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META-ANALYSIS

A Meta-Analysis of Differences in Thyroid and Cardiac Function Between Women with Normal Pregnancies and Gestational Diabetes Mellitus

Juan Guo, MM; Yinjian Zhou, MM; Qiongshan Li, MM; Ping Zhang, MD

ABSTRACT

Objective • This is a meta-analysis of thyroid function (TF) and cardiac function (CF) differences between women with normal pregnancies and gestational diabetes mellitus (GDM), in order to provide more reliable reference and guidance for the future clinical prevention and treatment of GDM.

Methods • Studies on the correlation of GDM with TF and CF were searched in PubMed, Cochrane Library, and other literature databases, and the literature for final analysis was confirmed after screening according to the eligibility criteria. Authors, publication time, research subjects, and endpoints were extracted for meta-analysis using Review 5.3 software.

Results • After screening, 10 studies with a total of 2554 subjects were selected, including 1125 GDM patients (GDM group) and 1429 normal pregnant women (control group). All the included papers scored 6-7 points on the Newcastle-Ottawa Scale used for literature quality evaluation, implying high-quality research. In the meta-analysis, the relationship between GDM and TF, TSH, and FT3 increased evidently in the GDM group, while FT4 decreased ($P < .05$). The meta-analysis of GDM and CF revealed lower LVEF and E/A while higher E/E' in GDM patients compared to the controls ($P < .05$). The funnel plot showed that the graphs of all the endpoints were basically symmetrical, indicating low publication bias.

Conclusion • Given the obvious thyroid dysfunction and cardiac dysfunction in GDM patients, symptomatic intervention measures should be taken actively and timely to improve the safety of GDM patients during pregnancy. (*Altern Ther Health Med.* 2024;30(4):66-70)

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INTRODUCTION

Gestational diabetes mellitus (GDM), defined as diabetes with normal glucose metabolism or underlying impaired glucose tolerance before pregnancy, only appears or is diagnosed during pregnancy, which is one of the most common medical complications during pregnancy.[1] The World Health Organization (WHO) reported a GDM incidence of about 1-14% worldwide, and in populous countries like China and India, the incidence can reach more than 5%.[2,3] Unlike simple diabetes mellitus, the glycometabolism of GDM patients mostly returns to normal after delivery.[4] Nevertheless, GDM patients are still at an increased risk of type 2 diabetes mellitus, with some patients hyperglycemic even remaining after childbirth.[5] For mothers, GDM may lead to macrosomia, significantly elevating the risk of dystocia and postpartum massive bleeding, and predisposing patients to various infections.[6] As far as the newborns are concerned, maternal hyperglycemic status may cause neonatal organ hypoplasia, endocrine disorders, and susceptibility to congenital diseases.[7]

On the other hand, thyroid diseases rank second among the endocrine diseases that women of childbearing age are susceptible to after GDM.[8] Thyroid function (TF) during pregnancy is influenced by the body's immune status and endocrine levels, resulting in a vicious circle of interaction between glycometabolism and hypothyroidism.[9] In most cases, GDM or thyroid diseases are treatable, but without proper evaluation and management, they can adversely affect mothers and fetuses, leading to multi-system metabolic abnormalities and even multiple adverse pregnancy outcomes.[10] GDM has also been reported to influence the structural and functional changes of the heart in pregnant women and newborns, and increase the occurrence of cardiovascular risk events.[11] However, at this stage, the clinical concern for GDM patients mainly focuses on glycometabolism, ignoring TF and cardiac function (CF) alterations, which also leads to the awkward situation that the incidence of GDM has been constantly rising while the

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treatment efficiency has not been significantly improved.[12] Therefore, this study will systematically evaluate and meta-analyze TF and CF in GDM patients, aiming at providing a more reliable and comprehensive reference for future clinical interventions to prevent and treat GDM.

MATERIALS AND METHODS

Document retrieval

By searching keywords "Gestational Diabetes" and "Cardiac Function", or "Gestational Diabetes" and "Thyroid Function" in the PubMed (URL: https://pubmed.ncbi.nlm.nih.gov/), Cochrane library (URL: https://www.cochranelibrary.com/), and Web of Science (URL: www.webofscience.com), related studies on TF and CF in GDM were screened. Then, the relevant journals and the references of the included studies were searched manually. After the retrieval, the documents with the same title, author(s), and publication years were checked and de-duplicated by using the document management software. The de-duplicated documents were screened for the first time according to the title and abstract to remove the irrelevant ones, followed by a second screening through reading the full text. In addition, literature types such as reviews, systematic reviews, and case reports were excluded.

