Review Article

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Pharmaceutical Care in Gestational Diabetes Mellitus

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Abstact

Gestational diabetes mellitus (GDM) is defined as diabetes diagnosed during pregnancy that is not clearly overt. Mild glucose intolerance during pregnancy has been linked to adverse pregnancy outcomes which affects both mother and fetus. As controversy continues concerning optimal strategy for diagnosing GDM, there also has been much confusion surrounding its management. It remains controversial whether treatment of GDM is effective and if treatment helps reduce the incidence of adverse pregnancy outcomes. Current evidence supports medical nutrition therapy (MNT) along with exercise and self-monitoring of blood glucose as cornerstone of GDM management. Although human insulin is the standard treatment for patients who cannot achieve desired glycemic levels with MNT and exercise, small scale studies with insulin analogues, lispro and aspart are also encouraging. In addition, glibenclamide and metformin have also displayed comparable efficacy to human insulin. Glibenclamide does not cross human placenta, therefore, it may be a safer alternative as compared to metformin which crosses human placenta but it is not teratogenic. However, higher incidence of preterm births have been reported in metformin-treated pregnant women, but this needs further confirmation. Present evidence greatly supports oral anti-diabetic therapy with glibenclamide and metformin besides insulin lispro and insulin aspart as alternatives to regular human insulin if MNT and exercise fails to achieve desired glycemic targets.

Key words: Gestational diabetes, pregnancy, macrosomia, insulin, glibenclamide, metformin.

INTRODUCTION

Gestational Diabetes Mellitus (GDM) is defined as diabetes diagnosed during pregnancy that is not clearly overt diabetes.[1] Mostly this disease condition terminates at the end of pregnancy; however such patients are at high risk for developing type 2 diabetes at a later stage in life. Consensus exists about the adverse maternal and perinatal outcomes associated with overt diabetes during pregnancy; however, there has been much controversy in the past about adverse pregnancy outcomes affiliated with mild glucose intolerance.[2] Hyperglycemia and adverse pregnancy outcomes (HAPO) study was a landmark study, conducted to identify the association of mild glucose intolerance with adverse maternal and perinatal outcomes. Results of the HAPO study indicated strong and continuous relationship of mild hyperglycemia with adverse pregnancy outcomes of GDM.[3] Maternal hyperglycemia causes increased glucose transfer from maternal circulation to the fetus causing hyperinsulinemia. This state is associated with overgrowth of adipose tissues surrounding the chest, shoulder and abdomen of the fetus, thus complicating pregnancies by increasing risk of shoulder dystocia, birth trauma and need for caesarean section.[4] Besides, there is increased risk for development of neonatal hypoglycemia, polycythemia, hyperbilirirubinemia and intra uterine fetal death. Risk

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for development of obesity and type 2 diabetes also increases in children born to GDM mothers.[2,5] In addition to caesarean section and increased risk of developing type 2 diabetes, maternal adverse outcomes include preeclampsia, pregnancy-induced hypertension and increased need for induction of labor.[2,3] Incidence of GDM ranges from 1% to 14 % depending upon the ethnic origin of the patient and the diagnostic tests used to identify such patients.[1]

Pathophysiology

During first trimester of pregnancy, insulin sensitivity increases due to increased binding of insulin to adipocytes. During this period, fasting, postprandial and HbA1c levels fall substantially due to increased fetal demand for glucose.[6] As the gestation advances, concentrations of cortisol, progesterone, estrogen, prolactin, tumor necrosis factor alpha and placental lactogen increases, and these contribute to increased insulin resistance. Reduction in insulin sensitivity is a physiological phenomenon and contributes to an increased supply of glucose to fetus and helps meet the increased nutrient requirement for fetal development.[7,8] Another form of insulin resistance is chronic in nature which antedates pregnancy and is aggravated by physiological changes during gestation period. Most GDM patients have both forms of resistance and considered to be more prone to development of disease. GDM develops when insulin production does not correspond to insulin demands thus elevating glycemic levels in the plasma. Reduction in insulin secretion may either be due to dysfunctional beta cells resulting from an autoimmune process or decrease in insulin release due to a genetic abnormality or defective beta cells which may be the result of chronic insulin resistance. The latter may be the predominant cause of decrease in insulin secretion.[9]

Target Glycemic Levels

Table 1 shows target plasma glucose levels recommended for GDM patients by the Fifth International Workshop Conference on Gestational Diabetes Mellitus.[10]

Table 1. Target glycemic levels

Fasting	<96 mg/dl
1-h postprandial	<140 mg/dl
2-h postprandial	<120 mg/dl

Excessive glycemic control (mean capillary glucose levels <87 mg/dl) is considered to be associated with high incidence for small for gestational age (SGA) babies.

