

## Chapter 36

# Pregnancy in Preexisting Diabetes

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### SUMMARY

Data from birth certificates in the United States indicate that maternal diabetes complicates 2%-3% of all pregnancies, but these data may underestimate the true prevalence of maternal diabetes in pregnancy. Two major forms of maternal diabetes may occur during pregnancy: preexisting or "pregestational" diabetes, and gestational-onset or gestational diabetes mellitus (GDM). Only the former is known prior to pregnancy, and this form constitutes ~10% of cases of maternal diabetes. Thus, prevalence rates for pregestational diabetes appear to be in the range of 0.1%-0.3% of all pregnancies. These pregnancies are at risk for both maternal and fetal complications.

Fetal complications of maternal diabetes can be divided into two major categories. Complications that arise from the effects of maternal diabetes on early fetal development (i.e., in the first trimester) include spontaneous abortions and major congenital malformations. In the absence of special preconceptional diabetes management, spontaneous abortions occur in 7%-17% of diabetic pregnancies and major malformations occur in 7%-13%. Rates of both complications are highest in women with the most marked hyperglycemia during the first trimester, and the rates of malformations appear to be decreasing in countries and medical centers where standards of diabetes care result in improved maternal blood glucose control prior to and during early pregnancy. The most prominent fetal complications that can arise during the second and third trimesters are stillbirth and

macrosomia (an excessively large infant). Stillbirths are now uncommon in diabetic pregnancies; congenital malformations and complications of maternal hypertensive disorders account for most of the 1.5- to 2-fold increase in perinatal mortality compared with nondiabetic pregnancies. Macrosomia appears to be the most frequent fetal complication, affecting 10%-33% of infants, depending on the definition used for macrosomia. Macrosomia increases the risk of birth trauma and has been associated with a long-term risk of obesity in offspring.

Maternal risks in diabetic pregnancies are greatest in the presence of preexisting microvascular disease (retinopathy and nephropathy). Diabetic retinopathy is present in 15%-66% of women early in pregnancy, and the retinopathy frequently worsens during gestation, especially when severe background or proliferative changes are present early on. Laser photocoagulation therapy prior to pregnancy can reduce the risk that proliferative retinopathy will worsen during gestation. Overt diabetic nephropathy is present before pregnancy in 5%-10% of patients; of these, two-thirds manifest hypertensive disorders during gestation. The hypertensive disorders precede pregnancy in approximately half of the cases and develop during pregnancy in the other half. Overt diabetic nephropathy in mothers increases the prevalence of intrauterine growth retardation and prematurity in infants; fetal morbidity and mortality increase as well. The long-term impact of pregnancy on diabetic retinopathy and nephropathy in mothers is not known.

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## INTRODUCTION

There is no national surveillance program for diabetes during pregnancy in the United States. As a result, it is not possible to determine true national prevalence rates for diabetes during pregnancy or for the various maternal and fetal complications that can occur when diabetes and pregnancy coexist. Data to help estimate prevalence rates for diabetes and its complications during pregnancy come from several sources. Since 1989, birth certificates in most states and the District of Columbia have included information on a variety of maternal and infant risk factors, including diabetes<sup>1</sup>. The birth certificate data provide the first national estimates of the prevalence of diabetes during pregnancy. However, the certificates do not distinguish between the focus of this chapter, diabetes that existed prior to pregnancy—pregestational diabetes, including insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM)—and diabetes that is first detected during pregnancy (GDM, discussed in Chapter 35). Birth certificate data may also suffer from inaccurate reporting of maternal and fetal complications (e.g., only 65% of maternal diabetes was recorded on birth certificates surveyed in Tennessee in 1989)<sup>2</sup>.

Other data sources include regional or statewide data derived from a combination of birth certificate and hospital record information and published reports from individual medical centers. The former source may be the most complete for a specific region, although the magnitude of inaccurate reporting on birth certificates and hospital discharge summaries is difficult to assess. The latter source may suffer from at least two forms of bias related to patterns of patient referral and care. First, the medical centers that have published their patient data were predominantly specialized referral centers. It is likely that these centers managed the most complicated cases of maternal diabetes, so that prevalence rates of various maternal complications may be overestimated compared with the entire population. Second, physicians in most of these centers have extensive experience in the management of diabetes during pregnancy, so that maternal and fetal outcomes might be better for a given severity of diabetes than would be true for less specialized medical centers.

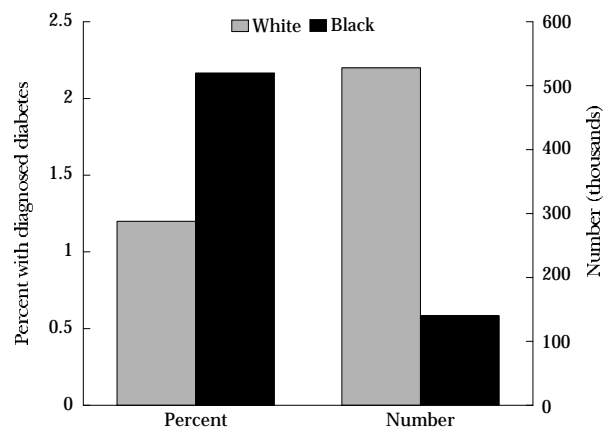
Because of the limitations imposed by the lack of national data for many aspects of pregestational diabetes in pregnancy in the United States, some information from other countries has been included in this chapter, particularly when the structure of the health care system in those countries has allowed the collec-

tion of reasonably good national data on pregnancies complicated by maternal diabetes.

## PREVALENCE OF DIABETES IN WOMEN OF CHILDBEARING AGE

Data from the 1991-92 National Health Interview Survey (NHIS)<sup>3,4</sup> on the prevalence of known diabetes in white and black women age 18-44 years are shown in Figure 36.1. These data are based on self-reporting of physician-diagnosed diabetes and they indicate that 1.2% of white women and 2.2% of black women in the age group (525,000 and 140,000 women, respectively) have been diagnosed by a physician as having diabetes. The responses did not distinguish between IDDM and NIDDM, which have different age distributions in the population (see Chapter 2). Data from the National Health and Nutrition Examination Surveys (NHANES), in which medical history and oral glucose tolerance testing were used to ascertain diabetes, indicate that an additional 0.7%-1.3% of women age 20-44 years have undiagnosed diabetes (Figure 36.2). Of the women without diabetes, many have impaired glucose tolerance (IGT) (Figure 36.2), a condition in which blood glucose concentrations are above normal but not in the diabetic range (Chapter 2). When diabetes and IGT estimates are combined, 10%-18% of non-pregnant women age 20-44 years have some type of abnormal glucose tolerance that would be associated with fetal or maternal risks if those women became pregnant.

