Hormones and Behavior 94 (2017) 84–92

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Maternal thyroid hormone trajectories during pregnancy and child behavioral problems☆

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ARTICLE INFO

Article history:
Received 11 January 2017
Revised 15 June 2017
Accepted 25 June 2017
Available online xxxx

Keywords:
Thyroid
Longitudinal
Pregnancy
Behavioral problems
Children
Sex difference

ABSTRACT

There is ample evidence demonstrating the importance of maternal thyroid hormones, assessed at single trimesters in pregnancy, for child cognition. Less is known, however, about the *course* of maternal thyroid hormone concentrations during pregnancy in relation to child behavioral development. Child sex might be an important moderator, because there are sex differences in externalizing and internalizing behavioral problems. The current study examined the associations between maternal thyroid hormone trajectories versus thyroid assessments at separate trimesters of pregnancy and child behavioral problems, as well as sex differences in these associations. In 442 pregnant mothers, serum levels of TSH and free T4 (fT4) were measured at 12, 24, and 36 weeks gestation. Both mothers and fathers reported on their children's behavioral problems, between 23 and 60 months of age. Latent growth mixture modeling was used to determine the number of different thyroid hormone trajectories. Three trajectory groups were discerned: 1) highest and non-increasing TSH with lowest fT4 that decreased least of the three trajectories; 2) increasing TSH and decreasing fT4 at intermediate levels; 3) lowest and increasing TSH with highest and decreasing fT4. Children of mothers with the most flattened thyroid hormone trajectories (trajectory 1) showed the most anxiety/depression symptoms. The following trimester-specific associations were found: 1) lower first-trimester fT4 was associated with more child anxiety/depression, 2) higher first-trimester TSH levels were related to more attention problems in boys only. A flattened course of maternal thyroid hormone concentrations during pregnancy was a better predictor of child anxiety/depression than first-trimester fT4 levels.

The importance of thyroid hormones for fetal brain development has been demonstrated in numerous studies over the past 50 years (for a review see, Henrichs et al., 2013). Many studies have demonstrated that even subtle impairments of thyroid function during pregnancy, such as maternal hypothyroxinemia (i.e., low free T4, normal TSH levels), can impede child cognitive development (Henrichs et al., 2013). Less is known about maternal thyroid function during pregnancy in relation to behavioral problems of children. Maternal thyroid dysfunction during pregnancy has been associated with cognitive developmental problems, such as language delays (Henrichs et al., 2010) and impaired executive functioning (Van Mil et al., 2012). Such cognitive problems have been found to be predictive of internalizing (i.e., depression, anxiety) and externalizing behavioral problems (i.e., aggression, attention problems, hyperactivity; Brownlie et al., 2004; Hagberg et al., 2010; Bornstein et al., 2013). Therefore, suboptimal maternal thyroid hormone functioning may also be associated with children's behavioral problems.

A series of studies within the Generation R project found evidence for this proposition. Thyroid dysfunction during pregnancy (i.e., higher maternal TSH levels, hypothyroxinemia, higher thyroid-peroxidase antibody levels) was found to be associated with more externalizing problems in infants (Ghassabian et al., 2011, 2012) and 6-year-olds (Ghassabian et al., 2014). In another study, child behavioral problems were examined in the context of iodine insufficiency during pregnancy (Vermiglio et al., 2004). In the iodine insufficient region, 50% of the mothers was hypothyroxinemic, and 88% of these hypothyroxinemic women had a child who was diagnosed with ADHD.

Moderating or mediating factors on the association between maternal thyroid hormones and child development are almost unknown (Henrichs et al., 2013). One such factor is child sex, which seems especially important in the context of child behavioral problems. Males are consistently more vulnerable to developing externalizing problems in the context of biological or environmental risk factors, whereas females are more vulnerable to developing internalizing problems (Zahn-

☆ This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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http://dx.doi.org/10.1016/j.yhbeh.2017.06.007
0018-506X/

Waxler et al., 2008). On the contrary, one recent study showed that higher maternal TSH levels were associated with more ADHD symptoms in girls, but not in boys, suggesting that girls might be more vulnerable to maternal thyroid deviations (Päkkilä et al., 2014). However, as this association was weak and the underlying mechanisms unclear, further study is warranted.

Little is also known about the *course* of maternal thyroid hormone concentrations during pregnancy in relation to child development, even though longitudinal thyroid assessments might be a more valid reflection of changes in thyroid hormones during pregnancy than assessments at one time point during pregnancy (Stricker et al., 2007). During normal pregnancy free thyroid hormones decrease while serum TSH levels correspondingly rise (Stricker et al., 2007). For most women, these changes are within the normal range but individual differences in the patterns of thyroid hormone changes during pregnancy (Stricker et al., 2007) may be predictive of child development (Pop et al., 2003). One small study by Pop and colleagues showed that children of mothers with low free T4 (fT4) levels early in pregnancy who showed an increase in fT4 later in pregnancy, and children of mothers with higher fT4 levels in early pregnancy that steeply decreased during pregnancy, scored within the normal range on the Bayley scales. However, mothers with low fT4 that further decreased during pregnancy had children with the lowest mental and motor development scores. The association between thyroid hormone trajectories during pregnancy and child outcomes needs to be replicated in larger studies and with more advanced statistical techniques, such as growth modeling.

