Comparison of Maternal and Neonatal Outcomes Among High-Risk Filipino Women With Gestational Diabetes Diagnosed Before and After 24 Weeks of Gestation

Kriselle Rae Dy and Christy Yao

Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, The Medical City, Pasig City, Philippines

Abstract

Objectives. This study determined the prevalence, clinical characteristics and pregnancy outcomes of high-risk women diagnosed with gestational diabetes mellitus (GDM) before and after 24 weeks of gestation.

Methodology. This retrospective study included all singleton deliveries with GDM at the Pasig City General Hospital from January 2018 to December 2019. Subjects were grouped into those who were diagnosed with GDM before 24 weeks of gestation (<24 weeks, n=61) and thereafter (≥24 weeks, n=219). Outcomes examined were preeclampsia, cesarean delivery, preterm birth, macrosomia, large-for-gestational age, small-for-gestational age, neonatal hypoglycemia, neonatal ICU admission, congenital malformations and perinatal mortality.

Results. The group diagnosed with GDM before 24 weeks was significantly older (33.0 ± 5.7 years versus 29.4 ± 5.9 years, $p<0.001$), had higher 2-hour 75 g oral glucose tolerance test (OGTT) results (158.2 ± 20.0 mg/dL versus 150.0 ± 23.7 mg/dL, $p=0.014$), and had more pregnancies with preeclampsia (23.0% versus 9.6%, $p=0.005$).

Conclusion. High-risk women diagnosed with GDM before 24 weeks of gestation had a higher incidence of preeclampsia compared with high-risk women diagnosed with GDM after 24 weeks of gestation.

Key words: prenatal screening, diabetes, gestational, pregnancy outcomes

INTRODUCTION

Gestational diabetes mellitus (GDM) is known to be associated with perinatal and maternal morbidity, including excessive fetal size, which leads to operative delivery and birth trauma. In a study done at the Philippine General Hospital in 2013, women diagnosed with GDM had an increased risk for primary caesarean section and infant admission to the neonatal intensive care unit (NICU).[1]

There are still many areas regarding GDM management that lack consensus among different authorities. These include the diagnostic criteria, classification, timing of screening and screening population (universal versus selective screening).

The International Association of Diabetes Pregnancy Study Group (IADPSG) proposed the following diagnostic criteria: fasting plasma glucose value ≥92 mg/dL and/or 1-hour glucose value ≥180 mg/dL and/or 2-hour glucose value ≥153 mg/dL in a 75 g OGTT. It should be noted that the screening criteria given by the IADPSG for the diag-

nosis of GDM at 24 to 28 weeks age of gestation (AOG) has not been validated in the first or early second trimester.[2]

Screening for GDM is usually performed between 24 to 28 weeks of gestation because insulin resistance increases during the second trimester, and glucose levels increase in women who do not have the ability to produce enough insulin to counter this resistance.[3] Presently, routine screening for GDM in the Philippines is done at 24 to 28 weeks of gestation.

The importance of early identification of dysglycemia in pregnancy arises from the effect of early maternal hyperglycemia on fetal growth and existing literature on early GDM reported poor outcomes.[4] The Philippine UNITE for Diabetes Clinical Practice Guidelines and the Philippine Obstetrical and Gynecological Society 2018 Clinical Practice Guidelines on Diabetes Mellitus in Pregnancy recommend that all pregnant women should be evaluated at the first prenatal visit for risk factors for diabetes. These risk factors include age ≥25 years old, overweight or obese before pregnancy, history of abnormal

Corresponding author: Kriselle Rae S. Dy, MD
Endocrine, Diabetes and Thyroid Center, The Medical City,
Ortigas Avenue, Pasig City, 1604, Philippines
Tel. No: +632-8-988-1000
E-mail: kriselledy@gmail.com
ORCiD: https://orcid.org/0000-0003-3818-8750

glucose metabolism, history of poor obstetric outcome (prior GDM, macrosomia, congenital malformations, recurrent abortions, unexplained intrauterine death), family history of diabetes among first degree relatives, intake of drugs affecting carbohydrate metabolism and glucosuria.[5] Having any of these risk factors confers a high risk for GDM, and a 75 g OGTT should be done as soon as possible. However, this is not universally followed and screening for GDM before 24 weeks remains at the discretion of the primary healthcare provider.

