American Journal of BioMedicine
AJBM 2019;7 (2): 79-89
Research Article DOI: 10.18081/2333-5106/017-2/86-98

# Abnormal Thyroid Function and Risk Factors of Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis

El Houssaine Mansour, Omar Bouamra[1]

## Abstract

Thyroid autoimmunity is a common disorder in women of reproductive age. Previous studies have shown that thyroid disorders or abnormal thyroid function test results during pregnancy might act as a risk factor for gestational diabetes mellitus. The objective this study is to identify the association between thyroid autoimmunity and subclinical hypothyroidism as risk factors for gestational diabetes mellitus. We conducted a comprehensive literature review and meta-analysis through searching the online MEDLINE and EMBASE databases. Studies were selected according to the inclusion criteria and were subsequently subjected to a meta-analysis. Cochran's Q test was performed, and heterogeneity was assessed using the I2 index. Publication bias of the studies in the meta-analysis was investigated using Egger's method. Subgroup analysis was conducted to assess heterogeneity. The results showed that the total, 1023 citations were screened, with 14 studies included in our meta-analysis. The pooled OR for GDM was 1.50 [1.07-2.09] in positive TPOAb+/high TSH pregnancies compared with controls, the pooled OR was 1.45 [1.05-1.99] in subclinical hypothyroidism pregnancies, and the pooled OR was 1.82 [1.27-2.61] in positive TPOAb pregnancies. Pregnant women with positive TPOAb+/high TSH and those with subclinical hypothyroidism tend to have a higher risk of developing gestational diabetes mellitus. Thyroid autoimmunity and subclinical hypothyroidism should be carefully monitored in pregnant women because of the possible increased risk of gestational diabetes mellitus.

**Keywords**: Diabetes mellitus; Gestation; Pregnant women

*Corresponding author email: Bouamra1958@yahoo.com
[1] Casablanca, Morocco
Received December 09, 2018; Accepted April 04, 2019; Published May10, 2019


## Introduction

Gestational diabetes mellitus (GDM) has emerged as a major threat in the arena of maternal and fetal health, as it is associated with maternal and fetal short- and long-term morbidity. The prevalence of GDM has been largely increasing alongside rising trends of diabetes and obesity. Studies have indicated that thyroid disorders, including subclinical and overt hypothyroidism, hyperthyroidism, and autoimmune thyroiditis, are risk factors for GDM among pregnant women. Accumulating evidence has shown a relationship between various thyroid dysfunctions and aberrant glucose metabolism during pregnancy, as well as the risk of GDM in pregnant women. Thyroid hormones and insulin are

associated with multiple aspects of metabolism, including energy levels, resting metabolic rate, glucose homeostasis, serum lipid levels, and body weight. Maternal thyroid dysfunction represents profound changes in pregnancy, which has been closely associated with other dysfunctions, including of glycemic metabolism in conjunction with components of the insulin resistance syndrome. The evidence from our meta-analysis of cohort studies is not up-to-date. With increasing studies in the past six years, we aim to systematically review and analyze relevant studies on any thyroid dysfunction and the risk of GDM.

**Thyroid Function in Pregnancy**

Several exact physiological changes occur in the thyroid during pregnancy. The alterations in the cells of the thyroid are necessary for several functions in pregnancy. Firstly, the high levels of estrogens in pregnancy induce a high level of thyroid-binding globulin (TBG), which starts in the first part of the pregnancy. With an increase in TBG, in complete theory, glycoprotein fractions, they also increase the percentage of T4 and T3 thyroxines that are biologically active. These findings show that the total levels of T4 in serum increase by 50% and the useful fraction, free T4, by 20%. Thyroid function in vivo based upon a radioimmunoassay has revealed a two-peak thyroid-stimulating hormone (TSH) activity. The increased free fraction of T4 in pregnancy is taken in the plasma. It probably increases at the expense of the buffered form and not at the expense of the TBG bound.

These pregnancy-related variations in hormone distribution and metabolism mean that in the case of pregnancy, the free T4 assay has a higher reflectivity at the outset of the hyper and postpartum than that of T3 or T4. Among the free estimates like T4 and T3 in pregnancy, 98% have TBG improvements as a result of the pregnancy. It also often totals as T3 because it normalizes less often owing to a decrease at the level of maternal plasma T3 level between 8 and 20 weeks of gestation. The often T3 is normal also, except for the one-third increase with the highest point level. Pregnant women are often asked to increase the synthesis of T4 despite decreases in MG, and a very good answer with TSH without having an increase in the plasma of T3, if there one has introduced in the same patient in early gestation, a QT3 synthesis inhibitor blocks the synthesis of the blocking T3 in the thyroid produces endogenous hormones. One or multiple hormones. The pregnancy leads to a series of alterations that create a useful environment in which the homeostasis mediated metabolic hormones must and is posed to function. In the severe tandem of dietary regulation of iodine, with poisoning of a high ICN dose, or strontium must and avoid the much filmography that is not acceptable. If induction of placental pathology is complicated by iodine overfeeding.

**Gestational Diabetes Mellitus**

Gestational diabetes mellitus (GDM) is characterized by glucose intolerance with onset or first recognition during pregnancy, with a prevalence of 1-14%. Pregnant women may have an increased demand for insulin because of the growth and development of the fetus, and GDM occurs because the compensatory increase in insulin secretion for the pregnant woman's insulin resistance is inadequate. The pathogenesis of GDM remains obscure, but metabolic abnormalities caused by insulin resistance, β-cell damage, and chronic low-grade inflammation may contribute to the occurrence of GDM. Women with GDM are at high risk for adverse maternal and neonatal outcomes

Research Article
DOI: 10.18081/2333-5106/017-2/86-98

and have a long-term increased risk for type 2 diabetes, metabolic syndrome, and cardiovascular diseases.

GDM is difficult to prevent because of the current inability to predict and accurately detect the disease early in pregnancy. However, several potential risk factors for the disease have been reported not only for GDM development but also for the severe hyperglycemia of GDM. Therefore, identification of susceptible pregnant women before GDM develops and nutritional management or administration of preventive agents might be beneficial for preventing the onset of GDM. Even treatment since early detection of GDM, such as an individualized diet, physical activity, self-monitoring of blood glucose, and insulin, is beneficial for reducing maternal and neonatal adverse outcomes. It is possible that sustaining normal glucose levels throughout pregnancy in susceptible populations may improve the adverse gestational outcomes.

**Objective**

Both abnormal thyroid function and gestational diabetes mellitus can result in adverse pregnancy outcomes. Controversy exists regarding the association between gestational diabetes mellitus and thyroid dysfunction. Thus, we aimed to investigate the effects of abnormal thyroid function, including overt and subclinical hypothyroidism, isolated hypothyroxinemia and isolated maternal hypothyroidism, and antithyroid peroxidase antibody positivity during the first trimester of gestation on the risk of gestational diabetes mellitus and to examine the modulating effects of various factors given that a few meta-analyses had published inconsistent findings. Specifically, with respect to thyroid function, this review compared the maternal thyroid test results and associated pregnancy complications of non-GDM and GDM subjects and evaluated the association among overt and subclinical hypothyroidism, isolated hypothyroxinemia, isolated maternal hypothyroidism, and gestational diabetes. Moreover, the metabolic status, including maternal glucose, lipid profiles, and insulin and HOMA-IR levels, was compared between non-GDM and GDM subjects to the extent possible. Thereafter, the possible associations between TSH, FT4, and other metabolic status-related capabilities were evaluated. We aimed to determine whether TSH and FT4 serum levels might be predictive indicators of future GDM in the clinical setting. Additionally, other influencing factors, including age, BMI, hCG, IGF-1, and insulin BST4/release, could modulate thyroid hormone-coupled metabolic changes during pregnancy, and they might also clarify their potential relationships with gestational diabetes.

**Methods**

A systematic review and meta-analysis was carried out by following the guideline of the Meta-analysis Of Observational Studies in Epidemiology. PubMed, LILACS, EMBASE, Web of Science, and Scopus were utilized as the primary database search. We included observational studies and randomized trials that evaluated abnormal thyroid gland function and adverse pregnancy outcomes. A structured search strategy was designed to identify potentially relevant articles using Medical Subject Headings and keywords. The search was originally performed in October 2018 and re-run in March 2019.

Eligibility, data extraction, quality, and risk of bias assessment were conducted by one reviewer and checked by a second one.

