CHAPTER 5

PREEXISTING DIABETES AND PREGNANCY

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SUMMARY

The prevalence of diabetes in adolescents and women of reproductive age has increased since 1995. However, no prospective national population-based data from the United States are available regarding women with preexisting diabetes in pregnancy (pregestational)—that is, type 1 diabetes or type 2 diabetes identified before pregnancy. Knowledge of the true prevalence depends on inclusion of women with early pregnancy losses, which are not available in birth certificate or hospital discharge data. In this chapter, prevalence data are presented from selected populations, including women who have recently given birth to a live infant, women who have used diabetes medications during pregnancy, women who have delivered in hospitals, and women enrolled in specific health plans. These reports, as well as population-based reports from other countries, suggest that diabetes during pregnancy *has at least doubled* since 1995, with increases in pregnancies affected by type 1 and type 2 diabetes and across all age groups.

Surveys of diabetes in female youth show that the prevalence of type 1 diabetes is greater than type 2 diabetes, but by the time in life of pregnancy, the ratio has reversed in population-based analyses of births. The former crude prevalence of preexisting diabetes mellitus in pregnancy of approximately 0.3% has risen to 1.0%–1.9% in major parts of North America, paralleling the diabetes prevalence in reproductive-age women, which was approximately 1.85%–3.0% between 2002 and 2009.

Preconception care of diabetes has consistently been reported to reduce major congenital malformations and perinatal complications by over 60%, thus rendering such care cost-effective. Utilization of preconception care is suboptimal, in part because of the high frequency of unplanned pregnancy, as well as lack of access to care. No national or regional surveillance systems are in place to prospectively monitor utilization of preconception care of diabetes and outcomes in the United States. Even though the risks of unplanned pregnancy are greater in women with diabetes than in nondiabetic women, women with diabetes are less likely to receive contraception counseling than women without diabetes.

Large prospective studies of diabetic women from the preconception period forward are needed in order to obtain reliable data on the prevalence of preconception care of diabetes and the use of contraception, as well as the number of diabetic women becoming and remaining pregnant. This effort might also have the effect of *better linkage of general diabetes care to enhanced preconception management of diabetic women.*

Severe maternal complications of pregnancy may be rare in the United States, but diabetes increases the relative risks of maternal mortality, ischemic stroke, myocardial infarction, preeclampsia-eclampsia, and possibly sepsis and venous thromboembolism. Prevention of diabetic ketoacidosis and severe maternal hypoglycemia is crucial; their frequencies should be monitored as indicators of quality of care, including self-care by the patient. Population-based systems to monitor these important comorbidities are lacking in the United States.

Proliferative retinopathy can progress during pregnancy, but risk of vision loss can be reduced by comprehensive ophthalmologic screening and photocoagulation as necessary. Data from other countries suggest that pregnancy does not exacerbate mild nephropathy in the long term, although the presence of nephropathy can contribute to poorer birth outcomes and worsen prognosis over the long term. Hypertensive disorders affect >10% of diabetic pregnancies, contributing to neonatal morbidity. Prospective data on treatment of hypertension during diabetic pregnancy are lacking.

First trimester glycosylated hemoglobin (A1c) levels >7.0% are associated with poorer birth outcomes. The teratogenic effects of hyperglycemia may be compounded by obesity, smoking, alcohol use, and/or poor nutrition. Fetal complications include a higher frequency of major congenital malformations, the most common of which are cardiovascular. It is controversial whether the use of medications

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common among women with diabetes contributes to the malformation risk, although insulin, antihyperglycemic medications, and oral contraceptives do not appear to do so. Stillbirths occur more frequently among women with poorer glucose control, and degree of risk increases with degree of A1c elevation. The prevalences of major malformations and stillbirths in surveys depend on the inclusion of terminations of pregnancy or late fetal losses at 20–23 weeks gestation, respectively.

Women with diabetes also have a 30%–60% higher risk of infants affected by preterm delivery and macrosomia with concomitant birth trauma events, such as shoulder dystocia with vaginal delivery. In 2009, approximately 56.5% of births to women with pregestational diabetes mellitus were by cesarean section, and 16%–27% of births resulted in birth weights >4,000 g. Other adverse events among infants of mothers with diabetes include infant mortality and neonatal hypoxic-ischemic encephalopathy, although such events are infrequent. Infants of diabetic mothers can experience a higher frequency of respiratory distress, polycythemia, hypoglycemia, hypocalcemia, and hyperbilirubinemia compared to infants of mothers without diabetes. In rare cases, these complications also can contribute to neonatal encephalopathy.

