

Management of Gestational Diabetes Mellitus

JMAJ 54(5): 293–300, 2011

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Abstract

Gestational diabetes mellitus (GDM) is a common metabolic disorder that occurs during pregnancy. GDM can cause significant problems, including maternal complications, perinatal complications, and metabolic disorders in offspring of mothers with GDM. The primary management method for women with GDM is nutritional therapy. Some women with GDM require diet therapy alone, while some women require both diet therapy and insulin therapy. Currently, there is no universal management method for GDM because there are no universal diagnostic criteria and genomic backgrounds differ according to ethnicity. However, consensus guidelines exist. This paper reviews these consensus guidelines for the optimal management of carbohydrate intolerant women in pregnancy.

Key words Gestational diabetes mellitus, Pregnancy, Diabetes mellitus, Management

Introduction

The basic cause of type 2 diabetes, whose prevalence is rapidly increasing worldwide, is genetic factors, with the addition of such acquired factors as lack of exercise, obesity caused by a high-fat diet, stress, and aging impairing insulin action, leading to the onset of diabetes. In Japan, there is a clear trend towards delayed marriage and child-birth, and in future the number of women with decreased carbohydrate tolerance who develop gestational diabetes mellitus (GDM) during pregnancy is expected to increase more and more. It is a fact that it is known that the incidence of GDM increases by approximately 8 times for pregnant women aged 35 years and over compared with women aged 25 years or under. As shown in **Table 1**, pregnant women with carbohydrate intolerance are known to develop various complications, and so blood glucose control is extremely important. Focusing particularly on GDM, this paper presents an outline of clinical issues as well as GDM diagnosis and management.

Definition of GDM

Originally, GDM was defined as decreased carbohydrate tolerance that develops or is first identified during pregnancy,¹ but in 2010 the definition was changed as following. Thus, GDM is a carbohydrate intolerance that is not diabetes that has developed or been discovered for the first time during pregnancy. The GDM definition therefore does not include overt diabetes in pregnancy.^{2,3} Accordingly, hyperglycemic disorders that are thought to have been overlooked until the pregnancy are excluded from the definition of GDM and are instead diagnosed as “overt diabetes in pregnancy.”

Diagnostic Criteria for GDM

Up until recently, the diagnostic criteria for GDM were not universal, with the criteria differing from country to country. In 2010, based on the results of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study,⁴ the International Association of the Diabetes and Pregnancy

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This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol.139, No.10, 2011, pages 2089–2094).

Table 1 Maternal and fetal complications in pregnancies with carbohydrate intolerance

Maternal complications	Fetal complications
Diabetes complications	Perinatal complications
Diabetic ketoacidosis	Fetal distress/fetal death
Deterioration of diabetic retinopathy	Congenital malformations
Deterioration of diabetic nephropathy	Macrosomia
Hypoglycemia (when using insulin)	Birth injury due to shoulder dystocia
Obstetric complications	Delayed fetal development
Spontaneous abortion	Neonatal hypoglycemia
Premature birth	Neonatal hyperbilirubinemia
Pregnancy-induced hypertension	Neonatal hypocalcemia
Hydramnios	Neonatal polycythemia
Shoulder dystocia	Newborn respiratory distress syndrome
	Hypertrophic cardiomyopathy
	Offspring's complications
	Obesity/diabetes

Table 2 Diagnostic criteria for gestational diabetes mellitus (GDM)

(75 g OGTT: [unit] mg/dl)		
Fasting OGTT	1-hour OGTT value	2-hour OGTT value
≥92 mg/dl	≥180 mg/dl	≥153 mg/dl
GDM diagnosis: one or more of the above values		

(Data source: Nakabayashi M, et al.²)**Table 3 Diagnostic criteria for overt diabetes in pregnancy**

Overt diabetes in pregnancy is diagnosed if any of the following apply.
(1) Fasting blood glucose level ≥126 mg/dl
(2) HbA1c values ≥6.5% [HbA1c(JDS)6.1%]*1
(3) Diabetic retinopathy is definitely present
(4) Casual blood glucose ≥200 mg/dl or 2-hour 75 g OGTT value ≥200 mg/dl*2

*1 From the standpoint of giving priority to international standards, for the new HbA1c values National Glycohemoglobin Standardization Program (NGSP) values, which add 0.4% to the Japan Diabetes Society (JDS) values previously used in Japan, have been adopted.