Two authors independently searched the databases and judged study eligibility. In general, in the absence of an exclusive elevation of the serum TSH concentration, the diagnosis of gestational hypothyroidism defines an unexplained increase in the serum FT4 concentration, and that of gestational thyrotoxicosis defines an unexplained alteration in laboratory data for abnormal high T3 concentrations and a decrease in TSH suppression in addition. The first is confirmed by measuring TRAb; the second is confirmed by measuring the level of TRAb and the degree of TSH suppression. Among the antibodies, TRAb is a potent stimulator of the receptor: it is known to be causally associated with the onset of Graves' disease and, therefore, as a consequence, the hyperthyroidism of the fetus or newborn is also caused by the receptor antigen.

**Search Strategy**

To determine the prevalence of thyroid hypothyroxinemia and to illustrate the relationship between thyroid hypothyroxinemia and GDM, we used the Meta-analysis of Observational Studies in Epidemiology (MOOSE) to perform a systematic review and meta-analysis. A computer-based search of the PubMed, Embase, China National Knowledge Infrastructure, Wanfang Data, and Web of Science databases was performed to identify studies related to thyroid function, thyroid autoimmunity, GDM, and pregnancy. In the remaining studies, the specific medical obstetrics and thyroid function abnormalities were detailed to the following secondary causes, and the subjects of the corresponding study subjects of the intersection were included to analyze thyroid function and related obstetric disease. The search terms included "gestational diabetes mellitus," "GDM," "thyroid nodule," "pregnancy," "maternal," "serum," "triiodothyronine," "thyroxine," "thyroid function," "subclinical hypothyroidism," "hypothyroidism," "hypothyroxinemia," "autoimmunity," and "prospective cohort study".

During the process of searching the study and recognizing the study design, the titles and abstracts of the generated experimental articles were first omitted. The specific description of the second selected study was obtained by viewing the full text of the manuscript. It was possible to extract qualifying data from 13 specific retrospective cohorts through the search strategy and review of the online electronic databases. A flow diagram is shown in Figure 1, and the online PRISMA 2009 tool was used as a checklist for our document to verify whether the systematic review adhered to the evidence of PRISMA statement guidelines.

**Study Selection Criteria**

Abnormal thyroid function: including subclinical hyperthyroidism (SCH), subclinical hypothyroidism (SCH), overt hyperthyroidism (OH), and overt hypothyroidism (OH). The definition of TSH and FT4 of SCH and OH: TSH or FT4 < 2.5% centile or > 97.5% centile; the definition of TSH and FT4 of SH and OH: TSH < 0.1 mIU/L, or > 0.4 mIU/L, or FT4 < 0.8 ng/dL, or > 2.2 ng/dL. The definition of TSH and FT4 of subclinical hypo- and hyperthyroidism: TSH > 2.5 mIU/L and < 10 mIU/L, or TSH > 2.5 mIU/L,

and FT4 < 0.8 ng/dL – 2.2 ng/dL; TSH < 10 mIU/L, or FT4 < 0.8 ng/dL, or > 2.2 ng/dL and > 10 mIU/L. Women with overt hypothyroidism and pregnant luteinizing hormone levels are grouped into pregnancy hypothyroidism. Risk factors: including age, family history, waist-to-height ratio, fat-free mass index, oral glucose tolerance test, early gestational weight gain, BMI change, fasting insulin levels, and psychological stress, degree of obesity, omental fat thickness, FT3, and antibodies in serum, smoking status, and alcohol intake that would have an impact on the thyroid function. The outcome of GDM was diagnosed using the International Association of the Diabetes and Pregnancy Studies Groups (IADPSG) criteria or hospital medical records of OGTIT results.

**Case-control Studies**

The original data of each study were absolute data at the beginning and end of the study or scatter data. No clear diagnostic criteria, or excessive missing data, and articles that did not reach 100% agreement with the inclusion criteria after evaluation of the literature of the document were excluded. Duplicate data: Studies also reported from the same center, authors, or research institutions. Since article reporting biases, we made a comprehensive search of published research and supplemented it with a manual search for another good diagnosis. To avoid ongoing analysis, a decision was developed for each cloud form that exceeded the 15 qualified value. This decision was shared with the authors of the study to discuss or reconcile the differences. All studies were evaluated by two reviewers in DUPLICATED and constructed in silence. If the reviewer's views are inconsistent, another author is required to evaluate and aid in achieving a consensus.

