

First Trimester Glycated Hemoglobin (HbA1c) Level As A Novel Predictor Of Gestational Diabetes Mellitus: A Systematic Review And Meta-Analysis

DOI: [10.52629/jamsa.v9i1.260](https://doi.org/10.52629/jamsa.v9i1.260)

Introduction Gestational diabetes mellitus (GDM) is a severe yet neglected threat to maternal and child health due to its association with multiple adverse pregnancy outcomes. Glycated hemoglobin (HbA1c) level is one of the most promising predictors of GDM in early pregnancy, based on several cohort studies done recently.

Purpose of study This systematic review and meta-analysis aim to evaluate the potency of HbA1c level in the first trimester as a novel predictor of GDM.

Methods This review selects cohort studies found by database searching systematically using previously determined inclusion criteria, such as pregnant women as the subject, assessment of HbA1c level in the first trimester, and assessment of odds ratio towards (GDM), and exclusion criteria such as assessment of outcome at postpartum, not assess GDM outcomes and studies written in languages other than English or Bahasa Indonesia. This review was arranged based on PRISMA guidelines.

Results and Discussion This review included seven cohort studies, with the pooled OR of 4.36 [95%CI: 3.66-5.20]. Quantitative analysis shows that HbA1c level in the first trimester is a significant risk factor of GDM development ($p < 0.00001$). However, heterogeneity analyses revealed that substantial heterogeneity is detected in the pooled studies. Therefore, to understand the significance of the HbA1c level and the development of GDM, further studies are needed.

Conclusion This study has proven the potency of first-trimester HbA1c level as a novel predictor of gestational

Ayers Gilberth Ivano Kalaij¹, Nathaniel Gilbert Dyson¹, Michael Sugiyanto¹

¹ Faculty of Medicine, Universitas Indonesia

Correspondence to:

Ayers Gilberth Ivano Kalaij
Faculty of Medicine,
Universitas Indonesia

ayers.gilberth@ui.ac.id

diabetes mellitus. Thus, it is necessary to integrate the use of HbA1c level screening as part of antenatal care in the first trimester of pregnancy.

Keywords *Gestational Diabetes Mellitus, First Trimester, Glycated Hemoglobin (HbA1c), Predictor*

Introduction

As Gestational diabetes mellitus (GDM) is a glucose intolerance condition that is first detected during pregnancy and usually disappears after giving birth.¹ It is a severe yet neglected threat to maternal and child health these days.² Ironically, according to the International Diabetes Federation (IDF), there were around 223 million women (20-79 years) living with diabetes today and this number is projected to increase to 343 million by 2045.³

GDM is associated with multiple adverse pregnancy outcomes. Hyperglycemia exposure to babies in a mother's womb increases their risk of being overweight or obese, which is associated with type 2 diabetes mellitus development. Other complications related to uncontrolled GDM are spontaneous abortions, major congenital anomalies, neonatal hypoglycemia, excessive fetal growth, polycythemia, jaundice, stillbirth, and respiratory distress syndrome.⁴

The global prevalence of GDM among women (20-49 years), as stated in the study by Guariguata et al in 2013, is 16.9%, or around 21.4 million live births. However, it was found that the South East Asian population is at the highest prevalence (25.0%) compared with other populations.

Furthermore, more than 90% of cases of gestational diabetes are estimated to occur in low- to middle-income countries.⁵

GDM is diagnosed during antenatal screening, rather than through reported symptoms.⁶ The American Diabetes

Association (ADA) and the American College of Obstetricians and Gynecologists (ACOG) suggested that all pregnant women should be tested for GDM between the 24th and 28th weeks of gestation, and those with any risk factors should get earlier screening.⁷ Nevertheless, late screening for GDM after the 24th gestational week has been questioned due to the possible delay in receiving the optimal effects of drug therapy, exercise, and diet to prevent maternal and neonatal complications.⁸ This issue leads to the global urge of finding potential early predictors to establish early prediction on GDM which aims to prevent obstetric and neonatal complications. Furthermore, this approach may help avoid a prolonged hospital stay, especially in the current COVID-19 pandemic.^{9,10}

Glycated hemoglobin (HbA1c) is a result of glucose attachment to the N- terminal valine of the hemoglobin β -chain. HbA1c level is linked to the glucose level in the blood and also the erythrocyte lifetime.¹¹ HbA1c itself has been known as a predictor and a diagnostic test for type 2 diabetes. However, this test has not been widely studied in GDM and no cutoff point has been defined for HbA1c in GDM.¹²

Recently, accumulating evidence has shown that glycated hemoglobin (HbA1c) level is a potential predictor of gestational diabetes mellitus in the early stage of pregnancy. However, the authors still wonder about the exact potency and association of HbA1c level as a predictor of GDM, and whether or not it can be integrated into current guidelines, as there

are no systematic reviews or meta-analyses regarding the topic so far. Therefore, we decided to conduct a systematic review and meta-analysis to conclude the potential use of HbA1c as a GDM predictor. We aim to prove the potency of first-trimester HbA1c level as a novel predictor of GDM, thus it can be integrated as part of antenatal care in the first trimester of pregnancy to reduce the GDM complications prevalence and promote a healthy pregnancy

