

Thyroid antibodies and gestational diabetes mellitus: a meta-analysis

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Objective: To determine whether thyroid antibodies are associated with an increased risk of gestational diabetes mellitus (GDM) in pregnant women.

Design: Meta-analysis.

Setting: Not applicable.

Patient(s): Twenty cohort and case-control studies involving pregnant women with positive thyroid antibodies were the exposure of interest, and GDM was the outcome.

Intervention(s): None.

Main Outcome Measure(s): A fixed-effects model was used to evaluate the relationship between thyroid antibodies and the risk of GDM. Subgroup analyses were performed among different types of study design, different thyroid antibodies, and patients with specific thyroid dysfunction.

Result(s): The search strategy identified 167 potentially relevant publications, of which 20 were included in the meta-analysis. A significant association between thyroid antibodies and GDM was observed. A meta-analysis of the 11 cohort studies with pregnant women with positive thyroid antibodies in their first trimester suggested no obvious risk of GDM compared with the reference group. In subgroup meta-analyses, no significant association between thyroid antibodies and GDM was found in euthyroid pregnant women, whereas a significant positive association was identified in women with a thyroid dysfunction.

Conclusion(s): Based on the currently available evidence, there is a significant but not strong association between thyroid antibodies and the risk of GDM, and thyroid antibodies in the first trimester lack predictive value for the risk of GDM. In addition, thyroid antibodies may not increase the risk of GDM in euthyroid pregnant women. (Fertil Steril® 2015;■:■-■. ©2015 by American Society for Reproductive Medicine.)

Key Words: Thyroid, autoimmunity, antibodies, gestational diabetes mellitus

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Gestational diabetes mellitus (GDM) is defined by the World Health Organization as having "any degree of glucose intolerance with onset or first recognition during pregnancy" (1). The prevalence of GDM in pregnant women varies substantially, ranging from 1.7% to 11.6% in advanced economies (2). In Asian countries, the prevalence varies

according to the screening strategy and diagnostic criteria and ranges from 1% to 20%, with an increasing trend in recent years (3). GDM is one of the most common pregnancy complications associated with a number of adverse outcomes, including miscarriage, delivery, excessive fetal growth, birth trauma, and neonatal metabolic abnormalities (4). In addition, women

who have been exposed to GDM during pregnancy are at an exceptionally high risk of developing type 2 diabetes, chronic hypertension, and vascular disease later in life (5, 6). GDM has undoubtedly become an important public health issue worldwide.

Studies have shown that GDM is caused by β -cell dysfunction and insulin resistance (7). A high prevalence of elevated thyroid antibodies have appeared in patients with a history of insulin resistance, such as pregnant women with GDM (8). The link between autoimmune disorders and insulin resistance could be the inflammatory events that are associated with both conditions. Autoimmune thyroid dysfunction was found to be associated with insulin resistance, suggesting a potential relationship between

Received January 22, 2015; revised and accepted June 4, 2015.

Y.Y. has nothing to disclose. Q.L. has nothing to disclose. Q.W. has nothing to disclose. X.M. has nothing to disclose.

Y.Y. and Q.L. should be considered similar in author order.

Supported by Operation Expenses for Basic Scientific Research of Central Authorities (grant no. 2012GJSSJKC03), International Science and Technology Cooperation Program of China (grant no. 2012DFB30130), and National Natural Science Foundation (grant no. 81402757).

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Fertility and Sterility® Vol. ■, No. ■, ■ 2015 0015-0282/\$36.00

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autoimmune thyroid dysfunction and GDM. The prevalence of thyroid antibodies in pregnant women is approximately 10%–15% (8). In recent years, many epidemiologic studies have investigated the links between thyroid antibodies, including thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb), and risk of GDM (9–28). However, these studies have apparently yielded conflicting results. Both obstetricians and endocrinologists pay great attention to whether euthyroid pregnant women with positive thyroid antibodies have a higher risk than women with negative thyroid antibodies and how their condition should be managed. Therefore, to clarify the evidence, we conducted a meta-analysis of available case-control and cohort studies of thyroid antibodies and GDM.

