

Diabetes Mellitus in Pregnancy: An Update on the Current Classification and Management

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ABSTRACT

BACKGROUND: Diabetes mellitus is a common medical disorder in pregnancy. It contributes particularly to perinatal morbidity / mortality, and maternal morbidity. This review aims at improving maternal and neonatal health care especially in Sub-Saharan Africa by improving the knowledge of health practitioners on current evidences in the classification and management of diabetes mellitus in pregnancy.

METHODS: Relevant texts as well as online data bases including Pubmed, Google scholar, and African journal online, were searched for literatures related to the subject.

RESULTS: Classification of diabetes in pregnancy has been revised to reflect the various aetiological factors. Also, the diagnostic value of fasting plasma glucose has been lowered to mark the point at which dramatic increase in the microvascular complications of diabetes mellitus occurs. Morbidity and mortality associated with the condition would be reduced through proper management that involves preconception care, early antenatal booking, dedicated multidisciplinary antenatal care, and delivery in a center with neonatal facility. Furthermore, some oral glucose lowering agents have shown some safety after the first trimester and they have been found to give comparable result to insulin therapy.

CONCLUSION: The classification of diabetes mellitus in pregnancy has been revised. Its optimal management should involve multi-disciplinary inputs and may include oral hypoglycaemic agents. Knowledge of these by clinicians would improve maternal and neonatal health.

KEY WORDS: Diabetes mellitus, pregnancy, diagnosis, preconception, antenatal, delivery, oral glucose lowering agents

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.¹ In pregnancy, DM can either predate the pregnancy (pre-gestational) or be discovered first during the pregnancy (gestational). Whichever is the scenario, the risks are similar for the mother and the fetus(es). Slight difference is only related to what will happen in gestational diabetes mellitus

(GDM) after delivery thus: whether the disorder will persist or revert and if it reverts, what happens in future?

There are lots of controversies surrounding the management of diabetes mellitus in pregnancy.² Likewise, worrisome low knowledge of diabetes in pregnancy and high level of patients' mismanagement have been observed among health practitioners involved in maternal health. This review is an elaborate update of an earlier review on the subject.³ It describes the current evidences in the classification, diagnosis and treatment of diabetes mellitus in pregnancy. As the world struggles to meet the targets of Millennium Development Goals (MDG) 4 and 5,⁴ it is hoped that the review would assist clinicians to improve maternal and newborn care, especially in Sub-Saharan Africa.

METHODS

In-depth search for literatures related to the subject area was made manually and electronically. This included the search of relevant texts and online databases for information on the subject. For the databases thus - Pubmed, Google scholar, and African journal online, the search was done using a combination of the key words. Literatures identified were studied and relevant information retrieved. The information was further organized and presented in sub-headings.

CLASSIFICATION OF DIABETES IN PREGNANCY

Pre-gestational diabetes mellitus

This is diabetes mellitus that antedates pregnancy. It is referred to as *Diabetes Mellitus and pregnancy*¹ and is sub-classified aetiologically into types 1 and 2. The use of the terms *Insulin Dependent Diabetes Mellitus (IDDM)* and *Non Insulin Dependent Diabetes Mellitus (NIDDM)* has been eliminated because they are confusing and are based on treatment instead of pathogenesis.¹

Type 1 Diabetes mellitus, formally referred to as *Insulin Dependent Diabetes Mellitus (IDDM)* is largely due to autoimmune destruction of pancreatic beta islets cells while type 2 Diabetes mellitus (also formerly known as *Non-Insulin Dependent Diabetes Mellitus (NIDDM)*) is due largely to insulin resistance. Because of the presence of insulin, individuals with type 2 DM are not easily prone to ketosis unlike type 1 diabetic patients.

Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is carbohydrate

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intolerance of varying severity with onset or first recognition during pregnancy.⁵ It does not exclude the possibility that the glucose intolerance may antedate pregnancy but has been previously unrecognized. The definition applies irrespective of whether insulin is used for treatment or the condition persists after pregnancy.¹

Prevalence of Diabetes Mellitus in Pregnancy

Worldwide prevalence of diabetes in pregnancy is 3–7 per 1000 pregnancies.^{6–8} Of these, about 90% are classified as GDM, 7% are previously diagnosed type 2 DM, and 4% are type 1 DM.⁸ In Nigeria, prevalence of DM in pregnancy varies but are generally less than 3 per 1000 deliveries;^{9,10} however, a recent report from Ibadan, Nigeria suggested that the prevalence might be on the increase (13.9%) and the diagnosis in first trimester was common (17.4%).¹¹ The upward trend in prevalence may not be unconnected to the current global pandemic of obesity and diabetes even among women of childbearing age.¹²

