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DIABETES MELLITUS AND PREGNANCY

INTRODUCTION

Pregnancy and diabetes mellitus is a common medical problem, although those of us in the practice of internal medicine seem to be called on infrequently to aid in the care of this type of patient. But, with the changing philosophy regarding the management of such patients the internist is surely going to be asked, with increasing frequency in the future, to aid the obstetrician with these problems.

Personally, I have had little experience with this clinical entity and thus I thought this would be a timely subject for this Grand Rounds Presentation.

Diabetes mellitus is observed in approximately 1-2% of all pregnancies. Although this is one of the most common medical complications seen in obstetrical practice there remains considerable controversy as to the exact definition of the disorder and what is regarded as proper management. Furthermore, the exact pathophysiological abnormalities responsible for much of the perinatal morbidity and mortality inherent in diabetic pregnancies is poorly understood. I will attempt, in this review to examine and discuss all aspects of this problem and hopefully, put each one into perspective.

TABLE 1

CLASSIFICATION OF DIABETES MELLITUS IN PREGNANCY

1. Class A - Asymptomatic (diagnosis based on abnormal OGTT); gestational
2. Class B - Onset of overt diabetes after age 20; duration less than 10 years, no vascular lesions (may also be gestational)
3. Class C - Onset of overt diabetes before age 20, duration less than years
4. Class D - Onset of overt diabetes before age 10 or greater than 20 years duration; or calcification of vessels of legs, hypertension, or benign retinopathy
5. Class E - Calcification of pelvic blood vessels (not used presently)
6. Class F - Nephropathy
7. Class G - Many failurs
8. Class H - Arteriosclerotic Heart Disease
9. Class R - Proliferative retinopathy
10. Class T - Renal transplantation

Class A diabetes includes those groups of patients with "chemical" diabetes that is, those who have a normal fasting plasma glucose level but whose response to oral glucose exceeds an acceptable limit. According to the new NIH Diabetes Study Group classification (3) these patients are asymptomatic prior to pregnancy and have developed "gestational diabetes" as a result of the intracurrent pregnancy. After termination of the pregnancy they will require re-classification into some other group. Some will, of course, revert to normal glucose tolerance and thus fall into the classification of Previous Abnormal Glucose Tolerance, while others will continue to have impaired glucose tolerance and, there will be some who will remain diabetic.

The term "gestational diabetes" is really a confusing one. According to the NIH report, this category is restricted to pregnant women in whom the onset or recognition of diabetes occurs during pregnancy. Therefore, diabetic women who become pregnant are not included in this category. The White Class A diabetic is a "gestational diabetic" in that her impaired glucose intolerance occurs with pregnancy. However, it is important to realize that patients who fall into White Class B can also be considered "gestational diabetics". Their fasting hyperglycemia may remit with the termination of the pregnancy.

Is Class A diabetes really a justifiable classification? As I will discuss later there appears to be little if any increased perinatal mortality in this class of diabetic pregnancy and treatment of the "diabetes" is usually limited to dietary management only. From an obstetric point of view there appears to be no need for early delivery either. So why have such a classification? Although perinatal mortality is probably normal in this group, there continues to be an increased incidence of neonatal morbidity. The infant of the Class A diabetic pregnancy should receive special care by the pediatrician. Thus, this classification is warranted in order to alert the pediatrician. Furthermore, what I feel is most important about this classification is the careful observation of the pregnancy. Sometimes there is a very thin line between true Class A diabetes and the subsequent development of persistant hyperglycemia (Class B diabetes). One should be aware of the patient's history for those indicators of potential problems. Such things as a family history of diabetes, previous delivery of a large baby or an unexplained stillbirth should alert the clinician to the situation.

Class B diabetics are those who have the onset of diabetes after the age of 20, or those who have it for less than 10 years and have no microvascular lesions. Development of Class B diabetes can also be a form of "gestational diabetes". Women who fall into Class C are those who developed diabetes between the ages of 10 and 19, or those who have had the disease for a duration of 10 - 19 years but who are free of microvascular lesions. Class D diabetics are those who were less than 10 when their diabetes began or who have had diabetes for more than 20 years. Also included in this classification are those diabetics of any age of onset or duration of the disease who have calcification of blood vessels in their legs, hypertension or benign diabetic retinopathy. Class E diabetics were originally placed in this category if they were found to have calcification of their pelvic arteries. This classification is no longer in used. Patients fall into Class F if they have diabetic nephropathy. Class G diabetics are those with multiple organ failures. Class H diabetics have arteriosclerotic heart disease. Class R diabetics have proliferative diabetic retinopathy and Class T are those pregnant diabetic women who

have had a prior renal transplantion (4)

The Diagnosis of Diabetes Mellitus During Pregnancy

For those patients who would fall into the diagnostic classification of diabetes B-T is simple, and in most cases, the diagnosis of diabetes has been established prior to the onset of pregnancy. Fasting hyperglycemia present on two or more occasions is all that is needed to establish the diagnosis according to the criteria recently established by the NIH Diabetes Study Group fasting hyperglycemia is defined as a fasting plasma glucose level in excess of 140 mg/dl. It is important to note that according to the NIH group the acceptable limit of fasting plasma glucose levels is lowered to 105 mg/dl during pregnancy.

The diagnosis of Class A diabetes (patients with normal fasting plasma glucose levels, i.e., less than 105 mg/dl) according to the NIH Diabetes Study Group requires the use of the oral glucose tolerance test. They use the diagnostic criteria of O'Sullivan and Mahan (5) to establish the diagnosis. The diagnosis of "gestational diabetes" can be made when two of more of the following plasma glucose values are met or exceeded (after 100 g glucose dose) fasting 105 mg/dl, 1 hour, 90 mg/dl, 2 hours 165 mg/dl, 3 hours 145 mg/dl.

As seems to be case generally in establishing a diagnosis of diabetes, the true incidence of "gestational diabetes" is difficult to ascertain. Amankwah, Prentice, and Flerry (6) using criteria established by O'Sullivan and Mahan (5) (these happen to be the diagnostic criteria utilized by the NIH Diabetes Study Group) were able to determine that the incidence of gestational diabetes was 6% in private patient population. It is of interest to note that when one examines, in a retrospective fashion, the previous pregnancy history of these gestational diabetic patients, one finds an incidence of congenital abnormalities of 13.6% and a total incidence of perinatal abnormalities of 4.5%, suggesting that patients with "gestational diabetes" are at greater risk for an unhappy outcome of their pregnancy than their non-diabetic counterpart.

