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Review

DIABETES AND PREGNANCY

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FUEL METABOLISM IN DIABETIC PREGNANCY

The effect of diabetic pregnancy on fuel metabolism is one of underutilization of exogenous fuel in the fed state (facilitated anabolism reduced) and over-production from endogenous source in the fasted state (hyperaccelerated starvation). The first sign of pregnancy in a diabetic (particularly in type 1 diabetes) as early as the first week of gestation and even before nausea or vomiting sets in may be early morning fasting ketonuria. A minor proportion of women lack the necessary B-cell reserve to maintain euglycemia during pregnancy, and develop impaired glucose tolerance (IGT). They have significantly lower insulin responses at 30 and 60 min after oral glucose load compared with glucose-tolerant controls (1), while insulin sensitivity is similarly reduced in the second trimester (1,2). The C-peptide response to intravenous glucagon is also significantly reduced in women with IGT in pregnancy (3), while serum proinsulin concentrations are increased (4). The need for insulin treatment in gestational diabetes mellitus (GDM) is associated with raised circulating proinsulin levels, implying that greater B-cell dysfuction leads to worse glucose intolerance (5). IGT in pregnancy can vary in severity but even mild degrees are accompanied by other disturbances, including abnormalities of glycerol and nonesterified fatty acid metabolism (6). Women with a previous history of GDM who become glucose-tolerant postpartum show continuing B-cell dysfunction, characterized by impaired insulin release in response to oral glucose, and impaired lipolysis despite normal insulin sensitivity (7,8). This points to a decreased B-cell function in GDM women, which makes them susceptible to the future development of type 2 diabetes (9). Carbohydrate intolerance deteriorates early in pregnancy in diabetic women, in parallel with the physiological decrease in insulin sensitivity. Women with type 1 diabetes are dependent on increased insulin dosage to maintain glycemic control. On an average, lasting from 12th week to 37 weeks of gestation, they may require weekly increments of 6% of insulin dosage from their preconceptional dose. Late pregnancy is associated with a threefold incidence of newly presenting type 1 diabetes (c.f. type 2 gestational diabetes) (10). This may occur because the insulin resistance of pregnancy imposes an additional burden on the beta cells of women who are in the prolonged but subclinical stage of 'prediabetes' with active insulinitis but enough residual B-cell mass to prevent overt hyperglycemia beyond pregnancy. Maternal diabetes also affects the placenta, both structurally and functionally. The placental glycogen content and insulin-binding capacity are higher in pregestational diabetic than in nondiabetic pregnancies (11).

Pregnancy-induced lipolysis makes women with type 1 diabetes more susceptible to diabetic ketoacidosis. It

may develop quickly and with relatively mild hyperglycemia (12). If left untreated, it may cause fetal death (13).

The mother with type 2 diabetes also has to increase her insulin production to counteract the pregnancy related insulin resistance. Before pregnancy these women have already had decreased insulin sensitivity. Further demands on their compromised beta cell function cause in most diet-treated type 2 women to require insulin (or oral agents, in those parts of the world where insulin is not available) early in pregnancy.

CLASSIFICATION OF DIABETES IN PREGNANCY

A uniform classification of diabetic pregnancies is still needed for both epidemiological and clinical purposes. Both the World Health Organization (WHO) (14) and the National Diabetes Data Group (NDDG) (15) of the National Institutes of Health (NIH) have endorsed a classification based on the etiology. WHO classification differs only by recognizing IGT before pregnancy. This is simple but of no prognostic value.

Classification of maternal diabetes in pregnancy:

- Pregestational diabetes: pre-existing type 1 or type 2 or secondary
- Gestational diabetes: diagnosis is made post-gestationally; normal glucose tolerance
- Any type of diabetes mellitus occurring first in pregnancy

Pregestational diabetes mellitus

This term denotes an already established diabetic marching through pregnancy. It has been long known that the incidence of maternal and fetal complications are greatly influenced by the severity of maternal diabetes. On assessing the severity, the following factors have to be taken into consideration: duration of diabetes, maternal age at the onset of diabetes, presence or absence of vascular complications, and methods of treatment. On the basis of preconceptional factors, Priscilla White established a clinical classification method in 1949 (16) and subsequently modified it in 1965 and 1971. This classification attempted to predict the outcome of pregnancy according to various metabolic, obstetric and other risk factors, and graded the prognosis from A (best) to F (worst). Subsequently, attempts to update the classification and incorporate ischemic heart disease and renal transplantation (17) have rendered it too cumbersome for general use.

Another system of classification using the prognostically unfavorable signs in pregnancy is based on the risk factors encountered during the pregnancy itself (18). These are toxemia, clinically manifested pyelonephritis, severe acidosis, lack of patient cooperation, and markedly unfavorable social conditions. A combination of these two classifications predicts fetal outcome more accurately (19), however, their complexity has made them obsolete.

Most European centers apply White classification modified by Pedersen (20) (Table 1):

Table 1. **White's classification of diabetes during pregnancy**

Class A	Diet alone sufficient, any duration or age at onset
Class B	Age at onset ≥20 years and duration <10 years
Class C	Age at onset 10-19 years or duration 10-19 years
Class D	Age at onset <10 years or duration ≥20 years or background retinopathy or hypertension (not preeclampsia)
Class R	Proliferative retinopathy or vitreous hemorrhage
Class F	Nephropathy with proteinuria >500 mg/day
Class RF	Criteria for both R and F classes coexist
Class H	Arteriosclerotic heart disease clinically evident
Class T	Prior renal transplantation

Note: Women in classes below A require insulin therapy. Women in R, F, RF, H and T classes have no criteria for age at diabetes onset or duration of diabetes but usually have long-term diabetes. The development of complication moves the patient to the next class.

