Parity and Risk of Thyroid Autoimmunity Based on the NHANES (2001–2002, 2007–2008, 2009–2010, and 2011–2012)

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Context: Autoimmune thyroid disease is more common in women than in men. Fetal microchimerism has been implicated as a potential explanation for this disparity.

Objective: The objective of this study was to evaluate the relationship between parity and thyroid autoimmunity in the US population.

Design, Setting, Patients: The National Health and Nutrition Examination Survey was used to identify females with antithyroperoxidase (TPOAb) and antithyroglobulin antibody (TgAb) measurements and parity data. Subjects (n = 4864) were categorized as never pregnant (n = 909) or previously pregnant (n = 3955). The association of parity with thyroid autoantibodies was examined both qualitatively and quantitatively. Thyroid autoimmunity was defined as TPOAb and/or TgAb titers above the reference limits.

Results: Previous pregnancy carried an odds ratio (OR) of 1.55 [95% confidence interval (CI): 1.26 to 1.91] for thyroid autoimmunity compared with never pregnant. Number of pregnancies was associated with thyroid autoimmunity: OR = 1.37 (95% CI: 1.02 to 1.84); 1.4 (95% CI: 1.08 to 1.81); 1.52 (95% CI: 1.18 to 1.96); and 1.73 (95% CI: 1.38 to 2.18) for 1, 2, 3, and ≥4 pregnancies, respectively. Because ever-pregnant women differed in several variables—age, race, smoking status, history of thyroid disease, and urinary iodine level—from never-pregnant women ($P < 0.001$), a multivariate regression analysis was performed, which showed no association of pregnancy with thyroid autoimmunity. The association was further examined utilizing an age-matched analysis, which confirmed the absence of an association between thyroid autoimmunity and parity.

Conclusion: Although we initially observed a strong association between parity and thyroid autoimmunity, after controlling for age and other variables, we were unable to identify an association. (***J Clin Endocrinol Metab*** **102: 3437–3442, 2017)**

Autoimmune thyroid disease (AITD) is more common in women than in men and increases in prevalence with increasing age (1, 2). Fetal microchimerism, the transplacental passage of fetal cells into the maternal circulation and tissues, has been implicated in the pathogenesis of AITD (3). If the hypothesis that these heterologous fetal cells serve as a maternal immune target is correct, women with a history of pregnancy would be expected to have higher rates of thyroid autoimmunity than women who have never been pregnant.

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Abbreviations: AITD, autoimmune thyroid disease; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; TgAb, antithyroglobulin antibody; TPOAb, antithyroperoxidase.

Fetal microchimeric cells have been identified as more prevalent and abundant in maternal thyroids with AITD than in unaffected thyroid glands (4). A number of hypotheses have been proposed to explain the potential mechanisms by which fetal microchimerism relates to thyroid autoimmunity, including the induction of a graft-vs-host reaction or alternatively a host-vs-graft reaction (3).

Four population-based studies have analyzed the association between thyroid autoimmunity and parity. Two of these studies, one performed in Denmark and the other in Australia, failed to show a relationship between parity and thyroid autoimmunity (5–7). However, two other single-institution studies from the United States and Germany (8, 9) demonstrated a positive association between parity and thyroid autoimmunity. We examined a large database representative of the US population to determine whether a correlation exists between a history of pregnancy and thyroid autoimmunity.

Subjects and Methods

Study population

We conducted a retrospective analysis of a cohort of the US population using data from the National Health and Nutrition Examination Survey (NHANES). NHANES was designed to reflect the noninstitutionalized civilian US population. Data were analyzed for survey years 2001 to 2002, 2007 to 2008, 2009 to 2010, and 2011 to 2012. The surveys for these years contain information regarding parity as well as thyrotropin, antithyroperoxidase (TPOAb), and antithyroglobulin antibody (TgAb) for 4864 females who were ethnically and geographically representative of the US population (Fig. 1). We included women who had provided information on their number of prior pregnancies and had been randomly chosen to have serum analyses of both TPOAb and TgAb. Women with known thyroid disease were included unless the thyroid disease was known prior to the age of fecundity (age, 12 years), in which case they were excluded (n = 19).