Should all asymptomatic pregnant women be screened for diabetes? If so, should the clinician do anything more sophisticated than to measure the urine glucose? Should he (she) do a fasting plasma glucose or oral glucose tolerance test? The answer is no, but there are things in the patients' history or initial evaluation that would suggest that a fasting plasma glucose or even an oral glucose tolerance test be performed. These would include glycosuria on more than one random sample; a strong family history of diabetes (one or both parents), particularly in an obese samples; a previous infant weighing greater than 10 pounds at birth; and a history of recurrent unexplained stillbirth, neonatal death, or congenital anomalies.

In my opinion what the clinician is looking to primarily identify is not the gestational diabetic who falls into the White Class A category but those would have asymptomatic fasting hyperglycemia and are in Class B. These are the patients who would be at risk for an unhappy outcome to their pregnancy should their diabetes go undiscovered.

The Effect of Diabetes on the Pregnancy

In general there is an increased fetal wastage (perinatal mortality) in diabetic pregnancies. This increase seems to be in proportion to the severity of the diabetes as indicated by the White classification of the diabetes (7, 8, 9). For example, Table 2 shows the results of a large Scandinavian series of 1332 pregnancies in women with diabetes followed at a single center from 1946 to 1972 (7). As can be seen, the perinatal mortality increased significantly from 5% in Class A diabetics to 35.4% in those women who fall into Class F. The overall perinatal mortality was 16.3%. They found that congenital malformation were the most important single cause of perinatal death. Although perinatal mortality in each White classification declined significantly in the period from 1966 - 1972 as compared to that period from 1946 - 1965 it is clear that the more severe the diabetes the greater the perinatal mortality (Table 3). Table 4 from another study (8) shows the incidence of congenital malformation in infants of diabetic mothers according to the White classification. In this study the risk of congenital abnormalities in patients in Class A was not increased, however, more severe diabetes (White classification B, C, D, F) was associated with a high incidence of congenital malformation. Women whose diabetes began before age 20 had a higher incidence of infants with malformations that were fatal than women who developed diabetes at an older age. In this study the risk of congenital malformation was similar for Class B, C, D, and F, affecting one in ten infants, while one in 13 had major malformations. Fetal malformation accounted for the death of one in every 75 infants and the risk was twice as high in Classes C, D., and F. as was in Class B.

TABLE 2

Perinatal mortality among 1,332 infants as related to White's classes

White's class	Total no. of infants	Perinatal mortality No.	Perinatal mortality %
A	181	9	5.0
B	316	44	13.9
C	331	60	18.1
D	425	76	17.9
F	79	28	35.4
Total	1,332	217	16.3

TABLE 3

Perinatal mortality relative to White's classes in two periods. 1,332 infants

White's class*	1946-1965 Perinatal mortality %	1966-1972 Perinatal mortality %
A	5.0	5.4
B	16.2	6.8
C	23.5	8.5
D	19.8	15.4
F	44.2	18.5

* The number of infants is given in table 2.

TABLE 4

Incidence of infants congenital malformation according to White's classification

	A	B	C	D + F
Total number of women	116	281	173	131
Infants with congenital malformations (%)	2 (1·7)	23 (8·2)	18 (10·4)	14 (10·7)
Infants with fatal malformations (%)	0 (0)	9 (3·2)	9 (5·2)	8 (6·1)

Hare and White have reviewed the Joslin Clinic experience for diabetic pregnancies in 1975 (Table 5) (9). In 72 pregnancies of more than 20 weeks gestation the overall perinatal survival rate was 94.4%. Most of the problems occurred in the more severe diabetic pregnancies. This same study also reported their results of pregnancies in diabetic women who had vascular disease (Class R, F, RF, E. H. and T.) They divided the data from the total of 416 (Table 6) into the time period from 1924 to 1962 (271 cases) and from 1963 to 1975 (145 cases). In both groups, maternal survival in pregnancies complicated by diabetes is practically assured except in those women with atherosclerotic heart disease. Three of the four diabetic women in Class H died during the course of pregnancy and/or delivery. One woman died undelivered, two died within the four week period after delivery. The only maternal survivor in this group was a patient who had coronary artery bypass surgery performed three months prior to her pregnancy. Two of the three children survived their mothers. In other diabetic pregnancies viable fetal survival in their series now approches that of women without diabetes delivery in the same hospital, but not if vascular disease is present despite improvement in care. The other vascular complications of diabetes seem unaffected by pregnancy. For example, there appears to be no progression of diabetic retinopathy during the course of pregnancy (10).

TABLE 5

Joslin diabetic pregnancies, 1975
perinatal survival rate: 94.4 per cent

N	Class	Fetal distress	Neonatal serious	Morbidity mild
6	A	0	0	1
10	B	2	1	5
33	C	4	2	21
17	D	5	2	12
5	F	2	3	1

71 Reaching 20 weeks' gestation
Spontaneous abortion rate: 15%

TABLE 6

Viable fetal survival—vascular series 416 cases

Class	1924-1962 No.	Survival (%)	1963-1975 No.	Survival (%)
R	34	74	48	84
F	126	65	59	72
RF	53	54	30	81
E	58	76	4	100
H	0	—	4	75
T	0	—	(1 previable)	—
Total	271		145	

Pederson et al (7), have slightly refined the prognostic capablities of the White Classification by adding what they refer to as a PBSP (Prognostically Bad Signs in Pregnancy) classification. This classification relates prognosis to factors that become evident only during the pregnancy. The factors which indicate a poor prognosis include:

(1) Clinical pyelonephritis: urinary tract infection with an acute elevations of temperature exceeding 39°C, confirmed by urine culture

(2) Precoma: Diabetic acidosis with a venous plasma bicarbonate level below 10 meq/L

(3) Severe acidosis: Venous plasma bicarbonate levels between 10-17 meq/L

(4) Severe toxemia: Two of the following three signs must be present.

   a) P.B. $\geq$ 150/100 for at least 5 days before delivery.
   b) More than 0.1% albuminuria for at least 24 hours before delivery
   c) Severe edema or weight gain $\geq$ 20 kg.