Materials and Methods

This systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, which can be accessed through

<http://www.prisma-statement.org/>

Search strategy

A systematic review and meta-analysis of cohort studies were conducted among the global population focusing on the correlation between Hemoglobin A1C levels and acquired gestational diabetes as its outcome. The initial literature search was performed by three independent reviewers with multiple electronic databases including PubMed, Scopus, and EBSCOhost, up to 28 October 2020. The keywords used in the search were "Hemoglobin A1C" OR "HbA1c" OR "hemoglobin" OR "A1c", "prediction" OR "marker" OR "predictor" and "gestational diabetes". Where applicable and available, appropriate advanced search techniques were applied to narrow the search.

Search Eligibility Criteria

Search results were assessed for duplicate removals, which was performed using EndNote X9 software. Moreover, studies were screened according to the following inclusion and exclusion criteria. Our inclusion criteria were

1. Cohort studies,
2. Pregnant women among the general population as the intervention subject;
3. Assess HbA1c level in the first trimester, and
4. Assess odds ratio towards gestational diabetes mellitus (GDM) prediction as the study outcome.

Exclusion criteria:

1. Assess outcome at postpartum;
2. Not assess GDM outcomes,
3. Studies that did not have a full-text version, and
4. studies written in languages other than English. Furthermore, screening of titles and abstracts of studies was carried out according to criteria of accessibility by three independent reviewers. Any disagreements were discussed into consensus. The planned procedure is illustrated in **Figure 1**.

Quality Assessment

All included studies were assessed using the Newcastle-Ottawa Scale designed for Cohort Studies (NOS-Ottawa) which were then converted into the Agency of Healthcare Research Quality (AHRQ)

standard into good, fair, or poor quality, which is shown in **Table 2**.

The quality assessment was done by three reviewers, with each other blinded on others' scoring, then discussed until consensus was reached.¹³

further in a table. Data were extracted from the included studies based on the following aspects: author and year of publication, study location, study design, participants, study period, and outcomes stated in HbA1c cut-off value with its

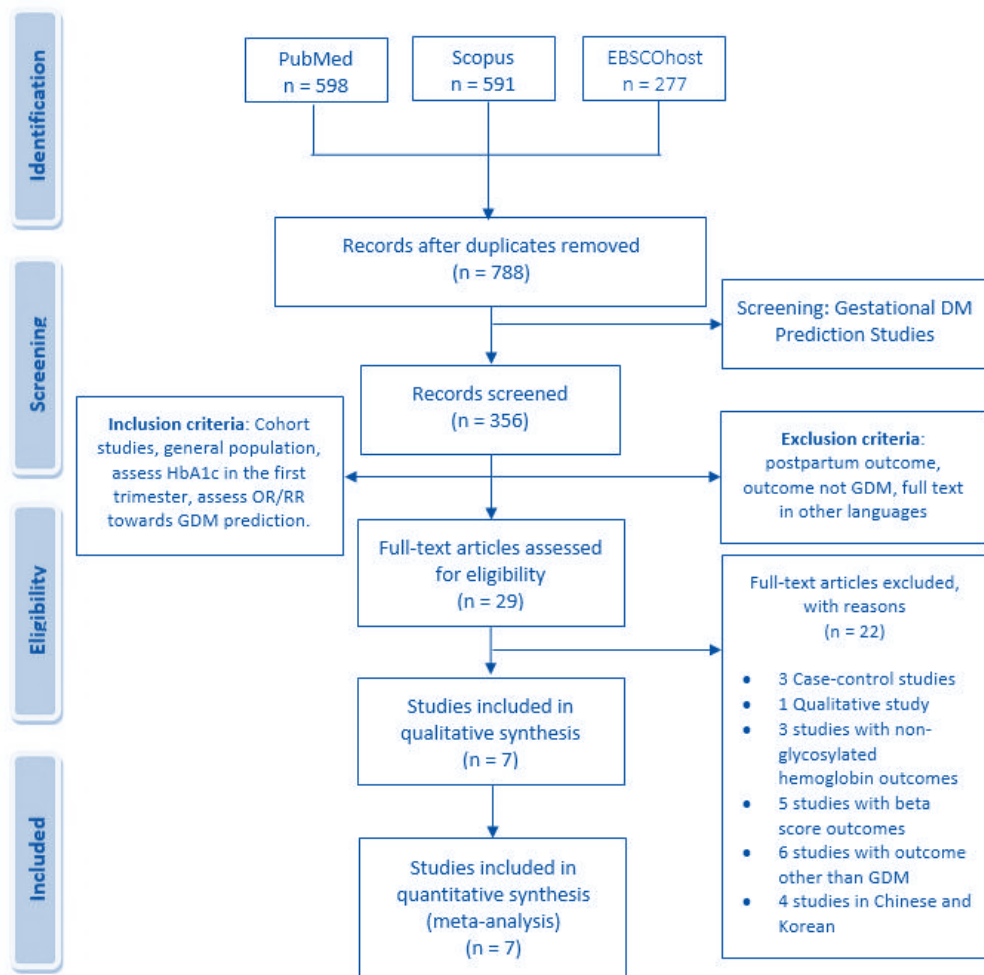


Figure 1 Literature search strategy

Summary measures and data analysis

Evidence-based analysis was conducted in this systematic review and meta-analysis. Outcome assessment was done by three reviewers independently, then discussed

respective odds ratio and p-value. The results of the study were stated as not correlated and correlated using the odds ratio ($p < 0.05$).