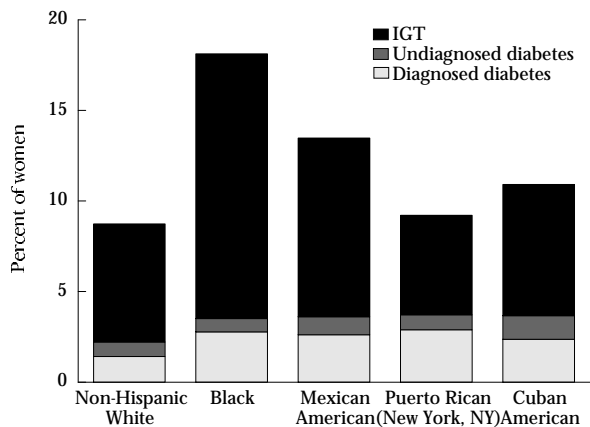
Figure 36.1  
Prevalence of Diagnosed Diabetes in Women Age 18-44 Years, U.S., 1991-92



Data are based on self-reported information on physician-diagnosed diabetes in the 1991-92 National Health Interview Surveys.

Source: References 3 and 4

**Figure 36.2**  
Prevalence of NIDDM and IGT in Women Age 20-44 Years, U.S., 1976-82

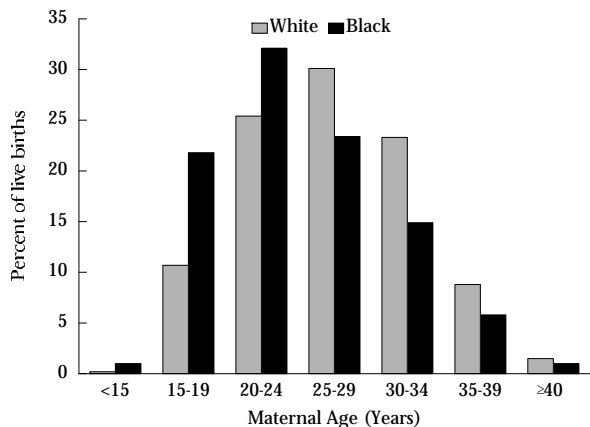


Diagnosed diabetes is based on self-reported information on physician-diagnosed diabetes; undiagnosed NIDDM and impaired glucose tolerance (IGT) were determined by a 75-g, 2-hour oral glucose tolerance test interpreted according to World Health Organization criteria.

Source: 1976-80 Second National Health and Nutrition Examination Survey and 1982-84 Hispanic Health and Nutrition Examination Survey

Precise details on the age distribution of diabetes in women of childbearing age are not available. However, data have been collected on the maternal age distribution for all live births and on birth rates according to maternal age in the entire U.S. population<sup>5</sup>. In 1992, 39% of births occurred to women age <25 years and only 10% occurred to women age ≥35 years (Figure 36.3). The birth rate was highest for white

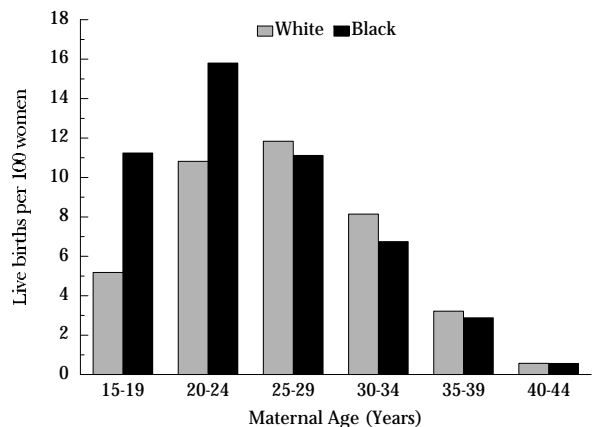
**Figure 36.3**  
Distribution of All Live Births by Maternal Age for Black and White Women, U.S., 1992



Data are from all birth certificates filed in the U.S. in 1991. Rates are expressed as the percent of births at all ages that occurred to women in each age group.

Source: Reference 5

**Figure 36.4**  
Birth Rates by Maternal Age for All Black and White Women, U.S., 1992



Rates were determined from data on all birth certificates filed in the U.S. in 1992.

Source: Reference 5

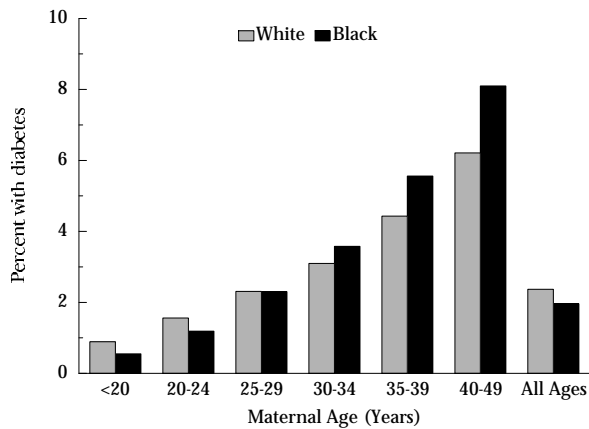
women age 25-29 years, and for black women age 20-24 years and birth rates declined almost linearly at older ages (Figure 36.4). This decline contrasts with the rising prevalence rates of diabetes with increasing age among women who are pregnant, as presented below.

**PREVALENCE OF PREGESTATIONAL DIABETES IN PREGNANT WOMEN**

Data from birth certificates indicate that 2%-3% of pregnancies in the United States are complicated by some form of maternal diabetes<sup>1,6-8</sup>. These data do not distinguish between pregestational diabetes and GDM. However, since prevalence rates for the latter condition are in the range of 2%-4% when routine blood glucose screening is employed during pregnancy<sup>9,10</sup> (see Chapter 35), it is likely that: 1) the birth certificate data underestimate the overall prevalence of maternal diabetes during pregnancy<sup>2</sup>; and 2) a minority of diabetic pregnancies occur in women with pregestational diabetes.

