Update : Diagnosis, Pathogenesis and Management of Gestational Diabetes Melitus.

By

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INTRODUCTION

Traditionally, diabeteces in pregnant women are classified according to the system propoed by White 1 (Table 1) where risk of a poor outcome increased with increasing severity of the diabetic desease as indicated by presence or absence of the microvascular complications.

Table 1. White's classification

White's Class	Age at onset (yrs)	Duration (yr)	Angiopathy
A	any		
B	>20	<10	
C	10-19	10	
D	<10	>20	benign retinopathy
E	any	any	calcification of pelvic vesels
R	any	any	proliferative retinopathy
F	any	any	nephropathy
H	any	any	atherosclerotic heart disease
T	any	any	pregnancy after renal transplantation

However, since maternal blood glucose control has a hugely significant impact on pregnancy outcome, the classification of maternal diabetes has been revised, and most hospitals in the UK and probably elsewhere, now use the guidelines proposed by King's College Hospital, London [2], as follows:

- Gestational diabetes
- Pregestational diabetes, either:
- Uncomplicated
- Complicated by vascular disease (micro or macro- vascular)

There are many recent excellent reviews and articles on pregestational diabetes [3,4,5,6,] which should indeed be seen as a regular complication of established diabetes. More intriguing in onset, significance, pathophysiology and management aspects is gestational diabetes (GDM), which will form the exclusive focus of this review.

GESTATIONAL DIABETES MELLITUS

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy[7].

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THIS DEFINITION APPLIES WHETHER OR NOT:

- insulin or dietary modification is used in primary therapy
- the condition persists after pregnancy
- unrecognized glucose intolerance antedated or began concomitantly with pregnancy.

It is important to detect gestational diabetes because:

- Pregancies complicated by GDM are at increased risk for foetal macrosomia, neonatal metabolic abnormalities (hypoglycaemia, hypocalcaemia, polycythaemia and hyperbilirubinaemia) and birth trauma.
- Maternal complications of GDM include an increased caesarean section delivery rate (from foetal growth disorders and current obstetric practice) and hypertensive disorders;
- Gestational diabetic women intensively managed can achieve near normal rates of macrosonia and neonatal hypoglycaemia
- GDM predicts the development of diabetes later in life.

PREVALENCE

Worldwide, GDM is present in about 4% of all pregnancies or about 135,000 annually with a prevalence range of 1 14% depending on population studied and diagnostic tests employed[8]. In Nigeria, the incidence rate of diabetic pregnancy (gestational and pre gestational) was reported as 0.64/1000 deliveries/yr.[9]

DIAGNOSIS OF GDM

This is a multi staged procedure of increasing sophistication and sensitivity, based on the individual risk status and findings in the initial glycaemic assessment.

RISK CATEGORIZATION:

Risk assessment for GDM should be ascertained at the first prenatal visit. The individual subject's risk could then be categorized as: [10,11]

Low Risk subjects in this category must satisfy all the following criteria:

- Member of ethnic/racial group with low prevalence of diabetes. The racial groups well recognized to have high prevalence of diabetes include: American minority populations, migrant Indians, Asians and Africans to Western countries, pacific Islanders and some urbanized Africans but typically not rural Africans
- No history of diabetes in first degree relatives
- Age <25 yr.
- Normal pre-pregnancy weight and weight gain during pregnancy.
- No history of abnormal glucose metabolism
- No history of poor obstetric outcome.

Here, blood glugose testing is not routinely recommended and is generally not cost effective.

Average risk includes women who do not meet any of the listed criteria for the low- or high- risk subjects. Blood glucose screening should be performed in this group at 24 28 weeks' gestation.

High risk includes women who meet one or more of the following criteria.

- Marked obesity
- Diabetes in first degree relative
- History of glucose intolerance
- Previous infant with macrosomia
- Current glycosuria
- Member of one of the high risk ethnic

group indicated above

- Here, blood glucose testing should be performed at the initial antenatal visit or as soon as feasible. If GDM is not confirmed then, repeat blood glucose testing should be performed at 24-28 weeks gestation or with development of symptoms suggestive of hyperglycaemia.