5. Mild toxemia: Two of the following three signs present

   a) B.P. 140/90 for at least three days before delivery
   b) More than 0.05% albuminuria for at least 24 hours before delivery
   c) Moderate edema or weight gain $\geq$ 15 kg.

6. Neglect: Failure to follow the recommended regimen, irrespective of the cause, e.g., "psychopathy" low intelligence, first attendance late in pregnancy (at delivery), poor social circumstances and lack of proper information.

Table 7 (7) shows the perinatal mortality combining both the White and PBSP classification. As can be seen when the PBSP are present there is a marked increase in perinatal mortality at each White classification.

TABLE 7

PBSP and White's classifications combined. 920 infants (1959-1972)

White's class	PBSP present				PBSP absent			
	No. of cases	Perinatal mortality No.	%		No. of cases	Perinatal mortality No.	%	
A	35	5	14.3	17.1	132	4	3.0	3.4
B	47	9	19.1		132	5	3.8	
C	68	20	29.4	26.7	155	14	9.0	9.8
D	119	30	25.2		171	18	10.5	
F	48	18		37.5	13	4		30.8
Total	317	82	25.9		603	45	7.5	

Fuel Homeostasis in Pregnancy

In order to discuss the metabolism of fuels during pregnancy it is appropriate to look at this from two points of view. That is we must discuss in metabolism of pregnancy in both the basal (fasted state) and fed state. A summary of maternal-fetal fuel and hormone exchange is seen in Figure 1 (11). Maintenance of glucose homeostasis in the fasted, post absorptive state in the non-pregnant condition depends upon a balance between the utilization and production of glucose. This control as suggested by Unger (12) is bihormonal in nature, i.e., insulin, the beta cell hormone controls the rate of glucose utilization by its effects on insulin sensitive tissues such as fat, liver, and muscle, while glucagon, the hormone of the alpha cell regulates glucose production through its glycogenolytic and gluconeogenic actions on the liver. During pregnancy there is a continous loss of glucose and amino acids from the maternal to fetal circulation. It is thought that the fuel requirements of the developing fetus are met almost entirely by the consumption of glucose (13). Thus, glucose is needed both to provide energy for protein synthesis and also constitutes the precursor for the synthesis of fat for the formation of glycogen. The overall level of glucose utilization as determined by measurements in the fetal man (14) and the lamb (15) is about 20 mg/minute at term (16), which is in considerable excess than the 2-3 mg/kg/minute in adult men. Glucose moves easily from the maternal to the fetal circulation. The fetal plasma glucose concentration is generally 10 to 20 mg/dl less than what is in the maternal circulation. Since, the rate of glucose exchange from maternal to fetal circulation is greater than can be explained on the basis of simple diffusion, the process of glucose transfer has been described as one of "facilitated diffusion".

MATERNAL-FETAL FUEL AND HORMONE EXCHANGE

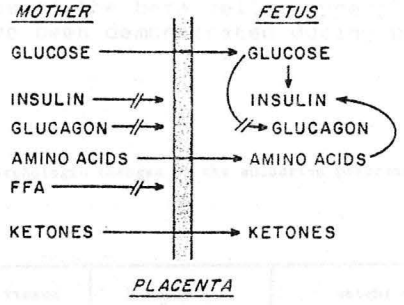


Figure 1 : Maternal-fetal fuel and hormone exchange. Glucose, amino acids and ketones are transferred from mother to fetus while insulin, glucagon, and free fatty acids (FFA) are not. Glucose in the fetal circulation stimulates secretion of insulin and inhibits secretion of glucagon by fetal islet cells. Amino acids are also potent stimuli of fetal insulin secretion.

Because, maternal insulin fails to traverse the placenta (17), fetal glucose metabolism is independent of maternal insulin availability, but fetal insulin is thought to play a central role in the development of the consceptus (16) being present and responds approximating to glucose by 12 weeks of gestation (18) (19).

In addition to the transfer of glucose, amino acids are actively transported by the placenta from the maternal to the fetal circulation resulting in maternal hypoaminoacidemia (20). Since amino acids espe-

cially alanine are key precursors in the basal state for gluconeogenesis by the maternal liver the pregnancy results in a drain of glucose as well as, glucose precursor from the mother.

Because of these changes in the maternal circulation the metabolic profile of the mother in the fasted state is characterized by hypoglycemia, hyperketonuria and hypoaminoacidemia. Ketones probably transverse the placenta and can be used by the fetus for fuel in brain tissue. The maternal hyperketonuria probably is the result of the hypoglycemia which in turn results in lower plasma insulin levels. The fall in plasma insulin levels stimulates lipolysis providing substrate for ketone synthesis.

Glucagon does not cross the placenta in either the maternal to fetal or fetal to maternal direction. And, although maternal and neonatal alpha cells respond to various stimuli fetal alpha cells do not (21).

In the nonpregnant individual, the response to ingested nutrients such as a mixed meal results in an increase in both insulin and glucagon levels. This increase in insulin levels results in uptake of the glucose in the diet into a variety of tissues. The most important of these tissues are the liver where glucose may be stored as glycogen or converted to fatty acids and triglycerides.

In the pregnant woman the metabolic response to feeding is characterized by hyperinsulinemia, hyperglycemia, hypertriglyceridemia, and insulin resistance (22). This hyperinsulinemic effect is most marked in the first trimester of pregnancy and can be seen in response to either glucose or amino acids (23). The hyperinsulinemia occurs even when plasma glucose levels are no higher than in nonpregnant controls (22). Thus a change in the responsiveness of the islets rather than an alteration in the circulating signal appears to be the responsible factor for the hyperinsulinemia of pregnancy. In keeping with this hyperresponsiveness of the beta cells, hyperplasia and hypertrophy of the beta cells have been demonstrated during pregnancy in rodents (24) (Table 8).

TABLE 8

: Morphologic changes of the endocrine pancreas in pregnant rats (mean $\pm$ S.D.)