Age-specific prevalence rates for all types of diabetes in white and black pregnant women, based on U.S. birth certificate data, are shown in Figure 36.5. Combined prevalence rates rise from <1% for women age <20 years to >6% for women age >40 years. Prevalence rates are higher for white women at age <25 years, when IDDM predominates and NIDDM and GDM are relatively uncommon. Rates are higher for black

**Figure 36.5**  
**Percent of Birth Certificates Listing Diabetes in the Mother, U.S., 1991**



Rates were determined from birth certificates that contained a checkbox for the presence of maternal diabetes (most states and the District of Columbia). The checkboxes do not distinguish among IDDM, NIDDM, and gestational diabetes in the mother. Other limitations of birth certificate data that may have led to an underestimation of diabetes rates are discussed in the text.

Source: Reference 1

women at age >30 years, when NIDDM and GDM are more common complications of pregnancy. This pattern is consistent with the relative prevalence rates of IDDM and NIDDM or GDM in the two ethnic groups: IDDM is more common in whites, while NIDDM and GDM are more common in blacks.

Population-based data from hospital records in the state of Washington<sup>11</sup> indicate a prevalence rate for pregestational diabetes (both IDDM and NIDDM) of 2.1 per 1,000 live births in 1979-80. This figure is close to the prevalence rate for IDDM of 1.8 per 1,000 live births reported for 1982-85 in Sweden, where national data for IDDM in pregnancy are available. A slightly lower rate of diabetes has been reported from a population-based study (birth certificate data followed up by telephone interviews) of congenital malformations in Georgia; 1 per 1,000 pregnancies were complicated by pregestational diabetes in that study, which included both live-born and stillborn infants rather than live births alone<sup>12</sup>.

On the basis of these limited population data, it appears that preexisting diabetes complicates pregnancies at a rate of ~1-3 per 1,000 births. A slightly higher prevalence rate would be expected if all pregnancies complicated by preexisting diabetes were considered, since 10%-20% of such pregnancies end in spontaneous abortions (discussed below) and an unknown number end in elective terminations. Even if these two factors are taken into account, the prevalence rate for pregestational diabetes appears to be somewhat

less than predicted by the background prevalence of diagnosed diabetes in women of reproductive age (14 per 1,000 women age 18-44 years in 1991-92)<sup>3,4</sup>. Whether the discrepancy represents an underestimation of the rates of pregestational diabetes in pregnancy or a true reduction in the fertility rates of diabetic women is not known.

The relative proportion of IDDM compared with NIDDM in pregestational diabetes is likely to vary according to the ethnicity of the population and the background prevalence of IDDM and NIDDM. For example, only NIDDM complicates pregnancies in Pima Indians with pregestational diabetes<sup>13</sup>, since IDDM does not occur in that ethnic group. By contrast, ~25% of pregestational diabetic pregnancies were complicated by NIDDM in the Washington state<sup>11</sup> and Georgia<sup>12</sup> studies. A large majority (>80%) of women with pregestational diabetes at California's Los Angeles County/USC Medical Center, which provides care for a predominantly Latino population, have clinical characteristics consistent with NIDDM<sup>14</sup>.

## FETAL COMPLICATIONS OF MATERNAL PREGESTATIONAL DIABETES

Maternal diabetes may be associated with abnormal fetal development and excess fetal morbidity and mortality compared with nondiabetic pregnancies (discussed below). The frequencies of fetal abnormalities vary according to the type and timing of medical care delivered to women with diabetes. As a result, frequencies of fetal morbidity and mortality in diabetic pregnancies have been changing over the past six decades<sup>15</sup>, and the frequencies vary according to the intensity of maternal medical care provided during specific developmental periods. Thus, it is difficult and perhaps inappropriate to derive a single prevalence rate for any fetal complication of maternal diabetes in the absence of some knowledge of maternal health care. In the discussion below, an attempt had been made to express fetal risks in relation to measures of maternal health care such as glycemic control or access to specialized prenatal centers.

## SPONTANEOUS ABORTIONS

Published data on overall rates of spontaneous abortion (SAB, generally defined as spontaneous loss prior to 20 weeks gestation) in pregestational diabetic pregnancies reveals no clear answer regarding whether the rates are increased compared with nondiabetic pregnancies. Some studies in the past<sup>16,17</sup> reported rates

**Table 36.1**  
**Rates of Spontaneous Abortion in Recent Series of Pregnancies Complicated by Pregestational Diabetes and in Nondiabetic Pregnancies**

Ref.	Years of study	Nondiabetic		Diabetic	
		No.	%	No.	%
18	1980-85	70/432	16.2	62/386	16.1
19	1982-85	16/222	7.2	41/532	7.7
20	1983-87			52/303	17.2
21	1982-88			12/122	9.8

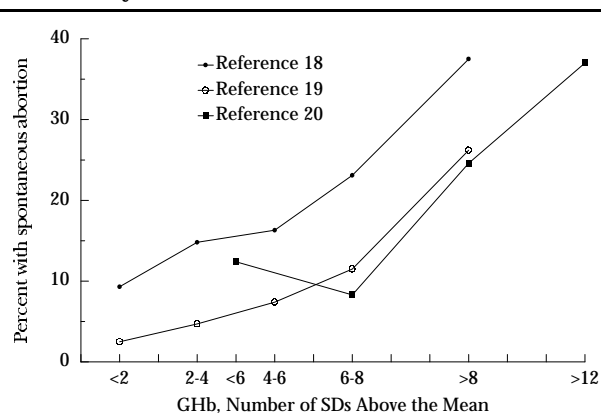
Nondiabetic control subjects were recruited prospectively in Reference 18 and were selected at random from one of the 36 hospitals at which diabetic women received care in Reference 19. Spontaneous abortion rates did not differ significantly between diabetic and nondiabetic groups in these two studies. No data from nondiabetic pregnancies were presented in References 20 or 21.

Source: References are listed within the table

that were twice as high as rates in nondiabetic women. More recent reports conclude that overall rates are no higher than observed<sup>18,19</sup> or expected<sup>20,21</sup> in the absence of maternal diabetes (Table 36.1).

Some of the conflicting results may be attributed to methodological differences (e.g., ascertainment of SAB, recruitment of nondiabetic controls). However, in most studies there is a clear pattern of increased SAB rates when maternal metabolic control in early pregnancy is poor. For example, the Diabetes in Early Pregnancy Study reported SAB rates of 16.2% and 16.1% in prospectively recruited nondiabetic control subjects and patients with IDDM, respectively<sup>18</sup>. Among the diabetic women, the minority with evidence of poor metabolic control during the first trimester (as indicated by elevated blood glucose and glycosylated hemoglobin levels) had increased SAB rates (Table 36.2 and Figure 36.6). In a study of 303 women referred for management of pregestational dia-

**Figure 36.6**  
**Rates of First Trimester Spontaneous Abortion in Pregnancies Complicated by Pregestational Diabetes, by Maternal GHb Levels**



GHb, glycohemoglobin; SD, standard deviation. Maternal GHb concentrations were measured during the first trimester or early second trimester of pregnancy. GHb is expressed as SDs above the mean of nondiabetic individuals (References 18 and 19) or as SDs above the mean of the entire diabetic group (Reference 20). See Table 36.2 for numbers of subjects in each study by GHb category.

