Sweet Success With Diabetes

The development of insulin therapy and glycemic control for pregnancy

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Marking a decade of use of human insulin to treat diabetes mellitus provides a welcome opportunity to review the development of insulin therapy for glycemic control in pregnancy. Since the time of the pioneers of medical care for pregnant diabetic women, gratifying progress has occurred in the prevention of serious maternal and fetal complications. After World War II, special diabetes and pregnancy treatment centers focused on generalized methods of reducing the tragically high levels of perinatal mortality. In the 1960s and 1970s, advances in understanding fetal physiology led to new methods of fetal diagnosis and surveillance. Coupled with established diabetes treatment regimens, application of perinatology techniques reduced perinatal mortality to near normal, and the focus shifted to the many forms of perinatal morbidity associated with maternal hyperglycemia and altered fuel balance. In the 1980s, the crucial technological advance of self-monitoring of blood glucose allowed many diabetic women to achieve near-normoglycemia as outpatients, and investigators demonstrated that tight glycemic control could prevent excess rates of fetal macrosomia and birth trauma, congenital malformations, and neonatal respiratory distress syndrome. Indeed, compared with the grim outlook a few decades ago, diabetic women participating in intensive, guided self-management programs usually can anticipate the delivery of completely healthy infants.

One objective in writing this historical review is to emphasize the key principles of diabetes care for pregnancy, which continue to guide our daily work and which must be taught to our students. Another is to discuss unsolved pregnancy problems, which future investigations of management of diabetes and pregnancy will need to address.

Dietary therapy is the keystone of diabetes management. Space does not allow a detailed analysis of dietary therapy for pregnancy, but an excellent review of the subject has been provided by Ney and Hollingsworth (1).

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PNM, perinatal mortality; SMBG, self-monitoring of blood glucose; PPBG, postprandial blood glucose; KTA, ketoacidosis; BG, blood glucose; RDS, respiratory distress syndrome; type I diabetes, insulin-dependent diabetes mellitus; type II diabetes, non-insulin-dependent diabetes mellitus; FBG, fasting blood glucose; MBG, mean blood glucose; LGA, large for gestational age; FFA, free fatty acid; β-HB, β-hydroxybutyrate; MAGE, mean amplitude of glycemic excursion; CSII, continuous subcutaneous insulin infusion.

PIONEERING EFFORTS AT CENTRALIZED MANAGEMENT OF DIABETES AND PREGNANCY—Elliott Joslin's clinic in Boston has been a center of excellence for treatment of diabetic people, even before the advent of insulin in 1922. Priscilla White, a physician at the Joslin Clinic, was devoted to the care of children and women with diabetes of juvenile onset, which gave her the opportunity to personally follow a very large number of pregnancies. By 1949, she had reported 439 consecutive cases with infants >1,000 g and had analyzed the causes of fetal wastage (spontaneous abortion 25%, PNM 18%) (2,3). Of these infants, 80% were larger than average with increased fat and visceromegaly (2). Stillbirth (43% of losses) and neonatal death (57%) were most common in the group with evidence of renal disease or hypertensive disorders (nearly half of the total population). Because vascular disease seemed inevitable if duration of diabetes exceeded 15 yr (2), PNM was higher in pregnant women with earlier onset of diabetes (3). Two-thirds of stillbirths occurred at 36–40 wk gestation, which led to White's insistence on planned preterm delivery "before the dreaded late intrauterine accident occurred," even though she recognized that maturation to "viability" occurred later than normal in pregnancies complicated by diabetes (3). Of course, this policy of preterm delivery to circumvent stillbirth resulted in an extraordinary cesarean section frequency of near 80% and in neonatal deaths from hyaline membrane disease.

Dr. White gave first priority to "good treatment of diabetes" (3). Patients were seen weekly by both obstetrician and physician. They were taught to weigh amounts of food, using a diet plan of 30 kcal/kg body weight, distributed over 3 meals and 3 snacks. Enough insulin was given to prevent glycosuria and "ketosis," with a basic dose of long-acting insulin before breakfast, supplemented by 3–4 doses of short-acting

Regular insulin before meals and the evening snack. By the third trimester, the average 2-h PPBG was ~8.3 mM (150 mg/dl) (4). This close attention to the details of diabetic management yielded low frequencies of diabetic ketoacidosis in 2% of pregnancies (6 of 8 fetuses died during the episode), and hypoglycemic coma occurred in 1% (no fetal deaths) (3).

White noted that the majority of pregnant diabetic women had an "imbalance of female sex hormones" (2,3). Today, we recognize that the elevated human chorionic gonadotropin at 23–35 wk was probably attributable to fetal-placental macrosomia, and that low urinary estrogen and progesterone were related to utero-placental vascular insufficiency. In 52 diabetic women with "normal hormone balance," there were no preterm deliveries, only 2% preeclampsia, and 96% perinatal survival, compared with figures of 40, 50, and 60%, respectively, in 38 women with abnormal hormone measurements (2). Therefore, she used the controversial sex hormone replacement therapy with daily injections of stilbestrol and progesterone (by partner at home), along with diuretics for edema and hydramnios. She claimed that this regimen was most effective in women with vascular disease, and that it lowered overall PNM to 10% (5), which was the best in the world at that time, and reduced preeclampsia from 26 to 16% (3,4). Others commented that the improvements were more likely related to meticulous diabetic management throughout pregnancy (6,7) and to early hospitalization by 34 wk gestation (5). Hurwitz (8) pointed out the lack of a proper control group for hormone therapy, because women who registered too late to receive it were likely to be "careless about their diabetes." In England, a multicenter controlled trial of oral stilbestrol was conducted by the Medical Research Council (9), but this study was flawed by the exclusion of diabetic women with vascular disease, "the lack of individual and constant care and attention" (4), and the high PNM in both treated (30%) and untreated (32%) groups (9). White raised a still unanswered question: Could estrogens protect uterine arteries as they do coronary arteries? (4). Subsequent experiments demonstrated that estrogen administration increases uterine blood flow in pregnant animals, which might have had something to do with White's impressive results. Of course, the therapy also had serious delayed effects on the reproductive tracts of female offspring.

In the 1950s, other American reports confirmed White's observations on the natural history of diabetes complicating pregnancy, as the workers applied her principles of diabetes management in a teaching hospital environment without the use of hormone therapy (8–11). Preeclampsia (or latent diabetic nephropathy) was commonly observed (29–43%) (8,11). PNM varied from 14–30% (Table 1) and was often associated with KTA or preeclampsia before 35 wk, whereas the risk of unexplained fetal death rose as term approached. Long et al. (10) at Johns Hopkins believed that "a mild to moderate degree of maternal acidosis contributes significantly to late fetal death in utero". They and others sounded modern themes when they observed that *1*) major congenital anomalies were more frequent in infants of diabetic mothers (10,11), *2*) excellent

Table 1—*PNM in large, nonselected series of pregnant women with pregestational diabetes*

Author	Date	Pregnancies	Years	PNM(%)
Pioneering efforts with centralized management				
White	1945	181	1936–1944	16.0
Peel; Oakley	1949	141	1942–1942	17.0
Jones	1953	184	1927–1951	29.6
Nelson; White	1953	128	1950–1952	9.6
Long; Eastman	1954	118	1942–1952	18.0
Pedersen	1956	265	1946–1955	21.9
Pedersen	1965	306	1959–1963	17.9
Oakley	1969	425	1958–1968	10.1
Pedersen	1974	255	1966–1969	12.9
Drury	1977	600	1951–1976	9.5
Impact of antepartum fetal surveillance and neonatal care				
Pedersen	1974	231	1970–1972	7.4
Persson	1975	170	1966–1973	4.7
Gabbe	1977	260	1971–1975	4.6
Kitzmiller	1978	137	1975–1976	5.8*
Jervell	1979	222	1970–1977	4.1
Roversi	1979	199	1963–1975	4.0
Schneider	1980	108	1973–1978	2.8
Tevaarwerk	1981	110	1972–1980	0.9
SMBG				
Jovanovic	1981	52	unknown	0
Langer	1988	103	1986–1987	0
Mimouni	1988	162	1978–1986	1.9
Cousins, CDAPP	1991	374	1986–1988	2.4

Before 1975, PNM excluded infants <1,000 g and >10 days after birth. See text for comments regarding series.

*Includes 3 cases of anencephaly aborted at 20–22 wk gestation.

diabetic control was needed to carry the pregnancy safely to term, 3) lack of diabetic control led to frequent ketonuria (one goal of therapy was to keep the premeal urine free of ketones [8,10]), and 4) they needed a method for estimating fetal size in utero and a yardstick for measuring fetal maturity (9).

In Europe, the pioneers of diabetes and pregnancy management included Oakley and Peel in London (12,13), Drury in Dublin (14), and Jorgen Pedersen in Copenhagen (15). They generally used lower calorie diets than the Americans (1,600–1,900 kcal), watched weight gain closely (14), and championed the split mix regimen of insulin therapy, which was a mixture of Regular and intermediate insulin administered before breakfast and supper with doses based on BG responses rather than urine glucose measurements, because of the variability of the latter in pregnancy. The goal of glycemic control was premeal BG <8.9 mM (160 mg/dl) at King's College Hospital in London (12,13) and 2-h PPBG <7.2–7.8 mM (130–140 mg/dl) in Copenhagen and Dublin (14, 15). The value of pre- vs. postmeal BG surveillance still has not been tested in a prospective comparative trial. Oakley and Pedersen (12,15) emphasized the importance of hospitalization at 32 wk gestation for strict diabetic control and believed this explained their success in dropping PNM from 20–30% to 11–13% by the end of the 1960s. Drury (14) hospitalized only those patients with complications before 38 wk, and the overall perinatal survival was 90.5%.

Pedersen, like White, maintained detailed records on a very large number of diabetic women he personally cared for during pregnancy. In 1952, he reported on the course of diabetes during the different stages of gestation (16). He observed an average reduction in insulin dosage of 33% in the first trimester (attributable to hypoglycemic reactions), followed by a 75% increase in insulin requirements after 20 wk to maintain mean 2-h PPBG <7.2 mM (130 mg/dl). In this early study, insulin coma occurred in 14% of pregnancies, usually in the first trimester, but was not associated with fetal death. On the other hand, KTA (16% of pregnancies) had its maximum frequency at 24–30 wk gestation and had a fetal mortality of 30%. At this early date he stated that coma and acidosis could be prevented by adequate supervision. He drew attention to the causes of the increased tendency to ketonemia in pregnancy: "loss of glucose in the urine due to reduced threshold, loss of glucose to the fetus, occasionally a too low caloric intake, and presumably increased burning of fat" (16).

Pedersen continued to make key contributions to our understanding of diabetes and pregnancy. The importance of good diabetic control and adequate antenatal supervision with a combined internist-obstetrician approach was illustrated by his observation of threefold higher PNM with only short-term treatment (<53 days before calculated term) or no centralized, organized care (17, 18a), a finding repeated by Zorowitz (18b), Farquhar (19), Peel (13,20), and Essex (21). In 1965, Pedersen reported a strikingly low PNM (6.9%) in 176 pregnancies without the prognostically bad signs of KTA, preeclampsia, pyelonephritis, or a neglect of prenatal care, compared with a loss rate of 31.5% when one of these signs was present in 130 pregnancies (22,23). Certainly his most famous contribution was his postulate of the relation of maternal BG levels and increased fetal insulin to the increased weight and length at birth of most infants of diabetic mothers (24). He summarized this hypothesis in the 1977 edition of his classic book on diabetes and pregnancy: "The key to many problems is the fact that the fetal homeostasis has been disturbed and reset due to maternal hyperglycemia and the ensuing fetal hyperinsulinism. One consequence is the finding that, as a group, they are at the same time 'heavy for dates' and 'premature for dates' " (15).

Although all writers before 1965 had stressed the importance of strict diabetes control in reducing perinatal loss, no one had related specific BG levels to risk of PNM. Studying patients in the 3rd trimester, Harley and Montgomery in Belfast (25), Delaney and Ptacek in Iowa City (26), and Karlsson and Kjellmer in Gothenburg (27) reported a gradation of PNM according to levels of glycemic control (Table 2). The "K and K paper" was especially important in stimulating attempts at tight glycemic control in the U.S., because the normoglycemic group of patients also had significantly less neonatal RDS, jaundice, and congenital anomalies (27).

Table 2—*Glycemic control in the third trimester and PNM*

	Level of glycemic control (premeal BG)		
	Good	Fair	Poor
Harley, 1965			
BG range (mM, [mg/dl])	<8.3 (150)	8.4–11.1 (151–200)	>11.1 (200)
PNM (%)	7.6	21	37.5
Delaney, 1970			
BG range (mM, [mg/dl])			>11.1 (200)
PNM (%)		10.6	33.6
Karlsson, 1972			
BG range (mM, [mg/dl])	<5.6 (100)	5.6–8.3 (100–150)	>8.3 (150)
PNM (%)	3.8	16	24

IMPACT OF ANTEPARTUM FETAL SURVEILLANCE AND INTENSIVE NEONATAL CARE — In the late 1960s and early 1970s, biochemical monitoring of fetal-placental function with estriol and human placental lactogen measurements was first applied to pregnancies complicated by diabetes, followed by the biophysical techniques of electronic fetal heart rate monitoring and profiling fetal movements and amniotic fluid volume with real-time ultrasound. These techniques for surveying risk of fetal asphyxia and death were coupled with predelivery amniotic fluid assays to predict risk of RDS, and all were used to help plan timing of delivery. In this era, the period of fetal viability was extended back to 24 wk gestation in calculating PNM, a result of the striking improvements in care of the premature newborn infant.

Although the new methods were never rigorously tested in strictly controlled clinical trials, investigators such as Persson and Lunell in Stockholm (28,29), Beard and Brudenell in London (30,31), Gabbe in Los Angeles (32), Kitzmiller in Boston (33), Roversi in Milan (34), and Tevaarwerk in Ontario (35) reported dramatic reductions in rates of stillbirth in large series of diabetic women hospitalized near the end of pregnancy (Table 1). Overall, PNM declined to 1–5% despite the lack of rigid glycemic control in many subjects, a point made by many other authors at the time (36–42). The developing confidence in fetal surveillance allowed investigators to achieve good results with weekly outpatient management until shortly before delivery (43–46).

With improvements in perinatology and neonatology in the 1970s, the leading causes of mortality in infants of diabetic mothers became congenital anomalies, severe fetal growth delay with diabetic vascular disease, and preterm birth at <28 wk gestation (33,47,48). The decline in stillbirths and neonatal deaths meant that perinatal morbidity became the end point for evaluating changes in diabetic management (23, 32,33).

INTENSIFIED INSULIN THERAPY — With the aim of reducing pregnancy morbidity, Lewis (49), Roversi (34), and Coustan (50) reported detailed analyses of the glycemic and perinatal effects of intensified conventional insulin regimens. Lewis determined the diurnal pattern of BG and insulin levels before and after standardized meals in normal pregnant women, then chose combinations of NPH and Regular insulin 30 min before meals to simulate the normal responses: the morning total dose (NPH:Regular, 2:1) was approximately twice that given in the evening (NPH:Regular, 1:1) (49). From this starting point, he stressed the need to individualize the regimen. Some type I patients required Regular insulin before lunch, others needed the evening NPH at bedtime to prevent nocturnal hypoglycemia, and a single injection sufficed in some women with diabetes of short duration and endogenous insulin secretion. A schedule of insulin dose adjustments by 20% increments was followed at weekly outpatient visits (49). Using these regimens, 7 diabetic women had normal glucose profiles (4.3 mM [78 mg/dl] premeal, 6.7 mM [120 mg/dl] peak postbreakfast at 1 h, and 5.6–6.1 mM [100–110 mg/dl] after other meals) when hospitalized in the third trimester (51). Gillmer (52) and Persson and Lunell (53) also compared glycemic profiles of normal pregnant control and diabetic women using standard diets and split mix insulin regimens, but noted the latter had higher BG 1 h after breakfast (9.7 mM, 178 mg/dl) and lower BG at 0200–0400 (2.5 mM, 45 mg/dl).

Coustan applied the Lewis split mix regimen in 73 diabetic women to determine if tight metabolic control (a set of 3 daily BGs measured weekly) would prevent fetal jeopardy and allow pregnancies to go full term (50). Insulin requirements increased 148–253% in class F to B patients (the biggest increase was for type II diabetic women), and average peak pregnancy doses >120 U/day achieved an average FBG of 5.4 mM (98 mg/dl), 2-h postbreakfast of 6.6 mM (119 mg/dl), and presupper of 5.9 mM (106 mg/dl) for the third trimester. MBG was normalized in 77% of the treated subjects, and 42% never required antepartum hospitalization. This level of glycemic control resulted in only 1.4% antepartum fetal distress, 4% PNM (2 malformations, 1 birth trauma), and 11% fetal macrosomia (50).

Roversi administered regular insulin before each meal in maximal tolerated doses (reduced 5 U from level producing perspiration) to 199 overt diabetic women (34). Patients selected their own eating plan with the aid of a dietitian, and the average caloric content was 1,900 kcal/day. With insulin given to tolerance, the frequency of hospitalization for maternal hypoglycemia was 9.5%, but 90% of the women went into spontaneous labor at term, and only 8.5% of infants were LGA (>90th percentile birth weight for gestational age) (34). Of the 8 perinatal losses (4.5%), 6 were associated with severe diabetic vascular disease and 2 with CNS anomalies.

Other authors used split mix insulin therapy, measuring BG at weekly outpatient visits until hospital admission at 32–36 wk gestation (33,39,41,54–56), and reported fetal macrosomia rates of 24–42%. With hindsight we can say that daily BG measurements and dietary-insulin adjustments came too late in gestation, because ultrasound studies demonstrate fetal macrosomia by 28 wk in pregnancies complicated by diabetes (57–59). Another factor could have been the use of premeal BG testing as the end point of diabetes management (27,35,36,39,56,57), because peak postprandial glycemic excursions were not accounted for.

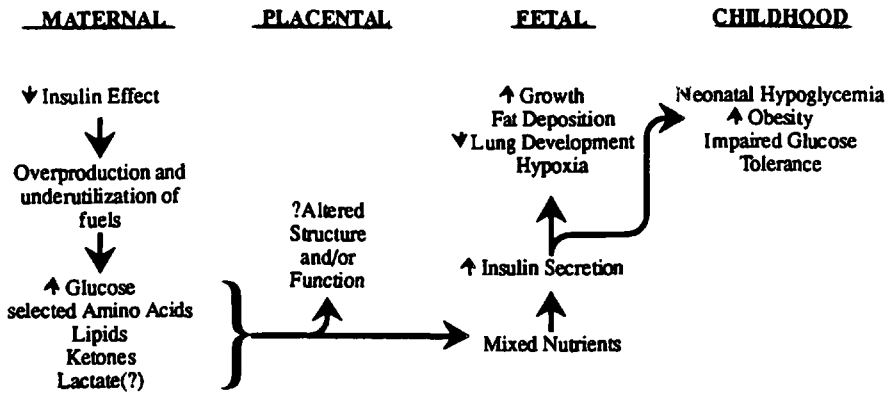

Figure 1—*Model of fetal development in pregnancies with insufficient maternal insulin secretion or action. Adapted from Freinkel and Metzger (62) and Milner (64).*

MIXED FUEL RESPONSES TO INSULIN AND FETAL MACROSOMIA— Pedersen's hypothesis to explain fetal macrosomia is the causal chain of maternal hyperglycemia to fetal hyperglycemia to fetal hyperinsulinemia equals growth and fat deposition (15). This implies that tight glycemic control should prevent the high frequency of LGA babies with their accompanying risks of shoulder dystocia and birth trauma. The observation that diabetic women with normal glycohemoglobin levels (an insensitive measure of normoglycemia) still delivered macrosomic infants raised questions whether Pedersen's hypothesis was sufficient to explain macrosomia in infants of diabetic mothers (55,60,61). Freinkel and Metzger (62,63), Milner (64), Kalkhoff (65), Thomas (66), and others expanded the concept to include the possibility that other fuel alterations related to insufficient maternal insulin action could contribute to fetal macrosomia (Fig. 1), in addition to the well-known influences of maternal obesity and weight gain. This leads us to consider data on insulin action and metabolic profiles in pregnancies complicated by diabetes.

Several investigators determined that the kinetics of injected insulin in blood is not affected by pregnancy (67–69), despite the presence of insulin-binding receptors and degrading enzymes in the placenta. Yet, the glucose disappearance rate after insulin injection is slowed in diabetic women in pregnancy compared with the nonpregnant state (69,70), despite fetal-placental utilization of glucose, suggesting gestational insulin resistance of glucose uptake by muscle and perhaps adipose tissue. This is thought to be attributable to postreceptor influences of placental hormones (human placental lactogen, progesterone, increased free cortisol secondary to estrogen-induced reductions in cortisol clearance) (71). I am not aware of studies of glucose transporters or of transcapillary-interstitial fluid insulin kinetics as determinants of insulin resistance in pregnancies complicated by diabetes (72). At any rate, the insulin resistance of pregnancy must be responsible for the widely observed progressive increase in insulin doses (range of 20–150%) required to maintain glycemic control after 14–20 wk gestation (2,3,16,29). Insulin requirements throughout pregnancy were systematically studied by Langer (73), who compared previously poorly controlled type I and II diabetic patients after initial adjustment of prepregnancy doses to achieve stability of ambulatory glycemia. In 63 type I diabetic patients, average insulin requirements rose from 0.86 U/kg before 24 wk to 1.19 U/kg at term (10% increase in second trimester, 25% more in third trimester) compared with dosage increases from 0.86 U/kg before 20 wk to 1.62 U/kg at term in 40 mostly overweight type II diabetic patients (37% increase in second trimester, 37% more in third trimester) (73).

An important point made in diurnal studies of insulin administration in pregnancy is that hyperinsulinemia is produced by clinical methods of insulin treatment of diabetic women (49,74). Postprandial peak blood levels from premeal injections may be similar to postprandial peaks of endogenous insulin in normal pregnant control subjects, but premeal plasma insulin levels may be 2–5 times normal in the diabetic women. There has been little investigation of the effects of this iatrogenic hyperinsulinemia on placental physiology, blood vessels, or the tendencies toward hypertension in pregnant diabetic women.

Stangenberg et al. (70) measured metabolic responses to intravenous injected insulin (0.1 U/kg) in 9 well-controlled diabetic women (4 without residual C-peptide secretion) at 34–36 wk gestation compared with 1 yr postpartum. Insulin produced an ~50% fall in glucose and a 20% rise in plasma lactate over 30 min (both responses were greater in the nonpregnant state), a 35% fall in FFA without change in glycerol and a 46% decline in β-HB. The insulin-induced lipid changes were similar during and after pregnancy; amino acid levels were unaffected by insulin during pregnancy; and leucine, isoleucine, and tyrosine decreased significantly in the nonpregnant state. The authors interpreted their findings to mean that 1) high doses of insulin required for normoglycemia lead to suppressed lipid mobilization, 2) pregnancy does not change insulin-induced hepatic uptake of FFA and insulin-reduced output of β-HB in diabetic women, and 3) there is decreased sensitivity to insulin restraint on

net skeletal-muscle release of amino acids during gestation (70).

Another approach is to measure diurnal changes in amino acids and lipids during standardized dietary and insulin therapy of diabetic women at different stages of pregnancy. In moderately well-controlled lean diabetic women, Kalkhoff (75) found higher premeal total plasma amino acids and six individual amino acids compared with control subjects, but branched chain amino acids did not differ. Of the amino acids, serine had the strongest correlation with infant birth weight. Gillmer (76) observed that mean diurnal FFA concentration was ~34% lower in 11 insulin-treated diabetic women with mean diurnal BG of 6.0 mM (108 mg/dl) than in pregnant control subjects.

Persson and Lunell (53) conducted three related metabolic studies in diabetic women in the third trimester. Weekly fasting FFA and β-HB (0.24–0.33 mM) were significantly higher in 21 diabetic women with MBG of ~6.5 mM (117 mg/dl) than in control subjects, but there was no correlation of MBG levels with FFA and β-HB. They considered the lack of an inverse correlation between FBG and fasting FFA, "an expression of the complex and dissociated action of exogenous insulin on lipid and carbohydrate metabolism." They also measured short-term changes throughout the day in 7 type I diabetic patients in the third trimester on their usual insulin doses and a 1,600 kcal diet. The average glucose profile ranged from 3.7 to 6.7 mM (66–120 mg/dl) premeal and 7.8–10 mM (140–180 mg/dl) postprandial. MBG was 6.9 ± 2.1 mM (125 ± 38 mg/dl) in type I compared with 5.8 ± 1.1 mM (105 ± 19 mg/dl) in 5 nondiabetic pregnant control subjects; MAGE 5.3 mM (95 mg/dl) vs. 2.5 mM (45 mg/dl). With this level of glycemic control, fasting and diurnal FFA and glycerol did not differ in diabetic patients and control subjects, but fasting β-HB was higher in type I diabetic patients (0.29 vs. 0.12 mM). Interestingly, diurnal β-HB declined by ~10 mM in the insulin-treated diabetic women, but rose before lunch and supper in diet-treated gestational diabetic women (53). Fasting β-HB levels were somewhat higher (0.6 mM) in the second trimester, especially in diabetic women without residual C-peptide secretion (77). In the third phase of the study, BG (29), FFA, and β-HB levels in 24 overtly diabetic women without ketonuria were compared with 27 patients with ketonuria (>25% of samples) (Table 3). Persson (29) concluded that "the presence of ketonuria seems to be a sensitive index of the degree of control."

Table 3—*BG, FFA, and β-HB in third trimester type I diabetes with and without ketonuria*

	With ketonuria	Without ketonuria	P value
n	27	24	0
FBG (mM)	5.6 ± 0.3	4.1 ± 0.2	<0.01
MBG* (mM)	7.2 ± 0.3	6.7 ± 0.2	NS
Fasting FFA (mM)	0.60 ± 0.03	0.55 ± 0.03	NS
Fasting β-HB (mM)	0.26 ± 0.02	0.13 ± 0.02	<0.001

Data from Persson, 1975 (29).
*Mean of 5 pre- and postmeal values.

Studying responses to a standardized meal in 15 tightly regulated pregnant type I diabetic women in the second and third trimesters, Reece et al. (74) reported that fasting and postprandial plasma branched chain amino acids, alanine, and FFA were similar to levels in nondiabetic pregnant control subjects. Fasting cholesterol and triglycerides increased to the same extent during pregnancy in women in both groups. Mean third trimester fasting blood ketones were 0.07 ± 0.05 mM in control subjects and 0.17 ± 0.23 mM in the diabetic women, but the differences were not significant, perhaps because of the small sample size. Reece et al. (74) concluded that normalization of circulating amino acids and lipids is possible in conjunction with correction of hyperglycemia in intensively treated diabetic women.

Despite the widely recognized progressive increase in insulin requirements during pregnancy, several investigators have observed that the amplitude of glycemic excursions (78) seems to become less in the third trimester (77,79). A "buffering effect" on brittleness has been speculated, but is hard to separate from the motivational effect of pregnancy on achieving smooth, regimented dietary control.

MATERNAL INSULIN-INDUCED HYPOGLYCEMIA— The most important limiting factor in intensified insulin therapy of diabetic women is the maternal CNS danger from hypoglycemic coma, which seems to come on more quickly and often without warning signs during gestation (2,3). In pregnancy, the fetal-placental unit continues to consume glucose and alanine in postabsorptive periods, and exogenous insulin may limit alternative fuel sources by restraining lipolysis (71). Fortunately, the fetus seems to be protected from maternal hypoglycemia. We have known for a long time that fetal death is not associated with severe insulin reactions (3,16). Although an early report noted developmental problems in infants of some psychiatric patients treated with insulin shock therapy in early pregnancy (80), investigators in preconception and early pregnancy trials have not noted an association between clinical insulin-induced hypoglycemic reactions and congenital malformations (81).

Possibly because of more stringent attempts at normoglycemia during

pregnancy, trials of intensified insulin therapy (34,50) revealed that symptomatic hypoglycemic episodes are more frequent (average 1–2/wk per subject) than in similar trials in nonpregnant diabetic subjects (82). The observation of Mintz et al. (83) that the growth hormone response to hypoglycemia was impaired in insulin tolerance testing of pregnant diabetic women was confirmed by Diamond et al. (84) who studied 9 well-controlled subjects at term (diabetes >10 yr in 8, autonomic neuropathy excluded) with hypoglycemic insulin clamps (2 $mU \cdot kg^{-1} \cdot min^{-1}$, BG lowered from 5.8 mM [105 mg/dl] to 2.5 mM [45 mg/dl] by 200 min). Compared with nonobese, nonpregnant, nondiabetic control subjects, they found that basal glucagon, epinephrine, and norepinephrine levels were similar in the groups, but basal growth hormone was very suppressed in late pregnancy. During hypoglycemia, glucagon declined in the pregnant diabetic women but rose in control subjects when BG reached ~3.3 mM (~60 mg/dl); cortisol rose in the diabetic women at 40 min; the rise in epinephrine was sluggish until 220 min. Hypoglycemia produced no changes in human chorionic gonadotropin or human placental lactogen in the pregnant diabetic patients. These findings indicate that pregnant diabetic patients have even more limited counterregulatory responses to hypoglycemia than type I diabetic patients in the nonpregnant state. In the latter, recent studies indicate that defective glucose counterregulatory responses, improved glycemic control (85), and glucagon suppression by persistently elevated circulating insulin levels from subcutaneous injections (86) contribute to decreased awareness of symptoms and impaired physiological defenses against hypoglycemia.

Despite the problems and risks of hypoglycemia in pregnancy, many investigators have demonstrated the safety and efficacy of intensified insulin treatment of diabetic women using frequent self-monitored capillary BG measurements and timely meals and snacks.

SMBG AND PERINATAL OUTCOME— The advent of reflectance meters for measurement of capillary BG revolutionized ambulatory diabetes care for pregnancy in the 1980s (87–89), thus enabling large numbers of women to apply self-management skills to correct hyperglycemia and prevent hypoglycemia. This advance emphasized the need for a multidiscipline team approach to teach the self-management skills, adjust the eating plan to glycemic responses and weight gain, and deal with the frequent psychological problems that may block smooth metabolic control (Fig. 2). These approaches have been outlined in detail by Freinkel, Dooley, and Metzger (90); Hollingsworth, Ney, and Moore (91); and Kitzmiller et al. (92,93).

Jovanovic and Peterson (88) used SMBG and intensive diabetes education and care to demonstrate the feasibility of achieving normal glucose profiles with split mix insulin therapy in pregnant diabetic women (5 type I, 5 type II) with high school educational backgrounds. The subjects were taught a three-step protocol to prevent episodes of hypoglycemia and caloric overcorrection (~1 symptomatic episode/wk with only 1 leading to unconsciousness throughout pregnancy). The authors observed that as

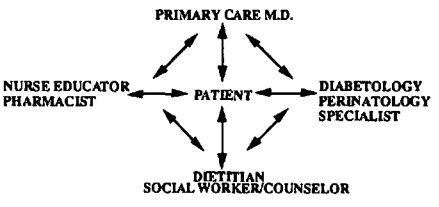

Figure 2—*Multidiscipline team approach for intensive diabetes management for pregnancy. If necessary, 24 h telephone availability is provided. Diagram developed by Gabbe and Kitzmiller.*

euglycemia was established, the BG level stimulating symptoms declined to 2.8 mM (50 mg/dl), and the sense of maternal well being was enhanced. In a subsequent report, euglycemia and appropriate perinatal management in 31 pregnant women with established diabetes normalized perinatal outcome (no perinatal loss, macrosomia, RDS, or polycythemia, and only 1 case of neonatal hypoglycemia) (94). Average insulin requirements for euglycemia (using a 30 kcal/kg desirable body weight diet) in pregnancy for lean diabetic women were 0.7 U/kg actual weight at 7 wk gestation, 0.9 U/kg at 26 wk, and 1.0 U/kg at 36 wk, compared with 1.2–3.0 U/kg at term in obese patients.

In another clinical trial of SMBG and diet-insulin therapy throughout pregnancy, Landon and Gabbe (95) taught 75 diabetic subjects to keep premeal capillary BG <6.7 mM (120 mg/dl), and 74% succeeded. The investigators found that the glycemic threshold for minimal perinatal complications (9% LGA, 2% RDS, 19% neonatal hypoglycemia) was premeal capillary BG <6.1 mM (110 mg/dl). MBG remained above that level in 32 subjects, and the outcomes were 34% LGA, 22% RDS, and 41% neonatal hypoglycemia.

Other investigators combined SMBG with dietary and insulin therapy designed to keep postprandial glycemic excursions within the normal range for pregnancy. Weiss and Hofmann (96) reported a detailed analysis of four insulin regimens in 33 Austrian subjects, including Regular insulin 4 times a day and different combinations of Regular with intermediate or long-acting insulin. Normoglycemia was achieved after 1 wk of intensive treatment; thereafter, women were taught to self-adjust insulin doses based on the pattern of BG profiles. No diabetic fetopathy was observed. Insulin requirements usually dipped 10% between 10 and 16 wk gestation and rose progressively above baseline after 26 wk gestation, by 50% at 36 wk. The rise in insulin requirement was greatest for

short-acting Regular insulin. After 35–36 wk, insulin requirements often declined (96), an observation made by many investigators (73–97). Equivalent perinatal results were achieved by Langer et al. (73), who compared responses in 63 type I diabetic patients with those of 40 type II diabetic patients, achieving rates of LGA < 10% in both groups.

In the multicenter Diabetes in Early Pregnancy Study, investigators compared mean FBG and 1-h PPBG levels in relation to infant birth weight in more than 300 pregnant women (98). After adjusting for confounding factors, PPBG at 28–32 wk was most strongly related to birth weight, and the threshold for increased risk of macrosomia seemed to be PPBG > 7.2–7.8 mM (130–140 mg/dl) and FBG > 6.7 mM (120 mg/dl). Fetal macrosomia also was common in diabetic women with weight gain >20 kg by 32 wk gestation. On the other hand, low mean PPBG levels <6.7 mM (120 mg/dl) were associated with increased frequency of small-for-gestational-age infants (<10th percentile of birth weight for gestational age and sex) (98). This result of persistently low maternal BG also was noted by Langer in insulin-treated gestational diabetic women (99), and Beischer in pregnant women with low values on glucose tolerance tests (100). Returning to the multicenter study, Jovanovic-Peterson et al. (98) concluded that "monitoring only fasting and premeal glucose concentrations, which reflect the lowest glucose levels of the day, does not provide an adequate indication of overall metabolic control and the risk of macrosomia."

The availability of SMBG and diabetes educators makes possible the use of individualized algorithms for self-adjustments of insulin dosages by pregnant diabetic women (88,89,93,101). After basic doses of Regular and intermediate insulin are established, patients can add or subtract units of Regular insulin based on premeal BG values, level of physical activity, stress, and meals in restaurants. For this system to work smoothly in pregnancy, patients must pay close attention to variability in food choices and review food and BG records with dietitians.

Cautionary words are now in order. Some programs using postprandial SMBG reported LGA frequencies of 16–29%, perhaps because strict glycemic control was only achieved after 28 wk gestation (97,102). Langer and Mazze (103) stressed the importance of using glucose meters with memory chips, because they found that 25% of 13 women with pregestational diabetes omitted capillary BG values, and 28% added glucose values that were not determined by the reflectance meter. Sequential measurement of glycoproteins is useful to detect patients who are falsifying SMBG. Finally, Diamond (104) reported that despite modern diabetes and obstetrical care, women classified as "neglectors" still have high rates of PNM and perinatal morbidity, often related to poor prepregnancy control and major congenital malformations.

The advent of human insulin allowed investigation of the role of antibodies to animal-source insulin in affecting glycemic control and pregnancy outcome. Persson (29) found no relation between levels of insulin antibodies and changes in porcine insulin requirements or degree of metabolic control in pregnancy. Weiss (96) observed no differences between the effects of human or porcine insulin in achieving normoglycemia. Based on the demonstration by Bauman and Yalow (105), that maternal immunoglobulin G insulin antibodies can transport insulin across the placenta into fetal blood, Sperling et al. (106) reported that diabetic women with insulin antibodies were more likely to have macrosomic infants, although glycemic control was not analyzed. A subsequent report from the same institution negated the idea that women treated with human insulin (with presumably lower levels of insulin antibodies) had less risk for fetal macrosomia (107). In the only prospective controlled trial of human versus animal insulin during pregnancy, maternal or infant insulin antibody levels were not related to type of insulin used (108). However, the group of type I diabetic patients randomized to human insulin before 20 wk gestation had fewer BG values beyond therapeutic range, fewer LGA infants, and lower infant C-peptide response to glucose/amino acid challenge at 3 mo of age (108).

INNOVATIVE INSULIN DELIVERY SYSTEMS IN PREGNANCY—

Several investigators established the feasibility of obtaining normoglycemia with CSII pump therapy in type I diabetic women in early (109) and later pregnancy (110–114). Coustan et al. (115) randomized 22 comparable pregnant diabetic women to intensive conventional or insulin pump therapy in the 1st trimester. MBG (premeal and postprandial) was <6.7 mM (120 mg/dl) in the majority of women in both treatment groups, and there was no significant difference in the glycohemoglobin values or the frequency of moderate or severe hypoglycemic episodes. Insulin requirements were lower with the insulin pump therapy in the 2nd (1.02 vs. 1.40 $U \cdot kg^{-1} \cdot day^{-1}$) and 3rd trimesters (1.26 vs. 1.63 $U \cdot kg^{-1} \cdot day^{-1}$) (115), but pump therapy still produced hyperinsulinemia compared with nondiabetic pregnant women (74). Fasting and postprandial amino acid and lipid levels were comparable in the two insulin treatment groups and in a nondiabetic pregnant control group (74). Workers in this field conclude that insulin pump therapy can be advantageous in a minority of cautious, responsible, type I diabetic pregnant women. The indications include convenience of flexible timing of insulin bolus doses and meals; tendency toward wide glycemic excursions from low to high despite adherence to the eating plan; and trouble with nocturnal hypoglycemia or the dawn phenomenon of increasing insulin requirements after

0400, although the presence of the latter during pregnancy is disputed by Hollingsworth (91).

Irsigler (116) has studied the feasibility of intraperitoneal insulin infusion systems in type I diabetic women before and during pregnancy in Vienna. His indications were similar to those given for CSII therapy. I am not aware of controlled studies comparing this method with intensified conventional insulin therapy in pregnant women.

Table 4—*Prevention of major congenital malformations in infants of diabetic women, particularly in preconception clinical trials*

		Preconception group		Registered already pregnant	
Author	Date	Infants	Anomalies* (%)	Infants	Anomalies* (%)
Fuhrmann	1983, 1984	185	2 (1.1)	473	31 (6.6)
Goldman	1986	44	0	31	2 (6.5)
Damm	1989	197	2 (1.0)	61	5 (8.2)
Steel	1990	143	2 (1.4)	96	10 (10.4)
Kitzmiller	1991	84	1 (1.2)	110	12 (10.4)
Total		653	7 (1.1)	771	60 (7.8)

Estimated costs of neonatal care for infants with anomalies were $400,600 for the preconception group and $3,430,900 for the registered already pregnant group. Types of anomalies taken from Kitzmiller et al. (131). Costs in 1990 dollars taken from Elixhauser A and Weschler JM: Battelle—CDC report on *Cost Benefit Analysis of Preconception Care for Women with Established Diabetes Mellitus.*

* Includes pregnancy terminations for anencephaly and prosencephaly.

FUTURE DIRECTIONS: PRECONCEPTION CARE, DEVELOPMENT OF OFFSPRING, PREECLAMPSIA

— At present, major congenital malformations are the leading cause of PNM and serious morbidity in infants of diabetic mothers. Experimental work with rodent embryos indicates that high glucose and β-HB concentrations are teratogenic (117). Insulin therapy in diabetic animal models can prevent the embryopathy (118). Many clinical studies (119–124), with only one exception (125), link a high risk for malformations with poor control of diabetes early in pregnancy, as marked by greatly elevated glycohemoglobin values in the first trimester. Because the malformations occur by 5–8 wk from the last menstrual period, investigators reasoned that organized preconception care of diabetes will be necessary to reduce the frequency of major anomalies to the "normal" level of 2%. In the last decade, seven preconception clinical trials demonstrated this result (Table 4) (126–131). Normalizing the increased frequency (25–40%) of early pregnancy loss associated with poor control of diabetes (132,133) is another benefit of preconception care (134,135), as is the opportunity to evaluate maternal vascular disease and prevent the development of proliferative retinopathy, which may be associated with a too rapid correction of hyperglycemia. In our own preconception trial, the level of glycemic control before and in the first weeks of pregnancy that was sufficient to prevent anomalies averaged 1-h PPBG < 10 mM (180 mg/dl) and produced near normalization of glycohemoglobin (131).

The problem remaining is how to achieve this result for an entire population of diabetic women and sexually active girls. Success has been reported in Denmark (129) and Sweden (123) based on intensive public and professional education campaigns and generalized improvement in glycemic control. In the United States, investigators have had limited success in recruiting diabetic women for preconception care (~20% in areas with public campaigns). One approach is to convince third-party payers to make it in the financial interest of their clients to participate in preconception care, because prevention of major congenital anomalies will save huge medical costs. Another is to convince practitioners that it is worth the time, effort, and motivational techniques required to improve glycemic control for all individuals with diabetes. To accomplish this, the old insistence of White and Pedersen on the importance of centralized care of diabetes for pregnancy will probably not work in North America. In Maine, a traveling team of diabetes educators has taken preconception care to rural towns (136). Another state health department funded the California Diabetes and Pregnancy Program, which has had success establishing patient education and treatment programs in >35 communities and is backed by regional perinatal centers. As reported by Cousins (137) for the California Diabetes and Pregnancy Program, for 572 pregnant women with pregestational diabetes (two-thirds type I, 40% women of color), this model of decentralized care was effective in lowering frequencies of PNM (2.4%), hypoglycemic coma (0.9%), KTA (3.1%), and hospital admissions for diabetes control (28.4%, compared with nearly 100% 20 yr ago). However, neonatal morbidity was still too common, with 6.1% major congenital anomalies and 31% LGA infants (137).

Another challenge for the future is to determine the level of diabetic control necessary to produce normally developing offspring, assuming congenital malformations can be prevented. Obesity in children has been linked to prior in utero fetal islet stimulation (138). Older, controversial data on childhood intellectual function should receive renewed attention based on recent studies. In 1969, Farquhar of Edinburgh (19) reported on a follow-up of 210 children of insulin-treated diabetic women. Only 5 children had "educational subnormality," but 20 had congenital abnormalities, 10% were

less than the 3rd percentile for height, and >20% had excessive weight by adolescence. Yssin (139) examined 152 Danish children of diabetic women 2–10 yr after birth (mean 4.5) in the 1960s. Major cerebral dysfunction was found in 16.5%, and 12% had minor problems with speech and reading or behavior disorders. The dysfunctions were strongly associated with low maternal estriol excretion in the index pregnancies, suggesting an association with poor diabetic control, uteroplacental vascular insufficiency, and intrauterine growth retardation. More recent reports from Molsted-Pedersen et al. (140,141) in Copenhagen link subnormal performance on developmental tests at 4–5 yr of age to early fetal growth delay on ultrasound measurements at 8–14 wk gestation (140), a problem associated with poor diabetes control in early pregnancy (141).

Churchill et al. (142) found lower neuropsychological test scores at 4 yr of age in children of 55 diabetic mothers with ketonuria in late pregnancy, but there was no association with insulin-induced maternal hypoglycemia. Infants <2,000 g were excluded from the study. Children of 18 acetone-negative diabetic mothers did not differ from control subjects. The authors postulated that ketonuria may signal episodes when maternal FFA and amino acids are being catabolized to increase the ketoacid pool for use as energy, which may decrease amino acids available for fetal cerebral development (142). Alternatively, evidence exists that β-HB crosses the placenta and is metabolized by fetal brain (143). Churchill's results were disputed when reanalysis of the data suggested that amnionitis could explain the results (144). However, Stehbens (145) also reported lower IQ at 5 yr of age, when controlled for birth weight, in 23 children of diabetic mothers who had experienced acetonuria in the last trimester.

In the last two years, Rizzo et al. (146,147) at Northwestern University reported results of their long-term studies of the relationship of perturbations of maternal fuels in diabetic and control subjects to development of offspring. In diabetic women, mean maternal FBG (range 3.8–8.3 mM [69–150 mg/dl]) and glycohemoglobin in the second and third trimesters, but not β-HB, had inverse correlations with three newborn behavior assessments (interactive, motoric, and physiological control) when controlled for perinatal events and socioeconomic status (146). In the child follow-up study (147), maternal hypoglycemia (average 1/wk) and infrequent maternal ketonuria were not related to IQ performance of offspring at 4 yr of age, but a significant correlation was noted with mean fasting β-HB in the second and third trimesters (range, 0.004–0.72 mM). The authors postulated that childhood IQ performance is affected by poor lipid metabolic regulation during pregnancy (147). Now that ketone meters are available, investigators should be able to determine the association between the usual indicators of diabetic control and diurnal ketonemia in large numbers of diabetic women, to test its association with embryopathy in early pregnancy and development of the brain in later gestation.

One constant over the 50 years of development of treatments for diabetes and pregnancy has been the persistently high frequency (12–39%) of the maternal preeclamptic syndrome (8,14,22,25, 35,42,95,137). It often is superimposed on chronic hypertension and diabetic nephropathy (47,48) (which makes diagnosis difficult), but also is frequent in normotensive diabetic women without microproteinuria (148–150). At present, the syndrome is still a common factor in perinatal death and early preterm delivery, which brings us back to the pioneer days of White (2,3) and Pedersen (22,23), who demonstrated the importance of toxemia as a determinant of PNM for infants of diabetic mothers. We do not know why preeclamptic toxemia is so common in these women. One theory focuses on lesions of the uterine arteries, which could reduce uteroplacental blood flow (151). But could aspects of glycemic control affect blood vessels and set up diabetic women for preeclampsia? There is new interest in the idea that endogenous (type II diabetes, gestational diabetes mellitus) or exogenous hyperinsulinemia (all types) may be a culprit (152–154).

References

1. Ney D, Hollingsworth DR: Nutritional management of pregnancy complicated by diabetes: historical perspective. *Diabetes Care* 4:647–55, 1981
2. White P: Pregnancy complicating diabetes. *JAMA* 128:181–82, 1945
3. White P: Pregnancy complicating diabetes. *Am J Med* 7:609–16, 1949
4. White P, Gillespie L, Sexton L: Use of female sex hormone therapy in pregnant diabetic patients. *Am J Obstet Gynecol* 71:57–69, 1956
5. Nelson HB, Gillespie L, White P: Pregnancy complicated by diabetes mellitus. *Obstet Gynecol* 1:219–25, 1953
6. Reis RR: Discussion of White's "Use of female sex hormone therapy." *Am J Obstet Gynecol* 71:68–69, 1956
7. Eastman NJ: Diabetes mellitus and pregnancy. *Obstet Gynecol Surv* 1:3–31, 1946
8. Hurwitz D, Higano N: Diabetes and pregnancy. *N Engl J Med* 247:305–309, 1952
9. Reis RA, deCosta EJ, Allweiss MD: The management of the pregnant diabetic woman and her newborn infant. *Am J Obstet Gynecol* 60:1023–39, 1950
10. Long NW, Hartmann WL, Futcher PH, Eastman NJ: Diabetes mellitus and pregnancy. *Obstet Gynecol* 3:160–68, 1954
11. Jones WL: Diabetes in pregnancy. *Am J Obstet Gynecol* 66:322–34, 1953
12. Oakley WG: The evolution of the management of diabetic pregnancy. *Postgrad Med J* 45:802–805, 1969
13. Peel J: A historical review of diabetes and pregnancy. *J Obstet Gynaecol Br Commonw* 79:385–95, 1972

14. Drury MI, Greene AT, Stronge JM: Pregnancy complicated by clinical diabetes mellitus: A study of 600 pregnancies. *Obstet Gynecol* 49:519–22, 1977
15. Pedersen J: *The Pregnant Diabetic and Her Newborn: Problems and Management*. Baltimore, Williams & Wilkins, 1977
16. Pedersen J: Course of diabetes during pregnancy. *Acta Endocrinol* 9:342–64, 1952
17. Pedersen J: Fetal mortality in diabetics in relation to management during the latter part of pregnancy. *Acta Endocrinol* 15:282–94, 1954

18a. Pedersen J, Brandstrup E: Fetal mortality in pregnant diabetics: strict control of diabetes with conservative obstetric management. *Lancet* i:607–12, 1956

18b. Zorowitz H, Motz A: Management of diabetes in pregnancy. *Obstet Gynecol* 27:820–26, 1966

19. Farquhar JW: Prognosis for babies born to diabetic mothers in Edinburgh. *Arch Dis Child* 44:36–47, 1969
20. Oakley WG: Prognosis in diabetic pregnancy. *Brit Med J* 1:1403–15, 1953
21. Essex NL, Pyke DA, Watkins PJ: Diabetic pregnancy. *Br Med J* 4:89–93, 1973
22. Pedersen J, Molsted-Pedersen L: Prognosis of the outcome of pregnancies in diabetics: a new classification. *Acta Endocrinol* 50:70–78, 1965
23. Pedersen J, Molsted-Pedersen L, Andersen B: Assessors of fetal perinatal mortality in diabetic pregnancy. *Diabetes* 23:302–305, 1974
24. Pedersen J: Weight and length at birth of infants of diabetic mothers. *Acta Endocrinol* 16:330–42, 1954
25. Harley JMG, Montgomery DAD: Management of pregnancy complicated by diabetes. *Br Med J* 1:14–18, 1965
26. Delaney JJ, Ptacek J: Three decades of experience with diabetic pregnancies. *Am J Obstet Gynecol* 106:550–56, 1970
27. Karlsson K, Kjellmer I: The outcome of diabetic pregnancies in relation to the mother's blood sugar level. *Am J Obstet Gynecol* 112:213–20, 1972
28. Persson B, Lunell N, Carlstrom K, Furuhjelm M: Urinary oestriol excretion in strictly controlled diabetic pregnancies. *Acta Obstet Gynecol Scand* 49:379–84, 1970
29. Persson B: Treatment of diabetic pregnancy. *Isr J Med Sci* 11:609–18, 1975
30. Brudenell M, Beard R: Diabetes in pregnancy. *Clin Endocrinol Metab* 1:673–95, 1972
31. Brudenell M: *Care of the Clinical Diabetic Woman in Pregnancy and Labour*. Sutherland HW, Stowers JM, Ed. New York, Churchill Livingstone, 1975, p. 221–29
32. Gabbe SG, Mestman JJ, Freeman RK, Goeblesmann UT, Lowensohn RI, Nochimson D, Cetrulo C, Quilligan EJ: Management and outcome of pregnancy in diabetes mellitus, classes B to R. *Am J Obstet Gynecol* 129:723–31, 1977
33. Kitzmiller JL, Cloherty JP, Younger MD, Tabatabaii A, Rothchild SB, Sosenko I, Epstein MF, Singh S, Neff RK: Diabetic pregnancy and perinatal morbidity. *Am J Obstet Gynecol* 131:560–80, 1978
34. Roversi GD, Gargiulo M, Nicolini U, Pedretti E, Marini A, Barbarani V, Peneff P: A new approach to the treatment of diabetic pregnant women. *Am J Obstet Gynecol* 135:567–76, 1979
35. Tevaarwerk GJM, Harding PGR, Milne KJ, Jaco NT, Rodger NW, Hurst C: Pregnancy in diabetic women: outcome with a program aimed at normoglycemia before meals. *Can Med Assoc J* 125: 435–40, 1981
36. Gugliucci CL, O'Sullivan MJ, Opperman W, Gordon M, Stone ML: Intensive care of the pregnant diabetic. *Am J Obstet Gynecol* 125:435–41, 1976
37. Ayromlooi J, Mann LI, Weiss RR, Tejani N, Paydar M: Modern management of the diabetic pregnancy. *Obstet Gynecol* 49:137–43, 1977
38. Gyves MT, Rodman HM, Little AB, Fanaroff AA, Merkatz IR: A modern approach to management of pregnant diabetics: a two-year analysis of perinatal outcomes. *Am J Obstet Gynecol* 128: 606–12, 1977
39. Leveno KJ, Hauth JC, Gilstrap LC, Whalley PJ: Appraisal of "rigid" blood glucose control during pregnancy in overtly diabetic women. *Am J Obstet Gynecol* 135:853–62, 1979
40. Jervell J, Moe N, Skjaeraasen J, Blystad W, Egge K: Diabetes mellitus and pregnancy: management and results at rikshospitalet, Oslo. 1970–1977. *Diabetologia* 16:151–55, 1979
41. Lavin JP Jr, Lovelace DR, Miodovnik M, Knowles HC, Barden TP: Clinical experience with one hundred seven diabetic pregnancies. *Am J Obstet Gynecol* 147: 742–52, 1983
42. Mimouni F, Miodovnik M, Siddiqi TA, Khoury J, Tsung RC: Glycemic control and prevention of perinatal asphyxia. *J Pediatr* 113:345–53, 1988
43. Cassar J, Gordon H, Dixon HG, Cummins M, Joplin GF: Simplified management of pregnancy complicated by diabetes. *Br J Obstet Gynecol* 85:585–91, 1977
44. Schneider JM, Curet LB, Olson RW, Shay G: Ambulatory care of the pregnant diabetic. *Obstet Gynecol* 56:144–49, 1980
45. Law SW, Gibbons W, Poindexter AN: Patient cooperation: a determinant of perinatal outcome in the pregnant diabetic. *J Repro Med* 24:197–201, 1980
46. Diamond MP, Vaughn WK, Salyer SL, Cotton RB, Fields LM, Boehm FH: Efficacy of outpatient management of insulin-dependent diabetic pregnancies. *Am J Perinatol* 5:2–8, 1983
47. Kitzmiller JL, Brown ER, Phillippe M, Stark AR, Acker D, Kaldany A, Singh S, Hare J: Diabetic nephropathy and perinatal outcome. *Am J Obstet Gynecol* 141: 741–51, 1981
48. Reece EA, Coustan DR, Hayslett JP, Holford T, Coulehan J, O'Connor TZ, Hobbins JC: Diabetic nephropathy: pregnancy performance and fetomaternal outcome. *Am J Obstet Gynecol* 159: 56–66, 1988
49. Lewis SB, Wallin JD, Kuzuya H, Murray WK, Coustan DR, Daane TA, Rubenstein AH: Circadian variation of serum glucose, C-peptide immunoreactivity and free insulin in normal and insulin-treated diabetic pregnant subjects. *Diabetologia* 12:343–50, 1976
50. Coustan DR, Berkowitz RI., Hobbins

JC: Tight metabolic control of overt diabetes in pregnancy. *Am J Med* 68:845–52, 1980
51. Lewis SB, Murray WK, Wallin JD, Coustan DR, Daane TA, Tredway DR, Navins JP: Improved glucose control in nonhospitalized pregnant diabetic patients. *Obstet Gynecol* 48:260–67, 1976
52. Gillmer MDG, Oakley NW, Brooke RM, Beard RW: Metabolic profiles in pregnancy. *Isr J Med Sci* 11:601–608, 1975
53. Persson B, Lunell NO: Metabolic control in diabetic pregnancy. *Am J Obstet Gynecol* 122:737–45, 1975
54. Adashi EY, Pinto H, Tyson JE: Impact of maternal euglycemia on fetal outcome in diabetic pregnancy. *Am J Obstet Gynecol* 133:268–74, 1979
55. Miller JM: A reappraisal of "tight control" in diabetic pregnancies. *Am J Obstet Gynecol* 147:158–60, 1983
56. Lin C, River J, River P, Blix P, Hoawad A: Good diabetic control early in pregnancy and favorable fetal outcome. *Obstet Gynecol* 67:51–56, 1986
57. Willman SP, Leveno KJ, Guzick DS, Williams ML, Whalley PJ: Glucose threshold for macrosomia in pregnancy complicated by diabetes. *Am J Obstet Gynecol* 154:470–75, 1986
58. Weiss PAM, Winter R, Pürstner P: Insulin levels in amniotic fluid. *Obstet Gynecol* 51:393–97, 1978
59. Bochner CJ, Mediaris AL, Williams J, Castro L, Hobel CJ, Wade ME: Early third trimester ultrasound screening in gestational diabetes to determine the risk of macrosomia and labor dystocia at term. *Am J Obstet Gynecol* 157:703–708, 1987
60. O'Shaughnessy RJ, Zuspan FP: Glycosylated hemoglobins and diabetes mellitus in pregnancy. *Am J Obstet Gynecol* 135:783–90, 1979
61. Stubbs SM, Leslie RDG, John PN: Fetal macrosomia and maternal diabetic control in pregnancy. *Br Med J* 282:439–40, 1981
62. Freinkel N, Metzger BE: Pregnancy as a tissue culture experience: the critical implications of maternal metabolism for fetal development. In *Proceedings CIBA Foundation Symposium*. Elliot K, O'Connor M, Another AM, Eds. 63:3–23, 1979
63. Freinkel N: Of pregnancy and progeny. *Diabetes* 29:1023–35, 1980
64. Milner RDG: Amino acids and beta cell growth in structure and function. In *The Diabetic Pregnancy: A Perinatal Perspective*. Merkatz IR, Adam PAJ, Eds. New York, Grune and Stratton, 1979, p. 145–53
65. Kalkhoff RK: Impact of maternal fuels and nutritional state on fetal growth. *Diabetes* 40 (Suppl. 2):61–65, 1991
66. Thomas CR: Placental transfer of non-esterified fatty acids in normal and diabetic pregnancy. *Biol Neonate* 51:94–101, 1987
67. Burt L, Davidson IWF: Insulin half-life and utilization in normal pregnancy. *Obstet Gynecol* 43:161–64, 1974
68. Bellmann O, Hartmann E: Influence of pregnancy on the kinetics of insulin. *Am J Obstet Gynecol* 122:829–32, 1975
69. Lind T, Bell S, Gilmore E, Huisjes HJ, Schelly AV: Insulin disappearance rate in pregnant and non-pregnant women, and in non-pregnant women given GHRIH. *Eur J Clin Invest* 7:47–51, 1977
70. Stangenberg M, Persson B, Fredholm BB, Lindblad BS, Stange L: Insulin-induced hypoglycaemia in diabetic women during late pregnancy and one year post partum. *Br J Obstet Gynecol* 88:619–27, 1981
71. Norton M, Buchanan T, Kitzmiller JL: The endocrine pancreas and maternal metabolism. In *Maternal-Fetal Endocrinology*. 2nd ed. Tulchinsky DT, Little B, Eds. Philadelphia, PA, Saunders. In press
72. Ader M, Poulin RA, Yang YJ, Bergman RN: Dose-response relationship between lymph insulin and glucose uptake reveals enhanced insulin sensitivity of peripheral tissues. *Diabetes* 41:241–53, 1991
73. Langer O, Anyaegbunam A, Brustman L, Guidetti D, Levy J, Mazze R: Pregestational diabetes: insulin requirements throughout pregnancy. *Am J Obstet Gynecol* 159:616–21, 1988
74. Reece EA, Coustan DR, Sherwin RS, Tuck S, Bates S, O'Connor T, Tamborlane V: Does intensive glycemic control in diabetic pregnancies result in normalization of other metabolic fuels? *Am J Obstet Gynecol* 165:126–30, 1991
75. Kalkhoff RK, Kandaraki E, Morrow PG, Mitchell TH, Kelber S, Borkowf HI: Relationship between neonatal birth weight and maternal plasma amino acid profiles in lean and obese nondiabetic women and in type I diabetic pregnant women. *Metabolism* 37:234–39, 1988
76. Gillmer MDG, Beard RW, Oakley NW, Brooke FM, Elphick MC, Hull D: Diurnal plasma free fatty acid profiles in normal and diabetic pregnancies. *Br Med J* 2:670–73, 1977
77. Stangenberg M, Persson B, Fredholm BB, Lunell NO: Profiles of intermediary metabolites in insulin-dependent pregnant diabetic women with or without endogenous insulin production. *Diabetes Care* 5:409–13, 1982
78. Artal R, Golde SH, Dorey F, McClellan SN, Gratacos J, Lirette T, Montoro M, Wu PYK, Anderson B, Mostran J: The effect of plasma glucose variability on neonatal outcome in the pregnant diabetic patient. *Am J Obstet Gynecol* 147: 537–41, 1983
79. Lev-Ran A, Goldman JA: Brittle diabetes in pregnancy. *Diabetes* 26:926–30, 1977
80. Impastato DJ, Gabriel AR, Lardaro HH: Electric and insulin shock therapy during pregnancy. *Dis Nerv Syst* 25:542–46, 1964
81. Combs CA, Kitzmiller JL: Spontaneous abortion and congenital malformations in diabetes. *Clin Obstet Gynecol* 5:315–32, 1991
82. DCCT Research Group: Diabetes control and complications trial (DCCT): results of feasibility study. *Diabetes Care* 10:1–19, 1987
83. Mintz DH, Stock R, Finster JL, Taylor AL: The effect of normal and diabetic pregnancies on growth hormone responses to hypoglycemia. *Metabolism* 17:54–61, 1968
84. Diamond MP, Reece EA, Caprio S, Jones TW, Amiel S, DeGennaro N, Laudano A, Addabo M, Sherwin RS, Tamborlane WV: Impairment of counterregulatory hormone responses to hypoglycemia in pregnant women with insulin-dependent diabetes mellitus.

Am J Obst Gynecol 166:70–77, 1992
85. Clarke WL, Gonder-Frederick LA, Richards FE, Cryer PE: Multifactorial origin of hypoglycemic symptom unawareness in IDDM: association with defective glucose counterregulation and better glycemic control. *Diabetes* 49:680–85, 1991
86. Liu D, Adamson U, Lins P, Kollind M, Moberg E, Andreasson K: Inhibitory effect of circulating insulin on glucagon secretion during hypoglycemia in type I diabetic patients. *Diabetes Care* 15:59–65, 1992
87. Irsigler K, Bali-Taubald C: Self-monitored blood glucose: the essential biofeedback signal in the diabetic patient's effort to achieve normoglycemia. *Diabetes Care* 3:163–70, 1980
88. Jovanovic L, Peterson C, Saxena B, Dawood MY, Saudek C: Feasibility of maintaining normal glucose profiles in insulin-dependent pregnant diabetic women. *Am J Med* 68:105–12, 1980
89. Skyler JS, O'Sullivan MJ, Robertson EG, Skyler DL, Holsinger KK, Lasky IA, McLeod AGW, Burkett G, Mintz DH: Blood glucose control during pregnancy. *Diabetes Care* 3:69–76, 1980
90. Freinkel N, Dooley SL, Metzger BE: Care of the pregnant woman with insulin-dependent mellitus. *N Engl J Med* 313:96–101, 1985
91. Hollingsworth DR: *Pregnancy Diabetes and Birth: A Management Guide*. 2nd ed. Baltimore, Williams & Wilkins, 1992
92. Kitzmiller JL: Sweet success: teaching diabetes and pregnancy management. *Diabetes Educator* 19:5s–47s, 1983
93. Kitzmiller JL, Gavin LA, Gin GD, Iverson M, Gunderson E, Farley P, Cohen H, Scheerer L: Managing diabetes and pregnancy. *Curr Prob Obstet Gynecol Fertil* 11:105–67, 1988
94. Jovanovic L, Druzin M, Peterson C: Effect of euglycemia on the outcome of pregnancy in insulin-dependent diabetic women as compared with normal control subjects. *Am J Med* 71:921–27, 1981
95. Landon M, Gabbe S, Piana R, Mennuti M, Main E: Neonatal morbidity in pregnancy complicated by diabetes mellitus: Predictive value of maternal glycemic profiles. *Am J Obstet Gynecol* 156: 1089–95, 1987
96. Weiss PAM, Hofmann H: Intensified conventional insulin therapy for the pregnant diabetic patient. *Obstet Gynecol* 64:629–37, 1984
97. Rayburn W, Piehl E, Lewis E, Schork A, Sereika S, Zabrensky K: Changes in insulin therapy during pregnancy. *Am J Perinatol* 2:271–75, 1985
98. Jovanovic-Peterson L, Peterson C, Reed G, Metzger B, Mills J, Knopp R, Aarons J, National Institute of Child Health and Human Development Diabetes in Early Pregnancy Study: maternal postprandial glucose levels and infant birth weight: the diabetes in early pregnancy study. *Am J Obstet Gynecol* 164:103–11, 1991
99. Langer O: Prevention of macrosomia. *Clin Obstet Gynecol* 5:333–48, 1991
100. Abell DA, Beischer NA: Evaluation of the three-hour oral glucose tolerance test in detection of significant hyperglycemia and hypoglycemia in pregnancy. *Diabetes* 24:874–80, 1975
101. Jovanovic L, Peterson CM: Optimal insulin delivery for pregnant diabetic patients. *Diabetes Care* 5 (Suppl. 1):24–31, 1982
102. Budhraja M, Danel I: Control of overt maternal diabetes during pregnancy in a county hospital. *Arch Intern Med* 146: 311–15, 1986
103. Langer O, Mazze R: Diabetes in pregnancy: evaluating self-monitoring performance and glycemic control with memory-based reflectance meters. *Am J Obstet Gynecol* 155:635–37, 1986
104. Diamond MP, Salyer SL, Vaughn WK, Cotton R, Boehm FH: Reassessment of White's classification and Pedersen's prognostically bad signs of diabetic pregnancies in insulin-dependent diabetic pregnancies. *Am J Obstet Gynecol* 156:599–604, 1987
105. Bauman WA, Yalow RS: Transplacental passage of insulin complexed to antibody. *Proc Natl Acad Sci USA* 78:4588–90, 1981
106. Menon RK, Cohen RM, Sperling MA, Cutfield WS, Minouni F, Khoury JC: Transplacental passage of insulin in pregnant women with insulin dependent diabetes mellitus: its role in fetal macrosomia. *N Engl J Med* 323:309–15, 1990
107. Rosenn B, Miodovnik M, Combs CA, Williams T, Wittikind C, Siddigi TA: Human versus animal insulin in the management of insulin dependent diabetes: lack of effect on fetal growth. *Obstet Gynecol* 78:590–93, 1991
108. Jovanovic-Peterson L, Kitzmiller JL, Peterson CM: Randomized trial of human versus animal species insulin in diabetic pregnant women: improved glycemic control, not fewer antibodies to insulin, influences birth weight. *Am J Obstet Gynecol.* 167:1325–30, 1992
109. Kitzmiller JL, Younger MD, Hare JW, Phillippe M, Vignati L, Fargnoli B, Grause A: Continuous subcutaneous insulin therapy during early pregnancy. *Obstet Gynecol* 66:606–11, 1985
110. Potter JM, Reckless JPD, Cullen DR: Subcutaneous continuous insulin infusion and control of blood glucose concentrations in a diabetic in third trimester of pregnancy. *Br Med J* 1:1099–101, 1980
111. Rudolf MCJ, Coustan DR, Sherwin RS, Bates SE, Felig P, Genel M, Tamborlane WV: Efficacy of the insulin pump in the home treatment of pregnant diabetics. *Diabetes* 30:891–95, 1981
112. Cohen AW, Liston RM, Mennuti MT, Gabbe SG: Glycemic control in pregnant diabetic women using a continuous subcutaneous insulin infusion pump. *J Reprod Med* 27:651–54, 1982
113. Edwards CQ, Cannon RB, Haug PJ, Farnsworth KW: Control of diabetes during pregnancy using continuous insulin infusion. *West J Med* 136:249–51, 1982
114. Hertz H, King KC, Kalhan SC: Management of third-trimester diabetic pregnancies with the use of subcutaneous insulin infusion therapy. *Am J Obstet Gynecol* 149:256–60, 1984
115. Coustan DR, Reece EA, Sherwin RS, Rudolf MC, Bates SE, Sockin SM, Holford T, Tamborlane WV: A randomized clinical trial of the insulin pump vs. intensive conventional therapy in diabetic pregnancies. *JAMA* 255:631–36, 1986

116. Irsigler K, Leodolter S, Rosenkranz A, Bali C, Kritz H, Rost I, Fuch G, Marcovich M, Fuernkranz H: Different approaches toward normoglycemia in pregnancy: the Vienna experience. In *Diabetes and Pregnancy*. Jovanovic L, Peterson CM, Fuhrmann K, Eds. New York, Praeger 1986, p. 263–90
117. Eriksson UJ: Diabetes in pregnancy: Effects on post-implantation embryos. *Isr J Med Sci* 27:478–86, 1991
118. Eriksson RSM, Thunberg L, Eriksson UJ: Effects of interrupted insulin treatment on fetal outcome of pregnant diabetic rats. *Diabetes* 38:764–72, 1989
119. Miller E, Hare JW, Cloherty JP, Duan PJ, Gleason RE, Soeldner JS, Kitzmiller JL: Elevated maternal hemoglobin A in early pregnancy and major congenital anomalies in infants of diabetic mothers. *N Engl J Med* 304:1441–43, 1981
120. Ylinen K, Alua P, Stenman U-H, Kesaniemi-Kuokkanen T, Teramo K: Risk of minor and major fetal malformations in diabetes with high haemoglobin A values in early pregnancy. *Br Med J* 4:345–46, 1984
121. Miodovnik M, Minouni F, Dignan PS, Berk MA, Ballard JL, Siddiqi TA, Khoury J, Tsang R: Major malformations in infants of IDDM women: vasculopathy and early first-trimester poor glycemic control. *Diabetes Care* 11: 713–78, 1988
122. Key TC, Giuffrida R, Moore TR: Predictive value of early pregnancy glycohemoglobin in the insulin treated diabetic patient. *Am J Obstet Gynecol* 156:1096–1100, 1987
123. Hanson U, Persson B, Thunell S: Relationship between haemoglobin AIC in early Type I (insulin-dependent) diabetic pregnancy and the occurrence of spontaneous abortion and fetal malformation in Sweden. *Diabetologia* 33: 100–104, 1990
124. Greene MP, Hare JW, Cloherty JP, Benacerraf BR, Soeldner JS: First trimester hemoglobin AI, and risk of major malformation and spontaneous abortion in diabetic pregnancy. *Teratology* 39:225–31, 1989
125. Mills JL, Knopp RH, Simpson JL, Jovanovic L, Metzger BE, Holmes LB, Aarons JH, Brown Z, Reed GF, Bieber FR, Van Allen M, Holzman I, Ober C, Peterson CM, Withiam MJ, Duckles A, Mueller-Heubach E, Polk BF, The National Institute of Child Health and Human Development Diabetes in Early Pregnancy Study: Lack of relation of increased malformation rates in infants of diabetic mothers to glycemic control during organogenesis. *N Engl J Med* 318:671–76, 1988
126. Fuhrmann K, Reiher H, Semmler K, Fischer F, Fischer M, Glockner E: Prevention of congenital malformations in infants of insulin-dependent diabetic mothers. *Diabetes Care* 6:219–23, 1983
127. Fuhrmann K, Reiher H, Semmler K, Glockner E: The effect of intensified conventional insulin therapy before and during pregnancy on the malformation rate in offspring of diabetic mothers. *Exp Clin Endocrinol* 83:173–77, 1984
128. Goldman JA, Dickerd D, Feldberg D: Pregnancy outcome in patients with insulin-dependent diabetes mellitus with pre-conceptual diabetic control: a comparative study. *Am J Obstet Gynecol* 155: 193–97, 1986
129. Damm P, Molsted-Pedersen L: Significant decrease in congenital malformations in newborn infants of an unselected population of diabetic women. *Am J Obstet Gynecol* 161:1163–67, 1989
130. Steel JM, Johnstone FD, Hepburn DA, Smith A: Can prepregnancy care of diabetic women reduce the risk of abnormal babies? *Br Med J* 301:1070–74, 1990
131. Kitzmiller JL, Gavin LA, Gin GD, Jovanovic L, Main EK, Zigrang WD: Preconception care of diabetes: glycemic control prevents congenital anomalies. *JAMA* 265:731–36, 1991
132. Miodovnik M, Skillman C, Holroyde JC, Butler JB, Wendel JS, Siddiqi TA: Elevated maternal glycohemoglobin in early pregnancy and spontaneous abortion among insulin-dependent diabetic women. *Am J Obstet Gynecol* 153:439–42, 1985
133. Mills JL, Simpson JL, Driscoll SG, Jovanovic L, Van Allen M, Aarons JH, Metzger B, Bieber FR, Knopp RH, Holmes L, Peterson CM, Withiam-Wilson M, Brown ZP, Ober C, Harley E, Macpherson TA, Duckles A, Mueller-Heubach E, The National Institute of Child Health and Human Development: Diabetes in Early Pregnancy Study: incidence of spontaneous abortion among normal women and insulin-dependent diabetic women whose pregnancies were identified within 21 days of conception. *N Engl J Med* 319: 1617–23, 1988
134. Dicker D, Feldberg D, Samuel N, Yeshaya A, Karp M, Goldman JA: Spontaneous abortion in patients with insulin-dependent diabetes mellitus: the effect of preconceptional diabetic control. *Am J Obstet Gynecol* 158:1161–64, 1988
135. Rosenn B, Miodovnik M, Combs CA, Khoury J, Siddiqi TA: Pre-conception management of insulin-dependent diabetes: Improvement of pregnancy outcome. *Obstet Gynecol* 77:846–49, 1991
136. Willhoite B, Bennert H: The impact of preconception counseling on pregnancy outcomes: the experience of the Maine Diabetes in Pregnancy Program. *Satellite Symposium to 14th International Diabetes Foundation Congress*, Newport, Rhode Island, poster 22, June 1991
137. Cousins L: The California Diabetes and Pregnancy Program: a statewide collaborative program for the preconception and prenatal care of diabetic women. *Clin Obstet Gynecol* 5:443–60, 1991
138. Silverman BL, Rizzo T, Green OC, Cho NH, Winter RJ, Ogata ES, Richards GE, Metzger BE: Long term prospective evaluation of offspring of diabetic mothers. *Diabetes* 40:121–25, 1991
139. Yssing M: Oestriol excretion in pregnant diabetes related to long term prognosis of surviving children. *Acta Endocrinol* 182:95–104, 1974
140. Peterson JB, Pedersen SA, Greisen G, Pedersen JF, Molsted-Pedersen L: Early growth delay in diabetic pregnancy: relation to psychomotor development at age 4. *Br Med J* 196:598–600, 1988
141. Pedersen JF, Molsted-Pedersen L, Mortensen JB: Fetal growth delay and maternal hemoglobin AIC in early pregnancy. *Obstet Gynecol* 64:351–52, 1984

142. Churchill JA, Berendes HW, Nemore J: Neuropsychological deficits in children of diabetic mothers. *Am J Obstet Gynecol* 105:257–68, 1969
143. Miodovnik M, Lavin JP, Harrington DJ, Leung L, Seeds AE, Clark KE: Cardiovascular and biochemical effects of infusion of beta hydroxybutyrate into the fetal lamb. *Am J Obstet Gynecol* 144: 594–600, 1982
144. Rudolf MCJ, Sherwin RS: Maternal ketosis and its effects on the fetus. *Metabolism* 12:413–28, 1983
145. Stehbens JA, Baker GL, Kitchell M: Outcome at ages 1, 3, and 5 years of children born to diabetic women. *Am J Obstet Gynecol* 127:408–13, 1977
146. Rizzo T, Freinkel N, Metzger BE, Hatcher R, Burns WJ, Barglow P: Correlations between antepartum maternal metabolism and newborn behavior. *Am J Obstet Gynecol* 163: 1458–64, 1990
147. Rizzo T, Metzger BE, Burns WJ, Burns K: Correlations between antepartum maternal metabolism and intelligence of offspring. *N Engl J Med* 325:911–16, 1991
148. Greene MF, Hare JW, Krache M, Phillippe M, Barss VA, Saltzman DH, Nadel A, Younger DM, Heffner L, Scherl E: Prematurity among insulin-requiring diabetic gravid women. *Am J Obstet Gynecol* 106–11, 1989
149. Siddiqui T, Rosenn B, Mimouni F, Khoury J, Miodovnik M: Hypertension during pregnancy in insulin dependent diabetic women. *Obstet Gynecol* 77: 514–19, 1991
150. Combs CA, Wheeler B, Gunderson E, Gavin L, Kitzmiller JL: Significance of microproteinuria in the first trimester of pregnancies complicated by diabetes. *Diabetes* 39:36A, 1990
151. Kitzmiller JL, Watt N, Driscoll SG: Decidual arteriopathy in hypertension and diabetes in pregnancy: immunofluorescent studies. *Am J Obstet Gynecol* 141: 741–51, 1981
152. DeFronzo RA, Ferrannini E: Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 14:173–94, 1991
153. Sowers JR, Saleh AA, Niyogi T, Standley P, Bottoms SF, Norman GS, Zemel MB, Zemel PC, Johnson BB, Sokol RJ: Mid-gestational hyperinsulinemia and development of pre-eclampsia. *Am J Obstet Gynecol* 166(Part 2):294, 1992
154. Rey E, Bonin A: Insulin concentrations in chronic hypertensive pregnant women. *Am J Obstet Gynecol* 166(Part 2):295, 1992