Insulin Detemir Versus Glibenclamide in Gestational Diabetes Mellitus: A Retrospective Cohort Study

Dorit Ravid MD[1,3], Michal Kovo MD PhD[1,3], Sophia Leytes MD[2,3], Yael Yagur MD[1,3], Maty Fakterman MD[3], and Omer Weitzner MD[1,3]

[1]Department of Obstetrics and Gynecology, Meir Medical Center, Kfar Saba, Israel
[2]Department of Obstetrics and Gynecology, Wolfson Medical Center, Holon, Israel
[3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT **Background:** Treatment of gestational diabetes mellitus (GDM) has been shown to improve both maternal and neonatal outcomes. For women with GDM who require glucose-lowering medication, insulin is regarded as the drug of choice by most medical societies. Oral therapy, with metformin or glibenclamide, is a reasonable alternative in certain medical circumstances.

Objectives: To compare the efficacy and safety of insulin detemir (IDet) vs. glibenclamide for GDM when glycemic control cannot be achieved through lifestyle modification and diet.

Methods: We conducted a retrospective cohort analysis of 115 women with singleton pregnancy and GDM treated with IDet or glibenclamide. GDM was diagnosed via the two-step oral glucose tolerance test (OGTT) of 50 grams glucose, followed by 100 grams. Maternal characteristics and outcomes (preeclampsia and weight gain) and neonatal outcomes (birth weight and percentile, hypoglycemia, jaundice, and respiratory morbidity) were compared between groups.

Results: In total, 67 women received IDet and 48 glibenclamide. Maternal characteristics, weight gain, and the incidence of preeclampsia were similar in both groups. Neonatal outcomes were also similar. The proportion of large for gestational age (LGA) infants was 20.8% in the glibenclamide group compared to 14.9% in the IDet group ($P = 0.04$).

Conclusions: In pregnant women with GDM, glucose control on IDet yielded comparable results as on glibenclamide, except for a significantly lower rate of LGA neonates..

IMAJ 2023; 25: 398–401

KEY WORDS: detemir, gestational diabetes mellitus (GDM), glibenclamide, glycemic control, insulin detemir (IDet) large for gestational age (LGA)

Treatment of gestational diabetes mellitus (GDM) has been shown to improve both maternal and neonatal outcomes [1,2]. Most women achieve euglycemia with nutritional therapy alone and only 30% require drug therapy [3].

For women with GDM who require glucose-lowering medication, insulin is regarded as the drug of choice by most medical societies. Oral therapy with metformin or glibenclamide is a reasonable alternative in certain medical circumstances [1-3]. Glibenclamide, a second-generation sulfonylurea, is commonly used for the treatment of GDM [4]. Both the American Diabetes Association (ADA) [1] and the American College of Obstetricians and Gynecologists (ACOG) [2] consider its use acceptable.

Reassuring safety and efficacy data of insulin detemir (IDet) for treating pregnant women with type 1 diabetes were published in 2012 [5], which led the U.S. Food and Drug Administration to reclassify IDet from C to B. Although IDet appears to be safe for use in pregnancy [6], information regarding the efficacy of this insulin for treating GDM is scarce.

A randomized controlled trial of 55 women with GDM reported similar glycemic control; as well as perinatal outcomes with NPH insulin vs. IDet, but with significantly fewer maternal hypoglycemic events in the IDet arm [7].

A retrospective study of 91 women with GDM [8] compared IDet to glibenclamide. Glycemic control was comparable. Women treated with glibenclamide had higher incidences of hypoglycemia and gestational weight gain (GWG).

Two systematic reviews and a meta-analysis of randomized trials [9,10] comparing glibenclamide with insulin (NPH and short acting agents) found a higher rate of neonatal hypoglycemia and macrosomia in women assigned to glibenclamide. Another concern regarding glibenclamide is the possible higher rate of maternal hypoglycemia compared to insulin [11]. However, only one small retrospective trial [8] provided direct comparison of glibenclamide to IDet in GDM.

In our study, we compared the efficacy and safety of IDet to glibenclamide in the treatment of GDM.