Source: References 18-20

betes, an overall SAB rate of 17% was found<sup>20</sup>. The SAB rate in nondiabetic control pregnancies was not determined, but diabetic women with poor glycemic control (elevated glycohemoglobin levels) in early pregnancy had much higher SAB rates than did women with good early-pregnancy control (Table 36.2). Population-based data from Sweden on SAB rates also indicate increased rates when maternal glycemic control is poor in early pregnancy. A study was made on 532 pregnancies complicated by pregestational IDDM, representing ~80% of all such pregnancies in Sweden during a 4-year period<sup>19</sup>. The SAB rate in these pregnancies was 7.7%, nearly the same as the 7.2% rate in

**Table 36.2**  
**Rates of Spontaneous Abortion in Pregnancies Complicated by Pregestational Diabetes, by Maternal GHb During the First Trimester**

Reference 18			Reference 20			Reference 19		
GHb SD>mean	No.	Spontaneous abortion (%)	GHb SD>mean	No.	Spontaneous abortion (%)	GHb SD>mean	No.	Spontaneous abortion (%)
<2	108	9.3	<6	113	12.4	<2	118	2.5
2-4	182	14.8	6-9	85	8.3	2-4	150	4.7
4-6	43	16.3	9-12	61	24.6	4-6	135	7.4
6-8	26	23.1	12-15	28	35.7	6-8	87	11.5
>8	16	37.5	>15	16	37.5	>8	42	26.2

GHb, glycohemoglobin; SD, standard deviation. GHb was determined during the first trimester or early second trimester and is expressed as SDs above the mean of nondiabetic individuals (References 18 and 19) or above the mean of the entire diabetic group (Reference 20). "No." denotes the number of diabetic women in each GHb category. Spontaneous abortion (%) denotes the percent of women in each GHb category who had a spontaneous abortion. Rates increased significantly with increasing GHb level in each study.

Source: References are listed within the table

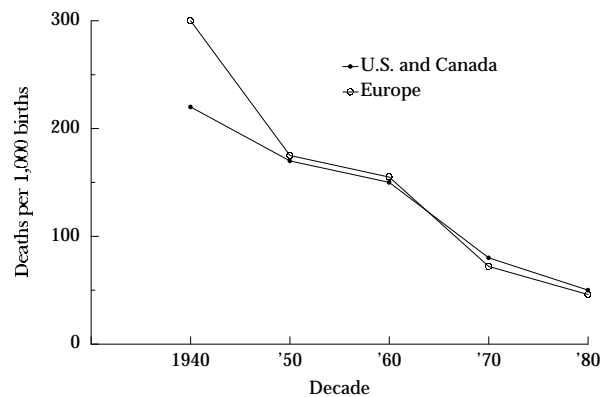
a group of randomly selected, concurrent controls. However, the survey revealed that there was a progressive increase in the SAB rate among diabetic women as glycohemoglobin levels increased above normal (Table 36.2).

Thus, it seems clear that the prevalence of SABs in women with pregestational diabetes is increased when blood glucose control is poor during the first trimester of pregnancy. Women with good control, whether recruited into a prospective program of preconceptional diabetes management or not, do not appear to have increased rates of SAB compared with nondiabetic women. Populations in which overall diabetes control is good (e.g., in Sweden<sup>19</sup>) can be expected to have no excess of SABs even in the absence of preconceptional diabetes management programs. By contrast, populations in which many diabetic women of reproductive age have poor metabolic control may be expected to have an increased rate of SABs unless specific programs of planned pregnancy and preconceptional diabetes management are implemented. It is important to note that, although the type of diabetes was not noted in all studies, most of the data cited above were derived from studies on patients with IDDM.

## PERINATAL MORTALITY

Data from pregnancies complicated by maternal diabetes in 225 hospitals in North America and Europe reveal a large decline in the perinatal mortality rate, from 250-300 per 1,000 live births in 1940 to 30-50 per 1,000 live births in 1988<sup>22</sup> (Figure 36.7). Perinatal mortality also fell in nondiabetic pregnancies during the same period, but the magnitude of the fall was not as great. For example, in the United States, overall perinatal mortality declined from 60 per 1,000 in the 1940s to 15 per 1,000 in the 1980s. Specific disease processes that accounted for the higher perinatal mortality in diabetic pregnancies in past decades were not given. However, the number of perinatal deaths that were related to congenital malformations (discussed below) remained relatively constant over this period, so the reduction in overall mortality must have resulted from a progressive lowering of deaths not related to congenital malformations. Prevention of stillbirths in non-malformed infants and improvement in maternal diabetes management and neonatal care likely accounted for much of the reduced mortality. As a result of the reduction in mortality not related to congenital malformations, the contribution of malformations to overall perinatal mortality in diabetic pregnancies has risen from 10%-15% in the 1940s to ~50% in the 1980s (Figure 36.8).

**Figure 36.7**  
**Perinatal Mortality Rates in Pregnancies Complicated by Insulin-Treated Diabetes, 1940-88**

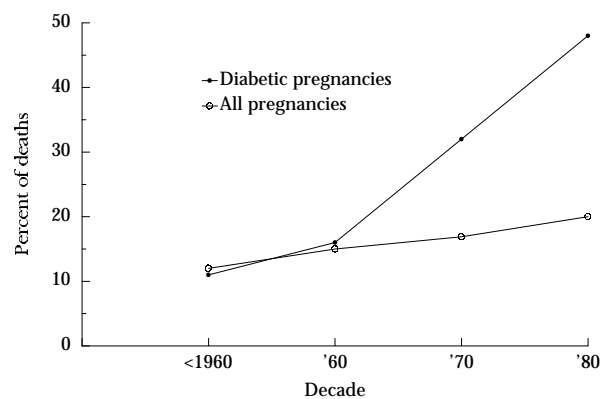


Data are from 225 hospitals in the United States and Canada (12,893 pregnancies) and Europe (17,538 pregnancies).

