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Original Article

Maternal hypothyroidism may be associated with CHD in offspring

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Abstract *Objectives:* This study tested whether mothers with maternal hypothyroidism have increased odds of CHD in their offspring, and examined the relationship between CHD, maternal thyroid function, and nausea and vomiting in pregnancy. *Background:* Maternal hypothyroidism increases the risk for foetal demise and prematurity and can have a negative impact on neurodevelopment. Prior studies have postulated a relationship between maternal thyroid function, CHD, and maternal nausea and vomiting in pregnancy. *Methods:* A cross-sectional case–control study was conducted over a 17-month period to obtain a history of maternal thyroid status and nausea and vomiting in pregnancy. Paediatric echocardiograms were evaluated for CHD by a blinded paediatric cardiologist. Logistic regression analysis was performed to examine the association between CHD and maternal hypothyroidism. *Results:* Of the 998 maternal–child pairs, 10% (98/998) of the mothers reported a history of prenatal hypothyroidism. The overall prevalence of CHD in the study sample was 63% (630/998). Mothers with a history of hypothyroidism were significantly more likely to have offspring with CHD compared with mothers without a history of hypothyroidism (72 versus 62%; $p = 0.04$). The adjusted odds ratio (95% confidence interval) of CHD in offspring associated with reported maternal hypothyroidism was 1.68 (1.02–2.78). *Conclusion:* This study suggests that maternal hypothyroidism is a risk factor for the development of CHD. Further prospective investigations are necessary to confirm this association and delineate pathogenic mechanisms.

Keywords: CHD; maternal hypothyroidism; nausea and vomiting in pregnancy

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CHD HAS A PREVALENCE OF 1% OF LIVE BIRTHS AND represents one-third of all major birth defects.[1] Abnormalities in maternal hormone status are associated with various congenital anomalies, including CHD.[2,3] Maternal hypothyroidism is known to increase the risk for foetal loss and prematurity and have a negative impact on postnatal learning and development.[4] There is also a link between maternal hypothyroidism and complete congenital heart block in infants.[5] Few studies have sought to directly assess the relationship between structural CHD and maternal hypothyroidism, and population-based studies examining general prenatal risk factors for CHD have yielded conflicting results regarding the risk of thyroid disorders.[6–10]

A relationship has also been described between nausea and vomiting in pregnancy, CHD, and maternal *hyper*thyroidism. Mothers with hyperthyroidism have an increased risk of nausea and vomiting in pregnancy, and increased nausea and vomiting in pregnancy is associated with a 30% reduction in CHD.[11–16] These links led us to propose a hypothetical model of the converse situation, where maternal hypothyroidism is associated with a decreased risk of

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nausea and vomiting in pregnancy, and decreased nausea and vomiting in pregnancy is related to an increased rate of CHD.[17]

Thus, we sought to test the hypothesis that maternal hypothyroidism is associated with an increased risk for CHD in offspring. Our secondary objectives were to test the hypotheses that maternal hypothyroidism is associated with decreased nausea and vomiting in pregnancy, and that decreased nausea and vomiting in pregnancy is related to an increased risk of CHD.

Material and methods

We conducted a cross-sectional case–control study examining the relationship between treated maternal hypothyroidism and CHD in offspring. Patients were included if they were undergoing their first cardiac assessment at The Hospital for Sick Children, Toronto, Canada. Many patients underwent previous echocardiograms from peripheral centres. Children whose mothers did not provide informed consent were excluded. Data were collected over a 17-month period between May, 2001 and September, 2002. The Health Research Ethics Board at The Hospital for Sick Children, Toronto, Canada, approved the study protocol, and written informed consent was obtained from each mother.

Data collection

Before echocardiography, mothers were surveyed with a standardised questionnaire to collect information on maternal history of hypothyroidism, use of thyroid-replacement hormone therapy, use of other medications during pregnancy, prenatal health status, child health, and demographic data. Information was also obtained regarding maternal nausea and vomiting status throughout the pregnancy, as assessed by the Motherrisk program.

Table 1. Categories of CHD for umbrella and specific cardiac diagnoses with proposed embryologic pathogenesis.