PATIENTS AND METHODS

We conducted a retrospective cohort analysis of women with GDM treated with either IDet or glibenclamide at two universi-

ty-affiliated hospitals. All pregnancies were singleton. GDM was diagnosed by the two-step procedure of 50 grams glucose followed by 100 grams OGTT. Diagnosis of GDM was established if two or more of the values were abnormal (fasting ≥ 95 mg/dl, 1 hour ≥ 180 md/dl, 2 hours ≥ 155 md/dl, 3 hours ≥ 140 md/dl) [8]. IDet or glibenclamide were prescribed if target glucose levels could not be maintained after one to two weeks of dietary adjustment. The choice of agent was based on clinical judgment and the patient's preference. The dose of glibenclamide was 2.5–20 mg/d. IDet was given as 0.1 mg/kg at bedtime and titrated until the glucose target was reached. If needed, a rapid acting insulin analog (insulin lispro or aspart) was added before meals when the 2-hour postprandial blood glucose levels were 120 mg/dl. Exclusion criteria included GDM controlled with lifestyle modification and medical nutritional therapy alone, pregestational diabetes (defined as fasting plasma glucose levels 126 mg/dl, a random glucose of 200 mg/dl, or blood glucose levels 200 mg/dl 2-hours post-OGTT), and multifetal gestation.

Maternal characteristics and outcome (preeclampsia, GWG) and neonatal outcomes (birth weight and percentile, neonatal hypoglycemia defined as blood glucose below 40 mg/dl, neonatal jaundice defined as bilirubin above 7.5 mg/dl, and respiratory morbidity) were compared between the groups. Maternal and neonatal data were extracted from electronic medical records.

Maternal variables included age, height, weight, parity and gravidity, preeclampsia, and gestational weight gain.

Neonatal variables included gestational age at delivery, birthweight, and percentile. Acute neonatal events (respiratory morbidity, neonatal jaundice, and neonatal hypoglycemia) were also evaluated. Neonatal hypoglycemia in the first 24 hours of life.

DATA ANALYSIS

Data are presented as numbers and percentages for categorical variables and as means and standard deviations for continuous variables. Student's *t*-test and Mann-Whitney U-test were used to compare continuous variables with and without normal distribution between the IDet and glibenclamide groups, respectively. Chi-square and Fisher's exact tests were used for categorical variables. We used multivariate logistic regression analysis to assess the correlation between each variable.

A sample size of 65 women was estimated to be sufficient to detect a 10% difference in neonatal outcomes between the medications under the assumptions of a 5% type I error (two-sided) at least 80% power.

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 21 (SPSS, IBM Corp, Armonk, NY, USA).

ETHICS APPROVAL

The study was conducted according to good clinical practice guidelines and was approved by Meir Medical Center and Wolfson Medical Center institutional review boards. Patient informed consent was not required due to the retrospective nature of the data collection.

RESULTS

The cohort included 115 women who met the study inclusion criteria, 48 (42%) received glibenclamide and 67 (58%) IDet.

Table 1 presents the baseline characteristics of the study patients. There were no significant differences between the two groups with respect to age, gravidity, parity, or body mass index (BMI). The average BMI in both groups was in the overweight range (BMI ≥ 25).

Table 2 presents maternal outcomes. There were no significant differences between the groups in the prevalence of preeclampsia and GWG. Preeclampsia occurred in 8.3% of the women taking glibenclamide and in 11.9% taking IDet, $P = 0.75$. The women who were treated with glibenclamide gained 11.7 ± 5 kg as compared to 13.4 ± 1.7 kg in the IDet group, $P = 0.64$. Gestational age at delivery was similar in both groups, as well as the rate of preterm labor (18% vs. 13% in the glibenclamide and IDet groups, respectively).

