Insulin Analog Use and Pregnancy Outcomes Among Women with Gestational Diabetes Mellitus (GDM): A Retrospective Analysis at the University of Santo Tomas Hospital

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Abstract

Introduction: Approximately 40% of women with gestational diabetes mellitus (GDM) will require insulin when diet failed to reduce glycemic levels. Insulin analogs have been noted to result in an improved glycemic control and an acceptable safety profile in diabetes mellitus. Our general objective was to evaluate the efficacy, safety, and pregnancy outcomes of insulin analog versus human insulin in women with GDM.

Methods: Retrospective cohort analysis of women with singleton pregnancy and GDM from January 2013 to March 2016 at the University of Santo Tomas Hospital was performed. Women were grouped into Group A (diet-controlled), Group B (supplementary insulin analog), Group C (supplementary human insulin), and Group D (combination of supplementary insulin analog and human insulin). Maternal characteristics, glycemic data, and outcomes and neonatal outcomes were compared among the treatment groups. Parametric data were expressed as mean, standard deviation, frequency, and percentage. Chi-square and one-way analysis of variance were utilized to analyze data.

Results: Of 144 women with GDM, 59 received insulin analog and 19 received human insulin. Good glycemic control and low rate of hypoglycemia in Group B were comparable to other groups. Maternal outcomes (hypertensive disorders of pregnancy and primary cesarean section) in Group B were not increased and similar to other groups. Neonatal outcomes (birth weight, large for gestational age, neonatal hypoglycemia, neonatal jaundice, and acute respiratory distress syndrome) in Group B were also not increased and comparable to other groups. Rates of prematurity were higher in Groups A and B.

Conclusion: Our study demonstrated that insulin analog was comparable to human insulin in terms of non-increased rates of adverse pregnancy outcomes with the exception of prematurity, and can be safely used as a viable treatment option without increased risk of hypoglycemia while achieving optimal glycemic control throughout pregnancy in Filipino women with GDM.

Keywords: gestational diabetes mellitus; insulin analog; pregnancy outcome

Introduction

The marked increase in the incidence of diabetic patients presenting at an earlier age has led to the increasing trend of patients with diabetes during pregnancy. An estimated 76 million women, 20 to 39 years of age who have diabetes or pre-diabetes may give rise to increased prevalence of pregestational or gestational diabetes mellitus (GDM).[1]

The prevalence of GDM in the Philippines is 6.7% which is nearly similar to the prevalence of GDM at the University of Santo Tomas Hospital Clinical Division (USTH CD) which is at 7.5%.[2] Presence of GDM increases the risks of maternal and fetal complications that manifest even after pregnancy. Women with elevated blood glucose levels have a greater risk of having adverse maternal and fetal outcomes, including preeclampsia, premature birth, primary cesarean section (CS), macrosomia, birth injury, neonatal hypoglycemia, congenital anomalies, and future type II diabetes mellitus (DM).[2,3] Macrosomia or delivery of a baby with a weight of eight pounds (3.6 kilograms) is the most common and significant neonatal complication as maternal glycemia increases.[3,4,5,6] The risk of macrosomia increases with increasing post-meal glucose.[3,4,5] De Veciana had shown in his study that improved fetal outcomes manifested by less neonatal hypoglycemia, macrosomia, and cesarean delivery were seen among GDM patients with controlled post-meal glucose.[7] The UNITE for Diabetes Philippines Guidelines recommends that all pregnant women should be evaluated at the first prenatal visit for risk factors for the development of diabetes.[3] High-risk women should be screened at the soonest possible time using the criteria set by the International Association of Diabetes & Pregnancy Study Groups (IADPSG).[3]

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GDM is initially managed with medical nutrition therapy in conjunction with monitoring of blood glucose and physical activity. The criteria for the initiation of pharmacologic therapy (insulin) is fasting plasma glucose ≥95 mg/dL in conjunction with post-meal levels ≥120 mg/dL after two-hours or 130 mg/dL after one-hour.[8,9]

During pregnancy, increased insulin requirement occurs because of the anti-insulin hormones from the placenta, increased maternal cortisol concentration together with increasing weight gain, and decreasing exercise. These metabolic changes lead to a greater demand for short-acting insulin and optimum doses of intermediate-acting insulin to guarantee a constant basal rate.[10] The current human insulin therapies cannot mimic the complex physiology required to maintain normal blood glucose levels and are limited by the danger of hypoglycemia.

The characteristics of the new insulins in the market can considerably help in the attainment of the desired metabolic control level during pregnancy. Insulin analogs currently available in the market and approved by the Philippine Food and Drug Authority for pregnancy are rapid-acting insulin lispro and insulin aspart and long-acting insulin detemir.

