

Gestational Diabetes Mellitus and Ademolus Classification of Hypoglycaemia-A Review

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Abstract

According to the World Health Organization, hyperglycaemia first detected at any time during pregnancy should be classified as either diabetes mellitus in pregnancy, or gestational diabetes mellitus. Current definitions of gestational diabetes include women with diabetes and women with intermediate hyperglycaemia impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) as defined in non-pregnant adults. The use of insulin in gestational diabetes mellitus is a category B level of recommendation while the use of oral hypoglycaemic agent is category C. Whichever glucose lowering agent is used whether injectable or oral, the risk of hypoglycaemia in both mother and fetus and in the immediate neonatal period cannot be overemphasised, this fact is what makes Ademolus Classification of Hypoglycaemia (ACH) a valuable tool in evaluating hypoglycaemia complicating the management of gestational diabetes mellitus. It is noticed that studies reported on maternal hypoglycaemia had varying results due, in part, to differences in the definition of hypoglycaemia. This is one of the gap in knowledge and controversies that will be addressed usefully by Ademolus Classification of Hypoglycaemia in gestational diabetes mellitus management complication worldwide, it will help to unify definition of hypoglycaemia irrespective of race and also allow for comparing of data objectively. The more we use ACH, the more we will see the gap in our existing knowledge, the more insight we will get in hypoglycaemia complicating gestational diabetes mellitus and the more scientifically knowledgeable we will become as it will open up new path of scientific understanding of fetomaternal pathophysiology for the benefit of mankind.

Keywords: Gestational diabetes mellitus; Hypoglycaemia; Classification

Introduction

According to the World Health Organization, hyperglycaemia first detected at any time during pregnancy should be classified as either diabetes mellitus in pregnancy, or gestational diabetes mellitus [1]. Current

definitions of gestational diabetes include women with diabetes and women with intermediate hyperglycaemia impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) as defined in non-pregnant adults. Therefore, gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. The definition applies

whether insulin or only diet modification is used for treatment and whether or not the condition persists after pregnancy. The use of insulin in GDM is a category B level of recommendation, meaning the use of insulin may be acceptable as either animal studies shows no risk but human studies not available or animal studies showed minor risks and human studies done and showed no risk while the use of oral hypoglycaemic agent is category C meaning they are to be used with caution if benefits outweigh risks, animal studies show risk and human studies not available or neither animal nor human studies done.

In practice the use of insulin in gestational diabetes mellitus is more common than use of oral hypoglycaemic agent. Whichever glucose lowering agent is used whether injectable or oral, the risk of hypoglycaemia in both mother and fetus and in the immediate neonatal period cannot be overemphasised [2].

In 2013, Ademolus Classification of Hypoglycemia (ACH) was first described by me and featured in my abstract presented at the Endocrine Society meeting in Chicago Illinois, United States of America in 2014 before it was eventually published in an open access journal for international perusal [3]. ACH classifies hypoglycaemia to Grade 1 to 4. Grade 1 has predominantly adrenergic features and is a blood sugar level between 55 to 70mg/dl,, grade 2 has adrenergic features with neuroglycopenic feature overlap and is a blood sugar level between 40 to 54.9mg/dl, grade 3 has predominantly neuroglycopenic features that are majorly reversible and is a blood sugar level of 10 to 39.9mg/dl while grade 4 has predominantly neuroglycopenic features with majorly irreversible brain damage and is a blood sugar level of less than 10mg/dl. (Table 1).

	Blood Sugar Level(mg/dl)
Grade 1(Mild)	55-70
Grade 2(Moderate)	40-54.9
Grade 3(Severe)	10-39.9
Grade 4(Very Severe)	<10
N:B Symptomatic Hypoglycaemia Above 70mg/Dl Is A Subset Of Grade 1	
N:B Asymptomatic Grade 4 Is Ademolusphenomenon	

Table 1: Ademolus Classification of Hypoglycaemia.

It is noticed that studies reported on maternal hypoglycaemia had varying results due, in part, to differences in the definition of hypoglycaemia. This is one

of the gap in knowledge and controversies that will be addressed usefully by Ademolus Classification of Hypoglycemia in gestational diabetes mellitus management complication worldwide, it helps to unify definition of hypoglycaemia irrespective of race and also allow for comparing of data whether within or between Americans, European, Asians or Australian. It has worldwide application. It also help to know the grade at which hypoglycaemia occur in the fetus irrespective of the gestational age or trimester of occurrence. Since the physiological serum glucose values in healthy newborns range between 3.3 and 5 mmol/L (59.4 to 90mg/dl), Ademolus Classification of Hypoglycemia will help to know the grade at which hypoglycaemia occurs in neonatal hypoglycaemia involving small for gestation age babies, macrosomic babies, preterm babies, and termed babies all of which can be a product of gestational diabetes mellitus. This gives room for objective comparison for prognostic purposes. The more we use ACH, the more we will see the gap in our existing knowledge, the more insight we will get in hypoglycaemia and the more scientifically knowledgeable we will become.