Source: Reference 22

The perinatal mortality rates shown in Figure 36.7 are hospital-based and may reflect the favorable impact of high-level medical, obstetrical, and neonatal care on infant mortality in diabetic pregnancies. Analyses of vital records and hospital discharge data from the states of South Carolina in 1978<sup>6</sup> and Washington in 1979-80<sup>11</sup> revealed perinatal mortality rates of 182 per 1,000 and 108 per 1,000 births, respectively. The data from South Carolina included all insulin-treated patients, some of whom may have had gestational diabetes. The data from Washington state were limited to

**Figure 36.8**  
**Contribution of Congenital Anomalies to Overall Perinatal Mortality in Diabetic and Nondiabetic Pregnancies, 1940-88**



Data are from 12,893 pregnancies in insulin-treated diabetic women at hospitals in the United States and Canada; data for all pregnancies were derived from published hospital-based data for all women.

Source: Reference 22

women with pregestational diabetes and indicated an increased perinatal mortality in both IDDM and NIDDM compared with the overall state perinatal mortality rate of 14 per 1,000. The apparently greater perinatal mortality in statewide data compared with data from specific medical centers (Figure 36.7) suggests that access to specialized medical centers may have an important beneficial impact on perinatal mortality in diabetic pregnancies. However, since no specific information on management practices or metabolic regulation were available from any of the three studies, it is not possible to ascertain the impact of different medical practices on the reported perinatal mortality rates.

### CONGENITAL MALFORMATIONS

Data collected during the past five decades from centers specializing in the care of pregnant women with diabetes indicate that major congenital malformations (generally defined as malformations that are fatal, require surgical correction, or lead to marked physical or psychological handicaps) occur in 7%-13% of pregestational diabetic pregnancies in the absence of special preconceptional diabetes care (Table 36.3)<sup>20,21,23-28</sup>. These data suffer from the potential bias created by patterns of referral to specialty centers. However, the fact that the prevalence rates are remarkably similar across centers and over time suggests that the bias may be relatively small.

The precise types of anomalies that occur in excess in diabetic pregnancies remains controversial. In 1971,

data on >7,000 pregnancies in diabetic women in Europe, North America, Australia, and South Africa were summarized<sup>29</sup>. Congenital malformations were reported in 4.8% of those pregnancies, compared with only 0.65% of nondiabetic pregnancies in different published series. Malformations of the spine, skeleton, kidneys/ureters, and heart, along with situs inversus, were significantly increased in the diabetic pregnancies. The study suffers from a lack of population-based data and appropriate nondiabetic control pregnancies, as well as a lack of systematic methods for ascertainment of malformations. However, the study is frequently cited in reference to the types of anomalies in diabetic pregnancies because of the large number of pregnancies considered.

Most subsequent reports on malformations in diabetic pregnancies have involved too few women to determine whether specific anomalies were increased. However, a population-based, case-control study in the metropolitan Atlanta, GA area found that the risks of anomalies of the central nervous system and the cardiovascular system were increased significantly (15- to 18-fold) in infants of women with pregestational diabetes compared with nondiabetic women<sup>12</sup>. Anomalies of these two systems were also among the most frequently reported in most of the series in Table 36.3, so it appears very likely that the cardiovascular and central nervous systems are specifically affected by maternal diabetes. The caudal regression syndrome has also been reported to be much more frequent in diabetic compared with nondiabetic pregnancies, so the risk of that rare abnormality is likely to be increased by maternal pregestational diabetes as well. Whether major malformations of other organ systems are related specifically to maternal diabetes in the United States remains in question. Prevalence rates of minor congenital anomalies (those not requiring surgical or medical intervention and not causing significant morbidity) do not appear to be increased by the presence of maternal diabetes<sup>28,30,31</sup>.

The above discussion considers pregnancies in which no special preconceptional diabetes management was provided. Data from at least five studies<sup>21,28,32-34</sup>, two of which were conducted in the United States, indicate that rates of major congenital malformations are lower in offspring of women who participate in special preconceptional diabetes management programs than in offspring of diabetic women who first seek medical attention while they are pregnant (Table 36.4). This suggests that careful metabolic regulation prior to and during early pregnancy can lower the incidence of malformations in diabetic pregnancies. However, it is also possible that women who participate in preconceptional care programs are more health conscious

**Table 36.3**  
**Rates of Major Congenital Malformations in Offspring of Women with Pregestational Diabetes**

Ref.	Years of study	% with anomalies in infants of:	
		Diabetic mothers	Nondiabetic mothers
23	1946-78	8	3
24	1961-70	11	
26	1971-75	7	
27	1977-80	13	
25	1977-81	8	2
28	1980-85	9	2
20	1983-87	8	
21	1982-88	11	

Definitions of a major malformation vary among studies but usually require significant impact on the well-being of the infant. A control group of nondiabetic women was recruited prospectively only in References 25 and 28; malformation rates were significantly higher in the diabetic groups in these studies. The nondiabetic malformation rate in Reference 23 is the rate in nondiabetic women at the same hospital.

Source: References are listed within the table

Table 36.4

**Rates of Major Congenital Malformations in Infants of Women with Pregestational Diabetes, by Participation in a Preconception Care Program**

Ref.	Malformation rate (%) in infants of women who:	
	Did not participate	Participated
32	7.5	0.8
33	9.6	0.0
34	10.4	1.4
21	10.9	1.2
28	9.0	4.9

Those who did not participate received no special preconceptional care; those who participated were enrolled in a diabetes care program prior to conception (up to the third week postconception in Reference 28). In References 21 and 32-34, attempts were made to maintain maternal glycemia as close to normal as possible prior to conception; no special preconception glycemic goals were used in Reference 28. The infants of women who participated in a preconceptional care program had significantly lower malformation rates in each study.

