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Research paper

Thyroid peroxidase antibodies during early gestation and the subsequent risk of first-onset postpartum depression: A prospective cohort study

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ABSTRACT

Background: During the postpartum period, women are at risk for the new onset of both auto-immune thyroid disorders and depression. The presence of thyroid peroxidase antibodies (TPO-ab) during early gestation is predictive for postpartum auto-immune thyroid dysfunction. The aim of this study was to investigate the association between TPO-ab status during early gestation and first-onset postpartum depression.

Methods: Prospective cohort study (n = 1075) with follow-up during pregnancy up to one year postpartum. Thyroid function and TPO-ab status were measured during early gestation. Depressive symptomatology was assessed during each trimester and at four time points postpartum with the Edinburgh Depression Scale (EDS). Women with antenatal depression were not eligible for inclusion. Self-reported postpartum depression was defined with an EDS cut-off of ≥ 13.

Results: The cumulative incidence of self-reported first-onset depression in the first postpartum year was 6.3%. A positive TPO-ab status was associated with an increased risk for self-reported first-onset depression at four months postpartum (adjusted OR 3.8; 95% CI 1.3–11.6), but not at other postpartum time points. Prevalence rates of self-reported postpartum depression declined after four months postpartum in the TPO-ab positive group, but remained constant in the TPO-ab negative group.

Limitations: Depression was defined with a self-rating questionnaire (EDS).

Conclusions: Women with an increased TPO-ab titer during early gestation are at increased risk for self-reported first-onset depression. The longitudinal pattern of self-reported postpartum depression in the TPO-ab positive group was similar to the typical course of postpartum TPO-ab titers changes. This suggests overlap in the etiology of first-onset postpartum depression and auto-immune thyroid dysfunction. Thyroid function should be evaluated in women with first-onset postpartum depression.

1. Introduction

Postpartum depression is a disabling and heterogeneous disorder with a huge variety in biological, psychological and social risk factors (Howard et al., 2014). In addition, there is substantial difference in the onset timing, severity and course of postpartum depression (Putnam et al., 2017; Fisher et al., 2016). The most important risk factor for postpartum depression is a depressive episode earlier in life or during pregnancy. In a large study among women with postpartum depression, approximately 60% of women reported an onset of their episode before pregnancy or during the antenatal period (Wisner et al., 2013).

Antenatal depression occurs during an entirely different immune and endocrine state than postpartum depression and may therefore have a different origin (Osborne and Monk, 2013). Interestingly, the postpartum period is a high risk period for more severe and first-onset episodes of depression (Munk-Olsen et al., 2016). Therefore, it is important to consider onset timing when studying risk factors for postpartum depression (Wisner et al., 2013). The postpartum period is also associated with an increased risk for the new onset of auto-immune thyroid disorders (Andersen et al., 2016). The presence of thyroid peroxidase antibodies (TPO-ab) during early gestation is a clear marker for the occurrence of postpartum auto-immune thyroid dysfunction, induced by the typical postpartum rebound phenomena of TPO-ab titers (Balucan et al., 2013; Fung et al., 1988; Jansson et al., 1984; Stagnaro-Green et al., 1992). Interestingly, TPO has also been named as a predictor for postpartum depression (Dama et al., 2016).

Four studies reported an association between an increased TPO-ab titer during early gestation and depression postpartum (Groer and Vaughan, 2013; Harris et al., 1992; Kuijpens et al., 2001; Lazarus et al., 1996). However, none of these studies focused on first-onset depression

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and three out of four studies did not take into account antenatal depression (Groer and Vaughan, 2013; Harris et al., 1992; Lazarus et al., 1996), while one study only briefly mentioned this in a sub analysis (Kuijpens et al., 2001). Together, as acknowledged by Dama and colleagues in their recent review, in previous studies antenatal depression may have confounded the association between a TPO-ab positive status during pregnancy and postpartum depression (Dama et al., 2016). Accordingly, the current study was designed to investigate the association between a positive TPO-ab status during early gestation and first-onset postpartum depression. We hypothesized that women are particularly at increased risk for first-onset depression three to four months postpartum, during the typical rebound of TPO-ab titers.

2. Method

2.1. Participants

Participants were included in the Holistic Approach to Pregnancy and the first Postpartum year (HAPPY) study, a large prospective cohort that is described in detail elsewhere (Truijens et al., 2014). In sum, the HAPPY-study focuses on maternal wellbeing during pregnancy and the postpartum period. During a recruitment period of 18 months (2013–2014), Dutch-speaking pregnant women were informed about the study during their first trimester appointment at 17 community midwives offices in the South-East of the Netherlands. Women with a non-singleton pregnancy or history of a severe psychiatric disorder were not eligible for inclusion. We excluded women with a self-reported lifetime history of depression as well as all women with depression during the full course of their pregnancy. In addition, women with a known thyroid disease at baseline as well as other endocrine/auto-immune disorders were not eligible for inclusion. The HAPPY-study was approved by the Medical Ethical Committee of the Maxima Medical Centre Veldhoven and the Psychology Ethics Committee of Tilburg University (protocol number EC-2012.25).