The current study examined whether individual differences in thyroid hormone trajectories (fT4 and TSH levels) during pregnancy were a better predictor of child behavioral problems than maternal thyroid hormone concentrations assessed at one trimester of pregnancy. We also examined whether there were sex differences in the associations between maternal thyroid hormone trajectories or thyroid assessments at one trimester of pregnancy and child behavioral problems.

1. Methods

1.1. Sample

This study is part of a prospective research line examining the influence of prenatal maternal emotional symptoms and parental interaction styles on the self-regulation and behavioral adjustment of toddlers and preschoolers. Between July 2002 and May 2005, midwives working in seven community midwifery practices in the southern regions of the Netherlands (Kempen) invited healthy Dutch-Caucasian pregnant women on their first antenatal check-up (10–12 weeks gestation) to participate in a study on maternal thyroid hormone and delivery (Wijnen, 2005). See Fig. 1 for a flow-chart of the sample recruitment and exclusion criteria. Information was available for 1093 women. After pregnancy, the women were asked again by one of the midwives (HAAW) to participate in our research. In total, 444 mothers agreed to participate and returned questionnaires about the behavioral problems of their children (De Bruijn et al., 2009). Two families had missing thyroid data, resulting in a final sample of $N = 442$. The sample included six late preterm babies (between 34 and 36.9 weeks). As exclusion of these children did not change the results, they were retained in the current dataset. See Table 1 for sample characteristics.

1.2. Assessments

1.2.1. Maternal thyroid function parameters

Serum levels of TSH, fT4 and TPO-Ab were measured at 12, 24, and 36 weeks gestation. TSH was measured using a solid-phase, two-site, chemiluminescent enzyme immunometric assay (IMMULITE third generation TSH, Diagnostic Corporation, Los Angeles, CA). TSH reference range for women 20 to 40 years was 0.15–2.0 mIU/l. The inter-assay coefficients of variation were 9.8, 6.9, and 4.60–0, at concentrations of 0.02, 0.15, and 11 mIU/l, respectively. The fT4 concentration was also measured by means of a solid-phase immunometric assay (IMMULITE Free T4). fT4 reference range for women 20 to 40 years was 8.7–19.6 pmol/l. The inter-assay coefficients of variation for this technique were 20, 5.3, and 5.20 ~ o at concentrations of 3.1, 19.8, and 55 pmol/l, respectively. TSH levels had to be square-root transformed to achieve a normal distribution on all three measurements. The IMMULITE Anti-TPO Ab kit was used for the determination of antibodies against thyroid peroxidase. The inter-assay coefficients of variation for this analysis were 9% and 9.5% for concentrations of 40 kU/l and 526 kU/l, respectively. The TPO assay was standardized in terms of the International Reference Preparation for TPO MRC 66/387. Women with TPO-Ab

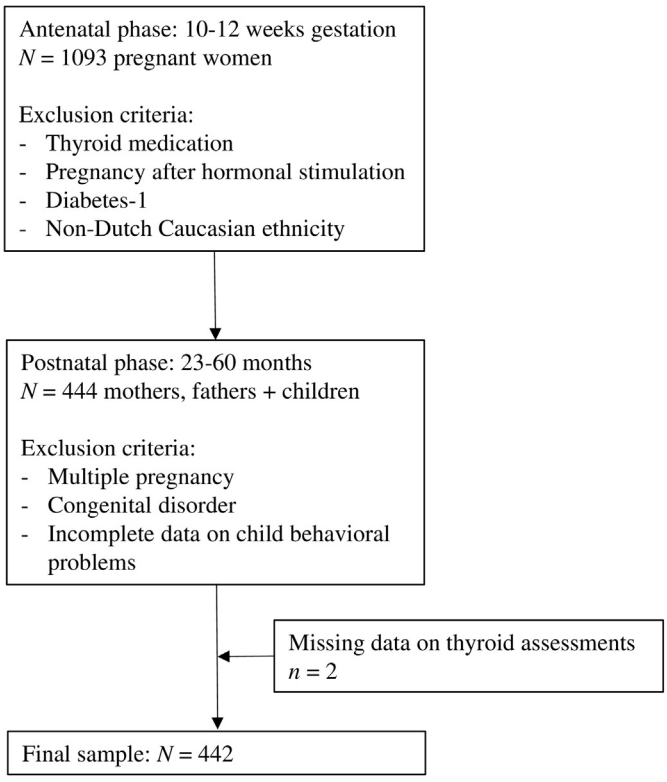

Fig. 1. Flow chart of sample recruitment.

Table 1
Sample characteristics of 442 women and their offspring.

	Overall sample
	M (*SD*)
Maternal characteristics	
Age at birth	30.69 (3.72)
Educational level (%)	
Low	11
Middle	46
High	43
Prenatal psychopathology symptoms[a]	
Depression	14.41 (3.39)
Anxiety SCL	12.38 (2.76)
Anxiety STAI	30.27 (7.27)
Child characteristics	
Male sex(%)	51
Birth weight	3538 (476)
Gestational age (weeks)	39.85 (1.33)
Age at assessment (months)	29.31 (10.38)

[a] Prenatal psychopathology symptoms were assessed with the Edinburgh Depression Scale (range: 0–30), State-Trait Anxiety Inventory (range: 20–80), Symptom Checklist anxiety scale (range: 10–50). Scores were standardized and averaged to create an overall psychopathology score.