Umbrella diagnosis	Specific primary diagnosis	Pathologic diagnosis
Conotruncal septation defects	Double outlet right ventricle	Ectomesenchymal tissue migration abnormalities
	Tetralogy of Fallot	
	Pulmonary atresia with ventricular septal defect	
	Aortopulmonary window	
	Common arterial trunk	
Abnormal conotruncal cushion position	Transposition of the great arteries	
Branchial arch defect	Interrupted aortic arch type B	
	Double aortic arch	
	Right aortic arch	
Left heart obstruction (non-hypoplastic left heart syndrome)	Bicuspid aortic valve	Abnormal intracardiac blood flow
	Aortic stenosis +/– dysplasia	
	Coarctation of the aorta	
	Interrupted aortic arch type A	
Hypoplastic left heart syndrome	Hypoplastic left heart syndrome	
Septation defects	Secundum atrial septal defect	
Right heart obstruction	Bicuspid pulmonary valve	
	Pulmonary stenosis +/– dysplasia	
	Pulmonary atresia, intact ventricular septum	
	Tricuspid atresia	
Tricuspid valve abnormality	Ebstein anomaly of tricuspid valve	Cell death
Endocardial cushion defects	Primum atrial defect	Extracellular matrix abnormalities
	Balanced atrioventricular septal defect	
	Unbalanced atrioventricular septal defect	
Pulmonary vein abnormality	Anomalous pulmonary venous return	Abnormal targeted growth
Heterotaxy	Left atrial isomerism	Abnormal situs or ventricular looping
	Right atrial isomerism	
L-looping of the ventricles	Congenitally corrected transposition of the great arteries	
Ventricular septal defect (perimembranous and muscular)	Ventricular septal defect (perimembranous and muscular)	Variable
Patent ductus arteriosus	Patent ductus arteriosus	–
Other	Other*	–

Based on Clark's[18] study

*Includes univentricular connections, sinus venosus defects, and situs inversus

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Cardiologists blinded to maternal thyroid status prospectively evaluated echocardiograms.

Study outcomes

The primary study outcome was the prevalence of CHD diagnosed using echocardiography. Pathologic cardiac lesions were categorised into one or more of 15 umbrella diagnoses and one or more of 30 specific cardiac pathologies, based on the embryological classification scheme of Clark[18] (Table 1). Lesions that are normal variants, such as isolated patent foramen ovale, patients less than 1 year of age with a hemodynamically insignificant atrial septal defect, and patients less than 1 month of age with a patent ductus arteriosus not requiring intervention, were classified as normal.

Statistical analysis and sample size calculation

All data analyses were performed using SAS 9.1 (SAS, Cary, North Carolina, United States of America) and SPSS (SPSS, College Station, Texas, United States of America). Counts and percentages were used to describe child, maternal, and family characteristics at baseline. Comparisons were made using Fisher's exact tests, and logistic regression analysis was used to explore associations between maternal history of hypothyroidism, nausea and vomiting in pregnancy, and CHD. The following risk factors for CHD were purposefully forced into each model owing to their clinical relevance: child aneuploidy, maternal diabetes mellitus, advanced maternal age (>35 years), family history of CHD, maternal chromosomal disorder, rubella, lithium use, and isotretinoin use.

Specific rates of maternal hypothyroidism for patients referred for echocardiography were unknown. Assuming an α of 0.05, 80% power and a maternal hypothyroidism rate of 1% in the population,[19] 1000 mother–child dyads (500 cases, 500 controls) would be required for logistic regression to detect a minimum odds ratio of ~4.

Results

Baseline characteristics

During the study period, 998 mother–child pairs were enrolled. Of these, 798 (80%) patients underwent previous echocardiograms at other institutions and 630 (63%) patients had CHD (Table 2). The median age of patients with and without CHD was 2.6 and 2.8 years, respectively (NS). In patients with CHD, 71 (11.3%) mothers reported a history of maternal hypothyroidism. In the 368 patients without CHD diagnoses, 27 (7.3%) mothers had a history of maternal hypothyroidism. All mothers with maternal hypothyroidism were treated with synthetic thyroid supplements.

Table 2. Baseline characteristics of the 998 maternal–child dyad included in the study.