In our country, the percentage of GDM patients on insulin therapy is higher than the 15% observed in internationally-published data.[1] The current practice of early initiation of insulin for tighter glycemic control is to prevent the adverse effects of hyperglycemia resulting in adverse maternal and fetal outcome. Rapid-acting analogs such as insulin lispro and aspart, achieve a higher peak insulin concentration in less time and with a short duration of action than regular human insulin thus, making it more appropriate in the treatment of post-meal hyperglycemia of pregnancy.[11-17] Pettit and colleagues compared the short-term efficacy of insulin aspart, regular insulin, or no insulin in patients with GDM. The post-meal glycemic control was significantly improved by insulin aspart compared with no exogenous insulin administration, while regular insulin did not show a significant difference from no exogenous insulin administered.[18] The same investigators randomized 27 women to either insulin aspart or regular insulin for prandial treatment of their carbohydrate intolerance. Both treatment groups maintained good overall glycemic control. Insulin aspart was effective in reducing post-meal glucose concentrations from baseline, lowering C-peptide values than regular insulin with no major reported hypoglycemic events. Neonatal birth weights were similar in both groups and no case of macrosomia was reported. These studies demonstrate that the overall safety and effectiveness of insulin aspart was comparable to regular insulin in pregnant women who have GDM.[18,19] The authors also concluded that insulin aspart is a convenient premeal insulin for use by patients requiring mealtime insulin, and furthermore, due to its favorable pharmacokinetics, insulin aspart blunts the post-meal glucose concentration as well as regular human insulin. The fetal outcome using insulin aspart was comparable with human insulin with a tendency toward fewer fetal losses and premature deliveries. Colatrella and colleagues reported that use of insulin lispro in GDM in comparison to neutral protamine Hagedorn (NPH) insulin resulted in achievement of fasting blood sugar (FBS) of < 95 mg/dL.[20] But a systematic review and meta-analysis of lispro versus regular insulin identified a higher rate of large for gestational age (LGA) infants, despite similar glycosylated hemoglobin (HbA1c) in the lispro group (relative risk,1.38 (95% CI 1.14-1.16)) but no differences in the rate of small for gestational age (SGA) infants. No advantage of lispro was demonstrated.[21] The current published rates of the major anomalies in infants born to mothers who have DM treated with insulin are between 2.1% and 10.9%. The study of Wyatt and colleagues showed that the rate of major congenital anomaly was 5.4% for offspring of mothers who had DM treated with insulin lispro before and during pregnancy which did not differ from the published major congenital anomaly rates for other insulin treatment.[22] A multi-national, open-label, randomized, parallel group, prospective study compared detemir, a long-acting insulin analog, with NPH in the treatment of women with preexisting DM who were pregnant or planning a pregnancy. Insulin detemir as compared with NPH resulted in less nocturnal hypoglycemia and achieved better glycemic control particularly in the preconception period. This study also reported reassuring safety and efficacy results.[23] In another study, insulin detemir was compared with glyburide in women with GDM study.[24] The long-acting insulin analog did not have a pronounced peak effect and cause less nocturnal hypoglycemia. In addition, insulin analog use was found to be associated with good patient acceptability and satisfaction[25] with its dosing convenience.[26,27] Although other investigators have reported that insulin analog was more effective than human insulin in providing post-meal glycemic control,[11,15,16,18,28] some studies concluded that insulin analogs offer little benefit than human insulin.[20,25,27,29-32] In both the lispro and aspart studies, there was a trend toward less hypoglycemia in the insulin analog group, but the differences were not statistically significant.

There are a few data on pregnancy outcomes of both fetus and mother among Asian women with GDM and on insulin analogs. Majority of the information on insulin analogs were obtained from pregnant women with pregestational diabetes and often extrapolated to women with GDM.[26,33] There are differences among various ethnic groups in terms of GDM prevalence, response to treatment, and pregnancy outcomes.[34-37] Moreover, the results of available studies have been conflicting. In our institution, insulin analogs have been increasingly used during pregnancy in the last decade, and so it is important to assess their safety. To our knowledge, this is the first study on insulin analog treatment for Filipino patients with GDM. Therefore, the general objective of this study was to evaluate the efficacy, safety and pregnancy

outcomes of supplementary insulin analog versus human insulin in women with GDM. Specific objectives were a.) to compare the glucose levels and rates of hypoglycemia in women with GDM who received either insulin analog (aspart or lispro and detemir) or human insulin, b.) to compare the maternal outcomes namely, hypertensive disorders of pregnancy (which included preeclampsia, eclampsia, and gestational hypertension) and primary CS in women with GDM who received either insulin analog (aspart or lispro and detemir) or human insulin and, c.) to compare the neonatal outcomes namely rates of prematurity, birth weight, LGA, neonatal hypoglycemia, neonatal jaundice, and acute respiratory distress syndrome (ARDS) in women with GDM who received either insulin analog (aspart or lispro and detemir) or human insulin. Nonetheless, the authors hypothesized that supplementary insulin analog use was comparable with human insulin in terms of efficacy, safety, and pregnancy outcomes.