*2 • In all cases, diagnosis should be confirmed with either fasting blood glucose or HbA1c values.

• In the case that HbA1c < 6.5% [HbA1c(JDS) < 6.1%] and 2-hour 75 g OGTT value ≥ 200 mg/dl, a diagnosis of overt diabetes in pregnancy is difficult. Accordingly, a diagnosis of high-risk GDM should be made and management for diabetes in pregnancy needs to be provided, with strict follow-up after the birth as there is a high risk of developing diabetes.

(Data source: Nakabayashi M, et al.²)

Study Groups (IADPSG) proposed a universal standard for GDM diagnosis.⁵ In Japan, the Japan Society of Obstetrics and Gynecology (JSOG)² and Japan Diabetes Society³ also recognized the universal diagnostic criteria in May–June 2010. As explained above, there are two hyperglycemic disorders in pregnancy: GDM and overt diabetes in pregnancy (**Tables 2 and 3**). The greatest difference between the universal criteria and the previous criteria is that a diagnosis of GDM is made if any one of the three cut-off values for the 75 g oral glucose tolerance test (OGTT) (fasting OGTT value, 1-hour OGTT value, 2-hour OGTT value) is abnormal. Up until now the frequency of GDM was 2.92%,⁶ however, this is expected to increase approximately four-fold with the new diagnostic criteria.

Complications in Pregnancy with Carbohydrate Intolerance (Table 1)

(1) Increased risks of maternal complications: In the case of women with diabetes complications, during pregnancy there are risks that diabetic retinopathy and diabetic nephropathy could deteriorate and ketoacidosis could increase.

(2) Increased risks of obstetric complications: Increased incidence of pregnancy-induced hypertension, caesarean section, bradytocia due to macrosomia, and induction of childbirth.

(3) Increased risks of perinatal complications: increased incidence of macrosomia, delayed intra-uterine fetal development, neonatal complications

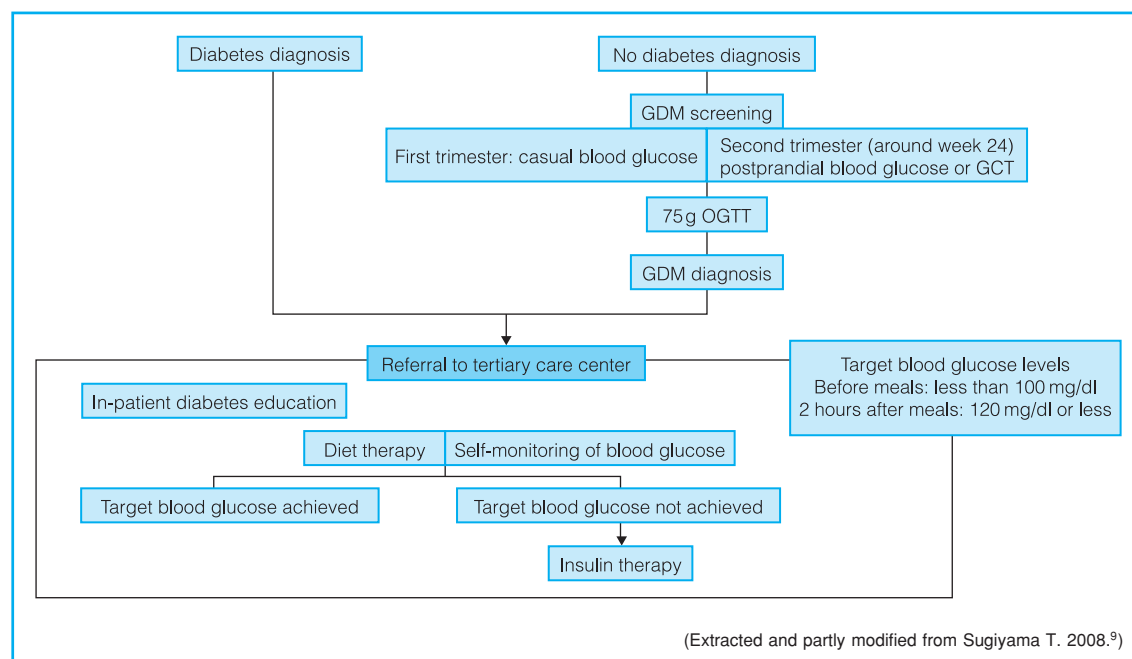


Fig. 1 Diagnosis of and management procedures for pregnant women complicated with carbohydrate intolerance

(hypoglycemia, polycythemia, hyperbilirubinemia, etc.).