	All patients (%)	CHD (%)	No CHD (%)	p-value*
Study sample	998	630 (63.1)	368 (36.9)	
Child characteristic				
Median age in years (range)	2.7 (0–18)	2.6 (0–18)	2.8 (0–18)	0.098
Chromosomal disorder	99 (10.4)	68 (11.3)	31 (8.8)	0.229
Maternal history				
Maternal age over 35 years	151 (15.1)	98 (15.6)	53 (14.4)	0.648
Comorbidities history				
Diabetes mellitus**	48 (5.0)	24 (3.9)	24 (6.7)	0.059
Chromosomal disorder	7 (0.7)	4 (0.7)	3 (0.8)	0.744
Rubella	2 (0.2)	1 (0.2)	1 (0.3)	0.702
Lithium use	1 (0.1)	1 (0.2)	0 (0.0)	1.00
Isotretinoin use	3 (0.3)	2 (0.3)	1 (0.3)	1.00
Hypothyroidism	98 (9.8)	71 (11.3)	27 (7.3)	0.044
NVP level				
No sickness	276 (30.0)	170 (29.6)	106 (30.7)	0.087
Mild	305 (33.2)	207 (36.0)	98 (28.4)	
Moderate	248 (27.0)	147 (25.6)	101 (29.3)	
Severe	91(9.9)	51 (8.9)	40 (11.6)	
Family history				
CHD	283 (29.3)	183 (30.0)	100 (28.0)	0.512

NVP = nausea and vomiting during pregnancy
*T-test for continuous variables and Fisher's exact test for categorical variables
**Type I, II, or gestational

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CHD and maternal hypothyroidism

Table 3 describes the distribution of the specific CHD outcomes by history of maternal hypothyroidism. Women with hypothyroidism were significantly more likely to have a child with CHD than those without hypothyroidism (72.4 versus 62.1%; p-value 0.044). There was also a significantly increased rate of heterotaxy in offspring of mothers with hypothyroidism; however, the prevalence of this lesion was low overall (3.1 versus 0.4%, p-value 0.013).

CHD, maternal hypothyroidism, and nausea and vomiting in pregnancy

The odds (odds ratio, 95% confidence interval) of having a child with CHD were statistically higher in mothers with hypothyroidism, in both bivariate (1.61, 1.01–2.55) and multivariate (1.68, 1.02–2.78) analyses (Table 4). In the adjusted analysis, there was no relationship between CHD and nausea and vomiting in pregnancy, or maternal hypothyroidism and nausea and vomiting in pregnancy.

Table 3. Prevalence of CHD (stratified by primary umbrella* diagnosis) in patients with and without MHOH.

	Status of MHoH			
	No MHoH (%)	**MHoH (%)**	**Total (%)**	**p-value**
Overall sample	900	98	998	
Children with CHD	559 (62.1)	71 (72.4)	630 (63.1)	0.044
Umbrella Diagnosis				
Conotruncal septation defects	79 (8.7)	12 (12.2)	91 (9.1)	0.091
Abnormal conotruncal cushion position	43 (4.8)	6 (6.1)	49 (4.9)	0.255
Branchial arch defect	4 (0.4)	0 (0.0)	4 (0.4)	1.000
Left heart obstruction (non-hypoplastic heart syndrome)	112 (12.4)	11 (11.2)	123 (12.3)	0.562
Hypoplastic left heart syndrome	17 (1.9)	1 (1.0)	18 (1.8)	1.000
Secundum atrial septal defect	51 (5.7)	9 (9.2)	60 (6.0)	0.074
Right heart obstruction	61 (6.8)	9 (9.2)	70 (7.0)	0.151
Tricuspid valve abnormality	8 (0.9)	0 (0.0)	8 (0.8)	1.000
Endocardial cushion defects	64 (7.1)	7 (7.1)	71 (7.1)	0.468
Pulmonary vein abnormality	8 (0.9)	2 (2.0)	10 (1.0)	0.174
Heterotaxy	4 (0.4)	3 (3.1)	7 (0.7)	0.013
L-looping of the ventricles	8 (0.9)	0 (0.0)	8 (0.8)	1.000
Ventricular septal defect	129 (14.3)	12 (12.2)	141 (14.1)	0.710
Patent ductus arteriosus	32 (3.6)	6 (6.1)	38 (38.1)	0.108
Other	49 (5.4)	8 (8.2)	57 (5.7)	0.115

MHoH = Maternal history of hypothyroidism

Per cent in bracket represent the proportion relative to the overall sample within each group

*Some children had two or more unrelated diagnoses

Table 4. Relationship between CHD, NVP, and MHoH based on bivariate and multivariate regression analysis.