Looking into the pregnancy outcomes associated with earlier identification of GDM in the local setting can help reinforce the recommendations for earlier screening for high-risk women, especially in primary care.

OBJECTIVES

This study aimed to determine the prevalence, clinical characteristics and pregnancy outcomes among Filipino women who delivered at Pasig City General Hospital from January 2018 to December 2019. Women who were diagnosed with GDM before 24 weeks of gestation were compared with women who were diagnosed after 24 weeks of gestation. Maternal outcomes included incidence of preterm delivery, primary caesarean section and preeclampsia. Neonatal outcomes included incidence of macrosomia, large-for-gestational age (LGA) and small-for-gestational age (SGA), hypoglycemia, neonatal ICU admission, congenital malformations and perinatal mortality.

METHODOLOGY

This was a retrospective cohort study of Filipino women diagnosed with GDM at the Pasig City General Hospital from January 1, 2018 to December 31, 2019. Institutional review board approval was obtained.

Starting 2018, it was mandated that all pregnant women seen at the institution's Outpatient Department (OPD) were to be screened for risk factors for diabetes based on the UNITE CPG during their first prenatal visit. Women who had at least one risk factor were considered high-risk and were advised to undergo 75 g OGTT immediately. If they tested negative, they underwent a repeat 75 g OGTT at 24 to 28 weeks. Patients who did not have any identified risk factors underwent 75 g OGTT at 24 to 28 weeks of gestation. Patients were diagnosed with GDM according to the IADPSG criteria based on their 75 g OGTT results.

High-risk women diagnosed with GDM were immediately referred to a multidisciplinary team comprising a dietician, a nurse educator and an endocrinologist. They received individualized dietary advice and self-monitoring of blood glucose education. On follow up after two weeks, insulin therapy was started if fasting blood glucose levels were more than 95 mg/dL and 2-hour postprandial glucose levels were more than 120 mg/dL.[6] Medications

and subsequent blood sugar monitoring were adjusted at the discretion of the attending endocrinologist. Obstetric care was in accordance with local standards of care.

Subjects included were women diagnosed with GDM using the IADPSG criteria with singleton pregnancies seen at the OPD and who delivered at the Pasig City General Hospital with complete prenatal, obstetric and offspring neonatal records. Women diagnosed with and treated for diabetes before pregnancy, diagnosed with overt diabetes (FBS ≥126 mg/dL or 2-hour blood glucose levels ≥200 mg/dL post-glucose intake) and those with twin or multiple pregnancies were excluded.

Maternal data included age, parity, prior caesarean section and indication, gestational age at first prenatal visit, gestational age at diagnosis of GDM, 75 g OGTT results, need for insulin treatment, development of preeclampsia, gestational age at delivery, mode of delivery and indication. Neonatal outcomes included APGAR scores, birth weight, birth length, admission to NICU, neonatal hypoglycemia, congenital malformations and perinatal mortality.

Descriptive statistics were used to summarize the general and clinical characteristics of the patients. Categorical variables were reported as frequency and percentage. Continuous quantitative data that met normality assumption by Shapiro-Wilk test were summarized using mean and standard deviation (SD), while those that did not were described with median and range. The two screening groups were compared in terms of their baseline characteristics, maternal outcomes and neonatal outcomes using the following statistical tests: independent samples t-test for continuous data with normal distribution, Mann-Whitney U test for continuous data that deviates from the normal distribution, chi-square test for ordinal/nominal variables and Fisher's exact test for ordinal/nominal variables with expected frequencies less than 5%. Statistical significance was set at $p \leq 0.05$.

Logistic regression was used to determine the association of timing of screening with maternal and neonatal outcomes. Crude odds ratio (OR) and its corresponding 95% confidence intervals (CI) were reported.

STATA version 15.0 (StataCorp SE, College Station, TX, USA) was used for data analysis.

RESULTS

From 2018 to 2019, the institution recorded 5072 deliveries, of which 561 were associated with GDM. This was equivalent to a period prevalence of 11.06 (95% CI, 10.21 to 11.96) per 100 births.