Methods

Study design

A retrospective cohort analysis involving paired chart review of both pregnant women with GDM and their neonate seen at the USTH from January 2013 to March 2016 was done. Implementation of the study began upon receipt of approval from the USTH Institutional Review Board and Ethics committee. All patient information remained anonymous and kept confidential.

The diagnosis of GDM was made with 75-gram OGTT (oral glucose tolerance test) according to the IADPSG criteria recommended by the Philippines UNITE for Diabetes Clinical Practice Guidelines or the Philippine Obstetrical and Gynecological Society (POGS) diagnostic cut-offs.[3] The IADPSG criteria require at least one abnormal result for the following glycemic parameters to be diagnosed as having GDM: FBS of ≥92 mg/dL, one-hour post load blood glucose of ≥180 mg/dL, and two-hour post load blood glucose of ≥153 mg/dL.[3] For the threshold values set by the POGS, at least one abnormal result is also required for GDM diagnosis: FBS ≥92 mg/dL, and two-hour post load blood glucose ≥140 mg/dL.[3]

Study population

Filipino women with GDM and singleton pregnancy, aged 18 years old and above, were included in the study. Exclusion criteria for this study were the following: those who had previously diagnosed DM, with overt DM, with twin or multiple pregnancies, and medical charts with insufficient data for analysis. The corresponding medical charts of their newborns were also reviewed and analyzed. Demographic information and clinical outcomes were extracted. A review of the blood glucose diary was also done. Blood glucose profile reviewed consisted of fasting/pre-meal capillary blood glucose (CBG), and one-hour post-meal CBG every week from the time of diagnosis to 38 weeks or every two weeks from 28 to 38 weeks gestation.

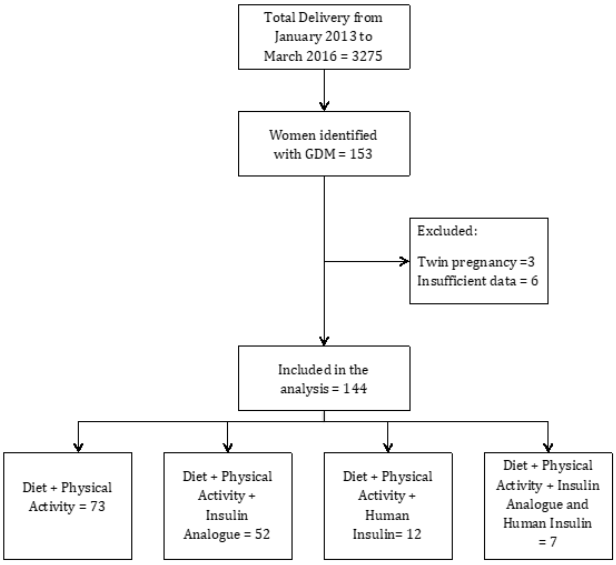

Figure 1. Algorithm of the selection process from initial screening to grouping according to treatment.

Subjects were then categorized according to the given treatment or independent variable: Group A: diet-controlled (along with physical activity); Group B: supplementary insulin analog (aspart or lispro, detemir); Group C: supplementary human insulin (regular insulin or NPH); and Group D: combination supplementary insulin analog (aspart or lispro and detemir) and human insulin (regular insulin and NPH insulin). Figure 1 shows the flow of the selection process.

Insulin therapy was initiated when: a.) fasting venous plasma glucose is ≥100 mg/dL at initial visit, or b.) fasting CBG level of >95 mg/dL and one-hour post-meal CBG value of >140 mg/dL were obtained on two occasions while on diet and physical activity. Supplementary insulin analogs prescribed to patients were rapid-acting insulin aspart or lispro, and long-acting detemir while human insulin includes NPH and regular insulin.