Variables		**Bivariate analysis**		**Multivariate analysis**	
Dependent	**Independent**	**OR (95% CI)**	**p-value**	**OR** (95% CI)**	**p-value**
CHD	MHoH	**1.61 (1.01, 2.55)**	**0.046**	**1.68 (1.02, 2.78)**	**0.042**
CHD	NVP Overall	0.75 (0.50, 1.14)	0.179	0.91 (0.57, 1.46)	0.707
CHD	NVP level*				
	Mild	1.32 (0.94, 1.85)	0.114	1.35 (0.80, 2.27)	0.262
	Moderate	0.91 (0.64, 1.29)	0.588	1.62 (0.96, 2.70)	0.072
	Severe	0.80 (0.49, 1.28)	0.349	1.14 (0.67, 1.92)	0.632
NVP Overall	MHoH	0.72 (0.35, 1.50)	0.383	0.98 (0.46, 2.08)	0.950
NVP Level*	MHoH				
Mild		1.64 (0.95, 2.86)	0.078	**3.28 (1.51, 7.11)**	0.003
Moderate		0.96 (0.51, 1.82)	0.895	1.29 (0.64, 2.59)	0.470
Severe		**2.10 (1.03, 4.30)**	**0.043**	1.86 (1.01, 3.47)	**0.049**

Bold values indicates p-value <0.05

CI = confidence interval; MHoH = maternal history of hypothyroidism; NVP = nausea and vomiting during pregnancy; OR = odds ratio

*Reference is no experience of nausea and vomiting during pregnancy

**Adjusted for age and risk of child chromosomal disorder, maternal diabetes mellitus, maternal age (>35 years), and family history of CHD

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Discussion

Our results suggest that there is an association between maternal hypothyroidism and CHD. Mothers with a history of maternal hypothyroidism were significantly more likely to have children with CHD compared with mothers without a history of hypothyroidism, with an odds ratio of 1.68. Specifically, heterotaxy was statistically more likely to occur in patients exposed to maternal hypothyroidism. There was no relationship between nausea and vomiting in pregnancy and CHD or maternal hypothyroidism.

Previous studies have reported conflicting data regarding maternal hypothyroidism and CHD.[6–10] To the best of our knowledge, no study has examined the relationship between maternal hypothyroidism and patients already referred for, or diagnosed with CHD. Thus, our design has the advantage of examining the relationship between maternal hypothyroidism and rare CHD that will not be well represented in a general population sample. There are several potential embryologic mechanisms whereby a maternal hypothyroid state may be teratogenic (Fig 1).

Maternal hypothyroidism, nitric oxide synthase, and calcium regulation

Animal models of maternal hypothyroidism have revealed abnormalities in the foetal expression of nitric oxide synthase. The nitric oxide synthase enzymes include neuronal, endothelial, and inducible nitric oxide synthase. Neuronal nitric oxide synthase contributes to intracellular signalling, and endothelial and inducible nitric oxide synthases are prominently expressed during cardiomyogenesis.[20] Sinha et al[21] showed that progeny of rat models of maternal hypothyroidism were deficient in neuronal nitric oxide synthase. Although the role of neuronal nitric oxide synthase in cardiac development is unclear, it is known to contribute to calcium regulation in the heart and contractility,[22] which, if altered in animals, leads to structural cardiac malformations and to arrhythmias including heart block (reviewed in [23,24]). Moreover, animal studies have shown that maternal exposure to calcium channel blockers predisposes foetuses to a slightly higher risk for cardiac malformations.[25,26] Hypothyroid states further impact on calcium regulation in the heart by downregulation of the sarcoplasmic reticulum calcium ATPase and upregulation of the sodium calcium exchanger, NCX-1.[27] It is not known how these derangements in calcium regulation affect cardiac development.

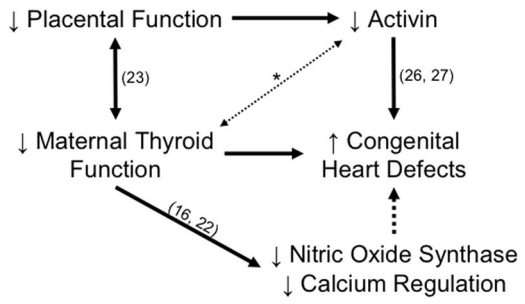

Figure 1.
*Proposed mechanisms of the relationship between maternal hypothyroidism and CHD. ( ) Supported references; *possible relationship (inferred from maternal hyperthyroid data).*

Activin and inhibin in maternal hypothyroidism

Mothers with hypothyroidism have been found to have placentas of lower weight,[28] which is relevant as placental growth factors such as activin and inhibin have been implicated in thyroid status as well as cardiac development. While it has been shown that hyperthyroidism is associated with increased levels of activin, the reverse has yet to be explored. Activin is an important part of the transforming growth factor pathway and is known to stimulate thyroid growth. It is located throughout the body, including the placenta and foetal–maternal intrauterine membranes,[29,30] and importantly, mutations in activin in both mice and humans have been associated with heterotaxy.[31,32] Although our numbers were small, there was a significant increase in the risk of heterotaxy in mothers with hypothyroidism, suggesting a possible role of altered activin levels. While the role of inhibin is less clear, triiodothyronine (T3) has been found to stimulate mRNA expression of inhibin[29] and it has also been linked to cardiac morphogenesis.[33]