Oral Hypoglycaemic Agents Use in Gestational Diabetes Mellitus and ACH

The sulfonylurea and meglitinide are insulin secretagogues. The sulfonylurea bind to sulfonylurea receptors in β -cells, stimulating insulin secretion at all blood glucose levels. Meglitinides are structurally different from sulfonylurea, but act similarly via a different receptor [4].

If insulin secretagogues cross the placenta, they would be expected to stimulate insulin production in the fetus. The resultant fetal hyperinsulinism in fetus of diabetic mother can predispose to fetal hypoglycaemia [5-7]. Presumably this would make diabetic fetopathy worse, even if circulating glucose levels were lowered. In one study, which measured tolbutamide levels in mothers taking tolbutamide as well as their newborns, drug concentrations in placental samples and in neonatal blood samples obtained about 3 h after birth were similar to maternal levels [8]. Using an isolated perfused human placental cotyledon model, Elliott (9) demonstrated minimal placental transfer of glyburide, but greater transport of glipizide and particularly chlorpropamide and tolbutamide, from maternal to fetal compartments [9-10]. Glyburide could not be detected in the cord blood of offspring whose mothers took the drug as part of a randomized trial [11]. The aforementioned goes to show that there is possibility of fetal hypoglycaemia in women on oral hypoglycaemic agent either occurring alone or co

existing with maternal hypoglycaemia complicating gestational diabetes mellitus management.

Available data including poor transplacental passage support the use of an insulin secretagogue, glyburide, to treat gestational diabetes.

Over the past decade, glyburide a second generation sulfonylurea has been widely accepted as a viable treatment option in gestational diabetes mellitus (GDM) when pharmacologic intervention is required. This is supported by national and international societies and by multiple authorities in the field of Maternal Fetal Medicine [12-13].

In a paper that estimate whether there is a relationship between glyburide dose (2.5mg, 5mg, 10mg, 15mg or 20mg) and the rate of hypoglycaemic episodes in women with gestational diabetes mellitus, it was reported that 33% had 1-7% of their total blood glucose values within the hypoglycaemic range and that all recordings of hypoglycaemic episodes were asymptomatic and no patient reported a severe, or symptomatic hypoglycaemic episode [14]. It is worth noting that this paper uses blood glucose level less than 50mg as their definition of hypoglycaemia, this cut off translate to grade 2 hypoglycemia in Ademolus Classification of Hypoglycemia and also implies that all gestational diabetic in this study with grade 1 hypoglycemia (which the study did not recognised) had asymptomatic hypoglycaemia. This study is also valuable as it confirms that asymptomatic hypoglycaemia occurred at grade 2 even in gestational diabetes mellitus patient which were delivered in St Luke's Roosevelt Hospital, New York as far back as year 2000 since the study reviewed women who delivered between year 2000-2009. Now their findings in the paper are clinical findings which could be more objectively stated and scientifically meaningful if the grades of hypoglycaemia in the asymptomatic group were characterised, the fact that all the hypoglycaemia caused by glyburide in this gestational diabetes mellitus patient were asymptomatic does not mean there was no progression in grades from grade 1 to grade 2 (the progression from grade 1 to 2 was hundred percent in this study as all unrecognised grade 1 hypoglycaemia in this study were asymptomatic), this was a knowledge gap absent in the writing of the paper but now revealed by Ademolus Classification of Hypoglycemia, it follows that the more we use ACH, the more we will discover the existing gap in our present knowledge of hypoglycaemia complicating gestational diabetes management. Likewise the asymptomatic hypoglycaemia in this study does not mean there was no progression from grade 2 to grade 3 neither does it mean that they all have the same grade of

hypoglycaemia using the Ademolus Classification of Hypoglycaemia, some could have had grade 2 while some grade 3 since asymptomatic hypoglycaemia has been reported in grade 3 patients with diabetes mellitus in Africans.