(4) In the case of GDM, there is an increased risk of the mother developing type 2 diabetes in future.

(5) The incidence of developing lifestyle-related diseases in offspring of mothers with GDM.

Treatment Policy

Figures 1 and 2 provide flow charts for diagnosis of and management procedures for pregnant women complicated with carbohydrate intolerance and management methods for pregnant women with carbohydrate intolerance.

Medical Interview/Examination/Testing Items

Medical interview

When the patient is first examined, her medical history with regard to diabetes should be checked. Furthermore, the following risk factors for GDM are also checked and it is determined whether or not the patient is at a high risk for GDM.

- Age: particular risk if the patient is aged 35 years or over

- Does the patient's history indicate decreased carbohydrate tolerance?
- Family medical history: particular risk if the patient has a first-degree relative with diabetes
- Obesity: this is an important risk factor for GDM
- History of abnormal delivery: particular risk if the patient has previously had a macrosomic baby
- Patients are screened for GDM in their first trimester or second trimester (around 24 weeks) (Table 4).

The Guidelines for Obstetrical and Gynecological Medical Care⁷ recommend the screening methods shown in Table 4.

In the case that the patient tests positive for the screening tests shown in Table 4, 75g OGTT for diagnosis is carried out. If GDM is diagnosed (Tables 2 and 3), the patient is referred to a tertiary care center where the following tests are performed and the management methods shown in Figs. 1 and 2 are implemented.

Examination/testing items

Physical findings: blood pressure, heart rate, weight (measured every day while the patient is hospitalized)

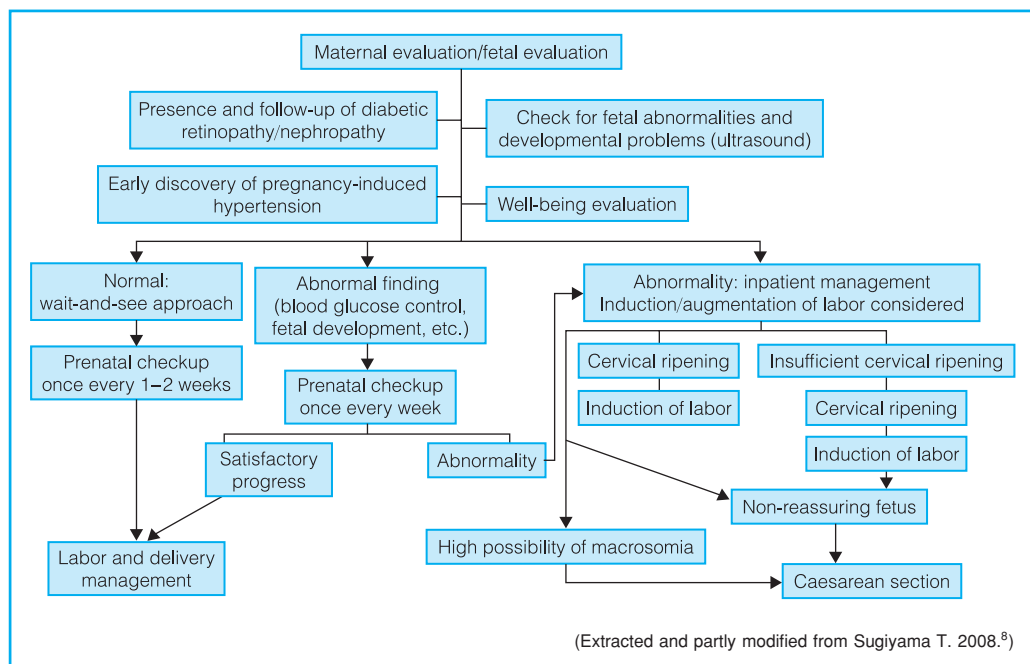


Fig. 2 Management methods for pregnant women with carbohydrate intolerance

Table 4 Gestational diabetes mellitus (GDM) screening methods

1. All pregnant women are screened for GDM.
2. For the following pregnant women with a high risk of developing GDM, it is recommended that GDM screening be omitted and diagnostic testing (75 g OGTT) carried out from the first.
 - 1) In the first trimester, a casual blood glucose test is carried out. Individual medical institutions may set their own cut-off values.
 - 2) A 50 g glucose challenge test (GCT) is carried out in the second trimester (weeks 24–28); the cut-off value is 140 mg/dl.