Group	Endocrine tissue %	B cells %	weight of pancreas mg	weight animals g
non-pregnant	0.88 $\pm$ 0.32	70.8 $\pm$ 2.7	411.7 $\pm$ 37.3	166.3 $\pm$ 10.3
pregnant	2.20 $\pm$ 0.55	82.1 $\pm$ 3.3	432.7 $\pm$ 43.2	201.5 $\pm$ 31.1
P	$<$ 0.001	$<$ 0.001	N.S.	$<$ 0.005

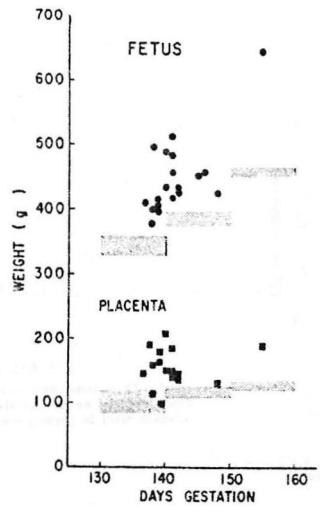
The presence of insulin resistance during pregnancy is reflected by higher blood glucose response to either oral or intravenous glucose than in the nonpregnant state despite the presence of hyperinsulinemia. The diminished responsiveness to intravenously administered insulin suggest peripheral insulin resistance as well.

There are several factors which seem to be responsible for the "diabetogenic" effects of pregnancy, which often results in the unmasking of diabetes in pregnancy (gestational diabetes). These include human placental lactogen (HPL) progesterone and estrogen all of which are secreted by the placenta. Glucagon physiology appears to be normal in pregnancy (22, 25).

Pathophysiology of Fetal Abnormalities in Diabetes Mellitus

It seems clear that many of the fetal abnormalities that occur in the diabetic pregnancy result from fetal hyperglycemia and subsequent fetal hyperinsulinemia. Since glucose freely passes from the maternal to fetal side of the placenta, maternal hyperglycemia results in fetal hyperglycemia and subsequent fetal hyperinsulinemia. Mintz et al, in elegant experiments (26) studied fetal and maternal glucose and insulin responses to the intravascular administration of glucose or amino acid in subhuman primate pregnancies in which diabetes had been induced in the mother by the administration of streptozotocin.

Fetal and neonatal baseline insulin levels were significantly elevated compared to those of controls. The administration of intravascular glucose to the fetus, mother or neonate was associated with a prompt two to five fold rise in fetal or neonatal plasma insulin concentrations. The intravenous infusion of a relatively low concentration of mixed amino acids to the conceptii from the streptozotocin-treated pregnancies was also associated with an elevation in fetal and neonatal plasma insulin levels, whereas normal monkey fetuses and neonates required a 10-fold greater concentration of amino acids in the infusate for a similar response. Furthermore, in this study both the neonates and the placentas of the streptozotocin-treated pregnant animals were significantly heavier than average for the period of gestation (Figure 2), polyhydramnios was consistently present and there was an increase in the incidence of third trimester stillbirths. Thus, studies in the pregnant streptozotocin-induced diabetic subhuman primate seems to be a good model in which to study diabetic pregnancy. Maternal hyperglycemia results in fetal hyperglycemia and fetal hyperinsulinemia. This metabolic milieu results in increased perinatal mortality.



The fetal-neonatal and placental weights of the streptozotocin-treated pregnancies (●, ■) compared to the reported means ±2 SEM (stippled areas) of 473 fetus-neonates and 131 placentas delivered from normal rhesus pregnancies (20-24).

Figure 2

Similar findings have been noted in man. Obenshani et al, showed a clear relationship between maternal hyperglycemia and fetal hyperinsulinemia (19). Another important fact in attempting to understand the pathophysiology of fetal abnormalities in diabetic pregnancies is that fetal macrosomia (excessive fetal size for gestation age), which is common in Class A - C diabetics, is the result, not of edema, but is primarily a consequence of increased deposition of fat and glycogen. Table 9 shows the increased skin fold thickness (an indicator of body fat) in infants of diabetic mothers as compared to those from nondiabetic pregnancies. Whitelaw (28) has provided strong evidence that it is the fetal hyperglycemia and hyperinsulinism which contributes to increased triglyceride synthesis in fetal adipose cells and increased deposition of subcutaneous fat. He showed close correlation between maternal fasting blood glucose and mean blood-glucose levels with neonatal skin fold thickness. The fattest babies had the largest adipose tissue cells and there was significant positive correlation between maternal blood-glucose levels and neonatal cell diameter (Figure 3 and 4).

TABLE 9

SKIN FOLD MEASUREMENTS IN NEWBORN INFANTS OF DIABETIC MOTHERS (Diab. inf.) AND NEWBORN INFANTS OF NORMAL MOTHERS (Norm. inf.)

	Diab. inf.	Norm. inf.
Number of infants	12	25
Gestational age (days)	258	275
Body weight (g)	3420	3300
Body length (cm)	51	52
Skin fold thickness (mm)	6.3	4.4
Skin fold thickness (range)	4.8-8.5	3.1-6.5

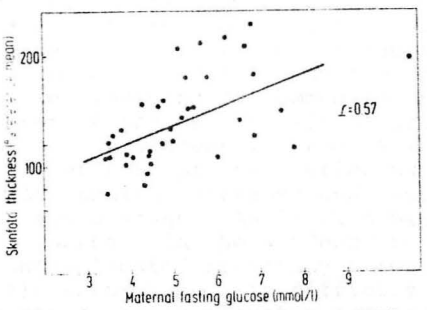


Fig. 3—Sum of skinfold thickness at eight sites in 37 infants expressed as a percentage of reference mean for gestational age, plotted against fasting blood-glucose of their diabetic mothers.

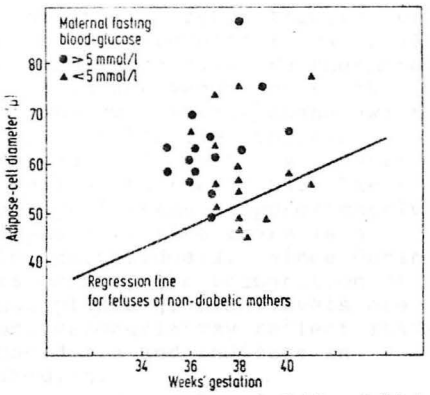


Fig.4—Mean adipose-cell diameter in 31 infants of diabetic mothers.