Eligibility criteria

Inclusion criteria: (1) published papers whose research years were from 2010 to now; (2) articles with the main research content involving the correlation of GDM with TF and CF; (3) randomized controlled studies or cohort studies; (4) papers with clear and correct standards for the included research subjects; (5) papers with complete original data. Exclusion criteria: (1) duplicate or suspected duplicate articles; (2) documents with possible conflicts of interest among researchers; (3) literature with selective reporting risks; (4) literature with obvious defects or logical errors in the research design.

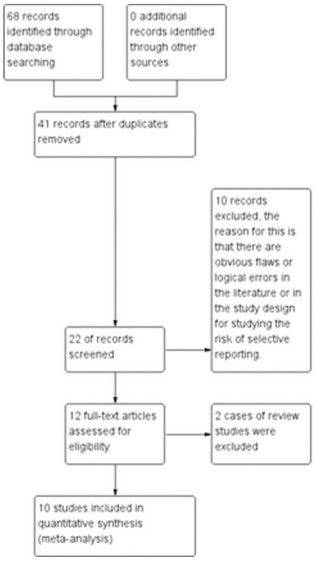
Literature screening

The literature, centrally managed by EndNoteX9, was independently screened by two research members. After removing the duplicate literature, the final judgment was made after reading the title, abstract, and full text. The literature agreed by two research members to meet the requirements was included in the final analysis, and in case of disagreement, a third research member would help to make the final decision. In order to prevent subjective factors from affecting literature evaluation, the information of all authors was blinded during the screening.

Literature quality evaluation

The quality of the included literature was evaluated with reference to the Newcastle-Ottawa Scale (NOS),[13] a document quality evaluation tool, from the domains of adequate with independent validation, representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of controls, compatibility of cohorts on the basis of the design or analysis, ascertainment of exposure, determination of exposure of cases and controls by the same method, and non-response rate. On a scale ranging from 0 to 9 points, a score above 6 points indicated good literature quality, while a score below 5 suggested poor quality, in which case the literature would be excluded.

Figure 1. Flow Chart of Literature Screening



Data Extraction

The author(s), publication years, and basic data (age, gestational age, etc.) of research participant were extracted from the literature, and the endpoints mainly included thyroid function [thyroid stimulating hormone (TSH), free triiodothyronine (FT3) and free thyroxine (FT4)] and cardiac function [left ventricular ejection fraction (LVEF), E/E', and E/A].

Statistical processing

Meta-analysis was performed using Review 5.3 software, and the significance threshold was $P < .05$. The included data were first tested for heterogeneity ($\alpha = 0.1$). When $I^2 < 50\%$, it was considered that there was no heterogeneity among papers, in which case the fixed-effects model would be adopted for analysis. The presence of heterogeneity among documents was indicated by $I^2 > 50\%$; in this case, analysis would be first carried out using a fixed-effects model, and validation analysis using the fixed-effects model would be further performed on indexes with differences. Finally, publication bias was observed by drawing the funnel plot. The publication bias was considered small if the two ends of the plot were basically symmetric; while little or no symmetry suggested large bias and no reference value.

RESULTS

Search results

According to the keyword-based search results, 68 related papers were initially found, 41 of which selected for further evaluation, after checking and de-duplication by EndNote. After reading the full text and screening according to the eligibility criteria, 10 papers were finally included for this meta-analysis.[14-23] See Figure 1 for literature screening process.

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Table 1. NOS Scores of Literature Used

Author	Domains of adequate with independent validation	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of controls	Compatibility of cohorts on the basis of the design or analysis	Ascertainment of exposure	Determination of exposure of cases and controls by the same method	Non-response rate	Total Score
Demiral Sezer S 2022	1	1	1	1	1	1	1	0	7
Raets L 2022	1	1	0	1	1	1	1	0	6
Rawal S 2018	1	1	0	1	1	1	1	0	6
Xu C 2018	1	1	0	1	1	1	1	1	7
Yanachkova V 2021	1	1	0	1	1	1	1	1	7
Aguilera J 2020	1	1	0	1	1	1	1	0	6
Calabuig AM 2021	1	1	0	1	1	1	1	1	7
Meera SJ 2017	1	1	0	1	1	1	1	0	6
Sonaglioni A 2022	1	1	0	1	1	1	1	1	7
Winhofer Y 2014	1	1	0	1	1	1	1	0	6

Evaluation of literature quality

The NOS scores of the included studies were all 6-7 points, indicating that they were high-quality studies with high reference value and therefore suitable for meta-analysis. See Table 1 for detailed scoring results.

