Proper therapy in pregnancy complicated by diabetes mellitus affords the physician an opportunity that is unparalleled in immediate impact and over-all therapeutic dimension for his or her patient. The immediate survival of the mother can be virtually assured and that of the unborn child brought close to that of the child of the nondiabetic gravida. Further, the benefit of this care extends considerably beyond these traditional clinical targets. Such relatively remote events as intellectual and psychologic performance in offspring from these pregnancies may be jeopardized by inadequate attention to details of medical management during pregnancy. Lastly, an opportunity is presented to both physician and patient to beneficially influence future diabetes therapy. The intense motivation of the mother, together with her positive experiences, can be channeled to promote an enduring attitudinal and behavioral approach to future diabetes care.

This communication will present briefly the rationale underlying the therapeutic regimen that we currently use. Details regarding the medical management of both pregestational and gestational diabetes mellitus will be presented. There are, undoubtedly, some arbitrary features to our program, and we are properly moved to acknowledge that some are under continuing evaluation. References are cited that provide the interested reader both a broader basis for understanding current notions about therapy and further insights into the controversies that still remain.

PERINATAL MORTALITY

Perinatal survival reported from a number of centers continues to show steady improvement.1-5 The experiences at the Joslin Clinic,1 Royal Maternity Hospital in Copenhagen,2,3 and MacDonald House in Cleveland4 have recently been reviewed. Favorable outcomes can now be expected in greater than 90 per cent of all pregnancies complicated by diabetes mellitus. Moreover, the experiences at some centers demonstrate that further improvement in over-all survival rates can still be achieved.4,5

These experiences with respect to both therapeutic accomplishments and limitations are instructive models. Clear conclusions emerge. Patients with pregestational or gestational diabetes who enter pregnancy without clinically detectable vascular disease and who acquire no new complications during pregnancy (pyelonephritis, pregnancy-induced hypertension) can, as a group, achieve pregnancy outcomes no different from those of nondiabetic gravid patients. By contrast, pregestational insulin-dependent patients who enter pregnancy with established macrovascular and/or microvascular disease fare less well and may suffer perinatal losses of approximately 20 per cent, despite disciplined and enlightened approaches to therapy. However, if fatal fetal congenital malformations in this last group are excluded from consideration, their over-all fetal salvage rates would approach 95 per cent.6

These results highlight important issues for clinicians. One relates to whether our current level of knowledge and technical skills can be expected to result in further improvement, since no less than 40 per cent of the perinatal mortality presently encountered results from fatal fetal congenital malformations.6 Whether this fact represents an immutable constraint to further improvement in outcome is a clinical research hypothesis that requires further investigation. We believe, but do not know, that preconceptional and early pregnancy control of diabetes mellitus is a crucial factor determining this figure. It is within this time frame that the primary-care physician has a special responsibility. Effective care can be provided during the earliest stages of embryogenesis if planned pregnancies are encouraged only when diabetes mellitus is well controlled. It is a way to obviate a problem that is frequently caused by late identification or late referral of the pregnant patient with diabetes mellitus. In addition, it is particularly important in the first trimester that morning sickness and hyperemesis complicated by ketonuria and either hyperglycemia or hypoglycemia be rigorously avoided.

Further evaluation of these large series1-5 requires careful analyses of several other factors that, either alone or in combination, could contribute to the remarkable progress.
that was reported. Two factors do not easily lend themselves to quantitation—regionalization and improved perinatal care of all high-risk pregnancies. For example, the Copenhagen group has most recently reported a responsibility for over 100 pregnant patients with diabetes mellitus each year. The impact of this regional concentration of patients and the experience derived therefrom must be pervasive in development of subtle and sophisticated nuances characteristic of optimal clinical judgment. This opportunity cannot exist for most physicians who provide care for only an occasional patient in any single year.

What does lend itself to quantitation is the present knowledge of the association and importance of maternal hyperglycemia to perinatal outcome. The basis for this accomplishment is the axiom that normal blood glucose levels during pregnancy are substantially different from normal nonpregnant levels. The goals of therapy must therefore be defined by normal gestational standards, not by the usual nongravid indices.

**GESTATIONAL METABOLISM**

Dynamic alterations in the availability and distribution of energy substrates occur during pregnancy in order to meet the nutritional requirements of the growing fetus. These needs are served by an organized sequence of interrelated hormonal adaptations that insulate that glucose, the primary fuel of the fetus, is readily available. During early pregnancy, glucose is transferred across the placenta to the conceptus by a process of facilitated diffusion. Amino acids, by contrast, are actively transported by the placenta to the fetus. Of particular significance to the regulation of blood glucose levels is the gluconeogenic amino acid, alanine. In partial response to the active transport process, alanine levels in maternal plasma decrease. The effect of this new distribution of glucose and gluconeogenic substrate is relevant during the normal fasting state between dinner and breakfast. Normal basal whole-blood glucose concentrations are 55–65 mg per dl throughout pregnancy. These levels, in turn, define one therapeutic goal for treatment strategies in the pregnant patient with diabetes mellitus.

The decrease in the level of fasting blood glucose and gluconeogenic amino acids is associated in early pregnancy with an appropriate decrease in plasma insulin levels and normal levels of glucagon and growth hormone. Keto genesis is facilitated by these adaptations. For reasons to be developed subsequently, we wish to avoid any significant degree of ketonemia in the pregnant patient. We have found that to do so in patients with diabetes requires added carbohydrate calories in the form of at least a 25-gm. feeding before bedtime.