SCREENING TEST

This is typically done at 24-28 weeks of gestation. The currently acceptable procedure is a 50g oral glucose challenge test, which can even be performed in the non fasting state. Blood samples are taken fasting and at 1 h post glucose ingestion. A 1hr glucose value >140 mg/dl (7.8 mmol/L) has a diagnostic sensitivity of 80% for GDM and justifies the performance of a full diagnostic 3h 100g OGTT in the fasting state [10,11].

Recently, peruchinni et al [12] proposed using only the fasting plasma glucose value as the screening test for GDM. They proposed a glucose concentration of 4.8mmol/L which has a tolerable sensitivity of 81% and specificity of 76% as an initial screening test, before performance of the specific diagnostic test. An accompanying editorial [13] considered this proposal attractive, as the test is easy to administer, well tolerated,inexpensive, reliable and highly reproducible. Comfirmation is however still desirable from other medical centers.

DIAGNOSTIC TEST

- There are 2 types of oral glucose tests (OGTT)for the diagnosis of GDM. For either procedure, important precautions need to be taken to ensure useful results. These conditionalities include:
- Use of venous plasma glucose concentrations
- Two or more of the targets must be met or exceeded for diagnosis
- Test must be performed in the morning after an overnight fast >8h and <14h
- Physical activity and diet in the three days preceding the test should be unrestricted (>150g carbohydrate.day)
- Subject must remain seated and not smoke during the test.

A. DIAGNOSTIC CRITERIA WITH 100G ORAL GLUCOSE LOAD

The diagnostic cut-off values (Table 2) are based on the recommendations of the 4th International workshop-conference on Gestational Diabetes which in turn are derived from the Carpenter and Coustan modification of the O'Sullivan and Mahan criteria [10,11,14,15].

Table 2. Diagnostic cut-off values for GDM with 100g glucose load.

Venous serum/plasma glucose		
	mg/dl	mmol/L
Fasting	95	5.3
1 h	180	10.0
2h	155	8.6
3h	140	7.8

B. DIAGNOSTIC CRITERIA WITH 75G GLUCOSE LOAD

These values (Table3) are essentially based on the recommendations of a WHO Study Group [16].

Table 3. Diagnostic values for GDM with 75 glucose load

	ACOG criteria [4]		WHO criteria [16]	
	mg/dl	mmol/L	mg/dL	mmol/L
Fasting	95	5.3	110	6.1
1h	180	10.0	--	--
2h	155	8.6	140	7.8

Famuyiwa et al [17] investigated 75g OGTT responses in 20 healthy pregnant Nigeria women in each trimester of pregnancy and in the puerperium, and found lower early glucose response (0-60min) and higher late glucose responses (90-120min) in comparison to 31 age and parity matched non pregnant women. They further identified the upper limits of normal for venous whole blood glucose in pregnant Nigerian women as (Table 4)

These are however whole blood values plasma values are typically 10 15% higher than whole blood values depending on fasting feeding state. Nonetheless, it was concluded that the values obtained in this group of Nigerian women were lower than those recommended for the diagnosis of GDM by both the O'Sullivan and Mahan/Carpenter and Coustan criteria [14,15] and the WHO[16]. the authors therefore pleaded for caution regarding uncritical application of data from one racial group to others.

Amadin et al[18] further reported that there was little diference in maximal glycaemic responses to either a 75g or a 100g glucose load in 20 healthy Nigerian women investigated during the 3rd trimester of pregnancy.

Table 4. OGTT Responses in Pregnant Nigerian Women.

	mg/dL	mmol/L
Fasting	90	5.0
30 min	135	7.5
60 min	150	8.3
90 min	145	8.1
120 min	125	6.9

CLASSIFICATION AFTER PREGNANCY

New American Diabetes Association Criteria [6]

Fasting plasma glucose:

- >126 mg/dL (7.0 mmol/L on 2 occassions = diabetes
- 110 125 mg / dL (6.1-6.9 mmol/L) impaired fasting glucose (IFG)
- <110 mg/dL (6.1 mmol/L) = normal glucose tolerance

OGTT (75G) WHO CRITERIA [16]

- Normal glucose tolerance = 2h value < 140 mg/dl (7.8 mmol/L)
  Classification: previous abnormality of glucose tolerance GDM
- diabetes = 2h value > 200 mg/dl (11.1 mmol/L)
- impaired gluscose tolerance IGT = 2h value 140 199 mg/dl (7.8 11.00 mmol/L