Basic information about the literature

A total of 2554 subjects were studied in all these papers, among which 1125 GDM patients were considered as GDM group, and the rest 1429 normal pregnancies were considered as the control group. Detailed information of all subjects is shown in Table 2. Five of the articles observed differences in TF between GDM patients and normal pregnant women and 5 observed differences in CF.

Meta-analysis

Correlation of GDM with TSH. By testing the heterogeneity among the five articles reporting the comparison of TSH, it was found that the I^2 value was not less than 50%, implying heterogeneity among the papers. The analysis results using the random-effects model revealed a 0.28 elevation in TSH in GMD patients compared to controls, with statistical significance ($P < .05$). Further, when the analysis model was replaced with a fixed-effects model, it also showed higher TSH levels in GDM group ($P < .05$), confirming the accuracy of the above results (Figure 2).

Correlation of GDM with FT3. Analysis of the results showed that FT3 was higher in the GDM group than in the control group ($P < .05$). After validation of the fixed-effect model, the same showed that FT3 was higher in the GDM group than in the control group ($P < .05$) (Figure 3).

Correlation of GDM with FT4. The analysis results using the random-effects model revealed 0.24 decrease in FT4 in GMD patients compared to controls, with statistical significance ($P < .05$). Further, the analysis model was replaced with a fixed-effects model, which also showed lower FT4 levels in GDM group ($P < .05$), confirming the accuracy of the above results (Figure 4).

Correlation of GDM with LVEF. Similarly, five studies on cardiac function were first analyzed for heterogeneity among the literature ($I^2 \geq 50\%$), using a random effects model. After analysis, it was seen that LVEF was lower in the GDM group compared to the control group, by approximately 2.70 ($P < .05$). The results of the fixed-effects model validation analysis were also consistent with the results above ($P < .05$) (Figure 5)

Table 2. Evaluation of Literature Quality

Authors	Main study content	Pregnant women with GDM (GDM group)	Normal pregnant women (control group)
Demiral Sezer S 2022	thyroid function	78	82
Raets L 2022	thyroid function	199	398
Rawal S 2018	thyroid function	107	214
Xu C 2018	thyroid function	50	50
Yanachkova V 2021	thyroid function	412	250
Aguilera J 2020	cardiac function	73	73
Calabuig AM 2021	cardiac function	123	246
Meera SJ 2017	cardiac function	18	72
Sonaglioni A 2022	cardiac function	30	30
Winhofer Y 2014	cardiac function	35	14

Abbreviations: GDM, Gestational diabetes mellitus.

Figure 2. Correlation of GDM with TSH

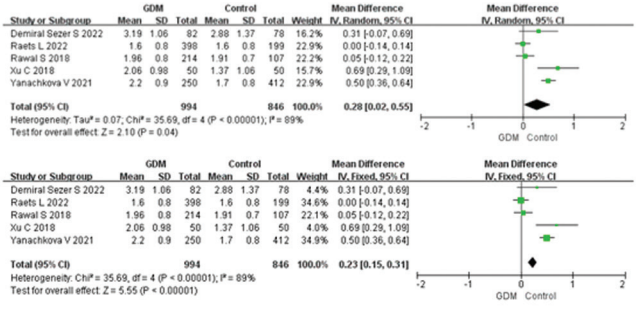

Figure 3. Correlation of GDM with FT3

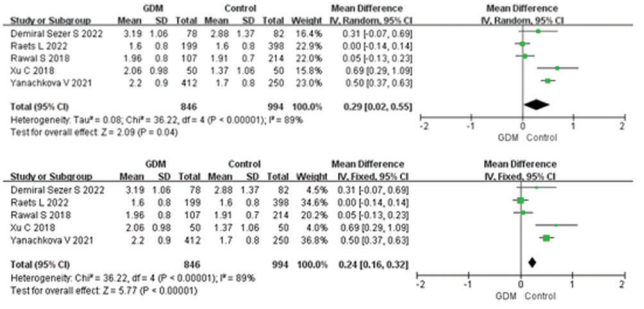

Figure 4. Correlation of GDM with FT4

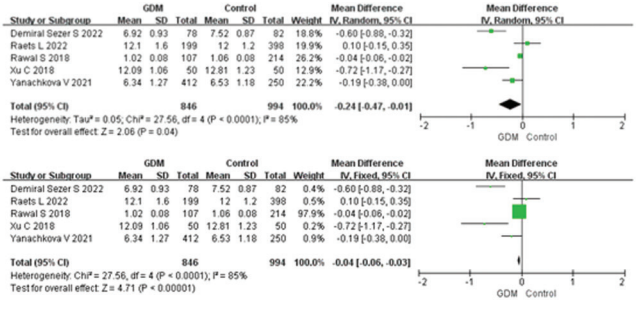

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Figure 5. Correlation of GDM with LVEF

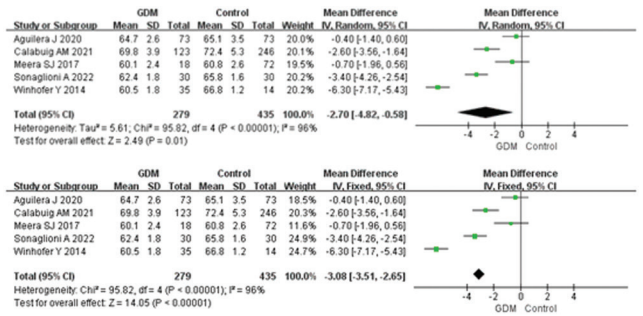


Figure 6. Correlation of GDM with E/A

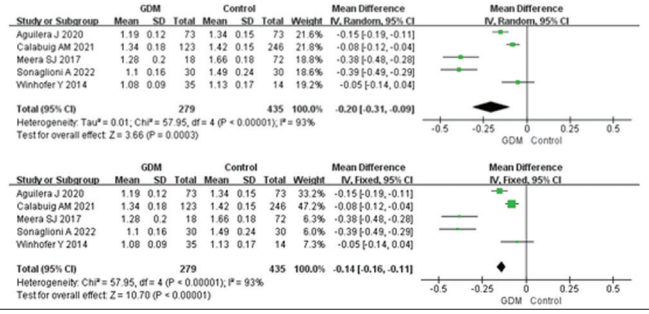


Figure 7. Correlation of GDM with E/E'

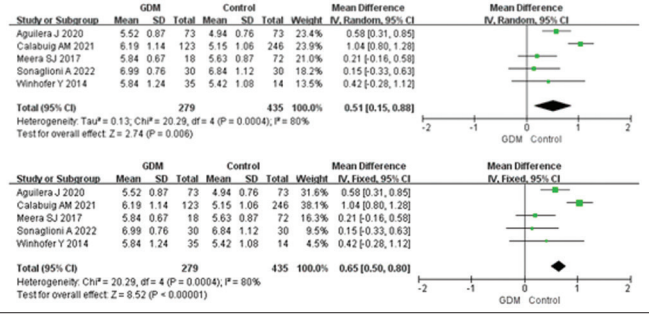
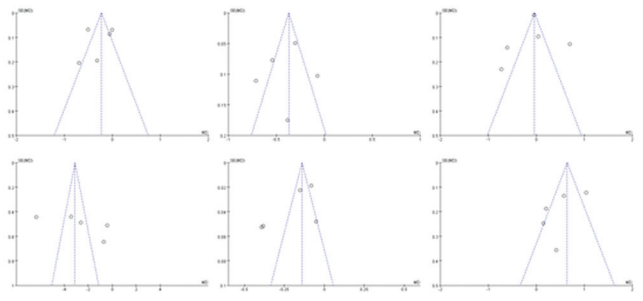


Figure 8. Publication Bias (The First Row from Left to Right is TSH, FT3, and FT4, the Second Row from Left to Right is LVEF, E/A, and E/E')



Correlation of GDM with E/A. The results of the random-effects model analysis showed that E/A was lower in the GDM group compared to the control group, by approximately 0.20 ($P < .05$). The results of the validation of the fixed-effects model analysis also showed lower E/A in the GDM group ($P < .05$) (Figure 6).

Correlation of GDM with E/E'. The analysis showed that E/E' was higher in the GDM group by approximately 0.51 compared to the control group ($P < .05$). The results of the fixed-effects model analysis also showed that E/E' was higher in the GDM group than in the control group ($P < .05$), verifying the results of the above analysis (Figure 7).

Publication bias

Funnel plots of all endpoints were drawn, and it can be seen that both sides of the funnel plots were basically symmetric, which indicates that the literature included in this analysis has low publication bias and high reference value (Figure 8).