The increasing frequency of type 1 and type 2 diabetes in young women and increasing maternal age at conception are likely to further increase the risk of adverse maternal, birth, and infant outcomes. Population-based data are needed to track conception, miscarriage, major malformations, and livebirth and stillbirth frequencies among women with diabetes. Such data would guide the optimal timing and tailoring of preconception interventions. Interventions are needed that quantify the optimal amount of surveillance during fetal development (balancing costs and benefits), along with interventions that examine long-term risk to mothers and offspring.

The subject matter in this chapter is necessarily broad, as it not only discusses prevalence of pregestational diabetes mellitus in pregnancy but also prevalence of diabetes in reproductive-age women; preconception care and contraception; complications in the mother, fetus, infant, and developing offspring; and methodologic issues related to assessment of outcomes in the mother, fetus, and infant. The beauty and the devil is in the details. The definitions and management of pregnancy-related conditions can vary considerably among studies and, in many cases, are controversial.

INTRODUCTION

OBJECTIVE

This chapter presents population-based or multicenter data on: (1) the growing prevalence of type 1 and type 2 diabetes before and during pregnancy in North America, (2) preconception care and contraception among those with diabetes, (3) maternal complications of preexisting diabetes in pregnancy, and (4) fetal, neonatal, and offspring outcomes among women with diabetes. Information on diabetes with onset or recognition during pregnancy is provided in Chapter 4 *Gestational Diabetes*. This chapter focuses on data published in peer-reviewed journals since 2000. If ample U.S. data are not available on the different topics, relevant international population-based or multicenter studies are cited. If population-based data are sparse, reports from regional centers may be cited, especially if they provide data that can guide future epidemiologic surveys. (Note to reader: selected additional multicenter and regional/national population based studies published from January 2016 to July 2017 appear in Appendix 5.1, in the same order as topics in this chapter. Commentary is provided by the lead author of this text.)

HISTORICAL CONTEXT

Prior to the application of (a) medical nutrition therapy, self-monitoring of maternal blood glucose, and individualized insulin regimens, (b) technologies of fetal assessment, and (c) intensive neonatal care, pregnancy in women with type 1 diabetes (then defined as child-onset, insulin-dependent) was a frightening affair (1). Maternal risks included diabetic ketoacidosis (DKA), hypoglycemic coma, and progression of vascular disease, including superimposed preeclampsia. Excess rates of early fetal loss, major congenital malformations, fetal growth restriction, stillbirth, birth trauma, and neonatal death from hyaline membrane disease were observed. Reports of striking improvements in outcomes since 1975 were based on multidisciplinary care at single medical centers with a regional referral system. This experience has been widely reviewed and updated (2).

Persisting problems include access to care, wider dissemination and adoption of standards of care, patient-related barriers to effective care, and the rising tide of obesity and type 2 diabetes. The latter is too often unrecognized until pregnancy is well established. Regional or national surveillance of diabetes and pregnancy outcomes at the community level in the United States has not kept pace with achievements at centers of excellence. These problems gain even more importance with the recognition of the lifelong influences of preconception, fetal, and neonatal processes on many features of health or disease.

In the 1980s–1990s, two national prospective studies included a focus on type 1 diabetes and pregnancy. The Diabetes in Early Pregnancy study (DIEP) (3,4,5) was a multicenter study of pregnant women with probable type 1 diabetes, then defined as young adult-onset, insulin-dependent diabetes; 347 diabetic women and 389 control nondiabetic women were enrolled within 21 days of conception (76% of women in these “early entry groups” enrolled prior to conception) and an additional 279 diabetic women entered after 5 postmenstrual weeks gestation (“late entry

group"). The DIEP was designed to evaluate whether metabolic control (assessed by colorimetric glycosylated hemoglobin [A1c], glycated protein, fructosamine, and fasting beta-hydroxybutyrate levels) correlated with early fetal loss, major congenital malformations, fetal macrosomia, and diabetic retinopathy among other outcomes. These outcomes are mentioned where appropriate in this chapter.

