Meta-analysis of the effect of positive thyroid peroxidase antibody on spontaneous abortion in pregnant women

Yang Zhisen[1], Liang Xinke[1], Wang Pengfei[1], Geng Li[2]

[1]Staff Hospital of Handan Iron & Steel Group Co. Ltd Thyroid Department, Handan, Hebei Province, 056000, China

[2]General Hospital of Handan Mining Group Internal Medicine Department, Handan, Hebei Province, 056000, China

Keywords: Thyroid antibody positive; abortion; Spontaneous abortion; Meta-analysis

Abstract: Aim: The effect of thyroid antibody positivity on spontaneous abortion in pregnant women was evaluated by Meta-analysis. Methods: PubMed, The Cochrane Library, China Biology Medicine disc, Chinese sci-tech journal database, China National Knowledge Infrastructure full-text database, and Wanfang academic journal full-text database were searched. (Search until November 20, 2018) Literature on the effect of thyroid antibody positivity on spontaneous abortion in pregnant women was comprehensively searched, methodological quality of the included literature was evaluated, and RevMan 5.3 was used for statistical analysis. Result: A total of 9 articles were included. Meta-analysis results showed that the abortion rate of the experimental group (TPO antibody positive) with normal thyroid function and the control group (antibody negative) was 2.35, 95% CI (1.46, 3.77), with statistically significant difference. While the abortion rate with normal thyroid function and levothyroxine intervention was OR=1.27, 95% CI (0.70, 2.28), and there was no significant statistical difference. Conclusion: The abortion rate of pregnant women with positive TPO antibody was significantly higher than that of women with negative antibody. Levothyroxine intervention did not significantly reduce the risk of miscarriage.

1. Introduction

Thyroid gland is an important endocrine organ of human body. The biological role of thyroid hormone is very extensive. Its main role is to promote the metabolism of substances and energy and promote the growth and development. In the past 20 years, people began to pay attention to the thyroid function of pregnant women, and gradually understood the influence of abnormal thyroid function, such as hyperthyroidism and hypothyroidism on mother and fetus, and also understood that thyroid immune antibodies may lead to adverse pregnancy outcomes1. There are many forms of thyroid antibodies, and the mechanism of action is not completely clear. Especially when thyroid function is normal and TPO positive, the outcome of pregnant women is still controversial. More studies have shown that women with positive TPO antibodies have a higher risk of miscarriage than women with negative antibodies. The purpose of this study was to include the existing reliable evidence to clarify the relationship between TPOAb and adverse pregnancy outcomes before 10 weeks, and to conduct a Meta-analysis on the effectiveness of the intervention with levothyroxine.

2. Materials and Methods

2.1 Document Retrieval PubMed, The Cochrane Library, Chinese sci-tech journal database (VIP), China National Knowledge Infrastructure full-text database (CNKI), and Wanfang academic journal full-text database were searched. The retrieval date is from the time of database construction to November 10th, 2018. Index word are “thyroid autoantibodies“ and “miscarriage OR spontaneous abortion OR early pregnancy loss“.

2.1 Criteria of inclusion and exclusion

Inclusion criteria: (1) All subjects were diagnosed as pregnant women; (2) The literature types

  DOI: 10.25236/icbcme.2019.005

were randomized controlled studies, case control studies or cohort studies; (3) Endpoint criteria in research report included abortion rates; (4) There are clear scientific records.

Exclusion criteria: Summary and meta-analysis, in vitro experiments, animal experiments, short reports and incomplete reports.

2.2 Data extraction and literature quality evaluation

The extraction of literature data was completed by two researchers independently, including experimental design, population, intervention measures and outcome indicators including abortion rate, and the data was extracted by cross comparison. The contents of extraction include: author, published time, experimental design, sample size, and intervention. Quality assessment of randomized controlled trials were performed using the modified Jadad scale, with a score below 3 (including 3) as low quality and a score of 4 or above as high quality. Non-randomized controlled studies were evaluated by the NOS scoring scale (full score: 9 points), and those above 5 points indicated good quality and could be used in the study. Disagreements may be resolved by discussion or with the assistance of a third investigator.