The following maternal antepartum characteristics were gathered: age, parity, gestational age at initiation of insulin (whether started at <26 weeks age of gestation or ≥26 weeks age of gestation), pregestational body mass index (BMI) in kg/m^2, and smoking history. Also included were risk factors for GDM such as: family history of DM in the first-degree relative, presence of chronic hypertension, impaired fasting glucose (IFG) prior to pregnancy, polycystic ovary syndrome (PCOS), GDM in previous pregnancy, LGA infant in previous pregnancy, use of glucocorticoid (given to those at risk for premature birth), and polyhydramnios defined as amniotic fluid index of >24 cm or having a notation of such in the chart.[38]

Primary maternal outcomes or dependent variables were recorded as follows: hypertensive disorders of pregnancy which included gestational hypertension, preeclampsia and eclampsia; and primary CS.

Primary neonatal outcomes or dependent variables included were prematurity (having gestational age at delivery of <37 weeks), birth weight in kilograms, LGA, neonatal hypoglycemia (defined as having a medical record that contained a notation of neonatal hypoglycemia, or with symptoms and/or treatment with glucose infusion, or a laboratory report of a glucose value <30.6 mg/dL in the first 24 hours, and or <45 mg/dL after the first 24 hours[39]), neonatal jaundice, and ARDS.

Other maternal data recorded were patients who underwent normal spontaneous delivery (NSD), miscarriage, and death. Other neonatal data recorded were gestational age at delivery in weeks, CBG value taken at first hour of life in mg/dL, number of SGA, APGAR score taken at one minute and at five minutes, with low score defined as having an APGAR score of less than 7[40], neonatal intensive care unit (NICU) admission, congenital anomaly, infection and birth injury and perinatal death which included death in utero and infant deaths.[41]

Secondary outcomes or dependent variables were maternal glycemic control parameters (fasting CBG, one-hour post-meal CBG) in mg/dL, and hypoglycemia defined as blood glucose value of <70 mg/dL with or without symptoms or having a notation of such condition in the chart.

Data analysis

All data were encoded in Microsoft Excel for Mac 2011 (Version 14.6.5) and analyzed in STATA SE Version 13. Descriptive statistics included mean and standard deviation for quantitative and continuous variables. Frequency and percent distribution were used to present qualitative variables. Logistic regression analysis using binomial variables was performed to adjust for the impact of potential confounders such as age, pregestational BMI, parity, chronic hypertension, previous of LGA, PCOS, IFG, and glucocorticoid administration. Chi-square and one way analysis of variance (ANOVA) tests was used to compare categorical and numerical variables among the four groups of GDM treatment respectively. A *p*-value of <0.05 was considered significant.

Results

A total of 144 paired charts of both pregnant women with GDM and infants were included in the analysis after the screening process. Majority of these women belong to the older age group (more than 30 years old), mostly multiparous and with two to three risk factors for GDM. Sixty women had data on gestational age at initiation of insulin. Seventeen of these women were diagnosed before the 26th weeks age of gestation (AOG) and had used insulin analogs during the first trimester. Fifty-nine women received insulin analog (n=52 for aspart or lispro and n=7 for detemir) and 19 received human insulin in the form of NPH or regular. (Table I)

Table I. Maternal antepartum characteristics by treatment groups

Maternal characteristics	Group A n=73(50.69%)	Group B n=52(36.11%)	Group C n=12(8.33%)	Group D n=7(4.86%)
Age, years (SD)	31.52 ± 5.00	32.83 ± 5.24	31.75 ± 6.93	35.86 ± 4.14
Parity [n(%)] a. primiparous b. multiparous	 20 (27.4%) 52 (71.2%)	 16 (30.8%) 36 (69.2%)	 3 (25.0%) 9 (75.0%)	 4 (57.1%) 3 (42.9%)
Gestational age at initiation of insulin, weeks [n(%)] a. <26 weeks AOG b. ≥26 weeks AOG	 Not applicable Not applicable	 14 (31.8%) 30 (68.2%)	 1(10.0%) 9 (90%)	 2 (33.3%) 4 (67.7%)
Pregestational BMI, kg/m^2 (SD)	28.23±10.79	29.30±5.21	28.57±3.1	29.29±3.75
Smoker [n(%)]	1 (1.4%)	2 (3.8%)	0	0

Group A - diet-controlled
Group B - supplementary insulin analog
Group C - supplementary human insulin
Group D - supplementary insulin analog + human insulin