Hyperinsulinism may also contribute to the frequent appearance of the respiratory distress syndrome in the infant of the diabetic mother. Pulmonary maturation in the fetus is largely dependent upon the ability of the fetal lung to synthesize surfactant. The synthesis of lecithin is dependent in part to an elevation of fetal glucocorticoid secretion which occurs late in gestation (28). Insulin has recently been shown to be an antagonist of cortisol in induced synthesis of fetal lung cells (29).

The Effect of Pregnancy on the Diabetes

The course of diabetes in pregnancy is quite variable and depends in large part upon whether or not one is dealing with early or late pregnancy. A schematic drawing of the course of diabetes in pregnancy is presented in Figure 5 (30).

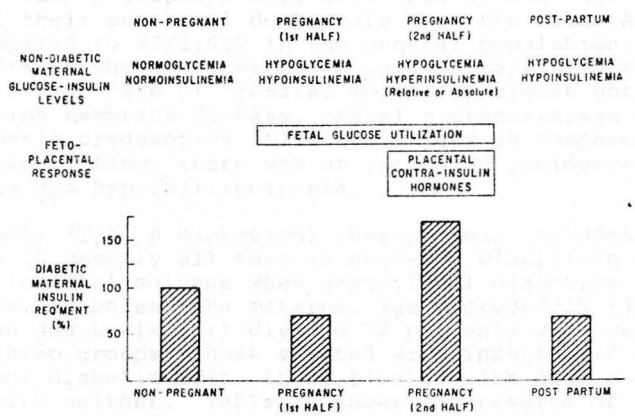


Figure 5

Influence of pregnancy on glucose and insulin levels in nondiabetic subjects and on insulin requirements in diabetic subjects. The prepregnancy insulin dose is shown as 100 per cent. The insulin requirement generally declines in the first half of the pregnancy and in the puerperium and is increased in the second half of pregnancy. (*From* Tyson, J. E., and Felig, P.: Med. Clin. N. Amer., 55:947-959, 1971.)

During the first half of pregnancy the major influence on maternal carbohydrate homeostasis results in the maternal to fetus transfer of glucose. This loss of glucose to the fetus often results in maternal hypoglycemia and requires a reduction of insulin dosage. Furthermore, this is complicated often by decreased food intake secondary to the nausea and vomiting so common in early pregnancy. Things change with the onset of the second half of pregnancy, when the diabetogenic action of the placental hormones (HPL, Estrogen, Progesterone) overcome the effects of the continuing glucose loss to the fetus. The need for insulin increases and insulin dosage increases approximately 67% on the average. As insulin becomes less effective there is a marked increase in the tendency to develop ketoacidosis. Since during even uncomplicated pregnancy ketonuria is common, the recognition of diabetic ketoacidosis is difficult because plasma glucose levels are often not markedly elevated. In addition, ketonuria may reflect starvation ketosis rather than diabetic ketoacidosis and indicate an increased need for glucose rather than insulin.

Postpartum, the rapid fall in the levels of HPL, estrogen and progeterone results in a reduction in maternal insulin requirements often to levels below the prepregnant course. It is not unusual for some women to undergo a remarkable postpartum remission which can last up to six weeks.

Management

In the Class A Diabetic

For those patients who have normal fasting plasma glucose values but have abnormal glucose tolerance tests during pregnancy, most recent studies show that this pregnancy is not associated with a perinatal mortality any greater than that of the general population (31, 32), provided that fasting hyperglycemia does not develop. Exceptions to this include women who have had a previous stillbirth, who develop preeclampsia during pregnancy, or those who require insulin during a prior pregnancy. For example, during the period from 1970 to 1972, 261 women with Class A diabetes were delivered at Los Angeles County Womens Hospital their perinatal death rate from the Class A group was 19/1,000 as compared to 32/1,000 in the general population. However, in those patients in whom the gestation was not permitted to go to term there was a high rate of neonatal mortality almost entirely related to hyaline membrane disease. Fetal macrosomia was more common in Class A diabetic pregnancies followed to term as compared to the general population. Also, there was an increased incidence of neonatal hypoglycemia and hyperbilirubinemia.

For these patients (Type A Diabetics) therapy that includes strict dietary control is usually all that is needed. O'Sullivan et al noted no improvement in fetal salvage when gestational diabetics were treated with insulin unless the maternal age exceeded 25 (33). However, Coustan and Lewis (34) divided 72 patients with gestational diabetes into three groups: those treated with insulin (20 u NPH and 10 u Regular) and diabetic diet, those treated with diet alone, and those treated with neither. Table 10 shows the results of the study of the 27 patients treated with insulin and diet alone two (7%) had

babies weighing more than 8½ lbs. Of the 11 patients treated with diet alone four (36.4%) had babies weighing more 8½ lbs and of the 34 patients treated with neither diet nor insulin 17 (50%) had babies weighing more than 8½ lbs. This effect of insulin on fetal size was independent of maternal age. However, this study is difficult to evaluate as they never separated those patients with gestational diabetes into those with or without fasting hyperglycemia.

TABLE 10

INCIDENCE OF MACROSOMIA AMONG 72 BABIES IN STUDY

	Control *N = 34* (%)	*Insulin* *N = 27* (%)	*Diet* *N = 11* (%)
Babies > 8½ pounds	17 (50)	2 (7)*	4 (36.4)
Average weight (kg)	3.625 ± 0.990	3.281 ± 0.600	3.418 ± 0.624
Average weight (lb/oz)	7/15½	7/3½	7/8½
Maternal age ≥ 25 birthweight above 8½ pounds	17 7 (41.2)	15 1 (6.7)‡	2 1 (50)
Maternal age < 25 birthweight above 8½ pounds	17 10 (58.8)	12 1 (8.3)§	9 3 (33)
Babies with corrected weight > 75% percentile	16 (47.1)	3 (11.1)¶	3 (27.2)

* = $P < 0.005$ from control group
† = $P < 0.025$ from diet group
‡ = $P < 0.05$ from control and diet groups
§ = $P < 0.05$ from control group
= Tables published by Tanner and Thomson (1976) correcting weight for sex, gestational age, maternal height, maternal weight, and parity
¶ = $P < 0.01$ from control group

Class A diabetics may be safely followed to term, If they are undelivered at this time fetal surveillance may be indicated. Each fetus must be evaluated individually for macrosomia and delivery by cesarean section should be considered when the estimated fetal weight is near 4000 - 4500 grams.