2.3 Statistical analysis

Revman 5.3 software was adopted for statistical analysis, and Weighted Mean Difference (WMD) was adopted as the evaluation index for measurement data and its 95% confidence interval was calculated; The odds ratio (OR) was used as the evaluation index for enumeration data and 95% confidence interval was calculated. Heterogeneity test was carried out with I2 test. If I2 < 50%, the heterogeneity between included studies was considered to be small, and fixed effect model was used for analysis. On the contrary, if I2> 50%, the heterogeneity between the included studies is considered to be large, and the random effect model is adopted for analysis. Publication bias of all included studies were assessed using funnel plots.

3. Results

3.1 Retrieved result

Through the above retrieval strategy, a total of 263 literatures were retrieved. A total of 32 duplicates and 7 in vitro experiments were selected. After reading the full text, 9 references were included, including 7 in English and 2 in Chinese. The NOS scores of the included literatures were all above 5 points, or the scores of the Jada scale were above 4 points. The characteristics, quality evaluation and basic baseline data of the included literatures are shown in Table 1.

Table 1 Basic characteristics and quality evaluation of the included literature

Included in the study	Published time	Study design	Main observational indicators	Outcome indicators	Age (years)	Quality of the literature
Carlo Ticconi et.al[2]	2011	case-control	TG-Ab、TPO-Ab	abortion	31.7±6.3	NOS:6
Haixia Liu et.al[3]	2014	prospective	TPOAb、TgAb、TSH	abortion	29.86–3.51	NOS:8
Mandakini Pradhan et.al[4]	2013	prospective	TPOAb、TSH	abortion	20~40	NOS:6
Mathis Grossmann[5]	2013	prospective	TPOAb、Vitamin-D	abortion	28~37	NOS:7
Meena Aruna Nagar Pushpa[6]	2015	observational	TPOAb	abortion、safe delivery	25~35	NOS:8
Roberto Negro et.al[7]	2016	RCT computer-generated concealed randomized	TPOAb、TSH	abortion、premature-baby	29.9±5.1	Jada:6
Rosa Vissenberg et.al[8]	2015	retrospective	TPOAb	abortion	34±4.6	NOS:8
Yang Xiu ping et.al[9]	2016	retrospective	TSH、FT4 and TPOAb	abortion、premature-baby et.al	27.6±3.4	NOS:8
Chen Sheng ping et.al[10]	2016	retrospective	TPOAb、TRAb、TSH et.al	abortion、premature-baby et.al	27.9±6.2	NOS:7

3.2 Analysis of outcome indicators

1) The thyroid function was normal, and the 9 studies included in the positive TPO antibody were pregnant women with normal thyroid function and antibody positive, and the outcome indicators included abortion rate. Heterogeneity test results I2=78%, P=0.0001, with greater

heterogeneity. Meta-analysis using random effects model suggested that there were significant statistical differences between the two groups, indicating that TPO antibody was positive when thyroid function was normal. The risk of miscarriage in pregnant women is significantly greater than that of pregnant women with negative antibodies. The results are shown in Figure 1. This conclusion is consistent with the findings in the included literature. Funnel plot was used to analyze the bias of published articles, and it was found that the included articles were distributed on both sides, indicating that the bias was small and the included literatures were reliable. The analysis results are shown in figure 2.

