

Thyroid Function and Autoimmunity Versus Number of Pregnancies

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Abstract

Background: Thyroid autoimmunity may be linked to infertility, in both thyrotropin (TSH)-dependent and TSH-independent fashion. The aim of the present study was to assess this presumed reciprocal relationship of thyroid autoimmunity and pregnancy.

Methods: TSH and antithyroid peroxidase autoantibodies (anti-TPO) were evaluated retrospectively over an eight-year period in 444 Greek women who had previously none or at least one pregnancy (>28 weeks). Statistics were done with analysis of covariance (ANCOVA) and the Chi square test.

Results: Thyrotropin was higher in women with one pregnancy and lower in those with two or more pregnancies compared to women with no pregnancies. Furthermore, significantly more women with no pregnancies were anti-TPO (+), compared to women with one or those with at least two pregnancies.

Conclusion: Because pregnancy might contribute to the development of thyroid autoimmunity, women should be monitored for development of thyroid autoimmunity long after their pregnancies, even after an uneventful first conception, pregnancy and delivery of a live infant.

Keywords: Fertility, Pregnancy, Thyroid, Thyrotropin.

To cite this article: Boufas D, Vryonidou A, Mastorakos G, Ilias I. Thyroid Function and Autoimmunity Versus Number of Pregnancies. *J Reprod Infertil*. 2016;17(4):240-242.

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Received: Nov. 5, 2015

Accepted: Feb. 2, 2016

Introduction

The causes of infertility (as well as pregnancy loss) are multiple; anatomical variations, endocrine diseases, alterations in thrombosis, autoimmune, hereditary and infectious diseases and other idiopathic or unknown etiologies. Thyroid autoimmunity (expressed with the presence of anti-thyroid antibodies) is prevalent in 4% of women of reproductive age (1) and may be linked to infertility, even in the absence of clinically apparent autoimmune disease, in both TSH-dependent and TSH-independent fashion (1-3). Women with endometriosis, polycystic ovarian syndrome or premature ovarian failure have very often high levels of antithyroid autoantibodies. The latter may coexist and may be associated with antiphospholipid antibodies (linked with gestational complications and pregnancy loss). Furthermore, women of childbearing age with positive antithyroid

autoantibodies, even when euthyroid, carry a substantial risk of miscarriage; one in four women with recurrent miscarriage is indeed antithyroid autoantibody positive (1, 2). The aim of the present study was to assess this presumed reciprocal relationship of thyroid autoimmunity and pregnancy.

Methods

Thyroid function (thyrotropin, TSH) and presence of thyroid autoimmunity (anti-thyroid peroxidase autoantibodies, anti-TPO) were evaluated in this retrospective study over an eight-year period in 444 Greek women (55±16 years old) who had previously none or at least one pregnancy (>28 weeks) among consecutive outpatients of an endocrine department of one of the largest hospitals in Greece. Women on any kind of thyroid

Table 1. Thyroid parameters of studied women

Pregnancies	n	TSH ($\mu\text{IU/ml}$)	Positive anti-TPO
0	147	3.81 \pm 2.87	69 (46%) ^{#, ##}
1	68	9.34 \pm 2.96 ^{*, **}	22 (32%)
≥ 2	229	3.29 \pm 2.06	69 (30%)

*P=0.038; women with 1 pregnancy vs. 0 pregnancy and ** p=0.004; women with 1 pregnancy vs. women with ≥ 2 pregnancies; post-hoc ANCOVA tests

#P=0.003; women with 0 pregnancy vs. 1 pregnancy, ## p=0.003; women with 0 pregnancy vs. women with ≥ 2 pregnancies; Chi square test

hormone treatment either at present or in the past were excluded. Age and number of pregnancies (>28 weeks) were noted. Thyrotropin and anti-TPO were measured by electrochemiluminescence. Analysis of covariance (ANCOVA) and chi square (χ^2) was employed for statistical analysis, with TSH taken as the dependent variable and number of children (0, 1 or ≥ 2) and positivity of thyroid autoantibodies taken as independent factors, and age as a covariate. The number of pregnancies vis-à-vis anti-TPO positivity was also assessed with the chi square test. Based on literature data (4-7), it was estimated that at least 39 women were required in each group for assessment of TSH differences of 2.0 $\mu\text{IU/ml}$ and SD=0.5 MIU/ml , with error levels (Type I & II) set at alpha=5% and beta=10%, respectively, thus the number of women studied exceeded this limit (8, 9).