In summary, the Class A diabetic probably requires no treatment except diet and provided that she does not develop fasting hyperglycemia she is at a low risk for a sudden intrauterine death. Thus, she should be allowed to go into labor spontaneously. Early delivery in these patients is associated with a high incidence of neonatal death related to hyaline membrane disease. However, fetal macrosomia will be more common at term in these patients so delivery by cesarean section should be considered when the fetal size exceed 4000 gms. Neonatal hypoglycemia and/or hyperbilirubinemia should be anticipated.

Management of Classes B-R Diabetes

There seems to be little question that reasonable metabolic control in these patients is necessary to achieve a successful outcome of the pregnancy. However, there seems to be some disagreement between those in the field, about the importance of instituting the most rigid type of diabetic control with diet and insulin therapy in order to reduce the incidence of perinatal mortality in gravid women with Class B-R diabetes mellitus. Karlsson and Kjellmer (35) were the first investigators to report a relationship between the degree of maternal diabe-

tic regulation and the eventual outcome of the pregnancy in regard to the perinatal mortality. Their study was based on 167 hospitalized pregnant diabeteics followed at the Obstetric Clinic Sahlgren's Hospital from 1961 to 1970. All patients were hospitalized during the final weeks of pregnancy and all had whole blood glucose measurements done three times daily. In those women whose average blood glucose levels were below 100 mg/dl (equivalent to 115, mg/dl plasma) the perinatal mortality was 3.8%. When the mean blood glucose level was between 100-150 mg/dl the perinatal mortality increased to 16% and when the mean blood glucose level exceeded 150 mg/dl perinatal mortality increased to 24%. They also reported a much lower incidence of congenital malformation and neonatal morbidity (hypoglycemia, hyperbilirubinemia, and RDS) in those pregnancies in which the average blood glucose level was less than 100 mg/dl (Table 11). Other investigators as well, have suggested that the degree of maternal diabetic control was an important determinent of perinatal mortality, i.e., the better the maternal diabetic control the lower the rate of perinatal mortality and morbidity. (36, 37, 38, 39, 40). However, in a recent study Soler et al (32), were unable to show any difference in any neonatal problems when his women were divided in groups with mean blood glucose values less than or greater than 110 mg/dl (Table 12).

TABLE 11

Perinatal deaths, neonatal morbidity, and malformations in relation to maternal blood glucose values

		< 100 mg./100 ml.	100-150 mg./100 ml.	> 150 mg./100 ml.
Perinatal deaths	1961-65	1/12	5/36	7/28
	1966-70	1/40	7/41	2/10
	Totals	2/52 (3.8%)	12/77 (16%)	9/38 (24%)
Hypoglycemia*	1961-65	1/12	1/36	3/28
	1966-70	5/40	7/41	1/10
	Totals	6/52 (12%)	8/77 (10%)	4/38 (11%)
Jaundice†	1961-65	0/12	5/36	3/28
	1966-70	0/40	1/41	0/10
	Totals	0/52 (0%)	6/77 (8%)	3/38 (8%)
Respiratory distress‡	1961-65	2/12	10/36	7/28
	1966-70	7/40	14/41	2/10
	Totals	9/52 (17%)	24/77 (31%)	9/38 (24%)
Malformation§	1961-65	0/12	8/36	2/28
	1966-70	2/40	4/41	3/10
	Totals	2/52 (3.8%)	12/77 (16%)	5/38 (13%)

*Includes infants with recorded blood glucose values at or below 20 mg. per 100 ml. Only three infants had obvious clinical signs of hypoglycemia.

†Includes severe jaudice that required exchange transfusion. Corresponds to bilirubin levels above 25 mg. per 109 ml. of serum in 6 cases and 20 to 25 mg. per 100 ml. in the remaining 3 babies, who were all born 4 week or more before term.

‡Includes both idiopathic respiratory distress (hyaline membrane disease) and severe aspiration.

§Includes both perinatally dead infants and those surviving the neonatal period.

TABLE 12

Neonatal morbidity in relation to mean maternal blood glucose during the third trimester

Mean maternal blood glucose (mg./dl.)	No. (%) of infants with individual neonatal problems				
	Major congenital malformations	Respiratory distress syndrome	Hypoglycemia	Hypocalcemia	Hyperbilirubinemia
<110 n = 49	6 (12)	2 (4)	10 (20)	3 (6)	7 (14)
>110 n = 51	3 (6)	7 (14)	9 (18)	5 (10)	12 (24)

In another study Persson (41), suggested that, while attention to the maternal level of control was important, the final answer on how rigid the control should be was not in. Further complicating this issue is the fact that in the study by Kitzmiller, et al (40) even though they reported excellent results with regard to perinatal mortality, the degree of maternal glucose control was suggested by the Scandinavian study (35) was not achieved in all women. The same is true of another large series reported by Gabbe, et al (43).

Because of the importance of this issue, the question of the relationship between maternal diabetic control and perinatal outcome has recently been evaluated by Dr. Peggy Whalley and her colleagues, here at Southwestern Medical School and Parkland Hospital (43). The basis for their study were 120 overtly diabetic women hospitalized on a High Risk Pregnancy Ward at Parkland. Patients (White's classification B-F) were initially hospitalized following their initial referral at which time the severity of the diabetes was assessed and to provide education to the patient regarding the importance of dietary management (which was an ADA diabetic diet providing 30 to 35 calories per kg of actual body weight) and insulin therapy during the pregnancy. All patients were begn on a suitable diet and insulin treatment program prior to discharge. After the initial hospitalization all were followed at weekly intervals in the outpatient department. Patients were routinely hospitalized at 32-34 weeks gestation for the remainder of the pregnancy unless complications prompted earlier admission. The purpose of this final hospitalization was to achieve optimal diabetic control while closely watching the progress of the pregnancy. Plasma glucose was measured at least four times per day at least one a week (more often if needed) and intermediate and short-acting insulin were administered as single or split doses as need to achieve the goal of therapy which was a fasting plasma glucose value of less than 115 mg/dl with comparable preprandial values.

