



Original research paper

Childhood maltreatment is associated with increased risk of subclinical hypothyroidism in pregnancy



Nora K. Moog^{a,b,c}, Christine M. Heim^{a,b,d}, Sonja Entringer^{a,e,f}, Norbert Kathmann^{b,c}, Pathik D. Wadhwa^{e,f,g,h,i}, Claudia Buss^{a,e,f,*}

^a Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health

^b Berlin School of Mind and Brain, Humboldt-Universität zu Berlin, Luisenstrasse 56, 10117 Berlin, Germany

^c Institute of Psychology, Humboldt-Universität zu Berlin, Rudower Chaussee 18, 12489 Berlin, Germany

^d Department of Biobehavioral Health, Pennsylvania State University, College of Health and Human Development, 219 Biobehavioral Health Building, University Park, PA, 16802, USA

^e University of California, Irvine, Development, Health, and Disease Research Program, 333 The City Drive West, Suite 1200, Orange, CA, 92868, USA

^f Department of Pediatrics, University of California, Irvine, School of Medicine, 505 S. Main St., Suite 525, Orange, CA, 92868, USA

^g Department of Psychiatry and Human Behavior, University of California, Irvine, School of Medicine, 101 The City Drive South, Building 3, Route 88, Orange, CA, 92697, USA

^h Department of Obstetrics and Gynecology, University of California, Irvine, School of Medicine, 200 S. Manchester Ave, Suite 600, Orange, CA, 92868, USA

ⁱ Department of Epidemiology, University of California, Irvine, School of Medicine, 224 Irvine Hall, Irvine, CA, 92697, USA

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ABSTRACT

The critical importance of thyroid hormones for fetal development is well established. The developing fetus is dependent on the mother for adequate thyroid hormone supply, and maternal thyroid dysfunction in pregnancy may result in suboptimal fetal development. Because exposure to childhood maltreatment (CM) has been associated with thyroid dysfunction in the non-pregnant state, we sought to test the hypothesis that exposure to CM may represent a risk factor for the development of maternal hypothyroidism in pregnancy. The study was conducted in a healthy cohort of 102 pregnant mothers who were followed across the entire course of pregnancy. At each trimester thyroid-stimulating hormone (TSH) and free thyroxine (fT4) were measured in maternal serum. Experience of CM was assessed using the Childhood Trauma Questionnaire. After adjusting for potentially confounding variables, CM exposure was associated with increased TSH concentrations across pregnancy ($F_{1,94.6} = 11.52, p = 0.001$) and with a 4- to 7-fold increased risk of TSH levels above the trimester-specific clinical cut-off values. Women with clinically elevated TSH concentrations did not differ in fT4 concentrations from women with normal TSH concentrations ($p > 0.1$), suggesting subclinical hypothyroidism. Our findings suggest that there is a substantial and clinically relevant increased risk for thyroid dysfunction during pregnancy among women exposed to abuse or neglect in their childhood. This could potentially have adverse consequences for fetal brain development. Thus, these findings highlight the critical importance of considering CM exposure as a potential risk factor for (subclinical) hypothyroidism in pregnancy.

1. Introduction

The thyroid hormones (THs), triiodothyronine (T_3) and thyroxine (T_4), are highly evolutionarily conserved tyrosine-based hormones produced by the thyroid gland that play a major role in the regulation of metabolism. During embryonic and fetal life THs also play an obligatory role in many fundamental processes underlying brain development, including neuronal proliferation, migration, neurite outgrowth and guidance, synaptogenesis, and myelination (Moog et al., 2017). The developing embryo/fetus is completely dependent on the mother for TH

supply until around mid-gestation, at which time the fetal thyroid gland becomes functional (Williams, 2008). Even during the second half of gestation, a significant proportion of THs in the fetal compartment is obtained from the maternal compartment (Vulsma et al., 1989).

The hormonal and metabolic adaptations produced by the state of pregnancy induce major changes in maternal thyroid physiology. Free thyroxine (fT4) concentrations are typically highest in the first trimester and decrease slightly across gestation, whereas thyroid stimulating hormone (TSH) levels are typically suppressed in the first trimester and increase later in pregnancy. Overall, there is an increased demand on

* Corresponding author at: Department of Medical Psychology Charité – Universitätsmedizin Berlin, Luisenstr. 57, 10117 Berlin, Germany.
E-mail address: claudia.buss@charite.de (C. Buss).

Box 1

Definitions and prevalence of maternal thyroid dysfunction in pregnancy (De Groot et al., 2012; Stagnaro-Green et al., 2011).

Overt hypothyroidism (0.3–0.5%)

■ Serum TSH levels above the trimester-specific reference range (2.5–3.0 mU/l) in conjunction with a decreased fT4 concentration.

Subclinical hypothyroidism (2–2.5%)

■ Serum TSH levels above the trimester-specific reference range (2.5–3.0 mU/l) with normal fT4 concentrations.

Hyperthyroidism (1–3%)

■ Serum TSH levels below the trimester-specific reference range (0.1–0.3 mU/l) with (i.e. overt hyperthyroidism) or without (i.e. subclinical hyperthyroidism) elevated levels of fT4 and/or fT3, often transient in the first half of pregnancy.