Of the 561 patients with GDM, 280 met the inclusion criteria for this study. Twenty-five patients were excluded as they were diagnosed with GDM not using the IADPSG criteria. Two hundred fifty-six patients were excluded
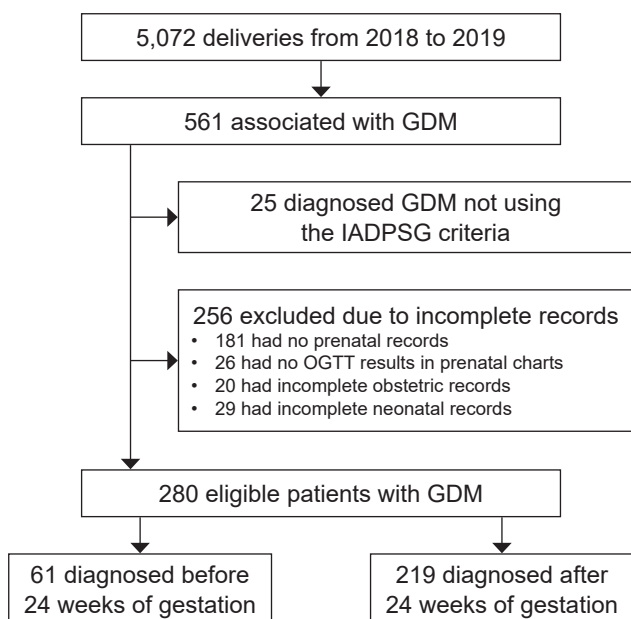
Figure 1. Study design and eligibility of patients.

GDM, gestational diabetes mellitus; IADPSG, International Association of the Diabetes and Pregnancy Study Groups; OGTT, oral glucose tolerance test.

due to incomplete records: 181 delivered at the institution but had no OPD prenatal records, 26 did not have OGTT results in their prenatal charts, 20 had incomplete obstetric records, and 29 had incomplete neonatal records of their offspring (Figure 1).

The 280 eligible patients were reviewed and analyzed: 61 (22%) were diagnosed with GDM before 24 weeks and 219 (78%) were diagnosed with GDM after 24 weeks of gestation (Table 1). Women diagnosed earlier were significantly older (mean 33.0 ± 5.7 years versus 29.4 ± 5.9 years) with 41% older than 35 years of age. They also had higher 2-hour OGTT results (mean 158.2 ± 20.0 mg/dL versus 150.0 ± 23.7 mg/dL) compared to those who were diagnosed after 24 weeks.

On the other hand, FBS, 1-hour OGTT, gravidity, parity and history of prior cesarean section (CS) were comparable between the two patient groups.

There were significantly more women with preeclampsia in the group diagnosed with GDM before 24 weeks (23.0% versus 9.6%, p=0.005) than in the group diagnosed with GDM after 24 weeks gestation. It is notable that there were nearly twice more preterm deliveries among those diagnosed earlier (14.8% versus 7.8%), although this was not statistically significant. The mode of delivery and requirement for insulin was not significantly different between the two groups (Table 2).

Women diagnosed with GDM before 24 weeks had proportionately more neonates born preterm (defined as AOG before 37 weeks) compared with women diagnosed with GDM after 24 weeks (16.4% versus 8.3%) but this did not reach statistical significance. Although the size

Table 1. Maternal baseline characteristics by timing of diagnosis of gestational diabetes mellitus