Other potential influences of maternal hypothyroidism

Maternal hypothyroidism influences metabolism and may alter the foetal epigenetic state. Hypothyroidism is well known to increase triglyceride and low-density lipoprotein cholesterol level. Recently, an abnormal maternal lipid profile was shown to be a risk factor for CHD in offspring.[34] Maternal lipid profiles were not measured in this study, but may have influenced CHD risk in this population. Maternal hypothyroid states also cause histone modifications and alterations in DNA methylation.[35,36] These changes have not been well described in human foetuses exposed to maternal hypothyroidism, or those with treated maternal hypothyroidism. However, they represent additional mechanisms by which maternal hypothyroidism may be associated with increased risk of CHD.

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CHD, maternal hypothyroidism, and nausea and vomiting in pregnancy

Contrary to the work of Boneva et al,[11] there was no significant difference in the odds of CHD with nausea and vomiting in pregnancy. There is no standardised questionnaire for measuring nausea and vomiting in pregnancy, and differences between our results and prior studies could be explained by alternate methods of measurement. It is also possible that there was recall bias for symptoms of nausea and vomiting, although this bias would be expected to be equal between groups. There was no relationship between maternal hypothyroidism and generalised maternal nausea and vomiting during pregnancy. Although analysis showed a relationship between different severities of nausea and vomiting and maternal hypothyroidism, there is no biochemical explanation for this parabolic relationship, and this finding is likely spurious for the same reasons discussed above.

Strengths and limitations

Our study had several strengths and limitations. A fundamental strength of the design was that the cases and controls were identified in the same setting and represented the same underlying population such that the two groups were indistinguishable from each other until the echo results were known. Mothers were asked to participate and asked about their pregnancy history before echo results being known by the observers, and thus any selection bias that might have existed was equally distributed between the groups.

Given that recruitment was carried out in patients already referred to paediatric cardiology, the total population in this study will be biased towards a diagnosis of CHD. Our population was also biased to a diagnosis of maternal hypothyroidism, as the prevalence was 10% in our study population, with an estimated 1% prevalence in the general population. Because of this selection bias, we cannot comment on the overall prevalence of CHD in mothers with maternal hypothyroidism. However, differences between mothers with and without hypothyroidism can nevertheless be examined.

This sample is susceptible to recall bias. Although the gold standard for diagnosing CHD was used, there is no validated tool to measure maternal nausea and vomiting in pregnancy, and maternal thyroid status was not verified biochemically. In some patients there was also a large time period between the clinic visit and pregnancy. Therefore, our sample is subject to recall bias and underestimates the number of women with subclinical hypothyroidism. Although women are less likely to recall nausea in pregnancy, there is better medical history recall for women receiving prescribed thyroid supplementation.[10,37] Recall bias may have been important for the reporting of nausea and vomiting, but may have been less significant for the reporting of maternal hypothyroidism.

As all women diagnosed with hypothyroidism were treated, it is difficult to be certain that the associated malformations are attributable to the thyroid dysfunction as opposed to the hormone-replacement therapy. However, as thyroid-replacement therapy is biochemically identical to endogenous hormone, it seems an unlikely cause for the increased CHD in hypothyroid mothers.

Finally, because it is difficult and impractical to acquire controls for rare conditions, we obtained the data and then carried out post-hoc analysis with adjustment for potential confounders, that is, we controlled for factors that have an impact on both exposure and outcome.[38] The finding of differences in the prevalence of heterotaxy between groups was not anticipated, and the findings became apparent in exploratory post-hoc analysis. Future studies are required before a more definitive relationship can be confirmed.

Conclusions

This retrospective study suggests that there may be an increased risk of CHD in the offspring of mothers with maternal hypothyroidism, with an odds ratio of 1.68. The pathogenic mechanism remains unclear, although there is some evidence that a maternal hypothyroid state can cause alteration in key proteins that contribute to cardiac morphogenesis. Prospective clinical and translational studies are required to further define this relationship.

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Conflicts of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the Health Research Ethics Board at The Hospital for Sick Children, Toronto, Ontario.

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