- White's group A: Diabetes existing prior to or detected during pregnancy, needing only diet, no insulin treatment being necessary.
- White's group A/B: Diabetes appearing before or during pregnancy, insulin treatment becoming necessary during pregnancy.
- White's group B: Diabetes pre-existing and necessitating insulin treatment before conception, onset of diabetes after maternal age of 20 years, and/or duration of diabetes shorter than 10 years.

- White's group C: Duration of 10-19 years and/or onset of diabetes between 10-19 years of maternal age, insulin dependent diabetes. (These four groups are characterized by the absence of diabetic angiopathy).
- White's group D: Onset of insulin dependent diabetes before the age of 10 years and/or duration exceeding 20 years. All pregnant mothers with discernible but not proliferative diabetic retinopathy are classified as group D.
- White's group F: Severe proliferative diabetic retinopathy and/or diabetic nephropathy before or during pregnancy.

CONSEQUENCES OF THE CHANGES IN FUEL METABOLISM DURING DIABETIC PREGNANCY

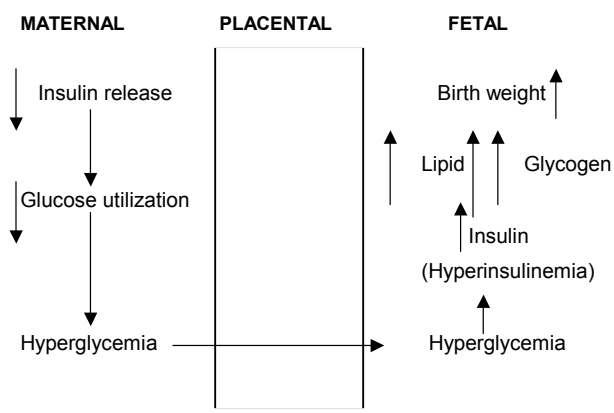
If hyperglycemia is present during the first trimester of pregnancy when organogenesis is taking place, congenital malformations may occur. The incidence is said to be as high as 8% in uncomplicated diabetic pregnancies (uncontrolled during the first 8 weeks of pregnancy), which is two- to threefold that in the general population (21). The malformations often involve the heart and central nervous system, and are potentially lethal. Apart from congenital anomalies, there can be fetal loss through early spontaneous abortion (22). In contrary to the earlier belief that maternal hypoglycemia is an early gestational cause of disturbed organogenesis, Pedersen found a significant negative correlation between the incidence of congenital malformations and that of severe hypoglycemia occurring during the first trimester of pregnancy (23). In addition to maternal hypoglycemia, several other factors may be involved in the etiology of malformations due to maternal diabetes (23). The role of other factors has been demonstrated in animal experiments of maternal ketonemia (24), fetal zinc depletion (25), and inhibited somatomedin action (26). The role of genetically determined susceptibility needs further elucidation. It seems probable that the high incidence of malformations in newborns of diabetic mothers is multifactorial in origin. The malformations develop in the genetically susceptible individuals as the result of a number of teratogenic factors (23). Fetal complications are classified according to the trimester of pregnancy in a poorly controlled diabetic (Table 2).

Table 2. **Fetal problems associated with maternal hyperglycemia according to trimesters of gestation**

First trimester	Second trimester	Third trimester
Malformations	Hypertrophic cardiomyopathy	Hypoglycemia
Growth retardation	Polyhydramnios	Hypocalcemia
Fetal wastage	Erythremia	Hyperbilirubinemia
	Placental insufficiency	Respiratory distress syndrome
	Preeclampsia	Macrosomia
	Fetal loss	Hypomagnesemia
	Low IQ	Intrauterine death

Hyperglycemia during second trimester may cause impairment of intellectual performance in the offspring. The fetal pancreas is capable of secreting insulin by 8th to 11th week of gestation. Maternal glucose that crosses the placenta stimulates beta cells, and mixed nutrients would have similar effects (modified Pedersen's hypothesis) (Fig 1). Consequently, the fetal beta cell activity depends on the maternal blood glucose and amino acid level. Once stimulated, the fetal pancreas continues to secrete insulin in an autonomus fashion regardless of glucose stimulation. Maternal glucose and fetal hyperinsulinemia result in macrosomia (weight >4 kg) and hypokalemia, the latter producing fatal cardiac arrhythmias. Unexplained intrauterine death in the third trimester, although rare, may be due to fetal

Figure 1. **Result of maternal hyperglycemia modified Pedersen's hypothesis**



hypoxia (placental insufficiency). This life threatening metabolic state could be prevented by maintaining maternal euglycemia throughout the period of gestation.

Hypoglycemia

Due to endogenous hyperinsulinemia and suppression of endogenous glucose production, the infant of a diabetic mother (IDM) is at an increased risk of hypoglycemia at 1 to 3 hours after birth. The factor mainly protective against fetal hypoglycemia is optimal control of maternal hypoglycemia, especially during the third trimester and during labor. It has been shown that a mean maternal plasma glucose >6 mmol/L during the last four hours in a diabetic mother leads to a higher incidence of neonatal hypoglycemia.