	Total (N=280)	<24 weeks (n=61)	≥24 weeks (n=219)	p value
Age, years	30.2 ± 6.0	33.0 ± 5.7	29.4 ± 5.9	<0.001*
<35	208 (74.3)	36 (59.02)	172 (78.5)	0.002‡
≥35	72 (25.7)	25 (40.98)	47 (21.5)	
Gravidity				0.252†
G1	86 (30.7)	14 (22.95)	72 (32.9)	
G2 to G5	185 (66.1)	46 (75.41)	139 (63.5)	
≥G6	9 (3.2)	1 (1.64)	8 (3.7)	
Parity				0.543†
P1 to P4	263 (93.9)	56 (91.8)	207 (94.5)	
≥P5	17 (6.1)	5 (8.2)	12 (5.5)	
Previous CS[a]	61 (21.8)	15 (24.6)	46 (21.0)	0.549‡
FBS[b], mg/dL	89.9 ± 12.3	91.0 ± 11.7	89.6 ± 12.4	0.406*
75 g OGTT[c], mg/dL				
1-hour	176.4 ± 30.3	182.2 ± 29.6	174.8 ± 30.3	0.094*
2-hour	151.8 ± 23.1	158.2 ± 20.0	150.0 ± 23.7	0.014*

Data presented are mean ± SD, frequency (%), or median (range)
*Independent samples t-test
‡Chi-square test
†Fisher's exact test
[a]CS, cesarean section
[b]FBS, fasting blood sugar
[c]OGTT, oral glucose tolerance test

Table 2. Maternal outcomes by timing of diagnosis of gestational diabetes mellitus

	Total (N=280)	<24 weeks (n=61)	≥24 weeks (n=219)	p value
Preterm delivery	26 (9.3)	9 (14.8)	17 (7.8)	0.096‡
Mode of delivery				0.726‡
NSD[a]	157 (56.1)	33 (54.1)	124 (56.6)	
CS[b]	123 (43.9)	28 (45.9)	95 (43.4)	
Primary	64 (52.0)	15 (53.6)	49 (51.6)	0.853‡
Need for insulin	10 (3.6)	4 (6.6)	6 (2.7)	0.232†
Preeclampsia	35 (12.5)	14 (23.0)	21 (9.6)	0.005‡

Data presented are frequency (%)
‡Chi-square test
†Fisher's exact test
[a]NSD, normal spontaneous delivery
[b]CS, cesarean section

for gestational age appeared to be associated with timing of diagnosis (p=0.038), pairwise comparisons based on Bonferroni adjusted p-values indicated comparable proportions between the two groups (Table 3). Macrosomic babies were delivered by the group diagnosed after 24 weeks (6.0% versus 0.0%). NICU admissions rate was higher in the group diagnosed before 24 weeks (13.3% versus 7.8%, p=0.188), although this did not reach statistical significance. Hypoglycemia was noted in one neonate in the group diagnosed with GDM after 24 weeks of gestation.

Other neonatal outcomes (proportions of live births; congenital anomaly; neonatal hypoglycemia; NICU admission and APGAR scores at 1, 5 and 10 minutes) were not significantly different between the two groups.

There were three neonates with congenital malformations (congenital heart disease, fetal hydrocoele and diaphragmatic hernia), all born to mothers diagnosed with GDM after 24 weeks gestation.

Table 3. Neonatal outcomes by timing of diagnosis of gestational diabetes mellitus

	Total (N=280)	<24 weeks (n=61)	≥24 weeks (n=219)	p value
Neonate sex				0.987‡
Male	148 (53.4)	32 (53.3)	116 (53.5)	
Female	129 (46.6)	28 (46.7)	101 (46.5)	
Live birth	277 (98.9)	60 (98.4)	217 (99.1)	0.523†
Gestational age at birth				
Preterm (≥37 weeks)	28 (10.0)	10 (16.4)	18 (8.3)	0.062‡
Term (<37 weeks)	251 (90.0)	51 (83.6)	200 (91.7)	
Birthweight, kg	3 (0.6–4.2)	3 (0.6–3.7)	3 (1.5–4.2)	0.338§
Birth length, cm	50 (31–56)	50 (31–55)	50 (38–56)	0.230§
Macrosomia	3 (1.1)	0	3 (1.4)	0.999†
APGAR score				
1-minute	8 (3–9)	8 (3–9)	8 (3–9)	0.851§
5-minute	9 (4–9)	9 (5–9)	9 (4–9)	0.123§
Size for GA				0.038†a
Small	6 (2.17)	3 (5.0)	3 (1.4)	
Appropriate	259 (93.5)	57 (95.0)	202 (93.1)	
Large	12 (4.3)	0	12 (5.5)	
Congenital anomaly	3 (1.1)	0	3 (1.4)	0.999†
Neonatal hypoglycemia	1 (0.4)	0	1 (0.5)	0.999†
NICU admission	25 (9.0)	8 (13.3)	17 (7.8)	0.188†