Risk Factors

Following are the risk factors for GDM development[11]:

- BMI above 30 kg/m^2,
- History of macrosomia and GDM,
- Diabetes in first degree relatives, or
- Ethnic origins with high prevalence of disease which includes South Asian (especially Pakistan, India or Bangladesh), Black Caribbean and Middle Eastern countries.

Screening and Diagnosis

Controversy surrounds the different diagnostic and screening procedures used to identify a GDM patient. Nearly six different diagnostic criteria are now in use. Based upon the findings of the HAPO study, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) in 2010 revised the diagnostic criteria for GDM which was also adopted by the American Diabetes Association (ADA).[1] Two discrete phases are included in the new criteria.

Initially pregnant women with high risk factors for GDM are offered measurement

for FPG, random plasma glucoseor HbA_{1c} during the first prenatal visit.If results of the test are indicative of overt diabetes i.e. FPG ≥ 7.0 mmol/l (126 mg/dl) or random plasma glucose ≥ 11.1 mmol/l (200 mg/dl) or HbA_{1c} value ≥ 6.5%, then patient is considered to have pre-existing diabetes. If FPG levels ≥ 5.1 mmol/l (92 mg/dl) but remains below 7.0 mmol/l (126 mg/dl), then patient is given a diagnosis of GDM.

In the second phase, all pregnant women including those with FPG below 5.1 mmol/l (92 mg/dl) during initial assessment, are offered a 75-g OGTT at 24 to 28 weeks of gestation. Patient is given diagnosis of overt diabetes if FPG levels ≥ 7.0 mmol/l (126 mg/dl). GDM shall be diagnosed if one or more of the values indicated in Table 2 are either equaled or exceeded.[1]

Table 2. Diagnostic Criteria for the 75-g 2 hour Oral Glucose Tolerance Test

Status	Glucose concentration threshold	
Fasting	92 mg/dl	5.1 mmol/l
1 hour	180 mg/dl	10.0 mmol/l
2 hour	153 mg/dl	8.5 mmol/l

Treatment

Treatment of GDM based upon available evidence can be: 1) medical nutrition therapy and exercise, 2) insulin, and 3) oral anti-diabetic agents.

Medical Nutrition Therapy and Exercise

Evidence from high quality trials and meta-analysis studies have demonstrated medical nutrition therapy (MNT) and exercise along with self-monitoring of blood glucose (SMBG) as the cornerstone of GDM management.[12-16] Exercise reduces postprandial glucose levels, HbA_{1c} and insulin requirements in overweight women.[17] Both ACOG and NICE guidelines recommend nutritional intervention and exercise in women with GDM.[11,18] ADA, prior to changing diagnostic criteria for GDM, also recommended nutritional counseling but the new guidelines does not recommend any specific intervention and further studies are suggested based upon new diagnostic criteria.[1] Goals of dietary interventions are to achieve normo-glycaemia while avoiding ketoacidosis and risk of hypoglycemia.

Patients should be advised to keep a balance between polyunsaturated and monounsaturated fats and use low glycemic index carbohydrates with a focus on lean proteins which also includes oily fish. If pre-pregnancy BMI of a patient is above 27 kg/m², caloric intake should be restricted to 25 kcal/kg/day or less and moderate exercise of at least 30 minutes should be done on daily basis.[11] Clinician should avoid ketonuria and not more than 33% of caloric restriction is desired.[18] Physical activity can consist of brisk walking or a seated arm exercise, for at least 10 minutes, after each meal.[9]

Insulin

Hypoglycemic therapy is recommended if desired blood glucose levels could not be maintained with diet and exercise interventions during a period of 1-2 weeks.[11] Human insulin is considered standard hypoglycemic therapy in such patients;[19,20] however, small scale studies with insulin analogues lispro and aspart are also promising.[21-23] Presently there is no available evidence in support of insulin glulisine, hence it is not used in clinical practice. Controversy also exists regarding appropriate plasma glucose levels for initiating insulin. Either FPG levels above 95 mg/dl or above 105 mg/dl are considered appropriate. Mostly 1 hour post-prandial glucose levels above 140 mg/dl and/or 2 hour post-prandial glucose levels above 120 mg/ dl is considered the threshold value to initiate insulin therapy.[18]

The initial dose of insulin may be 0.7 U/kg/d during 1st trimester, often increasing to 0.8 U/kg/d for weeks 18 to 26, 0.9 U/kg/d for weeks 26 to 36, and 1.0 U/kg/d for weeks 36 to term. Obese women may need higher doses of 1.5 U/kg/d to 2.0 U/kg/d due to a combined effect of pregnancy and obesity on insulin resistance.[24] Insulin requirements may decrease at 9 to 12 weeks of gestation and during 38 to 40 weeks of gestation.[25] Half of the total dose is given as a basal dose, using an insulin infusion pump or NPH insulin, divided into two to three daily injections with intervals of 8 to 12 hours.[24] High quality evidence in support of long acting insulin, glargine is unavailable therefore NPH is the agent of choice.