Screening for Gestational Diabetes Mellitus

Screening for GDM can be selective or universal (routine) depending on the setting.^{13,14} It is selective at the authors' center. According to the position statement of American Diabetes Association (ADA), selective screening is still recommended as soon as feasible or during the first prenatal visit for women at risk,¹⁵ and should be repeated between 24–28 weeks of gestation if results of testing do not demonstrate diabetes.¹⁶ Risk factors for screening include past obstetric history of macrosomic baby(ies), gestational diabetes mellitus and, unexplained perinatal death(s). Others are family history of diabetes mellitus, maternal age above 35 years, estimated fetal weight greater than 4kg, polydipsia, polyuria, polyhydramnios, repeated or heavy glycosuria, and maternal obesity. Furthermore, ADA also recommended the screening for GDM at 24–28 weeks of gestation in pregnant women not known to have DM, using a 75-g 2-hour OGTT and applying the diagnostic cut-off points of fasting, 1 hour, and 2-hour blood glucose values =5.1mmol/l, =10mmol/l, and =8.5mmol/l respectively.

The aforementioned recommendations have a higher level of evidence (level B: Supportive evidence from well-conducted cohort studies). On the other hand, two other recommendations, though of lower level of evidence (level E: Expert consensus or clinical experience), suggest the screening of women with GDM for persistent diabetes within 6–12 weeks postpartum; and at least a 3 yearly lifelong screening for DM in women with a history of GDM.¹⁵ Interestingly, a report from Ibadan, Nigeria, showed that the incidence of overt diabetes mellitus and GDM among obese women did not differ significantly from that of non-obese women.¹⁷ It is important to note that all screening guidelines for diagnosis of GDM are based on at least level III evidence.²

This may not be unrelated to the observation that some centers and specialists neither screen nor treat GDM.¹⁸ Furthermore, some clinicians challenge the existence of GDM.¹⁹ The latter is supported by a report in *the Cochrane Library* which did not show evidence that screening or treatment of GDM made an appreciable difference in perinatal outcomes.²⁰ Nevertheless a recent systematic review of eight trials comparing any specific treatment with routine management of GDM showed that specific treatments significantly reduced the risks of maternal and perinatal morbidity.²¹ The above conflicting reports expose the uncertainties surrounding this clinical entity. However, since obstetrics is a high-risk part of medical practice, it makes sense that we screen and treat for GDM until it is universally declared benign.²

Screening Methods for Gestational Diabetes Mellitus

The following methods can be used to rule-out or rule-in gestational diabetes mellitus depending on the plasma glucose level obtained. The methods and their accompanying normality and diagnostic values are shown in Table 1. Individuals with plasma glucose values within the prediabetic stages (see the 'Remark' section in Table 1) should be subjected to 75g 2-hr Oral Glucose Tolerance Test (OGTT)¹ or 100g 3-hr OGTT.²²

Table 1: Classification threshold for establishing normal Glucose tolerance (NGT) or Diabetes mellitus using various methods

Method of testing	Normal (mmol/l)	Diabetes mellitus	Remarks (values within these ranges requires OGTT)
50g non-fasting 1hr glucose challenge (gold standard). ⁵	<7.8 (140mg/dl)	e10.3 (185 mg/dl)*	7.8–10.2 mmol/l
Random Plasma Glucose	<7 (126mg/dl)	e11.1	7–11
Fasting Plasma Glucose	4–6	e7.0 ¹	6.1–6.9
2-Hour Plasma Glucose (2-HPG)	<9	e11.1	

*may be considered diagnostic of DM²³

The diagnostic value of fasting plasma glucose of greater than or equal to 7.0 mmol/l marks the point at which the prevalence of microvascular complications of diabetes mellitus (retinopathy and nephropathy) increases dramatically.¹

Fasting plasma glucose (FPG) in combination with 2-Hours Post Prandial (2-HPP) is the method mostly used in authors' center for screening and diagnosis of GDM. For clinical purposes however, the diagnosis of diabetes mellitus using the FPG and 2-HPP should be confirmed on a subsequent day, and precludes the need for OGTT.^{1,16,24} On the other hand, the diagnostic criteria using OGTT are shown in Table 2.

Table 2: Diagnostic thresholds for GDM using Oral glucose tolerance test (OGTT)

Venous plasma glucose	100g OGTT in mmol/l (mg/dl)	75g OGTT in mmol/l (mg/dl)
Fasting	5.3 (95)	5.3 (95)
1-hour	10.0 (180)	10.0 (180)
2-hour	8.6 (155)	8.6 (155)
3-hour	7.8 (140)	Not indicated

Two or more of the venous plasma concentrations in OGTT must be met or exceeded for positive diagnoses. Sensitivity of OGTT is 80% while the specificity is 85%.²³ One abnormal OGTT result is associated with fetal macrosomia and when such women undergo repeat OGTT, nearly one-third will demonstrate a positive diagnoses.²⁵

Furthermore, FPG alone when compared with OGTT, has similar sensitivity (80%) but high false positive rate (specificity 57%).²⁶ This low specificity improves when combined with 2-HPP.