Hypocalcemia

About 25% of IDMs may present with serum calcium <7 mg/dl, and this may remain mostly asymptomatic and is usually detectable during the second and third day of birth. Asphyxia and prematurity, operating through elevated cortisol, induce vitamin D antagonism at the intestinal level.

Respiratory distress and fetal metabolic acidosis may result in calcium being shifted from intracellular to extracellular pools, and reversal of this shift during correction of the acidotic event may produce hypocalcemia. Hypomagnesemia may coexist and may require correction.

Respiratory distress syndrome (RDS)

The incidence is six-fold for any given gestational age compared with nondiabetic pregnancies (27). It is thought to be due to poor diabetic control (28), which interferes with the production of the surfactant resulting in hyaline membrane disease of fetal lungs. It is postulated that fetal hyperinsulinemia inhibits the synthesis of the surfactant phospholipid component (29), although this theory is not universally accepted.

Polycythemia

It is relatively common in IDM and is mostly due to the hypoxic stimulus by the placental insufficiency and elevated glycohemoglobin. Overtransfusion from a large placenta of diabetic pregnancy may also contribute. The resultant hyperviscosity may induce congestive heart failure and vascular thrombosis accounting for the increased risk of renal vein thrombosis in these infants.

Hyperbilirubinemia

This common abnormality is due to the increased bilirubin production and increased life span of the RBCs with glycosylated cell membranes. Hepatic conjugation of bilirubin may be impaired due to an immature liver.

Macrosomia

The infant of a diabetic mother is often large for gestational age (LGA) (growth promoted) due to increased maternal-fetal nutrient transfer (30). Abnormalities include excessive abdominal fat deposition, organomegaly (notably of the liver, spleen and heart), and accelerated skeletal maturation. The basis of LGA infants in diabetic pregnancies is fetal hyperinsulinemia (31).

Stillbirth in diabetic pregnancy

Historically diabetic pregnancies often terminated in late unexpected intrauterine death. The exact cause is still unknown. The theories implicated include fetal hypoxia and acidosis (32), and hypokalemia leading to dysrhythmias, and placental dysfunction and competition for essential nutrients (33-35).

GESTATIONAL DIABETES MELLITUS

Definition

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy (36). The definition applies whether insulin or only diet modification is used for treatment, and whether or not the condition persists after pregnancy. It does not exclude the

possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy.

Approximately 7% of all pregnancies are complicated by GDM, resulting in more than 200,000 cases annually. The prevalence may range from 1% to 14% of all pregnancies, depending on the population studied and the diagnostic tests employed.

Detection and diagnosis

Risk assessment for GDM should be undertaken at the first parental visit. Women with clinical characteristics consistent with a high risk of GDM should undergo glucose testing as soon as feasible. If they are found not to have GDM at that initial screening, they should be retested between 24 and 28 weeks of gestation. Women at an average risk should have testing undertaken at 24-28 weeks of gestation.

High risk patients

- GDM during previous pregnancy
- Diabetes in a first degree relative
- High weight babies born from a previous pregnancy
- The baby born from a previous pregnancy showing any complications known to be associated as arising from maternal GDM
- A history of stillbirth or infants with congenital abnormalities
- Poor obstetric history including recurrent fetal wastage, hypertension, eclampsia, hydramnios, etc.
- A history of repeated or persistent urinary tract infection
- Glycosuria manifesting during pregnancy
- Age >30 years

However, screening using clinical risk factors fails to diagnose one third to one half of patients with GDM (37,38). Low-risk status requires no glucose testing but this category is limited to those women meeting all of the following characteristics:

- age<25 years
- weight normal before pregnancy
- member of an ethnic group with a low prevalence of GDM
- no known diabetes in first-degree relatives
- no history of abnormal glucose tolerance
- no history of poor obstetric outcome

A fasting plasma glucose level >126 mg/dl (7.0 mmol/L) or a casual plasma glucose >200 mg/dl (11.1 mmol/L) meets the threshold for the diagnosis of diabetes if confirmed on a subsequent day, and precludes the need of any glucose challenge. In the absence of this degree of hyperglycemia, evaluation for GDM in women with average or high-risk characteristics should follow one of two approaches.

- One-step approach: diagnostic oral glucose tolerance test (OGTT) without prior plasma or serum glucose screening. The one-step approach may be cost-effective in high-risk patients or population (e.g., some native-American groups).
- Two-step approach: initial screening by measuring plasma or serum glucose concentration 1 hour after a 50-g oral glucose load (glucose challenge test (GCT)) and a diagnostic OGTT in the subset of women exceeding the glucose threshold value on GCT. When the two-step approach is employed, a glucose threshold value >140 mg/dl (7.8 mmol/l) identifies approximately 80% of women with GDM, and the yield is further increased to 90% by using a cutoff of >130 mg/dl (7.2 mmol/l).

With either approach, the diagnosis of GDM is based on OGTT. Diagnostic criteria for the 100-g OGTT are derived from the original work of O'Sullivan and Mahan, modified by Carpenter and Coustan, and are shown in Table 3. Alternatively, the diagnosis can be made using a 75-g glucose load and the glucose

Table 3. **Diagnosis of GDM with 100-g oral glucose load**

	mg/dl	mmol/l
Fasting	95	5.3
1-h	180	10.0
2-h	155	8.6
3-h	140	7.8

Table 4. **Diagnosis of GDM with 75-g oral glucose load**

	mg/dl	mmol/l
Fasting	95	5.3
1-h	180	10.0
2-h	155	8.6

threshold value listed for fasting, 1 h, and 2 h (Table 4); however, this test is not as well validated for detection of at-risk infants or mothers as the 100-g OGTT.