As pregnancy progresses, the placenta manufactures increasing amounts of the major contra insulin factor of pregnancy, human placental lactogen (hPL), also known as human chorionic somatomammotropin (hCS). As a result, the rate of disposal of either orally or intravenously administered glucose is slowed. The normal pancreatic beta cells adapt to this alteration by potentiated secretion of insulin in response to orally administered meals or glucose. To the extent that the functional reserve of the islet cell is adequate, tolerance to glucose remains within physiologic limits. To the extent that pancreatic functional reserve is exceeded, gestational diabetes mellitus will emerge.

The levels of hPL in the maternal circulation are a direct function of placent al size. It would be expected, therefore, that placent al hypertrophy, one reflection of poorly controlled diabetes, would be revealed by high maternal plasma levels of hPL. Alternatively, small placentas that accompany extensive uteroplacental vascular disease in long-standing pregestational diabetes would be indirectly revealed by a low level of maternal plasma hPL.

In addition to protecting a fetal claim on glucose by its contra insul in activity, hPL has a servoregulatory function as well. Throughout pregnancy, it is believed to directly or indirectly selectively suppress the maternal hypothalamic-hypophyseal growth-hormone-secretory mechanism. During the first trimester, estrogens inhibit this feedback system, and growth hormone secretion in response to stress, hypoglycemia, or arginine infusion is normal. Thereafter, as hPL levels continue to rise, maternal growth-hormone secretion in response to similar stimuli is completely inhibited.

**TABLE 1**

| Class | Description |
|-------|-------------|
| Class A | Glucose tolerance test abnormal. No symptoms. Euglycemia maintained with treatment by appropriate diet but without insulin. |
| Class B | Adult onset (age 20 or older) and short duration (less than 10 years). |
| Class C | Relatively young onset (age 1–19) or relatively long duration (10–19 years). |
| Class D | Very young onset (age less than 10) or very long duration (20 years or more) or evidence of minimal vascular disease (e.g., background retinopathy). |
| Class E | Pelvic vascular disease (determined by x-ray). |
| Class F | Renal disease. |
| Class G | Multiple failures in pregnancy. |
| Class H | Arteriosclerotic heart disease. |
| Class T | Pregnancy after renal transplantation. |
Following parturition and removal of the placenta, maternal plasma hPL levels rapidly disappear, but in both normal subjects and patients with diabetes, there is a delayed return of normal hypophyseal regulation of growth-hormone secretion.\textsuperscript{21}

The normal fetus has a relatively immature system for control of its own blood glucose levels.\textsuperscript{22} It is not in this respect a miniature adult. Thus, although present in the fetal

| TABLE 2 |
| --- |
| Prognostically bad signs during pregnancy (PBSP) |

1. **Clinical pyelonephritis**
   - Urinary tract infection (culture positive) with acute temperature elevation exceeding 39°C.

2. **Precoma or severe acidosis**
   - Precoma: diabetic acidosis with venous bicarbonate below 10 mEq./L.
   - Severe acidosis: venous bicarbonate 10–17 mEq./L.

3. **Pregnancy-induced hypertension**

4. **Neglecters**
   - Pregnant diabetic women who are in labor when first admitted or who are psychopathic or of low intelligence, or women in poor social circumstances who present themselves less than 60 days before term.

When maternal diabetes mellitus is not well regulated and hyperglycemia is present, the fetus will be exposed to either sustained or meal-related intermittent waves of hyperglycemia. By mechanisms that remain unresolved, the fetal pancreatic beta cell adapts to this setting by developing a linkage between its glucose sensors and the insulin-secretory mechanism.\textsuperscript{28} The result is prematurely induced and inappropriately sustained or intermittent fetal hyperinsulinemia that parallels the prevailing blood glucose level in the mother and fetus.\textsuperscript{23} As Pedersen predicted 25 years ago,\textsuperscript{29} many of the physical and morbidity complications experienced by infants of mothers with diabetes mellitus can be attributed to fetal hyperglycemia and hyperinsulinemia. Thus, fetal hyperinsulinemia can result in increased fetal body fat (macrosomia), accounting for the cherubic appearance of these infants at birth. Fetal hyperinsulinemia may also inhibit the pulmonary maturation processes required for surfactant production and contribute, by this mechanism, to the increased incidence of pulmonary distress syndrome experienced by these neonates.\textsuperscript{30} Moreover, a persistence of enhanced responsivity of the fetal beta cell into neonatal life also contributes to the propensity for the development of neonatal hypoglycemia once the fetus is removed from a constantly delivered maternal source of glucose.\textsuperscript{23,31,32}

Lastly, although macrosomia may complicate vaginal delivery due to dystocia, it does not by itself account for the precipitous death in utero that is occasionally seen. The mechanism underlying unexplained intrauterine death in patients with diabetes is still unknown. Whether this represents a complication of fetal hypoglycemia,\textsuperscript{33,34} a fatal fetal cardiac arrhythmia in response to altered myocardial metabolism (perhaps secondary to altered sensitivity of insulin receptors), a sudden change in fetal oxygenation and acid-base balance due to some acquired defect in the respiratory exchange function of the placenta, or entirely other causes also requires clinical research commitment.

