THYROID AUTOIMMUNITY IS ASSOCIATED WITH AN INCREASED RISK OF SPONTANEOUS MISCARRIAGE IN EUTHYROID WOMEN

Chen L, Hu R. **Thyroid autoimmunity and miscarriage: a meta-analysis.** Clin Endocrinol (Oxf) 2011;74:513-9.

SUMMARY • • • • • • • •

BACKGROUND

According to epidemiologic research, 31% of pregnancies end in abortion. Because human chorionic gonadotropin is measured to detect early gestation, about one third of miscarriages could be discovered in time. The prevalence of two consecutive abortions is approximately 2% to 4%, whereas the prevalence of three consecutive abortions is <1%. Many factors have been associated with miscarriage, such as hereditary defects, developmental deformities, peripartum infection, environmental exposure (smoking, alcohol abuse, and intoxication) and some endocrine disorders (diabetes mellitus, thyroid diseases, and hyperprolactinemia).

Recurrent spontaneous abortion has been associated with several autoimmune diseases, especially systemic lupus erythematous and antiphospholipid syndrome.

In 1990, Stagnaro-Green (1) initially reported that euthyroid women with positive thyroid autoantibodies (TA) are more liable to have a spontaneous abortion. Since then, numerous studies on the association between thyroid autoimmunity (TAI) and miscarriage have been published. Considering the heterogeneity of the design and methodology of these studies and the conflicting study results, the authors have conducted a meta-analysis to provide more persuasive evidence for clinical practice.

METHODS

A systematic evaluation of the association between TAI and miscarriage was based on a search and data analysis of published case–control studies and cohort studies. TAI prevalence was compared between women who had had a spontaneous abortion and controls in case–control studies. The pooled odds ratio (OR) and its 95% confidence interval (CI) were

then calculated. Likewise, the abortion rates for TA-positive and TA-negative groups were compared, and the pooled relative risk (RR) and its 95% CI were calculated.

Inclusion criteria for the analysis were as follows:

- 1. All published studies were included, regardless of their publication language or date.
- 2. The cohort studies had to be prospectively designed.
- 3. Overt thyroid dysfunction in gestation was excluded, while euthyroidism was defined as a serum thyrotropin (TSH) level between 0.3 and 5.0 mIU/L.
- 4. TAI was defined as one or more types of positive TA. TA refers to thyroid microsome antibody, thyroglobulin antibody, and thyroid peroxidase antibody.
- 5. OR or RR and its 95% CI were calculated from the raw data extracted from the original literature.
- 6. The studies involving multiple in vitro fertilization procedures were excluded.

RESULTS

The search strategy identified 53 potentially relevant studies, 22 of which were included in the meta-analysis; 8 of these were case–control studies and 14 cohort studies.

Case–Control Studies: The 8 case–control studies included in the systematic review were published between 1993 and 2008. They reported data on 1077 women who had had recurrent spontaneous abortions, all of whom were white. Most of these women had had two or more consecutive miscarriages (n = 1341), while women with no history of abortion (n = 747), female blood donors (n = 300), and parous women (n = 284) served as most of the controls.

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In six studies, both thyroglobulin antibody (TgAb) and thyroid peroxidase antibody (TPOAb) were detected. Only in one study were thyroid microsome antibody (TmAb), TgAb, and TPOAb all tested. One study measured only TPOAb.

Six studies reported the prevalence of TAI in women with recurrent spontaneous abortion (RSA, three or more consecutive miscarriages), of which five studies concluded that the prevalence of TAI in women with RSA is significantly higher than in controls. Only one study claimed that the prevalence of TAI in RSA women is lower than in controls. Overall, the incidence of consecutive abortions was 25.3%, as compared to 11.8% in the control group (OR, 2.55; 95% CI, 1.42 to 4.57).