Data presented are frequency (%) or median (range)
‡Chi-square test
†Fisher's exact test
§Mann-Whitney U test
aNon-significant on pairwise comparisons using Bonferroni adjusted p values.
bNICU, neonatal intensive care unit

Table 4. Effect of timing of screening on maternal outcomes and neonatal outcomes

Outcome	n	Crude OR[a] (95% CI[b])	p value
Composite			
Poor maternal outcomes		0.769 (0.42–1.41)	0.394
Adverse neonatal outcomes		0.806 (0.38–1.71)	0.574
Individual			
Preterm delivery	26	0.486 (0.21-1.15)	0.102
Primary CS[c]	64	0.884 (0.46-1.72)	0.716
Need for insulin	10	0.401 (0.11-1.47)	0.168
Preeclampsia	35	0.356 (0.17-0.75)	0.007
Birthweight <2500 g	36	0.375 (0.18-0.79)	0.010
SGA[d] or LGA[e]	18	1.411 (0.39-5.04)	0.596
NICU[f] admission	25	0.558 (0.23-1.36)	0.200

aOR, odds ratio
bCI, confidence interval
cCS, Caesarean section
dSGA, small for gestational age
eLGA, large for gestational age
fNICU, neonatal intensive care unit

DISCUSSION

The period prevalence of GDM in this two-year study was 11.06%, similar to those reported by other local studies.[7,8]

The mean age of women diagnosed with GDM before 24 weeks was significantly higher. Studies have shown that increasing maternal age is a risk factor for developing GDM thus older patients are more likely to be screened earlier.[9]

The 2-hour glucose results in the 75 g OGTT were higher in those who were diagnosed with GDM before 24 weeks of gestation. This observation might be considered when screening for glucose intolerance in early pregnancy using 75 g OGTT. The OGTT may be more sensitive than FBS alone to diagnose GDM in early pregnancy. However, there is paucity of data on OGTT values in early pregnancy and the IADPSG criteria are not validated for early pregnancy. Further studies on this topic are needed. Most of the current glucose thresholds for the diagnosis of GDM are derived from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study and are only validated for use between 24 and 32 weeks of gestation.[10-12]

There were more women with preeclampsia in the group diagnosed with GDM before 24 weeks. Several studies noted similar results, even after adjustment for maternal age, ethnicity, parity, weight and blood glucose control.[13,14]

The development of preeclampsia appears to be associated with insulin resistance and may explain its increased risk and incidence among women with GDM. Management of GDM patients diagnosed earlier, includes not only earlier glycemic control but also earlier blood pressure control.

The increased incidence and higher odds of developing preeclampsia among mothers who were diagnosed before 24 weeks of gestation may be attributed not only to GDM but also to other risk factors that predispose patients to developing preeclampsia such as previous history of preeclampsia, nulliparity, higher body mass index (BMI),

There were three stillbirths: one born to a woman screened early for GDM, and two from pregnancies diagnosed with GDM after 24 weeks.

To explore the impact of timing of screening on the maternal and neonatal outcomes, logistic regression analysis was performed.

We compared the maternal and neonatal composite outcomes between screening time groups. The maternal composite outcome included preterm delivery and primary caesarean section, while the neonatal composite outcome included macrosomia, SGA/LGA, hypoglycemia, NICU admission, congenital malformations and perinatal mortality.

After stratifying according to timing of screening, univariate analysis showed that timing of screening was not associated with the composite of poor maternal outcomes and the composite of adverse neonatal outcomes (Table 4).

On individual outcome analysis, timing of screening was statistically significant in predicting preeclampsia and low birth weight among those screened before 24 weeks of gestation. The crude OR of preeclampsia and low birth weight is 0.356 and 0.375 times, respectively, lower for those screened after 24 weeks of gestation (Table 4).

preexisting hypertension, advanced age (more than 40 years) and family history.[15] One limitation of our study is that the risk factors that may have prompted earlier screening were not included during the data collection and analysis.