Two or more of venous plasma concentrations must be met or exceeded for a positive diagnosis. The test should be done in the morning after an overnight fast of 8 to 14 h and after at least 3 days of unrestricted diet (>150 g carbohydrate *per* day) and unlimited physical activity. The subject should remain seated and should not smoke throughout the test.

The American Diabetes Association (ADA) and WHO diagnostic criteria for GDM were evaluated against pregnancy outcomes. The cohort study consecutively enrolled Brazilian adult females attending general prenatal clinics. All women were requested to undertake a standardized 2-h 75-g OGTT between their estimated 24th and 28th week of gestation and were then followed until delivery.

GDM based on a 2-h 75-g OGTT as defined by either WHO or ADA criteria was found to predict adverse pregnancy outcomes.

OBSTETRIC AND PERINATAL CONSIDERATIONS

The presence of fasting hyperglycemia (>105 mg/dl or >5.8 mmol/l) may be associated with an increase in the risk of intrauterine fetal death during the last 4-8 weeks of gestation. GDM of any severity increases the risk of fetal macrosomia. Neonatal hypoglycemia, jaundice, polycythemia and hypocalcemia may complicate GDM as well. GDM is associated with an increased frequency of maternal hypertensive disorders and the need of cesarean section.

Long-term impact of GDM on maternal health

Women with GDM are at an increased risk of the development of diabetes, usually type 2, after pregnancy. Obesity and other factors that promote insulin resistance appear to enhance the risk of type 2 diabetes after GDM, while markers of islet cell-directed autoimmunity are associated with an increase in the risk of type 1 diabetes. The offspring of women with GDM are at an increased risk of obesity, glucose intolerance and diabetes in late adolescence and young adulthood. Approximately 5% - 10% of women with GDM subsequently develop type 1 diabetes (39). Women with GDM have an increased lifetime risk of developing diabetes, being over 30% compared with 10% in normal controls at 16 years after the index pregnancy (40). The requirements of insulin in pregnancy, obesity and further weight gain postpartum are also associated with an increased risk of future diabetes, mostly type 2 (8,41). Other predictors are family history of type 2 diabetes, further pregnancies (42), and a relatively impaired response to oral glucose.

It is appropriate to target women who have had GDM with health education to reduce cardiovascular risk factors, as the morbidity and mortality from premature heart disease is markedly increased in diabetic women (43). The importance of weight maintenance and exercise should be stressed, both for cardiovascular protection and for delaying the onset of IGT and type 2 diabetes (44,45).

Monitoring fetal well-being

Fetal heart rate monitoring by cardiotocography is advised. An unreactive (abnormal) non-stress cardiotocogram (i.e. absence of accelerations of fetal heart) may warrant urgent delivery. In many centers, a biophysical score (BPS) is obtained when non-stress test (NST) is nonreactive. There are five components to BPS, all being given a score 2 if present and score 0 if absent. A total score of 8 or 10 is considered reassuring of fetal health, a score of 6 is considered equivocal, and resting should be done within 24 h. A score 4 or less is abnormal (46) (Table 5).

Table 5. **Biophysical profile score**

Component	Criterion	Score
1. Non-stress test	Reactive	2
2. Fetal movements	3 within 30 minutes	2
3. Fetal tone	1 or more episodes of extension and return to flexion	2
4. Fetal breathing movements	30 seconds or more of breathing movements within 30 min	2
5. Amniotic fluid volume	A single 2-cm x 2-cm pocket or a 5-cm sum of deepest vertical pocket in each quadrant	2

Autonomic neuropathy is usually accompanied by peripheral neuropathic disturbances. This condition can be diagnosed by conducting cardiovascular reflexes. The loss of sweating may precede abnormal cardiovascular tests.

Assessment of fetal maturity

Respiratory distress syndrome (RDS) has been a major cause of neonatal morbidity and mortality in diabetic pregnancies. Amniocentesis is done to assess pulmonary maturity by assessing the lecithin to sphingomyelin (L:S) ratio. If it is less than 2:1, prophylactic steroids are given to accelerate lung maturity (27).

MATERNAL COMPLICATIONS

Preeclampsia

It is more common than in non-diabetic pregnancies (10% *vs.* 4%) and increases to 30% in the presence of vascular disease (47). In women without pre-existing hypertension or nephropathy, preeclampsia becomes apparent when the classical signs of hypertension and proteinuria develop. At this time, the only curative treatment is delivery of the baby. In women with nephropathy in whom the diagnosis is unclear, delivery is usually indicated when renal function deteriorates and blood pressure becomes difficult to control, or if fetal compromise occurs.

Preterm labor

The most common cause is still iatrogenic for the management of preeclampsia (9%). Spontaneous rupture of membranes (6%) and spontaneous onset of labor (3%) possibly due to polyhydramnios also contribute to this high incidence (48). Conventional management of preterm labor in the absence of obstetric contraindications is with an intravenous infusion of beta-adrenergic agonist such as salbutamol or ritodrine, which inhibit uterine contractivity, usually given for 24 h. This is combined with high dose glucocorticoids (typically two doses of 12 mg dexamethasone given intramuscularly at 12 h apart) to encourage fetal lung maturation. The two doses of dexamethasone are repeated at weekly intervals while the risk of preterm delivery remains.