DISCUSSION

The WHO defines GDM as any degree of glucose intolerance during pregnancy. For pregnant women, GDM may cause convulsions, premature delivery and stillbirth, in addition to increasing the possibility of reproductive system infections.[24,25] Statistics show that preterm birth occurs in approximately 10% of patients diagnosed with GDM and puerperal infection in more than 20%.[26] In the long run, GDM not only adversely influences pregnancy, but also increases prognostic metabolic syndrome and cardiovascular diseases in patients that may eventually evolve into lifelong type 2 diabetes, thus requiring lifelong maintenance treatment.[27,28] For newborns, GDM may increase the likelihood of developing congenital diseases, cause developmental deformities, and reduce the quality of life of newborns.[29] Currently, the pathogenesis of GDM has not been fully defined, and an in-depth understanding and summary of the pathological characteristics of GDM will be of great significance for future clinical development of prevention and treatment strategies for GDM. At the present stage, there is still much clinical controversy about the correlation of GDM with TF and CF. By screening the related literature in recent years and conducting a meta-analysis, the current relationship between GDM and TF and CF can be preliminarily summarized, so as to lay a reliable foundation for subsequent studies.

We finally selected 10 articles for analysis after screening based on the eligibility criteria. There were 2554 subjects participating in these studies, including 1125 GDM patients. Through meta-analysis, we found markedly elevated TSH while reduced FT3 and FT4 in GDM patients versus normal pregnant women, confirming obvious alterations in TF in GDM patients. Many scholars have conducted studies on the correlation between GDM and thyroid dysfunction, pointing out that the association between the two is very likely to be caused by insulin resistance in the body, which leads to abnormal glycometabolism, and thus adverse effects.[30] Giannakou et al. also proposed a link between GDM and the occurrence of hyperthyroidism from two perspectives. On the one hand, hyperthyroidism not only affects insulin sensitivity, but also accelerates insulin degradation, which directly interrupts the normal operation of the islet function in pregnant women. On the other hand, GDM influences normal TF through autoimmune abnormalities and glucose toxicity of the thyroid, thereby further increasing the risk of hyperthyroidism or hypothyroidism.[31] Therefore, the

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interaction between GDM and TF mainly lies in the fact that TF further affects the normal endocrine function of pregnant women by regulating hormone secretion, which promotes the occurrence of GDM. Meanwhile, TF affects normal fat metabolism, which in turn influences glucose-lipid metabolism, thus accelerating the development of GDM.[32]

In terms of CF, we observed lower LVEF and E/A while higher E/E' in GDM patients compared to controls, which also suggests that GDM causes cardiac dysfunction. We believe that this may be related to the fact that GDM enhances the sensitivity of the heart to oxidative stress and affects vascular contraction, causing dysfunction of intracellular mitochondria and DNA, promoting the generation of hydroxyl, carboxyl, hydrogen peroxide, and other oxygen free radicals and aggravate myocardial cell damage, thereby inducing cardiac dysfunction.[33] Based on the above results, we can further speculate that the influence of GDM on CF may also be related to GDM-induced TF changes, which aggravates abnormal blood lipid metabolism or triggers inflammatory reactions, thus affecting myocardial contraction and heart rate. Previous studies have also shown that patients with GDM combined with hypothyroidism have a significantly increased risk of cardiovascular adverse events,[34] which can also preliminarily support our view.

Glycolipid metabolism has been repeatedly mentioned as one of the key indicators in the exploration of the correlation of GDM with TF and CF. A number of studies have also fully demonstrated that the primary pathogenic mechanism of GDM is through the modulation of glycolipid metabolism.[35] But due to the limited information reported in the included literature, patients' glycolipid metabolism was not discussed in this analysis, which requires further research and analysis. Besides, we should further explore the association between TF and CF in GDM patients, as well as the relationship among the three. Finally, regional differences in iodine intake due to different sources of the literature samples included in this study, as well as variations in test results caused by the difference in testing instruments and kits for TF, all contribute to the heterogeneity to a large extent. So, in addition to expanding the included literature for a more comprehensive analysis, we should also conduct clinical trials to analyze the relationship between GDM and TF and CF, so as to provide more reliable reference for subsequent research.

CONCLUSION

There is significant thyroid dysfunction and cardiac dysfunction in GDM patients, and these three clinical conditions interact with each other, further increasing the risk of adverse events during pregnancy. In future clinical practice, it is necessary to closely monitor TF and CF changes in GDM patients, to improve their pregnancy safety.

AUTHOR DISCLOSURE STATEMENT

The authors report no conflict of interest.

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