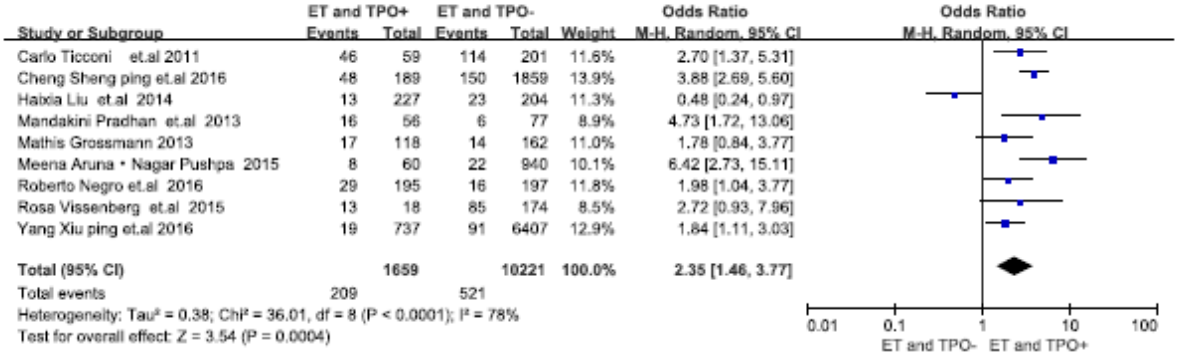

Figure 1 Abortion rate of normal antibody positive for thyroid function

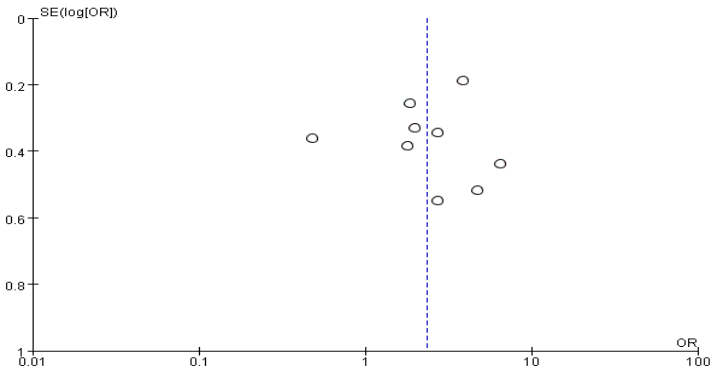

Figure 2 Funnel plot of abortion rate with normal antibody positive for thyroid function

2) TPO antibody positive, levothyroxine intervention in abortion The use of levothyroxine to interfere with TPO antibody-positive pregnant women is relatively rare. This paper also only included two articles, one for retrospective cohort study and the other for randomized controlled trials. The quality of the literature is high and has great reference value. Analyze that because pregnant women are special groups, there is no greater risk of applying any intervention factors in the absence of relative safety considerations, resulting in fewer related studies. The heterogeneity test results were I2=3%, P=0.31, and the heterogeneity was small. The meta-analysis was performed using the fixed effect model. The results showed that there was no statistical difference between the experimental group and the control group. When the TPO antibody was positive, Intervention with levothyroxine did not significantly reduce the risk of miscarriage in pregnant women. The results are shown in Figure 3. Due to the lack of literature, it is not suiTable for the application of funnel plots for bias analysis. At the same time, there are certain inaccuracies in its conclusions because of the less literature. The opinion on whether to treat levothyroxine in pregnancy and postpartum thyroid disease diagnosis and treatment is neither recommended nor opposed. To obtain more accurate conclusions, a lot of research is still needed.