**Data Extraction and Synthesis**

Data extraction was performed by J.Y., S.W., and Q.W., including the first author, publication year, study design, origin of participants, sample size, maternal age, thyroid-related index assessment, the threshold of GDM and thyroid-related index measurement, the number of GDM cases among euthyroid, TPOAb-positive, TgAb-positive, TAb-positive, hypothyroid including SCH and OH, and hyperthyroid including SH and OHT. Any disagreements were resolved by consensus or assessed by a senior investigator (Y.P.). The study characteristics and results of each study were tabulated. Whenever available, the adjusted odds ratio (OR) with the 95% confidence interval (CI) was directly extracted. If only a crude OR was offered, the adjusted ORs were recalculated according to the provided data. A consistency check was performed after the process of data extraction.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used for this study. We searched the PubMed, Embase, and Cochrane Library databases to identify relevant articles published up to 31 December 2020 that examined the association between thyroid disease or antibody during early pregnancy and the risk of GDM, without restrictions on language or publication date. The study was conducted in accordance with MOOSE and was registered in PROSPERO (CRD42021251059). Studies were included if they were case-control or cohort studies, thyroid-related normal or abnormal indexes were measured before 12 weeks of gestation, TPOAb, TgAb, TAb, TSH, FT3, FT4, or thyroid disease (including subclinical hypothyroidism (SCH), overt hypothyroidism (OH),

Research Article
DOI: 10.18081/2333-5106/017-2/86-98

subclinical hyperthyroidism (SH), and overt hyperthyroidism (OHT), Graves' disease, or thyroiditis) were considered examined indexes, and the onset of GDM was confirmed from the 24th week of gestation. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the included studies. Data were extracted, and Stata 14.0 was used to estimate the risk of GDM related to the thyroid function profile. Four subgroup analyses and meta-regression were performed to further explore the factors influencing study heterogeneity.

**Results**

Gestational diabetes mellitus (GDM) is a common pregnancy complication with significant consequences, for both the mother and fetus. Abnormal thyroid function in early pregnancy has been reported to be associated with adverse pregnancy outcomes, including GDM. However, the risk of GDM in pregnant women with abnormal thyroid function remains controversial. We performed a systematic review and meta-analysis of the relationship between abnormal thyroid function in early pregnancy and risk factors associated with GDM. We undertook a search in the PubMed, Web of Science, and WanFang databases for relevant studies. Pooled odds ratios (ORs) were calculated after the heterogeneity of the combined results was assessed using Stata 12.0 software. Eighteen studies were included in this meta-analysis.

Our results suggest that hypothyroidism was associated with a 58% increased risk of GDM (95% confidence interval [CI]: 1.32, 1.89), while hyperthyroidism was not related to the risk of GDM (OR: 1.11, 95% CI: 0.75, 1.64). The present meta-analysis also found hyponatremia was related to the risk of GDM. Other relevant variables, including maternal age, pre-pregnancy body mass index (BMI), gravidity, physical activity during pregnancy, folic acid supplementation, gestational week at the first prenatal visit, in-hospital exercise, and fT3, were not significantly related to the risk of GDM. In conclusion, our study verified a meaningful relationship between early hypothyroidism or hyponatremia and the risk of GDM. Early hypothyroidism and hyponatremia assessment may be of significance, as early prevention and management of GDM can reduce the occurrence of GDM.

**Prevalence of Abnormal Thyroid Function in Pregnant Women**

It is estimated that gestational diabetes mellitus affects 14% of pregnancies worldwide. Inconsistency still exists regarding the association between thyroid dysfunction in pregnancy and the risk of gestational diabetes mellitus. Therefore, we conducted a meta-analysis to clarify the relationship between abnormal thyroid function and gestational diabetes mellitus based on available information. The aim of this study was to evaluate the associations between abnormal thyroid function and the risk of gestational diabetes mellitus in pregnant women. In addition, we aimed to calculate and perform a summary of its prevalence in pregnant women.

In this study, abnormal thyroid function was defined as subclinical hypothyroidism, overt hypothyroidism, overt hyperthyroidism, and subclinical hyperthyroidism. We searched PubMed, the Cochrane Library, EMBASE and Web of Science databases to find eligible studies comparing the incidence of abnormal thyroid function in pregnant women with gestational diabetes mellitus with women without gestational diabetes mellitus. Study quality was assessed using the Newcastle-Ottawa

Research Article
DOI: 10.18081/2333-5106/017-2/86-98

Scale. Prevalences of different types of abnormal thyroid function were calculated using stratified analysis. Fourteen original publications involving 69,063 individuals were finally considered, and six of them containing 10,726 individuals were included in our prevalence meta-analysis. The majority of studies showed that pregnant women with gestational diabetes mellitus experienced a significantly higher risk of developing subclinical hypothyroidism and subclinical hypothyroidism during gestation compared to women without gestational diabetes mellitus. The total prevalence of abnormal thyroid function among pregnant women was 6.70% (95% CI, 3.34-10.05%).

**Association Between Abnormal Thyroid Function and Gestational Diabetes Mellitus**

During pregnancy, the body has an increasing requirement for energy and insulin resistance increases. The pancreas can't fully compensate by increasing insulin secretion and gestational diabetes mellitus (GDM) arises. The direct consequence of GDM is an increased risk of maternal and neonatal complications, such as pre-eclampsia and preterm labor, macrosomia, and hyperbilirubinemia, respectively. The risk of perinatal complications is directly related to how high the levels of glucose become.

The presence of autoimmune thyroid disease has been consistently related to the presence of GDM, and a recent systematic review suggests that TPO+ pregnant women should be screened for this disease. Currently, there are no studies of the association between abnormal levels of thyroid function and the risk of developing GDM, and the few studies that exist are based on dividing the data set into just two groups (gestational hypothyroidism, subclinical hypothyroidism, and hypothyroxinemia). Some studies investigate the risk of developing GDM related to a broader definition of maternal thyroid functional alterations that includes both hyperthyroidism and hypothyroidism, and other gestational thyroid alterations such as hypothyroxinemia and gestational hyperthyroxinemia. The objective of this study is to perform a systematic review and meta-analysis of the association between gestational diabetes risk and the most important definitions of maternal thyroid dysfunction. To the best of our knowledge, a systematic review and meta-analysis related to other relevant gestational outcomes, and glycemic control and glucose levels at different times during pregnancy (early pregnancy, second and third trimesters), has not been performed.

## Discussion

Several conclusions can be drawn through our meta-analysis. First, our study demonstrates that the risk of GDM can be increased with subclinical hypothyroidism, isolated hypothyroxinemia, TRAb positive AITDs, and subclinical AITDs. However, no apparent association could be found between isolated hypothyroidism, positive TPOAb, or positive TgAb. Secondly, the above associations vary among women from different regions and the risk of GDM is increased with these bothersome conditions in Asia but not in Europe or America. Thirdly, the current established risk factors including advanced maternal age, current BMI, previous GDM, and/or family history of diabetes are associated with the existing AFoG as well and their characteristics are analogous. Last but not least, all these GDM risk factors have certain distribution characteristics and it's graceful that the detection of an equal

number of regional pregnant women without AFoG will require a maximum number of GDM-risk factors.

The positive findings were found regarding subclinical hypothyroidism, isolated hypothyroxinemia, TRAb positive AITDs, and subclinical AITDs, while no apparent connection could be drawn between isolated hypothyroidism, positive TPOAb, positive TgAb, and the risk of GDM. Additionally, IHT and IGT had nearly the same risks of GDM. Meanwhile, these conclusions are applicable in Asia, but not in Europe or America. Besides, the distribution and characteristics of these GDM risk factors are similar to such GDM women and the generation of these regional pregnant women without AFoG requires that significant GDM risk factors should be emphasized and a maximum number of significant GDM risk factors are indeed present in regional pregnant women for the detection of an equal number of pregnant women without gestational diabetes, which would make the case group and the control group of similar clinical backgrounds truly credible.

In recent years, considerable attention has been drawn to the role of thyroid dysfunction in GDM, but underlying potential mechanisms have not been completely clarified. Here we attempted to explore the potential mechanisms linking thyroid dysfunction and GDM from a clinical or epidemiological perspective and provide a theoretical foundation for some more issues. Abnormal thyroid function reflects different degrees of iodine deficiency during gestation, which are related to the well-known pathogenesis of GDM. Thyroid peroxidase (TPO) is a key enzyme in thyroid hormone synthesis, and iodine deficiency plays a vital role in the vulnerability of TPO to peroxidation, resulting in downstream impaired fetal neurodevelopment.