The patients were closely monitored and these clinical finding were regarded as evidence of fetal jeopardy and prompted consideration for delivery irrespective of the gestational age:

1) development of pregnancy-induced hypertension
2) decreased fetal growth
3) polyhydrominos
4) decrease in fetal movements
5) sudden decrease in insulin requirements

In the absence of these features the pregnancy was allowed to progress to 37 weeks. Delivery was effected when the L/S ratio was 2:1 or greater. A pediatrician was always in attendance at delivery and the infant was closely observed in the neonatal ICU.

Table 13 shows the results of neonatal outcome in relation to maternal mean plasma glucose levels (mean of plasma glucose levels done during the final hospitalization) (43). As can be seen, there was no relationship between the level of maternal diabetic control and fetal perinatal mortality. Although in the groups with poorer diabetic control there were more perinatal deaths, these differences were not statistically significant. This point deserves comment. This is in reality a fairly small series. Enlargement of the total series might result in statistically significant differences between the groups not apparent with this size series. Table 14 shows the relationship of neonatal morbidity in relationship to maternal diabetic control (43). Although more than half of the neonates experienced some morbidity there was no relationship between the presence or absence of morbidity and the level of maternal control. Those women whose mean preprandial glucose values exceeded 172 mg/dl required earlier intervention for signs of fetal jeopardy. Dr. Whalley and her colleagues concluded that maternal hyperglycemia exceeding plasma glucose levels of 172 mg/dl is to be avoided but that mean plasma glucose levels of less than 115 mg/dl is unnecessary for a successful perinatal outcome.

TABLE 13

PERINATAL DEATHS IN RELATION TO MATERNAL GLUCOSE CONTROL

Mean Preprandial Glucose mg/dl	Total Pregnancies	Total Perinatal Deaths
Group I ‹ 115	18*	None
Group II 115-172	79	2
Group III › 172	24	3

*includes one set of twins

TABLE 14

DURATION OF PREGNANCY AND INDICATIONS FOR DELIVERY IN RELATION TO MATERNAL GLUCOSE CONTROL

	MEAN PREPRANDIAL GLUCOSE (mg/dl)		
	GROUP I < 115	GROUP II 115-172	GROUP III > 172
Mean Gestational Age at Delivery (Weeks ± S.E.M.)	36.8 ± 0.4	36.7 ± 0.1	35 ± 0.4[a]
Pregnancy-Induced Hypertension	4/17 (23%)	11/79 (14%)	14/24 (58%)[b]
Polyhydramnios	0/17 —	12/79 (15%)	5/24 (21%)
Decreased Fetal Movement	2/17 (12%)	8/79 (10%)	7/24 (29%)
Decreased Insulin Requirement	1/17 (6%)	9/79 (11%)	6/24 (25%)
Suspected Fetal Growth Retardation	2/17 (12%)	7/79 (9%)	5/24 (21%)

[a] Significantly shorter gestation when compared to either Group I or Group II ($p < .001$)

[b] $p < .05$

Insulin treatment in the pregnant diabetic is no different than of the non gravid diabetic in that rigid diabetic control must be pursued with extreme care upon the background that hypoglycemia is potentially life threatening and should be avoided at all costs. Recent studies in nondiabetic populations suggests that maternal hypoglycemia is associated with an increase in fetal mortality (44), and cerebral palsy and seizure disorders occurs two to three times more frequently in children of diabetic mothers (45). This may be related to maternal hypoglycemia (46).

Thus, while I feel that the best diabetic control possible should be the final goal, as I will mention shortly, this type of control using the present modalities of treatment is difficult to achieve. Since the risk of hypoglycemia is a real hazard, I think that a more moderate policy, such as that followed by our OB/Gyn Department, should be followed with regard to treatment of the Class B-T diabetic. Diet therapy should be insituted in all patients. It should consist of 30 cal/kg actual body weight divided between three meals and at least a bedtime snack. When necessary, additional midmorning and midafternoon snacks should be added. Carbohydrates should provide approximately 50% of the total calories with the remainder of the calories divided between protein and fat. As in the nongravid diabetic, the carbohydrates in the diet should mainly be in the form of complex starches rather than concentrated sweets. Although insulin regimines must be individualized usually two daily injections of a mixture of intermediate acting insulin (NPH or Lente) and regular insulin are required. The ultimate goal of diabetic control is to keep the urine free of glucose, and to have fasting plasma glucose

values below 115 mg/dl whenever possible. Mean preprandial plasma glucose levels should average less than 172 mg/dl (43). However, this goal should not be achieved at the expense of frequent and severe episodes of hypoglycemia. Measurement of glycosalated hemoglobin has recently been used to monitor diabetic control during the course of pregnancy and has proven to be a good predictor of both maternal glucose control and of birth weight. (47, 48).

For reasons that are not entirely clear to me, diabetic regulation in the gravid diabetic is somewhat more simply accomplished than has been the experience in the non-gravid diabetic (49). However, while many of those who report beneficial effects on perinatal mortality from rigid diabetic control most really do not achieve this goal in most of their patients. Most of their experience is similar to Dr. Whalley's in that only a relatively few patients (14% in Dr. Whalley's series) (43) was this really accomplished. However, treatment of the pregnant diabetic is not all that different from treatment of the nongravid diabetic (49), that is, rigid diabetic control is very difficult even while the patient is hospitalized.

In many centers, in order to carefully monitor the progress of the pregnancy and to attempt to achieve an optimal level of diabetic control, even the uncomplicated pregnant diabetics are hospitalized for varying periods of time during the last trimester of pregnancy. In any case, all diabetics should be admitted to the hospital at least one week prior to the anticipated date of delivery. Once hospitalized the patients should be carefully monitored and the diabetic control managed according to the principles outlined above. Some institutions have gone so far as to use a "closed loop" insulin delivery system (Biostator) during the third trimester of pregnancy to determine the patients' daily insulin requirement so as to make optimal diabetic control easier to achieve (50).