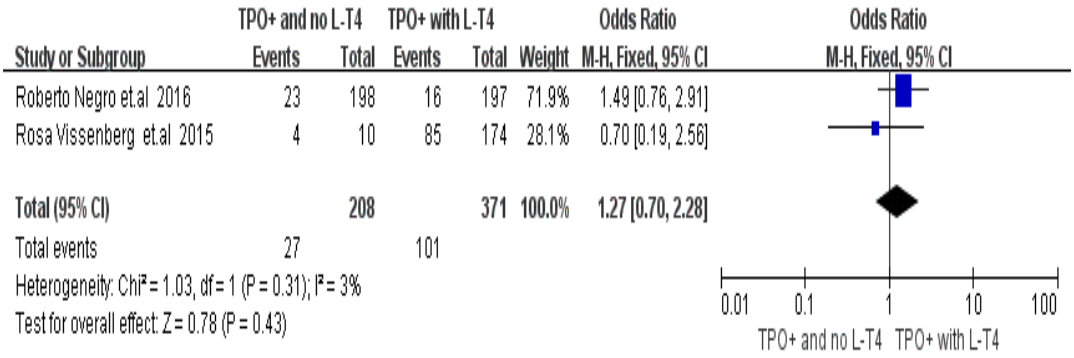

Figure 3 Abortion rate of TPO antibody-positive levothyroxine intervention

4. Discussion

TPO is an important enzyme that catalyzes thyroid hormones. It is synthesized by thyroid follicular cells and involved in the synthesis and release of thyroid hormones. TPO induces the body to produce high-affinity IgG antibodies, TPOAb, involved in thyroid infiltration and destruction. The presence of antibodies may be a sensitive indicator of maternal demand for thyroid hormones during pregnancy and a small deficiency of thyroid hormones. The use of levothyroxine for intervention to reduce abortion is based on this assumption, but this assumption is not supported by existing data. Thyroid antibodies cause abortion in many ways, and are generally recognized as: (1) abnormalities in autoimmunity. The production of antibodies indicates the activation of the immune system, which affects the whole process of pregnancy preparation, pregnancy and birth. The latest study shows that thyroid antibodies can be detected in the follicular environment of pregnant women, which may reduce the quality of oocytes and the fertilization environment. Th1 cell immune responses were observed in multiple miscarriages and in cases of embryo implantation failure. Th cells in antibody-positive women are activated, and Th1 cells secrete excessive interferon and other cytokines, which are associated with the cellular regulation of the immune response, which is thought to be highly correlated with abortion. (2) Damage to the placenta. Thyroid antibodies can also directly damage the placenta, or cause loss of pregnancy by affecting placental hormones such as human chorionic gonadotropin and human chorionic thyroid stimulating hormone.

The study has the following shortcomings: (1) Although the quality of the literature included in this study is high, the total number is only 9 and there are only 2 articles on the intervention of levothyroxine, which limits the reliability of the results to some extent. (2) Retrospective, prospective, and randomized controlled studies were included, and retrospective bias and selective bias were not completely excluded; (3) Non-English and Chinese literature on this study has not been screened and included, which may have an impact on the accuracy of the research results; (4) The outcome of the study is relatively small. On the one hand, it may be the selectivity of the research report. On the other hand, it may also set a relatively strict consistency standard for this study.

In conclusion, the abortion rate of pregnant women with normal thyroid function and antibody positive was significantly higher than that of pregnant women with negative antibody, which was statistically significant. However, as for whether the antibody-positive application of levothyroxine for intervention can reduce the risk of miscarriage, no positive results have been obtained in this study, and more large-scale studies are needed to evaluate the effectiveness of levothyroxine intervention in the future.

References

[1] Simone De Leo, Elizabeth N Pearce. Autoimmune thyroid disease during pregnancy [J]. Lancet Diabetes Endocrinol, 2018, 6 (7):575-586.

[2] Ticconi C, Giuliani E, Veglia M, Pietropolli A, Piccione E, Di Simone N. Thyroid Autoimmunity and Recurrent Miscarriage. Am J Reprod Immunol 2011;66:452-459

[3] Haixia Liu, Zhongyan Shan, Chenyan Li, etc. Maternal Subclinical Hypothyroidism, Thyroid Autoimmunity, and the Risk of Miscarriage: A Prospective Cohort Study [J]. Pregnancy and Fetal Development, 2014, 24(11):1642-1649.

[4] Mandakini Pradhan, Bhavna Anand, Neeta Singh, etc. Thyroid peroxidase antibody in hypothyroidism: It's effect on pregnancy [J]. The Journal of Maternal-Fetal and Neonatal Medicine. 2013, 26(6):581-583.

[5] Grossmann et al. Measuring thyroid peroxidase antibodies on the day nulliparous women present for management of miscarriage: a descriptive cohort study. Reproductive Biology and Endocrinology 2013 11:40

[6] Meena Aruna•Nagar Pushpa. Pregnancy Outcome in Euthyroid Women with Anti-Thyroid Peroxidase Antibodies [J].The Journal of Obstetrics and Gynecology of India, 2016, 66(3):160-165.

[7] Roberto Negro, Alan Schwartz, Alex Stagnaro-Green. Impact of Levothyroxine in Miscarriage and Preterm Delivery Rates in First Trimester Thyroid Antibody- Positive Women With TSH Less Than 2.5 mIU/L[J].J Clin Endocrinol Metab,2016,101(10):3685-3690.

[8] Rosa Vissenberg, Eric Fliers, Joris A. M. van der Post, Madelon van Wely, Peter H. Bisschop & Mariette Goddijn (2015):Live-birth rate in euthyroid women with recurrent miscarriage and thyroid peroxidase antibodies, Gynecological Endocrinology, DOI:10.3109/09513590.2015.1092513

[9] Yang Xiuping, Shu Libo, Xu Hongbo. Effect of thyroid peroxidase antibody positive status on pregnancy outcome in pregnancy [J].Modern Practical Medicine, 2016, 28 (12):1603-1604.

[10] Chen Shengping, Zhang Rui. Study on the relationship between thyroid peroxidase antibody positive and pregnancy events [J]. Chinese General Practice, 2016 (32): 3946-3949.