Results

Thyrotropin depended on the number of pregnancies (p=0.006) with significant differences in TSH among women with one pregnancy compared to those who had none (p=0.038) or at least 2 pregnancies (p=0.004) (Table 1); no dependency of TSH on either age (p=0.632) or anti-TPO autoantibodies positivity (p=0.139) was found. Women with no pregnancies had more often positive anti-TPO, compared to women with one or those with at least two pregnancies (p=0.003) (Table 1).

Discussion

It was found that women with increased frequency of thyroid autoimmunity had no pregnancy (46% were positive anti-TPO). Autoimmunity (with or without vasculitis) may have repercussions on fertility in various levels, including miscarriage, preterm deliveries, ovarian failure, implantation failure, and pregnancy loss (1, 2). Regarding thyroid autoimmunity, transcripts for TPO (and thyroglobulin, Tg) are required for thyroid hormone synthesis in the thyroid gland but it

is also expressed in the endometrium; the latter is thus susceptible to the action of anti-TPO and anti-Tg autoantibodies (10). Not surprisingly, clinical studies have shown that women with high levels of thyroid autoantibodies have compromised fertility (10). Thyroid autoimmunity in women has been associated with disturbed folliculogenesis, failure of fertilization, altered embryogenesis, implantation difficulties and subsequent overall fertility failure (11-15). Further mechanisms via which thyroid autoimmunity has effects on fertility include alterations in the secretory profile of endometrial T cells (with lowered secretion of IL-4 and IL-10 and increased secretion of interferon- γ), increased activation of polyclonal B cells, hyperactivity and increased migration of cytotoxic natural killer cells (leading to altered uterine immune and hormonal responses) (1); nevertheless, the exact mechanisms remain obscure (13-15).

On the other hand, in this study, women with two or more pregnancies showed lower frequency of thyroid autoimmunity (30% of positive anti-TPO antibodies) as compared to women with no pregnancy, indicating that lower levels of autoimmunity favor fertility (1). However, the most intriguing fact about the group in this study is that of women with one pregnancy and increased TSH (indicating subclinical or overt hypothyroidism) compared to women who had no history of pregnancy or women who had at least two pregnancies. Although subclinical hypothyroidism increases with age, the effect of age on thyroid function in our subjects was not significant. Thyroid hormone receptors and TSH-receptors are found in the normal endometrium (10). Their expression fluctuates along the menstrual cycle, showing an increase when apical uterine epithelial pinocytes appear (enabling endometrial receptivity) (10). The transcriptional regulation of factors for the synthesis of thyroid hormone receptors is in part-influenced by progesterone (10). The latter may be causally linked to the menstrual irregularity and subfertility of hypothyroid women. Additionally, hypothyroid women—by way of interaction of thyroid hormone receptors and estrogen receptors on estrogen-responsive promoters—show reduced endometrial thickness (10). Mature oocytes express thyroid hormone receptors. The maturation of oocytes involves—among others—interplay of thyroid hormones on these receptors (apparently this interplay is involved in nitric oxide synthase activity) (10). Our particular group rep-

resented women who developed thyroid autoimmunity with measurable destruction of thyroid during late pregnancy or, even most probably, during postpartum. Thus, following first pregnancy, these women seemed to become less capable of conceiving. Most previous relevant population studies in the literature (16) show no association between number of pregnancies and thyroid dysfunction or autoimmunity; in sharp contrast, there have also been reports of a positive association between number of births and thyroid autoimmunity (as shown with positivity of thyroid autoantibodies) (17). In this regard, the present study is in the same line with the latter work.

