http://www.banglajol.info/index.php/JNINB

Review Article

DOI: http://dx.doi.org/10.3329/jninb.v4i2.38931

Journal of National Institute of Neurosciences Bangladesh,
July 2018, Vol. 4, No. 2, pp: 145-149

ISSN (Online) 2518-6612
ISSN (Print) 2410-8030

Management beyond Insulin in Gestational Diabetes Mellitus: A Review Update

Sharmin Jahan[1], MA Hasanat[2]

[1]Assistant Professor, Department of Endocrinology, Bangbabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh; [2]Professor, Department of Endocrinology, Bangbabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

[**Received:** 2 March 2018; **Revised on:** 10 April 2018; **Accepted on:** 22 May 2018; **Published on:** 1 July 2018]

Abstract

Hyperglycemia is the most common endocrine disorder of pregnancy. As compared to Diabetes in pregnancy(DIP) the management of gestational DM(GDM) has always been a topic of controversy. Medical nutrition therapy(MNT) is the cornerstone of GDM management. 80-90% of GDM mothers can be treated by MNT alone and the rest will require drugs. Considerable controversy surrounds the use of oral anti-diabetic medications in pregnancy. The most widely studied drugs are glyburide and metformin. Conflicting results have been produced by different studies. However recent meta-analyses have shown that they can be an attractive alternative to insulin if long term safety data become available. Till then it might be too early to make a final comment on their use in GDM. *[Journal of National Institute of Neurosciences Bangladesh, 2018;4(2): 145-149]*

Keywords: Gestational Diabetes, MNT, Oral anti-diabetic drugs, Insulin

Correspondence: Dr. Sharmin Jahan, Assistant Professor, Department of Endocrinology, Bangbabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, Bangladesh; Email: sharmindmc@yahoo.com; Cell no.: +8801731061056

Conflict of interest: There is no conflict of interest relevant to this paper to disclose.

Funding agency: This research project was not funded by any group or any institution.

Contribution to authors: Jahan S, Hasanat MAinvolved from literature search. They have also prepared the manuscript and have revised it.

How to cite this article: Jahan and Hasanat. Management beyond Insulin in Gestational Diabetes Mellitus: A Review Update.J Natl InstNeurosci Bangladesh, 2018;4(2):145-149

Introduction

GDM is the most common medical condition women encounter during pregnancy. International diabetes federation (IDF) estimates that 16.8% live births are complicated with some form of hyperglycemia in pregnancy. Among them 84.0% are Gestational DM (GDM) and the rest 16% are Diabetes in pregnancy (DIP)[1]. Prevalence varies worldwide, among racial and ethnic groups and on testing methods used. Highest prevalence occurs in black Americans and Hispanic followed by South and East Asians. There is an alarming increase in the prevalence in Bangladesh, rising from 12.9% in 2013[2] to 36.6% in 2014[3].

GDM is a topic of controversy including the criteria, methods and timing of screening, optimum glycemic target and management with either oral anti-diabetic drugs (OAD) or insulin.As it is characterized by mild hyperglycemia occurring in later half of pregnancy that is not usually associated with congenital malformations so it is still debatable whether it requires strict control or not. However most of the studies over GDM mothers including the landmark Hyperglycemia and adverse pregnancy outcome study (HAPO) showed that optimum treatment leads to excellent peri-natal outcome and multi-disciplinary effort is advocated[4]. The components of management include medical nutrition therapy (MNT) that will suffice 80-90% of the GDM mothers and drug therapy in rest 10-20%. However, the role of OAD in GDM mothers is an arena of enormous controversy.