Table II. Maternal risk factors by treatment of GDM

Risk Factors n(%)	Group A	Group B	Group C	Group D	Total
Family history of DM in 1st degree relative	42 (57%)	29 (55.8%)	9 (75.0%)	5 (71.4%)	85
Previous LGA infant	5 (6.8%)	11 (21.2%)	1 (8.3%)	1 (14.3%)	18
PCOS	7 (9.6%)	6 (11.5%)	0 (0%)	1 (14.3%)	14
Chronic hypertension	3 (4.1%)	8 (15.4%)	2 (16.7%)	1 (14.3%)	14
IFG	2 (2.7%)	1 (1.9%)	0 (0%)	0 (0%)	3
History of GDM	9 (12.3%)	12 (23.1%)	2 (16.7%)	2 (28.65%)	25
Glucocorticoid administration	4 (5.5%)	9 (17.3%)	1 (8.3%)	0 (0%)	14
Polyhydramnios in present pregnancy	1 (1.4%)	4 (7.7%)	0 (0%)	0 (0%)	5

Group A - diet-controlled
Group B - supplementary insulin analog
Group C - supplementary human insulin
Group D - supplementary insulin analog + human insulin

Table III. Comparison of maternal glycemic control and hypoglycemia among four groups of GDM treatment

Glycemic parameters	Group A	Group B	Group C	Group D	*p*-value
Fasting CBG, in mg/dL, n=77 (SD)	83.17± 9.71	91.38± 19.20	90.55± 10.19	83.42± 5.40	0.15
1 hour post-meal CBG, in mg/dL, n=88 (SD)	121.11± 20.33	130.85± 25.05	120.01± 14.31	127.51± 17.21	0.26
Hypoglycemia n(%)	4 (5.5%)	5 (9.6%)	0 (0%)	2 (28.6%)	0.11

Group A-Diet-controlled
Group B-supplementary insulin analog
Group C-supplementary human insulin
Group D-supplementary insulin analog + human insulin

Table IV. Comparison of maternal data among four groups of GDM treatment

Maternal outcomes n(%)	Group A	Group B	Group C	Group D	*p*-value	Adjusted *p*-value*
Hypertensive disorders of pregnancy						
a) Preeclampsia	5 (6.8%)	4 (7.7%)	0 (0%)	1 (14.3%)	0.68	
b) Eclampsia	1 (1.4%)	0 (0%)	0 (0%)	1 (14.3%)	0.02	0.29
c) Gestational hypertension	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	0.81	
Mode of delivery						
a) NSD	33 (45.2%)	18 (34.6%)	5 (41.7%)	3 (42.9%)	0.17	
b) Primary CS	28 (38.4%)	25 (48.1%)	6 (50%)	4 (57.1%)	0.04	0.08
Miscarriage	0 (0%)	1 (1.9%)	0 (0%)	1 (14.3%)	0.02	0.29
Death	0 (0%)	1 (1.9%)	0 (0%)	0 (0%)	0.81	

**Adjusted for age, body mass index, parity, hypertension, previous large for gestational age infant, polycystic ovary syndrome, impaired fasting glucose, and glucocorticoid administration using logistic regression analysis.*

Table V. Comparison of perinatal data among four groups of GDM treatment

Perinatal data [n(%);SD]	Group A	Group B	Group C	Group D	*p*-value	Adjusted *p*-value
Gestational age at delivery, weeks	37.82 ± 2.00	37.71 ± 2.44	37.5 ± 1.38	37.5 ± 1.38	0.95	
Premature	7 (9.6%)	8 (15.4%)	2 (16.7%)	1 (14.3%)	0.01	0.03
Birth weight, in kilograms	2.99 ± 0.63	3.1 ± 0.69	2.91 ± 0.43	3.30 ± 0.67	0.36	
LGA	10 (13.7%)	11 (21.2%)	0 (0%)	1 (14.3%)	0.11	
SGA	11 (15.1%)	6 (11.5%)	3 (25%)	1 (14.3%)	0.06	
APGAR score						
a) 1 minute APGAR	7.70 ± 1.10	7.57 ± 1.14	7.42 ± 1.73	7 ± 2.45	0.79	
b) 5 minute APGAR	8.83 ± 0.70	8.75 ± 0.91	8.58 ± 1.44	9 ± 0	0.90	
CBG at first hour of life, mg/dL	61.42 ± 22.27	71.08 ± 34.61	61.92 ± 25.87	51 ± 11.35	0.10	
Neonatal hypoglycemia	0 (0%)	1 (1.9%)	0 (0%)	0 (0%)	0.81	
Jaundice	24 (32.9%)	24 (46.2%)	1 (8.3%)	2 (28.6%)	0.05	
Perinatal death						
a) death in utero	1 (1.4%)	0 (0%)	0 (0%)	1 (14.3%)	0.02	0.29
b) infant death	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	0.95	
NICU admission	13 (17.8%)	13 (25%)	3 (25%)	0 (0%)	0.03	0.60
ARDS	2 (2.7%)	1 (1.9%)	0 (0%)	0 (0%)	0.88	
Congenital anomaly	1 (1.4%)	4 (7.7%)	0 (0%)	0 (0%)	0.62	
Infection	13 (17.8%)	12 (23.1%)	3 (25%)	0 (0%)	0.05	
Birth injury	1 (1.4%)	1 (1.9%)	0 (0%)	0 (0%)	0.02	0.80