Oral Hypoglycemic Agent and Insulin Use in Gestational Diabetes Mellitus and ACH

Langer and colleagues did not specifically define maternal hypoglycaemia in their study, but reported a statistically significantly higher percentage of women with a blood glucose level less than 40 mg/dL in the insulin group than in the glyburide group (20% compared with 4%, respectively) [15]. By applying Ademolus Classification of Hypoglycaemia to this finding it means that statistically higher percentage of women had grade 3 hypoglycemia in the insulin group compared to the glyburide group, it means that grade 3 hypoglycemia is commonly seen in their study when gestational diabetes mellitus patients is treated with insulin compared to when treated with glyburide which perhaps causes more of grade 1 and grade 2 hypoglycaemia. Hence in such situation, in a patient who had hypoglycaemic episodes frequently before pregnancy irrespective of the aetiology who now has gestational diabetes mellitus, using glyburide (if not contraindicated) will be safer in such than using insulin in order to limit the risk of hypoglycaemia in an already at risk patient.

Anjalakshi and colleagues did not define maternal hypoglycaemia in their study; again it is emphasised that the era of such study is passed since now a definition can be given and interpretation of data can be objectively done [16]. Another randomised controlled trial defined maternal hypoglycemia based on the need for hospitalization and reported that no events required hospitalization, while this is a clinical approach, the use of a biochemical definition for hypoglycaemia induced by gestational diabetes mellitus management would have been a better approach Bertini also reported no difference in the percentage of women developing preeclampsia in the insulin compared with the glyburide group (6% in both groups) [17]. While Comparing use of insulin ,acarbose and glyburide in gestational diabetes mellitus, Bertini noted that glyburide showed a higher rate of macrosomia and neonatal hypoglycemia as compared to other therapies but was unable to objectively compare the grades of hypoglycaemia seen in those on acarbose compared to those on insulin and compared to those on glyburide for the purpose of future studies, comparing the outcome in such study using Ademolus Classification of Hypoglycemia is recommended.

In a prospective randomized comparative study of 150 antenatal women whose pregnancies had been complicated by GDM and did not respond to diet alone which were recruited from antenatal clinics at Obstetrics Department in Zagazig University Hospitals Egypt from November 2012 to December 2014 [18]. They were divided randomly into two groups, 75 patients in each, and were subjected to either insulin or metformin medication. Outcomes were comparing the effects of both medications on maternal glycemic control, antenatal complications, and neonatal outcome. The aim of The Study was to evaluate efficacy of metformin in comparison to insulin for managing GDM. It was found that hypoglycaemia developed in 7 babies of metformin group and 15 cases in insulin group with P- value 0.01 which is statistically significant.

Now this is an interesting finding especially as hypoglycaemia is not a common side effect of metformin compared to other oral hypoglycaemic agents especially the sulfonylurea, since it was recorded in this particular study, the grade and grades of hypoglycaemia it caused in neonates of diabetic mothers would have been an interesting thing to know though not looked into, actually this can be a research topic area in the near future in practices where metformin is used in gestational diabetes since the United Kingdom National Institute for Health and Clinical Excellence (NICE) recommends metformin use before and during pregnancy and supports metformin and glyburide as choices for handling of gestational diabetes (19) though The American College of Obstetricians and Gynecologists (ACOG) does not support or recommend against the use of oral antidiabetic agents in pregnancy [19,20]. Similarly it would have been more scientifically meaningful if the grades of hypoglycaemia in the insulin group was characterised and then comparatively analysed if metformin induced neonatal hypoglycaemia occur at a similar grade to insulin induced neonatal hypoglycaemia in this group of gestational diabetes mellitus patients and also to objectively determine which of the two agent causes more severe hypoglycaemia in neonates metformin or insulin? This vital but useful scientific information is needed for better understanding of hypoglycaemia as it affect fetomaternal wellbeing especially in the late third trimester of pregnancy.

GDM not only influences immediate maternal (preeclampsia, stillbirths, macrosomia, and need for caesarean section) and neonatal outcomes (hypoglycaemia, respiratory distress), but also increases the risk of future Type 2 diabetes in mother as well as the baby [21,22]. The questions that need to be addressed using ACH and GDM include what grade of hypoglycaemia

is not compactible with intrauterine life among Americans, Asians, Africans, and Caucasians? At what grade of hypoglycaemia does fetal distress starts commonly among ethnic group?

When mother has a grade 2 hypoglycaemia for instance, does the fetus have corresponding grade of hypoglycaemia or a grade lower or higher than that of the mother? Does the same grade of hypoglycaemia occurs in pre-existing diabetes before pregnancy at the same dosage and type of insulin with gestational diabetes?. These vital point need to be addressed worldwide comparatively using ACH.

This throws a research challenge to obstetrician/diabetologist with interest in gestational diabetes to address this research question using ACH. These are research questions/areas that the use of ACH will assist to shed more light on worldwide and will enhance further scientific understanding of fetomaternal pathophysiology as far as hypoglycaemia is concerned.

The more we use ACH, the more we will see the gap in our existing knowledge, the more insight we will get in hypoglycaemia complicating gestational diabetes mellitus and the more scientifically knowledgeable we will become. The questions to be answered are more as long as the tool is utilized, it will give detailed insight and open multiple new paths of scientific knowledge [23].

Insulin Use in Diabetes Mellitus in Pregnancy and ACH

It is well documented that tight glycemic control may increase the risk of hypoglycaemia with potential adverse maternal outcomes including coma, seizures, and maternal death [24-29]. In a study that analysed the use of insulin aspart compared to regular human insulin in 322 type I diabetic pregnant patient with the hypothesis that use of the rapid-acting insulin analog, insulin aspart (IAsp), for meal-related insulin replacement may be of benefit during pregnancy complicated by diabetes by providing better control of postprandial hyperglycaemia with less hypoglycaemia, compared with regular human insulin (HI), it was found that observed rates of major maternal hypoglycaemia were lower with IAsp than HI. A 28% lower risk for major hypoglycaemia (IAsp/HI; relative risk [RR] 0.720 [95% CI 0.36-1.46]) and a 52% lower risk for major nocturnal hypoglycaemia (0.48 [0.20-1.14]) was estimated for the IAsp versus HI groups, respectively, although this did not reach statistical significance. Risks for major daytime (0.85 [0.40-1.78]), all (0.97 [0.66-1.44]), and minor (0.97 [0.66-1.43]) hypoglycaemia were similar between treatments. The

estimated risk of any nocturnal hypoglycaemia was 24% lower on IAsp (0.76 [0.57–1.03]). Risk of all daytime hypoglycaemia was similar between treatments (1.08 [0.71–1.63]).

The findings in this paper are vital in the management of type 1 diabetes mellitus in pregnancy since use of oral hypoglycaemic agent is not widely acceptable in the management of type 1 diabetes mellitus. Though the findings are scientifically revealing, the lack of biochemical definition of “major hypoglycaemia” as used in the study design is a major limitation of the study that restricts its application when dealing with absolute values of severe hypoglycaemic episodes as contained in Ademolu Classification of Hypoglycaemia in pregnant type 1 diabetes mellitus patients.

Conclusion

Since gestational diabetes mellitus not only influences immediate maternal and neonatal outcomes but also increases the risk of future Type 2 diabetes in mother as well as the baby, then ACH should be used in hypoglycaemia complicating gestational diabetes mellitus management since the use of ACH will assist to shed more light on and will enhance further scientific understanding of fetomaternal pathophysiology as far as hypoglycaemia is concerned worldwide.

References

- World Health Organization (2013) Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy. pp: 1-62.
- Nicholson W, Bolen S, Witkop CT, Neale D, Wilson L, et al. (2009) Benefits and Risks of Oral Diabetes Agents Compared With Insulin in Women with Gestational Diabetes: a systematic review. *Obstet Gynecol* 113(1): 193-205.
- Ademolu AB, Ademolu AO, Ogbera AO, Fasanmade OA (2015) Hypoglycemia in Ikorodu. *Journal of Asian Health*.
- Donald R Coustan (2007) Pharmacological Management of Gestational Diabetes. *American Diabetes Association* 30(2): 1-3.
- Hawdon JM, Ward Platt MP, Aynsley-Green A (1994) Prevention and management of neonatal hypoglycemia. *Arch Dis Child Fetal Neonatal Ed* 70(1): F60-F64.
- Pettenati MJ, Haines JL, Higgins RR, Wappner RS, Palmer CG, et al. (1986) Beckwith syndrome: presentation of clinical and cytogenetic data on 22 new cases and review of the literature. *Hum Genet* 74(2): 143-154.
- Land JM (1994) Hypoglycemia in the neonate: how and when is it important. *Dev Neurosci* 16(5-6): 307-312.
- Miller DI, Wishinsky H, Thompson G (1962) Transfer of tolbutamide across the placenta. *Diabetes* 11: 93-97.
- Elliott BD, Langer O, Schenker S, Johnson RF (1991) Insignificant transfer of glyburide occurs across the human placenta. *Am J Obstet Gynecol* 165(4 pt 1): 807-812.
- Elliott BD, Langer O, Schenker S, Johnson RF, Prihoda T (1994) Comparative placental transport of oral hypoglycemic agents in humans: a model of human placental drug transfer. *Am J Obstet Gynecol* 171(3): 653-660.
- Langer O, Conway DL, Berkus MD, Xenakis EM, Gonzales O: A comparison of glyburide and insulin in women with gestational diabetes mellitus. *N Engl J Med* 343(16): 1134-1138.
- Gabbe SG, Graves CR (2003) Management of diabetes mellitus complicating pregnancy. *Obstet Gynecol* 102(4): 857-868.
- Saade G (2005) Gestational diabetes mellitus: a pill or a shot? *Obstet Gynecol* 105(3): 456-457.
- Lois Brustman, Oded Langer, Sophia Scarpelli, Manal El Daouk, Anna Fuchs, et al. (2011) Hypoglycemia in Glyburide-Treated Gestational Diabetes Is It Dose-Dependent?. *Obstet Gynecol* 117(2 Pt 1): 349-353.
- Langer O, Conway DL, Berkus MD, Xenakis EM, Gonzales O: A comparison of glyburide and insulin in women with gestational diabetes mellitus. *N Engl J Med* 343(16): 1134-1138.
- Anjalakshi C, Balaji V, Balaji MS, Seshiah V (2007) A prospective study comparing insulin and glibenclamide in gestational diabetes mellitus in Asian Indian women. *Diabetes Res Clin Pract* 76(3): 474-475.
- Bertini AM, Silva JC, Taborda W, Becker F, Lemos Beber FR, et al. (2005) Perinatal outcomes and the

- use of oral hypoglycemic agents. *J Perinat Med* 33(6): 519-523.
18. Hend S Saleh, Walid A Abdelsalam, Hala E Mowafy, Azza A Abd ElHameid (2016) Could Metformin Manage Gestational Diabetes Mellitus instead of Insulin?. *International Journal of Reproductive Medicine* pp: 8.
 19. National Diabetes Information Clearinghouse (NIDC) (2008) *Diabetes Overview*, NIH Publication.
 20. American College of Obstetricians and Gynecologists Committee on Practice Bulletins-Obstetrics (2001) ACOG practice bulletin. Clinical management guidelines for obstetrician-gynecologists. Number 30, September 2001 (replaces Technical Bulletin Number 200, December 1994). *Gestational diabetes Obstet Gynecol* 98(3): 525-538.
 21. Mithal A, Bansal B, Kalra S (2015) Gestational diabetes in India: Science and society. *Indian J Endocrinol Metab* 19(6): 701-704.
 22. Bellamy L, Casas JP, Hingorani AD, Williams D (2009) Type 2 diabetes mellitus after gestational diabetes: A systematic review and meta-analysis. *Lancet* 373(9677): 1773-1779.
 23. Ademolu AB (2017) Role of Ademolus Classification of Hypoglycemia in Blood Glucose and Diabetes Mellitus Management. *Gastroenterol Liver Clin Med* (2017) 1: 1-4.
 24. Rosenn B, Miodovnik M (2000) Medical complications of diabetes mellitus in pregnancy. *Clin Obstet Gynecol* 43(1): 17-31.
 25. Kimmerle R, Heinemann L, Delecki A, Berger M (1992) Severe hypoglycemia, incidence and predisposing factors in 85 pregnancies of type 1 diabetic women. *Diabetes Care* 15(8): 1034-1037.
 26. Rayburn W, Piehl E, Jacober S, Schork A, Ploughman L (1986) Severe hypoglycaemia during pregnancy: its frequency and predisposing factors in diabetic women. *Int J Gynaecol Obstet* 24(4): 263-268.
 27. Rosenn BM, Miodovonik M, Holcberg G, Khoury JC, Siddiqi TA (1995) Hypoglycemia: the price of intensive insulin therapy for pregnant women with insulin-dependent diabetes mellitus. *Obstet Gynecol* 85(3): 417-422.
 28. Evers IM, Ter Braak EWMT, de Valk HW, van Der Schoot B, Janssen N, et al. (2002) Risk indicators predictive for severe hypoglycemia during the first trimester of type 1 diabetic pregnancy. *Diabetes Care* 25(3): 554-559.
 29. Ter Braak EW, Evers IM, Willem Erkelens D, Visser GH (2002) Maternal hypoglycemia during pregnancy in type 1 diabetes: maternal and fetal consequences. *Diabetes Metab Res Rev* 18(2): 96-105.