2.2. Data collection, procedures and definitions

This study is reported in line with the STROBE guidelines (von Elm et al., 2007). Questionnaires were used to collect baseline demographic information, as well as relevant medical, obstetric, psychological and lifestyle data. If applicable, data were verified with medical records. Standardized blood measurements were performed at 10–12 weeks gestation and included TPO-ab, as well as thyroid releasing hormone (TSH) and free thyroxine (FT4). Measurements were performed in Li-heparin plasma using electrochemiluminescence assays (Cobas® e 601, Roche Diagnostics, Mannheim Germany). We defined a positive TPO-ab status with the commonly used threshold of > 20 IU/ml (Prummel and Wiersinga, 2005). This cut-off is probably not appropriate throughout the full course of pregnancy (Dama et al., 2016). Therefore, we performed the TPO-ab measurement during early pregnancy, before downsizing of maternal auto-immune processes emerges (Balucan et al., 2013).

Depressive symptomatology was assessed repeatedly every trimester and four times during the postpartum period (6 weeks, and 4, 8, and 12 months) using the Edinburgh Depression Scale (EDS). The EDS is validated to detect women with a high probability of major depression both during pregnancy and postpartum. In this study, self-reported depression was defined with the following validated EDS cut-off scores: trimester 1, ≥ 11; trimester 2 and 3, ≥ 10; (Bergink et al., 2011); postpartum period ≥ 13 (Cox et al., 1987; Harris et al., 1989; Pop et al., 1992). Women who scored above the trimester cut-offs during the course of their pregnancy were not eligible for inclusion in our study.

Our primary outcome measure was the occurrence of first-onset self-reported depression (i.e. incidence of new cases) at four months postpartum. Women with an increased TPO-ab titer during early gestation show a subsequent decline of their titer throughout pregnancy, with a typically rebound between three to five months postpartum and a gradual decline afterwards (Fung et al., 1988; Jansson et al., 1984; Stagnaro-Green et al., 1992). Therefore we considered four months postpartum to be the most optimal time point available to assess a possible association between a positive TPO-ab status during early gestation and the occurrence of first-onset self-reported depression postpartum. First-onset self-reported depression at other postpartum time points (6 weeks, 8 and 12 months) were used as secondary outcome measures.

2.3. Statistical methods

SPSS (version 24, IBM) was used for the statistical analyses. Binary logistic regression was used to evaluate the association between TPO-ab status during the first trimester (exposure) and the incidence of new cases of self-reported depression at four months postpartum (primary outcome), and at 6 weeks, 8 months and 12 months postpartum (secondary outcomes). To facilitate interpretation of the results, we plotted point prevalence rates of self-reported postpartum depression (EDS ≥ 13) over time (at 6 weeks, 4, 8 and 12 months postpartum) according to TPO-status. A multiple logistic regression analysis was performed to adjust for potential confounders. Based on previous literature, we included the following confounding variables: anxiety during pregnancy (Generalized Anxiety Disorder (GAD-7) scale sum score at 12 weeks gestation, continuous), age (years, continuous) and preterm delivery (< 37 weeks of gestation, dichotomous) (Dama et al., 2016), primiparity (dichotomous) (Greer et al., 2011; Howard et al., 2014) and recent life-events (self-reported, dichotomous) (Kuijpens et al., 2001). In addition, we considered the following confounding variables: mode of delivery (vaginal delivery or cesarean section), health problems of the baby (self-reported, dichotomous) and social support during the postpartum period (Tilburg Support Scale sum score, continuous). All potential confounding variables were introduced both separately and simultaneously into the unadjusted model to verify a potential effect on our exposure of interest (TPO-ab status). Logistic regression analyses were evaluated with Wald tests (χ^2, distribution, $\alpha = 0.05$). Results are presented with crude and adjusted odds ratio's (OR's) together with corresponding 95% confidence intervals.

Additionally, we tested whether a positive TPO-ab status during pregnancy was associated with differences in mean TSH and FT4 concentrations by using T-tests. TSH data was log-transformed to meet the assumption of normality, and log transformed mean TSH values are reported. Cohen's d are used to report the size of the effect (Cohen, 1988). Finally, we used a sensitivity analysis to assess the robustness of the findings. For this aim, we changed the dichotomous TPO-ab variable into a categorical variable (3 categories: ≤ 20 IU/ml; 21–100 IU/ml; ≥101 IU/ml).

Women were included in the final study sample if 1) at least two out of three pregnancy EDS scores were available and 2) the EDS score at four months postpartum (primar outcome measure) was available.

As a result of our data selection strategy we did not have any missing data on our primary outcome measure (EDS score ≥ 13 at 4 months postpartum). During pregnancy, the proportion of missing EDS measures varied between 1.7% and 2.5%. Regarding the secondary outcome measures, the proportion of missing data varied between 8.3% and 23.3%. Missing data was handled with the multiple imputation algorithm as implemented in SPSS version 24 (IBM). Ten imputed datasets were created and all predictor and outcome variables were used for imputation modelling. Analyses were run on the imputed data and pooled estimates are reported (Rubin, 2008). To explore the impact of the imputation procedure on our results, we repeated all analyses using the original dataset.