Management of pregestational and gestational diabetes mellitus

An important predictor of fetal outcome either in pregestational or gestational diabetes is the glycemic control attained immediately before and during pregnancy. Complications for the mother or baby may arise from medical, obstetric or neonatal factors. Thus, a management team consisting of a diabetologist, an obstetrician, a pediatrician, a nurse educator, a dietitian and a social worker continues to be essential to achieve this goal.

Pregestational diabetes type 1 and type 2

All premenopausal diabetic women should be considered as potential mothers, and should be given contraceptive and pregnancy advice in the routine diabetic clinic. Once a woman expresses an interest in becoming pregnant, she should have access to the diabetic antenatal clinic for specific preconceptional advice. Any woman planning a pregnancy should take a folate-rich diet together with 400 μg folic acid daily from before conception until the 12th week of gestation to reduce the risk of neural tube defects. In view of the association of diabetic pregnancy with spina bifida and other neural tube malformations, it also seems sensible to treat diabetic women with high-dose folic acid. In addition, rubella immunity should be assessed, as should be sickle-cell or thalassemia carrier status in women from relevant ethnic groups, and the women's partners should be tested if she is a carrier. A young woman should be instructed on how to self-assess her diabetic status and achieve normoglycemia. Whenever possible this should be done before conception, otherwise as soon as pregnancy is confirmed, and maintained thereafter. The patient should be reassured of the pregnancy and diabetes being incompatible. She should be assured that vaginal delivery close to term is likely and that the baby will be normal and healthy. A multidisciplinary team should be formed, along with active participation of the mother and her family. Education about special issues related to pregnancy should begin at the time when a diabetic wants to conceive. Pregnancy should not be discouraged on genetic grounds. The patient must be informed about the risk of perinatal mortality, congenital anomalies, maternal mortality, diabetic complications in pregnancy, obstetric complications, inheritance of

diabetes in offspring, etc. She must be advised to come for frequent antenatal visits, strict glycemic control (through home blood glucose monitoring and optimized insulin regimen), to stop smoking and drinking alcohol, and to stick to the appropriate diet. All women with type 2 diabetes should switch to insulin, ideally before pregnancy or early in the first trimester, to achieve good glycemic control. Moreover, the oral hypoglycemic drugs cross the placenta and are thought to be potentially teratogenic. They also stimulate fetal beta cells directly, aggravating fetal hyperinsulinemia and macrosomia. Diabetic women with established nephropathy should be advised against pregnancy, since it can increase the risk for both the mother and the offspring (44). Patients with active proliferative retinopathy must postpone pregnancy until they will have undergone photocoagulation therapy.

Ischemic heart disease demands treatment prior to any decision about pregnancy. Myocardial infarction occurring during pregnancy carries a high mortality rate for both the mother and the fetus (49).

MANAGEMENT DURING PREGNANCY

Diet

There is no need to make fundamental changes to the diabetic diet because of pregnancy. Carbohydrate, fat and proteins are taken in appropriate proportions. It is important to avoid excessive dietary protein in women with nephropathy. The expected weight gain during pregnancy is 300 to 400 g *per* week and total weight gain is 10 to 12 kg by term. The diet schedule must be planned in such a way as to prevent postprandial hyperglycemia. Diabetic fetopathy which is the result of maternal postprandial hyperglycemia can be minimized when the peak postprandial response is blunted. Gestational diabetes is a disease of carbohydrate intolerance. Thus, the peak postprandial response is minimized in a woman with gestational diabetes if her meal plan is carbohydrate restricted. A caloric prescription therefore can be designed so as to achieve postprandial normoglycemia by minimizing carbohydrates in the meal plan. One diet that has been proved to provide the needs of pregnancy and not to result in excessive weight gain or hyperglycemia consists of 30 kcal/kg of present pregnant weight for normal weight women, 24 kcal/kg for overweight women, and 12 kcal/kg for morbidly obese women (50,51). Thus, the optimal diet for the gestational diabetic women is based on maternal glucose as a variable on which the success or failure of a dietary prescription is based. Approximately 30 to 40 kcal/kg ideal body weight or an increment of 300 kcal/day above the basal requirement are needed. Those who are not gaining weight as expected, particularly in the third trimester, require admission to ensure adequate nutrition to prevent low birth weight infants. Folic acid, 400 μg/day, is given from before conception till 12 weeks of gestation to prevent neural tube defects (52).

MANAGEMENT DURING FIRST TRIMESTER

All patients should be on insulin therapy. The women whose glycemia is not under control should be hospitalized till they achieve good glycemia. Patients should be screened for hypertension and heart disease. Additional investigations should include urine test for protein, serum creatinine, and glycated hemoglobin measurement to find the risk for congenital anomaly. All other routine investigations like blood group, Hb%, etc. should be done. Follow-up is generally at 2-4 weeks at this step, depending on diabetic control and presence of complications.

Ultrasound scan

Early ultrasound scan is important to estimate gestational age because of the risk of preterm delivery and because of macrosomia in the second trimester, which may make later dating less accurate. Also, early growth delay has been reported to be associated with a sevenfold incidence of congenital abnormalities (53). Early ultrasound is also important to detect gross congenital anomalies such as anencephaly, unexpected missed abortion, and multiple pregnancy.