This test should be administered to pregnant women who tested negatively on the first-trimester casual blood glucose test, or who tested positively on the first-trimester casual blood glucose test but were diagnosed as non-GDM on 75 g OGTT.
3. Screening is carried out using the following two-step method.

(Extracted from Japan Society of Obstetrics and Gynecology/Japan Association of Obstetricians and Gynecologists (eds). 2008.⁷⁾)

Height of uterine fundus measured once per week

Pelvic examination: check for indications of premature birth; vaginal culture

Blood and urine testing

(1) Self-monitoring of blood glucose (tertiary care center)

- As a rule, blood glucose is measured 7 times per day. Blood glucose testing times: before each meal, 2 hours after each meal (2 hours after the start of the meal), and before going to sleep at

night. Depending on the patient's symptoms, blood glucose may also be measured at 2 a.m. or 3 a.m.; in the case of mild glucose intolerance symptoms, blood glucose may be measured 4 times per day.

- In the case of patients with type 1 diabetes, blood glucose is measured 6–7 times per day throughout the pregnancy.
- While hospitalized, the values obtained with self-monitoring of blood glucose are checked against laboratory blood glucose values once to

check consistency.

(2) HbA1c, glycoalbumin, blood biochemistry, peripheral blood in general: measured once per month.

(3) Anti-insulin antibody, anti-GAD antibody, islet-cell antibody (ICA): carried out once as early in the pregnancy as possible.

(4) Uric protein, quantitative measurement of urinary glucose: twice per month

(5) Urine ketone bodies, protein, qualitative measurement of urinary glucose: twice per week

Blood ketone bodies: once per month

(6) Trace urinary albumin: early pregnancy

(7) Urinary NAG, urinary β_2 MG, and creatinine clearance to test for diabetic nephropathy in patients presenting with overt urinary protein: once per month; follow-up carried out by a nephrologist.

(8) Quantitative measurement of urinary C peptide (urine collection): once in first trimester, second trimester, and third trimester.

Fetal ultrasound

(1) Measurement of fetal development

- Using fetal ultrasound, the biparietal diameter (head circumference), abdominal circumference, and femur length of the fetus are measured at appropriate intervals to evaluate fetal development.

- In the case that the fetus is clearly too large for its gestational age, consideration is given to terminating the pregnancy by means of a planned delivery if gestational age is 37 or more weeks.

(2) Screening for fetal congenital malformations (anomalies): fetal structure that can be observed by ultrasound is checked, especially the central nervous system, spine, position of the stomach in relation to the heart.

(3) Checking the amount of amniotic fluid: check for presence of hydramnios.

(4) Evaluation of fetal well-being

- Non-stress Test (NST) (test measuring fetal heart rate): generally this test is carried out from 30 weeks gestation onwards, everyday in the case of in-patient GDM management and once every 1–2 weeks in the case of out-patient management. In the case of fetal dysfunction, an emergency caesarean section is considered.

- Biophysical profile scoring (BPS: indicator of fetal well-being): fetal ultrasound and fetal heart rate parameters are used. For a BPS score of 6 or lower, active fetal management is required. An emergency caesarean section must also be considered.

- Measurement of fetal blood velocity: resistance

index (RI) such as the umbilical cord artery, middle cerebral artery, and uterine artery is measured.

Examination of the ocular fundus

In the case of pregnant women with diabetes complications, ophthalmoscopy is carried out once per month. In the case of GDM, too, ophthalmoscopy is carried out once per month if blood glucose control is poor.

Treatment Policy for Pregnant Women with Carbohydrate Intolerance

In the majority of GDM cases, the frequency of the various complications that may affect mother or child can be controlled with appropriate diagnosis and management. As mentioned above, control of blood glucose levels during pregnancy is extremely important, and the reasons will be explained below.

Conventionally, it is desirable that, in the case that two or more 75g OGTT cut-off values are abnormal, the patient undergoes in-patient education with diet therapy, and if the target blood glucose levels given below are not achieved, the patient should be treated with insulin therapy. In contrast, in the case that only one 75g OGTT cut-off value is abnormal, it is thought to be possible to treat the patient with diet therapy on an out-patient level. In the case of obese women, however, as a general rule in-patient education is thought to be desirable. GDM management policy is an important topic requiring consideration going forward.

