positively associated with mental distress (e.g., stress, anxiety, and depression).[7]

Maternal mental distress is one of the most common complications of pregnancy.[8] The literature suggests a high prevalence of mental distress in women of high socio-economic status with otherwise healthy pregnancies, with more than one-quarter testing positive for stress and anxiety, and 11% for depression.[9] These rates were further elevated in women with high-risk pregnancies.[10–12] Congenital heart disease (CHD) is the leading cause of infant deaths from birth defects.[13] For pregnant women carrying foetuses with CHD, over half report elevated levels of stress and about one out of every four test positive for depression.[10,11] More importantly, elevated maternal mental distress in CHD has been associated with impaired in vivo foetal hippocampal and cerebellar growth in our recent study.[10] Maternal mental distress has also been associated with alterations in human foetal brain structure and metabolism in healthy pregnancies.[9] Whether maternal mental distress influences foetal brain development through changes in maternal cortisol levels is unclear.

Animal models have shown a positive association between maternal mental distress and cortisol levels during pregnancy.[14,15] Elevated maternal cortisol levels are thought to influence foetal development through activation of the foetal hypothalamic–pituitary–adrenal axis.[14,16] In healthy human pregnancies, both negative and positive associations,[2,17–19] as well as no

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association,[20–23] have been described between self-reported measures of maternal mental distress and cortisol levels. Differences in sample size, cortisol collection methods, random samples versus 24 hours collection may contribute to the variances in findings across studies.[2,17–19,21–23] Evidence that maternal experience of mental distress is associated with altered cortisol levels is inconsistent in healthy pregnancies, and remains lacking for pregnancies complicated by foetal CHD.

In this study, we aim to (1) compare maternal cortisol levels in pregnancies complicated by foetal CHD with healthy pregnancies; (2) determine the relationship between self-reported maternal mental distress scores and maternal cortisol levels in pregnancies with foetal CHD and healthy pregnancies.

Materials and method

Study design

This study was part of a larger study evaluating potential intrauterine mechanisms of adverse foetal neurodevelopment in CHD. Patients were consecutively recruited into a longitudinal prospective case–control study. Our cases were pregnant women with confirmed foetal CHD that would require open-heart surgery within the first 2–3 months after birth as determined by the attending foetal cardiologist at the Children's National Hospital, while controls were healthy volunteers with low-risk pregnancies enrolled from community obstetrical clinics. Exclusion criteria included: (1) foetuses with extracardiac anomalies noted on antenatal ultrasound or chromosomal abnormalities; (2) pregnant women with (i) pregnancy-related complications (e.g., pre-eclampsia, gestational diabetes); (ii) known medical disorders (e.g., genetic, metabolic, or psychiatric); (iii) drug abuse; (iv) medications for chronic conditions (e.g., enoxaparin, selective serotonin reuptake inhibitor, or levothyroxine); and (v) multiple pregnancies. Enrolled patients had two study visits in the foetal period between 22 and 40 weeks of gestation. Following approval by the institutional review board at our institution, informed written consent was obtained from all patients.

Maternal mental distress measures

Psychometrically sound questionnaires measuring stress (Perceived Stress Scale),[24] depression (Edinburgh Postnatal Depression Scale),[25] and anxiety (Spielberger State-Trait Anxiety Inventory)[26] were completed at each study visit. Perceived Stress Scale measures the degree of stressful feelings experienced during the last month and the 10-item version (range: 0–40) was used. Edinburgh Postnatal Depression Scale is a 10-item questionnaire (range: 0–30) designed to measure the severity of depression in the past 7 days, which is commonly used during pregnancy and postnatally.[27] The Spielberger State-Trait Anxiety Inventory was used to measure state anxiety (20 items; range 20–80) and trait anxiety (20 items; range 20–80), where state anxiety measures the feeling right now and trait anxiety measures the general feeling.

Cortisol measures

Two maternal cortisol samples (saliva) were collected at each study visit based on the convenience of the patients using a Salivette sampling device. Collection time was recorded for each sample (i.e., 6 am–8 pm), with a mean interval between time points of 2 hours. Saliva samples for cortisol measurements were sent via courier to a single laboratory (Quest Diagnostics).

Clinical factors

In addition to maternal mental distress scores and cortisol levels, we collected maternal data for gravidity, parity, age, weight, education, employment, and race as well as salivary collection time, gestational age at collection, and foetal sex.

CHD categories

The CHD cohort was categorised into functionally single-ventricle and two-ventricle CHD based on the diagnosis (Table S1).