Risk of miscarriage

The risk of miscarriage is higher with poor glycemic control than in those with good glycemic control (9% *vs.* 29%), insulin treatment and glucose monitoring (54). It is appropriate to tend to a mean blood glucose concentration between 5.6 and 6.7 mmol/L (55). All patients have to monitor blood glucose at home four times a day. The emphasis is on minimizing

postprandial peaks of glucose (to keep it below 7 mmol/L) and fasting level to below 5 mmol/L. To achieve this, virtually all women need shortacting insulin before each meal and an intermediate acting insulin at bed time. For many women insulin requirements do not begin to increase until second trimester, and some women need to reduce it in the first three months (56). An important family member should be instructed how to treat hypoglycemia at home.

MANAGEMENT DURING SECOND TRIMESTER

Monitoring diabetic control

Insulin requirements will often have doubled by the end of second trimester. The most problematic period of the day is between breakfast and lunch, because of the physiological tendency to hyperglycemia at this time. The morning dose of shortacting insulin is generally increased with careful adjustment of timing of meal, so to avoid hypoglycemia. Diabetic ketoacidosis occurs in up to 10% of pregnancies (57), often with relatively mild hyperglycemia. So, urine testing for ketones must be done in times of poor glycemic control or intercurrent infection.

Monitoring diabetic complications

Vascular, renal and retinal problems need to be followed carefully and appropriate treatment should be undertaken. Hypertension should be managed with drugs considered safe in pregnancy, usually methyldopa, and nifedipine if a second agent is required.

Monitoring the fetus

Detailed ultrasound scan has to be performed at 18-20 weeks to rule out structural abnormalities of the spine, skull, kidneys and heart. From 26 weeks onwards, scans are done to assess fetal growth as it may become apparent during this trimester.

Screening for chromosomal abnormalies

Diagnostic amniocentesis can be done to rule out neural tube defects. The test is unreliable. So, most centers depend on detailed ultrasound scanning. Ultrasound measurement of fetal nuchal translucency at 10-14 weeks of gestation may provide additional information regarding the role of chromosomal anomaly (58).

General review of obstetric progress

Most obstetric problems associated with diabetes, such as preeclampsia, polyhydramnios, preterm labor, macrosomia or growth retardation, and unexpected intrauterine death occur in third trimester, however, general surveillance for these factors is performed from 26 weeks of gestation.

MANAGEMENT DURING THIRD TRIMESTER

Monitoring diabetic control

Insulin requirements become stable or may even slightly decline at 34-36 weeks of gestation. Frequent ultrasound scan should be performed to assess fetal growth and liquor volume. Babies weighing more than 4000 g are said to be macrosomic, however, there may be variation of +20% of the actual weight in ultrasound formulas. So, birth weight can vary between 3200 g and 4800 g (59). Good glycemic control can reduce macrosomia in babies. Macrosomia is often of concern because of shoulder dystocia, which can lead to birth injury or even to fetal death. Presently there is no fully reliable way to predict which fetus will develop shoulder dystocia and which will not. Polyhydramnios may be detected at this time by ultrasound. It may be related to fetal polyuria secondary to fetal hyperglycemia (60). It may be associated with preterm labor, premature rupture of membranes, unstable lie, and cord prolapse. It is also associated with an increased risk of stillbirth in diabetic women (61). Nonsteroidal anti-inflammatory drugs such as indomethacin have been used to reduce fetal urine production, and consequently liquor volume tightening of diabetic control may also be helpful in some cases.

Timing of delivery

Delivery is advised at 38 weeks of gestation (62), while others allow the women with uncomplicated diabetes to go into spontaneous labor irrespective of the gestational age (63). In Murphy's retrospective review (63), 64% of 45 women went into spontaneous labor after 37 weeks of gestation, with a mean gestation of 39 weeks. All authors agree that pregnancy could terminate before 40 weeks of gestation. Uncomplicated diabetic pregnant women are allowed for spontaneous delivery by some practitioners. The patient has to be hospitalized during the last weeks of pregnancy. Before inducing labor with oxytocin and amniotomy, it is important to check uterine cervix which has to be ripe. When cervix is not ripe, labor is finished by cesarean section. Elective cesarean section is rare except in breech presentation, placenta previa, and other obstetric complications or fetal distress.

MANAGEMENT DURING DELIVERY AND PUERPERIUM

Pregestational diabetes

During spontaneous or induced labor, the objectives of medical management are to maintain plasma glucose within the physiologic range (3.9 to 6.7 mmol/L) and to prevent ketosis. Intravenous glucose is administered at 5 to 10 g/h by a constant infusion pump. All other intravenous fluids are devoid of glucose. Patients with type 2 diabetes often do not require insulin with this regimen. Those with type 1 diabetes are treated with small doses of subcutaneous regular insulin every 3 to 6 h (64), or by continuous intravenous infusion of regular insulin at rates of 0.02 to 0.04 IU/kg body weight (1.4 to 2.8 IU/h in a 70-kg woman) (65). Capillary blood sugar is measured every 1 to 4 hours (with periodic measurements of plasma glucose for confirmation). The glucose infusion may be delayed by 1 to 2 h when hyperglycemia is present at entry, whereas insulin administration may be withheld temporarily if the blood glucose level is less than 3.9 mmol/L.

Elective cesarean section is scheduled early in the morning when possible. Neither insulin nor glucose is administered if the blood sugar level before the procedure is between 3.9 and 7.8 mmol/L. Glucose, insulin or both are given when blood sugar levels are outside this range or the procedure is delayed significantly.