A basic understanding of the alterations that occur during and following normal gestation permits a number of predictions with respect to the clinical course of diabetes mellitus in association with pregnancy:

1. For reasons that were discussed, normal gestation is associated with a distinct and reproducible pattern of alteration in glucose metabolism. Therefore, when assessing glucose tolerance by laboratory means, normal nongravid blood glucose criteria will be irrelevant during pregnancy, and different criteria predictably will be required. O'Sullivan has met this need by a monumental effort that established new criteria for glucose tolerance testing from data derived from thousands of nondiabetic pregnant women.\textsuperscript{35,36} Normal glucose tolerance limits were defined as a fasting whole-blood glucose less than 90 mg. per dl., and one-, two-, and three-hour whole-blood concentrations that did not exceed 160, 145, and 125 mg. per dl., respectively. These criteria confirm that fasting blood glucose is lower and elevation of the blood glucose response to oral intake is more prolonged than in the nongravid state.

2. Since glucose removal is facilitated during the first trimester and acquired insulin resistance is minimal, gestational diabetes should rarely present itself during this stage of pregnancy. Rather, the prevalence of gestational diabetes will increase as a function of duration of pregnancy. Therefore, to detect gestational diabetes in a high-risk patient (positive family history for diabetes, excessive weight gain during pregnancy, previous high-birth-weight infants, previous obstetric history of stillbirths, prematurity, hydramnios, pregnancy-induced hypertension, or renal glyco-
The rationale for this approach seemingly depended upon stringent limitation on pregnancy weight gain (16—18 lb.). To replicate this pulsatile type of pregnancy response, maternal hypoglycemia is to be averted. As the diabetogenic influence of pregnancy becomes more manifest (from about the 24th week of gestation), increasing dosages of insulin will be required to attain the same level of control of the blood glucose. The absence of an anticipated rise in insulin requirements may indicate placental hypoplasia and a fetus that is small for gestational age, a high-risk complication that warrants special management considerations. Similarly, a sudden downward requirement for insulin suggests a fetus in jeopardy because of loss of placental viability. By contrast, detection of placental hypertrophy and fetal macrosomia (by ultrasonography) indicates that maternal insulin requirements are not being met and that significant maternal and fetal hyperglycemia is present.

4. Normal pregnant women, as a result of adaptive changes in pancreatic islet cell function, experience major physiologic shifts in response to food intake. There is normally an increased sensitivity of the pancreatic beta cell to glucose administration in late pregnancy that is characterized by a heightened initial insulin response that is also delayed and significantly prolonged. This adaptation, among others, permits a more prolonged maternal anabolic response to food intake. In addition, it blunts the amplitude of meal-related glycemic excursions and serves to clamp the glucose perturbation experienced by the fetus. To replicate this pulsatile type of pregnancy response, insulin-dependent patients will need to supplement long-acting insulins with multiple, meal-related dosages of regular insulin.

5. Following removal of the placenta, at the time of parturition, the source of the major contrainsulin influence of pregnancy is eradicated. Predictable downward shifts in the requirements for insulin will occur. Moreover, persistent inhibition of the maternal growth-hormone-secretory mechanisms results in a selective but transient postpartum state of functional hypopituitarism. These adjustments must be anticipated in management considerations if maternal hypoglycemia is to be averted.

DIETARY MANAGEMENT—GENERAL CONSIDERATIONS

The dietary management of pregnancy, whether complicated by diabetes mellitus or not, until recently has been an empiric, if not a mystical, exercise. Diet programs were designed to impose stringent limitation on pregnancy weight gain (16—18 lb.). The rationale for this approach seemingly depended upon the notions that maternal weight gains of this order ensured the adequacy of nutrition to both mother and fetus; that weight gains in excess of these standards could result in certain obstetric complications, notably hypertension and hydramnios; and that weight gains even substantially less than these arbitrary standards carried little risk to the unborn child. None of these notions is supported by evidence, and the latter two, at least, have been repudiated.

Although precise measurement of nutritional adequacy, as distinct from weight gain, is still not possible, much has been learned to support the need for a careful nutritional prescription if pregnancy outcome is to be favorable. Several recent reviews have addressed this issue and should be consulted for details. The energy cost of pregnancy has been estimated to be 75,000 kcal. This figure is derived from the energy expenditure required to accommodate the normal compositional changes of pregnancy, an expenditure that has been found to vary from 38 to 50 kcal. per kilogram. At present, 38 kcal. per kilogram is the lowest base for a diet prescription. Prescriptions below this level will neither achieve a desirable rate of weight accumulation nor allow for efficient utilization of protein supplements. In clinical terms, an increment of 300 kcal. per day above basal requirements should provide calories sufficient to meet the nutritional needs of pregnancy.

At least 45 per cent of calories are in the form of carbohydrate (no less than 200 gm.), following the nutritional guidelines of the American Diabetes Association. Supplements to this intake level of carbohydrate are required in those patients with significant renal glycosuria (in excess of 30 gm. per day). The intake of protein has been particularly singled out for attention. This follows from the special requirements in pregnancy to synthesize new tissue in great abundance. The total accumulation of protein during pregnancy, calculated from known sites of protein deposition in both mother and fetus at term, averages 925 gm. Current recommendations provide for this requirement by direct supplementation without consideration for the efficiency of conversion of dietary foodstuffs to tissue protein. Thus, 30 gm. of protein per day is prescribed to supplement the usual nonpregnant allowance. In a mature woman, 1.3 gm. per kg. of body weight will meet this requirement. Higher intakes are recommended for adolescent pregnancies (1.5—1.7 gm. per kg. body weight). The remainder of the calories are provided as fat (40—60 gm.).