Oral Anti-diabetic Agents

Oral antidiabetic therapy with glibenclamide and metformin is recommended by NICE guidelines if dietary intervention and exercise fails to achieve desired glycemic levels.[11] However, regulatory authorities around the globe, including the US FDA, have not approved oral antidiabetic drugs for use in pregnancy. These recommendations were based on the experiences with first generation sulfonylureas which were reported to be teratogenic and associated with neonatal hypoglycemia.[26,27] However, several studies that compared glibenclamide to human insulin, demonstrated that the human placenta is impermeable to glibenclamide[28,29] and it is as effective as regular human insulin in GDM patients.[29,30] Use of metformin in pregnancy remains controversial due to its ability to cross placenta and the risk of fetal anomalies.[31] Some trials have reported high incidence of preterm births in metformin treated arms.[32,33] Effects of metformin exposure on the infants in the long term are also unknown. However, metformin has not been reported to be teratogenic and efficacy of metformin has proven comparable to regular human insulin.[30,32,33] Dose of both glibenclamide and metformin is upward titrated to a maximum of 20 mg and 2,500 mg respectively based upon patient's response.[29,32]

Postpartum Care

Pregnant women suffering from GDM have a 35-60% chance of developing type 2 diabetes within a period of ten years.[9] They also have a high chance of developing GDM in subsequent pregnancies. A systematic review has reported this incidence to be 30-84%.[34] Results of 2.8 years of follow up in a diabetes prevention program (DPP) reported a reduction in chances of developing type 2 diabetes by 58% through lifestyle interventions and 31% for metformin-treated group as compared to placebo.[35] Therefore, GDM patients should focus on regular exercise and weight management to reduce the risk; life style interventions are also considered cost effective.[36]

A 75-g OGTT is recommended after 6–12 weeks of delivery in those, who do not develop type 2 diabetes mellitus immediately after child birth. Patients should be advised to repeat the test at 1 year and thereafter at a minimum interval of every 3 years to detect the disease in time.[9]

Pharmacist Role in GDM Management

Pharmacist as a part of the health care team needs to become more patient-centered, in providing pharmaceutical care. They should support the health care team by providing latest evidence-based information on pharmacotherapy issues on one hand, and by involving patient in therapeutic monitoring on the other. They need to make patient understand the purpose of therapy and involve the patient in the decision making process to reach therapeutic goals. Studies have shown that pharmacist-based medical therapy management programs improve adherence to therapy and reduce HbA_{1c}.[37] Patient also needs to be educated about the

adverse effects of therapy especially those on insulin or glibenclamide. These drugs are capable of producing severe hypoglycemia especially when caloric intake is restricted and/or following long exercise. Therefore, patient should know about the symptoms of hypoglycemia and its management. Patient should be advised to monitor plasma glucose levels strictly to avoid hypoglycemic risk and to keep the glycemic levels within the desired limits. Besides, insulin dose and time of administrationis also based upon glycemic parameters.[18] Patients on metformin therapy need counseling about the most common adverse effects like diarrhea, nausea, vomiting and flatulence. In addition, vitamin B_{12} levels should be checked especially if anemia is present as metformin decreases vitamin B_{12} levels in a small group of patients, thus associated with megaloblastic anemia. Besides educating the patient on pharmaco-therapeutic aspects, pharmacist should provide in depth advice to the patient on dietary management. A variety of educational strategies that includes verbal, written or audio-visual forms can be used to deliver the message effectively.[38] Patient should be provided information on importance of dietary control, body weight management and role of exercise in avoiding GDM complications. Besides, they need to be educated about risk of having macrosomic babies and associated complications. The patient should know that early feeding and glycemic control during labor plays an important role in reducing incidence of neonatal hypo-glycaemia[11]. Pharmacist working in the diabetes clinic should have detailed understanding of GDM management and diabetic complications especially of gestational diabetes mellitus.