Insulin requirements usually decline dramatically immediately following delivery (often by 50% to 75%) (31). The women who wish to breastfeed are maintained at or above their antepartum caloric intake. Because of the potential for oral agents to be secreted in breast milk and cause hypoglycemia in the infant, they are not prescribed for patients with type 2 diabetes if they wish to breastfeed. Those who do not breastfeed are returned immediately to a diet appropriate for nongravid women (30 to 32 kcal/ideal body mass). All patients are encouraged to use the diabetic management skills they have acquired during gestation.

Gestational diabetes

Therapeutic goals are the same as in pregestational diabetics. Insulin therapy is rarely required to maintain intrapartum normoglycemia in women with GDM. The vast majority of patients requiring insulin therapy antepartum can discontinue it at delivery.

INTRAPARTUM DIABETIC MANAGEMENT

The glucose utilization during labor in well controlled diabetics is uniformly 2.55 mg/kg/min. The best control achieved during pregnancy should not be lost at labor. Plasma glucose should be monitored hourly and maintained between 90 and 120 mg/dl (31).

MANAGEMENT OF GESTATIONAL DIABETES MELLITUS

Pregnant women with GDM have higher perinatal mortality, and they give birth to more macrosomic newborns weighing >4 kg. Strict glycemic control of GDM has been shown to decrease the proportion of macrosomic newborns (>4000 g) (67). Managing pregnant patients with GDM depends on obstetric problems. Bed rest is the need in patients with habitual abortion or preeclampsia. Hormonal therapy is needed in a situation with incipient abortion, and cerclage of uterine cervix is needed for incompetent internal cervical os. The treatment of GDM is diet. Pregnant

patients who need bed rest require no more than 1800 kcal *per* day, and those who continue working require 2100 kcal *per* day (25-35 kcal/kg desirable body weight). Insulin treatment is recommended when fasting blood glucose is higher than 6.1 mmol/L, or insulin >20 μU/L in amniotic fluid, in cases with macrosomic fetus, placenta or polyhydramnios, and in patients with glycosuria more than 2.0 mmol/L/24 h. Shortacting insulin before each meal may be enough, sometimes an intermediate acting insulin is added at night. The insulin dosage usually increases as the pregnancy progresses, particularly up to around 30 weeks of gestation. All women with GDM should have ultrasound scan for fetal size and volume soon after the diagnosis has been made; later they should have serial scans every four weeks. During the last three weeks of pregnancy it is important to monitor the fetus. Most authors recommend labor induction at 38th week of gestation, and all authors agree that pregnancy could terminate before 40th week of gestation.

We prefer spontaneous vaginal delivery induced with oxytocin infusion and amniotomy.

During labor it is important to monitor fetal heart rate with cadiotocography. Before starting labor induction it is important to check uterine cervix which has to be ripe. When uterine cervix is not ripe, the delivery is finished with cesarean section.

After delivery, the mother will not require further insulin but blood glucose levels should be monitored before leaving the hospital and OGTT should be performed within six weeks. Women with diagnostic OGTT for diabetes postpartum should be transferred to a diabetic clinic. Those with normal glcuose or IGT should be informed on the importance of attaining and maintaining an ideal BMI through diet and on the benefits of exercise. In any future pregnancy such a woman should book early and undergo OGTT; if normal, it should be repeated at 20-28 weeks of gestation.

All women with GDM should receive nutritional counseling by a registered dietitian when possible, consistent with ADA recommendations. Individualization of medical nutrition therapy (MNT) depending on maternal weight and height is recommended.

For obese women (BMI >30), a 30%-33% calorie restriction (to –25 kcal/kg of actual weight *per* day) has been shown to reduce hyperglycemia and plasma triglycerides with no increase in ketonuria (68). Restriction of carbohydrate to 35%-40% of calories has been shown to decrease maternal glucose levels and to improve maternal and fetal outcome (69).

Insulin is pharmacological therapy that has most consistently been shown to reduce fetal morbidity when added to MNT.

The measurement of fetal abdominal circumference early in the third trimester can identify a large subset of infants with no excess risk of macrosomia in the absence of maternal insulin therapy. This approach has been tested primarily in pregnancies with maternal fasting serum glucose level <105 mg/dl (5.8 mmol/l).

Human insulin should be used when insulin is prescribed.

Oral glucose-lowering agents have generally not been recommended during pregnancy. However, one randomized, unblinded clinical trial compared the use of insulin and glyburide in women with GDM who were not able to meet glycemic goals on MNT (70).

Programs of moderate physical exercise have been shown to lower maternal glucose concentration in women with GDM.

Breast-feeding, as always, should be encouraged in women with GDM.

Longterm therapeutic considerations

Reclassification of maternal glycemic status should be performed at least 6 weeks after delivery and according to the guidelines from the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (71). Diagnostic criteria are shown in Table 6.

Table 6. **Criteria for diagnosis of diabetes mellitus**

Normoglycemia	IFG and IGT	Diabetes mellitus
FPG <110 mg/dl	FPG >110 mg/dl and <126 mg/dl (IFG)	FPG >126 mg/dl
2-h PG <140 mg/dl	2-h PG >140 mg/dl and <200 mg/dl (IGT)	2-h PG>200mg/dl
–	–	Symptoms of DM and casual plasma glucose concentration >200 mg/dl

Medications that worsen insulin resistance (e.g., glucocorticoids, nicotinic acid) should be avoided if possible.

Education should also include the need for family planning to ensure optimal glycemic regulation from the start of any subsequent pregnancy. Low doses of estrogen-progestogen oral contraceptives may be used in women with prior histories of GDM, as long as no medical contraindication exists.