Odds ratio (OR) with a 95% confidence interval and p-value below 0.05 was used to determine the association between high glycated hemoglobin (HbA1c) serum level at first trimester and incident prediction in gestational diabetes patients. Factors were put as study code, log of odds ratio, and standard of error which will be calculated for study weight, fixed odds ratio, and its 95% confidence interval (CI) which will be presented in a forest plot. Studies were also assessed using Cochrane's chi-squared test and the Higgins I-squared statistical test in terms of heterogeneity of the included studies. If the p-value of the chi-squared test results is <0.05 and the I-squared statistic is over 50%, the study will be considered heterogeneous. Thresholds for the interpretation of I-squared referred to Cochrane Handbook for Systematic Reviews of Interventions is as follows: 0% to 40% considered as not important; 30% to 60% represent moderate heterogeneity; 50% to 90% represent substantial heterogeneity; 75% to 100% considered as strong heterogeneity.¹⁴ All forms of statistical tests of this study including heterogeneity were carried out using Review Manager (RevMan) v5.3.

Furthermore, sensitivity analysis was conducted through Duval and Tweedie's trim-and-fill analysis which are specific for situations where the heterogeneity is too large. This method was conducted to re-ensure the pooled effect size after removing any studies to minimize the publication bias.¹⁴ However, we did not conduct further subgroup analysis due to

similar characteristics of each study indicated in the study characteristics table which is shown in **Table 1**.

Results

Search results and study selection

Comprehensive literature searches from PubMed, Scopus, and EBSCOhost databases using the search strategy mentioned above resulted in a total of 1,466 studies. Among them, 678 were deduplicated. Moreover, 432 were excluded after screening the titles and abstracts in terms of gestational diabetes mellitus prediction studies. In addition, 327 studies were filtered based on inclusion and exclusion criteria which resulted in 29 studies being assessed by full-text reading. Subsequently, 22 studies were further excluded since 3 were case-control studies, 1 was a qualitative study, 3 were studies with non-glycated hemoglobin outcomes, 5 studies assessed only beta score as their outcomes, 6 studies had outcomes other than GDM, and lastly, 4 were not written in English. Finally, the search yielded 7 studies, consisting of all cohort studies to be included in the qualitative and quantitative synthesis.

Study Characteristics and design

The data extracted and characteristics of included studies are shown in **Table 1**. Overall, this review included a total of 13,930 subjects. Study locations varied across three continents: Asia (n=4) and America (n=3). The mean age of all included studies was distributed from 22 to 39 years. All studies enrolled assessed

Table 1. Characteristics of selected studies

Study Characteristics								
Studies, year	Location	Design	Participants	Range/Mean age (year)	Study Period	HbA1c Cut-off Value	Odds ratio (95% CI)	P-Value
Kansu-Celik et al, 2019	Ankara, Turkey	Retrospective cohort	608	31.11 ± 6.93	Jan 2010 – Jan 2018	HbA1c ≥ 5.6%	4.69 [2.66–8.29]	<0.001
Pezeshki et al, 2019	Zanjan, Iran	Prospective cohort	356	26.4 ± 4.3	Apr 2015 – Apr 2016	HbA1c ≥ 5.3%	9.73 [3.85 – 24.55]	0.001
Punnose et al, 2019	New Delhi, India	Retrospective cohort	2275	28.57 ± 3.76	Jan 2011 – Dec 2016	HbA1c ≥ 5.6%	2.6 [1.486–4.547]	<0.001
Chen et al, 2018	Washington, USA	Retrospective cohort	7020	Normal: 31 ± 5.1 Prediabetic: 32.5 ± 5.2	Jul 2011 – Dec 2014	HbA1c 5.7–6.4%	7.723 [5.916–10.081]	<0.05
Kumru et al, 2016	Istanbul, Turkey	Prospective cohort	333	28.6 ± 4.6	Jan 2011 – Jan 2013	NR	1.11 [0.22–5.57]	<0.05
Osmundson et al, 2016	Palo Alto, California, USA	Retrospective cohort	2812	34.2 ± 4.3	Jan 2011 – Dec 2012	HbA1c 5.7–6.4%	2.194 [1.572–3.064]	<0.001
Fong et al, 2014	Long Beach, California, USA	Retrospective cohort	526	28.8 ± 6.4	Jan 2011 – Jan 2013	HbA1c 5.7–6.4%	2.38 [1.01–5.63]	0.048
NR = Not Reported								