The unique requirements for mineral and vitamin supplementation have been extensively reviewed in a series of recent papers. It is important, however, to single out one other area of dietary concern—namely, sodium intake. This is because current thinking regarding sodium intake also represents a break from the routine of the recent past. Pregnancy is normally associated with dynamic alterations in the renin-angiotensin-aldosterone system.
The purpose served by these specific adaptations is to preserve an effective circulating blood volume. Plasma renin activity and renin substrate both increase, but the pressure effect of angiotensin is attenuated. Although the initiating event in this physiologic chain is still unknown, it results in increased aldosterone production, avid renal sodium retention, and, ultimately, in a preservation of the enhanced intravascular volume. In all pregnant patients, and specifically in those with diabetes mellitus, this sequence should be considered a normal, healthy physiologic response. Thus, sodium restriction has no place in the routine dietary management of the pregnant patient. Similarly, the presence of dependent edema, a common finding in pregnant patients with and without diabetes, should not automatically trigger an alarm reaction with the introduction of diuretics. Diuretics clearly represent a potential danger to both the mother and fetus, are ineffective in preventing pregnancy-induced hypertension, and should be limited to the treatment of such rare specific conditions as congestive heart failure.

Recent studies have shown that an average weight gain of 27.5 lb. (12.5 kg.) during the course of pregnancy is associated with the lowest incidence of hypertension, prematurity, and perinatal mortality. The Committee on Maternal Nutrition of the National Research Council recommends a slightly lower average weight gain, of 24 lb. (10 to 12 kg.). The presence of diabetes should not influence this projection in any way. However, attention must also be directed to the pattern of weight gain throughout the pregnancy. The diet prescription should result in minimal weight gain in the first trimester, followed by a progressive, linear rate of weight gain of 350 to 400 gm. per week through the last two trimesters. AWRATIONAL DIETARY MANAGEMENT—CLINICAL APPLICATIONS

In our clinics, the majority of patients with gestational diabetes are overweight (preconception weight 20 per cent or more above standard for height and weight). In prescribing a diet for these women, however, our principal concern is to ensure that the diet is adequate in qualitative as well as quantitative terms. Thus, caloric restriction to secure weight reduction or no net weight gain would be qualitatively unacceptable. Although fat catabolism resulting from caloric restriction might provide a sufficient reservoir of available calories, it would do so at tremendous risk. Many lines of evidence indicate that the fetus may suffer irreparable central nervous system damage as a result of maternal ketonemia, an inevitable complication of caloric restriction. Pregnancy, in our view, is not the time to initiate a weight reduction program. These patients are prescribed a diet to support the usual pattern of weight gain, but excessive gain (greater than 3 kg. per month) is firmly discouraged.

The goals of dietary therapy in the patient with gestational diabetes are twofold. One is to meet the nutritional needs of the mother and fetus as outlined above, and the other is to limit the extent of hyperglycemia. The latter is monitored by frequent determinations of both fasting and preprandial blood glucose levels. If either the fasting or preprandial blood glucose level exceeds 100 mg. per dl. on more than three occasions, insulin will be introduced. It must be acknowledged, however, that this is still an arbitrary clinical judgment. Some reports conclude that treatment with diet or diet and insulin yields comparable fetal salvage rates, except when maternal age exceeds 25 years. These patients require careful repetitive dietary treatment. If the pattern of weight gain remains inadequate, particularly in the third trimester, we do not hesitate to recommend hospitalization to insure that protein and/or caloric supplements are taken.

INSULIN THERAPY

Standards of assessment. The standard for assessing diabetic control during pregnancy should be the nondiabetic pregnant blood glucose levels rather than nonpregnant values, which has been the general custom. Normal fasting whole-blood glucose values during pregnancy average 65 ± 9 mg./dl., with daily nonfasting mean values of 80–87 ± 8–11 mg./dl., depending on the week of gestation. The mean range of diurnal values is 46 mg./dl.; rarely does the whole blood glucose exceed 100 mg./dl. The important observation is that normal pregnancy is associated with a significant lowering of the fasting blood glucose level and two-hour postprandial blood glucose levels that rarely exceed 100 mg./dl. Therapy, therefore, should be designed to reproduce this normal gestational blood glucose profile throughout the day and night.

Monitoring of diabetes. To achieve such a degree of blood glucose regulation, we have utilized daily home monitoring of blood glucose concentration. Our approach utilizes the
Eyetone/Dextrostix method, marketed by Ames Company. This glucose oxidase method gives a true glucose determination, in a drop of capillary blood obtained by fingerstick. The colorimetric change on the reagent strip (Dextrostix) reflecting blood glucose is detected with an electronic device (Eyetone dextrometer). Carefully calibrated (with frequent checking of calibration using a special calibration kit), such blood glucose estimates are valid within 10–15 per cent of true blood glucose. Patients can be readily taught to measure daily blood glucose levels at home. We follow a scheme wherein fasting blood glucose is obtained on a daily basis, along with at least one other periprandial blood glucose determination. On the average of once weekly, seven blood glucose measurements are obtained—before and two hours after each meal (breakfast, lunch, and supper) and before the patient's bedtime snack.

In addition to the blood glucose determinations, we ask patients to monitor their urinary glucose and ketone spills four times daily (before meals and before bedtime snack).

**Insulin therapy.** When insulin is required in the patient with *gestational diabetes*, a single dose of intermediate acting insulin taken once in the morning before breakfast may suffice. If blood glucose profiles taken in a home setting do not reach desirable levels, the insulin therapy will be altered to a multiple-component regimen. In such patients and in all insulin-requiring patients with *pregestational diabetes*, insulin is provided in a regimen with multiple components of insulin action, each having a peak at a different time of the day. This is done either by multiple doses of regular insulin (before meals and at bedtime) or as a split-and-mixed insulin regimen. The latter type of regimen both splits the insulin into two doses (one in the morning before breakfast and the other in the evening before supper) and mixes short-acting insulin (e.g., regular) and intermediate-acting insulin (e.g., NPH or lente) in each injection. As a guideline, the initial distribution of insulin provides two thirds of the total daily dose in the morning (divided as one part short-acting insulin to two parts intermediate-acting insulin) and one third of the total daily dose in the evening (divided in equal parts between short-acting insulin and intermediate-acting insulin). As patients begin this regimen, monitored by the home blood glucose determinations, they maintain daily telephone contact with the professional staff (physicians and diabetes nurse specialists), who together with the patient make appropriate adjustments in insulin dosage to achieve euglycemia. As the patient becomes more familiar with the adjustment program, an algorithm for insulin dose alterations is developed and contacts with the professional staff can be less frequent. Weekly, the patient is seen in the Diabetes Unit for full evaluation of diabetes regulation, review of progress, and discussion of any questions that have arisen. An example of the blood glucose regulation that can be achieved with this approach is shown in figure 1. Following home blood glucose monitoring with the use of the Eyetone instrument, this patient self-adjusted both the composition of her diet and her insulin dosages, resulting in a mean blood glucose level of 82 mg./dl. through the last six weeks of pregnancy. The 29th week of gestation was complicated by a severe upper respiratory tract infection, but hyperglycemia was nonetheless well managed.

There are a number of important observations that have emerged from this management program. The most significant of these is that it is possible to abolish completely the need for hospitalization of insulin-dependent patients prior to their predelivery confinement. The potential cost savings is significant and relevant. In addition, our initial experiences, both in pregnant and nonpregnant patients, suggests that insulin-dependent patients, even the most brittle, appear to stabilize their clinical lability with this self-directed regimen. Lastly, we have been increasingly impressed that the positive experience of effective self-regulation has clearly altered the patients' attitude about disease management even when not pregnant. They appear, at this juncture, to be among our best-regulated insulin-dependent patients.

This program of stringent control is based on the firm conviction that the maintenance of euglycemia will strengthen the probability of a successful pregnancy outcome. Several lines of evidence support this view. Centers that utilize stringent control criterion have clearly experienced the best currently available over-all results. Acknowledged earlier, however, caution in attributing these remarkable achievements to any single feature of a highly sophisticated treatment program. Nonetheless, some are persuaded that the major gain in fetal salvage rates experienced by these centers relates solely to improved overall obstetric care. Karlsson and Kjellmar, by contrast, have shown in a retrospective study that perinatal mortality can be directly related to mean blood sugar levels during the last weeks of pregnancy. In this study, a perinatal mortality of 24 per cent in the group with a mean blood glucose level over 150 mg. per dl. was reduced to 15 per cent when the mean blood glucose was between 100 and 150 mg. per dl. If the mean blood glucose level was kept below 100 mg. per dl., the perinatal mortality was dramatically reduced to 4 per cent. In further accord with the pernicious morbidity and mortality of maternal fetal hyperglycemia, these results are supported by the recent results from studies in pregnant animal models. Streptozotocin-induced maternal hyperglycemia in the nonhuman pregnant primate (rhesus monkey) reproduces many of the morbid features observed in human pregnancy complicated by poorly regulated diabetes mellitus. These
studies have demonstrated that fetal macrosomia, hydramnios, placental hypertrophy, fetal pancreatic islet cell hyperplasia, and fetal hyperinsulinemia all will be associated with untreated maternal hyperglycemia. Moreover, an unexpectedly large number of intrauterine fetal deaths (20–30 per cent) were encountered before delivery by cesarean section at the equivalent ratio of 36 weeks of human gestation, whereas stillbirths were never encountered in over 300 gestations in euglycemic animals. We believe that all of these experiences provide compelling evidence to support the value of stringent control of maternal hyperglycemia during pregnancy.

Maternal hypoglycemia in an insulin-treated patient is a theoretical threat that requires alertness. Fetal glucose levels are a direct function of maternal glucose levels, with the possible exception of extreme degrees of maternal hyperglycemia. The fetus does not have a compensatory capacity to protect against maternal hypoglycemia. One can be confident, therefore, that insulin-induced hypoglycemia is a coupled phenomenon in both maternal and fetal blood compartments. The issue of fetal adverse effects rests on what definition of hypoglycemia constitutes a severe insult for the fetus. Nonetheless, the fetus of the diabetic woman seems to withstand acute episodes of severe maternal hypoglycemia, as judged by our present clinical abilities. This, however, may be more a commentary on our inability to detect subtle damage than to its absence.

Home monitoring provides a unique opportunity for the patient to detect actual or impending hypoglycemia and respond to it during both day and night. This has proved particularly advantageous, since some workers report that hypoglycemia will be most commonly found during the early morning hours. Our patients have not experienced this, but the presupper dosages of regular insulin we employ are proportionately much less than used by those workers, and we provide a bedtime snack that includes both 25 gm. carbohydrate and some protein.

Insulin therapy at parturition. When the placenta has been delivered and the source of hPL thus removed, the patient becomes extremely sensitive to insulin for several days. As discussed above, this early postpartum (1–3 days) exquisite sensitivity to insulin is due to transient inhibition of the maternal growth-hormone-secretory mechanism. Therefore, common practice has been to withhold insulin therapy.
the morning of delivery, thus minimizing the threat of unrecognized maternal hypoglycemia post partum. There are two problems with this approach. First, the exact timing of delivery, even with induction of labor, cannot be accurately predicted. The induction may last greater than one day, and the withholding of insulin for such a period is clearly unacceptable. Second, and perhaps more important, by omitting insulin on the day of delivery, the level of metabolic control that was achieved throughout gestation is sacrificed. This will result in increased maternal and fetal hyperketonemia and hyperglycemia during labor and delivery. Hobel et al. have shown that the incidence of respiratory distress among a group of premature babies was significantly lower in those that did not become acidic during labor. Therefore, it has been our approach to use simultaneous continuous intravenous infusions of glucose and insulin to sustain metabolic regulation on the day of delivery. Insulin infusion is carefully regulated by an IVAC pump. The rates of both infusions are regulated by hourly blood glucose determinations. The usual insulin requirement has been 0.8–2.0 U. per hour after a loading dose of 0.02–0.05 U. per kilogram is given by bolus. The glucose infusion rate usually approximates 8–12 gm. per hour as per 5 per cent dextrose in water. Samples are obtained through an indwelling butterfly needle with heparin lock, and determinations are carried out with a Beckman glucose analyzer at the bedside. Our goal is maintenance of blood glucose between 60 and 100 mg./dl. Figure 2 depicts the therapy is then withheld until significant hyperglycemia can be achieved and may lead to a reduction in the incidence of neonatal hypoglycemia.

MATERNAL MORBIDITY AND MORTALITY

Table 1 provides a recent modification of White’s classification index for diabetes during pregnancy. It is based on the duration and status of diabetes prior to pregnancy, particularly the presence of vascular disease. Two new subgroups have been added, classes H and T; and two, classes E and G, have been essentially discarded. Class H comprises patients with clinically detectable coronary artery disease. Class T includes pregnant patients who have received kidney transplants for renal failure.

With a single exception, maternal mortality in these categories has been virtually excluded with current treatment programs. Although only limited data are available, class H patients appear to have a manifest threat to short-term maternal survival. Thus, in a recent Joslin Clinic series, only one of four mothers was alive four weeks following the pregnancy, and she had had coronary bypass surgery prior to pregnancy. Since coronary artery disease is a prominent feature of long-standing diabetes and its manifestations in the female patient can be atypical, cardiac status, including exercise stress tests, should be carefully evaluated in these pregnant patients.

The natural history of retinopathy in pregnancy follows an unpredictable clinical course for any individual patient. Prepregnancy background retinopathy or background retinopathy acquired during pregnancy is most commonly a benign process. It can remain stationary, remit, or, on occasion, progress to the proliferative stage. With a benign clinical course, we regard background retinopathy without concern. Patients undergo fluorescein retinography during the first trimester and thereafter, depending on the results of ophthalmoscopic retinal examinations performed at each visit. If lesions progress to a proliferative stage, they are treated with argon laser therapy. The limited experiences reported to date indicate that laser therapy can halt progress of proliferative lesions appearing during pregnancy and preserve vision. Patients with prepregnancy laser-treated proliferative retinopathy are now observed during pregnancy. We have not been convinced that disease so treated necessarily progresses during pregnancy.

The natural history of nephropathy is a more elusive clinical projection. No compilation of clinical experience has been reported to support the notion that these patients are at grave risk because of pregnancy alone. As a group, however, they do require the most demanding clinical management, including close control of hypertension and fluid and electrolyte balance, prolonged bed rest, and frequent hospitalizations. With this, maternal mortality is nil, although rare interruption of pregnancy is still required for decreasing renal function. Patients with kidney transplant can maintain a successful pregnancy despite continuing requirement for immunosuppressive therapy.

Macroangiopathy and extensive microangiopathy, and their complications, appear to also influence the maternal requirements for insulin therapy. Thus, in White’s classes B through D, most patients will require increasing dosages of insulin as a function of length of gestation. Some patients in class D and many in classes R, F, and RF will manifest stable and even decreasing requirements for

T

able 1 provides a recent modification of White’s classification index for diabetes during pregnancy. It is based on the duration and status of diabetes prior to pregnancy, particularly the presence of vascular disease. Two new subgroups have been added, classes H and T; and two, classes E and G,
insulin during pregnancy. Whether this is solely due to placental hypoplasia, a common complication in the presence of extensive maternal vascular disease, is still uncertain.

FETAL MORBIDITY AND MORTALITY

An additional demographic advantage of the White classification is the predictive value it lends to assessing fetal jeopardy. Thus, in the Copenhagen experience, perinatal mortality increased from 5 to 35 per cent through the White classification. Another independent and highly significant assessment is provided by Pedersen’s prognostic bad signs of pregnancy (PBSP, table 2). A statistically significantly higher mortality was encountered if PBSP were present in each of White’s classes except F.

Procedures for antenatal surveillance, along with disciplined regulation of maternal diabetes, have contributed to the steady improvement in perinatal survival in all White’s classes over the past decade. For these, ultrasonography, urinary estriol determination, amniotic fluid phospholipid assay, and intrapartum fetal monitoring are most commonly employed.

Ultrasonography in the mid-trimester provides valuable and reliable information concerning length of gestation. This information is specifically required, as many of these pregnancies will be electively terminated prior to term, and an objective index of gestational age is vital for this decision. Serial ultrasonography subsequently provides valuable information concerning the rate of fetal growth. The detection of macrosomia reflects on the inadequacy of control of maternal diabetes. The detection of a reduced rate of fetal growth forecasts the need for specialized techniques and procedures required in the management of fetuses at high risk. The likely cause of death in growth-retarded fetuses is placental insufficiency. Ultrasonography therefore provides a powerful noninvasive early alert mechanism to indirectly assess this function.

The most widely used and frequently abused test of fetoplacental function is the 24-hour urinary excretion of estriol. The clinical value of estriol assays remains a matter of dispute even after a decade of trials. Goebelsmann and his co-workers have provided a detailed analysis of factors influencing the discriminatory value of estriol excretion in detecting fetal jeopardy or well-being in pregnancy complicated by diabetes mellitus. Four separate issues were highlighted in detail. First, urinary estriol excretion is highly correlated with birth weight. Urinary estriol determination should therefore also correlate with the rate of fetal growth-retarded fetuses, a common complication in the presence of extensive maternal vascular disease.

To prevent intrauterine fetal death, preterm delivery of patients with complicated diabetes mellitus from the 33rd to 37th week of gestation has become a matter of routine in some centers. The managerial trade-off, under blind circumstances, is that of death in utero against death in the nursery from prematurity. Respiratory distress syndrome (RDS) and hyaline membrane disease, prominent causes of neonatal morbidity and mortality, are related to inadequate surfactant production, an ultimate product of maturation of the fetal lung. The concentration of lecithin and other phospholipids, phosphatidylinositol and phosphatidylglycerol, in amniotic fluid serially signals the progressive completion of this maturation process. The specific values of the latter phospholipids are under continuing study. Some reports suggest that normal values of the L/S ratio are less reliable in the presence of diabetes mellitus. The most recent large-scale study, however, clearly confirms that infants of diabetic mothers delivered soon after the determination of an L/S ratio considered mature for the normal (greater than 2.0) are not at greater risk for RDS than infants of the nondiabetic population. In considering this apparent controversy, account should be taken of differences in laboratory technical competence and the failure to appreciate that intrapartum asphyxia and neonatal acidosis may lead to RDS despite a mature L/S ratio.
Antepartum fetal heart-rate monitoring enjoys wide acceptance as a noninvasive procedure to rapidly assess the respiratory functional reserve of the placenta. Uterine contractions can transiently interfere with uteroplacental blood flow. Therefore, spontaneous or induced uterine contractions (oxytocin stress testing) can produce a transient ischemic challenge to the fetus. If uteroplacental blood flow is compromised, transient fetal hypoxia may result in an alteration of electrical activity controlling the fetal heart rate. A positive test consists of delayed deceleration of the fetal heart rate following uterine contractions. The absence of beat-to-beat variability and/or acceleration with fetal movement are other fetal electrocardiographic phenomena that may prove to be significant indices of fetal hypoxia. The test may be performed weekly from the 32nd week of gestation, depending on clinical circumstances. A negative test remains a reassuring prognostic signal that the fetus is not in imminent jeopardy, despite some recent reports that cast doubt on the predictive validity of a negative test. A negative test would be followed by weekly reassessment of the fetal heart-rate responses to uterine contraction in combination with daily urinary estriol levels and weekly amniotic fluid phospholipid determinations. The objective is to deliver an infant mature in all of its systems. The maintenance of physiologic maternal blood glucose levels and the absence of evidence for fetal compromise will permit the clinical judgment that these pregnancies can continue to term.

A positive test serves as a catalyst for further action. Thus, if a positive test is encountered, urinary estriol levels and amniotic fluid phospholipids are determined simultaneously. If urinary estriol levels are unchanged and amniotic fluid L/S ratios reflect fetal lung immaturity, the patient will be followed by daily estriol assays and fetal heart rate monitoring will be repeated, with or without oxytocin, on a weekly basis. If the L/S ratio is greater than 2, under these circumstances, the pregnancy will be terminated by induction and vaginal delivery, if possible, or by cesarean section. If urinary estriol levels, in the presence of a positive stress test, are low, the pregnancy will be terminated, irrespective of the L/S ratio. As a matter of completeness, and seemingly as a paradox, some patients with positive stress tests (approximately 25–45 per cent) will undergo vaginal delivery without evidence of intrapartum asphyxia.

Evidence can be marshaled to support the contention that vaginal delivery may play a dominant part in determining whether the newborn of the patient with diabetes develops respiratory distress. Thus, if the cervix is effaced and dilated, vaginal delivery should be given a trial. To do so, however, requires the availability of instruments and expertise to permit intrapartum monitoring. This is essential in the conduct of these trials of labor; if the presence of intrapartum asphyxia is to be detected and corrected early enough to avoid harm. The results of Beard and his co-workers suggest that a significant incidence of intrapartum asphyxia has previously been undetected and therefore may have been more of a contributory factor to problems of the neonatal period than was previously thought. We are convinced that the long-term prognosis for infants of diabetic mothers can be influenced not only by the quality of antepartum care but by intrapartum and neonatal complications as well.

**The Neonate**

Infants of diabetic mothers have an increased likelihood of neonatal hypoglycemia, hypocalcemia, and hyperbilirubinemia, as well as respiratory distress syndrome and hyalin membrane disease. All of these complications result from immaturity of organ systems and will be seen in premature babies whether maternal diabetes is present or not. Neonatal hypoglycemia is also related to a persistence of fetal hyperinsulinemia as a complication of uncontrolled maternal hyperglycemia. Thus, with careful medical therapy and obstetrical management that has as its goal the delivery of a mature infant, these complications should occur rarely. Because, on occasion, decisions to deliver early must be made, a neonatal intensive-care unit should be available for all potentially high-risk babies.