Medical Nutrition Therapy

Diet in pregnancy is to be developed by the woman and the registered dietitian that should be culturally

appropriate and individualized. Ideally it is a carbohydrate controlled meal plan that promotes adequate nutrition and appropriate weight gain with maintenance of normoglycemia and absence of ketosis[5]. Diet of a GDM mother differs in respect of spacing, types, glycemic load and glycemic index(GI) of carbohydrate. It should be equally distributed among three meals and three snacks spaced at 2.5 to 3.0 hours' interval. Foods with high glycemic index like processed, instant cereals, fruit juice, rice, potato, white bread, should preferably be avoided while intake of low GI foods like whole grain starch, brown bread & rice is encouraged. A meta-analysis in non-pregnant people with diabetes found that low GI foods led to an additional 0.4% lowering of glycated hemoglobin (HbA1c)[6]. The dietary reference intake (DRI) for CHO should be at least 33 g above the minimum level for non-pregnant women to ensure fetal brain development and function[7]. Fiber intake of minimum 28 g/day is recommended to avoid constipation and to promote satiety.

Calorie requirement in GDM: Excess weight gain in pregnancy is associated with maternal as well as foetal morbidities. On the other hand dieting is also not allowed though calorie can be curtailed by 30% for obese women without any ill effects. Adherence to healthy nutrient rich diet and small frequent feeds with a meal plan of at least 1800 cal is advocated to avoid ketonemia. ADA recommendation is approximately 1800 to 2200 calorie/day for a pregnant GDM. There is a simple eyeball technique for calorie assessment in GDM mothers: Small patient requiring 1800 calories, medium patient 2200 calorie and large patient 2400 calorie each day[8].

Gestational weight gain: Eastman et.al showed that there is a strong correlation between infant birth weight and maternal pregravid BMI for the normal and underweight categories[9]. However obese and overweight women tend to deliver large babies irrespective of the weight gain during pregnancy. Institute of medicine (IOM) has provided guideline for appropriate weight gain in pregnancy that should be between 12.5 to 18 kg,11.5 to 16 kg, 7 to 11.5 kg and 5 to 9 kg for the underweight, normal, overweight an obese BMI category respectively[10].

Exercise: It not only improves insulin sensitivity and glucose clearance but also increases calorie expenditure and BMR. It has been shown to reduce cardiovascular risk and improve weight control and overall wellbeing. The easiest exercise is 10 min activity session like brisk walking or upper limb exercise 30 min after each meal. Women physically active prior to pregnancy should be encouraged to continue previous exercise routine. However, the decision of exercise should be left to the discretion of the obstetrician as there are certain contraindications which are best judged by her. One study of the acute effect of exercise on glucose levels showed an impressive 1.3 mmol/l drop in glucose values at 30 min of exercise[11].

Monitoring of glycemic status: Glycemic status can be measured by glucometer at home or from venous plasma at the laboratory. However self monitoring of blood glucose (SMBG) have been found to be superior to intermittent office monitoring. Frequency of testing is determined by need of medication and control of diabetes. Measurement of postprandial glucose levels is more important than pre-prandial levels since the former correlates better with certain adverse neonatal outcomes like malformations, macrosomia, hypoglycemia, and shoulder dystocia. It is still debatable as to whether glucose should be measured at 1 or 2 hours after a meal and authors differs in this regards[12]. Suggested frequencies are fasting, 1 hr/2hr postprandial and bedtime, pre-prandial and 3AM (when indicated). Glycemic target is based on the recommendation of Fourth International Workshop-Conference on GDM: pre-prandial < 5.3 mmol/l,1-h post-prandial: <7.8 mmol/l and/or 2-h post-prandial: <6.7 mmol/l. These values were used as "upper boundary" treatment targets in clinical trials of GDM, and these trials achieved satisfactory clinical outcomes, including frequency of fetal macrosomia less than 11.0%, suggesting that the treatment targets were appropriate[13]. Currently controversy has arisen regarding stringent glucose control in GDM that might prove to be deleterious in terms of increased risk of small for gestational age (SGA) or IUGR[14].