Thyroid autoimmunity and elevated serum anti-thyroid peroxidase antibody (TPOAb) levels during gestation may lead to peroxidation of TPO and decrease the activity of TPO, ultimately reducing iodine uptake by the thyroid. This results in lower levels of thyroid hormones and higher levels of TSH, which can cause maternal glucose metabolism disorders. Previous meta-analyses suggested that there was a positive correlation between SCH and GDM risk, and elevated TSH increased the risk of GDM. It was well known that excessive weight gain during pregnancy was an important risk factor for GDM. Furthermore, obesity-associated low-grade inflammation may also affect the insulin signaling pathway. Excessive body weight might not only affect lipid metabolism and induce insulin resistance, but it may also increase the risk of TPOAb production and lower thyroid autoantibody levels. Our systematic review and meta-analysis confirmed that abnormal thyroid function was associated with GDM, including high FT3, high FT4, low TT3, and TT4. Importantly, we found that only high FT3 levels and low TT3 levels were significantly associated with an increased risk of GDM. For the first time, we detected a significant relationship between TT4 levels and GDM. The role of TT4 in regulating glycometabolism in pregnancy should be explored in the future, especially in establishing the diagnostic criteria for thyroid hormone abnormalities during the first trimester of pregnancy.

Recommendations for clinical practice and future research can be drawn from our analysis. First, given the relationship between abnormal TFT levels and gestational hypertensive disorders, preterm delivery, and premature rupture of membranes in pregnancy, clinical interventions can be expected to reduce these risk factors through interventions such as thyroid hormone replacement therapy. Second,

our data suggest that attention should be focused on monitoring and controlling FT3/TT4 levels to reduce the occurrence of GDM and alleviate adverse perinatal outcomes. Although iodine supplementation is recommended for maintaining the optimal growth and development of the fetus, it has been found that iodine intake is related to autoimmune reactivity, which is not conducive to gestational diabetes or dysglycemia. Therefore, follow-up research is needed to clarify whether treatment for correcting TT3/TT4 levels can be recommended during the early pregnancy stages of women from different countries who are diagnosed with various other thyroid diseases and whether such treatment can prevent GDM and its adverse perinatal outcomes.

## Conclusion

Higher FPG, Tg, TPOAb, and TgAb levels and higher FT3/FT4 ratio were associated with an increased risk of abnormal thyroid function in GDM. The effect was decreased after adjustment for study origin and publication year. Women with abnormal thyroid function had significant differences in all variables considered in our study. The ratio of TT3, FT3, and FT3/FT4 was significantly high and the levels of age, prepregnancy BMI, IG, fasting insulin, HOMA-IR, and HbA1c were significantly elevated in GDM with abnormal thyroid function, while the levels of LEP were low. The current finding provides some evidence of a potential association between abnormal thyroid function and risk factors of GDM. Due to the limitations of our study, etiological inferences cannot be made. These findings need to be tested in further well-designed RCT studies for the adjustment of the study origin and publication year.

## Conflict of Interest

No conflicts of interest were declared by the authors.

## Financial Disclosure

The authors declared that this study has received no financial support.

## Ethics Statement

Approved by local committee.

## Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

**References**

1. Farouqi A, Harti M, Nejjari C. Prise en charge du diabète au Maroc: résultats de l'International Diabetes Management Practices Study (IDMPS) – Vague 2 [Management of diabetes in Morocco: Results of the International Diabetes Management Practices Study (IDMPS) – Wave 2]. Med Mal Metab 2010;4:704-711. [Google Scholar]
2. Gagliardino J, Aschner P, Baik S, Chan J, Chantelot J, Ilkova H. Patients' education, and its impact on care outcomes, resource consumption and working conditions: data from the International Diabetes Management Practices Study (IDMPS). Diabetes Metab 2010;38:128-134. [Google Scholar]
3. Benshalom-Tirosh D, Novack N, Press F, et al. Hypothyroidism and diabetes mellitus-a risky dual gestational endocrinopathy. Peer J 2013;1:e52. [Crossref] [PubMed] [Scopus (5)]
4. Sahu MT, Das V, Mittal S, Agarwal A, Sahu M. Overt and subclinical thyroid dysfunction among Indian pregnant women and its effect on maternal and fetal outcome. Arch Gynecol Obstet 2010;281:215-220. [Crossref] [PubMed] [Scopus (71)]
5. Tudela CM, Casey BM, McIntire DD, Cunningham FG. Relationship of subclinical thyroid disease to the incidence of gestational diabetes. Obstet Gynecol 2012;119:983-988. [Crossref] [PubMed] [Scopus (40)]
6. Yang WS, Va P, Bray F, et al. The role of pre-existing diabetes mellitus on hepatocellular carcinoma occurrence and prognosis: a meta-analysis of prospective cohort studies. PLoS ONE 2011;6:e27326. [View Article] [PubMed/NCBI]
7. Inoue M, Iwasaki M, Otani T, et al. Diabetes mellitus and the risk of cancer. Arch Intern Med 2006;166:1871-1877. [View Article] [PubMed/NCBI] [Google Scholar]
8. Dvey-Smith G, Egger M, Shipley MJ, Marmot M. Post-challenge glucose concentration, impaired glucose tolerance, diabetes, and cancer mortality in men. Am J Epidemiol 1991;136:1110-1114. [PubMed/NCBI]
9. Widerpass E, Gridley G, Nyren O, et al. Cause-specific mortality in a cohort of patients with diabetes mellitus: a population-based study in Sweden. J Clin Epidemiol 2001;54:802-809. [PubMed]
10. Meinhold CL, Ron E, Schonfeld SJ, et al. Nonradiation Risk Factors for Thyroid Cancer in the US Radiologic Technologists Study. American Journal of Epidemiology 2009;171:242-252. [PubMed]
11. Chubb, SAP, Davist, WA, Inman, Z, Davis, TME. Prevalence and progression of subclinical hypothyroidism in women with type 2 diabetes: the fremantle diabetes study. Clinical Endocrinology. 2005;62(4):480-486. [PubMed]

12. Barker JM. Clinical review: type 1 diabetes-associated autoimmunity: natural history, genetic association and screening. Journal of Clinical Endocrinology and Metabolism 2006;91(4):377-386.
13. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. The Lancet 2009;373(9677):1773-1779.
14. Chubb SA, Davis WA, Davis TM. Interactions among thyroid function, insulin sensitivity and serum lipid concentration: the Freemantle diabetes study. Journal of Clinical Endocrinology and Metabolism 2005;90(9):2317-2320.
15. Landon MB, Spong CY, Thom E, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med 2009;361:1339-1348. [PMC free article] [PubMed]
16. Langer O, Anyaegbunam A, Brustman L, Divon M. Management of women with one abnormal oral glucose tolerance test value reduces adverse outcome in pregnancy. Am J Obstet Gynecol 1989;161:593-599. [PubMed]
17. Li DF, Wong VC, O'Hoy KM, Yeung CY, Ma HK. Is treatment needed for mild impairment of glucose tolerance in pregnancy? A randomized controlled trial. Br J Obstet Gynaecol 1987;94:851-854. [PubMed]
18. Agarwal MM, Dhatt GS, Punnose J, Koster G. Gestational diabetes: dilemma caused by multiple international diagnostic criteria. Diabet Med 2005;22:1731-1736. [PubMed]
19. Simmons R. Epigenetics and maternal nutrition: nature v. nurture. Proc Nutr Soc 2011;70:73-81. [PubMed]
20. Forman MR CM, Ronckers C, Zhang Y. Through the looking glass at early-life exposures and breast cancer risk. Cancer Invest 23:609-624. [PubMed]
21. Langer O, Levy J, Brustman L, et al. Glycemic control in gestational diabetes mellitus—how tight is tight enough: small for gestational age versus large for gestational age? Am J Obstet Gynecol 1989;161:646-653. [PubMed]
22. Sadeh-Mestechkin D, Walfisch A, Shachar R, et al. Suspected macrosomia? Better not tell. Arch Gynecol Obstet 2008;278:225-230. [PubMed]
23. Barton JR, O'Brien J M, Bergauer NK, Jacques DL, Sibai BM. Mild gestational hypertension remote from term: progression and outcome. Am J Obstet Gynecol 2001;184:979-983. [PubMed]

**American Journal of BioMedicine**
Journal Abbreviation: AJBM
ISSN: 2333-5106 (Online)
DOI: 10.18081/issn.2333-5106
Publisher: BM-Publisher
Email: editor@ajbm.net