Information regarding age, race, tobacco use, socioeconomic status, and known history of thyroid disease was collected. Tobacco use was evaluated by asking patients if they had smoked at least 100 cigarettes in their lifetime and if they currently smoked. Urinary iodine levels were also collected along with TPOAb and TgAb titers. Socioeconomic status was evaluated using the family poverty income ratio. Patients were asked if they had a known history of thyroid disease, and if so, the age of onset. Thyroid autoimmunity was defined as a level of TPOAb and/or TgAb above the reference limit for the assay.

Laboratory methods

The upper limits of normal for the assays, as denoted by the manufacturers' reference ranges for diagnosis of thyroid autoimmunity, were used to denote a positive TPOAb or TgAb titer. TPOAb titers were measured with the Beckman Access2 Immunoassay System (reference range, <9 IU/mL), and TgAb titers were measured with the Beckman Access2 Immunoassay System thyroglobulin antibody assay (reference range, <4 IU/mL).

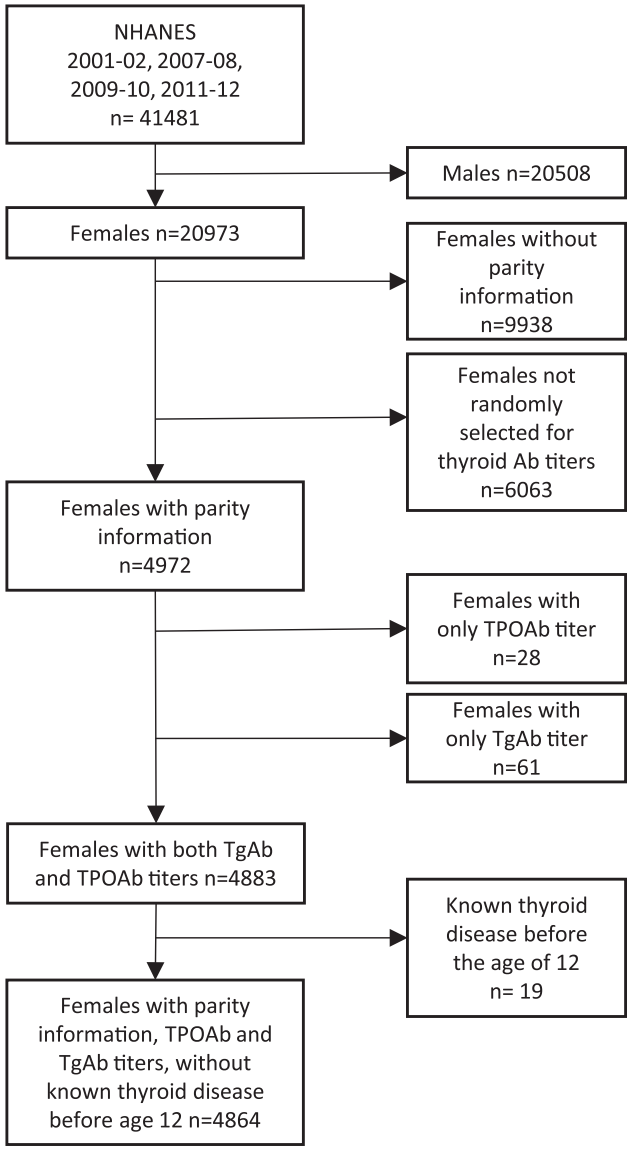

Figure 1. Flowchart shows selection of the study population.

Subjects with TPOAb titer <9 IU/mL and TgAb titer <4 IU/mL were considered negative. Information and laboratory manuals are available at https://wwwn.cdc.gov/nchs/nhanes/search/datapage.aspx?Component=Laboratory.

Statistical analysis

Statistical analysis was performed using Stata (version 14) and SPSS (version 24) software. Patient demographic and biological characteristics were compared between the two groups (ever- vs never-pregnant women) using a χ^2 test (Table 1). For binary outcomes such as positive thyroid autoantibodies, simple and multiple logistic regression models were used to examine the relationship between pregnancy and positive thyroid autoantibodies (Figs. 2 and 3). Positive thyroid autoantibodies were defined as levels of TPOAb and/or TgAb above the reference limit for the assay. In addition, raw values of both TPOAb and TgAb titers were used to investigate the relationship between pregnancy and TPOAb or TgAb titer value. The TPOAb and TgAb titers were log-transformed, and residuals were checked for the

