Pre-Conception Care of Diabetes, Congenital Malformations, and Spontaneous Abortions

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As noted by many previous reviewers (1–4), major congenital malformations remain the leading cause of mortality and serious morbidity in infants of mothers with established diabetes (IDM). In addition to the associated human suffering, the malformations are very expensive in both short- and long-term health care costs. The purpose of this technical review is to provide the detailed background to the American Diabetes Association's Position Statement on clinical guidelines for pre-conception care of women with diabetes (5–7a). The review is organized to discuss several related topics.

- Frequency of major congenital anomalies in IDM
- Association of congenital malformations with control of diabetes
- Spontaneous abortions and diabetes
- Animal studies of congenital malformations associated with diabetes (in vivo studies, potential mechanisms of diabetic teratogenesis, preimplantation and early postimplantation embryos)
- Clinical studies of pre-conception care of women with diabetes
- Cost-benefit of pre-conception care of women with diabetes
- Elements of pre-conception care of women with diabetes (recruitment of participants, evaluation of risks for pregnancy, counseling and motivation of patients for intensive treatment, patient training in diabetes self-management skills, contraception and planning pregnancy)
- Strategies for widespread implementation of pre-conception care

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CDAPP, California Diabetes and Pregnancy Program; CDCP, Centers for Disease Control and Prevention; DCCT, Diabetes Control and Complications Trial; DIEP, Diabetes in Early Pregnancy Study; IDM, infants of diabetic mothers; IUD, intrauterine device; NIH, National Institutes of Health; OC, oral contraceptive; PGE_2, prostaglandin E_2; STZ, streptozotocin; TNF, tumor necrosis factor.

FREQUENCY OF MAJOR CONGENITAL ANOMALIES IN IDM

— Although several pioneer investigators reported that birth defects were frequent in pregnancies complicated by diabetes (8–11), methodological problems affected the estimates of the incidence of congenital malformations in early studies of IDM (12). There were variations in the definition of major versus minor anomalies, in the time period of fetal development (e.g., including spontaneous abortions or only viable gestations >24 or >28 weeks from the last menstrual period), and in the duration of neonatal life (e.g., 1st week, 4 weeks, or 1st year of life) in which to make the diagnosis. In this review, gestational age is given as postmenstrual weeks. There was also variation in the diagnosis of maternal diabetes, prediabetes, or glucose intolerance; in the severity of diabetes in patients referred to major centers reporting the statistics; and in the selection of a nondiabetic control group. Rubin and Murphy (13) pointed out that the diagnosis of congenital anomalies was more likely in IDM, since they were more closely observed than control infants and more likely to die, so more likely to have an autopsy.

Given these limitations, Kucera (14) collated 47 reports appearing in 1945–1965 from nine geographic and ethnic areas with a total of 7,101 fetuses born to diabetic mothers. There were 340 anomalies (4.8%) (14). He compared this to an incidence of 0.65% in 431,764 pregnancies reported by the World Health Organization. Subsequent series from regional centers in Denmark, the U.K., North America, and Israel noted rates of major anomalies of 5.2–16.8% in IDM, compared with 1.2–3.7% in infants of nondiabetic city- or hospital-based control subjects (15–21). Major anomalies were those considered lethal, requiring surgery, or predicted to handicap the life of the child. Minor anomalies were inconsistently more common in IDM.

Farquhar's (22,23) two case-control studies were exceptional in not finding a higher rate of anomalies in IDM. However, in the first study, he eliminated lethal anomalies (22), and in the second study of stillbirths and neonatal deaths, he may have diluted the effect of diabetes by including minor anomalies (23). Subsequent case-control studies found a relative risk of 3.09–7.9 for major anomalies associated with maternal diabetes (24–27). Khoury et al. (28) demonstrated no significant effect from alleged recall bias by the use of affected control subjects in some of these case-control studies. Most recently, large population-based surveys in Australia (29) and Spain (30,31) have confirmed significantly elevated risks of major malformations in IDM.

Is the increased risk of major malformations in IDM associated with the maternal diabetic state, with its treatment, or with genetic influences? Regarding diabetes-associated genes, major malformations were not more common in five studies of the offspring of diabetic fathers (12,32–36) or in women who developed diabetes after their pregnancies (12,36). Diabetic mothers of malformed infants usually do not have a genetic predisposition to malformations, including cardiac anomalies (17), and normal or malformed IDM do not have a higher frequency of

Table 1—*Studies of major malformations in IDM: organ systems frequently involved*

Author/date	Ref.	Region	Design	IDM	Control subjects	Relative risk/odds ratio (NS) CNS	CVS	GI	GU	Skeletal
Kucera, 1971	14	Europe	Literature review	3,565	350,010	4.6	5.6	3.2	4.7	20.7
Neave, 1984	12	Eastern U.S. & Canada	Matched control subjects	2,592	2,592	3.3	6.1	4.3	2.3	15
McCarter et al., 1987	19	Baltimore, MD	Hospital discharges	312	914	3.1	(2.0)	3.7	3.2	2.0
Becerra et al., 1990	26	Atlanta, GA	Birth defects case control	28	3,029	15.5	18.0	—	—	- -
Bower et al., 1992	29	Western Australia	Birth defects registry	214	110,592	3.5	4.4	(1.5)	(1.0)	3.2
Martinez-Frias, 1994	31	Spain	Birth defects registry	76	18,683	2.9	2.8	(2.6)	3.8	5.2

Relative risk/odds ratio (as compared to nondiabetic population) was not significant, since the 95% confidence interval crossed 1.0. CNS, central nervous system, including neural tube defects; CVS, cardiovascular (mainly heart and outflow tracts); GI, gastrointestinal; GU, genitourinary. Data from Kucera are taken from Tables 2A, 3, and 4, comparing IDM from central Europe and Scandinavia and control subjects from Czechoslovakia, Germany, Spain, Sweden, and Yugoslavia. In this analysis of his review, CNS malformations included anencephalus, spina bifida, hydrocephalus, and other CNS anomalies; CVS included heart anomalies; GI included esophageal, anal, and rectal atresia; GU included cystic kidney, agenesis of kidney, aplasia of kidney, hydronephrosis, and ureter duplex; and skeletal included gross skeletal anomalies, caudal regression, and other spinal anomalies.

chromosomal abnormalities than control subjects (17,37). Racial/ethnic group and maternal age do not influence the incidence of malformations in IDM (32,36,38), and excess major anomalies are seen with both IDDM and NIDDM (32,36,39,40). Prospective studies of women with gestational diabetes usually have not shown increased rates of major malformations (16,21,32), and those few that did may have included pregnant women with undiagnosed NIDDM (26). Among IDDM patients, some early studies showed higher risks for malformations with increased duration or severity of diabetes (marked by vascular complications), although the authors could not discriminate whether the affected pregnancies had poor metabolic control (12,15,16,41).

Regarding the effects of treatment of diabetes, a few authors suggested that oral hypoglycemic agents might be teratogenic independently of the degree of diabetic control (16,42). However, there were no major malformations observed in a consecutive series of 25 women with NIDDM treated with oral hypoglycemic agents during embryogenesis between 1966 and 1991 in Copenhagen (43). In a larger study of 332 consecutive infants born to women with NIDDM, major anomalies were observed in 11.7%, but the risk was not related to the mode of antidiabetic therapy during early pregnancy (40). The analysis included 125 women treated with diet, 147 with oral hypoglycemic agents, and 60 with insulin. Since most of the reported major malformations have occurred in infants of insulin-treated diabetic women, it is difficult to separate the effects of insulin treatment from metabolic control. Pedersen and Molsted-Pedersen (44), however, determined that the most intensively managed IDDM patients had a lower risk of malformed infants (44), and Baker et al. (45) and Horii et al. (46) concluded that insulin per se does not cause malformations in experimental systems. It is controversial whether insulin-induced shock therapy produced malformations in offspring of a few nondiabetic pregnant women (2,47,48), but several investigators failed to find an association of clinical hypoglycemia early in pregnancy with increased risk for malformations in insulin-treated diabetic women (15,39,50–53).

In IDM, many malformations (24–74%) are severe multi-organ system birth defects (15,19,25,29,31,32,39,54), which have been considered lethal in 13–50% of cases (15,18,20,39). Several investigators (12,15,18,55,56) have emphasized the rising proportion of perinatal deaths due to major malformations in IDM, as total perinatal mortality declined in diabetic women.

Many authors speculated that the multiplicity of malformations observed in IDM indicated a teratogenic effect of diabetes very early in gestation (14, 32,39,54). The organ systems most commonly affected in IDM include skeletal (especially ribs and vertebrae), cardiac (especially septal and outflow tract lesions), central nervous and neural tube, gastrointestinal, and genitourinary (Table 1). Mills et al. (2,57) analyzed the types of malformations significantly more common in IDM with reference to known time periods of embryologic development. Assuming that no malformations develop after differentiation occurs, the authors estimated the latest gestational age for the induction of different types of malformations in IDM to be week 5 for sacral agenesis to week 8 for ventriculoseptal defects (57). This early time of occurrence fits with Opitz's (58) theory that the multisystem anomalies in IDM are primary-field abnormalities of blastogenesis, which represents the first 4 weeks of human development, from fertilization to the end of gastrulation (day 42 postmenses). "The primary field is the entire embryo during blastogenesis," and "midline and mesoderm formation at gastrulation is its most important function" (58). Opitz speculated that "diabetic hits" during blastogenesis produce complex multisystem anomalies, but that "mild hits" may linger in effect into morphogenesis (day 42–70 postmenses, formation of organs in secondary, epimorphic fields), producing simpler, localized defects (58).

ASSOCIATION OF CONGENITAL MALFORMATIONS WITH CONTROL OF DIABETES

— In the 1970's Jorgen Pedersen postulated that incomplete metabolic compensation of maternal diabetes during nidation and in early pregnancy is important in causing the increased frequency of major malformations in IDM. Noting the lack of a measure of the degree of compensation, he discussed the indirect evidence for an association with poor control (44). This included the strong negative correlation be-

Table 2—*Association of major malformations in IDM with initial maternal glycohemoglobin level*

Author, date	Ref.	*n*	Degree of elevation of glycohemoglobin (malformations/infants)		
			Moderate	High	Highest
Miller et al., 1981	62	106	<7 (2/48 [4.2])	7–9.8 (8/35 [22.9])	≥10 (5/23 [21.7])
Ylinen et al., 1984	65	142	<6 (2/63 [3.2])	6–9.8 (5/62 [8.1])	≥10 (4/17 [23.5])
Reid et al., 1984	64	127	<6 (2/58 [3.4])	6–9.9 (5/44 [11.4])	≥10 (6/25 [24.0])
Key et al., 1987	66	61	<5.8 (2/45 [4.4])	5.8–9.4 (4/13 [30.8])	≥9.5 (3/3 [100])
Greene et al., 1989	68	250	<6 (3/99 [3.0])	6–12 (6/123 [4.9])	≥12 (11/28 [39.3])
Hanson et al., 1990	70	491	<6 (3/429 [0.7])	6–7.9 (2/31 [6.5])	≥8 (5/31 [16.1])
Rosenn et al., 1994	71	228	<4 (4/95 [4.2])	4.0–9.9 (7/121 [5.8])	≥10 (3/12 [25.0])
Total		1,405	(18/837 [2.2])	(37/429 [8.6])	(37/139 [26.6])

Data are SD above normal mean (*n*/*n* [%]).

tween severe insulin reactions in the 1st trimester and malformations, suggesting that intensive treatment might be beneficial. He also noted that patients with diabetic vascular disease who were "more difficult to compensate" had the highest rates of anomalies but that when diabetes was well controlled in subsequent pregnancies in these patients, malformations did not occur (44).

Since most diabetic women registered for care after the time of embryogenesis, a retrospective measure of control was needed to test the metabolic hypothesis. This was provided by the various assays for glycohemoglobin, shown to be related to the previous level of maternal hyperglycemia in pregnancy (59–62). Leslie et al. (63) first noted an association of elevated HbA_1 with congenital anomalies in 1978 (63). Subsequently, many investigators observed that mothers of malformed IDM had significantly higher glycohemoglobin levels in the 1st trimester than did diabetic mothers of nonaffected babies (41,62,64–71). Women who had delivered a malformed infant but entered the subsequent pregnancy with low glycohemoglobin levels had a low rate of anomalies (41,62,67).

The association of poor control of diabetes reflected by elevated glycohemoglobin was strongest for infants with major, severe anomalies (41,62,64–67,70,71). The data on minor anomalies are more variable. Ylinen et al. (65), Hanson et al. (70), and Rosenn et al. (72) noted an association of glycohemoglobin levels with minor anomalies in IDM, but Stubbs et al. (67) did not. In the general population, there is great variation in the reported frequency of minor malformations (72), likely due to difficulties in accurate or complete diagnosis (73).

There has been debate about the degree of poor glycemic control (indicated by the level of glycohemoglobin in early pregnancy) that is associated with a significantly increased risk of major malformations (41,62,68). To compare data based on different assays of glycohemoglobin at various centers, it is useful to use the number of standard deviations above the mean for a nondiabetic population for a given laboratory (68,71). The concept of requiring a relatively high threshold of >10 SD for significantly increased risk of major malformations (68) is probably influenced by inadequate sample size in a single series. When the data are analyzed by SD and pooled from seven series (Table 2), it is clear that there is a moderately increased risk of anomalies (4–9%) with elevations of glycohemoglobin in the range of 6–10 SD and a very high risk (~27%) with very high levels of glycohemoglobin >10–12 SD above the mean (62,64–66,68,70,71). Most investigators find a low frequency of major malformations when the initial glycohemoglobin is <4 SD above the mean (62,65,66,68).

The report of the National Institutes of Health (NIH)-sponsored multicenter Diabetes in Early Pregnancy Study (DIEP), which appeared in 1988, gained notoriety and generated controversy by its title, which claimed a lack of relationship between glycemic control and the rate of malformations (49). The second report (74), focusing on general pregnancy outcome, provided the number of subjects enrolled in the study: 386 women with established diabetes and 432 nondiabetic control subjects were recruited to begin intensive monitoring by week 5 of gestation. In the early-entry diabetic group, there were 62 embryonic or fetal losses and 324 women delivered, including 2 stillbirths. Among the control subjects, there were 70 embryonic and fetal losses and 362 women delivered (74). However, the initial report (49) states that there were 347 pregnancies in the early-entry diabetic group and 389 in the early-entry control group for which data on malformations were available. The discrepancy is unexplained. Of the 347 babies delivered to early-entry diabetic women, 13 had major malformations commonly associated with diabetes, but only 11 of their mothers entering the study by 5 weeks' gestation had glycohemoglobin measured before 9 weeks of gestation. Of these women, seven had initial glycohemoglobin above the 50th percentile for early-entry diabetic women and nine were above the 90th percentile for the early-entry nondiabetic control subjects (49). Many commentators (68,75–80) have discussed the reasons that the title and conclusions were unjustified by the data in the first report (49), including that only ~10% of the early-entry diabetic subjects had the "exposure of interest" (68), i.e., very poor glycemic control. Comparison of data in the original paper with other reports was hampered by lack of definition of mean and SD for the glycohemoglobin assay in the early-entry nondiabetic control subjects (49), but this information was published in the second paper (74). If one limits the analysis to diabetic women with mean glycohemoglobin measured weekly at 5–8 weeks gestation, then major malformations of a type commonly attributed to

Table 3—*Spontaneous abortions in prospective studies of pregnant diabetic women*

Author, date	Ref.	Time of enrollment (weeks)	Pregnancies	Diagnosis of spontaneous abortion (weeks)	Frequency of spontaneous abortion	Glycohemoglobin threshold for highest in study
Wright et al., 1983	88	<14	58	Clinical (<15)	10 (17.2)	>6 (4/13 [30.8])
Miodovnik et al., 1985	90	<9	116	Clinical (<20)	26 (22.4)	>6 (12/27 [44.4])
Mills et al., 1988	74	<6	386	Symptoms and U/S (<21)	60 (15.5)	>6 (12/42 [28.6])
Greene et al., 1989	68	<13	303	Symptoms and U/S	52 (17.2)	>9 (3/105 [29.5])
Hanson et al., 1990	70	<16	532	Clinical	41 (7.7)	>8 (11/42 [26])
Rosenn et al., 1994	71	<9	99	Clinical (<20)	26 (26.2)	>6.5 (14/32 [43.8])
Total			1,494		(215 [14.4])	(84/261 [32.2])

Data are *n*, *n* (%), or SD above mean for nondiabetic population (*n/n* [%]). Diagnosis excludes ectopic and molar pregnancies. The analysis of Rosenn et al. (71) excludes 26 abortions in 116 pregnancies reported by Miodovnik et al. (90) in 1985. U/S, ultrasonography.

diabetes were observed in 1 of 119 (0.8%) pregnancies with glycohemoglobin <2 SD, 4 of 109 (3.7%) pregnancies with glycohemoglobin 2–4 SD, and 6 of 84 (7.1%) pregnancies with glycohemoglobin >4 SD (χ^2 5.53, $P = 0.06$). It seems that there is an association of major malformations with moderately elevated maternal glycohemoglobin levels in this controversial study, despite the misleading title. The rates of malformation and the relation to glycohemoglobin are consistent with those observed in other series (Table 2).

SPONTANEOUS ABORTIONS AND DIABETES

The incidence of spontaneous abortion in nondiabetic women is dependent on the method used to identify pregnancy and to diagnose spontaneous abortion. In a prospective evaluation of 197 normal women who wished to conceive, ~25% had "chemical pregnancies" (transient positive assays for human chorionic gonadotropin [hCG] in the urine) and 14% had spontaneous clinical abortion marked by cramps, bleeding, and passage of tissue (81). The latter figure is similar to the rate of 15.3% clinical spontaneous abortions before 20 weeks' gestation (excluding ectopic and molar pregnancies) in 432 nondiabetic women who served as control subjects in the DIEP study (74). Kalter (82) noted that the frequency of recognized pregnancies that spontaneously abort varies from ~10 to 25% depending on the method of study: 10–15% in "prospective surveys of already pregnant women in clinical settings" (74,83), 12–15% by retrospective investigations of pregnancy histories based on maternal recall (84,85), and 15–25% in analyses using life-table probability methods (86). Confounding variables affecting the early fetal loss rate in nondiabetic women include maternal age, gravidity, race, and possible environmental influences (82). Common causes of early fetal loss include severe chromosome defects, malformations, "blighted ova" with development of chorioamnion but no embryo (empty sac), and fetuses without cardiac motion (68). Diabetic women would be expected to suffer the usual frequencies of these processes, but in addition could have excess loss rates related to metabolic embryopathy.

The incidence of spontaneous abortion in women with diabetes diagnosed and treated before pregnancy has been difficult to establish with accuracy because of variation in time of registration for care and loss to follow-up of some women who miscarry. Kalter (82) discussed the methodological shortcomings in his historical review of 58 studies published in 1950–1986 and gave a 12.7% frequency for 1,890 pregnancies in diabetic women who were "observed during specifically stated extended periods." Using a retrospective approach, Sutherland and Pritchard (87) determined a 17.1% spontaneous abortion rate in 164 pregnancies in diabetic women in a defined area of Scotland. In prospective studies published since 1982, in diabetic women enrolled before 16 weeks of gestation, the "clinical" spontaneous abortion rate varied from 7.7 to 30% (68,70,74,88,89) (Table 3). The earlier in gestation patients enrolled, the higher the spontaneous abortion rate, suggesting that many early spontaneous abortions do not come to the attention of investigators in most studies.

The most definitive study of spontaneous abortions in diabetic women compared with nondiabetic control subjects was the NIH-sponsored multicenter DIEP reported by Mills et al. (74). In 386 pregnancies in diabetic women followed from the 5th gestational week, there were 60 pregnancy losses (15.5%) observed by 20 weeks' gestation, excluding 1 molar and 1 ectopic pregnancy. Spontaneous abortions were identified by clinical symptoms in 63% and by abnormal ultrasonography in 26% (by both or other in 11%). The losses occurred before 8 weeks' gestation in 30%, at 8–11 weeks in 58%, and at 12–19 weeks in only 12%. Diabetic women with pregnancy losses reported no exposures to abortifacient drugs, chemicals, or radiation; no physical or psychological trauma; and only minor exposures to infections in early pregnancy. Logistic regression analysis confirmed that greater maternal age and nonwhite race were significant risk factors for spontaneous abortion in the diabetic women as well as control subjects (74). Although the overall abortion rate in diabetic women was not higher than in the 432 nondiabetic control subjects also followed prospectively from 5 weeks' gestation, the small subgroup of diabetic women with poor control indicated by elevated glycohemoglobin had the greatest risk of early pregnancy loss.

This result is similar to that in five other studies of 1,108 diabetic women

(Table 3), in which the average overall spontaneous abortion rate was 14.3%, but the rate was 32.2% in the subset of diabetic women with substantially elevated glycohemoglobin levels (>6–9 SD above the mean) at early prenatal visits (68,70,71,88,90–92). The causes of the excess rates of spontaneous abortion in the women with poorly controlled diabetes were not identified in these clinical surveys, but the explanation may be found in experimental studies of the influence of diabetic factors on blastocyst and embryo development.

ANIMAL STUDIES OF CONGENITAL MALFORMATIONS ASSOCIATED WITH DIABETES

— Because of ethical limitations to the study of embryogenesis in humans, animal studies have provided most of the mechanistic information that is currently available regarding the effects of maternal diabetes on embryogenesis. The studies have been performed largely in rodents and have used in vivo and in vitro approaches to examine the mechanisms by which a diabetic environment alters normal embryo development. The animal models vary in the types and timing of malformations that can be studied, so no one model can be taken as a perfect representation of the spectrum of developmental abnormalities that occur in the face of maternal diabetes in early human pregnancy. Nonetheless, animal studies have already provided important information regarding the importance of good metabolic control in the prevention of diabetes-related malformations, and ongoing studies hold the potential for identifying basic mechanisms of diabetic teratogenesis that can be used to develop additional approaches for the prevention of birth defects.

In vivo studies

Most forms of spontaneous diabetes in humans and animals have a genetic component to their etiology, leaving open the possibility that inherited genetic abnormalities could explain the association between maternal diabetes and malformations in offspring. Evidence against this hypothesis in human diabetes was reviewed above. That the malformations can occur in the absence of a genetic predisposition to diabetes was proven in animal models of diabetes induced by streptozotocin (STZ) or alloxan. Endo et al. (93) first reported that induction of diabetes in mice by injection of alloxan *before* conception led to an increased rate of skeletal malformations in newborns. Since that time, a number of investigators have studied the effects of chemically induced diabetes on embryogenesis in vivo (45,46,94–97). Those studies reveal that chemically induced maternal diabetes can be associated with malformations in offspring. However, the effect is strain dependent; that is, some rodent strains manifest congenital malformations with overt diabetes in the mother (46,97), while other strains do not (95,98,99). Moreover, Eriksson (95) and Otani et al. (100) have used cross-breeding experiments to demonstrate that the genetic makeup of the embryo and the maternal metabolic environment both contribute to diabetes-related malformations. Thus, one important contribution of animal studies in vivo has been the demonstration that malformations in diabetic pregnancies result from exposure of genetically susceptible embryos to the abnormal intrauterine environment created by maternal diabetes.

The second major contribution of animal studies in vivo has been the demonstration that exogenous insulin therapy could reduce or eliminate the excess risk of congenital malformations in offspring. This was first demonstrated by Horii et al. (46), who observed a reduction in skeletal malformations in offspring of diabetic mice when the mothers were treated with insulin throughout gestation. Other investigators (45,94) have confirmed the beneficial effects of exogenous insulin treatment to reduce skeletal malformations in models of chemically induced diabetes in vivo. These studies provide a rationale for successful programs of prevention of malformations in human pregnancies through pre-conception metabolic control.

A third contribution of in vivo animal studies has been to identify potential periods of susceptibility of embryos to maternal diabetes. Eriksson et al. (101) used timed interruptions of insulin treatment in their model of skeletal malformations and embryonic resorptions to demonstrate a relatively narrow window of susceptibility to maternal diabetes during the stages of gastrulation and neurulation (analogous to days 32–49 postmenses in human embryogenesis). Several other groups have reported alterations in embryogenesis even earlier in diabetic pregnancies. Diamond et al. (102) first reported an apparent developmental delay in two-cell embryos recovered from mice with STZ- or alloxan-induced diabetes. Vercheval et al. (103) reported a similar delay in the progression of rat embryos from the two-cell to the blastocyst stage in the presence of maternal STZ-induced diabetes. However, Diamond et al. (102) reported that ovulation was also delayed in diabetic mice, providing a possible explanation for the apparent developmental delay at the two-cell and blastocyst stages. Beebe and Kaye (104) studied protein synthetic rates using two-cell, morula, and blastocyst stage embryos taken from pregnant mice with STZ-induced diabetes. They reported that protein synthesis was normal in the two-cell embryos but that morula and blastocyst stage embryos had reduced synthetic rates, suggesting an acquired developmental delay that could not be explained by a delay in ovulation. Pampher et al. (105) demonstrated that the reduction in cell number in blastocysts from diabetic rats was due to a reduced inner cell mass, the portion of the blastocyst that gives rise to the embryonic germ layers. Insulin treatment of diabetic mothers ameliorated the developmental delay observed by Diamond et al. (102) in diabetic mice and restored to normal the blastocyst inner cell mass in diabetic rats (105). These findings indicate that maternal diabetes can alter embryogenesis not only during the period of neural tube formation, but also much earlier in pregnancy, before implantation into the uterus. The long-term effects of these very early developmental changes are unknown.

The final contribution of animal studies in vivo has been a study of potential teratogenic factors related to maternal diabetes. Styrud et al. (106) used multivariate regression analysis to determine that circulating maternal concentrations of glucose, triglycerides, β-hydroxybutyrate, branched-chain amino acids, and creatinine were independently related to the risk of malformations and resorptions in late neurulation stage embryos in diabetic rats. Eriksson (107) and Uriu-Hare et al. (97) found reduced zinc concentrations in normal and malformed fetuses of diabetic rats of two different strains. The

latter group (108) also reported that maternal dietary zinc restriction accentuated the teratogenic effects of STZ-induced diabetes in Sprague-Dawley rats. However, zinc supplementation to normal diets did not reduce the teratogenicity of STZ diabetes, indicating that zinc deficiency alone could not explain the teratogenic effects of maternal diabetes. Giavani et al. (109) reported higher malformation rates in fetuses of rats with STZ-induced diabetes when mothers were maintained on a high-carbohydrate, low-protein diet as compared with a low-carbohydrate, high-protein diet during gestation.

These in vivo studies demonstrate that malformations in diabetic pregnancies are likely to be multifactorial in their etiology and that the risk of malformations may be modified by environmental factors such as maternal nutrition. Insulin-induced hypoglycemia has also been shown to be teratogenic to rat embryos in vivo (110), although an analogous effect has not been observed in recent human studies (49,50).

In vitro studies

Direct examination of potential mechanisms that lead to malformations requires an ability to control the environment of the embryo in a manner that cannot be achieved in vivo. Thus, many investigators have turned to in vitro studies in which embryos can be exposed to diabetes-like conditions during specific developmental stages in order to determine the effects of such exposure on overall development as well as on specific morphological and biochemical processes. Techniques have been developed that allow the study of embryogenesis during the preimplantation period (up to the blastocyst stage, analogous to the first 5–6 days of human embryogenesis) and during the period of neural tube development (analogous to days 18–35 of human embryogenesis, days 32–49 postmenses).

Preimplantation embryos. Preimplantation rodent embryos will develop normally, at least from the standpoint of morphology, in defined medium containing small proportions of serum. At least three groups have studied the effects of diabetes-like conditions on preimplantation embryos using in vitro culture techniques. Diamond and colleagues (111,112) reported that addition of D-glucose to create final glucose concentrations >440 mg/dl caused a delay in the development of normal mouse embryos from the two-cell stage to the blastocyst stage; addition of insulin or glucagon to the culture medium had no impact on the developmental impairment induced by high glucose concentrations. Ornoy and Zusman (113) reported that culture of preimplantation mouse embryos in medium containing serum from diabetic rats or humans resulted in significant toxic effects, as manifested by degeneration of the inner cell mass of the blastocyst. The severity of the embryotoxicity was correlated with concentrations of glucose, β-hydroxybutyrate, and acetoacetate in the test sera. Moreover, addition of glucose, β-hydroxybutyrate, and/or acetoacetate to the culture medium in the absence of diabetic serum was also embryotoxic, particularly when the substances were added in combination. De Hertogh et al. (114) reported that addition of glucose to normal culture medium inhibited development of the inner cell mass of preimplantation rat embryos in a dose-dependent fashion. Insulin at low concentrations (3 pmol/l) mitigated this toxic effect, while insulin at higher concentrations (30–600 pmol/l) exaggerated the embryotoxic effects of high glucose concentrations. Taken together, data from these three groups indicate that metabolic abnormalities known to be associated with maternal diabetes (e.g., hyperglycemia and hyperketonemia) can directly alter development of preimplantation embryos. The extent to which preimplantation embryos are exposed to those metabolic abnormalities before implantation (i.e., while developing in fallopian and uterine cavity fluids) remains to be determined.

Recently, Pampher et al. (115) reported that uterine cells removed from diabetic rats on days 5–8 of gestation (the peri-implantation period) produced more tumor necrosis factor (TNF)-α than did cells from normal rats at the same stage of gestation. Histological studies and mRNA analysis revealed that TNF-α was being produced by the uterine epithelium cells of the diabetic animals. Culture of normal preimplantation embryos in medium conditioned by uterine cells from diabetic animals resulted in a significant reduction of growth and development, which was mitigated by addition of anti–TNF-α antibodies to the culture medium (115). These findings raise the possibility that factors other than the traditional metabolic abnormalities of maternal diabetes may account for some of the early developmental disturbances that occur in embryos of diabetic mothers.

Early postimplantation embryos

Whole-embryo culture technique. In the late 1970s, New (116) developed an in vitro technique to study the development of rodent embryos during the period of neurulation. Embryos and their nutrient membranes (the parietal and visceral portions of the yolk sac) are removed from mothers at the beginning of neural tube development and grown in vitro for 24–48 h, during which time they undergo complete closure of the neural tube along with initial development of structures that will become the eyes, ears, heart, and great vessels, limbs, and axial skeleton. The mouse or rat embryos are usually grown in serum from normal or diabetic "donor" rats that can be modified by treatment of the donors in vivo before serum harvest or by modification of the serum in vitro after the harvest. Thus, the "whole-embryo culture" technique provides a powerful tool with which to examine mechanisms that may be involved in diabetic teratogenesis, particularly regarding abnormalities of neural tube development.

Effect of diabetic serum in vitro. A major development in the study of diabetic teratogenesis was the demonstration by Sadler (117) that in vitro exposure of early postimplantation mouse embryos to serum from rats made diabetic with STZ caused an excess of developmental malformations. This finding provided proof that some components or deficiencies in diabetic serum were teratogenic. Subsequent studies revealed that the effect of diabetic serum on embryo development varies among experimental preparations. Two groups (117,118) reported that mouse embryos develop malformations when exposed to diabetic rat serum in vitro during the early postimplantation period. Rat embryos may be less susceptible to the teratogenic effects of rat serum. For example, Styrud and Eriksson (119) reported that serum from diabetic rats caused no excess of malformations in embryos of a strain that is susceptible to skeletal malformations when exposed to maternal STZ-induced diabetes in vivo. Other investigators have reported malformations in rat embryos grown in serum from diabetic rats (120) or humans (121) during neurulation. Thus, studies of cultured early postimplantation embryos

demonstrate that diabetic serum per se can be teratogenic but, as with the in vivo studies of diabetic teratogenesis (above), embryos may vary in their genetic susceptibility to these toxic effects.

Potential mediators of diabetic teratogenesis. One early approach that was used to identify potential teratogenic factors in diabetic serum was to add the candidate factor(s) to normal serum, then test the modified serum for teratogenesis in a mouse or rat whole-embryo culture system. Glucose was the first substance tested (122), and several groups reported increased malformation rates in early postimplantation mouse or rat embryos after culture in glucose-supplemented serum from normal rats (118,123–125). In general, this approach has revealed that malformation rates increase with increasing glucose concentrations in the test serum, although glucose concentrations above those typically observed in diabetic serum have been required to induce an increase in malformation rates. A similar pattern has been observed after addition of the ketoacid β-hydroxybutyrate to normal serum before embryo culture (124–126). Malformation rates increase in a dose-dependent fashion above a threshold concentration that is higher than β-hydroxybutyrate concentrations in embryotoxic serum from diabetic animals. Addition of glucose and β-hydroxybutyrate in combination (124,127) causes malformations at lower concentrations of each substance than when they are added individually, indicating a synergistic embryotoxic effect of the two compounds. Eriksson et al. (125) reported that simultaneous addition of glucose, β-hydroxybutyrate, and the leucine metabolite α-ketoisocaproic acid in concentrations designed to mimic diabetic serum caused malformations in rat embryos, providing further evidence for synergism among excess oxidative substrates in the genesis of diabetes-related birth defects. Finally, studies in which low–molecular weight fractions (<1,000 kDa) of diabetic rat serum containing somatomedin-inhibitor activity were added to normal serum before embryo culture suggested a teratogenic role for as yet unidentified somatomedin inhibitors (128). The inhibitory serum fractions have been shown to have synergistic embryotoxicity with glucose and β-hydroxybutyrate (124,127). These studies provide strong evidence for a multifactorial etiology of diabetic teratogenesis in rodent embryo culture models.

A second approach to the identification of potential teratogenic factors in diabetic serum has been the use of insulin to modify the diabetes in vivo or the diabetic serum in vitro before embryo culture. Sadler and Horton (129) initially reported that the teratogenic activity of serum from STZ-induced diabetic rats was markedly reduced by chronic treatment of the diabetic rats to lower their blood glucose concentrations before serum harvest. Addition of insulin to diabetic serum in vitro did not ameliorate the teratogenic activity of serum from untreated diabetic rats, indicating that insulin deficiency per se was not responsible for the teratogenic activity of the diabetic serum. Travers and colleagues (130,131) showed that insulin deficiency created by removal of insulin from normal rat serum causes developmental anomalies in postimplantation embryos in vitro. While that observation suggests that insulin, presumably supplied from the maternal circulation, is important for normal embryonic development, the findings of Sadler and Horton (129) prove that factors other than insulin deficiency contribute to diabetic teratogenesis. Buchanan et al. (132) used intravenous insulin infusions to normalize glucose and β-hydroxybutyrate concentrations of STZ-induced diabetic rats. The teratogenic activity of serum from the acutely treated rats was reduced >50% compared with serum from untreated diabetic animals. However, the serum from acutely treated animals remained much more teratogenic than serum from normal animals, suggesting that teratogenic factors other than glucose and ketones are present in diabetic serum, at least as determined by a mouse embryo culture system. Thus, the existing evidence from in vitro studies indicates that glucose and ketones may be involved in the genesis of diabetes-related malformations, but that other factors must be involved as well.

Disruption of myo-inositol, arachidonic, and prostaglandin metabolism. *myo*-inositol, a normal component of cell membranes, serves as an important reservoir for several phosphoinositides that are, in turn, involved in intracellular signaling through diacylglycerol, arachidonic acid, and prostaglandin pathways. Depletion of intracellular *myo*-inositol has been implicated in the pathogenesis of several long-term diabetes complications in adults. As reviewed by Baker and Piddington (80), a growing body of evidence also implicates *myo*-inositol depletion in the pathogenesis of neural tube defects that occur under diabetic conditions. First, early postimplantation rodent embryos have a specific nutritional requirement for *myo*-inositol (133). The *myo*-inositol content of neuroectodermal tissue normally increases during neurulation (134), and neural tube closure defects occur if embryos are deprived of *myo*-inositol during this critical developmental period. Second, diabetes in vivo and hyperglycemia created by adding glucose to culture serum in vitro reduce the *myo*-inositol content of embryos (134–136). Weigensberg et al. (137) demonstrated that the reduction in *myo*-inositol content of rat embryos cultured in high-glucose serum was due to a specific and competitive inhibition by glucose of *myo*-inositol uptake. Reduced *myo*-inositol content was associated with a reduction in the content of other phosphoinositides (138) and with embryonic malformations (135,136). Competitive inhibition of *myo*-inositol uptake by in vitro exposure of embryos to *scyllo*-inositol, a nonmetabolizable isomer of *myo*-inositol, caused a similar disruption of inositide metabolism and embryonic development (138). Finally, dietary supplementation of *myo*-inositol to pregnant diabetic rats in vivo (139) and direct addition of *myo*-inositol to high-glucose serum (135,136,140) in vitro not only restored the embryonic content of *myo*-inositol toward normal, but also reduced the frequency of embryonic malformations. Thus, *myo*-inositol depletion appears to be an important link between hyperglycemia and the neural tube malformations that occur in several rodent models of diabetic embryopathy. Accumulation of sorbitol through the aldose reductase pathway also occurs in embryos in the presence of diabetes in vivo (134,139,141) or hyperglycemia in vitro (136). However, accumulation of sorbitol does not seem to be related to the genesis of embryonic malformations, since blockade of the aldose reductase pathway prevents sorbitol accumulation but does not protect against malformations (135, 136,141).

Studies by several groups of investigators suggest that *myo*-inositol depletion leads to neural tube closure defects through a disruption of arachidonic acid

and prostaglandin metabolism "downstream" to the depletion of *myo*-inositol. Goldman et al. (142) initially reported that arachidonic acid supplementation reduced the frequency of neural tube closure defects observed in mouse embryos after exposure to hyperglycemic serum in vitro. Pinter et al. (143) reported a similar protective effect from hyperglycemia when arachidonic acid was provided to rat embryos during neurulation in vitro. Baker et al. (140) tested the effects of several prostaglandins, which are produced from arachidonic acid through the cyclooxygenase pathway, on the development of mouse embryos under hyperglycemic conditions. These investigators reported complete protection from hyperglycemia-induced neural tube defects when embryos were supplemented with prostaglandin E_2 (PGE_2). Goto et al. (144) confirmed the protective effects of PGE_2 when mouse embryos were exposed to hyperglycemic conditions in vitro, and they observed similar protection from the teratogenic effects of diabetic serum during mouse embryo culture. Baker et al. (140) found that indomethacin reversed the protective effects of *myo*-inositol supplementation during culture of postimplantation embryos under hyperglycemic conditions. Since indomethacin inhibits the enzyme cyclooxygenase and thereby the production of prostaglandins from arachidonic acid, the observation of Baker et al. (140) shows a link between *myo*-inositol availability, prostaglandin production, and neural tube malformations induced by hyperglycemia. The available data suggest that neural tube defects can occur in the following manner in the presence of hyperglycemia or diabetes: *1*) Hyperglycemia leads to a competitive inhibition of *myo*-inositol uptake and an intracellular depletion of *myo*-inositol. 2) *myo*-inositol depletion reduces the availability and turnover of phosphoinositides for intracellular signaling. 3) Reduced phosphoinositide signaling limits the activity of phospholipase A_2, a major regulator of arachidonic acid production. 4) Reduced arachidonic acid production leads to reduced prostaglandin synthesis and defective neural tube closure. Supplementation to reverse the deficiencies of *myo*-inositol, arachidonic acid, or prostaglandins (especially PGE_2) can mitigate the effects of hyperglycemia or diabetes to produce neural tube closure defects in mouse or rat embryos. Whether this mechanism is relevant to other diabetes-related malformations in animal models or to any diabetes-related malformations in human diabetes remains to be determined.

Free oxygen radicals and diabetic teratogenesis. A series of observations by Eriksson and colleagues (94,125,126,145–148) provides strong evidence that free oxygen radicals can cause embryonic malformations. They initially identified a strain of Sprague-Dawley rats (U rats) whose offspring were susceptible to three developmental abnormalities when the mothers had overt STZ-diabetes induced before conception: an increased rate of resorptions and increased frequencies of jaw and sacral skeletal malformations (94). Inbreeding of the susceptible strain produced three lines of genetically homogenous rats that differed in susceptibility to skeletal malformations in the presence of maternal diabetes. Analysis of a series of biochemical markers from the three inbred strains revealed that they differed with respect to the erythrocyte catalase locus, *Cs-1* (145). Since catalase is known to be involved in the metabolism of free oxygen radicals, that observation led to a series of in vitro experiments to examine the role of free oxygen radicals in the genesis of embryonic malformations. The experiments have generally involved culture of embryos obtained from a cross between male outbred U rats and female Sprague-Dawley rats. Embryos from this cross develop multisystem malformations when exposed to very high glucose concentrations in vitro. The malformation rate can be lowered by co-culture with oxygen radical scavengers such as catalase, superoxide dismutase, and glutathione peroxidase or with citiolone, a compound that induces oxygen radical scavenging enzymes in the embryos (125,146). Subsequent studies have revealed that oxidative substrates other than glucose (i.e., β-hydroxybutyrate, pyruvate, and α-ketoisocaproic acid) act synergistically to induce embryonic malformations at concentrations that are relevant to concentrations found in diabetic rat serum, even though that serum is not teratogenic in this particular model. As was true for glucose-induced malformations, oxygen radical scavengers mitigate the teratogenic activity of the nonglucose substrates, an observation that has led Eriksson and Borg (125) to postulate that increased oxidative metabolism resultant from an increased substrate supply from maternal serum leads to excess generation of free oxygen radicals in embryonic mitochondria. The oxygen radicals become embryotoxic when their rate of production exceeds the capacity of the embryos to neutralize them, because of either immaturity or a genetic limitation in the expression of oxygen radical scavenging enzymes. The demonstration that an excess supply of oxidative substrates leads to severe morphological disruption of embryonic mitochondria in neuroectodermal tissue (126,147), combined with the observation that blockade of pyruvate transport into the mitochondria prevents pyruvate-induced malformations in embryo culture, supports the role of oxidative metabolism in the mitochondria in the genesis of malformations in this model of skeletal malformations and resorptions. Whether the mechanisms operative in this in vitro model are relevant to other types of embryonic malformations (e.g., neural tube or cardiac defects that have not been observed in excess in U rats in vivo) remains to be determined. However, the demonstration that free oxygen radicals can interfere with arachidonic acid and prostaglandin metabolism (148) suggests one possible link between the findings of Eriksson and colleagues (94, 125,126,145–148) and the alterations of *myo*-inositol, arachidonic, and prostaglandin metabolism discussed above in relation to the pathogenesis of neural tube defects in embryos.

Alterations in DNA synthesis and structure. Rapid rates of growth and differentiation during organogenesis require a continuous supply of nucleic acids, especially DNA. The pentose phosphate pathway of glucose metabolism is a major source of ribose molecules that can be used for DNA synthesis. In vitro studies of embryonic metabolism indicate that inhibition of the pentose phosphate pathway may be involved in the genesis of diabetes-related malformations in two settings. Sadler and colleagues (126,127,149) observed that exposure of 5- to 6-somite mouse embryos (i.e., embryos undergoing the early stages of neural tube closure) to high concentrations of β-hydroxybutyrate leads to a reduction in rates of glucose flux through the pentose phosphate pathway, reduced DNA synthesis in the cranial neural tube, and a high rate of neural tube closure defects. Supplementation of ribose molecules, the normal product of the

pentose phosphate pathway, restored DNA synthesis in the neural tube and reduced the rate of neural tube malformations (149). The same group of investigators (150) reported that β-hydroxybutyrate had no effect on the pentose phosphate pathway in younger embryos (i.e., at the 2- to 3-somite stage), but the ketone body inhibited DNA production by limiting de novo pyrimidine biosynthesis at this early stage. In either case, the reduction in DNA availability was postulated as a cause of the neural tube closure defects induced by β-hydroxybutyrate.

The second situation in which inhibition of the pentose phosphate pathway may be involved in the genesis of malformations related to maternal diabetes is the case of maternal insulin-induced hypoglycemia. That condition has been shown to induce malformations in rat embryos in vivo (110) and in rat and mouse embryos in vitro (151–154). Hunter and Sadler (155) reported that a reduction in glucose availability during in vitro culture of embryos undergoing neurulation led to two metabolic abnormalities: *1*) a reduction in the activity of the pentose phosphate pathway and nucleic acid synthesis and 2) a reduction in energy production from anaerobic glycolysis. The former mechanism was operative during exposure to relatively mild hypoglycemia (~80 mg/dl compared with ~140 mg/dl in normal rat serum), while the reduction in energy production from glycolysis was operative only in the presence of more severe hypoglycemia (~40 mg/dl). Embryonic malformations occurred in both settings. Since the time scale of fetal development in rodents is much shorter than human pregnancy, the relevance of these findings to clinical diabetes is uncertain.

Exposure to diabetes-like conditions may alter not only the amount of DNA available for growth and differentiation, but also the structure of the DNA itself. Endo and Ingalls (156) reported nearly 3 decades ago that tissues from malformed term fetuses of alloxan-induced diabetic mice had a higher frequency of chromosomal abnormalities than did analogous tissues from nonmalformed fetuses of normal or diabetic mice. The same group (157) subsequently reported similar chromosomal abnormalities in blastocysts removed from diabetic rats very early in pregnancy. More recently, Lee et al. (158) studied the effects of maternal diabetes in vivo on DNA mutation rates using a novel transgenic mouse strain. The strain overexpresses a reporter gene, *lacI*, that can be extracted from fetal tissues and assayed in vitro to quantify DNA mutations that occur during intrauterine development. Embryos from the *lacI* transgenic strain were implanted into uteri of pseudopregnant surrogate mothers with or without mild STZ-induced diabetes (blood glucose >150 mg/dl). Fetal tissues studied near the end of pregnancy revealed a twofold increase in *lacI* mutations in the fetuses that had developed in diabetic as compared with nondiabetic mothers. The mutations were predominantly base substitutions distributed throughout the *lacI* reporter gene. These findings indicate that maternal diabetes can alter the DNA structure of developing offspring in utero. Whether alterations in the structure of DNA contribute to the teratogenic effects of maternal diabetes remains to be determined.

Alterations in yolk sac function. Early postimplantation rodent embryos begin neural tube development before the establishment of the allantoic placenta. Thus, all of the developmental events that can be studied with whole-embryo culture in vitro take place before allantoic placentation. During this period, the embryos are surrounded by a two-layered yolk sac and an allantoic membrane, which provide a functional barrier between the embryo and maternal plasma. In vitro studies indicate that small molecules such as glucose may be transported across the membranes, presumably because of the presence of GLUT1 transporter molecules (159), so that the embryos take up glucose in proportion to the surrounding glucose concentrations over a physiological and pathological range (160). Larger molecules (e.g., peptides) may be degraded by the membranes (161) in order to supply amino acids to the developing embryo. The important role of the membranes in determining embryonic nutrition before allantoic placentation suggests a potential role for membrane abnormalities in the genesis of diabetes-induced malformations in vivo and in vitro. Available data support that suggestion. Reece and colleagues (162,163) have demonstrated structural and functional abnormalities of yolk sac membranes removed from early postimplantation embryos exposed to hyperglycemia in vitro. Balkan et al. (164) and Hunter et al. (165) reported that yolk sac abnormalities could be induced by in vitro exposure of neurulation-stage embryos to low–molecular weight serum fractions containing somatomedin-inhibitory activity. Moreover, the investigators demonstrated that proteins were taken up by the yolk sac but not delivered to the embryos in the presence of the somatomedin inhibitors and that supplementing amino acids in the culture medium mitigated the teratogenic effects of the somatomedin inhibitors (164). The findings suggest that somatomedin inhibitors disrupt embryogenesis at least in part through a toxic effect on protein processing by the embryonic membranes. Whether similar mechanisms could be operative during early human development is unclear, since the human embryo has a different anatomic relationship to the yolk sac than do rodent embryos (166).

Summary

Animal studies have provided a wealth of information regarding embryonic malformations that may occur in diabetic pregnancies. In vivo studies have revealed that metabolic abnormalities are important in the genesis of malformations and that insulin treatment can minimize the impact of maternal diabetes on embryogenesis. In vitro studies indicate that the teratogenic potential of diabetic serum is likely to depend on several metabolic abnormalities that act in concert to disrupt one or more biochemical processes in the embryo and its nutrient membranes. A major challenge that awaits investigators in the field of diabetic teratogenesis will be to determine whether one or more of the mechanisms that contribute to the genesis of malformations in animal models are operative in pregnancies of women with established diabetes. Identification of such mechanisms could lead to new strategies in the prevention of birth defects in IDM.

CLINICAL STUDIES OF PRECONCEPTION CARE OF WOMEN WITH DIABETES—

Stimulated by the concept of Navarrete et al. (167) and Pedersen and Molsted Pedersen (44) that incomplete metabolic compensation early in pregnancy causes the excess rate of major congenital anom-

Table 4—*Major congenital anomalies in infants of diabetic women participating in pre-conception clinical studies*

Author, date	Ref.	Pre-conception group		Registered already pregnant	
		Infants	Anomalies	Infants	Anomalies
Fuhrmann et al., 1983	172	128	1 (0.8)	292	16 (5.5)
Fuhrmann et al., 1984	173	56	1 (1.8)	144	6 (4.2)
Goldman et al., 1986	176	44	0	31	2 (6.5)
Mills et al., 1988	49	347	17 (4.9)	279	25 (9.0)
Damm and Molsted-Pedersen, 1989	174	283	7 (2.5)	148	15 (10.1)
Steel and colleagues, 1990, 1994	52, 171	196	3 (1.5)	117	14 (12.0)
Kitzmiller et al., 1991	50	84	1 (1.2)	110	12 (10.9)
Rosenn et al., 1991	177	28	0	71	1 (1.4)
Tchobroutsky et al., 1991	178	40	0	186	16 (8.6)
Willhoite et al., 1993	179	58	1 (1.7)	93	8 (8.6)
Total		1,264	31 (2.5)	1,471	115 (7.8)

Data are *n* or *n* (%). Anomaly data include therapeutic abortions for lethal anomalies. For Mills et al. (49), 14% of women did not register pre-conception but enrolled by 3 weeks postconception.

alies in IDM and armed with an understanding that the severe and often multiple malformations typical of IDM must develop by 3–6 weeks postconception (5–8 weeks postmenses) (57), investigators in Europe set out in 1976–1977 to test the hypothesis that intensified care of diabetes must start before pregnancy in order to reduce the rate of anomalies (52,168–173). Specific prepregnancy clinics for diabetic women were started at the Rikshospitalet in Copenhagen, Denmark, by Molsted-Pedersen and Pedersen (168) and colleagues, at the Royal Maternity Hospital in Edinburgh, Scotland, by Steel and coworkers (169,170), and at the Diabetes Institute in Karlsburg, East Germany, by Fuhrmann and colleagues (172,173). The Copenhagen outpatient diabetes clinic focused on planning of pregnancy, effective contraception, and achievement of optimal diabetic control (174). Patients were admitted to the hospital for a few days as soon as pregnancy was verified (175). Steel (169) stated that the objectives of her multidiscipline outpatient clinic were to assess suitability for pregnancy regarding complications of diabetes, to obtain maximum cooperation of husband and wife with the physicians teaching the diabetes self-treatment plan, and to provide contraception until optimum diabetic control was achieved. Her patients were trained to use multiple daily injections of insulin, with self-adjustment of doses to keep premeal blood glucose ~4 mmol/l (72 mg/dl) (170). Fuhrmann conducted a prepregnancy program for a large area of East Germany, using hospitalization to train patients in various insulin and dietary programs to keep daily plasma glucose at 3.3–7.2 mmol/l (60–130 mg/dl). His patients continued diabetes self-management at home, using basal body temperature charts until pregnancy was identified and were rehospitalized for weeks 5–7 of gestation (172,173).

Based on the reported association of elevated maternal glycohemoglobin levels with a high rate of major malformations in IDM (62–71), a second wave of clinical studies of pre-conception care of women with diabetes began in 1981–1982 (50,176–179). These five sets of investigators used outpatient multidisciplinary team approaches to train patients in diabetes self-management with diet, intensified insulin therapy, and self-monitoring of blood glucose, aiming for near-normoglycemia before stopping contraception. The results of all of the pre-conception studies of intensified diabetes treatment are summarized in Table 4. Most of the trials reported that >80% of subjects achieved normal glycohemoglobin levels before conception, and each showed a striking reduction in the rate of major malformations compared with infants born to diabetic women who reported for care when already pregnant. Each of the investigators concluded that "reasonably strict metabolic control, started well before conception, can prevent excess malformations in babies of diabetic mothers" (173). The decrease in malformations was not due to increased numbers of therapeutic abortions in these studies (50,175,180,181). Four of the investigators also reported that women in the pre-conception care groups had rates of spontaneous abortion not greater than expected for nondiabetic women (50,177, 179,182).

One limitation of all of the pre-conception studies is that they were not randomized, since each of the investigators believed it would be unethical to assign women to a poor-glycemic-control group before pregnancy. As noted, the diabetic control subjects used for these studies were women who did not respond to the recruitment campaign in the community, and they often had unplanned pregnancies with elevated glycohemoglobin levels (50,171,176). The frequencies and types of major malformations in infants born to the late-registrant diabetic women were similar to those in prior studies of congenital anomalies associated with maternal diabetes (Tables 1 and 2). The late-registrant control subjects had diabetes of similar duration and complications compared with the pre-conception participants; and many investigators noted that their "metabolic decompensation" (44) was not inherently more difficult to treat, in that after several weeks of program participation during pregnancy, they achieved a level of glycemic control similar to that of the pre-conception participants (50,171,172, 176,177).

Another criticism of the clinical trials of pre-conception care has been that the good results were due to the fact that the participants were well-motivated diabetic women who responded to the inves-

tigators' recruitment efforts and were able to plan their pregnancies. Indeed, some clinicians have suggested that prepregnancy clinics are not worthwhile because they attract diabetic women who are already in good control (183). These arguments are controverted by three observations. First, participants in several of the pre-conception studies had glycohemoglobin levels (at the time they entered the study) as high as the late-entry patients when they presented for care (50,171, 176). Second, many of the women who participated in the successful pre-conception studies had delivered babies with major malformations in prior pregnancies (50,171,172,177). Third, in a study of the determinants of women seeking pre-conception care in Michigan, only 27% of participants perceived that they were in very good diabetes control in the prior 6 months (184). Thus, the very low malformation rates observed in the pre-conception studies are difficult to explain simply on the basis of a selection bias.

Based on these clinical studies, what is the optimal level of glycemic control to be achieved before pregnancy? As noted, many of the investigators presented data to show that ~80% of the pre-conception participants had normal glycohemoglobin levels at the onset of pregnancy (50,171,176). In the first report of Fuhrmann et al. (172), mean daily blood glucose (before and after meals) was <8.4 mmol/l (151 mg/dl) during 5–7 weeks of gestation in 98% of the 128 pre-conception care participants. In the second report of 56 additional participants, 86% were "normoglycemic" during embryogenesis and 14% had "insufficient metabolic control" (40% of blood glucose values >7.7 mmol/l (140 mg/dl), and one of the latter group delivered an infant with a lethal heart defect (173). The group of Goldman et al. (176) of 44 pre-conception care participants achieved mean blood glucose concentrations in the 1st trimester of 6.1 mmol/l (110 mg/dl) and a mean glycohemoglobin level <3.5 SD above the mean for 20 nondiabetic control subjects also followed from the onset of pregnancy. Kitzmiller et al. (50) reported the mean of four daily capillary blood glucose levels (one fasting and three 1-h postprandial) for each of 6 weeks before and 7 weeks after conception in 84 pre-conception care subjects (50). The mean of these blood glucose levels was <10 mmol/l (180 mg/dl) before and at conception and <8.9 mmol/l (160 mg/dl) during 5–8 weeks gestation in 90% of the subjects. Initial pregnancy glycohemoglobin levels were within 5 SD above the normal mean in 93% of the participants (50). One can conclude that these levels of glycemic control were sufficient to prevent an excess rate of major congenital anomalies under the conditions of these studies.

Additional data on capillary blood glucose (one fasting and three 1-h postprandial) measured daily during 5–8 weeks of gestation in 347 diabetic women were reported by the DIEP Study Group (49). The mean of these blood glucose levels was <7.5 mmol/l (135 mg/dl) in 5% of subjects, >10.6 mmol/l (190 mg/dl) in 50%, and >12.9 mmol/l (232 mg/dl) in 5%. In this early-entry diabetic group, there were 17 infants delivered with major malformations (4.9%) and 13 infants with major malformations commonly associated with diabetes (3.7%), compared with 9.0% major malformations of all types and 6.1% malformations "commonly attributed to diabetes" in 279 late-entry diabetic women (49). Thus, the level of glycemic control was not as strict as that achieved in the pre-conception clinical studies, and the rate of major malformations was higher. It is difficult to compare the results of this large early pregnancy study to the clinical evaluations of pre-conception care of women with diabetes, since only 86% of the early-entry diabetic subjects were registered before pregnancy and no data were available on the intensity of diabetes management before and at conception (49).

Information on other diabetic factors (hypoglycemia, vascular disease) speculated to contribute to the excess rate of congenital anomalies is available by analysis of the pre-conception clinical studies. Symptomatic hypoglycemia was reported in 86 diabetic participants (26%) in early pregnancy in two of the trials, but only one infant had a major malformation (50,171). In the DIEP study of 347 early entry diabetic subjects, there was no increase in the frequency of hypoglycemia in weeks 5–12 of gestation in the 17 women delivering infants with malformations (49). Regarding diabetic vascular disease, there were 186 women of White's classes D, F, and R (185) participating in four of the pre-conception care studies (50,171,172,176), and none of their infants had major malformations, suggesting that pre-conception care is effective for women with diabetes of long duration with vascular complications.

COST-EFFECTIVENESS OF PRE-CONCEPTION CARE OF WOMEN WITH DIABETES

— In the mid 1980s, Hollingsworth et al. (186) and Steel (187) predicted that pre-conception care of women with diabetes would be cost-effective, since prevention of congenital malformations would mean that IDM could be cared for after birth in the regular nursery as opposed to the much more expensive intensive care nursery ($230/day vs. $1,350/day at that time) (186).

Using a case-control study design, Scheffler et al. (188) evaluated the cost-benefit of the California Diabetes and Pregnancy Program (CDAPP). The program uses a multidisciplinary team approach to care, emphasizing early recruitment before or in early pregnancy (189). Enrolled women receive diabetes self-management training specifically developed to meet the needs of diabetic women during pregnancy. To minimize the effect of selection bias, three control hospitals without a special program were chosen outside the catchment areas of three similar CDAPP hospitals (188). The costs of care were estimated by means of "time-motion" methodology on the basis of expected nonphysician staff time necessary to deliver patient care services as specified in the California Guidelines for Care of Diabetes and Pregnancy (190,191). The costs of patient training activities were estimated to be $800 for prenatal care after 12 weeks' gestation, compared to $1,300 for pre-conception plus prenatal care (188).

Data on total hospital charges and length of stay were collected on 102 CDAPP cases and 218 control-hospital diabetic cases cared for in 1986–1988 (188). Since the CDAPP cases were more likely to be women with advanced diabetes (57 vs. 18%), an analysis was conducted on 90 patients matched for age, ethnicity, duration of diabetes, and payer mix (~36% of cases in each group were funded by MediCal-California Medicaid). The results showed that mean hospital charges and length of stay were signifi-

cantly lower for both mothers and infants in the CDAPP.

For every dollar spent on the patient training services of CDAPP, there was an estimated savings of $5.19 in maternal-infant hospital charges. The cost-benefit pertained to women with indemnity as well as public insurance. Within the CDAPP cases, the greatest savings were realized by early enrollment, before 8 weeks' gestation. A secondary analysis looked at the effects of an all–pre-conception program under conservative assumptions, which indicated savings of $5,624 per participant. Scheffler et al. (188) concluded the report with this sentence: "In addition, there are many non-monetary benefits to healthy pregnancy outcomes."

In 1989, the Centers for Disease Control and Prevention (CDCP) contracted with the Battelle Memorial Institute for a study to determine whether the additional costs of pre-conception care for women with established diabetes are balanced by the savings from averted complications (192). A hypothetical model pre-conception care program was developed through a series of questionnaires sent to health care providers experienced in pre-conception care of diabetic women and by a series of meetings of a panel of six physicians in which consensus development techniques were used (193). The consensus pre-conception care program involved "close interaction between the patient and an interdisciplinary health care team, as well as intensified evaluation, follow-up, testing, and monitoring" (192). Program costs were based on personnel charges, laboratory and diagnostic tests, medications, and supplies and totaled $17,519 per delivery for pre-conception plus prenatal care, compared to $13,483 per delivery for prenatal care only, in 1989 dollars. Outcome measures included direct medical costs for maternal and infant hospitalization and long-term care costs for affected children. Using conservative estimates, the incidence of neonatal adverse outcomes was developed from published population-based studies of diabetic women. Elixhauser and colleagues (192) determined that the net savings of pre-conception care were $1,720 per enrollee compared to prenatal care only, and the benefit-cost ratio was 1.86 ($1 spent on pre-conception care, $1.86 saved in direct medical costs). As expected, the savings resulted largely from prevention of the most expensive adverse events–major congenital anomalies–and their long-term costs for care. Sensitivity analyses were performed to assess the impact of changes in a wide range of assumptions regarding incidence of adverse outcomes and program cost components, and the program always remained cost saving (192).

The benefit-cost ratio was 1.33 if outreach costs of $800 per woman enrolled in the pre-conception program were added, and it was 2.32 if the number of pre-conception visits was reduced because of more rapid attainment of glycemic control. The benefit-cost ratio was 1.84 if malformation rates were used from published studies of pre-conception care programs compared with late registrants into prenatal care (49,50,171–173, 176,177), but it rose to 2.25 if the one study with less stringent glycemic control (49) was excluded. The authors concluded that health insurance payers could realize significant cost savings by reimbursing for pre-conception care and for self-management training of women with established diabetes (192).

Costs for the long-term care of infants with debilitating anomalies may not be relevant to the current structure of managed health care insurance plans, whose members may change plans every few years. To deal with this criticism, Elixhauser et al. (194) reassessed the cost-benefit of pre-conception care, eliminating all post–neonatal intensive care unit infant costs. Including only the direct medical costs for the pregnant diabetic women and their infants in the NICU, the benefit-cost ratio was 1.24 (194). Thus, benefits of pre-conception care accrue during pregnancy and during the initial hospitalization of mother and infant, so immediate savings could be realized by reimbursement for participation in the program.

ELEMENTS OF PRE-CONCEPTION CARE OF WOMEN WITH DIABETES —

The elements of an organized program for pre-conception care are best based on the published clinical trials that were successful in preventing excess spontaneous abortions (50,177,179,182) and major malformations in infants of mothers with established diabetes (50,169–179). Steel and colleagues (50,169–171,188) and Kitzmiller et al. (50) presented detailed methods that were applied in heterogeneous populations of diabetic outpatients in the Edinburgh and San Francisco, California, areas, respectively; and Goldman et al. (176) adapted the aims and practices of Steel et al. (169) in his clinical trial in Israel. The landmark study of Fuhrmann and coworkers (172,173) in former East Germany preceded the widespread availability of glucose reflectance meters. Fuhrmann's model of care, emphasizing hospitalization before and again during early pregnancy, would be extremely costly today.

Although the components of diabetes self-management used by the investigators of pre-conception care (50,169–179) were not subjected to formal study to determine which facets of management were critical for the prevention of anomalies, the methods used were sufficient to achieve a level of glycemic control that prevented congenital malformations, so their use can be recommended. The treatment methods were similar to those used with the group of subjects with IDDM randomized to intensive treatment in the multicenter Diabetes Control and Complications Trial (DCCT) (195–197). The components of the pre-conception care programs were also similar to the elements of care developed by Elixhauser and colleagues (192,193), which are summarized in Table 5. As noted, to provide a basis for the cost-benefit analysis, this CDCP-sponsored study used a panel of physicians specializing in the care of women with diabetes and a targeted survey of other health care providers. The consensus goals of pre-conception care were stated: *1*) integrate the patient into the management of her condition, 2) postpone pregnancy until excellent blood glucose control is achieved by focusing on close interaction between the patient and a multidisciplinary health care team, and 3) identify, evaluate, and treat complications of diabetes such as retinopathy, nephropathy, and hypertension (193).

Recruitment of participants

Methods used to recruit subjects for clinical trials of pre-conception care included letters to physicians and presentations at continuing education conferences; announcements in newsletters and posters in clinics (50,177,187); announcements

Table 5—*Standards of pre-conception care for women with existing diabetes*

General principles of pre-conception care	Inform patient about the risks of pregnancy complicated by diabetes. Use contraception until an excellent blood glucose level is achieved. Identify, evaluate, and treat hypertension, nephropathy, and retinopathy. Train in glucose control and self-monitoring. Instruct in nutrition and meal planning. Provide social work intervention and counseling as needed.
Excellent blood glucose control	
Prevent hyperglycemia at beginning of pregnancy	GHb within 4 SD of mean or peak postprandial capillary blood glucose level <9 mmol/l (162 mg/dl).
Requirements for patient	Follow eating plan developed with dietitian. Monitor blood glucose levels with reflectance meter at least four times daily (once fasting and after each meal or before meals and bedtime snack). Self-adjust insulin dosage. Meet regularly with health care team to tune glucose control and diet. Identify and manage sources of stress that interfere with adherence to regimen.

Modified from Elixhauser et al. (192,193).

in newspapers, radio, and television (50,172,173); booths or programs at health fairs or other consumer-oriented gatherings, including cosmetic and fashion shows (198); and informational inserts with purchased diabetes supplies (50,189). These methods produced a yield of subjects for pre-conception care ranging from 28 to 62% of the total number of diabetic pregnant women in the clinical studies (50,169–179). In the study of Kitzmiller et al. (50), 58% of 189 women recruited for pre-conception care became pregnant; 51% of the subjects were referred by physicians, 33% responded to announcements in the print or electronic media, and 16% learned of the program by word of mouth. Kaufmann and coworkers (192,198) estimated outreach costs for their program in Illinois to be $800 per enrollee.

In a case-control study of diabetic women entering pre-conception versus prenatal care at five centers in southeastern Michigan, Janz et al. (184) sought to identify the sociodemographic characteristics, medical factors, knowledge, attitudes, and health-related behaviors of the 57 women who sought pre-conception care. Women were interviewed within 1 week of their first clinic visit. Patients not receiving pre-conception care were more likely to be nonwhite (36 vs. 0%) and to have NIDDM (19 vs. 7%) and were less likely to be living with a partner (60 vs. 93%), to have an education beyond high school (41 vs. 80%), to be employed (41 vs. 78%), or to have a partner who was employed (71 vs. 96%) (184). The demographic characteristics of the pre-conception patients were similar to those of the early-pregnancy registrants in the multicenter DIEP (49).

The health-related behavioral characteristics of the pre-conception and prenatal subjects in the Michigan study of Janz et al. (184) are listed in Table 6. Pre-conception subjects with IDDM were more likely to have discussed pre-conception care with their health care providers (98 vs. 51%) and to have been

Table 6—*Medical and behavioral characteristics of diabetic women seeking pre-conception (PC) versus prenatal care only (PN) in southeastern Michigan*

	PC subjects	PN subjects	
	IDDM	IDDM	NIDDM
n	53	79	18
Diabetes clinic visit in past year (%)	77.4	79.5	70.6
Patient perceived very good diabetes control in past 6 months (%)	26.9*	8.9	11.8
Discussed PC care with diabetes care provider (%)	97.6*	51.4	35.7
Health provider encouraged PC care (%)	77.4*	43.0	5.9
Gyn clinic visit in past year (%)	88.1	87.2	90.3
Discussed PC care with Gyn provider (%)	79.5*	34.4	38.5
Prior pregnancy with diabetes (%)	52.8	57.7	70.6
Awareness of PC care (%)	100.0	72.7	58.8
Believed high benefits to baby (%)	94.3*	73.1	82.4
Barriers to self-management (1 = big problem, 5 = no problem)	3.9	3.9	3.9
Self-efficacy score (0 = not confident, 10 = very confident)	8.9	8.8	8.5
Total social support score (1 = a lot, 5 = no support)	1.3	1.5	1.6
Adherence score with diet, insulin, blood glucose monitoring (1 = all the time, 5 = none)	1.8	2.6	3.9

Modified from Janz et al. (184). *$P < 0.05$, IDDM, PC vs. PN.

encouraged to obtain such care (77 vs. 43%). Pre-conception patients perceived greater benefits of pre-conception care, but only 27% perceived that they had been in "very good" diabetes control in the past 6 months. In a logistic regression model with sociodemographic variables excluded, significant factors that were associated with seeking pre-conception care were adherence to the diabetic regimen and encouragement by providers to participate in pre-conception care (184). The authors discussed several methods that might improve the frequency of diabetic women obtaining pre-conception care and pointed out the lack of attention paid to this in women of childbearing age with NIDDM. They concluded that "providers must regard every visit with a diabetic woman as a pre-conception visit. Contraception must be explicitly discussed, and pregnancies should be planned. In counseling, the benefits of pre-conception care should be stressed and the support of families and friends should be elicited" (184).

Molsted-Pedersen et al. (199) and many others (200) emphasized follow-up of women with gestational diabetes as one method of providing subjects for pre-conception care, since up to 60% of these women may develop diabetes by 5 years after pregnancy (201–206). Rosenn et al. (207) and Miodovnik et al. (208) emphasized follow-up of women with established diabetes after pregnancy to encourage re-enrollment in pre-conception care, but the problem of unintended pregnancies lowers the yield. The issue of contraception for diabetic women is discussed below.

Evaluation of risks for pregnancy

As diabetic women seek to enter pre-conception care, the first step is evaluation of medical risks for pregnancy. Glycemic control has generally been assessed by measurement of glycosylated hemoglobin (50,171,177) and by self-monitoring of premeal and postprandial capillary blood glucose (50,171, 172,176,177). The general targets for glycemic control discussed above may need to be individualized based on the patient's recognition of and response to hypoglycemia (207,211). Food records have been useful to evaluate the patient's ability to time meals and snacks in relation to insulin injections and exercise, to estimate the carbohydrate content of food choices, and to learn the relation of those food choices to glycemic responses (50,212). Review of symptoms after eating and the timing of postprandial glucose excursions can identify diabetic gastroparesis. Gastric emptying studies can be used for diagnosis before pregnancy (213). Diabetic gastroparesis can be a future problem when coupled with the stresses, hormonal changes, and potential hyperemesis of early pregnancy (214,215). Stimulants of gastric mobility, such as metoclopramide and cisapride, may be useful before and in early pregnancy (216), although the maternal benefit must be balanced against the unclear teratogenic potential of the drugs. Finally, careful review with the patient of the food and blood glucose records by physician, dietitian, and diabetes educator may uncover eating disorders in a proportion of women with either IDDM or NIDDM (217,218), who will need specific counseling and treatment if glycemic control is to be adequate for pregnancy.

Evaluation and treatment of hypertension is important in the pre-conception period, since blood pressure levels strongly influence progression of diabetic nephropathy (219–221) and the outcome of pregnancy (222–224). A 1993 Consensus Statement on treatment of hypertension in diabetes recommends that the goal of therapy is to maintain systolic blood pressure <130 mmHg and diastolic blood pressure <85 mmHg (225). These levels should also be optimal for pregnancy (222–224,226). Treatment is recommended for isolated systolic hypertension (>140 mmHg) (225). It is important to establish effective blood pressure control with antihypertensive agents that will be safe for pregnancy. The 1993 Consensus Statement recommends that ACE inhibitors, α-1 receptor blockers, calcium antagonists, and low-dose thiazide diuretics may be especially useful in the treatment of diabetic patients (225). However, ACE inhibitors are contraindicated in pregnancy because of serious adverse effects on fetal and neonatal renal function (227). There is a theoretic problem using calcium antagonists such as diltiazem in early pregnancy, since animal studies demonstrate an increase in fetal limb defects (228). Thiazide diuretics are usually not used during pregnancy, since chronic use in nondiabetic hypertensive pregnant women was associated with significant reduction in plasma volume (229), which could contribute to impaired utero-placental perfusion (230).

Antihypertensive agents that are safe and often effective in pregnancy include methyldopa, clonidine, and prazocin (231, 232). Methyldopa is little used outside of pregnancy because of poor compliance associated with drowsiness and because of a possible rise in blood pressure after 6–9 months of use associated with increasing plasma volume (231). However, methyldopa has been widely used during pregnancy, and no effects were noted on development of offspring (233). There is controversy whether β-adrenergic blockers can adversely affect fetal growth (231–232), and they should be used with caution in diabetic women because of potential adverse affects on lipid balance, glycemic control, and hypoglycemia awareness (225).

Evaluation of renal function and staging of nephropathy is part of the pre-conception management of every diabetic woman. A 24-h specimen should be collected for determination of microalbumin (234) or total protein excretion and creatinine clearance by a reference laboratory because technical problems can lead to invalid results in laboratories that perform microalbumin assays infrequently (285). A 24-h overnight collection is preferred to a shorter timed collection because protein excretion follows a diurnal rhythm, and use of a protein-to-creatinine ratio in a single voided spot urine can result in large errors (236). Creatinine clearance can be moderately reduced during pregnancy in spite of "normal" serum creatinine levels (222), which supports the use of 24-h urine collections. Effective therapy of diabetic nephropathy before pregnancy depends on the stage of renal involvement. Early hyperfiltration marked by glomerular filtration rate >150 ml/min (237) will usually reverse with improved glycemic control (238). Progression of microalbuminuria can be slowed by intensive glycemic control (197,239,240) and treatment of hypertension (241). Control of hypertension (221) and perhaps low protein intake (242) can slow the progression of overt diabetic nephropathy with macroproteinuria. Minimal protein intake for future pregnancy is calculated to be >60 g/day (212). Women bordering on end-stage renal disease with creatinine clearance <50 ml/min or serum creatinine >3 mg/dl are discouraged from attempting

pregnancy until there is stable renal function after transplantation (50,52,222–224). Diabetic women with renal transplants will usually have a successful pregnancy without an increased rate of transplant rejection, although about two-thirds will develop preeclampsia in late gestation (243).

Diabetic women are carefully evaluated for the presence of retinopathy with a retinal examination through dilated pupils before pregnancy. Counseling of these women is based on clinical studies of diabetic retinopathy in pregnancy. Phelps et al. (244) observed that 65% of 20 women with background retinopathy showed worsening during pregnancy and that 10% developed proliferative changes. Four of five women with proliferative retinopathy worsened during the course of pregnancy. Deterioration of background retinopathy correlated significantly with the levels of plasma glucose at entry and with the magnitude of improvement in glycemia during the first 6–14 weeks after entry. The authors warned that abrupt institution of improved glycemic control during pregnancy may be a risk for deterioration in retinopathy (197,244), which is an important reason for gradual attainment of stable tight control in the pre-conception period.

Klein et al. (245) compared gradable fundus photographs ~40 weeks apart in 133 pregnant and 241 nonpregnant diabetic women to determine the effect of pregnancy on diabetic retinopathy. Worsening of retinopathy in both groups was correlated with higher glycosylated hemoglobin levels and less strongly with diastolic blood pressure. When these variables were controlled for, pregnancy itself or rapid improvement in glycemic control was significantly associated with progression (adjusted odds ratio 2.3). The authors recommended a clinical trial to evaluate the effects of prescribed levels of glycosylated hemoglobin and blood pressure in preventing or minimizing the increased risk of progression conveyed by pregnancy (245).

The multicenter DIEP provided another opportunity to evaluate the effect of metabolic control in pregnancy on the progression of retinopathy (246). Fundus photographs were available both in early pregnancy and 1 month postpartum in 155 diabetic women, 15 of whom were excluded from analysis because of proliferative retinopathy at entry or prior laser photocoagulation. Of the remaining 140 women, in early pregnancy, 39 women had no retinopathy (10.3% developed background changes), 38 had microaneurysms only (21% had progression by postpartum), 32 had mild nonproliferative retinopathy (2 developed neovascularization and 12.5% had progression in background retinopathy by postpartum), and 31 had moderate-severe nonproliferative retinopathy at baseline. Of the latter group, 29% developed neovascularization and 26% had a progression in nonproliferative retinopathy (246). Chew et al. (246) determined that elevated glycosylated hemoglobin at baseline (>6 SD above control mean, adjusted odds ratio 2.7) and the magnitude of improvement of glucose control through week 14 were associated with a higher risk of progression. In univariate analysis, blood pressure and proteinuria were not significant risk factors for progression of retinopathy. The authors concluded that excellent metabolic control before conception may be required to avoid the increased risk for progression of diabetic retinopathy during pregnancy (246).

In a group of 18 diabetic pregnant women, retinal blood flow was measured by laser Doppler velocimetry in a major temporal retinal vein in each trimester and at 18–20 weeks postpartum and compared with that in 19 control subjects without diabetes (247). The patients who suffered the worst progression of retinopathy had the poorest glycemic control in early pregnancy and significantly greater retinal blood velocities in all 3 trimesters. Chen et al. (247) suggested that these patients did not exhibit the expected compensatory retinal vessel constriction (autoregulation) that the group without diabetes demonstrated in response to the hyperdynamic circulation of pregnancy. On the other hand, the mean improvement in HbA_{1c} in pregnancy was similar in diabetic women whose retinopathy did or did not progress. The data from this study also indicate that gradual achievement of tight glycemic control before pregnancy may protect against progression of diabetic retinopathy, as it does in nonpregnant patients with IDDM (197,240, 248).

There are few data available on evaluation for ischemic heart disease before pregnancy, but it is suspected that active coronary artery disease in diabetic women may have a high mortality rate during pregnancy (185). In a series of diabetic patients with end-stage renal disease being evaluated for transplantation by coronary angiography, Manske et al. (249) found virtually no significant coronary disease as long as age was <45 years, diabetes duration was <25 years, and there were no ST-T wave changes on electrocardiogram (249). This suggests that diabetic women in pre-conception care should have an electrocardiogram and, if risk factors are present, that evaluation by a cardiologist is indicated.

Counseling and motivation of patients for intensive treatment

The domain of counseling of patients coming to pre-conception care is broad and includes provision of information on *1*) pregnancy risks associated with the level of glycemic control and with diabetic complications, 2) maternal health risks associated with the metabolic and other stresses of pregnancy, and 3) appropriate methods of delaying or preventing pregnancy (50,52,176,177). The results of the assessment of metabolic compensation (glycohemoglobin, blood glucose and food intake pattern, recognition of hypoglycemia, weight and effects of exercise, lipid balance, thyroid function) are explained and treatment targets established. As noted by Steel and coworkers (169,170), Rosenn et al. (53), and Janz et al. (184), it is important to involve the patient's partner and other supporting individuals in this process, since the support is needed to achieve safe tight glycemic control. Patients with diabetic gastroparesis are informed that hyperemesis in early pregnancy can be severe and that hospitalization or total parenteral nutrition may be necessary (214,215). Patients with eating disorders need to deal with the issues of recognition, self-esteem, and behavior modification before pregnancy is attempted (250).

Patients with proliferative retinopathy are counseled to prevent pregnancy until laser phototherapy induces remission, since neovascularization worsens during pregnancy but risks of reactivation after successful treatment are minimal (244,251,252). Patients with background retinopathy are informed that there is a 7–10% risk of developing proliferative retinopathy during pregnancy, influenced by degree of preprolif-

erative changes, level of glycemic control, and perhaps blood pressure (244–246). Such patients should anticipate repeated ophthalmological examination during pregnancy and should know that laser phototherapy is usually successful during pregnancy when required (253).

Women in pre-conception care are informed whether they have incipient or clinical diabetic nephropathy and about the roles of glycemic control (197,238–240), antihypertensive therapy (219–221,241), and perhaps restriction of protein intake (242) in preventing or slowing progression of the disorder. They are informed that proteinuria will temporarily increase during pregnancy but that renal function worsens in only 8–30% of subjects with clinical diabetic nephropathy, at a rate probably no different than background as long as blood pressure can be controlled (222–225,254). Women with proteinuria >180 mg/24 h (256) are counseled about the increased risks of superimposed preeclampsia, fetal growth retardation, and preterm hospitalization or delivery (222–224), which are even greater in patients with reduced creatinine clearance (222,223). Women with overt nephropathy should understand their prognosis for eventual renal failure and its treatment by dialysis or transplantation and consider how the effects of the chronic disease will impact upon the responsibilities of child rearing (255). Women with incipient renal failure (serum creatinine >3 mg/dl, creatine clearance <50 ml/min) are counseled to avoid pregnancy unless renal function can be stabilized by kidney transplantation (52,222,224,243).

Women with evidence of coronary artery disease are usually advised to avoid pregnancy because of possible increased mortality. In the first 11 cases of ischemic heart disease in pregnant diabetic women reported up to 1977, there were eight maternal deaths (185). Six cases have been reported since 1980 without maternal mortality: four women had myocardial infarction 2 months to 2 years before conception, one had severe angina 2 years before pregnancy, and in one woman, an electrocardiogram during the 2nd trimester revealed an anteroseptal infarction of undetermined age (257). Improved glycemic control and medical management may have decreased the maternal risk in these patients. Three successful pregnancies have been reported in diabetic women who had coronary artery bypass surgery 3 months to 2 years before conception (185,258,259). Diabetic women with evidence of coronary artery disease should be counseled about this option in the pre-conception period (259).

For women with diabetes, coping with intensive treatment to achieve tight glycemic control for pregnancy is difficult, and motivation is an important factor in the long-term success of the regimen. Steel (52,187) and others (50,177,184) noted the powerful motivating force of the desire for procreation and that women coming to pre-conception care were self-selected but also were influenced by the encouragement of their health care providers. Steel (187), Fuhrmann et al. (172), Kitzmiller et al. (50), and Rosenn et al. (177) noted that motivation to cope with the rigors of intensive treatment improved still further as a result of the imparted understanding of why glycemic control is so important and of the rationale for the self-management methods that were taught. However, even well-motivated patients can be expected to have compliance problems with one aspect or another of treatment, based on common human characteristics such as denial, resistance to control, etc. Jacobsen et al. (260) noted the importance of psychosocial assessment to help identify patients at risk for compliance problems. In a prospective study of 57 patients newly diagnosed with IDDM at age 9–15 years, several psychosocial measures had significant correlations with compliance indexes. These included self-esteem and perceived competence, self-perceived locus of control of one's life (outside factors versus personal sense of control), social functioning, behavioral symptoms, and adjustment to diabetes (260–262). Attention must be paid to these psychosocial factors by the integrated diabetes care team, which includes the patient in the center, for maximal success of intensive diabetes ambulatory treatment. This was noted in the multicenter DCCT: for 463 participants in the intensive treatment arm, psychosocial distress and psychological symptoms were not significant predictors of glycohemoglobin level, although they were in the less well supported conventionally treated patients (263).

Patient training in diabetes self-management skills

A multidisciplinary integrated team approach (193) has been successful in the clinical studies of prevention of congenital malformations (50,176,177) and other complications of diabetes (195–197, 264). Patients have been trained in daily self-monitoring of capillary blood glucose using glucose reflectance meters with memory capacity. Once safe targets of glycemic control were selected, premeal blood glucose values were used to guide the dosage of short-acting and intermediate insulin (170,171). Postprandial blood glucose values were used to assess the response to individual food choices (50,212). The great majority of diabetic women in pre-conception care have been taught to self-adjust multiple daily insulin doses based on premeal blood glucose levels, anticipated carbohydrate intake, and anticipated level of exercise (50,52,187,173). Continuous subcutaneous insulin infusion therapy has been useful in a subset of IDDM patients in pre-conception care (10–25%) (50,187) who demonstrated problems with hypoglycemia (53), the dawn phenomenon (265), or wide glucose excursions in spite of good compliance with intensified dietary and conventional insulin regimens (50,266,267).

Diabetic women in pre-conception care are trained to use a meal plan that would be appropriate in early gestation in order to avoid loss of glycemic control caused by changing the treatment plan when pregnancy is diagnosed (50). Patients desiring weight loss are advised to complete or abandon that effort before stopping contraception and planning pregnancy, since ketonemia can result, which has possible effects on embryonic development (124,126) and childhood development (268). Energy intake is based on prepregnancy weight status. For women at a desirable body weight, 30 kcal/kg per day is suggested; for >120% desirable body weight, 24 kcal/kg per day; and for <90% desirable body weight, 36–40 kcal/kg per day is recommended (6,212). The percentage of carbohydrate (usually 40–45%) depends on individual eating habits and the effect on blood glucose levels. Avoidance of fruit juices and processed or refined starch products and sweet condiments may be necessary to achieve euglycemia in pregnancy–"unrefined, whole grain breads,

non-instant oatmeal, legumes and lentils are encouraged because of their lower glycemic response" (212). Steel et al. (170) taught pre-conception patients to weigh out the carbohydrate content of each meal; and Goldman et al. (176), Kitzmiller et al. (50), and Rosenn et al. (177) taught such patients to estimate grams of carbohydrate balanced with the dose of short-acting insulin. Women using rice-based meal plans need to measure the quantity of cooked rice, usually limited to 1 cup per meal. Protein intake is recommended to be at least 60 g/day, and <10% of energy should be from saturated fat (212). Caffeine intake is limited to <321 mg/day or <3 cups of coffee to lower the risk of early fetal loss (269). Folic acid (3,400 mg/day) is provided with multivitamins to lower the risk of neural tube defects in offspring (270–273), including in the setting of tight glycemic control.

Women with IDDM and their partners are taught to use glucagon for treatment of severe hypoglycemia and to use three or four well-timed snacks per day to avoid it (50,53,169–171). Periodically, blood glucose testing at 2:00–4:00 A.M. is necessary to identify and prevent nocturnal hypoglycemia. Hollingsworth and Ney (274) recommended eliminating daytime snacks in obese women with NIDDM to avoid food-stimulated maternal hyperinsulinemia. However, Jenkins et al. (275) measured lower blood glucose and insulin concentrations in patients with NIDDM who increased their meal frequency. Studies are needed of the effect of amounts and timing of food intake on glycemia and ketonemia in early pregnancy in this population. For women with IDDM, Reece and coworkers (276,277) demonstrated that normalization of blood glucose levels in pregnancy by intensified dietary and insulin therapy also resulted in lipid, ketone, and amino acid levels that were not different than those in healthy nondiabetic pregnant control subjects.

Contraception and planning pregnancy

Many contraceptive options are appropriate for the few months usually required to reach targeted levels of metabolic control in pre-conception care of diabetic women. These include abstinence, barrier methods, and oral contraceptive (OC) pills. The choice between these methods is largely a matter of patient preference rather than medical dictum. There is no evidence that the failure rates of any of these methods are any different in diabetic women than in nondiabetic women.

Periodic abstinence (the so-called rhythm method) requires regular menstrual cycles in a patient with a high degree of knowledge and compliance. For optimum efficacy, periodic abstinence requires ovulation prediction using basal body temperature measurement and cervical mucus evaluation.

Barrier methods, such as condoms, diaphragms, and cervical caps, have optimum efficacy when used in combination with a spermicidal gel or suppository. Condoms are the only barrier method that protects against sexually transmitted diseases.

Low-dose combination OCs. In recent years, the estrogen and progestin dosage in OCs has been lowered considerably, reducing morbidity and side effects while retaining pregnancy protection. The term low-dose refers to formulations that contain <0.050 mg of ethinyl estradiol or its methylated derivative, mestranol (278,279). With today's low-dose estrogen preparations, large prospective population studies of nondiabetic subjects have found no increased risk of myocardial infarction, pulmonary embolism, or cerebral vascular accident (280,281). Angiotensinogen is elevated by ethinyl estradiol in a dose-dependent fashion; even with the lowest dose preparations (0.030–0.035 mg), there is a mild but not usually clinically significant rise in blood pressure (282). In women with diabetes or previous gestational diabetes, pills with a low estrogen dose are selected and blood pressure is monitored regularly (283).

The progestin component in low-dose combinations varies widely in its dosage and potency. All formulations of progestin are 19-nortestosterone derivatives. Norethindrone and its two derivatives, ethynodiol diacetate and norethindrone acetate, which are metabolized to norethindrone, have equivalent biological effects per dose. Levonorgestrel is 10–20 times more potent and more androgenic than the norethindrones (284) and is marketed in a lower dose. Three new third-generation derivatives of levonorgestrel have been introduced: norgestimate, desogestrel, and gestodene. They look promising because of higher progestin activity with less androgenic activity (285,286), but further studies comparing their efficacy with the existing progestins in similar low-progestin-dose formulations and evaluating their use in diabetic women need to be done. Progestin-only OCs (mini-pills) may be a useful alternative for women who are lactating or who have a contraindication to estrogen-containing pills, such as a history of deep venous thrombosis. These preparations have minimal metabolic side effects (287). However, they cause irregular, unpredictable menses and thus have a high rate of discontinuation.

Lipid and carbohydrate metabolism with OCs. In diabetic women, the selection of the proper dose/potency of the progestin component is important because of the potential adverse effects on carbohydrate and lipid metabolism. Shortly after OCs became available, Waine et al. (288) reported a deterioration of glucose tolerance with the use of OCs, which at that time contained high estrogen and progestin doses. Subsequent investigations demonstrated that the progestin component, but not estrogen, was the culprit: decreasing the dose and potency of progestins resulted in decreasing blood glucose (289–292). In muscle and adipose cells, progestins exert a contra-insulin effect, while in the liver they appear to promote glycogen storage, an insulin-like effect. Estrogens oppose the peripheral action of progesterone and increase insulin sensitivity in muscle and adipose cells. When prescribed in combination, the net effect on carbohydrate metabolism appears to be dependent on the molar concentration ratio of estrogen to progestin (293). Today's low-dose combination OCs, whether containing the new progestins or the older preparations in lower dosages, tend to be estrogen dominant in their metabolic effect. They have been shown to have minimal effect on glucose tolerance and on serum insulin or glucagon levels in healthy women (285,294–297).

Selection of the proper progestin dosage for diabetic women should also be geared toward minimizing adverse effects on lipid metabolism. The degrees of increased LDL cholesterol and decreased HDL cholesterol are related to the dose and androgenic potency of progestins (298). In combination OCs, estrogen counterbalances this effect by favorably altering the lipid levels. As a result of low-

ering progestin content or decreasing androgenicity, the current low-dose estrogen-progestin formulations are largely estrogen dominant in their metabolic effects. Recent prospective studies in healthy women using these formulations have not found adverse changes in HDL or LDL cholesterol or in total cholesterol–to–HDL cholesterol ratios. Only the more androgenic progestin, the levonorgestrel in triphasic preparations, has been shown to lower HDL_2 compared with the norethindrone, gestodene, or desogestrel formulations (286,299,300). These findings have been confirmed in a large cross-sectional study examining women using seven different low-estrogen-dose formulations with varying progestin doses and types in contrast to women using no hormonal contraception (287).

OC use and diabetes. Prospective short-term (up to 1 year) studies evaluating the use of low-dose combination or progestin-only OCs in women with IDDM demonstrated little effect on glycemic control. In one study, a slight increase in insulin requirement was found, although no effect on blood glucose levels was noted (301). Other studies have not found significant changes in insulin requirement, glucose excretion, or glycemic control using various low-dose combination and progestin-only preparations. Similarly, these studies found no change or an improvement in total serum cholesterol and HDL cholesterol (302–307). Recently, a small controlled study in women with IDDM examined the new progestin gestodene in a combination formulation and found no adverse effects on lipoprotein level or direct endothelial function (308). Indirect measures of endothelial function suggested that OC therapy induced a procoagulant state, which was compensated for by enhanced fibrinolytic activity (309).

Currently there are no long-term prospective studies evaluating the effect of OC use on diabetic complications. Retrospective studies are difficult to evaluate secondary to selection bias and the inability to match the patient baseline health status before OC use. One such study examined 120 IDDM patients on OCs and 156 IDDM patients on nonhormonal contraception; all three cases of cerebral thrombosis and one case of myocardial infarction were found in the OC users (310). Conversely, in a more recent cross-sectional study of 384 women with IDDM, no association was found between current, past, or present use of OCs and the severity of retinopathy, hypertension, or glycosylated hemoglobin when other risk known factors were controlled for (311).

The intrauterine device and diabetes. Intrauterine devices (IUDs) available in the U.S. are the Paraguard copper-bearing device, which is now approved for 10-year usage, and the Progestasert progesterone-bearing device, which must be replaced annually. Some clinicians have been reluctant to prescribe IUDs for diabetic women because of a concern for the risk of pelvic infection, which could lead to ketoacidosis. However, the only IUD ever shown to cause infection was the Dalkon Shield, which has not been marketed for several years. Several controlled studies have shown the modern IUDs to be safe and equally effective in diabetic women (312–315). Rates of pregnancy, expulsion, and bleeding appeared to be similar to nondiabetic users. In none of the studies of IUD use in diabetic women has an increased infection rate been found, although the studies would not have had the power to detect an increased rate of pelvic inflammatory disease above the very low risk in the general population (1.6 per 1,000 woman-years) (316). These devices can be an excellent choice for multiparous diabetic women without a history of pelvic infections or tubal pregnancies and with a single sexual partner who are seeking long-term contraception.

Planning pregnancy. St. James et al. (319) studied factors related to the family planning behavior of 66 women with IDDM compared with 69 women with phenylketonuria and 68 healthy control subjects matched for age, level of education, and marital status (319). Of the sexually active diabetic women, 16–28% were using no contraception at intervals of the 5-year study period; 23 of the 66 women with IDDM became pregnant, but only 26% of the pregnancies were planned. Diabetic contraception users did not differ from nonusers on sociodemographic variables. The investigators evaluated four sets of variables possibly related to family planning behavior: *1*) knowledge about fertility and contraception and about diabetes; 2) locus of control and self-esteem; 3) attitudes about contraception, sex, and childbearing; and 4) degree of social support for birth control use (319). The diabetic contraceptive users had higher levels of social support and more positive attitudes about contraception than the nonusers. St. James et al. (319) concluded that the factors influencing consistent birth control use were amenable to intervention by clinicians, who should focus on attitudes and behavior, not just patient knowledge (319).

Many factors were identified that had a negative influence on the use of contraception by the diabetic women. Many of them questioned the advisability of contraception regarding risks to their health, and many nonusers believed they would have difficulty conceiving. Some diabetic women indicated that issues regarding future pregnancy were secondary to their concerns about their own health and fear of future complications (319). It was noted that convincing diabetic women of the risks of unplanned pregnancies was difficult, since the risks are not absolute, e.g., ~25% risk of major congenital anomalies in women with poor glycemic control. Without counseling, many diabetic women will simply hope and expect to be in the unaffected group.

St. James et al. (319) delineated specific stages of an optimal maternal diabetes life cycle: *1*) prevention of unplanned pregnancy, 2) reproductive decision-making, 3) initiation of intensified diabetes management, and *4*) achievement of pregnancy (319). Steel (52,187) has written about some of the problems that can occur in the period of intensified diabetes management after women and their partners have decided to proceed with pregnancy. Mildly elevated blood glucose values can occasion anxiety and depression in very conscientious patients who feel "they ought to be doing better." If there is a long delay in conception, women may become depressed and "reduce their efforts to maintain tight diabetic control" and then become pregnant at a risky time (187). These and other problems demonstrate the importance of the psychological counseling function of members of the diabetes care team.

STRATEGIES FOR WIDESPREAD IMPLEMENTATION OF PRE-CONCEPTION CARE

— Early investigators of pre-conception care of diabetes (168–178) assumed that patients would be recruited to attend a centralized

specialist diabetes clinic because, as noted by Steel (187), "tight control of diabetes is often quite difficult to achieve." We have seen that this strategy has been effective in preventing excess congenital malformations in infants of those women who participated, but many investigators (50,171,172) noted the "difficulties in persuading those patients most in need to attend the clinic" (187).

Funded by the CDCP or the California Department of Health Services, a few regional programs have attempted to improve access to pre-conception care for diabetic women living in wide areas. In Michigan, a network of five medical centers has recruited diabetic women for pre-conception care with a 35% frequency of success, as published by Janz et al. (184). The authors stated that the results of the usual outreach efforts "were generally disappointing" (184). In the rural sections of Maine, a unique dispersed network of providers caring for pregnant women with diabetes was developed (70 obstetricians, 400 family practice physicians, 30 outpatient diabetes education sites) using locally developed patient care guidelines (The Maine Guide for Preconception Care of Women With Established Diabetes) (179). A Maine diabetes registry was created to promote pre-conception counseling. In 1987–1990, there were 185 pregnancies in Maine in women with established diabetes, and 34% were considered to have had pre-conception care (58 liveborn infants, 1 major anomaly). Of the 93 liveborn infants born to diabetic women who did not receive pre-conception care, 8 babies had major malformations (8.6%). Of the total group of pregnant diabetic women, 17% attended publicly supported outpatient clinics, and none of this group received pre-conception care (179).

In California, for more than a decade, the Maternal and Child Health Branch of the Department of Health Services has funded a statewide diabetes and pregnancy program (CDAPP) based at nine regional perinatal medical centers supporting 68 local affiliate multidisciplinary patient training programs (called Sweet Success). Guidelines for care were published and widely distributed (190, 191), and a variety of outreach efforts were used to encourage diabetic women to enter pre-conception care (189). Of 280 pregnancies in women with established diabetes in 1987–1990, only 20% had pre-conception care. There were <2.0% major malformations in infants of women in this group, but the rate was 9% in infants of diabetic women receiving prenatal care only. Program coordinators in California noted several problems that contributed to the lack of pre-conception care: unplanned pregnancies, lack of awareness of the program, lack of encouragement by health care providers to enter pre-conception care, and financial barriers to intensified care (50,189).

From the experience reported so far, it is clear that additional strategies are needed to increase use of pre-conception care. Steel (187) stressed that as a part of continuing diabetes care, the subject of pregnancy must be "mentioned to diabetic girls at a fairly early age so that they understand the importance of planning, which includes the use of reliable contraception where appropriate." A school-based approach to educating and shaping the attitude of diabetic girls was considered important in achieving the 75% pre-conception care rate in Copenhagen reported by Damm and Molsted-Pedersen (174) in 1990.

Another strategy pursued by the Council on Diabetes in Pregnancy of the American Diabetes Association is to minimize financial barriers to obtaining pre-conception care by securing reimbursement for the costs of the necessary diabetic patient training activities and counseling. Since prevention of congenital malformations provides cost-benefit to pre-conception care programs, it is hoped that third party payers will find ways to encourage their diabetic health plan members to use these services. Financial incentives may be effective, as they have been in influencing women to make other types of disease-preventing behavioral modifications (320).

In spite of improved access to pre-conception care and increased knowledge of the risks of poor glycemic control at the beginning of pregnancy, the continuing problem with unplanned pregnancies may prevent the malformation rate from approaching normal in IDM. As noted by Gregory and Tattersall (183), general improvement in diabetes management in the population is probably responsible for the gradual but steady decline in the frequency of major congenital anomalies in IDM in Cincinnati (41,89,177) and Copenhagen (174,175). Both sites have been centers for diabetes and pregnancy with steady referral patterns for >30 years. Major malformation rates as low as 3% have been reported for 255 consecutive pregnancies of diabetic women delivered in 1976–1990 in the Northern Jutland county of Denmark (321) and in infants of 914 diabetic women entered into the Swedish Birth Registry in 1983–1986 (70,322). Both countries formerly reported the expected major malformation rates of 7–8% (15,70). The Swedish authors concluded that their comparatively low frequency of major anomalies supports the hypothesis of good metabolic control in their population, in which dissemination of information on prepregnancy planning has been intensive (70,322).

If general diabetic control were kept within the thresholds for prevention of diabetes complications established by the DCCT (glycohemoglobin <5 SD above normal mean, blood glucose <10 mmol/l [180 mg/dl]) (197,323), then perhaps unplanned pregnancies would not pose a problem for diabetic women. Indeed, the effects of intensive diabetes therapy on fetal outcomes were recently evaluated in 180 participants in the DCCT who completed 270 pregnancies (324). Of 92 live births, with one set of twins, in the intensive group, there was only one major congenital malformation (0.7%), compared with eight (5.9%) in 99 live births, with two sets of twins, in the conventionally treated group ($P = 0.06$). The good result in the intensive treatment group was obtained even though a minority of the pregnancies were planned. At conception, mean HbA_{1c} for the intensive group was 7.4 ± 1.3% (<5 SD above the normal mean) (195,324). The conclusion reached by investigators and readers of results of the DCCT (197,323,324) and by us is that implementation of intensified diabetes therapy before, during, and after pregnancy (i.e., all the time) should prevent the excess rate of major congenital malformations as well as other serious complications of diabetes.

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