Statistical analysis

Analysis was performed using SAS 9.3 and MATLAB R2019a. Patient characteristics in CHD and controls were compared using t-test and Fisher's exact test for continuous and categorical variables, respectively. Logarithmic transformation was used to transfer cortisol levels in linear models. Time of day for each salivary collection, gestational age at visit, foetal sex, gravida, parity, maternal age, weight, education, employment, and race were tested for associations with maternal mental distress scores and cortisol levels. Generalized estimating equations, which allow multiple measurements for each patient, were used to measure associations between maternal mental distress scores and maternal cortisol levels, controlling for salivary collection time and gestational age at measurements. p-values were adjusted for multiple testing using the false discovery rate,[28] and two-tailed adjusted p-values ≤ 0.05 were considered significant.

Results

Demographics

We studied 165 women (55 CHD, 110 controls) and collected 504 salivary cortisol samples (160 CHD, 344 controls). Foetal gender did not significantly differ ($p = 0.25$) in CHD (34 males foetuses; 21 female foetuses) versus controls (56 male foetuses; 54 female foetuses). In CHD/controls, the mean gestational age was $29.11 \pm 3.81/28.0 \pm 2.27$ weeks for the 1st visit and $35.46 \pm 2.43/35.78 \pm 1.82$ weeks for the 2nd visit. Maternal age was 31.07 ± 5.92 and 35.09 ± 5.69 years for CHD and controls, respectively. In CHD/controls, 74%/92% of women attended college, and 71%/85% reported professional employment. Demographic and characteristics of the patients in CHD and controls are shown in Table 1.

Foetal CHD diagnose groups

Of the 55 foetuses with CHD, 31 (56%) were two-ventricle CHD and 24 (44%) were functionally single-ventricle CHD. The most common CHD types were hypoplastic left heart syndrome (12 foetuses, 22%) and transposition of the great arteries (10 foetuses, 18%). The CHD diagnosis types are shown in Table S1 in Data Supplement.

Maternal stress, anxiety, and depression

In both CHD and controls, maternal stress, depression, and anxiety scores did not differ significantly based on foetal sex (all $p > 0.05$). Women carrying foetuses with CHD had significantly higher stress scores (15.80 versus 10.86; $p < 0.0001$), state-anxiety scores (36.86 versus 29.43; $p < 0.0001$), and depression scores (7.68 versus 4.69; $p = 0.0004$) compared to women carrying healthy foetuses (Table 2). Maternal trait-anxiety scores

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Table 1. Demographic and clinical characteristics of the patients in CHD and controls

Variable (mean ± SD or n (%))	CHD (55 patients)	Controls (110 patients)	p-value
Males/females	34/21	56/54	0.25
Gestational age, week			
Time point 1 (n = 286)	29.11 ± 3.81	28.0 ± 2.27	0.05
Time point 2 (n = 218)	35.46 ± 2.43	35.78 ± 1.82	0.49
Maternal characteristics			
Age, year	31.07 ± 5.92	35.09 ± 5.69	<0.0001
Primigravida	21 (38)	41 (37)	0.82
Primipara	23 (42)	60 (55)	0.1
Maternal educational level			0.002
≤High school	13 (24)	6 (5)	
Some college	3 (5)	5 (5)	
College graduate	18 (33)	30 (27)	
Graduate degree	20 (36)	66 (60)	
Unknown	1 (2)	3 (3)	
Maternal employment status			0.05
Professional	39 (71)	93 (85)	
Skilled/clerical/sales	5 (9)	4 (4)	
Unskilled labourer	1 (2)	0 (0)	
Unemployed or homemaker	9 (16)	9 (8)	
Unknown	1 (2)	4 (4)	
Maternal race/ethnicity			0.66
Asian or Pacific Islander	2 (4)	9 (8)	
Non-Hispanic Black	9 (16)	10 (9)	
Hispanic	5 (9)	11 (10)	
Non-Hispanic White	37 (67)	76 (69)	
Other or unknown	2 (4)	4 (4)	

p-value for difference between controls and CHD based on Fisher's exact test for categorical variables and two-tailed, unpaired t-test for continuous variables.