Medications in GDM: When a GDM mother fails to reach glycemic target after 2 weeks on lifestyle modification then without any delay she should be put on drugs. GDM that is detected early in pregnancy often requires medications. Though insulin because of its efficacy and long term safety is the undisputed medication in GDM it has got some disadvantages as well. It requires strong motivation and health education, multiple daily subcutaneous injections are often painful, cumbersome dose modification depending on BMI of patient is required. Occurrence of hypoglycemia, weight gain in mother is commonplace. So, oral drugs would pose to be satisfactory alternative to insulin with good patient compliance. However, till date there is no clear consensus on use of OAD in

GDM. Most international agencies (ADA,WHO,IDF) discourage their use. They are only approved by a few American associations (ACOG) & by the NICE Guideline under some special situation. However, in a large nationwide retrospective cohort study in the US including 10778 women with drug treated gestational diabetes, use of glibenclamide increased from 7.4% in 2000 to 64.5% in 2011, becoming the most common treatment since 2007[15].

Glyburide/glibenclamide, is a second-generation oral sulfonylurea that is pregnancy category C. The initial dose is 2.5 mg once or twice a day and can be increased after titration with blood glucose values up to a maximum of 20 mg/day, but no more than 7.5mg should be taken at a single time[16]. Besides metformin it is one of the few OADs that is experimented on GDM mothers widely. The land mark study by Langer et al included 404 GDM subjects between 11 to 33 weeks of gestation who were divided into insulin or glyburide treated group according to intensified treatment protocol. The primary and secondary end points were achievement of the desired level of glycemic control and maternal and neonatal complications respectively. Glyburide was not detected in the cord serum of infants of GDM mother and the cord insulin concentrations were similar between the treated groups proving the lack of transplacental passage of glyburide(3.9%) and suggesting insignificant fetal exposure of glyburide[17]. This was in contrast to older sulphonylurea that frequently crossed placenta (upto 28%) to the fetus. Short plasma half life of the drug, tight plasma protein binding and presence of placental transporter pumping the drug back quickly into maternal circulation even after transplacental passage were thought to be the responsible factors. Efficacy was almost equal as the daily blood glucose concentrations and HbA1c values were similar between groups.The failure rate was 4% in the glyburide patients.There were no differences in the large for gestational age(LGA) or with macrosomia, lung complications, hypoglycemia, admission to the neonatal intensive care unit, or fetal anomalies. Ultimately it was found to be a cost-effective medication with good patient compliance, satisfaction, and overall satisfactory maternal and neonatal outcome. Langer concluded that glyburide was a clinically effective alternative to insulin therapy in women with gestational diabetes. Similar recommendations were made by other researchers as well. Some investigators reported a higher rate of maternal hypoglycemia in insulin group (20.0%) in comparison glyburide (4.0%) while others reported similar hypoglycemia rates[17]. Neonatal hypoglycemia was reported by some to be higher among those women who received glyburide (33.0%) compared with those receiving insulin (4.0%) whereas others did not find such differences[16].

Metformin, a Biguanide derivative acting as an insulin sensitizer would be a logical approach in pregnancy as it does not cause weight gain or hypoglycemia. On the other hand, it crosses the placenta frequently, upto 50.0% was noted in the cotyledon model. Thereby fetal exposure of the drug and safety in pregnancy has been a concern. It is a pregnancy category B drug. Coetzee and colleagues[18] did the first studies on metformin during the 1970s. In 2000, Hellmuth and colleagues[19] performed a cohort study of type 2 DM pregnant women on metformin versus glyburide versus insulin. This study disfavored the use of metformin due to the increased rate of preeclampsia (32.0% metformin vs. 7.0% glyburide vs. 10.0% insulin) and intrauterine fetal death (8.0% vs. 0.0% vs. 2.3%, respectively) in metformin treated group. Later this study was widely criticized as women in the study were not sound matched. Those women who received metformin were morbidly obese and started the medication later in the pregnancy. Thus, the adverse outcomes were probably attributed to poor pregnancy status rather than to metformin[20-21]. MiG study, one of the largest trial till date with metformin randomly assigned 751 women with GDM at 20 to 33 weeks of gestation to open treatment with metformin with supplemental insulin if required or insulin[22]. The trial was designed to rule out a 33.0% increase from 30.0% to 40.0% in the composite primary and secondary perinatal outcome in infants of women treated with metformin as compared with those treated with insulin. The authors did not find any difference in efficacy in glycemic control and the primary and secondary composite outcomes were equal between the assigned groups except for increased frequency of prematurity. However, the failure rate was high about 46.3%. Frequency of neonatal hypoglycemia were similar and severe hypoglycemia occurred significantly less often in infants of women taking metformin[21]. Other investigators reported rate of maternal hypoglycemia between 0 to 21.0% in metformin treated women[23]. There was no increase in the rate of neonatal hypoglycemia after delivery compared with women who received insulin. In those who did develop neonatal hypoglycemia, it was determined that this outcome was related to maternal hyperglycemia at the time of delivery[22].

