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Full length article

The importance of declining insulin requirements during pregnancy in patients with pre-gestational gestational diabetes mellitus☆,☆☆

Maya Ram[a,b,*,1], Larissa Feinmesser[a,b,1], Shiri Shinar[a,b], Sharon Maslovitz[a,b]

[a] Department of Obstetrics and Gynecology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[b] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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ABSTRACT

Objective: In patients with pre-gestational and gestational diabetes mellitus (GDM), insulin requirements often increase during the third trimester of pregnancy in order to maintain proper glycemic control. However, a fraction of patients demonstrate a significant decrease in insulin requirements in late gestation. We aimed to evaluate the clinical significance of decreasing insulin requirements in patients with pre-gestational diabetes and GDM with respect to fetal wellbeing and pregnancy outcome.

Study design: We performed a retrospective cohort study in a single referral center for gestational diabetes between 1/2010 and 12/2014. Healthy pregnant women with pre-gestational diabetes and GDMA2 and a decrease of at least 30% in insulin requirements over a period of two weeks during the third trimester (group A) were compared to women with stable or increasing insulin requirements (group B). The primary outcome was a composite of situations associated with feto-placental dysfunction (fetal growth restriction, oligohydramnios and cesarean section due to category 2–3 monitor). Secondary outcomes were maternal oral glucose tolerance test (OGTT) results 6 weeks postpartum, neonatal intensive care unit (NICU) admission rates, Apgar scores $\leq$7 at 5 min, arterial blood pH $\leq$ 7.1, macrosomia, neonatal hypoglycemia and a composite adverse neonatal outcomes (defined as one or more of the following: respiratory morbidity, cerebral morbidity, phototherapy, need for blood transfusion, necrotizing enterocolitis or death).

Results: Group A consisted of 101 women and group B – of 203 women. There were no differences between the groups in demographic characteristics or diagnostic characteristics of diabetes. The frequency of conditions related to feto-placental dysfunction did not differ between the groups (7.9% vs. 8.4%, p = 0.61). Secondary outcome measures also did not differ between the groups, regardless of insulin requirements.

Conclusion: Decreasing insulin requirements during the third trimester are not associated with adverse perinatal outcome related to placental dysfunction.

Introduction

Insulin requirements may change frequently during the course of pregnancy. It is well established that during the latter half of pregnancy incremental doses of insulin are required in order to maintain proper glycemic control [1]. This may be attributed to increased production of pregnancy related hormones such as estrogen, progesterone, human placental lactogen (hPL) and prolactin, all of which are considered counter-regulatory hormones, opposing the hypoglycemic effect of insulin [2]. However, some studies report a significant drop in insulin requirements in late gestation [2–5]. The pathophysiological explanation for this decline focuses on a presumed failing feto-placental unit leading to decreased secretion of estrogen, progesterone and hPL [2]. Nonetheless, previous studies in women with type 1 diabetes

Abbreviations: GA, gestational age; IUGR, intrauterine growth restriction; AF, lamniotic fluid index; NICU, neonatal intensive care unit; SD, standard deviation.

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☆☆ This study was conducted in Tel-Aviv, Israel.

* Corresponding author at: Department of Obstetrics and Gynecology, Lis Hospital, Tel Aviv Sourasky Medical Center, 6 Weizmann Street, Tel Aviv 6423906, Israel.
E-mail address: maya3000@gmail.com (M. Ram).

[1] These author contributed equally to this work.

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failed to delineate an association between declining insulin requirements and adverse neonatal outcomes related to placental insufficiency [2,3].

To date, the vast majority of studies assessing the clinical significance of declining insulin requirements in patients with Type I diabetes are inconclusive. Similarly, studies on the more common form of diabetes – gestational diabetes mellitus (GDM) – are lacking. Even so, the common, non-evidence based, practice in many institutions is to induce delivery in cases of a significant reduction in insulin requirements, for fear of adverse fetal and neonatal outcomes due to a dysfunctional feto-placental unit [2].

The aim of this study was to evaluate clinical significance of decreasing insulin requirements in patients with GDM with respect to fetal wellbeing and pregnancy outcome.

Methods

A retrospective study conducted between January 2010 and December 2014 in a single referral center for diabetes in pregnancy. Electronic medical records of women with GDM or pre-gestational diabetes (PGD) requiring insulin in order to achieve a euglycemic state were reviewed. The diagnosis of PGD was made according to HA1C >6.5 or fasting glucose level >125 mg/dl or a random glucose level >200 mg/dl. The diagnosis of GDM was made according to abnormal Oral Glucose Tolerance Test (OGTT)- defined as any 2 abnormal values out of four (a pathologic OGTT was defined based on Carpenter & Coustan's threshold values [6]). The indications for OGTT were: Glucose tolerance Test (GCT)> 140, family history of diabetes mellitus (DM), fasting glucose level >100 at the beginning of pregnancy, history of delivery of a macrosomic newborn (above 4000 g).