AETIOLOGY AND PATHOGENESIS OF GDM

The suggested mechanisms are [19,20,21]:

1. Autoimmunity and heredity: There is no evidence of a higher frequency of HLA DR 3 and DR 4 antigens in G D M , except in those women who later develop type 1 DM.
   Similarly, islet cell antibodies and insulin autoantibodies and GAD antibodies have a low prevalence in GDM and are more typically seen in those women with yet undiagnosed pre-gestational type 1 DM. Many studies have also confirmed that most patient with GDM had neither parent nor siblings affected with IGT or NIDDM, questioning a direct role for heredity in

the pathogenesis of the disorder.

2. Defects in B cell function and insulin secretion. Studies in pregnant women with normal glucose tolerance (NGT) and those with GDM during pregnancy indicate that:

- Insulin secretion is considerably increased with both NGT and GDM, and highest in obese women with GDM
- Glucose induced insulin secretion is increased more in normal pregnant women than in those with GDM.
- Peak plasma insulin during an OGTT occurs later in women with GDM than in normal women.
- First phase insulin secretory response to an IVGTT increase more during pregnancy in normal women than in those with GDM
- Hyper-secretion of proinsulin occurs in some women with GDM, especially in the first trimester, and appears to be an indicator of significant further deterioration in glucose tolerance and need for insulin therapy later in pregnancy. Indeed the return of proinsulin levels to normal, postpartum, is significantly delayed in GDM and this serves as a good marker for risk of future development of typ2 DM. Hyperproinsulinaemia in GDM is believed to reflect B-cell secretory dysfunction
- Reduced insulin secretion in response to mixed meals in GDM
- Insulin resistance with impaired insulin-insulin receptor binding and impaired post-receptor insulin signaling. Indeed, insulin sensitivity is reduced to about one-third of non-pregnant values in GDM, and this abnormality may persist into the postpartum period in some of the women.

There are therefore many biochemical similarities between GDM and type 2 DM. GDM could therefore be considered an 'early onset type 2 DM'. Indeed many women with GDM develop type 2 DM later in life.

THERAPEUTIC INTERVENTION DURING PREGNANCY

Current practice has previously been very well discussed [10, 11, 22] and is only briefly summarized here. The goal is to prevent an adverse perinatal outcome. It is know that there is a continuous relationship between increasing maternal glycaemia and risk of perinatal morbidity, especially macrosomia. The ideal capillary blood glycaemic targets for significant risk reduction to close to general population levels are:

Fasting <95 mg/dL (5.3mmol/L)
Postprandial : 1 hr. < 140 mg/dl (7.8 mmol/L); 2hr. <120mg/dl (6.7 mmol/L)

These goals are best achieved using the following modalities:

MEDICAL NUTRITION THERAPY

This remains the cornerstone of treatment for GDM. The immediate objective is to provide adequate caloric and nutrient needs during pregnancy while achieving desirable glycaemic targets without inducing excessive ketonuria, ketosis or postprandial hyperglcaemia. The diatary prescription should be individualized to take into account the patient's body habitus, weight gain, physical activity and cultural background and should be modifiable throughout pregnancy to achieve the stated goals.

Normally, there is an inverse relationship between pre-pregnancy body weight and optimal weight gain during pregnancy. Therefore the expected weight gain during

pregnancy varies according to the pre-pregnancy weight. A relatively small weight gain of ~ 7kg is recommended for obese patients (BMI > 29kg/m2) when they become pregnant, and a proportionally greater weight gain, (up to 18kg) for patients who are underweight (BMI <20kg/m^2) at the onset of pregnancy.

There is currently a consensus that diets providing as little as 25kcal/kg actual body weight will result in attainment of glycaemic goals without inducing ketonuria. Carbohydrate intake can be limited to 35-45% of total calories (protein 20-25%, fat 35-40%) since diets higher in CHO content may worsen postprandial glycaemia, except they are rich in complex carbohydrates. Nutritional supplements such as iron and folic acid may also need to be prescribed according to individual needs.

Exercise

This useful adjunctive therapy in women with GDM can, prudently used with diet, improve glucose tolerance and obviate the need for insulin therapy. Insufficient evidence exists to recommend any specific form of exercise as being superior to others in the management of GDM. However, arm ergometry has been described as a form of exercise, which is safe and efficacious for sedentary, obese, unfit and aging pregnant women with GDM [23].

It should be noted however that the safest from of exercise is the one that will not cause fetal distress, low-infant birth weight and /or uterine contractions. It should also be in keeping with the socio-cultural and economic circumstances of the patient for her to be fully complaint. In African rural communities, brisk walking and daily duties on the household farm should just be enough. It is prudent, though, to avoid exercisethat induces maternal hypertension (BP > 140/90 mmHg).

The optimal frequency and intensity of exercise has not yet been determined. It however appears that a minimum of 3 episodes / week, each> 15min, for at least 2-4 weeks are required to achieve any lowering of maternal glycaemia.

Postpartum, women with GDM or even pre-gestational diabetes should be encouraged to resume an exercise programme as soon as they feel ready. This could be by 2 weeks after a SVD or 4-6 weeks after caesarean section.

METABOLIC MONITORING

The best procedure for metabolic monitoring in GDM is self-monitoring of blood glucose. It is certainly a lot more beneficial than the less frequent glucose measurements during clinic visits. Urine glucose assessment is essentially useless. Since the risk of fetal macrosomia correlates more with postprandial rather than fasting glycaemia, it typically is recommended that glucose monitoring include both postprandial (1,2,hr) and fasting/pre-meal assessent. Patients using home blood glucose meters should be re educated on the use of these maters at intervals and their values also regularly cross checked at the clinic labs to ensure adequate quality control . Stored glucose values can be electronically transmitted for review by the health care providers.

The usefulness of early morning urine ketone testing in patients on hypocaloric and / or carbohydrate restricted diets for the detection and treatment of ketonuria from accelerated fat metabolism is currently controversial. It is also currently unclear whether regular measurement of such parameters as glycated haemoglobin and other proteins such as fructosamine, which indicate longer-term glycaemic control, have any role currently in the management of GDM.

INTENSIFIED METABOLIC THERAPY

Treatment with insulin is indicated in patients

who:

- Fail to achieve or maintain glycaemic targets;
- Show signs of excessive fetal growth.

In these individuals insulin treatment has to be individualized. Conventionally, insulin is given as mixed soluble (short acting) and intermediate acting forms given twice daily, typically pre-break fast and before the evening meal. More recently however, it has been suggested that an intensified course of insulin consisting of a four times daily regimen (three doses of regular insulin before meals and an intermediate insulin dose at bedtime) resulted in improved glycaemic control during pregnancy. This is accompanied by a reduction in such adverse perinatal metabolic events as hyperbilirbinaemia and hypoglycaemia[24].

The newer rapid acting insulin preparation with peak hypoglycaemic activity 1-2 hr after injection are recommended as they offer the potential for improved control of postprandial glycaemic excursions. Similarly, the minimally antigenic insulin preparations should preferably be used, to minimize the trans-placental transport of anti insulin antibodies and also the risk of future allergic manifestations in women who develop diabetes requiring insuling therapy after pregnancy.

With the initiation of insulin therapy, the frequency of self-monitoring of blood glucose should be increased. It has been reported that monitoring glucose levels 6 times a day (before and I hr after each main meal) with the use of insulin dosage titration procedures ensures a smooth increase in insulin dose as pregnancy progresses. Insulin dosage at delivery will therefore be significantly higher than earlier on in pregnancy. This, in turn, will significantly decrease the fetal macrosomia rate.

LABOR AND DELIVERY

Maternal hyperglycaemia during labor should be avoided as it may potentiate the risk of neonatal hypoglycaemia and accentuate the rise in lactate and decline in pH that normally accompany any foetal hypoxia. A consensus conference [10,11] suggested that a target range of 80-120 mg / dL (4.4-6.7 mmo/L) for plasma and 70 110 mg/dL (3.9-6.1 mmol/L) for capillary whole blood should be considered optimal maternal glycaemia during labor.