The JSOG Committee on Nutrient and Metabolism Problems¹ recommends as target blood glucose levels venous plasma glucose values of 100 mg/dl or lower before meals and of 120 mg/dl or lower 2 hours after meals.

According to two randomized controlled trials (RCTs) concerning the management of GDM^{9,10} that were published recently, amongst the patients who received treatment intervention (diet therapy, self-monitoring of blood glucose, insulin therapy) there was a clearly lower incidence of complications for both the mother and newborn than for patients receiving no treatment intervention. The findings of these reports substantiate the need for blood glucose control in GDM.

Self-monitoring of blood glucose

Depending on the degree of hyperglycemic dis-

order in pregnancy, self-monitoring of blood glucose is carried out by the patient at a frequency of 4–7 times per day. As explained above, the target blood glucose levels are venous plasma glucose values of 100 mg/dl or lower before meals and of 120 mg/dl or lower 2 hours after meals. In the case that these target values cannot be achieved, the diet and insulin therapies described below are implemented. Furthermore, while the patient is hospitalized, checks should be made to ensure that the difference between blood glucose levels obtained through self-monitoring and by laboratory testing is no more than around 10%.

Diet therapy

The key strategies for achieving strict control of blood glucose levels are first of all frequent self-monitoring of blood glucose, followed by appropriate diet therapy, which is extremely important. During pregnancy, as pregnant women patients need to consume adequate energy, protein, and minerals. In Japan, according to the diet therapy recommended by the JSOG Committee on Nutrient and Metabolism Problems¹¹ in 1985, dietary intake for ideal pregnancy weight is 25–30 kcal/kg + 150 kcal for the first half of pregnancy and 25–30 kcal/kg + 350 kcal for the second half of pregnancy, with “+ 150 kcal” and “+ 350 kcal” the additional calorie intake recommended for pregnant women according to the dietary reference intakes prescribed by the then-Ministry of Health and Welfare. Under the nutritional guidelines recommended by the Ministry of Health, Labour and Welfare in 2010,¹² an additional calorie intake of 50 kcal, 250 kcal, 450 kcal is recommended for pregnant women during the first, second, and third trimester, respectively. Thus using these recommendations, it is reasonable to regard the currently recommended calorie intake for pregnant women as 25–30 kcal/kg + 50 kcal, 25–30 kcal/kg + 250 kcal, and 25–30 kcal/kg + 450 kcal for the first, second, and third trimester, respectively.

In the case that the target blood glucose levels described above cannot be achieved eating three meals a day, dividing each meal in a ratio of 2:1 or 1:1 and eating 4–6 meals per day can be effective.

Insulin therapy

In the case that target blood glucose levels cannot be achieved, insulin therapy should be actively implemented. Although there are RCTs

indicating that the oral antidiabetic, glyburide, does not affect the fetus, its safety cannot be said to have been established, and so as a rule treatment is changed to insulin therapy. In the case that a woman becomes pregnant while taking an oral antidiabetic, it is explained to the patient that there is no evidence that oral antidiabetics increase the incidence of congenital malformations. In the case of insulin therapy, due to the need for strict blood glucose control, it is important to keep blood insulin concentrations as close as possible to physiological insulin secretion patterns. That is to say, keeping in mind basal insulin secretion and after-meals insulin secretion, intensive insulin therapy is carried out by means of multiple injections of intermediate-acting and rapid-acting insulin or ultrarapid-acting insulin analog.

Points to note with regard to carbohydrate intolerance in pregnancy

Some changes in glucose metabolism during pregnancy have a negative effect on diabetes. For instance, worsening catabolization at the end of pregnancy can easily cause ketosis or ketoacidosis, while high post-meal blood glucose levels can easily occur due to worsening insulin resistance. Accordingly, even in the case of type 2 diabetes, ketosis or ketoacidosis can occur in the last trimester of pregnancy. Moreover, hyperemesis gravidarum occurring in the first trimester in the case of women with type 1 diabetes complications in particular can easily trigger ketoacidosis, while patients undergoing insulin therapy may develop hypoglycemia, and so care must be taken.

In the case that ritodrine hydrochloride—a drug used to treat threatened premature labor—is administered via venous circulation, ketosis or ketoacidosis can easily occur, and so meticulous care needs to be taken.