Thyroid autoimmunity (5–20%)

■ Presence of TPO- and/or TG-antibodies in the serum, with or without changes in TSH and fT4 concentrations.

the maternal thyroid throughout gestation, which is reflected in an enlargement of the maternal thyroid in pregnancy by approximately 20% (Braunstein, 2011). These gestational changes, alone or in combination with pre-existing conditions such as the presence of thyroid autoantibodies (which are present in 5–20% of women of childbearing age), may lead to the onset of thyroid dysfunction or an exacerbation of milder pre-existing dysfunction (Glinoe et al., 1991). Thyroid dysfunction, i.e. hyper- and hypothyroidism, is estimated to affect about 4–6% of all pregnant women (Stagnaro-Green et al., 2011). For definitions and prevalence of dysfunctional thyroid states during pregnancy refer to Box 1.

Severe forms of thyroid dysfunction, i.e. overt hypo- and hyperthyroidism, are often accompanied by marked symptomatology as well as fertility problems and increased embryonic morbidity, such that treatment is often necessary for a pregnancy to ensue or continue (Thangaratnam et al., 2011; van den Boogaard et al., 2011). On the other hand, more moderate forms of thyroid dysfunction, such as subclinical hypothyroidism, are less likely to be detected, and this may, therefore, paradoxically confer a higher burden of disease (risk to the developing fetus) from a public health perspective.

While a severe deficiency of maternal thyroid hormones during gestation produces grave cognitive, motor and sensory deficits in her child (Gilbert et al., 2012), even subtler forms of maternal hypothyroidism may produce long-lasting alterations in child brain structure and cognitive development, that confer increased risk for neurodevelopmental disorders (e.g., Ghassabian et al., 2011; Haddow et al., 1999; Pakkila et al., 2014; Williams et al., 2012; Willoughby et al., 2014). Moreover, these alterations appear to be largely irreversible by treatment after birth (de Escobar et al., 2004). Hence, the optimal regulation of maternal thyroid function during pregnancy is important not only for her own health, but likely also for the long-term health of her child.

Other than the presence of specific medical conditions (primarily thyroid autoimmunity) or iodine deficiency, relatively little is presently known about conditions and processes that confer increased risk of maternal hypothyroidism in pregnancy. We have previously advanced the hypothesis that maternal stress and stress-related biological processes during pregnancy may modulate maternal thyroid function (Moog et al., 2017). Here, we seek to test the hypothesis that exposure to stress that predates conception and extends back to the sensitive period of her own childhood may represent a novel and significant risk factor for the development of maternal hypothyroidism in pregnancy.

Substantial evidence in humans and animals demonstrates a tight coupling between the thyroid (hypothalamic-pituitary-thyroid (HPT)) and the stress (hypothalamic-pituitary-adrenal (HPA)) axes (for review see Moog et al., 2017). Based on the consideration that the onset and course of hypothyroidism is often insidious and may be precipitated by maternal states and conditions that precede pregnancy, we were particularly interested in considering the role of stress exposure from a maternal life course perspective. We selected exposure to childhood maltreatment (CM) as our primary variable of interest for the following reasons: a) CM represents among the most pervasive and pernicious

stressors affecting around one third of the general population, with life-long biological, psychological and behavioral consequences (e.g., Heim et al., 2010); b) we and others have previously demonstrated that a woman's exposure to CM can produce alterations in several features of gestational biology that relate to embryonic/fetal development (Cammack et al., 2011; Mason et al., 2016; Moog et al., 2016; Shea et al., 2007); c) CM exposure has been associated with reduced thyroid activity in the non-pregnant state (Haviland et al., 2006; Machado et al., 2015; Sinai et al., 2014), with thyroid dysfunction in the post-partum period (Plaza et al., 2010; Plaza et al., 2012), and, more generally, with a higher risk of autoimmune disorders (Dube et al., 2009; Goodwin and Stein, 2004); and d) children of women exposed to CM exhibit an increased risk of developing some of the same behavioral disorders that have been observed in children with moderate maternal thyroid dysfunction (Miranda et al., 2013; Rijlaarsdam et al., 2014; Thompson, 2007). In light of these observations, we hypothesized that women exposed to CM may exhibit an increased likelihood of thyroid dysfunction in pregnancy, a time period of particular importance for not only the mother but also for her developing fetus.

2. Materials and methods

2.1. Study design

The study was conducted at the University of California, Irvine, Development, Health and Disease Research Program in a clinical convenience cohort of 146 pregnant women. All participants had singleton, intrauterine pregnancies, with no known cord, placental, or uterine anomalies, fetal congenital malformations, or corticosteroid medication use. Participants were recruited in the first trimester of gestation and followed prospectively and serially through pregnancy. Study visits occurred in early (T1: 12.7 ± 1.8 weeks gestation, N = 134), mid (T2: 20.5 ± 1.5 weeks, N = 145), and late pregnancy (T3: 30.5 ± 1.4 weeks gestation, N = 142). Study visit procedures included administration of structured socio-demographic and psychosocial interviews and questionnaires, collection of biological samples, and fetal ultrasonography. All study procedures were approved by the university's institutional review board and all participants provided written informed consent.

2.2. Childhood maltreatment exposure

At the mid gestation study visit, exposure to CM was ascertained using the Childhood Trauma Questionnaire (CTQ, Bernstein and Fink, 1998), one of the most widely-used, reliable, and validated instruments for determination of abuse and neglect experiences in childhood and adolescence. This 28-item measure assesses five dimensions of childhood maltreatment: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. Cut-off values for moderate or greater exposure were used to create dichotomous variables of exposure for each CTQ subscale (emotional abuse ≥ 13; physical abuse ≥ 10;

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