DISCUSSION

Goal of GDM management is to keep optimum glucose levels and improve pregnancy outcomes. Excessive glucose control is thought to increase chances for SGA babies. Therefore, mean capillary glucose levels below 87mg/dl are not desired (Metzger BE, 2007). The recommended targets are to keep typical fasting glucose <95–96 mg/dl, 1 hour postprandial glucose 130–140 mg/dl, and 2 hour postprandial glucose <120 mg/dl.[1,10,18] Thus, GDM management is the art of keeping this delicate balance of glycemic control in these patients, if desired results are to be achieved. However, results of a recent pooled analysis of mean glucose levels in non-diabetic pregnant mothers indicated much lower plasma levels as compared to minimum threshold levels defined for glycemic control in GDM patients. The pooled estimates of glucose values (± SD) were as follows: fasting 71 ± 8 mg/dl, 1 hour postprandial 109 ± 13 mg/dl and 2 hour postprandial 99 ± 10 mg/dl.[39] These levels are 20-31 mg/dl lower than the current recommended targets of glycemic control. These findings may initiate a new debate to define normoglycemia in GDM patients. Results of the HAPO study confirm an association of mild glucose intolerance to adverse pregnancy outcomes and this relationship is continuous.[3] Thus, no threshold value can be defined for a particular outcome. Current studies on the topic have targeted a glycemic control in the range of 90-99 mg/dl at fasting, <140 mg/dl at 1 hour postprandial and <120-127 mg/dl at 2 hour postprandial. These glycemic levels have produced beneficial results without increasing the harm of treating GDM.

MNT with exercise and SMBG have been proven as an effective first line treatment option in achieving desired glycemic controls in GDM patients. In the ACHOIS trial, dietary counseling and SMBG was compared to the routine care group. Patients in the intervention arm had a statistically significant (P= 0.01) lower rate of serious perinatal adverse outcomes (1% vs. 4 %) and the incidence of

SGA babies was not more than the control group. Only 20 percent of the women received insulin therapy because they could not achieve the desired glycemic levels with dietary intervention alone.[12]

However, findings of another similar trial were different to some extent. Diagnostic criteria of this study were stricter and near to the new threshold levels established by ADA, but the mean FPG levels almost matched the ACHOIS population. Despite this, statistical significance for reduction in primary composite perinatal outcome which comprised of hypoglycemia, hyper-bilirubinemia, elevated cord-blood C-peptide level, still birth or neonatal death and birth trauma could not be achieved for the two study arms. However, there was a significant reduction in incidence of several secondary outcomes which includes mean birth weight (P = <0.001), LGA infants (P = <0.001), neonatal fat mass (P= 0.003), shoulder dystocia (P = 0.02) and cesarean delivery (P = 0.02). Study also found significant decrease in incidence of pre-eclampsia (P = 0.02) and gestational hypertension (P= 0.01) in the intervention arm. Only 7.6 percent of women in this study received insulin therapy because they could not achieve the desired glycemic levels with dietary intervention alone.[13]

Although results of these studies have some differences, there exists some conformity also. Incidence of adverse outcomes of critical importance like LGA babies, and pre-eclampsia remained low with statistical significance in intervention arms in both studies. Several meta-analysis studies[14-16] also found dietary advice effective in reducing these perinatal and maternal complications.

Evidence for human insulin comes from several studies where patients were treated with regular human insulin successfully if glycemic levels were not controlled adequately with dietary therapy.[12,13,19,20] It was found that transfer of insulin to fetus occurs as insulin-anti insulin antibody complexes and this transfer has correlation with fetal macrosomia. Human insulin was found to be least immunogenic, thus considered safe.[40] Therefore, insulin with lowest immunogenicity should be used in GDM and it remains standard therapy for treating diabetes in pregnant women.

Trials for synthetic insulin analogues, insulin lispro and insulin aspart are also reassuring. A randomized controlled trial in 42 women compared the safety and efficacy of insulin lispro to regular human insulin. Immunologic response to insulin lispro was a primary concern. Results indicated no difference in anti-insulin antibody levels between the two arms of study and drug was not measurable in the cord blood. Besides, no difference was observed in mean HbA1c levels, fasting and postprandial glucose levels in the two study arms.[21] Similar results were also observed in another study for insulin lispro and for insulin aspart.[22,23] Insulin aspart was more effective in providing postprandial glycemic control, and this was attributed to the better pharmacokinetic profile of insulin analogues. Evidence in support of the use of insulin glulisine in GDM is lacking, therefore this agent cannot be recommended at this stage.