Table 2. Maternal salivary cortisol levels and maternal mental distress scales in CHD and healthy pregnancies

Mean ± SE	CHD	Controls	p value
Cortisol collection time[a]	13.90 ± 0.46	12.89 ± 0.39	0.11
Cortisol level (mcg/dl)[b]	0.23 ± 0.01	0.25 ± 0.01	0.24
Stress[c]	15.80 ± 0.91	10.86 ± 0.53	<0.0001*
Depression[c]	7.68 ± 0.71	4.69 ± 0.37	0.0004*
State anxiety[c]	36.86 ± 1.56	29.43 ± 0.83	<0.0001*
Trait anxiety[c]	33.97 ± 1.33	31.13 ± 0.83	0.07

[a]p-value based on generalized estimating equations.
[b]p-value based on generalized estimating equations, controlling for saliva collection time and gestational age at measurements. Cortisol levels were logarithmic transformed in the model.
[c]p-value based on generalized estimating equations, controlling for gestational age at measurements.
*Significant after adjusting for multiple testing.

Table 3. Maternal mental distress scales in functionally single-ventricle versus two-ventricle CHD pregnancies

Mean ± SE	Single-ventricle CHD	Two-ventricle CHD	p-value
Stress	17.67 ± 1.73	14.36 ± 0.88	0.10
Depression	9.25 ± 1.34	6.42 ± 0.67	0.07
State anxiety	39.57 ± 2.86	34.77 ± 1.58	0.15
Trait anxiety	37.03 ± 2.70	31.73 ± 1.01	0.08

p-value based on generalized estimating equations, controlling for gestational age at measurements.

trended higher in CHD versus controls, but did not reach statistical significance (33.97 versus 31.13; $p = 0.07$). Within the foetal CHD cohort, maternal mental scores did not differ significantly between women carrying single-ventricle versus two-ventricle CHD foetuses (Table 3); however, maternal trait anxiety and depression trended higher in women with single-ventricle versus two-ventricle CHD foetuses (trait anxiety: 37.03 versus 31.73, $p = 0.08$; depression: 9.25 versus 6.42; $p = 0.07$). Maternal stress scores decreased significantly with advancing gestational age in healthy pregnancies ($\beta = -0.13$; $p = 0.008$), but not in CHD pregnancies. Maternal anxiety and depression scores did not change as gestational age increased in either group ($p > 0.05$). Maternal age, education, employment, and race were not significantly correlated with maternal mental scores. Gravida and parity were not correlated with maternal mental scores ($p > 0.05$).

Maternal salivary cortisol levels

As expected, salivary cortisol levels decreased from 6 am to 8 pm in both CHD and controls (both $p<0.0001$). Maternal cortisol levels trended higher with increasing gestational age in healthy pregnancies ($\beta = 0.01$; $p = 0.06$), but not in CHD pregnancies ($\beta = 0.003$; $p = 0.78$). Foetal sex, gravida, parity, maternal age, education, employment, and race were not associated with maternal cortisol levels in either group (all $p > 0.05$). The salivary collection time did not differ significantly between CHD and controls ($p = 0.11$). Maternal cortisol levels, adjusted for collection time and gestational age at measurements, did not differ significantly between the two groups ($p = 0.24$) (Table 2). Maternal cortisol levels were higher in women carrying single-ventricle versus two-ventricle CHD foetuses (0.23 versus 0.19 mcg/dl; $p = 0.03$), controlling for salivary collection time and gestational age at measurements.

Association between maternal mental distress and cortisol levels

There was no significant association between maternal stress, depression, or anxiety scores and maternal cortisol levels in either the CHD or control groups (Table 4) or single-ventricle and two-ventricle CHD (Table 5), controlling for salivary collection time and gestational age at measurements.

Discussion

In this study, we demonstrate that women carrying foetuses with CHD had higher self-reported mental distress, but no difference in random cortisol concentration compared to women carrying healthy foetuses. We also found that cortisol levels were higher in women carrying single-ventricle versus two-ventricle CHD foetuses. There was also no significant association between

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Table 4. Associations between maternal mental distress scores and salivary cortisol levels in CHD and controls

	CHD		Controls	
Mental distress measures	p-value	β	p-value	β
Stress	0.009	0.09	−0.003	0.59
Depression	0.003	0.64	−0.007	0.37
State anxiety	0.004	0.22	−0.005	0.08
Trait anxiety	0.004	0.32	−0.003	0.39

p-value based on generalized estimating equations, controlling for salivary collection time and gestational age at measurements.
Outcomes (i.e., cortisol levels) were logarithmic-transformed values.