Table 2. Quality assessment of selected studies.^{1,2}

Studies, year	Selection				Comparability	Outcome			AHRQ Standard
	1	2	3	4	1	1	2	3	
Kansu-Celik et al, 2019	a(*)	a(*)	a(*)	a(*)	b(*)	a(*)	a(*)	b(*)	Good
Pezeshki et al, 2019	a(*)	a(*)	a(*)	a(*)	b(*)	a(*)	a(*)	b(*)	Good
Punnose et al, 2019	a(*)	a(*)	a(*)	a(*)	b(*)	b(*)	a(*)	a(*)	Good
Chen et al, 2018	a(*)	a(*)	a(*)	a(*)	b(*)	a(*)	a(*)	d	Good
Kumru et al, 2016	a(*)	a(*)	a(*)	a(*)	b(*)	a(*)	a(*)	a(*)	Good
Osmundson et al, 2016	a(*)	a(*)	a(*)	b(*)	b(*)	a(*)	a(*)	a(*)	Good
Fong et al, 2014	a(*)	a(*)	a(*)	b(*)	d	a(*)	a(*)	a(*)	Good

¹Assessment form and complete version of AHRQ grading calculation are located in appendix 1.

²Study is considered:

- Good: 3 or 4 stars in selection domain AND 1 star in comparability domain AND 2 or 3 stars in outcome domain.
- Fair: 2 stars in selection domain AND 1 star in comparability domain AND 2 or 3 stars in outcome domain.
- Poor: 0 or 1 stars in selection domain AND 0 star in comparability domain AND 0 or 1 stars in outcome domain.

(*) Stars are given for each of the study aspects.

and reported HbA1c cut-off value at the first trimester which was involved in GDM prediction, except Kumru et al which did not report HbA1c cut-off value at the first trimester.¹⁵

Quantitative Analysis of High HbA1c Level and GDM Prediction

Our meta-analysis resulted that high glycated hemoglobin (HbA1c) serum level in the first trimester was significantly associated with gestational diabetes mellitus incident as it is a predictive factor and met minimum requirements for meta-analysis according to the Cochrane Handbook, although our study consists of studies with considerable heterogeneity.¹⁶ This meta-analysis has also shown the cumulative fixed-odds ratio of each study after calculating its weight and presented the final odd ratio of analysis with all respective study weights. According to this meta-analysis, high glycated hemoglobin (HbA1c) serum level increases the chance of having gestational diabetes mellitus by 4.36 (3.66-5.20) times. The forest plot is presented in **Figure 2**. Nevertheless, the p-value for the overall effect test ($z=16.41$) is $p < 0.00001$ which shows a significant association between the two factors.

Heterogeneity and sensitivity analysis

Pooled included studies showed that the p-value of the chi-square test was < 0.00001 and the I-square test was 87%. Those are indicative of significant heterogeneity studies. According to the Cochrane Handbook, the included studies in this meta-analysis are considered as substantial heterogeneity. Furthermore,

sensitivity analysis using Duval and Tweedie's trim-and-fill analysis revealed that one study is an outlier study. After the removal of Chen et al study on sensitivity analysis, the outcome was $OR = 2.81$ (2.22-3.55), $P < 0.000001$; $I^2 = 63\%$.¹⁷ This event could be due to larger samples used in this study compared to other included studies and due to variability in the diagnostic measurement criteria since this study was part of a larger research project evaluating clinical outcomes associated with the new GDM Guideline, IADPSG's guideline.

Publication Bias

Critical appraisal was conducted using the Newcastle-Ottawa Scale for cohort study criteria which transformed into the AHRQ criteria. Detailed critical appraisal was given in the appendix in the last part of this paper. From our systematic review and meta-analysis, all included studies show good quality studies based on AHRQ standard, which indicated that this review included a low risk of bias studies. However, according to the Cochrane Handbook, heterogeneity examination using funnel plot demands at least 10 studies to present sufficient power for studies heterogeneity.¹⁶ Therefore, funnel plot analysis assessing publication is not performed in this study. Thus, this study is still subject to publication bias which is limited to the number of publications. However,, this study is still currently applicable as it included all studies available at the moment, thus making it applicable in clinical settings.