It is already known that insulin has some adverse effects like hypoglycemia and weight gain and it is in the injectable form. Thus, skilled handling is required and also there is inconvenience while administration. Besides, high cost of therapy is another challenge. This is troublesome, particularly in a resource-constrained country where health insurance policies are not robust. Therefore, finding an efficacious, safe, cost effective and user friendly alternate therapy is necessary. In quest of such therapies, several randomized trials were conducted in the past, mostly with glibenclamide and

metformin. Nonetheless, experience with oral antidiabetic drugs for use in gestational diabetes is limited, therefore, regulatory authorities across the globe do not consider oral antidiabetic therapy a safe option in pregnancy.

However, trials with glibenclamide seem promising. An in vitro study had demonstrated that glibenclamide has a very low propensity for transfer across the placenta.[28] Findings of this study were the basis for another study which compared glibenclamide to insulin in 404 GDM patients. Results of this randomized control trial showedno significant differences in incidence of adverse perinatal outcomes between the two groups. Only 4% of patients were shifted to insulin because they could not achieve desired glycemic levels. In the cord serum of infants, study drug was not detectable, indicating its inability to cross the placenta; thus no difference was observed in insulin concentrations in cord serum between the two groups.[29] Another study found no difference in adiposity of infants between glibenclamide and insulin-treated group.[30] However, these studies were underpowered to detect many key outcomes of interest. Further studies with large sample sizes are required to confirm the findings of these studies.

Metformin is another oral antidiabetic drug of interest. It is not associated with weight gain and hypoglycemia and acts by increasing insulin sensitivity and by decreasing hepatic glucose production. Apprehensions with metformin use are due to its ability to cross the placenta. It can expose the fetus to concentrations equaling maternal circulation, which can affect fetal physiology.[31] Nonetheless, a meta-analysis study has shown metformin to be safe for use during first trimester of pregnancy. Safety was assessed in terms of major malformations only, but other outcomes such as stillbirth, spontaneous abortions, intrauterine growth retardation, minor anomalies, and preterm labor were not addressed in the study due to limited published data and further studies were recommended.[41] Although metformin is not considered teratogenic, a high quality study reported significant increase high incidence of preterm births (P= 0.04) in metformin-treated group.[32] Similar findings were also observed in metformin-treated arm in a recent study[33] but another study reported a lower incidence of preterm deliveries in the metformin-treated arm.[42] However, these two studies had limited power to detect low incidence variables. Long term complications associated with metformin use are unknown, nevertheless, results at 18 months of age in a study on 126 infants born to women with polycystic ovary syndrome treated with metformin seems promising due to absence of any effect of the drug on motor and social development of babies.[43] Further studies are required to establish long term safety of metformin.

In the Metformin versus Insulin for the Treatment of Gestational Diabetes (MiG) study, 92.6% of women continued to receive metformin in the intervention arm but 46.3% of patients could not achieve desired glycemic levels with metformin use and therefore received insulin supplements. Nonetheless, there was no significant difference in incidence of the primary composite outcome as well as secondary outcomes between the two study arms.[32] Another recent trial also evaluated the efficacy and safety of metformin in GDM patients in comparison to insulin. Two groups were similar in rates of maternal and perinatal complications and only 14% of the patients needed insulin supplements to achieve desired glycemic levels in metformin-treated arm.[33] Lower rate of insulin use in this trial may be attributed to lower BMI of patients in this study as compared to MiG trial. This is in line with the findings of two retrospective studies reporting 13% and 18% of women

receiving supplemental insulin.[44,45] Another study reported 31.9% of women receiving supplemental insulin. Higher BMI was noticed in the group of women receiving insulin supplements and this group of patients also had a higher incidence of LGA babies as compared to metformin only group.Thus individual patient characteristics play an important role in achieving desired therapeutic outcomes. Overall effect of metformin in decreasing neonatal and maternal complications was comparable to insulin.[42]

CONCLUSION

The above discussion highlights confusion in this area of health care because of conflicting results of studies. Ambiguities exist about treatments that are most effective in reducing incidence of adverse pregnancy outcomes and also it is not clear which complication can be addressed most effectively. Evidence suggests MNT along with exercise and SMBG as cornerstone of GDM management and human insulin remains the standard treatment option for the patients who cannot achieve desired glycemic levels with MNT and exercise. Although alternate therapeutic options are proven safe and effective, further studies of sufficient power are necessary to detect low incidence variables to confirm findings of earlier studies on the topic. Identification of a cost effective therapy will have a great impact on a low income country with an ethnic population at high risk for GDM.

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