Table 5. Associations between maternal mental distress scores and salivary cortisol levels in functionally single-ventricle and two-ventricle CHD pregnancies

	Single-ventricle CHD		Two-ventricle CHD	
Mental distress measures	p-value	β	p-value	β
Stress	−0.0002	0.97	0.008	0.49
Depression	−0.0005	0.93	−0.003	0.84
State anxiety	0.002	0.48	0.004	0.49
Trait anxiety	0.0004	0.88	0.005	0.65

p-value based on generalized estimating equations, controlling for salivary collection time and gestational age at measurements.
Outcomes (i.e., cortisol levels) were logarithmic-transformed values.

maternal depression, anxiety, or stress scores and maternal cortisol levels in either the CHD or healthy pregnancies. Finally, prenatal maternal salivary cortisol levels were negatively associated with salivary collection time in both healthy and CHD pregnancies, but were not correlated with gestational age at collection, foetal sex, gravida, parity, maternal age, education, employment, or race.

Maternal cortisol levels decreased from morning to evening in both CHD and healthy pregnancies, reflecting the known diurnal rhythm of cortisol with peak levels in early morning.[18,29,30] Maternal cortisol levels trended higher with advancing gestational age in controls but were not associated with gestational age in CHD pregnancies. Some,[21,31] but not all,[32] previous studies in healthy pregnancies have shown increased cortisol levels with increased gestation. Additional studies with larger sample sizes and consistent cortisol collection methods and timing are needed to confirm the influence of gestational age on maternal cortisol levels.

We report higher self-reported stress, anxiety, and depression scores in pregnant women with CHD versus healthy foetuses, a finding that corroborates previous studies.[10,11] Unlike our low-risk control group, in which maternal stress scores decreased with increasing gestational age, the elevated mental distress persisted across gestation in women carrying CHD foetuses. Considering the association between elevated maternal distress and adverse pregnancy outcomes, our data highlight the need for increasing mental health support for women carrying foetuses with CHD.

Our subgroup analyses showed that maternal trait anxiety and depression trended higher in women carrying functionally single-ventricle versus two-ventricle CHD foetuses, suggesting that more severe CHD diagnostic groups may increase maternal mental distress compared to other CHD types. We also found that maternal cortisol levels were higher in women carrying foetuses with single-ventricle versus two-ventricle CHD. Whether increased maternal cortisol levels in single-ventricle CHD is due to elevated maternal anxiety and depression in this study group needs further investigation using a larger sample size of CHD diagnostic groups.

Finally, we found that maternal salivary cortisol levels were not associated with self-reported/perceived levels of maternal stress, anxiety, and depression in either CHD or healthy pregnancies. Mechanisms linking maternal mental distress with adverse foetal neurodevelopment are not well elucidated, but are thought to be mediated in part by maternal cortisol changes. This theory is supported by studies of non-human pregnant models that suggest positive associations between mental distress and cortisol levels.[14,15] While less is known in humans, some previous studies of low-risk pregnancies also have shown no association between maternal distress and cortisol levels.[20–23] This discrepancy may be due to differences in the human hypothalamic-pituitary adrenocortical axis from most animal models, and the maternal hypothalamic–pituitary–adrenocortical axis becomes less responsive to mental distress as gestation increases in humans.[33] This work suggests that maternal mental distress may influence foetal neurodevelopment through mechanisms other than activation of maternal hypothalamic–pituitary–adrenocortical axis.[20,34] Potential mechanisms include, but are not limited to, altered placental flow and function, uterine artery resistance, cytokine production, and epigenetic modifications.[9,10,33,35,36] However, it is possible that very early exposure (before 22 weeks gestation), or cumulative exposure to prenatal mental distress may be associated with cortisol levels; however, this will need to be evaluated in future studies.

The limitations of this study include the lack of mental distress measures and salivary cortisol samples in early gestation; the random sampling of salivary cortisol between 6 am and 8 pm rather than cumulative cortisol measures; and the heterogeneous CHD diagnoses. These limitations are currently being addressed in our ongoing studies. We also plan to continue to increase our sample size of CHD diagnostic groups and will examine the relationship between prenatal maternal cortisol levels and foetal and child development.

Conclusions

Cortisol levels were higher in women carrying functionally single-ventricle versus two-ventricle CHD foetuses, however, our results show no significant difference in maternal salivary cortisol levels between CHD and healthy pregnancies. We also show no association between stress, anxiety and depression, and salivary cortisol levels in healthy pregnancies or those complicated by foetal CHD. Our findings suggest that the effects of maternal mental distress on foetal brain development in both CHD and healthy pregnancies may be mediated by pathways other than maternal cortisol concentrations. This study highlights the need for ongoing research into the mechanisms underlying altered human foetal brain development in healthy and high-risk pregnancies complicated by maternal mental distress.

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Conflict of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on

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human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional review board at Children's National Hospital.

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