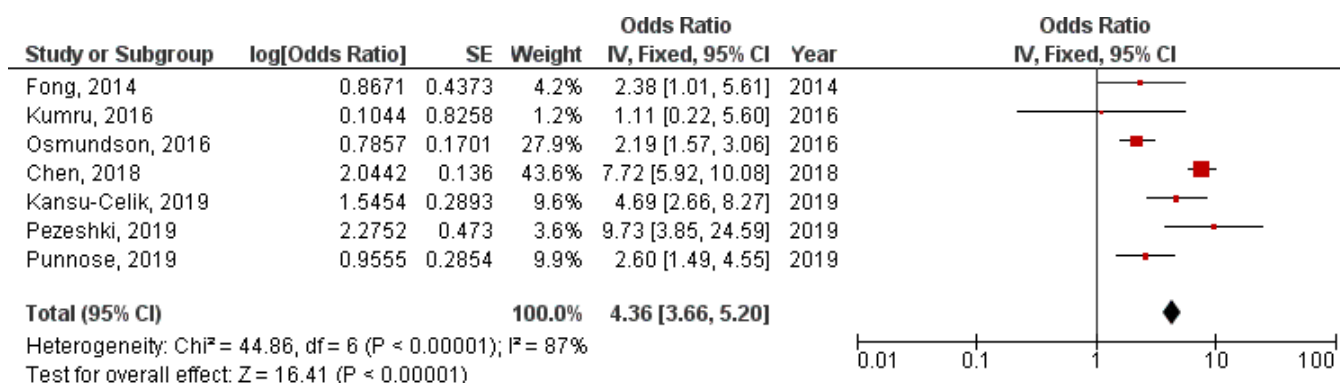


Figure 2 Forest plot presenting the association of HbA1c level in the first trimester of pregnancy and the of GDM

Discussion

The Development of Gestational Diabetes Mellitus and The Increasing of HbA1c Level

As gestation occurs, the human body adapts to prepare for the growth of the fetus, one of them being metabolic adaptation. During early gestation, insulin sensitivity increases to increase glucose uptake by various tissues to fulfill energy demands for the entire pregnancy. In the later gestation, insulin sensitivity decreases due to influence from various hormones, such as leptin, cortisol, estrogen, progesterone, placental lactogen, and placental growth hormone. This mild degree of resistance will also increase glucose production by the liver and the breakdown of fat stores in the tissues, further increasing the blood glucose level and free fatty acids concentration.¹⁸ However, the increased degree of insulin resistance or impaired compensatory pancreatic β -cells hyperplasia can result in gestational diabetes mellitus.¹⁹ The dysfunction of pancreatic β -cells causes the impaired response of increasing blood glucose level. A prolonged increase in blood glucose

level will decrease tissue insulin sensitivity to divert excess energy uptake to other tissues.^{20,21}

In GDM, the insulin-induced glucose uptake decreased by 54% compared to normal pregnancy.²² Once β -cells dysfunction occurs, the vicious cycle of it, hyperglycemia, insulin resistance, and further β -cells dysfunction is established. Progression of GDM involves many insulin signaling pathways and involves many organs throughout the body, such as the neurohormonal system, adipose tissue, liver, skeletal muscle, placenta, and gut.¹⁸

Glycated hemoglobin (HbA1c) is a hemoglobin that has glucose attached to the N-terminal valine of its β -chain. It can reliably reflect the blood glucose level for the preceding 8-12 weeks as the lifespan of erythrocytes is within that range.^{11,23} Measuring the HbA1c level within the first trimester of pregnancy can provide the estimation of maternal glycemic condition before pregnancy or in early pregnancy as the insulin sensitivity in that period should be higher. The HbA1c level is expected to drop by at least 0.5% as a result of higher

insulin sensitivity and shorter lifespan of erythrocytes during pregnancy.²⁴ High HbA1c level in the first trimester may indicate preconception dysfunction in maternal glycemic control which may result from a poor dietary pattern. This supports the study by Zhang that improvement in glycemic function before pregnancy decreases the risk of developing GDM.²⁵

The Utility of HbA1c Level Screening

The HbA1c cut-off value of GDM is $\geq 6.5\%$. However, some of the included studies use the prediabetic cut-off, $5.7-6.4\%$, to discriminate the GDM group from the non-GDM group. Our review proved that a high HbA1c level is a statistically significant risk factor for the development of GDM. HbA1c level can also predict the occurrence complication. A study by Osmundson stated that high HbA1c level is associated with the increased risk of excessive gestational weight gain, cesarean delivery, and large for gestational age, although was statistically significant only for the weight gain.²⁶ Study by Mañé stated that $\text{HbA1c} \geq 5.9\%$ is a statistically significant risk factor of macrosomia [OR=3.114; 95% CI 1.127- 8.063; $p=0.028$] and preeclampsia [OR=3.539; 95% CI 1.086-11.532; $p=0.036$].²⁷ Macrosomia results from the increase in glucose, fatty acids, and amino acids through the placenta due to GDM, stimulating the production of insulin and IGF-1. Macrosomia is also a risk factor of shoulder dystocia which will obstruct the labor process.¹⁸ It is believed that GDM and preeclampsia result from pregnancy maladaptation, such as endothelial

dysfunction, angiogenic imbalance, which result from high anti-angiogenic factors such as sFlt-1 and sEng and low pro-angiogenic factors such as PGF, oxidative stress, and dyslipidemia. Studies have proven that patients with GDM have low pro-angiogenic factors and high anti-angiogenic factors.²⁸ Women with a previous history of GDM have a higher risk of developing type 2 diabetes mellitus (T2DM) later in life. The altered vasculature in women with GDM history also predisposes them to cardiovascular disease. As soon as being delivered, neonates born from mothers with GDM are at risk of hypoglycemia as a result of fetal hyperinsulinemia. Children born from mothers with GDM also have a higher risk of childhood insulin resistance, which may result in obesity, T2DM, and cardiovascular disease.¹⁸