Table 1. Characteristics of participants

Characteristic	Glyburide (n=48)	Detemir (n=67)	*P*-value
Age in years, mean ± SD	33 ± 5.59	34 ± 4.37	0.3
BMI, mean ± SD	27.6 ± 4.27	29.7 ± 6.5	0.07
Gravidity, mean ± SD	3.22 ± 2.13	3.1 ± 1.68	0.799
Parity, mean ± SD	1.39 ± 1.32	1.46 ± 1.28	0.759
Abnormal OGTT, n (%)*			
0-hour	14 (29%)	22 (32%)	0.8
1-hour	17 (35%)	29 (43%)	0.6
2-hour	15 (31%)	27 (40%)	0.55
3-hour	3 (6%)	5 (7%)	0.77

*Abnormal blood glucose on OGTT: 0-hour > 5.2 nmol/L, 1-hour > 10 nmol/L, 2-hour > 8.5 nmol/L, 3-hour > 7.7 nmol/L

BMI = body mass index, OTGG = oral glucose tolerance test, SD = standard deviation

Table 2. Maternal outcomes

Characteristic	Glyburide (n=48)	Detemir (N=67)	*P*-value
Preeclampsia, n (%)	4 (8.3%)	7 (11.9%)	0.75
Weight gain, mean ± SD	11.74 ± 5.86	13.46 ± 7.3	0.64
Gestational age, mean ± SD	37.9 ± 0.8	37.7 ± 1.1	0.2
Preterm labor, n (%)	9 (18%)	9 (13%)	0.46

SD = standard deviation

Table 3. Neonatal outcomes

Characteristic	Glyburide (n=48)	Detemir (n=67)	*P*-value
Birthweight in grams, mean ± SD	3229.9 ± 488.2	3266.7 ± 468.27	0.68
Percentile, mean ± SD	63.6 ± 25.7	62.49 ± 25.68	0.82
Hypoglycemia, n (%)	7 (16.3%)	25 (37.3%)	0.018
Neonatal jaundice, n (%)	10 (23.3%)	11 (16.4%)	0.373
Respiratory morbidity, n (%)	0	3 (4.5%)	0.279
Large for gestational age, n (%)	10 (20.8%)	10 (14.9%)	0.04
Small for gestational age, n (%)	3 (4%)	2 (4%)	0.5

SD = standard deviation

There was no significant difference in birthweight or birth percentile (63.6% and 62.4%) in the glibenclamide and the IDet groups, respectively.

The proportion of large for gestational age (LGA) was 20.8% in the glibenclamide group compared to 14.9% in the IDet group ($P = 0.04$). The rate of small for gestational age neonates was similar (4% in both groups).

There was no difference between the groups in the rate of neonatal jaundice or respiratory morbidity. The rate of neonatal hypoglycemia was significantly higher in the IDet group (37.3% vs. 16.3%, $P = 0.018$).

Logistic regression analysis was used to assess the relationship between neonatal hypoglycemia and relevant independent variables. No association was found with the type of pharmacological treatment ($P = 0.176$), maternal age ($P = 0.455$), BMI ($P = 0.574$), or gestational age at delivery ($P = 0.932$).

DISCUSSION

Our data show that IDet is as efficacious as glibenclamide for the treatment of GDM. The risk of maternal preeclampsia and GWG, as well as neonatal complications, were similar in both treatment arms. Treatment with IDet was associated with a lower rate of LGA neonates.

Historically, insulin has been considered as the standard therapy for GDM in cases refractory to nutrition therapy and exercise, and this is still the recommendation of several organizations, including ADA [1], ACOG [2], and the Canadian Diabetes Association [12].

The mainstay of basal insulin in the treatment of GDM in pregnancy is the intermediate-acting insulin-NPH. IDet has been suggested as an option for type 1 diabetes in pregnancy [5]. IDet is a long-acting insulin analog with peak-less activity and duration of action of about 20 hours [13]. The benefits of IDet can be less frequent dosing and lower incidence of maternal hypoglycemia. The disadvantages include higher cost and lack of information regarding maternal and neonatal outcomes in GDM. For glycemic control, IDet is comparable to NPH or glibenclamide, with fewer episodes of maternal hypoglycemia [7,8].

Information on the perinatal outcomes of women with GDM treated with IDet is scarce. We found no difference in the risk of preeclampsia between women who were treated with IDet vs. glibenclamide (8.3% vs. 11.9%, respectively, $P = 0.75$). The incidence of preeclampsia in both treatment arms was in the range described previously in GDM [2,14].