MANAGEMENT OF DIABETES MELLITUS IN PREGNANCY

Effective treatment of GDM has been shown not only to reduce perinatal morbidity but also to likely improve the woman's quality of life.²⁷ Treatment targets presently remains the targets as set by the Fourth International Workshop-Conference on GDM thus: fasting capillary glucose of < 5.3 mmol/l (96 mg/dl), 1- and 2-hour postprandial of < 7.8 mmol/l (120 mg/dl) and < 6.7 mmol/l (120 mg/dl) respectively.²⁸ Evidence abounds that it may be better to measure postprandial than preprandial levels because postprandial glycaemic levels are better correlated with certain adverse outcomes such as congenital malformations, macrosomia, hypoglycaemia and shoulder dystocia.²⁹

The effective management therefore spans from preconception care to postnatal care as discussed below.

Preconception care

It is very necessary that pregnancy should be adequately planned for women with pre-gestational Diabetes mellitus. The goals of preconception care include:

- maintenance of blood sugar within normal level
- avoidance of teratogenicity from periconceptual hyperglycaemia
- involvement and empowerment of the patient in the management of her diabetes
- achievement of the lowest A1C test results possible without excessive hypoglycemia,
- ensuring effective contraception until stable and acceptable glycemia is achieved, and
- identification, evaluation, and treatment of long-term diabetes complications such as retinopathy, nephropathy, neuropathy, hypertension, and Coronary Heart Disease.^{15,30}

In view of the risks to which both the mother and fetus are exposed to, the importance of planning pregnancy in such women cannot be overemphasized. Unfortunately, diabetes mellitus was not part of reasons for accessing preconception care in Enugu, Nigeria.³¹

The standard practice is that oral glucose lowering agents

(OGLA) are usually converted to insulin therapy during pregnancy but current evidence(s) in support of the increasing use of OGLA in pregnancy abound. Nevertheless, caution should be exercised with the use of some oral antidiabetic drugs due to possible relative or absolute contraindications. In particular, Statins and Angiotensin Converting Enzyme inhibitors (ACEI) are contraindicated in pregnancy and should be discontinued before conception.³² Another oral agent for which concerns have been raised in pregnancy is Angiotensin Receptor Blockers because risk(s) cannot be ruled out in the first trimester, hence they should generally be discontinued before pregnancy. The oral antidiabetic agents which have been used for glycaemic control in pregnancy include glyburide (glibenclamide), metformin and acarbose.

Management of the pregnancy should also include attempts to rule out and/or assess extent of complications of DM such as retinopathy, and offer appropriate counseling or treatment. In addition, periconception folic acid supplementation should be offered, and the woman counseled on the need for socio-economic preparation for pregnancy and childcare.

Also, it should be highlighted that attention needs to be paid greatly to mothers' diet which contributes significantly to good glycaemic control. In pregnancy however, the goals of dietary control may differ a little to include provision of appropriate energy for reasonable weight gain, normal growth and development during pregnancy and lactation.³³ In less developed nations, this may pose some challenges due to several reasons.³³

Furthermore, attention to nutrition needs to be adequately supervised especially in such nations where maternal dietary intakes during pregnancy may be lower than the recommended daily allowances; more so as the level of nutritional intake is associated with the birth weight.³⁴ Medical Nutrition Therapy (MNT) which should be anchored by Dieticians constitutes a key fundamental treatment modality which does not only apply to preconception care but also cuts across all the trimesters. This is so because of the need to achieve good glycaemic goals without unnecessary weight gain or loss. The minimum nutrient requirements in pregnancy to achieve the above goals have been described by the Institute of Medicine.³⁵ MNT has been defined as "carbohydrate-controlled meal plan that promotes adequate nutrition with appropriate weight gain, normoglycaemia, and the absence of ketosis".³⁶

The term "carbohydrate-control" takes into consideration issues such as total amount of carbohydrate, carbohydrate distribution, foods with sugar, breakfast-time carbohydrate, fibers, glycaemic index and artificial sweeteners.

ANTENATAL MANAGEMENT

Management usually involve diet and/or insulin therapy, exercise, and patient education.¹⁶ The woman should be encouraged to register early in a dedicated diabetic antenatal clinic staffed by an Obstetrician with special interest in diabetic pregnancy, a Diabetologist/Endocrinologist, a diabetic nurse/midwife, and a dietician.^{6,25,37} She should be admitted at booking (for Pre-gestational DM) or at diagnosis of GDM for stabilization of diabetic control.³⁷

Initial treatment of DM in pregnancy is dietary however, insulin therapy should be commenced if initial FPG is greater or equal to 8 mmol/l, or when the FPG is consistently greater than 6 mmol/l despite diet therapy.⁷ Where indicated, twice daily or four times daily insulin with combinations of regular and intermediate / long acting preparations should be given; both regimen give good and comparable results. In addition, blood glucose checks should be carried out many times (4-6) per day.

Furthermore, antenatal clinic appointments should be more frequent after patient's stabilization; and anomaly ultrasound scan is recommended between 18 and 22 weeks of gestation.⁶ Fetal surveillance is necessary in third trimester and serial biophysical profile (BPD) is of great value.⁶ Finally, delivery plan should be formulated at 36 weeks gestational age.⁶

DELIVERY

Vaginal delivery is the method of choice for all cases of diabetes mellitus in pregnancy, whenever possible. For well-controlled cases and uncomplicated pregnancy, it should be possible to reach 39 completed weeks of gestation.^{6,16,37} Beyond this, there is little evidence of benefit and some evidence of harm.⁶ Poorly controlled diabetes mellitus may require earlier delivery however, amniocentesis for the assessment of fetal lung maturity may be necessary.²⁵

During labour or cesarean section, euglycaemia is maintained with infusion dextrose and sliding scale of insulin administration^{7,25} or Glucose/Potassium/Insulin (GKI) Infusion.³⁸ A less aggressive protocol which involves watchful waiting and institution of insulin therapy only when maternal blood sugar falls outside a pre-determined range of 4 - 7 mmol/l, has also been practised with good outcome for the management of diabetic woman during the peripartum period.³⁹ Pain elaborates catecholamines, which may impair plasma glucose control therefore, adequate analgesia is required during labour or cesarean section for good glycaemic control.⁶ After a cesarean delivery, good wound care and early ambulation should be ensured.³⁷

POSTNATAL CARE

Insulin requirement falls by half within 24 hours of

delivery then, by further one quarter if the woman breastfeeds.¹⁶ Adequate adjustments of insulin therapy are therefore necessary and in GDM, insulin may need to be stopped. Contraceptive counseling should be offered; barrier methods, mini-pills, low dose combine oral pill, and intra uterine contraceptive devices (UCD) are safe.^{6,16} Sterilization should be encourage if patient has completed her family.

At six weeks postnatal visit, GDM patients should be subjected to a repeat OGTT following which they should be reclassified accordingly.^{2,25} Afterwards, she should be referred to appropriate clinic(s) as necessary such as medical diabetic clinic and family planning clinic.

ORAL GLUCOSE LOWERING AGENTS AND DIABETES MELLITUS IN PREGNANCY

Non insulin management of GDM was very recently reviewed by Magon and Seshiah with a lot of potentials for OGLA.³⁶ In 1994, placental testing demonstrated that glibenclamide (glyburide), a second-generation sulfonylurea, did not cross the placenta.⁴⁰ No randomized controlled trial has focused on the use of OGLA during organogenesis in the first trimester.² However, when glibenclamide is used for DM in the second and third trimesters (beginning at 11 weeks' gestation), their outcomes were similar to those randomized to insulin treatment, and there was no risk to mother or fetus.⁴¹ In line with the above evidences, a survey of American obstetricians indicated that 13% of them began treatment of GDM with glyburide when diet and exercise fail.⁴²

Furthermore, studies of placental transportation of metformin and umbilical cord analyses in metformin-treated patients have not been done recently.² However, since the initial study by Coetzee et al,⁴³ evidence is beginning to accumulate about the effectiveness and safety of metformin in pregnancy.⁴⁴ It has been observed that non-diabetic women with polycystic ovary syndrome treated preconceptually and throughout pregnancy with metformin had a lower incidence of GDM and produced healthy, normal infants.^{45,46} It is possible that the teratogenic effects attributed to oral hypoglycaemics might be due to the effect of hyperglycaemia. More research is therefore required in this area.

CONCLUSION

The classification of diabetes mellitus in pregnancy has been revised and its optimal management should involve multi-disciplinary inputs. To enhance optimal maternal and neonatal healthcare, clinicians are encouraged to acquaint themselves with the current knowledge on DM in pregnancy as reviewed, including the use of oral hypoglycemic agent. Finally, continuing female education and empowerment as well as improved service delivery in our health facilities remain essential

ingredients for the attainment of optimal female reproductive health in general, and the proper management of diabetes in pregnancy in particular.

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