The use of HbA1c level as a risk factor screening is recommended as it is a simple and quick test; therefore, prolonged hospital stay is not required. Risk factor screening during early pregnancy, including risk for GDM, is heavily required, especially in low-income countries, where the access to adequate antenatal care is still limited, and in the current COVID-19 pandemic era, when the hospital visit should be limited. Early detection of risk factors of pregnancy complications can lead to a healthier maternal lifestyle and healthy pregnancy

Strength and Limitations

Our review has several strengths and limitations. To our knowledge, this is the

as the gestational age when the HbA1c level was measured. This review also consisted of a low number of eligible

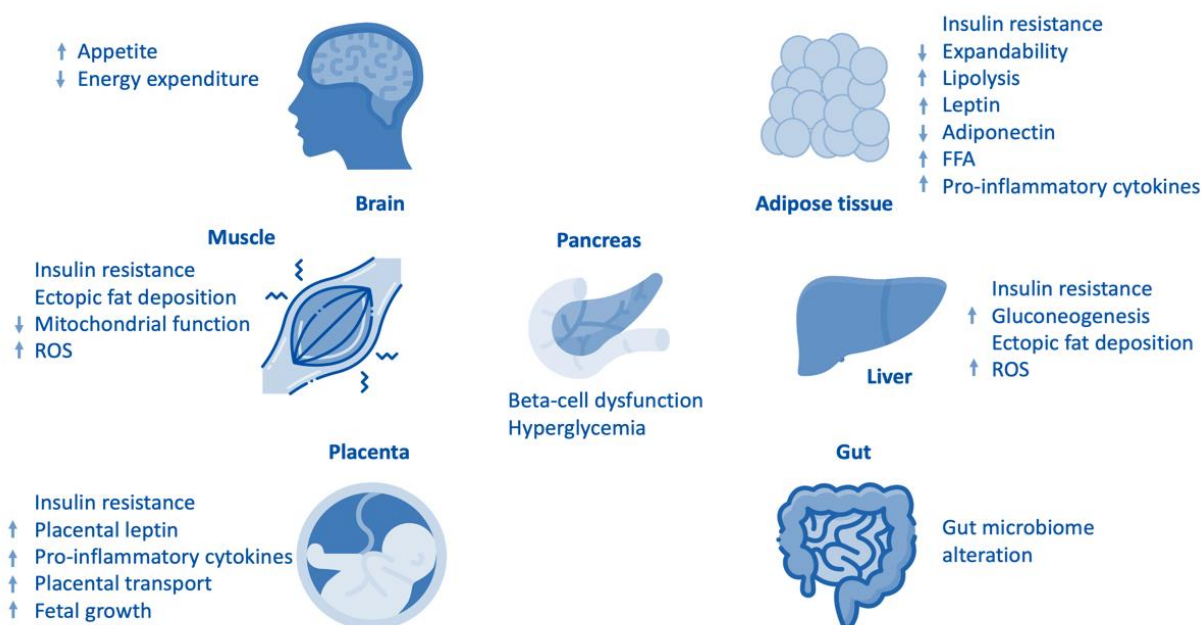


Figure 3 Organs involved in the pathophysiology of gestational diabetes

first systematic review and meta-analysis to assess the HbA1c level in the first trimester as a risk factor of gestational diabetes mellitus. Our meta-analysis also yielded a significant pooled odds ratio and was statistically significant, proving the significance of its correlation with the development of GDM. All of the studies included in this review are cohort studies, which is the main type of studies in assessing risk factors. The main limitation of our study was the high heterogeneity from the meta-analysis. This may be caused by the variation of the cutoff value of the HbA1c used and other variables such

studies since the study about this topic is still scarce. The publication bias analysis using a funnel plot cannot be made because of the limited number of studies. Furthermore, this review also included only studies written in English.

Conclusion and Recommendation

In conclusion, this systematic review and meta-analysis have proven the potency of HbA1c level in the first trimester as a novel predictor of gestational diabetes mellitus in pregnant patients. Thus, it is necessary to integrate the use of HbA1c level

screening as part of antenatal care in the first trimester of pregnancy, especially in Southeast Asian countries (e.g., in Indonesia), due to the high prevalence; however, further research should be done. Early detection of GDM risk factors using HbA1c level in the first trimester could increase glycemic control during pregnancy, thus decreasing the prevalence of pregnancy complications due to GDM and having a healthy pregnancy. We also encourage women of reproductive age to maintain their glycemic function to prepare for healthy pregnancies by consuming a healthy diet and maintaining an active lifestyle.

Acknowledgement

We have nothing to declare.