GDM management during labor and delivery

Timing and mode of delivery

In the case of diabetes or GDM alone, caesarean section is not indicated, but at the present time it cannot be said that there is sufficient data to support this. For example, it has been reported that in the case of a GDM patient undergoing insulin therapy where fetal development is thought to be within the normal range, there is no difference in the caesarean section rate between women for

whom labor is induced at 38 weeks and those for whom labor is not induced. Moreover, it has also been reported that there is no difference in the incidence of macrosomia or caesarean section between insulin-treated GDM patients for whom labor is induced at 38–39 weeks and insulin-treated GDM patients who electively waited for labor and childbirth to take their natural course. Although in general the rate of caesarean section for GDM patients is high, there are some reports that this is due to the concern of physicians about shoulder dystocia occurring as the result of macrosomia, which has a high rate of frequency amongst GDM patients. However, much of the data is from the United States, and the average birth weight of infants born in the United States is higher than that in Japan. Thus it is thought to be impossible to use overseas data as the Japanese standard from the standpoint of infant birth weights.

So far, in the case that the GDM patient has good blood glucose control and fetal development is thought to be within the normal range, as a general rule it is considered that the pregnancies of GDM patients may be managed in the same manner as those of normal glucose-tolerant women. In the case that birth weight is estimated at 4,000g or higher, an elective caesarean section is considered. However, in the case that the patient has poor blood glucose control, induced delivery at 38 weeks onward is considered.

GDM management during labor and delivery

When carrying out insulin therapy, special care is needed as the amount of insulin required during pregnancy, during delivery, and after birth differs tremendously. Thus, insulin requirements at the end of pregnancy increase by approximately two-fold. During first-stage labor the required amount decreases, while in second-stage labor it increases slightly and after birth decreases rapidly. Accordingly, attention needs to be paid to such changes in required insulin amounts during pregnancy and the amount of insulin administered reduces by half following delivery. In particular, since it becomes difficult for the patient to eat during first- and second-stage labor, especially careful management of blood glucose levels is necessary in the case that labor and delivery are prolonged. In many cases at Mie University, at the onset of labor the patient is administered an electrolyte fluid containing 5% glucose at a rate of 100–120 ml/hr, then administered insulin intra-

venously via an infusion pump. Depending on the individual case, blood glucose is measured at intervals of 1–2 hours. Insulin administration begins with a dosage of 0.5 units/hr and the insulin dosing rate is determined based on fluctuations in blood glucose levels.

Factors that can be ameliorated before and after pregnancy

In the case of women with diabetes complications, and especially in the case that diabetic retinopathy is present, the patient needs to undergo evaluation and treatment by an ophthalmologist. For example, if the patient was being treated before pregnancy for proliferative retinopathy using photo-coagulation therapy, pregnancy is possible. In addition, it is necessary to educate the patient about points to be careful about with regard to further pregnancies.

Obesity is an important risk factor for GDM, and so prior to pregnancy not only is it necessary for patients to take special care with their lifestyle, especially diet, but it is also vital that women suffering from infertility be checked for glucose intolerance. For women with carbohydrate intolerance as a complication of obesity, it is also necessary that the patient make lifestyle improvements after the birth.

GDM patients are encouraged to undergo 75g OGTT testing 6–12 weeks postpartum for reevaluation. In the case that a hyperglycemic disorder is confirmed, the patient is referred to a diabetes specialist for future follow-up. Many GDM patients drop out of medical care at the obstetric/gynecological level, and so patient education is also thought to be important.

Since obese women are at a high risk for developing a hyperglycemic disorder in pregnancy in the future, nutritional guidance and appropriate diet therapy should be considered, and this is a point I wish to particularly emphasize.

Conclusion

In the management of carbohydrate intolerance in pregnancy, the clinical condition of individual cases needs to be identified over time, and in addition to the cooperation of family members, multidisciplinary management and treatment are provided by obstetricians, gynecologists, nutritionists, pediatricians, cardiovascular specialists, nephrologists, ophthalmologists, and nursing staff.

As the trend towards delayed marriage and childbirth continues, the number of pregnant women with carbohydrate intolerance is increasing, and so it is imperative that medical institu-

tions implement measures to prevent the onset of lifestyle diseases not only during pregnancy but also postpartum.

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