Source: References are listed within the table

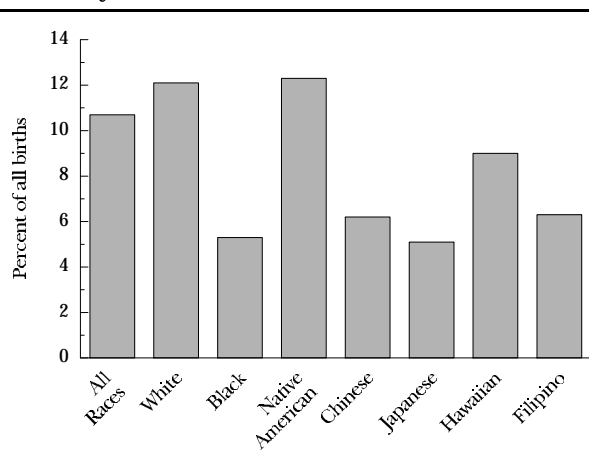
and at lower risk for a malformed infant for reasons unrelated to improved metabolic control. Data from countries such as Sweden<sup>19</sup>, Denmark<sup>31</sup>, and parts of England<sup>35</sup>, where diabetes care has improved in the population as a whole, suggest that improved metabolic control does contribute to reduction in malformations associated with participation in preconception care programs. Congenital malformation rates in diabetic pregnancies have declined in these regions in the last decade, even among women who do not participate in preconceptional care programs<sup>35</sup>. Thus, it is likely that at least some of the differences in anomaly rates in Table 36.4 are related to an effect of improved metabolic control during early pregnancy. Efforts to improve general diabetes care in the United States<sup>36</sup> are likely to result in an overall reduction in malformation rates in diabetic pregnancies similar to the reductions observed in Sweden, Denmark, and parts of England. A reduction in malformation rates would effect a significant reduction in the cost of diabetic pregnancies in the United States<sup>37</sup>.

**MACROSOMIA AND HYPOGLYCEMIA**

One of the major effects of maternal diabetes during the second and third trimesters is fetal overnutrition, which may result in excessive fetal growth (macrosomia) and fetal hyperinsulinemia with neonatal hypoglycemia. The reported prevalence of these two complications varies due to at least two factors: 1) lack of standard definitions for macrosomia and neonatal hypoglycemia, and 2) different approaches to clinical management of diabetic pregnancies. Prevalence rates reported from medical centers for infants that are large-for-gestational-age (LGA, >90th percen-

Figure 36.9

**Percent of All U.S. Births with Birthweight ≥4,000 Grams, by Race of Mother, 1992**



Data are from all birth certificates filed in the United States in 1992.

Source: Reference 5

tile weight for age) in pregestational diabetic pregnancies have been in the range of 29%-33% during the past decade<sup>38-40</sup>. These rates are significantly greater than the expected prevalence of 10% based on the definition of LGA as >90th percentile. Among all births in the United States in 1991, the proportion of infants weighing >4,000 grams at birth was 10.6% (Figure 36.9). Prevalence rates were highest in Native Americans (12.6%) and whites (11.9%) and lowest in blacks (5.2%) and Asian Americans (5.2%-8.9%)<sup>5</sup>.

At least two significant morbidities may result from fetal macrosomia. Birth trauma may result from fetal size that is disproportionate to the birth canal. This complication was reported to be twice as common in infants of diabetic compared with nondiabetic mothers in a statewide survey based on birth certificate data from North Carolina in 1989-90<sup>7</sup>. Reports from centers specializing in the care of diabetic pregnancies indicate lower rates of birth trauma<sup>41</sup>, although rates of cesarean delivery are often high in these centers (see below). The second major complication that may occur following fetal macrosomia is a long-term risk of obesity. When measured at age 7-8 years<sup>42</sup> or age 15-19 years<sup>43</sup>, offspring of mothers with diabetes (including NIDDM, IDDM, and GDM) were overweight compared with offspring of nondiabetic mothers. The long-term impact of this phenomenon on the prevalence of obesity in offspring of diabetic mothers remains to be determined.

Prevalence rates of neonatal hypoglycemia (i.e., serum or plasma glucose <30 mg/dl for term infants or <20 mg/dl for preterm infants) in infants of mothers



with pregestational diabetes have been reported to be in the range of 8%-37%<sup>6,40,44-47</sup>. The prevalence rates may vary according to degree of maternal metabolic regulation and intensity of neonatal glucose monitoring, since many infants show no physical signs of low blood glucose concentration. Hypoglycemia requiring glucose infusion was more common in diabetic than nondiabetic pregnancies in one study<sup>40</sup>. However, strict criteria for institution of glucose infusion were not provided in that study, so it is possible that knowledge of the maternal condition biased the treatment for hypoglycemia.

### OTHER MORBIDITIES IN OFFSPRING

Offspring of women with pregestational diabetes have been reported to be at increased risk for several other perinatal complications based on studies at single or multiple medical centers. These complications include polyhydramnios<sup>48</sup>, polycythemia<sup>44,47</sup>, neonatal jaundice<sup>40,44,47</sup>, hypocalcemia<sup>44,49</sup>, and respiratory distress syndrome<sup>44,47</sup>. The last three of these complications may be made more frequent by premature delivery<sup>44,50,51</sup>, which was a routine practice 10-15 years ago but has become less common with the advent of improved glycemic control and noninvasive techniques for fetal monitoring. Thus, the frequencies of most of these fetal complications have fallen in the past decade.

Population-based data for these perinatal complications are not available from diabetic pregnancies in the United States. However, data from a population-based study of IDDM in Sweden provides an estimate of the frequency of polycythemia, jaundice, hypoglycemia, and respiratory distress syndrome in neonates when diabetic mothers have ready access to specialized diabetes care before and during pregnancy<sup>47</sup>. In

this study, each of these four complications was more frequent in diabetic than nondiabetic pregnancies (Table 36.5). Gestational ages at delivery were slightly lower in diabetic compared with control pregnancies in the study, so prematurity may have contributed to the intergroup differences in fetal complications.

## MATERNAL COMPLICATIONS OF PREGESTATIONAL DIABETES

### MORTALITY

Prior to the advent of exogenous insulin therapy, maternal survival during pregnancy was severely compromised by the presence of preexisting diabetes. For example, survival was <50% in one small series reported from the early 1900s<sup>52</sup>. Today, maternal mortality is a rare event in diabetic and normal pregnancies. Commonly cited figures for maternal mortality during pregnancy have been in the range of 3-7 per 100,000 for diabetic women and 7-9 per 100,000 for the general population<sup>53</sup>. A lack of good population-based data makes it impossible to determine whether mortality rates differ between these two groups in the United States.

Women with maternal vascular disease, particularly coronary artery disease, do appear to be at increased risk for mortality during pregnancy. In a series of pregnancies managed at the Joslin Clinic in Boston, MA during 1963-75, only one of four diabetic women with symptomatic heart disease survived pregnancy and the perinatal period<sup>52</sup>. The only survivor had coronary bypass surgery prior to pregnancy. In a separate study, only three of 11 diabetic women with symptomatic heart disease survived pregnancy<sup>54</sup>. Data on survival of patients who have had successful coronary revascularization are largely anecdotal, so no firm conclusions can be drawn about maternal mortality in these women.