Although there was insufficient evidence to conclude statistical significance, we observed a trend towards more preterm deliveries in the group diagnosed with GDM before 24 weeks of gestation. The subsequent management following the diagnosis of GDM involves increased frequency of prenatal visits, with additional maternal and fetal monitoring.[16] An earlier diagnosis of GDM may have resulted in more obstetric interventions, taking into consideration conditions such as preeclampsia that may be present in the high-risk early screening group. It was noted that in the subgroup of mothers who developed preeclampsia, preterm delivery was more common among those who were diagnosed earlier (5/14 or 36%) compared to those diagnosed after 24 weeks of gestation (4/21 or 19%) (p=0.432).

The use of insulin was comparable between the two groups. Previous studies have observed more frequent and earlier use of insulin with higher daily doses in those diagnosed with early GDM without improved outcomes.[17-19]

The mode of delivery did not differ between groups, which was similar to the study of Hong et al., where early screening was not associated with significant reduction in the risk of caesarean section.[20]

Although not statistically significant, more neonates in the early GDM group had lower age of gestation at delivery. In the study by Hong et al., women who were screened earlier were more likely to deliver preterm. These women had a higher prevalence of increased BMI, previous GDM and chronic hypertension.[20] The risk factors that may have been present in the group diagnosed with GDM before 24 weeks of gestation in this study may have contributed to the preterm births in addition to increased monitoring of these high-risk patients. Studies that reviewed the benefits and harms of early screening showed that the diagnosis of glucose intolerance in early pregnancy led to more monitoring and interventions, including induction of labor, which may have led to preterm deliveries, without improvement in outcomes.[21,22]

The absence of LGA neonates and higher odds of having neonates with low birth weight in the group diagnosed with GDM before 24 weeks may be due to earlier interventions to control diet and hyperglycemia. Similar studies have concluded that timely restrictions and pharmacologic interventions are contributing factors to limited weight gain in the early screening group.[18,19]

In our study, there were three macrosomic neonates in the group diagnosed with GDM after 24 weeks. LGA neonates were observed to be born to younger mothers. The mothers who had LGA offspring had their screening done much later than the recommended 24 to 28 weeks AOG: six out of the 12 had their OGTT beyond 28 weeks age of gestation. This might have led to delayed interventions for GDM control. Two of the three mothers with macrosomic offspring sought first consult for GDM beyond 30 weeks AOG despite having been screened at 24 to 28 weeks AOG. The compliance to diagnostic requests and the health-seeking behavior of the subjects prove to be realistic limitations in the management of GDM in the local setting.

The limitations of this study include its retrospective design and short time frame of only two years. It was conducted in one institution, limited to women who had their prenatal consults and subsequent delivery at the same institution, excluding a significant number of women who delivered at this institution but did not have their prenatal checkups at the OPD. The risk factors that might have been present in our subjects that prompted early screening and may have contributed to pregnancy complications were not determined.

CONCLUSION

The group diagnosed with GDM before 24 weeks was significantly older and had higher 2-hour 75 g OGTT results compared to the group diagnosed with GDM after 24 weeks of gestation. There were more women in whom GDM was diagnosed earlier in pregnancy who developed preeclampsia and delivered preterm neonates compared to women in whom GDM was diagnosed later in pregnancy. Preeclampsia may be from earlier onset of GDM. There may have been other risk factors contributing to these outcomes in these high-risk patients.

Based on this study's results and limitations, we recommend a prospective study comparing differences in pregnancy outcomes in patients screened before 24 weeks AOG, at 24 to 28 weeks AOG and after 28 weeks AOG using the 75 g OGTT. It is also recommended that all risk factors affecting pregnancy outcomes be considered in future studies. Further research is also needed to determine if early screening for GDM should be done in all pregnant women regardless of the presence or absence of risk factors.

Statement of Authorship
Both authors certified fulfillment of ICMJE authorship criteria.

Author Contribution Statement
KD collected the data and wrote the manuscript. CY contributed to the discussion and reviewed and approved the final version of the manuscript.

Author Disclosure
Both authors declared no conflict of interest.

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