Two studies described GWG in women with GDM treated with IDet. One small randomized controlled trial by Herrera et al. [7] compared IDet (25 patients) to NPH (30 patients) and found no difference in GWG. A retrospective study that compared IDet to glibenclamide, found significantly greater GWG with Glibenclamide [8]. In contrast, we found no significant difference in GWG between IDet and glibenclamide (13.4 kg vs. 11.74 kg, $P = 0.64$). A recent systematic review and network meta-analysis suggested that detemir had a favorable weight profile compared to other long-acting insulin analogs in women with type II diabetes [15]. The weight sparing effect of IDet may be partly based on its central catabolic action in the central nervous system, as was shown in a rat model [16]. Appropriate GWG (according to the Institute of Medicine 2000 recommendations) in women with GDM can help avoid negative perinatal outcomes (LGA infant, preterm birth, and cesarean delivery) [17]. As weight gain is a common side-effect of sulfonylureas like glibenclamide, in women with type II diabetes [18], IDet may be safer for women with GDM.

In our study, only 14.9% (10/67) of the newborns whose mothers received IDet were LGA, compared to 20.8% (10/48) on glibenclamide. A significant difference ($P = 0.04$) was found in favor of IDet.

The mean neonatal weight in this cohort, as well as the weight percentiles were similar between IDet and glibenclamide and both were in the range appropriate for gestational age. Similar mean fetal weights and percentiles were described in two other small studies [7,8]. A systematic review of 33 studies that included 4944 mothers who were randomized to insulin, metformin, or glibenclamide for the treatment of GDM found that neonates exposed to glibenclamide were significantly heavier at birth compared to those whose mothers were randomized to insulin or metformin [19].

In this study, the rate of neonatal hypoglycemia was significantly higher in the IDet group (25/67, 37.3%) vs. glibenclamide (7/48, 16.3%; $P = 0.018$). Yet, multivariant analysis found no association between this result and the treatment agent. In another similar study on 29 women treated with IDet, the rate of neonatal hypoglycemia was similar to that of the glibenclamide group. There were no cases of neonatal hypoglycemia in the IDet group and 1/62 in the glibenclamide group [8]. Herrera et al. [7] also found no cases of neonatal hypoglycemia among 25 women with GDM who were treated with IDet vs. NPH (30 patients).

The main risk factors for neonatal hypoglycemia are GDM, LGA, small for gestational age, and prematurity. All these parameters were similar between both treatment groups, other than a higher rate of LGA neonates in the glibenclamide group. The rate of neonatal hypoglycemia described in our cohort is in the range described recently in a prospective Dutch cohort of 506 neonates born to women with GDM [20].

The current study provides some evidence in favor of the management of GDM with IDet regarding perinatal outcomes. IDet might be more expensive but, in most cases, a single daily dose is required with a predictable dosing profile. Gathering more information on the efficacy and safety of insulins other than NPH is also important in view of the concerns about the safety of oral hypoglycemic drugs that cross the placenta and their short- and long-term effects.

Although modest in size, this study is the largest to report on a direct comparison of IDet and glibenclamide in GDM. The limitations of this study are mainly its retrospective, non-randomized nature, lack of information on the glycemic status of the patients and absence of data regarding the time of treatment initiation.

CONCLUSIONS

In pregnant women with GDM, glucose control on IDet yielded results comparable to glibenclamide, except for a significantly lower rate of LGA neonates.

Correspondence

Dr. O. Weitzner
Dept. of Obstetrics and Gynecology, Meir Medical Center, Kfar Saba 4428164, Israel
Email: omer.w4@gmail.com