Only patients with comprehensive and well documented pregnancy follow up, as well as known obstetrical and neonatal outcomes were included. Inclusion criteria comprised of women aged 18–45 years with a singleton gestation and diabetes requiring insulin to maintain proper glucose control. Women were excluded if they had multiple gestations, chronic diseases such as hypertension, renal or rheumatologic disorders, received oral hypoglycemic agents during pregnancy (such as glyburide or Glucophage), had undergone pregnancy termination due to fetal malformations or delivered prematurely before 36 weeks.

Patients diagnosed with PGD or GDM were counseled by a dietician at the referral center regarding the recommended daily caloric intake and timing and composition of meals. Blood glucose level monitoring commenced thereafter as follows: fasting blood glucose (FBG) levels and 1 or 2-h post prandial levels after each meal. The target glucose values were: FBG <90 mg/dl, 1-h post prandial glucose <140 mg/dl and 2-h post prandial glucose <120 mg/dl. Failure in dietary treatment mandating insulin was defined as 6 deviations (any deviation) from the treatment goals over a 7-day period. The daily dose of Levemir (Generic name-insulin Detemir,Brand Names: Levemir, Levemir FlexPen), subcutaneous (SC) insulin, was initiated at bedtime if FBG was high and at 10:00 am if postprandial glucose levels were high. Increments of insulin doses were added by the patient according to a sliding scale – starting with 6 units at bedtime and increasing insulin dose by 4 units every other day if FBG remained >90 mg/dl for two consecutive days.

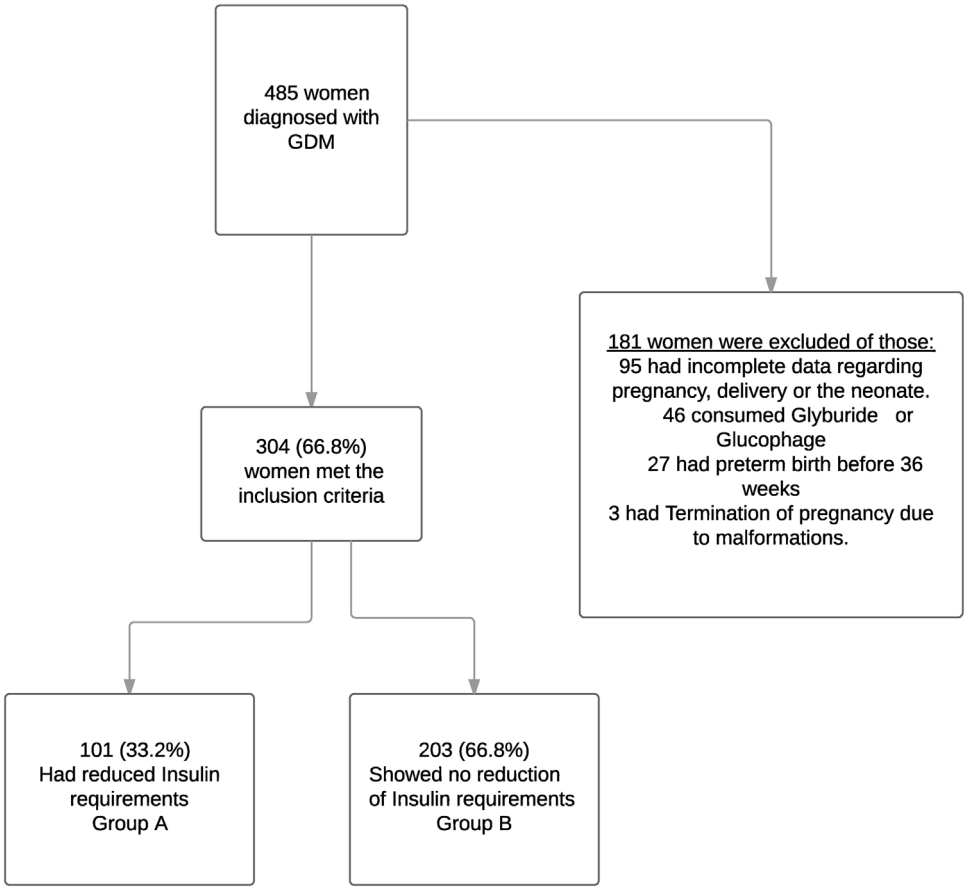

Fig. 1. Description of women comprising the study population.