Exogenous insulin is hardly required during labor in GDM even if insulin was needed for glycaemic control during the pregnancy. It is essential to monitor glucose levels possibly at 1-4 hr intervals and administer insulin only if values exceed the optimal range. Where elective caesarean delivery is contemplated, insulin is withheld on the morning of the operation, except with fasting hyperglycaemia. It is also necessary to provide glucose parenterally (e.g. as a 10-20% glucose infusion) to meet basal energy requirements (0.12-0.18g/kg body weight/.hr) and prevent hypoglycaemia. Insulin therapy may need to be restarted after delivery.

OBSTETRIC MANAGEMENT

The goal is opimal maternal and foetal outcome of GDM. In ensuring the realization of this objective, attention must be paid to the following issues:

FETAL SURVEILLANCE

The time of commencement and frequency of application of foetal surveillance procedures should ordinarily be influenced by:

Severity of maternal hyperglycaemia

Presence of other adverse clinical factors such as past poor obstetric history and hypertension.

Generally, fetal movements should be monitored by the mother through the last 8-10

weeks, and any abnormalities duly reported. In those intensively managed with insulin, cardiotocography is suggested at 32 weeks. Other foetal monitoring techniques such as biophysical profiling and Doppler ultrasonogrphy of umbilical blood flow are indicated in specific cases or with associated complications such as pre-eclampsia.

Ultrasonography to measure fetal abdominal circumference at 29-33 weeks gestation is useful for identifying the large subset of patients with maternal fasting glucose levels <105 mg/dl (5.8 mmol/L) at little risk of fetal macrosomia at term and monitored by dietary therapy alone. It is also occasionally indicated for the detection of congenital abnormaities in women whose GDM was diagnosed in the first trimester or who present with fasting serum glucose levels of> 120mg/dL (6..7 mmol/L).

Amniocentesis for the assessment of foetal lung maturity is typically not indicated in well-controlled patients after 38 weeks of gestation if there is reasonable certainty about the estimation of gestational age. Use of amniocentesis for this purpose before the 38th week of gestation should normally be dictated by specific needs.

MATERNAL SURVEILLANCE

Patients with GDM have a 2 fold increased risk of hypertensive disorders in pregnancy. Consequently, at each antenatal visit, they should have careful monitoring of blood pressure, urinary protein excretion and body weght.

ROUTE AND TIMING OF DELIVERY

Certain consensus views should probably guide practice.

- The presence of GDM should not of itself constitute an indication for elective caesarean section and preclude supervised vaginal delivery
- GDM should not be an indication for delivery prior to 38 weeks of gestation in the absence of objective evidence of foetal compromise. Surfactant deficient respiratory distress syndrome is rare in term infants of mothers with GDM. However, delay beyond 38 weeks may lead to an increase in the rate of large for gestational age infants without reducing the risk of caesarean delivery.
- There is currently no data regarding whether or not there is greater risk of perinatal morbidity/mortality in the infants of well controlled GDM if pregnancy is allowed to proceed past 40 weeks of gestation although beyond 40 weeks, fetal surveillance would definitely need to be intensified.

POST PREGNANCY MONITORING

This is in relation to both the offspring and the mother.

OFFSPRING

There is epidemiological evidence to the effect that people exposed to maternal diabetes (type 1, type 2 and GDM) in utero have an increased risk of obesity, abnormal glucose metabolism and the metabolic syndrome, as children and young adults [25,26]. These offspring should be evaluated at frequent intervals for height, weight, and blood glucose concentrations and appropriate dietary therapy and physical activity prescribed to reduce the likelihood of obesity developing.

MOTHER

Women with GDM have a 17-63% risk of non gestational diabetes within 5-16 years after the index pregnancy 27,28,29. At particular risk are those with:

Severe hyperglycaemia during or soon after pregnancy

- Obesity

- GDM diagnosed before 24 weeks gestation.

Since insulin resistance and accompanying defects in insulin secretion characterize the development of diabetes after GDM, treatment of women with a history of GDM should include measures to minimize insulin resistance i.e. exercise, maintenance of normal weight and avoidance of drugs that impair insulin sensitivity. It is essential to monitor blood glucose levels after delivery and at least at 3yr. intervals or sooner, if so warranted by findings of impaired fasting or post-challenge blood glucose concentrations.

Finally, women with a history of GDM should use effective contraception to minimize the chance that they will become pregnant with untreated hyperglycaemia. The consequences of that is a markedy increased risk of fetal birth defects.

CONCLUSION

It is thus clear that GDM is an important disorder but consensus is still developing regarding its aetio-pathogenesis and the best means of diagnosing and managing it. These aspects are important because of the potential morbidity and mortality for both mother and child associated with the disorder. There are still many controversial issues that should form the basis for future research. These include:

- Defining optimal glycaemic targets to eliminate excess fetal risks
- Identifying an optmal dietary management plan adaptable to local and cultural circumstances.
- Defining the role of self-monitoring of blood glucose in diet-treated patients specifically, and particularly, utility of this development in low technology, illiterate and poor countries.
- Comparison of maternal glucose levels with foetal measurements in selecting pregnancies for insulin therapy;
- Comparison of the different approaches to management: different insulin regimens, adjunctive exercise, timing, nature and frequency of foetal monitoring and timing and route of delivery;

Mapping out the cost-benefit ratio and psychological impact of the various diagnostic and management strategies.

Identifying the influence of maternal metabolic, intrauterine, genetic, lifestyle and other host risk factors on the lifetime susceptibility to obesity and diabetes, with the ultimate objective of developing strategies to prevent obesity, glucose intolerance and diabetes in the offspring of members with GDM.

Better understanding of the physiology of the intrauterine environment in normal and diabetic pregnancies.

A woman with GDM is a patient at a very high risk for future diabetes. Studying and understanding her physiology and metabolism can provide a very valuable insight into techniques for the development of intervention strategies that can be used in clinical trials aimed at delaying or preventing the onset of diabetes and its long-term consequences.

AN AFRICAN DIMENSION

This review article as presented information and suggestions on the best means for the optimal diagnosis and management of GDM. As much as possible, this information was interspersed with local Nigerian data, where immediately available. It is however recognized that practitioners even in some of the best Nigerian medical facilities labor under intense pressure from non-availability of technology considered basic and rudimentary in many other countries. Medical practice then is often a struggle between what is best and what is available / affordable.!

For instance, specialist physician and / or obstetric care are hardly uniformly available or affordable to many, especially in rural areas. Regular monitoring of glycemia with home glucose maters, and timely availability of blood glucose results to hospitalized patients, are often impossible even in tertiary centers. Urine examination, which has been dismissed as useless and unreliable elsewhere, is often what is routinely used even in some of the best centers the rural centers may not even have that option. Food is taken as available and as affordable, not as prescribed although there is an inherent advantage in the traditional high carbohydrate and low fat diet of many rural Nigerians. A pregnant village woman would laugh at your face if you tell her to jog as a form of exercise in the village indeed she would be considered mad and ostracized.

Furthermore, where insulin is prescribed,there are fundamental logistic issues on how the injections are given and how the medication is preserved for optimal potency, especially for the illiterate villager. And does anybody really have a choice in the type and antigenicity of insulin preparations - or people are forced to purchase what is available or affordable. Indeed, U40 and U80 beef and porcine insulins that have been discarded in many developed countries are often the forms still regularly available in Nigeria. And mono-component insulins are beyond the reach of all but a few privileged ones. Even where available, is there adequate health education to ensure compliance to dosage and dosage scheduling required for excellent glycaemic control? And in case of a necessity for prolonged admission for glycemic control and monitoring, who pays the bills?

Even where inpatient admission finally occurs, typically with such diabetic emergencies as ketoacidosis, prolonged labor or post-surgery, infusion pumps for accurate delivery of insulin dosage and other required infusions are hardly uniformly available. In many centers, titration of insulin dosage is based on a sliding scale determined by findings on 4 6 hourly urinalysis. This simply would be unacceptable elsewhere. The list of deficiencies is endless.

However, endlessly cataloguing the potential problems and difficulties in the optimal management of GDM (and of course other important diseases) in poor countries does not solve the problem. Often heroic measures have to be taken by practitioners on the spot.

It is impossible in a review of this nature to suggest guidelines, since, facilities and manpower availablility, differ between different hospitals, states and countries. What is necessary is for the various professional organizations in each of these countries to convene and supervise discussions in consensus conferences, at the end of which locally relevant and usable guidelines can be issued. These can be modified from the international guidelines-incidentally a lot of Nigerians attend international conferences where most of these universal guidelines are discussed and finalized.

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