Conclusion

Less autoimmunity-prone women (with lower TSH) seem to have more pregnancies whereas autoimmunity-prone (positive anti-TPO) women seem to have no pregnancies. Therefore, because gestation might contribute to the development of thyroid autoimmunity, women should be monitored for development of thyroid autoimmunity long after their pregnancies, even after an uneventful first conception, pregnancy and delivery of a live infant.

Conflict of Interest

Authors declare no conflict of interest.

References

1. Twig G, Shina A, Amital H, Shoenfeld Y. Pathogenesis of infertility and recurrent pregnancy loss in thyroid autoimmunity. *J Autoimmun.* 2012;38(2-3): J275-81.
2. Carp HJ, Selmi C, Shoenfeld Y. The autoimmune bases of infertility and pregnancy loss. *J Autoimmun.* 2012;38(2-3):J266-74.
3. Binita G, Suprava P, Mainak C, Koner BC, Alpana S. Correlation of prolactin and thyroid hormone concentration with menstrual patterns in infertile women. *J Reprod Infertil.* 2009;10(3):207-12.
4. Walsh JP, Bremner AP, Bulsara MK, O'Leary P, Leedman PJ, Feddema P, et al. Parity and the risk of autoimmune thyroid disease: a community-based study. *J Clin Endocrinol Metab.* 2005;90(9):5309-12.
5. Bülow Pedersen I, Laurberg P, Knudsen N, Jorgensen T, Perrild H, Ovesen L, et al. Lack of association between thyroid autoantibodies and parity in a population study argues against microchimerism as a trigger of thyroid autoimmunity. *Eur J Endocrinol.* 2006;154(1):39-45.
6. Phillips DI, Lazarus JH, Butland BK. The influence of pregnancy and reproductive span on the occurrence of autoimmune thyroiditis. *Clin Endocrinol (Oxf).* 1990;32(3):301-6.
7. McCanlies E, O'Leary LA, Foley TP, Kramer MK, Burke JP, Libman A, et al. Hashimoto's thyroiditis and insulin-dependent diabetes mellitus: differences among individuals with and without abnormal thyroid function. *J Clin Endocrinol Metab.* 1998;83(5): 1548-51.
8. Cohen J. A power primer. *Psychol Bull.* 1992;112 (1):155-9.
9. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods.* 2007;39(2):175-91.
10. Colicchia M, Campagnolo L, Baldini E, Ulisse S, Valensise H, Moretti C. Molecular basis of thyrotropin and thyroid hormone action during implantation and early development. *Hum Reprod Update.* 2014;20(6):884-904.
11. van den Boogaard E, Vissenberg R, Land JA, van Wely M, van der Post JA, Goddijn M, et al. Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. *Hum Reprod Update.* 2011;17(5):605-19.
12. Practice Committee of the American Society for Reproductive Medicine. Subclinical hypothyroidism in the infertile female population: a guideline. *Fertil Steril.* 2015;104(3):545-53.
13. Medenica S, Nedeljkovic O, Radojevic N, Stojkovic M, Trbojevic B, Pajovic B. Thyroid dysfunction and thyroid autoimmunity in euthyroid women in achieving fertility. *Eur Rev Med Pharmacol Sci.* 2015;19(6):977-87.
14. Vissenberg R, Manders VD, Mastenbroek S, Fliers E, Afink GB, Ris-Stalpers C, et al. Pathophysiological aspects of thyroid hormone disorders/thyroid peroxidase autoantibodies and reproduction. *Hum Reprod Update.* 2015;21(3):378-87.
15. Weiss RV, Clapauch R. Female infertility of endocrine origin. *Arq Bras Endocrinol Metabol.* 2014; 58(2):144-52.
16. Sgarbi JA, Kasamatsu TS, Matsumura LK, Maciel RM. Parity is not related to autoimmune thyroid disease in a population-based study of Japanese-Brazilians. *Thyroid.* 2010;20(10):1151-6.
17. Greer LG, Casey BM, Halvorson LM, Spong CY, McIntire DD, Cunningham FG. Antithyroid antibodies and parity: further evidence for microchimerism in autoimmune thyroid disease. *Am J Obstet Gynecol.* 2011;205(5):471.e1-4.