Cohort Studies: Fourteen prospective cohort studies published from 1990 to 2009 assessed the influence of TAI on pregnancy outcome. In all, 598 TA-positive pregnancies and 4870 TA-negative pregnancies were followed. The result was that 120 of 598 women in the TA-positive group (20.1%) and 313 of 4870 women in the TA-negative group (6.4%) had a spontaneous abortion (RR, 2.31; 95% CI, 1.90 to 20.82). Only one study was undertaken in Asia. Among the 14 cohort studies, four observed pregnancies

in which assisted reproduction technology had been used, while the rest surveyed spontaneous pregnancies.

Diversity in the methods applied to measure thyroid autoantibodies was also observed. Both TPOAb and TgAb were determined in five studies. In three studies, TgAb, TmAb, and TPOAb were detected, whereas only TPOAb was tested in five studies. In another study, only TmAb was detected. Nine studies drew a conclusion that TAI increased the risk of miscarriage. However, according to the remaining five studies, the abortion rate in the TAI group was higher than in controls, but not significantly different.

Meta-analysis: The pooled OR was 2.55 (95% CI, 1.42 to 4.57; P = 0.002), which means thyroid autoimmunity was more prevalent in women with RSA. The pooled RR was 2.31 (95% CI, 1.90 to 2.82; P<0.00001), which implies that thyroid-autoantibody-positive women were more liable to have a miscarriage.

CONCLUSIONS

Based on the currently available evidence, it appears that the presence of thyroid autoimmunity is associated with an increased risk of spontaneous miscarriage in euthyroid women.

COMMENTARY • • • • • • •

The present meta-analysis attempts to provide an estimate of the risk of miscarriage for euthyroid women in the presence of thyroid autoantibodies. The authors rightly state that although the presence of positive thyroid antibodies is significantly associated with miscarriage, it does not mean that the relationship is causal. Because thyroid antibodies may coexist with other autoimmune diseases, such as systemic lupus erythematosus and antiphospholipid syndrome, with spontaneous abortion rates of 7% to 8% and 22%, respectively, subjects affected with these conditions were excluded from the present analysis.

Although the authors considered the possibility that titer values of thyroid antibodies could be related to miscarriages, this association was mentioned in only one study.

One important point in this type of analysis is the definition of thyroid dysfunction in the first trimester of pregnancy. It is recommended that gestational-age-specific reference ranges be used in the diagnosis of thyroid dysfunction, particularly early in pregnancy. However, the range in values according to gestational age is not usually reported by the manufacturers or by commercial laboratories. Therefore, it is continued on next page

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recommended that medical practitioners follow the recommendations suggested by the Endocrine Society Guidelines in Thyroid Disorders in Pregnancy (2); a serum TSH over 2.5 mIU/L in the first trimester of gestation is considered diagnostic of hypothyroidism and is known to potentially affect the outcome of pregnancies, including miscarriages. In the present meta-analysis, serum TSH in the selected articles ranged from 0.3 to 5.0 mIU/L, therefore many of the miscarriages occurred in women suffering from mild hypothyroidism. It has to be kept in mind that many of the studies were published before 2007, when the recommendation for a serum TSH range was given. Serum TSH levels in the antithyroid-antibodypositive women were 0.61 mIU/L higher than in the antithyroid-antibody-negative women (95% CI, 0.51-0.71; P<0.00001).

The other issue discussed by the authors is patient age; women with positive thyroid antibodies in the 9 studies considered were, on average, 1.29 years older than those with negative antibodies; it is known that there is an increase in the incidence of spontaneous miscarriage with age.

In summary, the meta-analysis done by Chen and Hu supports the general medical concept of an increased rate of spontaneous miscarriages in women harboring positive thyroid antibodies, although other factors, such as age, mild thyroid dysfunction, and higher serum TSH values, albeit within normal limits, could contribute to it.

The dilemma for the practitioner in the presence of a euthyroid, antithyroid–antibody-positive woman who wishes to become pregnant or who is in her first trimester is to treat or not to treat with levothyroxine. This is a controversial issue among endocrinologists and obstetricians, with some benefit of treatment reported in the literature (3-5). Considering the higher risk for miscarriages in euthyroid women with thyroid autoimmunity and the potential benefits of levothyroxine therapy, could 50 or 75 μ g daily of levothyroxine be harmful to a healthy young woman?

— Jorge H. Mestman, MD

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