MATERIALS AND METHODS

Search Strategy and Study Selection

We followed the Meta-analysis of Observational Studies in Epidemiology guidelines to explicitly report this meta-analysis (29). To study the association between thyroid antibodies (TPOAb or TgAb) and GDM, an electronic search was conducted with the use of Pubmed and two Chinese databases, Wanfang and China National Knowledge Internet (CNKI), from inception to October 2014. The following search words were used: (1) thyroid antibody, thyroid antibodies, thyroid autoimmune antibody, thyroid autoimmune antibodies, thyroid autoantibody, thyroid autoantibody, TPOAb, TPOAb, thyroid peroxidase antibody, thyroid peroxidase antibodies, thyroid globulin antibody, thyroid globulin antibodies, TG-Ab, or TgAb; and (2) gestational diabetes, pregnancy diabetes, maternal diabetes, gestational diabetes mellitus, or GDM. An initial screening was based on the titles and abstracts of published papers, and the full texts were then reviewed carefully during the second screening. In addition, reference lists of the original studies and review articles were considered. Irrelevant studies, reviews, case reports, and letters to the editor were ineligible. Overlapping studies were also excluded. All of the literature searches were reviewed independently by two authors.

Data Extraction and Assessment of Quality of Methods

Relevant data were extracted from each paper with the use of standardized data collection forms. Any disagreements were resolved by discussion until an agreement could be found. We contacted the corresponding authors through email to obtain additional detailed information when necessary. The related data were extracted to calculate an odds ratio (OR) or relative risk (RR) for the association between thyroid antibodies and GDM. We also extracted study characteristics for further exploration in subgroup meta-analyses. The following characteristics were recorded: first author, year of publication, study period, study design, definition of GDM, definition of thyroid dysfunction, and exclusion criteria (Supplemental Table 1, available online at www.fertstert.org). The selected studies were assessed for quality with the use of the Newcastle-Ottawa scale (NOS) for cohort studies and

case-control studies (http://www.ohri.ca/Programs/clinical_epidemiology/default.asp). Studies with NOS scores of 0–3, 4–6, and 7–9 were considered to be of low, moderate, and high quality, respectively. Two investigators extracted the data and independently assessed the quality. Disagreements were resolved by consensus or arbitration by a third investigator.

Statistical Analyses

The RR was used as the common measure of association across the studies. ORs were transformed into RRs according to the following formula: $RR = OR / [(1 - P_0) + (P_0 \times OR)]$, where P_0 is the incidence of GDM in the thyroid antibodies-negative group (30). In addition, the Miettinen test-based approach was used to calculate the variance of logRR (variance $\log RR = \text{variance } \log OR \times [\log RR / \log OR]$) (31). The overall combined RR and 95% confidence interval (CI) was calculated with the use of logRR and variance of logRR. Heterogeneity across studies was assessed with the use of the Cochrane Q statistic (significance level at $P < .10$) and the I^2 statistic. If $I^2 < 50\%$, a random-effects model (DerSimonian-Laird method) was used to pool the results; otherwise, a fixed-effects model (Mantel-Haenszel method) was used. In addition, subgroup analyses were conducted stratifying by the type of study design, type of thyroid antibody (TPOAb or TgAb), and thyroid dysfunction exclusions. Sensitivity analyses were performed to detect the effects of individual study on the pooled result by omitting one study in each turn. Publication bias was assessed with the use of funnel plots and the Egger regression test. We conducted all analyses with the use of Stata software, version 12.0. Except where otherwise specified, a P value of $< .05$ was considered to be statistically significant.

RESULTS

Study Selection and Study Characteristics

The study selection process is shown in Figure 1. Initially, 167 unique citations were retrieved from the Pubmed, CNKI, and Wanfang databases. After the first screening of the abstracts and titles, 130 citations were excluded, primarily owing to being reviews, clearly irrelevant studies, or studies not focusing on GDM. Then we reviewed full-text articles for a more comprehensive evaluation. Two articles were excluded because the exposure was not relevant, and 15 articles were excluded because they did not focus on GDM. Finally, 20 articles (9–28) were included in our meta-analysis.

The meta-analysis included 10 cohort studies and 10 case-control studies conducted with 34,566 participants. The characteristics of the 20 articles are presented in Supplemental Table 1. The cohort sizes of the studies ranged from 49 to 7,641 and were published from 1997 to 2014. Among the studies, 11 (9–14, 19, 24–27), seven (15–17, 21–23, 28), and two (18, 20) were conducted in Asia, Europe, and America, respectively. The ascertainment of thyroid antibodies varied across studies. Among the 20 articles included here, nine studies evaluated TPOAb only (9–11, 20, 21, 23–25, 27), ten studies evaluated both TgAb and TPOAb (one type of positive antibody was considered to be a

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