The Role of Adding Metformin to Insulin Therapy in Insulin-Resistant Diabetic Pregnant Women
A Randomized Controlled Trial

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By

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بسم الله الرحمن الرحيم
وَأَنْزَلَ اللَّهُ
عَلَيْكَ الْكِتَابَ
وَالْحِكْمَةَ
وَعَلَّمَكَ مَا لَمْ
تَكُنْ تَعْلَمُ وَكَانَ
فَضْلُ اللَّهِ عَلَيْكَ
عَظِيمًا
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Before all, Thanks to GOD.

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List of Abbreviations

AACE	: American Association of Clinical Endocrinologists
ADA	: American Diabetes Association
ADA	: American Diabetes Association
AMP	: Activating adenosine monophosphate
BMI	: Body Mass Index
CHD	: Coronary heart disease
DM	: Diabetes mellitus
FPD	: Fasting plasma glucose
GDM	: Gestational diabetes mellitus
HELLP	: Hemolysis, elevated liver enzymes, and low platelet count
IADPSG	: Diabetes and Pregnancy Study Groups
IDDM	: Insulin-dependent diabetes mellitus
IDF	: International Diabetes Foundation
IFG	: Impaired fasting glucose
IQR	: Interquartile range
MiG	: Metformin in Gestational Diabetes Mellitus
MODY	: Maturity Onset diabetes of the Young
NAFLD	: Non-alcoholic Fatty Liver Disease
NDDG	: National Diabetes Data Group
NIDDM	: Noninsulin-dependent diabetes mellitus
OGTT	: Oral glucose tolerance test
OGTT	: Oral glucose tolerance test
PCOS	: Polycystic ovarian syndrome
PCOS	: Polycystic ovary syndrome
PDM	: Pre-existing diabetes mellitus
RDS	: Respiratory distress syndrome
SD	: Standard deviation

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Introduction

The proportion of pregnant women with gestational and pregestational diabetes mellitus (DM) is increasing, mainly from an increase in type 2 DM ***(Hedley et al., 2004; Metzger et al., 2007)***. Obesity, low level of physical activity, and, possibly, the exposure to diabetes *in utero* are major contributors to the increase in type 2 diabetes ***(Butte, 2000).***

Insulin has been the drug of choice for treating DM with pregnancy, because of its safety in pregnancy, lack of significant transplacental passage and long history of use ***(Pridjian and Benjamin, 2010)***.

Pregnant diabetic women not uncommonly show poor glycemic control that necessitates hospital admission during their antenatal follow-ups. Of them a significant proportion, particularly those who are obese with long-standing pregestational diabetes mellitus, show some insulin resistance, that requires further increase in insulin dose over variable periods of hospital stay. Prolonged hospital stay is known to be associated with several adverse events including a higher risk of nosocomial chest and urinary tract infections, venous thromboembolism, in addition to the high cost. Prolonged hospitalization, on its own, may even worsen glycemic control ***(ACOG, 2001)***. Moreover, insulin, in high doses, is associated with weight gain and bouts of hypoglycemia ***(Rowan et al., 2008)***.

In the 21st century, oral hypoglycemic agents have been included in the armamentarium of treatment modalities for gestational diabetes mellitus (GDM). Earlier concerns with use of these agents in pregnancy were the unknown risk of teratogenicity and neonatal hypoglycemia caused by transplacental passage ***(Pridjian and Benjamin, 2010)***. Several randomized controlled trials have been conducted on the use of different oral hypoglycemic drugs as a substitute to insulin in women with GDM; the results of all of which were promising. Glycemic control and neonatal outcome in women who received oral hypoglycemic agents, namely the sulfonylurea glyburide and the biguanide metformin, were comparable to those who received insulin ***(Rowan et al., 2008)***.

Metformin is a biguanide that improves insulin sensitivity, probably by activating adenosine monophosphate (AMP) kinase. In contrast to insulin, metformin is not associated with weight gain or hypoglycemia. Reported outcomes of its use during pregnancy have been favorable ***(Shao et al., 2000; Kirwan et al., 2002)***. The safety of use of metformin during pregnancy are mainly derived from reports of women with polycystic ovarian syndrome (PCOS) who got pregnant while using metformin ***(Pridjian and Benjamin, 2010)***. Metformin is now categorized by the FDA regarding its safety for use in pregnancy as category B ***(Pridjian and Benjamin, 2010)***. Metformin has been studied in treatment of GDM in two randomized controlled trials. Rowan et al. randomized a number of women with GDM to receive either

metformin or insulin. Of the 363 women who received insulin, 336 (92.6%) continued on metformin till delivery, but 168 (46.3%) required supplemental insulin to achieve euglycemia. Neonatal outcomes were similar in both groups, and women preferred to use metformin even if insulin was added ***(Rowan et al., 2008)***. In another randomized controlled trial, Moore et al. compared the use of metformin to glyburide for treatment of GDM. Euglycemia was achieved in 65.3% of women who received metformin, while 34.7% needed supplemental insulin ***(Moore et al., 2010)***.

To our best knowledge, oral hypoglycemic agents have not been suggested as alternative to insulin in women with pregestational DM. The current recommendation is to switch women with type 2 DM, who have been maintained on metformin and get pregnant, to insulin even if unexpected pregnancy occurs ***(Pridjian and Benjamin, 2010)***. The promising results of the few randomized trials on the use of metformin as an alternative to insulin in women with GDM, encourages us to try it, not as an alternative to insulin, but as an 'adjuvant' in women with DM with pregnancy who show insulin resistance.

Aim of the Work

The aim of the present study is to assess the impact of adding oral metformin to insulin therapy in pregnant women with resistant diabetes mellitus.

Gestational Diabetes Mellitus

Definition

Gestational diabetes mellitus (GDM), a common medical complication of pregnancy, is defined as "any degree of glucose intolerance with onset or first recognition during pregnancy"**.** The definition has applied whether or not insulin is used for treatment or hyperglycemia persists after pregnancy. The possibility that unrecognized glucose intolerance antedated the pregnancy is not excluded ***(Metzger et al., 1998; ADA, 2009).***

However, in 2010, the International Association of Diabetes and Pregnancy Study Groups (IADPSG), an international consensus group with representatives from multiple obstetrical and diabetes organizations, including the American Diabetes Association (ADA), recommended that women found to have diabetes at their initial prenatal visit, using standard criteria, receive a diagnosis of overt, rather than gestational diabetes ***(ADA, 2010).***

The rationale for this change is that more and more women have personal risk factors, such as obesity, for diabetes, and are therefore being screened early in pregnancy. Women diagnosed in the first trimester likely had pre-existing diabetes unrecognized prior to pregnancy rather than impaired glucose tolerance due to pregnancy-related hormonal changes, which are most pronounced later in gestation.