Conflict of Interest

We declare that we have no competing intention for completing this review.

References

1. American College of Obstetricians and Gynecologists. Gestational Diabetes Mellitus: Practice Bulletin No. 137. Obstet Gynecol. 2013;
2. Lee KW, Ching SM, Ramachandran V, Yee A, Hoo FK, Chia YC, et al. Prevalence and risk factors of gestational diabetes mellitus in Asia: A systematic review and meta-analysis. BMC Pregnancy Childbirth. 2018;
3. International Diabetes Federation. IDF Diabetes Atlas, 9th edn. Brussels, Belgium. Atlas de la Diabetes de la FID. 2019.
4. Buchanan TA, Xiang AH, Page KA. Gestational diabetes mellitus: Risks and management during and after pregnancy. Nat Rev Endocrinol. 2012;
5. Guariguata L, Linnenkamp U, Beagley J, Whiting DR, Cho NH. Global estimates of the prevalence of hyperglycaemia in pregnancy. Diabetes Res Clin Pract. 2014;
6. Garrison A. Screening, diagnosis, and management of gestational diabetes mellitus. Am Fam Physician. 2015;
7. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020;
8. Ray JG, Berger H, Lipscombe LL, Sermer M. Gestational prediabetes: A new term for early prevention? Indian Journal of Medical Research. 2010.
9. Rowan JA, Budden A, Ivanova V, Hughes RC, Sadler LC. Women with an HbA1c of 41-49 mmol/mol (5.9- 6.6%): A higher risk subgroup that may benefit from early pregnancy intervention. Diabet Med. 2016;
10. Powe CE. Early Pregnancy Biochemical Predictors of Gestational Diabetes Mellitus. Current Diabetes Reports. 2017.
11. Kansu-Celik H, Ozgu-Erdinc AS, Kisa B, Eldem S, Hancerliogullari N, Engin-Ustun Y. Maternal serum glycated hemoglobin and fasting plasma glucose predicts gestational diabetes at the first trimester in Turkish women with a low-risk pregnancy and its relationship with fetal birth weight; a retrospective cohort study. J Matern Neonatal Med [Internet]. 2019 Aug 12;1-8. Available from: <https://www.tandfonline.com/doi/full/10.1080/14767058.2019.1651837>
12. Selvin E, Steffes MW, Gregg E, Brancati FL, Coresh J. Performance of A1C for the classification and prediction of diabetes. Diabetes Care. 2011;

13. Luchini C, Stubbs B, Solmi M, Veronese N. Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale. *World J Meta-Analysis*. 2017;
14. Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series*. Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series. 2008.
15. Kumru P, Arisoy R, Erdogan E, Demirci O, Kavrut M, Ardic C, et al. Prediction of gestational diabetes mellitus at first trimester in low-risk pregnancies. *Taiwan J Obstet Gynecol*. 2016;55(6):815–20.
16. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. The Cochrane Collaboration. 2011.
17. Chen L, Pocobelli G, Yu O, Shortreed SM, Osmundson SS, Fuller S, et al. Early Pregnancy Hemoglobin A1C and Pregnancy Outcomes: A Population-Based Study. *Am J Perinatol*. 2019;36(10):1045–53.
18. Plows JF, Stanley JL, Baker PN, Reynolds CM, Vickers MH. The pathophysiology of gestational diabetes mellitus. *Int J Mol Sci*. 2018;19(11):1–21.
19. Egan AM, Dow ML, Vella A. A Review of the Pathophysiology and Management of Diabetes in Pregnancy. *Mayo Clin Proc* [Internet]. 2020;1–13. Available from: <https://doi.org/10.1016/j.mayocp.2020.02.019>
20. Hoy AJ, Brandon AE, Turner N, Watt MJ, Bruce CR, Cooney GJ, et al. Lipid and insulin infusion-induced skeletal muscle insulin resistance is likely due to metabolic feedback and not changes in IRS-1, Akt, or AS160 phosphorylation. *Am J Physiol - Endocrinol Metab*. 2009;297(1).
21. Weir GC, Laybutt DR, Kaneto H, Bonner-Weir S, Sharma A. Beta-cell adaptation and decompensation during the progression of diabetes. *Diabetes* [Internet]. 2001 Feb 1;50(Supplement 1):S154–9. Available from: <http://diabetes.diabetesjournals.org/cgi/doi/10.2337/diabetes.50.2007.S154>
22. Catalano PM. Trying to understand gestational diabetes. *Diabet Med* [Internet]. 2014 Mar;31(3):273–81. Available from: <http://doi.wiley.com/10.1111/dme.12381>
23. Hinkle SN, Tsai MY, Rawal S, Albert PS, Zhang C. HbA1c Measured in the First Trimester of Pregnancy and the Association with Gestational Diabetes. *Sci Rep* [Internet]. 2018 Dec 16;8(1):12249. Available from: <http://www.nature.com/articles/s41598-018-30833-8>
24. Arbib N, Shmueli A, Salman L, Krispin E, Toledano Y, Hadar E. First trimester glycated hemoglobin as a predictor of gestational diabetes mellitus. *Int J Gynecol Obstet*. 2019;145(2):158–63.
25. Zhang C, Tobias DK, Chavarro JE, Bao W, Wang D, Ley SH, et al. Adherence to healthy lifestyle and risk of gestational diabetes mellitus: prospective cohort study. *BMJ* [Internet]. 2014 Sep 30;349(1):g5450. Available from: <https://www.bmj.com/lookup/doi/10.1136/bmj.g5450>
26. Osmundson S, Zhao B, Kunz L, Wang E, Popat R, Nimbal V, et al. First Trimester Hemoglobin A1c Prediction of Gestational Diabetes. *Am J Perinatol* [Internet]. 2016 Apr 27;33(10):977–82. Available from: <http://www.thieme-connect.de/DOI/DOI?10.1055/s-0036-1581055>
27. Mañé L, Flores-Le Roux JA, Benaiges D, Rodríguez M, Marcelo I, Chillarón JJ, et al. Role of first trimester HbA1c as a predictor of adverse obstetric outcomes in a multi-ethnic cohort. *J Clin Endocrinol Metab* [Internet]. 2016 Nov 23;jc.2016-2581. Available from:

<https://academic.oup.com/jcem/article-lookup/doi/10.1210/jc.2016-2581>

28. Weissgerber TL, Mudd LM. Preeclampsia and Diabetes. *Curr Diab Rep* [Internet]. 2015 Mar 3;15(3):9. Available from: <http://link.springer.com/10.1007/s11892-015-0579-4>
29. Fong A, Serra AE, Gabby L, Wing DA, Berkowitz KM. Use of hemoglobin A1c as an early predictor of gestational diabetes mellitus. *Am J Obstet Gynecol* [Internet]. 2014 Dec;211(6):641.e1-641.e7. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0002937814005778>
30. Pezeshki B, Chiti H, Arasteh P, Mazloomzadeh S. Early screening of gestational diabetes mellitus using hemoglobin A1C: Revising current screening guidelines. *Casp J Intern Med*. 2019;10(1):16–24.
31. Punnose J, Malhotra RK, Sukhija K, Mathew A, Sharma A, Choudhary N. Glycated haemoglobin in the first trimester: A predictor of gestational diabetes mellitus in pregnant Asian Indian women. *Diabetes Res Clin Pract* [Internet]. 2020 Jan;159:107953. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0168822719312227>
32. Amaefule CE, Sasitharan A, Kalra P, Iliodromoti S, Huda MSB, Rogozinska E, et al. The accuracy of haemoglobin A1c as a screening and diagnostic test for gestational diabetes: a systematic review and meta-analysis of test accuracy studies. *Curr Opin Obstet Gynecol* [Internet]. 2020 Oct;32(5):322–34. Available from: <https://journals.lww.com/10.1097/GC>
O.00000000000000648

SUPPLEMENTARY MATERIALS

First Trimester Glycated Hemoglobin (HbA1c) Level As A Novel Predictor Of Gestational Diabetes Mellitus: A Systematic Review And Meta-Analysis

Ayers Gilberth Ivano Kalaij¹,
Nathaniel Gilbert Dyson¹,
Michael Sugiyanto¹

¹Faculty of Medicine, Universitas Indonesia

Appendix 1: Newcastle-Ottawa scale

Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1. Representativeness of the exposed cohort
 - a. Truly representative **(one star)**
 - b. Somewhat representative **(one star)**
 - c. Selected group
 - d. No description of the derivation of the cohort
2. Selection of the non-exposed cohort
 - a. Drawn from the same community as the exposed cohort **(one star)**
 - b. Drawn from a different source
 - c. No description of the derivation of the non-exposed cohort
3. Ascertainment of exposure
 - a. Secure record (e.g., surgical record) **(one star)**
 - b. Structured interview **(one star)**
 - c. Written self-report
 - d. No description
 - e. Other
4. Demonstration that outcome of interest was not present at start of study
 - a. Yes **(one star)**
 - b. No

Comparability

1. Comparability of cohorts on the basis of the design or analysis controlled for confounders
 - a. The study controls for age, sex and marital status **(one star)**
 - b. Study controls for other factors (list)_____ **(one star)**
 - c. Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome

1. Assessment of outcome
 - a. Independent blind assessment **(one star)**
 - b. Record linkage **(one star)**
 - c. Self-report
 - d. No description
 - e. Other
2. Was follow-up long enough for outcomes to occur
 - a. Yes **(one star)**
 - b. No

Indicate the median duration of follow-up and a brief rationale for the assessment above:___

3. Adequacy of follow-up of cohorts
 - a. Complete follow up- all subject accounted for **(one star)**
 - b. Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. **(one star)**
 - c. Follow up rate less than 80% and no description of those lost
 - d. No statement

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

- **Good quality:** 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
- **Fair quality:** 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
- **Poor quality:** 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain