The Role of First Trimester HbA1c as a Predictor of Gestational Diabetes Mellitus and Adverse Maternal and Perinatal Outcomes among Non-Diabetic Pregnant Filipino Women

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Abstract

Objectives: This study aims to determine the role of HbA1c level during first trimester in predicting gestational diabetes mellitus in Filipino non-diabetic women. Hence, to identify those will be at increased risk of its adverse maternal and perinatal outcomes, and who will benefit from early intervention. This will aid in preventing maternal and perinatal morbidity and mortality and reducing health care cost by avoiding strategies which can result in false positive cases.

Methodology: A cross-sectional study conducted in a tertiary hospital in the Philippines. Seventy-one Filipino pregnant women were included in the final analysis. HbA1c levels were taken during the first trimester and routine screening of gestational diabetes mellitus (GDM) utilizing 75 grams OGTT during 24th-28th weeks age of gestation. Binary logistic regression modeling was performed to determine if HbA1c was a predictor of gestational diabetes mellitus. The calculated median for Hba1c was then utilized as a threshold value to predict GDM. Odds ratio, relative risk and corresponding 95% confidence intervals from binary logistic regression were computed to determine the association of variables.

Results: In this study the prevalence rate of GDM is 38%. It showed that first-trimester HbA1c level is not a predictor of GDM and adverse maternal and perinatal outcomes. However, in utilizing an HbA1c threshold of ≥ 5.2%, there is a two-fold increase risk of developing hypertensive disorders, requiring insulin during pregnancy, and macrosomic newborns and a four-fold increase risk of having large for gestational age newborns. It has a positive predictive value (PPV) of only 16%. However, it has a high negative predictive value (NPV) of 88% therefore it can be used to rule out risk of GDM as early as in the first trimester.

Conclusion: The association of HbA1c level and the occurrence of GDM was not observed in this study. However, by using an HbA1c threshold of ≥ 5.2%, as opposed to the standard reference range for diagnosing type 2 diabetes mellitus and gestational diabetes mellitus in Caucasians, the relative risk of developing GDM in 24th-28th weeks AOG is 1.26 (0.6865, 2.3242).

Keywords: HbA1c, gestational diabetes mellitus, pregnancy, insulin

Introduction

Gestational diabetes mellitus (GDM) is defined as a form glucose intolerance that is first recognized during pregnancy.[1] It is associated with short- and long-term adverse health outcomes both to the mothers and their newborns. Mothers affected with GDM are known to have decreased quality of life and increased risk of caesarean section, gestational hypertension, pre-eclampsia and type 2 diabetes mellitus (T2DM). The newborns on the other hand are associated with macrosomia, neonatal hypoglycemia and T2DM. It has emerged as a global public health concern.[2]

The worldwide prevalence of GDM varies significantly, from 1% to 28%, depending on the population characteristics (e.g., maternal age, socioeconomic status, race/ethnicity, or body composition), screening methods, and diagnostic criteria.[2] Majority of the data regarding GDM prevalence has shown an increasing trend over time. Also, multi-ethnic studies have emphasized its increased risk among the different Asian populations.[1] In the largest maternity hospital in Singapore, the prevalence of GDM has increased significantly from 2.8% in 1994 to 5 to 15% in 2016.[3] In Japan, an increasing number of pregnant women have

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GDM, with an estimated prevalence rate of 2.6% in 2006 to 12.08% in 2012.[4] In the Philippines, it affected 14% of pregnancies. A tertiary hospital in Metro Manila, Philippines, reported a prevalence of 7.5%.[5]

GDM cases may be undetected due to inadequate and inappropriate screening methods which in turn lead to an increase in the maternal and neonatal morbidity, that are mostly preventable.[6]

The one step strategy of 75-gram oral glucose tolerance test (OGTT) derived from the International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria is currently the standard diagnostic test for GDM at 24-28 weeks AOG recommended both by international and local guidelines.[7] Thus, GDM can only be detected once the pregnancy has reached approximately the second or third trimester. In addition, OGTT is an inconvenient and time-consuming procedure since the pregnant woman has to fast for at least 8 hours and wait for a total of 2 hours to have at least 3 venipuncture. Not only that, most pregnant women complain of nausea and vomiting because of the unpleasant taste of the 75-gram glucose and because of delayed gastric emptying related to pregnancy. Therefore, there is still a need for a universally acceptable, simpler and accessible test for gestational diabetes screening during early pregnancy or first trimester.[6]

HbA1c testing is a simple, reliable and widely available tool in assessing blood glucose control. Hence, it is one of the valuable tools for diagnosing T2DM. However, the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study suggested that the measurement of HbA1c is not a useful alternative to an OGTT in pregnant women. Hb1Ac levels during the study were taken together with the 75-gram OGTT between 24 and 32-week AOG or during the second to third trimester already.[8]

Anemia in pregnancy combined with hemodilution and increase in red cell turnover, and unknown blood disorders such as hemoglobinopathies have prevented the acceptance of HbA1c as a screening tool in GDM. However, anemia in pregnancy usually occurs during the later stage of gestation and hemoglobinopathies are more prevalent in Caucasian and African population.[6]

A target Hb1Ac level of 6-6.5%, as proposed by several studies, seems to be inappropriate for the pregnant woman. Maternal and perinatal adverse outcomes were observed appreciably on much lower levels of HbA1c and there is a substantial variability between different population and ethnicity.[9]

Due to the growing burden of GDM worldwide particularly in Southeast Asia, and given that we have limited data regarding its true prevalence in the Filipino population, it is valuable that we further investigate how to accurately diagnose GDM.[10]

This study aims to determine the role of HbA1c level during the first trimester of pregnancy, to avoid the effect of anemia during late gestation, in predicting GDM in Filipino non-diabetic women and identifying those who will be at increased risk of its adverse maternal and perinatal outcomes, and therefore may benefit from early intervention. This can potentially help in preventing maternal and perinatal morbidity and mortality and reduce health care cost by helping avoid false positive cases.

Operational Definition of Terms

1. Gestational diabetes mellitus (GDM) - any degree of glucose intolerance that is first recognized during pregnancy, regardless of whether the condition may have predated the pregnancy or persisted after the pregnancy.[1]
2. Glycosylated A1c (HbA1c) - provides the average glucose levels in an individual's blood as hemoglobin becomes glycosylated.[11]
3. 75-gram oral glucose tolerance test (OGTT) - procedure utilized for diagnosing GDM; plasma glucose measurement when patient is fasting at least 8 hours and at 1 and 2 h after intake of 75 grams oral glucose, at 24–28 weeks of gestation in women not diagnosed with overt diabetes previously (cut-off values: Fasting 92 mg/dl, 1 hour 180 mg/dl, 2 hours 153 mg/dl, 1 value above the cut-off will diagnose GDM)[1]
4. First trimester - the first 12 weeks $\pm$ 6 days of pregnancy[12]
5. Second trimester - 13-27 weeks $\pm$ 6 days of pregnancy[12]
6. Third trimester - 28 weeks until full term of pregnancy[12]
7. Ballard score - used to assess the gestational maturity of newborns[12]
8. Macrosomia - newborns with a birth weight of $\geq$ 4000 grams or > 95th percentile[12]
9. Small for gestational age (SGA) refers to an infant that is smaller for age and gender or with a birth weight below the 10th percentile[12]
10. Large for gestational age (LGA) - refers to an infant that is larger than expected for age and gender or with a birth weight above the 90th percentile[4]
11. Preterm delivery - delivery of infant that occurred before 37 completed weeks, that is, ≤ 36 weeks.[6,7,12]
12. Hypertensive disorders of pregnancy - include gestational hypertension and pre-eclampsia/ eclampsia[4]
    a. Gestational hypertension - blood pressure of 140/90 mmHg after 20 weeks gestation in a previously normotensive woman without proteinuria[4]
    b. Pre-eclampsia – new conditions: proteinuria (protein/creatinine ratio > 30 mg/mmol), other maternal organ dysfunction, or fetal growth restriction[12] onset or worsening hypertension after 20 weeks gestation with the coexistence of one or more of the following new-onset[12]
    c. Eclampsia - new-onset or worsening hypertension after 20 weeks 'gestation with the coexistence of one or more of the following new-onset conditions: proteinuria (protein/creatinine ratio >30 mg/mmol), other maternal organ dysfunction, or fetal growth restriction; and seizure[12]

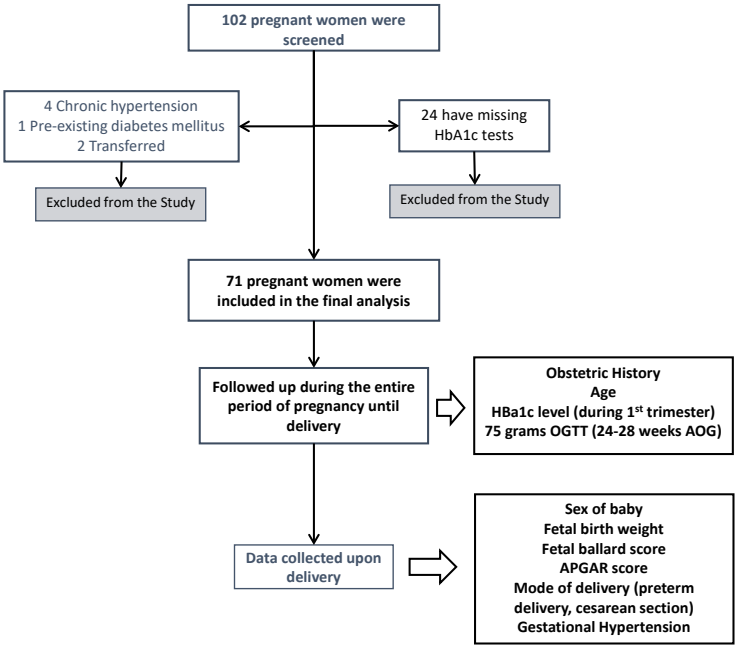

Figure 1. Data Collection Procedure

13. Ceasarean delivery - delivery of a fetus through surgical incisions made through the abdominal wall (laparotomy) and the uterine wall (hysterotomy)[12]

Methods

Study Design. This is a cross-sectional study conducted to determine the role of first trimester HbA1c level in predicting GDM and adverse maternal and perinatal outcomes in Filipino non-diabetic women. The study was conducted in the Outpatient Department of Chong Hua Hospital, a tertiary hospital, in Cebu City, Philippines. Informed consent was secured from all participants.

Study Population. The study population are all pregnant women in their first trimester. Recruitment of the participants started March 2019 which lasted until May 2019. They are all enrolled as Charity patients in the Outpatient Department Obstetrics Charity Service in Chong Hua Hospital.

Inclusion Criteria. All Filipino women (18 years old and above) with singleton pregnancy not diagnosed to have diabetes.

Exclusion Criteria

- Fasting blood sugar ≥ 126 mg/dl
- Patients with pre-existing diabetes mellitus (type 1 or 2)
- Patients with history of GDM
- Patients with multiple gestation (e.g., twins, triplets, quadruplets, etc.)
- Patients with history of miscarriage and abortion
- Patients with obstetrical history of SGA and LGA pregnancy
- Patients with comorbidities such as hypertension, liver disease, kidney disease and blood dyscrasia
- Patients with history of prolonged intake of steroid

Data Collection. Upon completion of their informed consent, data were collected during the patient's 1st visit at the Outpatient Department-Obstetrics Gynecology Department (*Figure 1*).

Data included age, comorbidities with maintenance medications such as hypertension, dyslipidemia, and thyroid disorders, obstetrics, family, personal and social history.

HbA1c level was requested upon initial visit on the first trimester and was taken at Chong Hua Hospital Laboratory only. The institution utilized *Dimension Flex Reagent Cartridge HbA1c-GMDN*. It is a process of collection of reagents and other associated materials to be used for the qualitative and/or quantitative detection of HbA1c in a specimen using a nephelometry or turbidimetry method. This clinical chemistry system calculates an NGSP and DCCT standardized % HbA1c result.