### DIABETIC RETINOPATHY

Virtually all data on diabetic retinopathy in pregnancy are based on diabetic women whose pregnancies were managed at medical centers. Thus, it is impossible to determine the true population-based prevalence rate for diabetic retinopathy among pregnant women with pregestational diabetes. Published data indicate that 15%-66% of women with pregestational diabetes have retinopathy at the start of pregnancy<sup>26,47,48,55-57</sup>. To the extent that patients with diabetic complications are preferentially referred to specialized centers, these fig-

Table 36.5  
Neonatal Morbidity in Pregnancies Complicated by Pregestational IDDM, Sweden, 1982-85

Neonatal morbidity	Infants with morbidity (%)		p
	Diabetic mothers (n=491 births)	National data (n=279,000 births)	
Idiopathic respiratory distress syndrome	1.6	0.6	<0.01
Hypoglycemia	8.0	0.2	<0.001
Jaundice	16.3	3.9	<0.001
Polycythemia	2.2	0.1	<0.001

Data from diabetic mothers come from ~80% of all pregnancies with IDDM in Sweden during the study period. Hypoglycemia denotes blood glucose <30 mg/dl with signs of hypoglycemia. Jaundice denotes serum bilirubin >300 μmol/L. Polycythemia denotes a central venous hematocrit >70%.

Source: Reference 47

ures may represent an overestimate of the prevalence of retinopathy among all women with pregestational diabetes.

While data from specialized referral centers may not provide accurate estimates of the prevalence of diabetic retinopathy in pregnant women, these data are useful for assessing changes in retinopathy during pregnancy. Data from many published series indicate that retinopathy often worsens during pregnancy and the risk of worsening is greatest for women who enter pregnancy with existing retinopathy. Thus, incidence rates for development of background retinopathy in women with no retinopathy prior to pregnancy were reported to be 0%-33%<sup>55,56,58,59</sup>. Progression from background to proliferative changes occurred in 10%-65% of patients and worsening of proliferative changes occurred in 14%-100% of patients<sup>55,56,58,59</sup>. Three additional facts are of note. First, many of the new background and mild proliferative changes regressed without laser therapy within 1 year after delivery, so the deterioration that occurred during pregnancy was not necessarily permanent. Second, it is likely that some of the deterioration was related to rapid improvements in glycemic control<sup>60</sup> that are often initiated to protect the fetus. Thus, the incidence of new retinal changes may be altered by the degree of metabolic control at the start of pregnancy, with worse control predisposing to a higher risk of retinopathy<sup>55</sup>. Finally, incidence rates for retinal complications during pregnancy may be altered by prior treatment. For example, of six diabetic women who had laser therapy for proliferative changes prior to conception, worsening of proliferative changes during pregnancy occurred in only one (17%)<sup>59</sup>. This rate was much lower than the 86% rate in women with untreated proliferative changes at the beginning of pregnancy. The long-term status of vision in women who have had diabetic retinopathy during pregnancy is not known.

## DIABETIC NEPHROPATHY

As was true for retinopathy, most data on diabetic nephropathy during pregnancy in the United States come from specialized referral centers, so the data may overestimate the true prevalence of nephropathy in women with pregestational diabetes. The data suggest that 2%-22% of diabetic women have overt nephropathy (generally defined as proteinuria >300-500 mg/24 hours during the first half of gestation)<sup>21,26,47,61-64</sup>. The study with a 2% prevalence of nephropathy involved Latino patients, most of whom had NIDDM<sup>26</sup>. The later age at onset of NIDDM compared with IDDM may explain the relatively low prevalence of overt nephropathy in this study.

Population-based data from Sweden<sup>47</sup> indicate that ~5% of women with IDDM have proteinuria consistent with overt nephropathy in early pregnancy. State-wide data from Washington<sup>11</sup> indicate that ~10.5% of women with IDDM have diabetic nephropathy or retinopathy, but the exact prevalence of nephropathy is not clear from these data. On the basis of these two studies, it appears that 5%-10% is a reasonable estimate for the overall prevalence of overt nephropathy in women with IDDM who become pregnant. Similar data for women with NIDDM are not available.

Several obstetrical and perinatal complications are common in women with overt nephropathy. These women have a high prevalence (13%-48%) of chronic hypertension antedating pregnancy<sup>26,62,64-66</sup>. In addition, patients without preexisting hypertension frequently (21%-52% of cases) develop pregnancy-induced hypertension or preeclampsia (see below)<sup>47,62,65,67</sup>. Thus, a majority of patients with overt nephropathy have elevated blood pressure by the third trimester. Premature delivery is common. Delivery at <37 weeks gestation occurs in 23%-60% of women with nephropathy and 9%-31% are delivered at <34 weeks gestation<sup>65,68,69</sup>. Hypertensive disorders account for 17%-63% of deliveries before 37 weeks<sup>62,65,66,69</sup>. Prematurity is associated with a variety of neonatal complications, including respiratory distress syndrome, intracranial bleeding, jaundice, hypocalcemia, and hypoglycemia. Infants have been reported to be small-for-gestational-age at birth in 10%-21% of pregnancies with overt nephropathy<sup>64,66,68</sup>. The growth retardation may be related to hypertensive disorders, placental vascular abnormalities, or undetermined factors. Maternal anemia has been reported in ~40% of women with overt diabetic nephropathy<sup>62,64</sup>.

The effect of pregnancy on renal function in women with overt diabetic nephropathy has been studied primarily during and shortly after pregnancy. Many patients with overt nephropathy experience a rise in protein excretion during the last half of gestation<sup>62,66,70</sup>. For example, in one study about two-thirds of patients manifested a >3g/24 hour increase in proteinuria between the first and third trimesters; most of the increase occurred during the third trimester<sup>62</sup>. Patients with marked proteinuria often develop significant fluid retention and edema. Protein excretion has been reported to return to prepregnancy or early pregnancy levels soon after delivery in 66%-100% of patients<sup>62,66,70</sup>. Creatine clearance often remains stable or declines slightly during gestation<sup>62</sup>, in contrast to the increase in creatinine clearance that normally occurs during pregnancy.

Whether pregnancy causes any long-term deterioration in renal function is largely unknown. Two uncontrolled studies measured renal function in a small number of women with overt nephropathy for several years after delivery<sup>62,64</sup>. In both, rates of decline in renal function were consistent with the natural course of diabetic nephropathy, suggesting that pregnancy per se did not accelerate the decline. Nonetheless, the natural history of diabetic nephropathy dictates that women who have overt nephropathy during pregnancy are likely to experience a worsening of renal function in the years following delivery. Actual rates of development of renal failure in these patients remain to be determined, particularly with the implementation of renal protective therapy such as blood pressure control<sup>71</sup> or angiotensin converting enzyme inhibition<sup>72</sup>.