Table 1. Demographic and Clinical Characteristics of Study Population (N = 4864)

Characteristic	Never Pregnant No. (%)	Median (Range)	Previously Pregnant No. (%)	Median (Range)	*P* Value
Age, y	909	23 (12 to ≥85)	3955	51 (16 to ≥85)	<0.001
≤31	622 (68.4)		598 (15.1)		
32–47	103 (11.3)		1128 (28.5)		
48–63	96 (10.6)		1123 (28.4)		
>63	88 (9.7)		1106 (28)		
Race/ethnicity	909		3955		<0.001
Hispanic	230 (25.3)		1162 (29.4)		
Non-Hispanic White	433 (47.6)		1819 (46)		
Non-Hispanic Black	171 (18.8)		786 (19.9)		
Other	75 (8.3)		188 (4.7)		
Family poverty income ratio	849	2.1 (0 to ≥5)	3618	2 (0 to ≥5)	0.99
0–1	188 (22.1)		802 (22.2)		
>1	661 (77.9)		2816 (77.8)		
Self-reported history of thyroid disease	627		3909		<0.001
No	570 (90.9)		3332 (85.2)		
Yes	57 (9.1)		577 (14.8)		
Age were told have thyroid disease, y[a]	57	40 (14 to ≥80)	567	43 (12 to ≥80)	0.11
12–29	21 (36.8)		133 (23.5)		
30–42	10 (17.6)		143 (25.2)		
43–55	15 (26.3)		140 (24.7)		
>55	11 (19.3)		151 (26.6)		
Current knowledge of thyroid disease[b]	56		562		0.85
No	14 (25)		147 (26.2)		
Yes	42 (75)		415 (73.8)		
Smoking status	629		3916		<0.001
Smoked <100 cigarettes in life	467 (74.2)		2341 (59.8)		
Smoked ≥100 cigarettes not currently smoking	69 (11)		828 (21.1)		
Smoked ≥100 cigarettes currently smoking	93 (14.8)		747 (19.1)		
Iodine, μg/L	886	135 (5 to 762,010)	3864	138 (6 to 136,161)	<0.001
<99	344 (38.8)		1294 (33.5)		
99–199	235 (26.5)		1305 (33.8)		
>199	307 (34.7)		1265 (32.7)		

P values comparing proportions between ever- and never-pregnant women were obtained by χ^2 tests.

[a]For age when told they have thyroid disease, 10 women were missing data.

[b]For current knowledge of thyroid disease, 16 women were missing data.

normal assumption. For multivariate analyses, potential confounding variables were compared between the two groups (ever- vs never-pregnant women), as shown in Table 1, and those found to be statistically significant were included in the aforementioned multivariate models. As part of the sensitivity analysis, the age-matched analysis was done using one-to-one matching (Fig. 4) (n = 630 for each group).

Results

Demographic and clinical characteristics of the study population

The study population was composed of 4864 female subjects, including 909 never-pregnant and 3955 ever-pregnant women (Table 1). The demographics were analyzed for each group and then compared. Age, race, self-reported history of thyroid disease, smoking status, and urinary iodine measurements were statistically significantly different between the two groups.

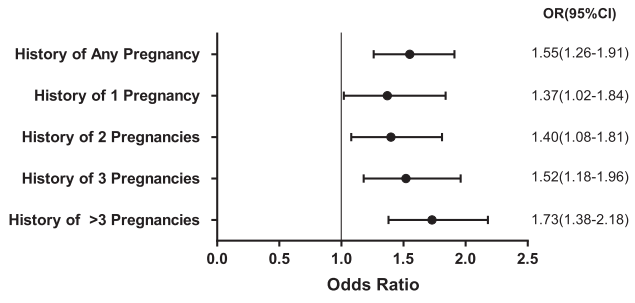

Figure 2. Thyroid autoantibody positivity in previously pregnant women compared with never-pregnant women (univariate analysis). Error bars represent 95% CI.

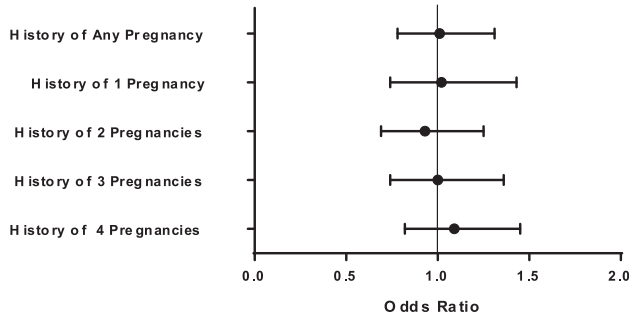

Figure 3. Thyroid autoantibody positivity in previously pregnant women compared with never-pregnant women (multivariate analysis). *P* value for all comparisons, *P* = nonsignificant. Error bars represent 95% CI.

Association of parity with thyroid autoantibodies: univariate analysis

According to a univariate analysis, a history of pregnancy carried an odds ratio (OR) of 1.55 [95% confidence interval (CI): 1.26 to 1.91] for thyroid autoimmunity compared with no history of pregnancy. The ORs for antibody positivity trended upward with increasing number of pregnancies (Fig. 2). When positivity for TPOAb and TgAb was analyzed individually for each antibody, ever pregnancy was a risk factor for both TPOAb (OR: 1.64; 95% CI: 1.29 to 2.08) and TgAb (OR: 1.32; 95% CI: 1.00 to 1.74). There was a significant association between the number of pregnancies and a positive TPOAb value (OR: 1.59; 95% CI: 1.15 to 2.20); 1.53 (95% CI: 1.15 to 2.03); 1.58 (95% CI: 1.19 to 2.11); and 1.76 (95% CI: 1.36 to 2.29) for 1, 2, 3, and ≥4 pregnancies, respectively, compared with women without prior pregnancy. For ever-pregnant women, the log-transformed TPOAb titer ($P = 0.002$) but not the TgAb titer ($P = 0.09$) was significantly higher than that of never-pregnant women (data not shown).

Association of parity with thyroid autoantibodies: multivariate analysis

Because age and several other factors in the cohort of previously pregnant women were statistically significantly different from those in the cohort of never-pregnant women, a multiple logistic regression analysis was performed using age, race, self-reported thyroid disease, smoking status, and urinary iodine level as covariates. After adjustment for these covariates, there was no association between history of pregnancy and the presence of antithyroid antibodies ($P = 0.91$) (Fig. 3). Furthermore, no association was noted when TPOAb ($P = 0.92$) and TgAb ($P = 0.65$) were analyzed individually. Similarly, when we adjusted only for age, the association between parity and thyroid autoantibodies observed in the univariate analysis was lost.

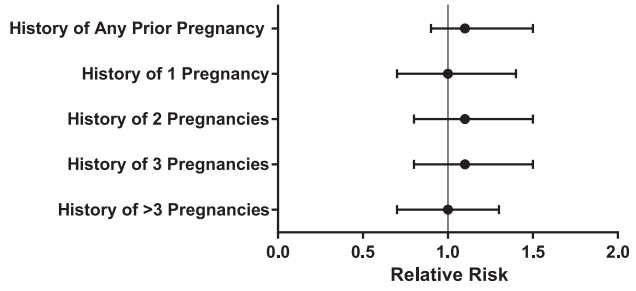

Figure 4. Relative risk of positive thyroid autoantibodies in previously pregnant women compared with never-pregnant women (age-matched analysis). *P* value for all comparisons, *P* = nonsignificant. Error bars represent 95% CI.

Association of parity with thyroid autoantibodies: age-matched analysis

An age-matched analysis was performed using 630 never-pregnant women for whom an age-matched, previously pregnant woman was available. When the age-matched analysis was used, the relative risk of thyroid autoimmunity in previously pregnant women was 10% higher than the risk in never-pregnant women, but the difference did not reach statistical significance. The risk of thyroid autoimmunity after one, two, three, or at least four pregnancies was also analyzed (Fig. 4), but a statistically significant association was not found. When TPOAb positivity and TgAb positivity were individually analyzed, similar results were observed (data not shown).

Discussion

One proposed mechanism for the female vs male disparity in prevalence of AITD is fetal microchimerism. The feto-maternal transfer of cells has been observed as early as the fourth week of gestation (10), and fetal cells have persisted in the maternal circulation decades after pregnancy (11). One hypothesis suggests that fetal microchimerism plays a role in the development of autoimmune disease, including AITD, by eliciting an intraorgan graft-vs-host process, whereas another proposal suggests that fetal cells residing in the thyroid gland induce a host-vs-graft response by inciting a maternal immune response.