Patient was monitored during the entire pregnancy. Diet, lifestyle, blood pressure and glucose monitoring, and necessary therapeutic intervention were advised and documented, accordingly. Insulin therapy was initiated when blood glucose target levels were not met according to the American Diabetes Association (ADA) Standards of Medical Care in Diabetes 2019: fasting glucose of 95 mg/dL (5.3mmol/L) and either, one-hour postprandial glucose of 140 mg/dL (7.8 mmol/L) or two-hour postprandial glucose of 120 mg/dL (6.7 mmol/L).

At 24-28 weeks AOG, all participants were requested for a 75 grams OGTT. All the results of 75 grams OGTT were interpreted using the IADPSG criteria. Hence, the diagnosis of gestational diabetes is made when any of the following blood glucose levels is met or exceeded: Fasting blood glucose of 92 mg/dl, one hour blood glucose level of 180 mg/dl and two hours blood glucose level of 153 mg/dl.

And upon delivery of the baby, data were collected which included sex, fetal birth weight, fetal ballad score, APGAR score, and mode of delivery (preterm delivery, caesarean section) and complications during delivery, if present.

Figure 1 depicts the schematic diagram of the study design from inclusion of participants.

Data Analysis. Descriptive statistics were utilized to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were used for categorical variables. For continuous variables, the *Shapiro Wilks test* for normality was performed to determine the more appropriate summary statistics to use. The parameters age, hemoglobin and hematocrit were normally distributed; hence, the mean and

Table I. Summary Statistics of Continuous Demographic Variables, Tests and Clinical Outcomes

Parameter	Mean n=71	Standard Deviation	Median n=71	Quartile Range	Shapiro-Wilks Test for Normality p-value [a]
Age	31.34	4.87	31.00	6.00	0.2920
HbA1c	5.15	0.38	5.20	0.40	<0.0001
FBS	84.03	12.72	83.00	12.00	<0.0001
Blood Glucose Level 1 hour after intake of 75g sugar	140.27	34.75	137.00	53.00	0.0522
Blood Glucose Level 2 hours after intake of 75g sugar	128.89	30.55	123.00	42.00	<0.0001
Hemoglobin	12.45	0.89	12.40	1.20	0.1657
Hematocrit	37.47	2.58	37.20	3.60	0.0901
Age of Gestation	38.35	1.42	39.00	1.00	<0.0001
Fetal Weight	2885.99	525.18	2900.00	470.00	0.0071
APGAR Score (1 minute after birth)	8.30	1.52	9.00	1.00	<0.0001
APGAR Score (5 minutes after birth)	8.90	0.72	9.00	0.00	<0.0001

Table II. Distribution of population based on the different variables

Variable	Frequency	Percent (%)
Gestational Diabetes mellitus (GDM)		
No	44	61.97
Yes	27	38.03
Obstetrician Score		
Primigravida	36	50.70
Multigravida	49	49.3
Fetal Weight Category		
Appropriate for Gestational Age	62	87.32
Large for Gestational Age	2	2.82
Small for Gestational Age	7	9.86
Macrosomia	1	1.014
Insulin Requiring Therapy		
No	64	90.14
Yes	7	9.86
Mode of Delivery		
Primary Caesarean	14	19.72
Non-Spontaneous Vaginal Delivery	47	66.20
Repeat Caesarean	6	8.45
Vacuum Assisted	4	9.86
Hypertensive disorder (Pre-eclampsia or Gestational hypertension)		
No	63	88.73
Yes	8	11.27

standard deviation of the said parameters better characterize the samples' measure of central location and dispersion, respectively. For the rest of the parameters, non-normality was established; therefore, the median and interquartile range were used to determine the measure of central location and dispersion of the parameters, respectively.

For this study, factors deemed to be affected by HbA1c level were investigated for the purpose of statistical analyses. For the primary outcome, binary logistic regression modeling was performed to determine if HbA1c was a predictor of GDM. Subsequently, using the same method, secondary outcomes such as cesarean delivery, hypertensive disorders in pregnancy, and insulin requiring therapy during pregnancy (maternal outcomes), small or large for gestational age, macrosomia and preterm delivery (perinatal outcomes), and HbA1c as the predictor variable were analyzed. Odds ratio and corresponding 95% CI from binary logistic regression were computed. The values generated provided an estimate on the change of odds ratio for a positive outcome for every percent change in HbA1c level. Missing observations were neither replaced nor estimated. Null hypotheses were rejected at $p<0.05$ level of significance.

The calculated median for Hba1c was then utilized as a threshold value to predict GDM. Thereafter, the participants were then divided into two groups based on this value. Relative risk and corresponding 95% CI for the occurrence of GDM were then calculated.

Ethical Considerations. The research protocol was submitted to the Institutional Review Board of Chong Hua Hospital for review and approval prior to the

Table III. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value Using 5.2% HbA1c Threshold

Parameters	Estimate	95% CI
HbA1c threshold	5.2%	
Sensitivity	42.11%	26.31-59.18%
Specificity	67%	48.17-82.04%
Positive predictive value	16%	10.05-27.45%
Negative predictive value	88%	83.11-91.05%

Table IV Demographic and Clinical Profile of the Study Population in Accordance with HbA1c values of ≥ 5.2% and < 5.2%.

Clinical Characteristics	HbA1c <5.2 n=33	HbA1c ≥ 5.2 n=38	*p-value*
Age, years	30.78 ± 5.19	31± 4.51	0.8515
HbA1c	5 ± 0.17	5.4 ± 0.17	<0.001
FBS (mg/dl)	81.9 ± 16.64	85.87 ±7.67	0.215
Blood glucose level after intake of 75 grams oral glucose (mg/dl)			
1 hour	136.87 ±36.0	143.21±33.84	0.449
2 hours	129.54 ±27.6	123± 33.27	0.369
Hemoglobin (g/dl)	12.62 ± 0.90	12.3 ±0.87	0.134
Hematocrit (%)	37.66 ± 2.92	37.3± 2.27	0.568
Ballard score (weeks)	39± 1.20	39± 1.588	1
Birth weight (g)	2900 ± 511.04	2915.26 ±542.25	0.95

Table V. Comparison of Pregnancy Outcomes According to the First Trimester HbA1c Levels Using a Threshold of ≥ 5.2%.

Pregnancy outcomes (n= 71)	HbA1c < 5.2 n=33 (%)	HbA1c ≥ 5.2 n=38 (%)	RR (95%CI)	OR (95% CI)
Gestational diabetes mellitus (+ 75 grams OGTT at 24-28 weeks)	11(33)	16(42)	1.26 (0.6865, 2.3242)	1.45 (0.55, 3.83)
Caesarean section	7(21)	11(29)	1.36 (0.5981, 3.1138)	1.513 (0.508, 4.5)
Assisted delivery	4(12)	0	0.1 (0.0054, 1.7349)	0.1 (0.004, 1.64)
Preterm delivery	2 (6)	2 (5)	0.87 (0.1294, 5.827)	0.86 (0.1145,6.47)
Hypertensive disorders in pregnancy	2(6)	5 (13)	2.2 (0.4507,10.45)	2.35(0.4241,13.0)
Insulin-requiring therapy	2(6)	5 (13)	2.2 (0.4507,10.45)	2.35(0.4241,13.0
Small for gestational age	4(12)	3 (8)	0.65 (0.157, 2.70)	0.62 (0.13, 3.0)
Large for gestational age	0	2 (5)	4.36 (0.2167, 87.67)	4.6 (0.21, 99.0)
Macrosomia	0	1 (3)	2.62(0.11, 62.1)	2.68 (0.11, 68.0)

initiation of the study. It was approved with Reference code 1219-01. All information was kept confidential and data gathered were utilized exclusively for the purpose of the research only.

All of the participants were enrolled as charity patients both by the OB residents and researcher. Hence, the cost of the examination was covered by the charity service of the institution.

Results

One hundred and two pregnant women were initially recruited in this study. Four participants were excluded due to chronic hypertension, one subject was excluded due to pre-existing diabetes mellitus with an HbA1c level of 11.5%, and two participants transferred to another institution.

A total of 95 participants fulfilled the inclusion criteria; however, 24 (25.2%) have missing HbA1c levels and were excluded. Hence, 71 participants were included in the final analysis. These participants had a mean age of 31.34 years, hemoglobin level of 12.45 g/dl and hematocrit level of 37.47%, with median HbA1c level of 5.2%, fasting blood sugar 83 mg/dl, 1 hour and 2 hours blood glucose level after intake of 75 grams oral glucose of 140.27 and 123 mg/dl, age of gestation 39 weeks, fetal weight 2900 grams, and APGAR score 1 and 5 minutes after birth of 9 (*Table I*).

Majority of the participants did not have GDM (61.97%). Meanwhile, 50% of the samples were primigravid and approximately 90% of the samples did not have insulin-requiring therapy and had pregnancies which resulted to appropriate for gestational age (AGA). Also, majority of delivery were via non-spontaneous vaginal delivery (66.2%) and the gender of the babies were boys

Table VI. Association of HbA1c level to the Occurrence of Gestational Diabetes mellitus, Maternal and Perinatal outcomes

	Mean ± SD	Odds ratio (95% Wald CI)	p-value
Gestational Diabetes Mellitus			
With GDM (n=27)	5.17 (± 0.286)	1.232 (0.329,4.622)	0.7568
Without GDM (n=44)	5.14 (± 0.427)		
Maternal Outcomes			
Insulin-Requiring Therapy			
With insulin-requiring therapy (n=7)	5.20 (± 0.342)	1.608 (0.139, 18.609)	0.7036
Non-insulin requiring therapy (n=64)	5.14 (± 0.383)		
Cesarean Delivery			
Caesarean Delivery (n=20)	5.25 (± 0.280)	3.654 (0.562, 3.746)	0.1593
NSVD/Vacuum Assisted Delivery (n=51)	5.11 (± 0.406)		
Hypertensive disorders in Pregnancy			
With Pre-eclampsia (n=8)	5.31 (± 0.275)	8.282 (0.464, 7.816)	0.1504
Without Pre-eclampsia (n=63)	5.13 (± 0.386)		
Perinatal Outcomes			
SGA Fetal Weight			
With SGA Fetal Weight (n=7)	5.04 (± 0.331)	0.521 (0.099, 2.741)	0.4418
Without SGA Fetal Weight (n=64)	5.16 (± 0.383)		
LGA Fetal Weight and HbA1c Level			
With LGA Fetal Weight (n=2)	5.45 (± 0.071)	69.267 (0.143, >999.999)	0.1791
Without LGA Fetal Weight (n=69)	5.14 (± 0.379)		
Macrosomia and HbA1c Level			
With Macrosomia (n=1)	5.20	1.549 (0.003, 773.922)	0.8902
Without Macrosomia (n=70)	5.15 (± 0.380)		
Preterm Delivery			
With Preterm Delivery (n=6)	5.20 (± 0.346)	1.587 (0.091, 27.605)	0.7512
Without Preterm Delivery (n=66)	5.15 (± 0.382)		

(67.61%). Meanwhile, 11.27% of the samples were diagnosed with hypertensive disorders such as pre-eclampsia and gestational hypertension (*Table II*).

Table III shows the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) using the calculated median HbA1c of 5.2% as threshold. It showed that an HbA1c level of 5.2% had a sensitivity of 42.11% and specificity of 67% to predict GDM. It has a NPV of 88% and a PPV of 16%.

Table IV presents the demographic and clinical profile of the study population in accordance with glycosylated hemoglobin HbA1c values of ≥ 5.2% and < 5.2%.

In utilizing HbA1c threshold of ≥ 5.2%, there is a two-fold increased risk of developing hypertensive disorders in pregnancy, requiring insulin during the course of gestation and having macrosomic newborns, and four-fold increased risk of having LGA newborns.

Table V shows the comparison of pregnancy outcomes according to the first trimester HbA1c levels using a threshold of ≥ 5.2%.

Table VI shows the association of HbA1c level to the occurrence of GDM, maternal and perinatal outcomes.

The results suggest that comparable HbA1c is observed for the sample with GDM and those who do not have GDM. The binary logistic regression analysis further suggested that the association between HbA1c and GDM has an OR of 1.232 (95% CI: 0.329,4.622), which means that for every 1% increase in HbA1c, the odds of having gestational diabetes increases by 1.232. Nevertheless, this association is not statistically significant (*p=0.7568*).

The association between HbA1c and maternal outcomes, specifically the requirement of insulin in the participants' therapy, the occurrence of caesarean delivery, the diagnosis of hypertensive disorders in pregnancy: pre-eclampsia and gestational hypertension, were also investigated.

As for the insulin-requiring therapy, similar HbA1c were observed between participants with insulin-requiring and non-insulin requiring therapy. The odds ratio suggested for a 1% increase in the HbA1c, the odds of having an insulin-required therapy increases by 1.608. However, the *p-value* and 95% CI show that HbA1c is not predictive of the maternal outcome pertaining to insulin-requiring therapy.

Furthermore, similar HbA1c are demonstrated for the participants who had caesarean delivery and those who did not. Also, the same conclusions are drawn on the insignificance of HbA1c level as a predictor of having a cesarean delivery.

The presence or absence of a hypertensive disorder is also of interest as a variable that can potentially be predicted by HbA1c. The results, however, suggested that hypertensive disorder (specifically pre-eclampsia and gestational hypertension) cannot significantly be determined by HbA1c. The inclusion of 1.0 in the 95% CI

as well as the p-value supports this conclusion. This can also be supported by the comparability in HbA1c levels on the groups with hypertensive disorder and those without.

Therefore, it can be concluded that there is no association between the maternal outcomes considered and the HbA1c levels based on the data in this study.

The associations of HbA1c levels and perinatal outcomes, specifically SGA and LGA fetal weights, macrosomia, and preterm delivery were also investigated.

Comparable HbA1c levels were observed between participants with SGA fetal weights and those who do not. The same conclusions were drawn for the HbA1c levels between groups with and without large for gestational age fetal weight, as well as those with and without macrosomia and those who had preterm delivery and its compliment. The OR suggest that for every 1% increase in HbA1c, the OR for a positive outcome for LGA fetal weight, SGA fetal weight, macrosomia and preterm delivery increase by 0.521, 69.267, 1.549, and 1.587, respectively. Meanwhile, the *p-value* and 95% CI of the calculated OR show that the HbA1c level is not a significant predictor of the perinatal outcomes considered.

Discussion

Approximately 14% of Filipino pregnant women are diagnosed with GDM.[5] It is a health burden that affects significantly the mother and the unborn child in which it imposes greater morbidity and mortality risks and additional health care cost. Currently, its prevalence is growing worldwide due to the increasing trend of obesity, dyslipidemia, metabolic syndrome and T2DM. In fact, GDM is one of the major predisposing factors for the development of T2DM.

Screening test using 75 grams OGTT, is recommended for all pregnant women who are at risk of developing GDM. However, due to multiple blood extractions and the glucose drink being unpalatable, this test has a drawback of being unappealing to pregnant women. Hence, the potential of an alternative screening tool such as HbA1c is studied.

In this study, it was demonstrated that an HbA1c level of ≥ 5.2 % had a sensitivity of 42.11%, specificity of 67% and NPV of 88% for the detection of GDM. This is in concordance with a prospective cohort study, in which HbA1c level of ≥ 5.2% was noted be the optimal threshold for detecting GDM among Singaporean women with sensitivity of 82% and specificity of 72% as well as NPV of 97%.[3] In fact, in our study, GDM patients with HbA1c of ≥ 5.2% are two times more likely to require insulin therapy than those with lesser HbA1c, which therefore warrants stricter compliance to diet and closer sugar monitoring.

Moreover, those participants with HbA1c level of ≥ 5.2%, regardless of whether they are diagnosed to have GDM or not based on 75 grams OGTT, are two times more likely to develop hypertensive disorders of pregnancy and to have macrosomic newborns, and four times more likely to have LGA newborns. In a study by Wang, et. al, in Taiwan, a lower HbA1c threshold of > 5.0% during mid-trimester was noted to be associated with adverse outcomes including preterm delivery, pre-eclampsia, caesarean delivery and macrosomia.[11] Another study in Brazil showed that an HbA1c > 5.9% had a three-fold increased risk of having a macrosomic newborns and developing pre-eclampsia.[9] Likewise, a study conducted by Hughes, et. al in New Zealand and by Osmundson, et. al., in North America also reported a threshold of HbA1c 5.9% and 5.7%, respectively, to detect pregnant women at significantly greater risk of developing GDM along with its adverse maternal and perinatal outcomes.[12,13]

The incongruence of cutoff points for HbA1c between Asian and Caucasian pregnant women suggested the need for a different threshold and/or reference range of HbA1c among different ethnic groups. Whether these variations are related to differences in the prevalence of conditions affecting erythrocyte turnover, genetic glycation differences, or differences in glycemia that are not represented by the fasting and 2-hour plasma glucose levels of OGTT, needs to be elucidated further.

There are also conflicting results regarding the true correlation of HbA1c levels and GDM and its adverse maternal and perinatal outcomes. As previously mentioned, it was shown that an early pregnancy HbA1c level 5.9% was utilized to identify women with diabetes in pregnancy and predicted increased risk of adverse pregnancy outcomes, including major congenital anomaly, preeclampsia, shoulder dystocia, and even perinatal death.[12] Another study likewise concluded that an HbA1c of 5.9% taken at the time of diagnosis of GDM despite subsequent treatment still predicts an increased risk of several adverse pregnancy outcomes including macrosomia, LGA, caesarean section, and hypertensive disorders of pregnancy.[14] In contrast, the HAPO study group showed poorer correlation of HbA1c with 75 grams OGTT in diagnosing GDM and its adverse pregnancy outcome.[15] Only caesarean section, pre-eclampsia and preterm delivery showed comparable OR risk between HbA1c levels and 75 grams OGTT.

Although diagnosis of GDM and adverse pregnancy outcomes were significantly higher in terms of proportion using the threshold HbA1c level of ≥ 5.2%, the *p values* for their association are not statistically significant in our study. HbA1c level of ≥ 5.2% had a PPV of only 16.05% hence it is insufficient to replace 75 grams OGGT as a screening test for GDM. However, it does have a high NPV of 88% which means it can be used to rule out risk of GDM as early as in the first trimester, and pregnant women can do away with 75 grams OGTT during the 24-28weeks age of gestation.

The lack of association of HbA1c and the occurrence of GDM in this study may be due to the small sample size as reflected by the wide 95% CI in the results presented. Hence, to further support the result of this study and to

gather more information with regards to this association, a bigger sample size is recommended for future studies.

Limitation of the Study

This study was limited in terms of the number of participants since the recruitment was voluntary. Detecting participants with unknown blood dyscrasias specifically, hemoglobinopathies, that can alter their HbA1c levels was not done. Other confounding factors that were not considered in the study were the participants' BMI and history of polycystic ovarian syndrome which can influence insulin sensitivity hence HbA1c level.

Also, since the study population was not placed in a controlled environment during the entire pregnancy, variables such as diet and exercise, that can greatly affect glucose metabolism, were not monitored. However, proper diet and exercise using the 2019 American Diabetes Association guidelines were advised during the initial and follow up visits.

Clinical Implications

Although HbA1c cannot be used as a screening tool to diagnose GDM due to its low PPV based on the results of this study, it can be used to rule out the risk for GDM as early as in the first trimester of pregnancy. Moreover, HbA1c of ≥ 5.2% can be used as an additional risk stratification tool among GDM patients for potential need of insulin therapy along the pregnancy course as well as risk of poor pregnancy outcome.

Conclusion

The association of HbA1c level and the occurrence of GDM was not observed in this study. However, by using an HbA1c threshold of ≥5.2%, as opposed to the standard reference range for diagnosing T2DM and GDM mellitus in Caucasians, the relative risk of developing GDM in the 24-28 weeks AOG is 1.26 (*p=0.6865*, 2.3242). As with the secondary outcomes such as hypertensive disorders in pregnancy, requiring insulin therapy during pregnancy, macrosomic newborns and large for gestational age newborns, the relative risk is 2.2, 2.2, 2.6 and 4.6, respectively.

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