A current comprehensive meta-analysis onrandomized

controlled trials comparing insulin with either glibenclamide or metformin provided robust evidence for the researchers[22]. This meta-analysis showed that in comparison to insulin birth weight was about 100 g higher, neonatal hypoglycaemia was twofold higher, and macrosomia was more than twofold higher in the glibenclamide group.Failure in the glibenclamide group was 6.37%. These findings were in sharp contrast to that by Langer et al[17] in respect to glibenclamide in GDM and the putative explanation was significant maternal to fetal transfer of glibenclamide that was proven by Hebert et al[23] and showed a maternal to fetal transfer ratio of 0.7. These diverging results were attributed to the use of a method with a detection limit of 0.25 ng/mL, while that of the method of Langer et al[23] was 10 ng/mL.On the other hand, in the metformin group, maternal outcomes were better in terms of total weight gain, weight gain since study entry, postprandial blood glucose, and pregnancy induced hypertension, whereas fetal outcomes were worse in terms of gestational age at delivery and preterm birth and better in terms of severe neonatal hypoglycaemia in comparison to insulin. Regarding potential mechanisms mediating differences with metformin use, the lower postprandial blood glucose observed with metformin (0.14 mmol/L) seemed insufficient to accountfor the lower rate in pregnancy induced hypertension and severeneonatal hypoglycaemia. The effect of metformin on maternal weight gain could be expected considering the effect ofmetformin outside pregnancy, while that on pregnancy induced hypertension could be attributed to improvements in insulinresistance, inflammation, or endothelial function. The effect ofmetformin on gestational age-small, but sufficient to increasethe rate of preterm birth by 50.0% could be attributed to metformin itself though the neonatal outcomes were unaffected by prematurity. The authors concluded that glyburide was clearly inferior whereas metformin with or without insulin was slightly superior to insulin in GDM mothers[22].

Studies comparing metformin and glibenclamide on pregnant mothers are scanty. Two open label, head to head trial on metformin versus glibenclamide on GDM in USA and Brazil found that metformin was associated with less maternal weight gain, lower birth weight, less macrosomia and fewer large for gestational age newborns.The average treatment failure was 26.8% in the metformin group versus 23.5% in the glibenclamide group[24-25].

Reports on evidence of safety and efficacy of other OAD in pregnancy is lacking. Some drugs like beta-glucosidase inhibitors do not have any systemic absorption. However long term safety data on these as well as other newer agents still remain undetermined.

Conclusion

MNT is the mainstay of management of GDM. Oral anti-diabetic drugs pose as lucrative alternative to insulin. Till now no drug has been proven to be clearly superior to insulin therapy in pregnancy and long term safety data are yet unavailable. If sofound, they will open up new avenues in GDM management.

References

1. International Diabetes Federation Diabetes Atlas, Seventh Edition, 2015;48 -63

2. Jesmin S, Akter S, Akashi H, Al-Mamun A, Rahman MA, Islam MM, et al. Screening for gestational diabetes mellitus and its prevalence in Bangladesh, Diabetes Research Clinical Practice 2014;103(1):57-62

3. Sandesh-Panthi MA, Hasanat MH, Yasmin-Aktar NS, Sharmin-Jahan MF. Frequency of gestational diabetes mellitus in Bangladesh impact of WHO 2013 screening criteria: Efficiency DIPSI & WHO 1999 criteria. Journal of Clinical Diabetology 2015;2(2):13-9

4. Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, et al. HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991-2002

5. Medical Nutrition Therapy, Evidence-Based Guides for Practice: Nutrition Practice Guidelines for Gestational Diabetes Mellitus (CDROM). Chicago, IL: American Dietetic Association; 2001

6. Brand-Miller J, Hayne S, Petocz P, Colagiuri S. Low-glycemic index diets in the management of diabetes: A meta-analysis of randomized controlled trials. Diabetes Care 2003;26:2261-7

7. Food and Nutrition Board, Institute of Medicine: U.S. DietaryReference Intakes: Energy, Carbohydrates, Fiber, Fat, Fatty Acids,Cholesterol, Protein, and Amino Acids. Washington, DC: NationalAcademies Press; 2002

8. American Diabetes Association. Gestational Diabetes Mellitus (Position Statement). Diabetes Care 2004;27 Suppl1:S88-90

9. Eastman NJ. Weight relationship in pregnancy. ObstetGynecolSurv1968;23:1003-25

10. Institute of Medicine. Dietary reference intake for carbohydrates, fiber,fat, fatty acid, cholesterol, protein and amino acid.Food and nutrition board. Washington Dc: national academy press; 2002

11. Avery MD, Walker AJ. Acute effect of exercise on blood glucose and insulin levels in women with gestational diabetes. J Matern Fetal Med 2001;10:52-8

12. Jovanovic-Peterson L, Peterson CM, Reed GF, Metzger BE, Mills JL, Knopp RH, et al. Maternal postprandial glucose levels and infant birth weight: Diabetes in Early Pregnancy Study: The National Institute of Child Health and Human Development –Diabetes in Early Pregnancy Study. Am JObstetGynecol1991; 164:103-11

13. Metzger BE, Buchanan TA, Coustan DR, de Leiva A, Dunger DB, Hadden DR, et al. Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. Diabetes Care 2007;30(Suppl 2):S251-60

14. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS. Effect of treatmentof gestational diabetes mellitus on pregnancy

outcomes. N Engl J Med. 2005;352(24):2477–86
15. Camelo-Castillo W, Boggess K, Sturmer T, Brookhart MA, Benjamin DK Jr, Jonsson-FunkM. Trends in glyburide compared with insulin use for gestational diabetes treatment inthe United States, 2000-2011. ObstetGynecol2014;123:1177-84
16. Anjalakshi C, Balaji V, Balaji MS, Seshiah V.A prospective studycomparing insulin and glibenclamide in gestational diabetes mellitusin Asian Indian women. Diabetes Res ClinPract2007;76:474-5
17. Langer O, Conway DL, Berkus MD, Xenakis EM, Gonzales O. Acomparison of glyburide and insulin in women with gestationaldiabetes mellitus. N Engl J Med 2000;343:1134-8
18. Coetzee EJ, Jackson WP. Pregnancy in established non-insulindependent diabetics: A five-and-a-half year study at Groote SchuurHospital. S Afr Med J 1980;58:795-802
19. Hellmuth E, Damm P, Molsted-Pedersen L. Oral hypoglycaemicagents in 118 diabetic pregnancies. Diabet Med 2000;17:507-11
20. Norman RJ, Wang JX, Hague W. Should we continue or stop insulinsensitizing drugs during pregnancy? CurrOpinObstetGynecol2004;16:245-50
21. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP.MiG TrialInvestigators. Metformin versus insulin for the treatment of gestationaldiabetes. N Engl J Med 2008;358:2003-15
22. 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
23. Hebert MF, Ma X, Naraharisetti SB, Krudys KM, Umans JG, Hankins GD, et al. Are weoptimizing gestational diabetes treatment with glyburide? The pharmacologic basis forbetter clinical practice. ClinPharmacolTher2009;85:607-14
24. Silva JC, Fachin DR, Coral ML, Bertini AM. Perinatal impact of the use of metformin andglyburide for the treatment of gestational diabetes mellitus. J Perinat Med 2012;40:225-8
25. Moore LE, Clokey D, Rappaport VJ, Curet LB. Metformin compared with glyburide ingestational diabetes: a randomized controlled trial. ObstetGynecol2010;115:55-9