Histologic studies examining the association between parity, fetal microchimerism, and AITD offered contrasting results. Klintschar *et al.* (4) found a significant correlation between the presence and quantity of maternal thyroid fetal cells in those with a diagnosis of Hashimoto thyroiditis compared with healthy controls. However, an Italian study by Cirello *et al.* (12) found that women with AITD had fewer fetal microchimeric cells in their circulation than healthy controls. The number of fetal cells in the peripheral blood, however, may not accurately reflect the presence of fetal cells and the autoimmune response at the tissue level. Fetal cells may respond to inflammatory signals (3) and migrate to and

engraft in damaged and injured tissue in a graft-vs-host reaction. When engrafted fetal microchimeric cells invoke a host immune response, they may involve the host tissue via a phenomenon such as epitope sharing (13), and one would expect females with a history of parity to have a higher prevalence of AITD than nulliparous females.

In a univariate analysis, we noted a statistically significant increase in thyroid autoimmunity with increasing number of pregnancies in US women. However, after adjusting for age, race, self-reported thyroid disease, tobacco use, and urinary iodine concentrations, we noted no difference in the incidence of thyroid autoimmunity between previously pregnant and never-pregnant women. We confirmed the association between race and prevalence of thyroid autoantibodies (14), but the association between parity and thyroid autoimmunity remained significant after accounting for race. When we adjusted only for age, the significant association between parity and thyroid autoantibodies observed in the univariate analysis was lost. Likewise, when performing an aged-matched analysis, we found no relationship between prior pregnancy and thyroid autoimmunity.

Our results support the findings of Australian and Danish cohort studies (5–7) examining this same hypothesis. The DanThyr study cohort was composed of women in specific age groups (18 to 22, 25 to 30, 40 to 45, and 60 to 65 years) for whom parity information was collected and thyroid autoantibodies were evaluated. No association was found between the presence of thyroid autoantibodies in the serum and history of pregnancy. The results were similar both when the cutoff was set at the functional sensitivity of the assay (TPOAb >30 U/L and TgAb >20 U/L) and at a higher arbitrary cutoff of >100 U/mL for both antibodies.

Recently, a longitudinal follow-up of the original survey was published in which nulliparous women with negative TPOAb and TgAb results were reevaluated after 11 years. Subjects were queried as to interval pregnancies or births. No association was found between interval parity and the development of TPOAb positivity (6). Walsh *et al.* (7) evaluated an Australian cohort of 1045 female patients and similarly found no relationship between positive thyroid autoantibodies and prior parity. In contrast, Friedrich *et al.* (9) analyzed a cohort of German women using either an abnormal ultrasound or positive serology to diagnose AITD. The authors found that women with at least one prior pregnancy had an increased risk of AITD.

Greer *et al.* (8) analyzed serum collected from women during pregnancy. Similar to our results, Greer *et al.* (8) found that the incidence of thyroid autoantibodies increased as the number of prior pregnancies increased; however, this difference was not statistically significant after they adjusted for additional population characteristics. However, the authors did find a statistically significant correlation between parity and a high TPOAb level when using a high cutoff of >500 IU/mL.

Shortcomings of our study include a lack of information regarding family history of thyroid disease, an important predictor of thyroid autoimmunity. In addition, only known parity was accounted for; women in our population may have had early spontaneous loss of pregnancy without their knowledge. This is important because fetal microchimerism is known to occur as early as the first trimester; thus, some women may have been erroneously classified as nulliparous. Finally, our study used thyroid autoantibodies as the sole criterion for diagnosis of thyroid autoimmunity because thyroid ultrasonographic data were not available. Thus, we may have underdiagnosed thyroid autoimmunity in our population.

Conclusion

Our study used a large cohort of the US population to examine the association between a history of pregnancy and thyroid autoimmunity as defined by the presence of thyroid autoantibodies. A strong association between parity and antithyroid antibody positivity was initially observed. However, after controlling for age and other variables, we were unable to identify an association between parity and thyroid autoimmunity.

Acknowledgments

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