References

1. American Diabetes Association. 14. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020; 43 (Suppl 1): S183-S192.
2. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. *Obstet Gynecol* 2018; 131 (2): e49-e64.
3. Society of Maternal-Fetal Medicine (SMFM) Publications Committee. Electronic address: pubs@smfm.org. SMFM Statement: Pharmacological treatment of gestational diabetes. *Am J Obstet Gynecol* 2018; 218 (5): B2-B4.
4. Camelo Castillo W, Boggess K, Stürmer T, Brookhart MA, Benjamin DK Jr, Jonsson Funk M. Trends in glyburide compared with insulin use for gestational diabetes treatment in the United States, 2000-2011. *Obstet Gynecol* 2014; 123 (6): 1177-84.
5. Mathiesen ER, Hod M, Ivanisevic M, et al; Detemir in Pregnancy Study Group. Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes. *Diabetes Care* 2012; 35 (10): 2012-7.
6. Callesen NF, Damm J, Mathiesen JM, Ringholm L, Damm P, Mathiesen ER. Treatment with the long-acting insulin analogues detemir or glargine during pregnancy in women with type 1 diabetes: comparison of glycaemic control and pregnancy outcome. *J Matern Fetal Neonatal Med* 2013; 26 (6): 588-92.
7. Herrera KM, Rosenn BM, Foroutan J, et al. Randomized controlled trial of insulin detemir versus NPH for the treatment of pregnant women with diabetes. *Am J Obstet Gynecol* 2015; 213 (3): 426.e1-7.
8. Koren R, Ashwal E, Hod M, Toledano Y. Insulin detemir versus glyburide in women with gestational diabetes mellitus. *Gynecol Endocrinol* 2016; 32 (11): 916-19.
9. Song R, Chen L, Chen Y, et al. Comparison of glyburide and insulin in the management of gestational diabetes: a meta-analysis. *PLoS One* 2017; 12 (8): e0182488.
10. Balsells M, García-Patterson A, Solà I, Roqué M, Gich I, Corcoy R. Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. *BMJ* 2015; 350: h102.
11. Sénat MV, Affres H, Letourneau A, et al; Groupe de Recherche en Obstétrique et Gynécologie (GROG). Effect of glyburide vs subcutaneous insulin on perinatal complications among women with gestational diabetes: a randomized clinical trial. *JAMA* 2018; 319 (17): 1773-80.
12. Diabetes Canada Clinical Practice Guidelines Expert Committee; Robinson DJ, Coons M, Haensel H, Vallis M, Yale JF. Diabetes and mental health. *Can J Diabetes* 2018; 42 (Suppl 1): S130-S141.
13. Owens DR, Bolli GB. Beyond the era of NPH insulin--long-acting insulin analogs: chemistry, comparative pharmacology, and clinical application. *Diabetes Technol Ther* 2008; 10 (5): 333-49.
14. Yogev Y, Xenakis EM, Langer O. The association between preeclampsia and the severity of gestational diabetes: the impact of glycemic control. *Am J Obstet Gynecol* 2004; 191 (5): 1655-60.
15. Madenidou AV, Paschos P, Karagiannis T, et al. comparative benefits and harms of basal insulin analogues for type 2 diabetes: a systematic review and network meta-analysis. *Ann Intern Med* 2018; 169 (3): 165-74.
16. Vasselli JR, Pi-Sunyer FX, Wall DG, John CS, Chapman CD, Currie PJ. Central effects of insulin detemir on feeding, body weight, and metabolism in rats. *Am J Physiol Endocrinol Metab* 2017; 313 (5): E613-E621.
17. Cheng YW, Chung JH, Kurbisch-Block I, Inturrisi M, Shafer S, Caughey AB. Gestational weight gain and gestational diabetes mellitus: perinatal outcomes. *Obstet Gynecol* 2008; 112 (5): 1015-22.
18. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: a meta-analysis. *JAMA* 2016; 316 (3): 313-24.
19. Tarry-Adkins JL, Aiken CE, Ozanne SE. Comparative impact of pharmacological treatments for gestational diabetes on neonatal anthropometry independent of maternal glycaemic control: A systematic review and meta-analysis. *PLoS Med* 2020; 17 (5): e1003126.
20. Voormolen DN, de Wit L, van Rijn BB, et al. Neonatal hypoglycemia following diet-controlled and insulin-treated gestational diabetes mellitus. *Diabetes Care* 2018; 41 (7): 1385-90.

Compassion is not weakness and concern for the unfortunate is not socialism.
Hubert Horatio Humphrey Jr. (1911–1978), American pharmacist and politician who served as the 38th vice president of the United States

The best portion of a good man's life is his little, nameless, unremembered acts of kindness and of love.
William Wordsworth (1770–1850), English Romantic poet