MNT for diabetes has been proven to lower HbA_{1c} concentration by 1%-2% and is crucial for effective care (72,73). MNT is recommended for the management of GDM, and it is often the only diabetes treatment offered to women with this condition.

FAMILY PLANNING IN DIABETES MELLITUS

The timing of childbearing is an important question in a diabetic woman. There are teenaged mothers on the one hand and mothers in their late thirties or even early forties on the other hand. In any, it is best to conceive within ten years of the onset of diabetes, before the development of vascular complications. It is desirable that the planned child or children be born from the first successful pregnancy or pregnancies of the mother. Therefore, contraception before (and between) the pregnancies is recommended.

In contraception, the advantage of barrier methods is the virtual absence of adverse side effects. The intrauterine device is safe and more comfortable, and diabetics in good metabolic balance run no more risk of complications than healthy women. Oral contraceptives can be used safely in low doses in uncomplicated diabetics (74). But since oral contraceptives may increase blood pressure and enhance platelet aggregation, they are not recommended in cases of diabetes complicated by angiopathy or other risk factors such as smoking, hypertension, age (if over 35 years), etc. (68).

For patients in whom there is a medical reason against pregnancy or who do not want to become pregnant anymore, sterilization can be offered.

There is no medical reason against pregnancy in a diabetic woman if she has no complications, no additional disease, and her metabolic state is near normoglycemic. In other cases, treatement of accompanying disorders should be considered, and pregnancy can only be recommended with caution since it may carry a risk to maternal and fetal health. This decision is obviously influenced by some circumstances such as whether she is already pregnant or only planning to have a child, if pregnant at an appropriate age, and whether she already has a healthy child. The decisions can be summarized as follows:

- pregnancy is not suitable or its continuation cannot be recommended in the following cases:
  - marked diabetic nephropathy, severe hypertension, pronounced albuminuria, reduced renal function
  - progressive therapy resistant proliferative retinopathy impairing visual function
  - severe ischemic heart disease
  - severe diabetic ketoacidosis at the time of conception or during the first week of gestation (and only one subsequent pregnancy can be recommended, after receiving preconceptional care)
- pregnancy maintenance may be considered in case of:
  - pronounced hypertension, albuminuria
  - advanced proliferative retinopathy threatening vision
  - demonstrable ischemic heart disease
  - marked hyperglycemia, glycosuria, acetonuria during the first weeks of pregnancy (a subsequent pregnancy may be recommended after preconceptional care)
  - lack of cooperation
- no further pregnancy is recommended if the mother with retinopathy has a healthy child and her diabetes has existed for more than 20 years

DIABETIC PREGNANCY OUTCOMES IN INDIA

India is a developing country with its own population profile that is different from other countries. Although the problems related to pregnancy outcomes in diabetic women are the same throughout the world, there are some economic and sociocultural conditions that modify the severity of the problem from one part of the world to the other. The level of literacy, different economic status of the people, place of residence (rural or urban), etc. influence the outcome of pregnancy in

diabetic women in India. Sixty-five percent of the people live in rural areas lacking modern amenities of life, communication, roads, rails and health care facilities. In India, the inadequate budget for health care precludes health departments from giving proper and adequate attention to these patients. There are no specialized clinics for diabetic pregnancies and no health educators to explain the problems of diabetes in pregnancy. Because of the highest rate of illiteracy in Indian women, they do not show much interest to understand the nature of their disease and its possible impact on pregnancy. Even now some of the rural women deliver at home by the help of a midwife or sometimes even by the help of an elderly woman from the household, which makes the outcome worse for both the mother and the child, especially in diabetics. Although preconceptional counseling is available at medical teaching institutions, they are very few in number and far from the reach of rural population. Even when they are within reach in some areas to the rural population, they do not utilize these services because of their illiteracy. Home blood glucose monitoring, which is the most important part in diabetic pregnancy, is not carried out by nearly all patients because of the high cost of the device. There is no health insurance scheme in India which could provide for these devices and the cost of treatment. Although some private health insurance schemes are coming up now, only the people from the upper middle class (economically) can afford it. Nowadays, the majority of people utilize the services of private medical practitioners, where they are followed up in a better way. However, poor people cannot even afford the cost of consultations. Although private practitioners provide a better medical care, they are poor in record keeping, which is important in diabetic pregnancy, especially in a gestational diabetic for the future follow-up.

Ultrasound scan, which is most important in the follow-up of fetal development and growth throughout the gestational period, is not within reach of some of rural population. Even when it is within reach, most of these people cannot afford it because of poverty. Some of those who can afford it are ignorant of its importance.

In general, the pregnancy outcome in diabetic women is poor in India when compared with the developed world. The time has come for the government of India to implement an effective plan to the benefit of pregnant women with diabetes and those who develop diabetes during pregnancy. Since India is a developing country with many other problems in hand to deal with, it can start this with a small budget. As the majority of people live in rural India and since midwife is the primary health care worker in rural India, the government can start this program by educating midwives on how to advise a pregnant diabetic. They (midwives) must be able to recognize the high risk group of pregnant women that are prone to develop gestational diabetes, so that they can advise the patient about the importance of antenatal checkup by an obstetrician. Also, they (midwives) must be able to teach an already diabetic patient about the importance of preconceptional counseling by an obstetrician in order to avoid maternal and fetal complications during pregnancy. Also, they must follow up the patients after delivery and advise them on the importance of diet and exercise from time to time.

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