Diabetic nephropathy may be detected prior to the development of overt proteinuria by measuring the urinary albumin excretion rate. Patients who do not have overt proteinuria detectable by indicator strips but who excrete albumin at greater-than-normal rates (i.e., microalbuminuria) are at risk for developing overt nephropathy and renal failure. The prevalence of microalbuminuria has not been reported in women with pregestational diabetes. However, in one report the prevalence rates for hypertensive disorders of pregnancy and for premature deliveries were increased in women whose albumin excretion rates were 190-299 mg/24 hours (i.e., in the range of microalbuminuria) in early pregnancy<sup>65</sup>. This finding may account for some of the increased prevalence of hypertensive disorders of pregnancy observed in diabetic women without overt nephropathy (see below).

## DIABETIC NEUROPATHY

No prevalence rates are available for any form of diabetic neuropathy during pregnancy. One cross-sectional study in Finland suggests that pregnancy does not increase the prevalence of diabetic autonomic neuropathy<sup>73</sup>, although symptoms of autonomic neuropathy may worsen during pregnancy<sup>74,75</sup>.

## HYPERTENSIVE DISORDERS

Definitions of pregnancy-induced hypertension (PIH) vary among studies. The definitions apply to women who do not have hypertension at the beginning of pregnancy and usually are based on the development of a defined level of elevated blood pressure (e.g., systolic >140/90 mmHg or diastolic >105 mmHg) or an increase in blood pressure above a first trimester

value (e.g., by  $\geq 20$  mmHg in mean arterial pressure). Preeclampsia is generally defined as PIH with overt proteinuria. Population-based data from Sweden<sup>47</sup> indicate that PIH and preeclampsia occur three to four times more frequently in women with pregestational diabetes than in nondiabetic women. Undoubtedly, some of the increase is due to women with overt diabetic nephropathy, since approximately half of these women develop hypertensive disorders during pregnancy. However, even women without overt nephropathy are at increased risk for PIH and preeclampsia. For example, in a Swedish study hypertensive disorders occurred in 18.7% of pregnant women with IDDM who did not have overt diabetic nephropathy in early pregnancy<sup>47</sup>. This prevalence was significantly higher than the 5% prevalence of hypertensive disorders in nondiabetic women in Sweden.

At least two factors might explain the association between pregestational diabetes and hypertensive disorders in the absence of overt nephropathy: 1) the presence of incipient nephropathy with microalbuminuria in some patients, and 2) an association between diabetes (especially NIDDM) and hypertensive disorders in general<sup>76,77</sup>. The relative contributions of these factors to hypertensive disorders of pregnancy in women with IDDM and NIDDM and in women from different ethnic groups remain to be determined.

## PRETERM AND CESAREAN DELIVERY

The prevalence of cesarean deliveries has consistently been reported to be higher in pregestational diabetic pregnancies than in nondiabetic pregnancies in patients at specialized medical centers. Cesarean rates have been in the range of 24%-66% in diabetic patients<sup>48</sup>, rates that were three to five times the rates in nondiabetic women<sup>26,45,47,78</sup>. Cesarean rates are higher in women with retinopathy or nephropathy than in women without these complications<sup>48</sup>. Reasons for cesarean delivery are seldom specified in published reports, so it is difficult to determine factors that underlie the increased cesarean rates. Undoubtedly, the practice of early delivery to avoid fetal demise contributed to the high rate of cesarean delivery in the past. However, recent information indicates that rates of cesarean delivery are still three to four times the rates in nondiabetic pregnancies<sup>44</sup>. The relative contributions of hypertensive disorders, fetal distress, and fetal macrosomia to the excess of cesarean deliveries remain to be established.

Preterm deliveries have also been reported to be more frequent in diabetic compared with nondiabetic preg-

nancies. Recent population-based data from Sweden<sup>47</sup> revealed a 25% rate of preterm delivery (<37 weeks gestation) in women with IDDM, compared with only 6% in the general population. At the University of Cincinnati<sup>69</sup> in Ohio and McMaster University in Canada<sup>40</sup>, preterm delivery rates in patients with pregestational diabetes were 24% and 30%, respectively. The diabetic rate was greater than the 12% rate of preterm delivery in nondiabetic women in the Cincinnati study. Hypertensive disorders accounted for 48% of preterm deliveries in the McMaster series but only 16% of preterm deliveries in Cincinnati. In the latter, 54% of the preterm deliveries resulted from spontaneous preterm labor. Other factors that may contribute to preterm deliveries in diabetic pregnancies include fetal distress (16% at the University of Cincinnati) and suspected fetal macrosomia.

### **MATERNAL HYPOGLYCEMIA**

Strict glucose regulation in diabetic patients is known to increase the frequency of hypoglycemic episodes<sup>79</sup>. Relatively few recent data are available to define the prevalence of symptomatic hypoglycemia in pregestational diabetic women during pregnancy; none of the prevalence rates comes from population-based studies. Of 165 women with IDDM managed at the University of Cincinnati during 1978-86, 34% experienced symptomatic hypoglycemia<sup>80</sup>. A similar frequency of hypoglycemia (35% of patients) during the first trimester was reported for women with IDDM who received care during 1982-88<sup>21</sup>. Hypoglycemia that required assistance treatment from others was found in 72% of a small group of intensively treated patients

with IDDM; 36% of these women had hypoglycemia requiring intravenous glucose<sup>81</sup>. No adverse effects of maternal hypoglycemia on fetal outcome were noted in these studies.

### **CONCLUSION**

Although a large amount of information has been published regarding pregnancy in women with diabetes, very few population-based data are available to reveal true prevalence rates for maternal pregestational diabetes or its complications during pregnancy. The information presented in this chapter, derived largely from specialized referral centers, provides strong evidence that several fetal and maternal complications are increased in women with pregestational diabetes. Few of the studies made any distinction between IDDM and NIDDM; those that did presented data primarily on pregnancies complicated by IDDM. Very little of the information is reported on the basis of specific ethnic groups. Thus, although it seems clear that maternal diabetes is an important health risk during pregnancy, much additional information is needed to assess the true impact of pregestational IDDM and NIDDM on maternal and fetal well-being in different ethnic groups in the United States.

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