Macrosomia is a common problem in offspring of mothers with gestational diabetes and with uncomplicated diabetes of relatively short duration, e.g., White classes A, B, and perhaps C. It has been shown that insulin treatment of gestational diabetes will markedly decrease the occurrence of macrosomia, as well as reduce viable losses.

In contradistinction to the large babies seen in White classes A, B, and C, patients with vascular disease often have babies that have low birth weights and are small for gestational age. This is presumably secondary to compromised placental function. Such infants have a greater risk of both perinatal and postnatal mortality.

Pedersen and Yssing have found a threefold increase of congenital malformations in infants of diabetic mothers over that of the population at large. Skeletal defects and congenital heart disease were the most frequently recognized abnormalities. Major malformations (i.e., those of documented clinical significance) were correlated with genetic factors, White classification (highest in classes D and F), complications during pregnancy, and low birth weight. Women with uncomplicated pregnancies (i.e., none of the PBSP of table 2) had no major malformations. Pedersen noted a strong negative correlation between insulin reactions during the first trimester and congenital malformations, implying that malformations were more likely with a
CONSTANT LOW DOSE INSULIN INFUSION DURING LABOR

BLOOD GLUCOSE (mg/dl)

INSULIN (units/hr — I.V.)

GLUCOSE (g/h — I.V.)

EPIDURAL BLOCK

DELIVERY

FIG. 2. Record of insulin and glucose infusion rates and blood glucose responses during induction of labor in the patient described in figure 1. The patient had two trials of labor, with oxytocin induction, on two successive days. On the second day, epidural block was associated with hyperglycemia that was managed by increasing the insulin infusion rate.

Mother. A follow-up of mothers who had established vascular disease during pregnancy was reported in 1971. It covered a series of cases seen at the Joslin Clinic from 1924 to 1962. Thirty-two of 144 women who had had 271 pregnancies had died. Their mean survival after pregnancy was eight years. Therefore, one child in five had lost a mother before reaching 10 years of age. This information requires confirmation from more current longitudinal studies. It raises great concern on our part and may seriously influence family planning for such patients.

It is doubtful, in our view, that pregnancy itself significantly alters the natural history of diabetes already complicated by extensive vascular disease (i.e., classes D, F, R, and RF). Whether this is so for classes A, B, and C—without manifest vascular disease—is unclear. Such a conclusion can be established with certainty only if there is demonstration that pregnancy alone can accelerate the progress of vasculopathy, independently of its effects on blood glucose regulation. The latter can be controlled, but the former cannot. Such a demonstration would undoubtedly influence the advice given to prospective mothers concerning the advisability of conception.

Child. In 1969, Churchill, Berendes, and Nemore reported that there was a significant lowering of intelligence quotient (I.Q.) in offspring of diabetic mothers who manifested acetonuria during pregnancy. Patients with acetonuria were matched by hospital for birth, race, sex, maternal age, birth order, and socioeconomic index with acetonuria-free control patients. The neuropsychiatric deficits were manifested by lower Bayley mental and motor scores at age eight months and lower Stanford-Binet I.Q. scores at age four years. The deficits were not related to severity of diabetes or degree of prematurity, only to acetonuria, and were seen in both gestational and overt diabetes. These investigators also found that there was a decrease in I.Q. scores of offspring of nondiabetic mothers with acetonuria, particularly if manifested during the third trimester.

The adverse effect on intellectual states of offspring of diabetic mothers with acetonuria during pregnancy has been confirmed by Stehbens et al., who found impairment in I.Q. scores at age five. These authors also found that infants with birth weight of less than 3,000 gm. had significant I.Q. decreases at both ages three and five. They concluded that the significant relationship between acetonuria, birth weight, and intellectual status was further evidence that continuous prenatal care to control maternal diabetes is a most important factor influencing morbidity. Of importance, Churchill et al. found, is that maternal hypoglycemic episodes had no impact on later neuropsychiatric status.

Yssing found that major cerebral handicaps of definite clinical significance were strongly associated with a complicated course in any of three periods: prenatal, delivery, or neonatal. Minor abnormalities were found independently of the prenatal and neonatal course but were to some extent dependent on delivery per se. Cerebral dysfunction was progressively more common in White classes...
C, D, and F and was increased if there were pregnancy complications. Dysfunction also seemed related to genetic predisposition, low birth weight, low gestational age, and either high or low maternal age. Biberghil et al. found correlations between degree of metabolic compensation (control) and speech development. These authors also noted that diabetic vascular complications were associated with decreased somatic and psychosomatic development and that urinary tract infections during pregnancy were related to severe cerebral defects.

The offspring of women with diabetes are exposed to an increased risk of death in both the perinatal and postneonatal periods. Provided they survive, they are more likely than other children to have congenital malformations: juvenile diabetes mellitus or cerebral dysfunction. Many of these long-term complications can be minimized by careful metabolic control of maternal diabetes, adequate prenatal and perinatal care, careful monitoring and execution of delivery, and use of a well-equipped and well-staffed neonatal intensive-care unit.

We are persuaded that pregnancy in patients with diabetes should be a carefully planned event by the patient and her physician, supervised by a specialized team experienced in the frequent management of pregnancy in diabetic women, and supported by modern laboratory and inpatient facilities.

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