**Adjusted for age, body mass index, parity, hypertension, previous large for gestational age infant, polycystic ovary syndrome, impaired fasting glucose, and glucocorticoid administration using logistic regression analysis.*

The strongest risk factors for GDM in our study were the family history of DM followed by the previous history of GDM and history of LGA. (Table II)

There was no significant difference among the four treatment groups in terms of glycemic parameters namely, fasting CBG and one-hour post-meal CBG and hypoglycemic events. (Table III)

As shown in Table IV, there was no significant difference among the four groups in terms of hypertensive disorders of pregnancy, mode of delivery specifically CS and NSD, miscarriage, and death. Maternal mortality was reported due to septic shock secondary to overwhelming infection.

Neonates of mothers with GDM and were treated with diet and exercise alone (Group A) and supplementary insulin analog (Group B) had significantly higher rates of prematurity compared to those women with GDM who received either supplementary human insulin or a combination of human insulin and insulin analog remaining significant after adjustment for age, pregestational BMI, parity, hypertension, previous LGA infant, PCOS, IFG, and glucocorticoid

administration (p=0.03). There was no significant difference among the four treatment groups with respect to gestational age at delivery, birth weight, LGA, SGA, APGAR scores, CBG taken at the first hour of life, neonatal hypoglycemia, jaundice, death in utero, infant death, congenital anomaly, infection, and birth injury. (Table V)

The results partially supported the hypothesis that supplementary insulin analog use was comparable with human insulin in terms of efficacy, safety, and pregnancy outcomes, with the exception of prematurity which was higher in the former.

Discussion

Our study had shown that use of supplementary insulin analog was comparable to human insulin for GDM in terms of efficacy in achieving glycemic control and can be safely used as a viable treatment option without increased risk of hypoglycemia. Likewise, the occurrence of adverse maternal outcomes was not increased and not significantly different from other treatment groups. We also noted that the rates of occurrence of adverse neonatal outcomes (birth weight, LGA, neonatal hypoglycemia, neonatal jaundice, and ARDS) were not increased. However, rates of prematurity were increased with supplementary analog as well as in women whose GDM was diet-controlled.

The recent Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study has established a continuum of risk between glycemic levels obtained during a glucose tolerance test and various adverse maternal and fetal outcomes.[42] The poor maternal and fetal outcomes are largely related to the degree of maternal glycemic control. GDM women had perinatal mortality rates similar to women with pre-existing DM. In our study, 17 women were diagnosed with GDM before the 26th week of gestation. This carbohydrate intolerance was perhaps induced by pregnancy or an alternative explanation is that, GDM was type II DM discovered during pregnancy. In one study, the subgroup of women whose GDM was diagnosed at the first antenatal visit had a higher perinatal rate than those in whom hyperglycemia was identified later.[43] This may be due to higher mean blood glucose levels either due to inadequate treatment or higher severity of GDM.

Review of patients' self-monitored CBG was done instead of HbA1c. This is because most studies found poor to low correlation between HbA1c and mean fasting/pre-meal and post-meal blood glucose values.[44] There is also a poor association between HbA1c and pregnancy outcomes. Though in a previous study, the normal HbA1c for the pregnant non-diabetic in our institution is found to be five percent, the lack of uniformity among different laboratories was a deterrent for routine use. Using HbA1c as a tool for monitoring and adjusting glucose levels to manage GDM is not effective.

Majority of the women with GDM are readily controlled by diet (along with physical activity) alone which was demonstrated in our study by the treatment Group A. However, some women with GDM may have difficulty in attaining the glycemic target. During pregnancy, the secretion of the anti-insulin hormones from the placenta, increased maternal cortisol concentration, and increased weight will result in increased insulin requirement. Traditionally, insulin therapy is initiated when CBG levels exceed 105 mg/dL (5.8 mmol/L) in the fasting state and 140 mg/dL (6.7 mmol/L) one-hour after meals. These cut-off values are derived from guidelines for managing insulin in pregnant women who have type I DM. In a prospective study of 471 women with GDM, a more aggressive goal of a fasting CBG level below 95 mg/dL (5.3 mmol/L) showed a decrease in the rates of LGA neonates, from 28.6 to 10.3% (relative risk, 5.99; 95% CI, 1.37 to 8.88).[45] Langer and colleagues have recognized that different glycemic thresholds are needed to minimize different complications, and a mean blood glucose <100 mg/dL is associated with a complication rate similar to that of the non-GDM population.

Particularly in the late first and third trimesters, blood glucose control is more unstable with low fasting plasma glucose and high post-meal excursions and occurrence of nocturnal hypoglycemia. Pregnancy-induced nausea and vomiting can also predispose to hypoglycemia. During the second and third trimesters, there is further increase production of placental anti-insulin hormones that cause a progressive increase in insulin requirements. In the last month of pregnancy, there could be a decrease in insulin requirement particularly at night because of transfer of maternal glucose and amino acid through the placenta to the fetus which accelerates growth.[46] Nonetheless, these events lead to a greater demand for short-acting insulin, which will cover the meal and optimized doses of intermediate-acting insulin for a constant basal rate. These metabolic demands can be addressed with special characteristics of the new insulin analogs. The fasting hyperglycemia (which reflects the level of disease severity) in pregnant women is traditionally treated with human NPH but the new long-acting insulin analog, detemir, may provide a better basal glycemic profile since it has no pronounced peak effect as NPH insulin and therefore causes less nocturnal hypoglycemia. On the other hand, two rapid-acting analogs, aspart and lispro, are safe and efficacious pre-meal insulin for use by pregnant diabetic women requiring mealtime insulin. Due to their favorable pharmacokinetics, post-meal blood glucose concentrations are improved compared with human regular insulin or no insulin treatment. In our study, Group B represented the GDM women on supplementary insulin analogs. Whereas, if the patient has elevated fasting and post-meal blood glucose levels, and requires multiple daily injections to achieve good

glycemic control, a basal-bolus regimen is done.

Similar to other modes of treatment for GDM in this study, glycemic targets (fasting CBG of ≤95 mg/dL and one-hour post-meal CBG of ≤140 mg/dL) based on American Diabetes Association (ADA) recommendations[47] were achieved by the addition of insulin analog to diet and physical activity, as indicated by the mean fasting CBG and mean one-hour post-meal CBG. This result is almost identical with other study findings which showed that insulin analogs and human insulin were equally efficacious in terms of achievement of overall glycemic control.[27,30,31] A study by Deepaklal et al.[17] which focused on insulin lispro use in GDM demonstrated that it was able to achieve mean fasting blood glucose values at 85.7 mg/dL and one-hour post-meal blood glucose values at 116.5 mg/dL, which are within the targets set by the ADA . There was no increased rate of hypoglycemia across the four groups of treatment. It was noted that insulin analogs and human insulin were comparable in terms of occurrence of minimal hypoglycemia.[20,23,30,31] This is particularly important in achieving glycemic targets since hypoglycemia is one of the barriers to attaining optimal glycemic control. In contrast, other studies noted that compared with human insulin, insulin analogs provided better control of hyperglycemia with lesser hypoglycemia.[12-16] The incidence of less hypoglycemia among basal insulin analogs is attributed to the absence of peak effect.[15]

Our study had shown that in women with GDM treated either with insulin analogs (aspart, lispro, and detemir) or human insulin (NPH and regular) had no difference in maternal outcomes (hypertensive disorders of pregnancy and primary CS). Additionally, we did not find a trend toward a significant increase in the rate of occurrence of these adverse maternal outcomes with supplementary insulin analogs. Our finding is somewhat similar to the results of a study by Colatrella et al. which concluded that insulin analog and human insulin were equal in terms of reduction of hypertensive disorders of pregnancy and primary cesarean section.[20] Bhattacharyya et al.[25] demonstrated no increase in the occurrence of pregnancy loss and CS among women with GDM who were either treated with insulin analogs, human insulin or diet. We also noted this finding in our study as there was a very negligible rate of occurrence of miscarriage. In another study, Koning et al.[48] found no difference in the development of hypertensive disorders between diet-controlled and insulin-treated women with GDM. Both diet and insulin therapy resulted in reduction of this adverse maternal outcome. On the other hand, Landon et al.[49] noted that treatment of GDM with diet and insulin resulted in lower risk of having CS and hypertensive disorders than non-treatment of GDM.

We noted a higher rate of prematurity in the diet-controlled group as well as those in the supplementary insulin analog group. This finding could be partly due to the possibility that physicians of women belonging to these groups decided to deliver the infant at an earlier gestational age to reduce the chance of occurrence of any serious perinatal outcomes brought about by comorbid conditions namely chronic hypertension, preeclampsia, and eclampsia. As shown in the results, although not significant, the rate of hypertensive disorders in the diet-controlled group and the supplementary insulin analog group was higher compared to the groups that received supplementary human insulin and combination of supplementary human insulin and insulin analog. It is established that hypertensive disorders have been associated with insulin resistance. The insulin resistant state in these groups was further worsened by the presence of GDM. Although diabetes during pregnancy is a recognized major risk factor for poor pregnancy outcomes, the occurrence of these conditions can be minimized by the timely institution of treatment.[50] It is possible that treatment of these groups of women with diet and physical activity and supplementary insulin analog had been enough to prevent the significant increase in the number of individuals who would develop hypertensive disorders which is one of the maternal complications of GDM. Another reason for this result could be the knowledge of the attending physician of insulin analog use by the patient may have led to the assumption that glycemic control had been difficult, and in order to prevent adverse effects of hyperglycemia to the offspring and to achieve optimal pregnancy outcome, chose to have earlier delivery of the infant. Lastly, other fetal and maternal medical conditions such as that of the heart and kidney which are beyond the scope of this study could be present in women belonging to these groups and responsible for premature birth.

With respect to birthweight, the occurrence of LGA, SGA, APGAR scores, neonatal hypoglycemia, jaundice, perinatal death, NICU admission, ARDS, congenital anomaly, infection, and birth injury, supplementary insulin analog was comparable to the other modes of GDM treatment. Moreover, we found no significant increase in the rates of occurrence of these events across four groups. The mean values for gestational age at delivery, birthweight, APGAR score, and CBG taken at first hour of life were unremarkable. This finding had some resemblance with the results of the study done by Bhattacharyya et al.[25] which reported no increase in adverse fetal outcomes specifically congenital anomalies, neonatal hypoglycemia, and neonatal hyperbilirubinemia whether women with GDM were treated with diet alone, insulin analog or human insulin. On the other hand, two studies have demonstrated that both non-pharmacologic and insulin treatment of GDM were effective in terms of reduction in perinatal mortality and morbidity such as birth injury, hyperbilirubinemia, hypoglycemia, SGA, LGA, macrosomia, low APGAR score, the requirement for respiratory support, prematurity, and NICU admission.[48,49] Colatrella et al.[20] have shown in their study that insulin analog and human insulin were equal

in terms of delivery of premature infants, LGA, APGAR score at five minutes, congenital malformations, neonatal hypoglycemia, and hyperbilirubinemia. Rezai et al.[30] found that human insulin and insulin analog were similar in terms of minimal occurrence of adverse perinatal outcomes such as LGA and congenital malformations. In contrast, Trujillo et al.[50] reported that insulin analogs were generally more efficacious in reducing hyperglycemia and neonatal complications. As shown in the study of Lim et al. there is a considerable number of patients who received insulin in our study and this could probably explain the low rate of macrosomia among those with GDM.[2]

Attainment of optimal glycemic control during pregnancy leads to the reduction in the incidence of adverse pregnancy outcomes secondary to GDM. With the exception of prematurity, this is the most likely reason why we did not find a significant increase in the rates of other adverse maternal and perinatal outcomes. Insulin analogs were reported to reduce peak glucose concentration and overall fetal macrosomia.[12] Achievement of target blood glucose values improves several perinatal outcomes in terms of macrosomia, prematurity and postmaturity, complicated modes of delivery, congenital anomaly, and neonatal hypoglycemia.[11,50] In the light of these facts, full cooperation between the patient and physician in GDM management is indispensable.

To the best of our knowledge, this is the first study on the use of insulin analogs in Filipino women with GDM. This study also included first-trimester exposure to insulin analog which was not found to be associated with an increased rate of congenital anomaly.

Our results should be interpreted in the context of limitations inherent in its design. Our study is a retrospective cohort with information based on medical records which limited the availability of certain information such as weight gain during the period of pregnancy, information on lifestyle factors (smoking, alcohol, protein intake), and folic acid supplementation (which is known to lower the risk of a congenital anomaly). The number of subjects is small to render significant conclusions. Further trials on a larger scale and multicenter are therefore required.

Conclusion

Our study demonstrated that insulin analog was comparable to human insulin in terms of non-increased rates of adverse pregnancy outcomes with the exception of prematurity, and can be safely used as a viable treatment option without increased risk of hypoglycemia while achieving optimal glycemic control throughout pregnancy in Filipino women with GDM.

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