Delivery

Diabetic management on the day of delivery also results in special problems because of the rapid fall in insulin requirements that occurs with delivery (the result of a fall in concentration of the diabetogenic placental hormones). Several methods have been suggested, the most common one being to fast the patient, and to give a reduced dose of insulin in the morning of the day of delivery, and begin a glucose infusion. Soler and Malins (51) use the following protocol. The patients are fasted and infused with 10 g of glucose per hour throughout labor and after delivery until normal eating is resummed. They give a fixed dose of intermediate acting insulin (NPH 24 units) at 0800. They find this dose suitable for women whose insulin requirements during pregnancy ranged from 60 to 250 units/day. This protocol is effective for women whose delivery was induced or for those having cesarean section. West and Lowy (52) carried 14 diabetic patients through labor and delivery using a combined glucose (approximately 10 g/h) and insulin infusion (1-2 U/h). Others have used a "closed loop" insulin infusion system to control glucose levels during labor and delivery (53).

The major challenge in the management of the pregnant diabetic is the timing of the delivery. It has long been known that the risk of intrauterine fetal death in the diabetic pregnancy increases if the pregnancy is delayed beyond 36 weeks (55). However, the incidence of respiratory distress syndrome (RDS) is greater the more premature the fetus. Herein, lies the dilemma faced by the obstetrician. He (she) is faced with the problem of detecting fetal jeopardy which could lead to intrauterine death should delivery be delayed while assessing fetal maturity to avoid neonatal deaths due to RDS if delivery is premature.

TABLE 15

METHODS OF ASSESSMENT

1. Ultrasound determination of biparietal diameters
2. L/S (lecithin/sphingomyelin) ratio in amniotic fluid
3. Urinary estriol measurement
4. Oxytocin challenge test (OCT)

Table 15 shows the methods of fetal assessment which are helpful in resolving this dilemma (55). Fetal growth is determined by ultrasound determination of biparietal diameters. Vaginal delivery is to be avoided in the case of fetal macrosomia and cesarean section considered when fetal size is in excess of 4000 gms. The maturity of the fetal lung is determined by measurement of the L/S (lecithin/sphingomyelin) ratio in amniotic fluid. The increase in this ratio to 2.0 which occurs at 35 weeks in nondiabetics, is often delayed in diabetics in Classes A - C. A L/S ratio greater than 2.0 is rarely associated with RDS in the neonate regardless of gestational age, except in diabetic pregnancies where a ratio exceeding 2.0 can be associated with RDS in the infant (56). For this reason some workers suggest that measurement of the amniotic fluid phospholipid levels also be performed in an attempt to identify those patients in whom fetal RDS may occur despite mature L/S ratios. Amniotic fluid phospholipids were found to be absent in 5 of 6 infants of diabetic mothers who had RDS despite having L/S ratios greater than 2.0 (57).

Fetal jeopardy is evaluated by measurement of urinary estriol excretion (biweekly determinations at over 32 to 35 and daily beyond 35 weeks). A fall in urinary estriol excretion of 50% indicates fetal jeopardy. The oxytocin challenge test (58) which measures the response of the fetal heart rate to an oxytocin infusion is done weekly after 32 weeks of gestation or as necessary if there has been a 50% fall in the urinary excretion of estriol.

Individual management of each pregnancy is necessary. The diabetic with Class B-T diabetic should be delivered as close to 38 weeks as possible if fetal pulmonary maturity has been established. If estriol determination (50% fall) or a positive OCT indicates fetal deterioration and the L/S ratio was in excess of 2.0, then immediate induction or cesarean section should be performed. Cesearan section should only be done for the usual obstetric indication.

The Infant of the Diabetic Mother

Once the gravid diabetic is delivered of a viable infant the burden of reponsibility quickly shifts from the obstetrician to the pediatrician. It is interesting to remember that the infant of the diabetic mother is already abnormal at birth, the result of forces extended by maternal diabetes and often medical manipulation. As discussed above, there have been tremendous advances in the outcome of diabetic pregnancies. And, although perinatal loss is much less than it once was, there are particular problems that relate to the IDM.

Congenital malformation have emerged as the most important cause of perinatal mortality the risk of such occurance is about three or four times higher than the risk in an infant of a nondiabetic mother. Table 16 shows the types of congenital abnormalities in a series of 100 consecutive diabetic pregnancies reported by Soler and Malins (32). This represented a 9% incidence.

TABLE 16

Congenital malformations

Fatal major malformations	
(B) Ellis van Crevald syndrome	
(C) Renal agenesis	
(C) Cor triloculare	
(D) Hydrocephalus and coarctation of aorta	
Nonfatal malformations	
Major	Minor
(C) Imperforate anus	(A) Cystic hemangioma face
(C) Atrial septal defect	(B) Midline defect superior alveolar margin
(C) Meningomyelocele	(C) Bifid thumb
(F) Ventricular septal defect	(D) Hypospadias
(F) Cleft palate	

White class is shown in parentheses.

Other problems which are confronted by the IDM include macrosomia which can often result in trauma to both infant and mother during vaginal deliery. As mentioned above the increase in fetal size is due to a fat accumulation. In fact, Farquhar (59) has described the IDM as a "cherubic" overweight infant which is easily picked out in the nursery. Other problems encountered by the pediatrician in the IDM are listed in Table 17. All require the immediate attention of the pediatrician.

TABLE 17

CLINICAL FEATURES OF IDM

1) Congenital Malformation
2) Macrosommia
3) Repiratory Distress Syndrome
4) Hypoglycemia
5) Hypocalcemia
6) Hyperbilirubinemia

With the marked improvement in obstetrical care in the past years and the progressive fall in perinatal mortality in diabetic pregnancies, it remains the challenge of those in the health care team to reduce or effectively treat these postnatal complication of diabetic pregnancies. They will continue to represent the largest part of the problem (60) facing those of us interested in diabetes and pregnancy.

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