The Diabetes Control and Complications Trial (DCCT) was a multicenter controlled clinical trial in North America that compared intensive treatment with conventional diabetes therapy among patients with type 1 diabetes (age 13–39 years; diabetes duration 1–15 years); 94 of 345 women in the original intensive treatment group became pregnant at least once during the 10-year trial. Of the total 135 pregnancies in women in the intensive treatment group, 96 progressed ≥20 weeks gestation (6). Among 335 women originally randomized to conventional treatment, 26 women anticipating pregnancy switched to intensive therapy (per DCCT protocol) prior to conception for 52 pregnancies (n=42, >20 weeks), but 60 women in the conventional treatment group had 83 unplanned pregnancies (n=58, >20 weeks). Mean (±standard deviation) A1c at conception was 7.4%±1.3% (57±14.2 mmol/mol) for the 135 beginning pregnancies in the intensive treatment group compared to 6.9%±1.0% (52±10.9 mmol/mol) for the 52 pregnancies in women in the conventional treatment group who initiated intensive therapy prior to conception and 8.8%±1.7% (73±18.6 mmol/mol) for the 83 unplanned pregnancies in the conventional treatment group. Pregnancy outcomes (6) and frequencies of microvascular complications during and after pregnancy (7) are presented later in this chapter.

In 1988, the National Maternal Infant Health Survey was a multistaged cross-sectional probability sample of 7,366 live births recorded in the United States for women age 15–49 years. This was used to estimate the prevalence of pregnancy complicated by preexisting diabetes (8). Data were obtained from birth records, hospital medical records, and questionnaires sent to mothers and their health care providers. The weighted prevalence of pregnancies affected by juvenile-onset diabetes was 0.17% compared to 0.31% for pregnancies affected by adult-onset diabetes. The prevalences of both types of preexisting diabetes in pregnancy have increased greatly since 1988.

DATA SOURCES AND LIMITATIONS

Beyond the two pioneering national prospective studies including a focus on type 1 diabetes and pregnancy that are cited above, few national population-based diabetes outcome data for pregnancy in the United States have been published in peer-reviewed journals since 2000. The limited number of United States-based studies that focused on pregnancy outcomes are cited later in the chapter. Most notably lacking are data from the growing numbers of pregnant women with type 2 diabetes. Mainly international population-based studies of preexisting (pregestational) diabetes mellitus in pregnancy are available after 2000, and these are cited where appropriate.

Due to the limited U.S. data, prospectively collected data from the Kaiser Permanente Northern California (KPNC) multicenter health care system were analyzed for *Diabetes in America, 3rd edition*. KPNC is a large group practice prepaid health plan comprising 44 medical centers with 544,687 deliveries in 1996–2011. Analysis of U.S. census data demonstrates that KPNC members are similar to the general population with regard to ethnicity and education and differ only slightly with regard to income (9). Whether preconception care is better in the KPNC compared to the general population is uncertain. A potential barrier to preconception care for women with diabetes is access to care, which in turn might be sensitive to lower household income.

The methods of KPNC data collection and analysis have been published (10,11). Briefly, the KPNC diabetes registry gathers data from electronic medical records and identifies patients based on primary hospital discharge diagnoses, two or more outpatient visit diagnoses of diabetes, any prescription for a diabetes-related medication, and any record of an A1c test result >6.7% (>50 mmol/mol). References to unpublished data from KPNC in this chapter rely on this diabetes and pregnancy registry.

The National Vital Statistics System (NVSS) contains data from birth and death certificates that are provided by the states, compiled and prepared by the U.S. National Center for Health Statistics, and presented in national statistical files (12). In 2009, the 2003-revised birth certificate was used in 28 states, New York City, and the District of Columbia. The 2003-revised birth certificate discriminates preexisting diabetes in pregnancy from gestational diabetes. The NVSS tables presented in this chapter were analyzed specifically for *Diabetes in America*. Only "national-average" data are used in this chapter. Of 2,689,579 births in 2009 (~66% of all U.S. births), 17,784 cases were listed as preexisting diabetes (0.66%). Birth certificates are known to underrepresent complicating conditions, and other population-based data sets reviewed in this chapter yield higher rates of preexisting diabetes in the same time period.

When possible, definitions of maternal and fetal outcomes used in this chapter are consistent with those proposed by the Working Group on Outcome Definitions of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) (13). In this chapter, use of the term *preconception diabetes* refers to women with type 1 or type 2 diabetes studied prior to pregnancy, and the term *preexisting diabetes* refers to women with type 1 or type 2 diabetes studied during pregnancy, but with data not specified for either type of diabetes. Some authors prefer the term pregestational diabetes, and that term may be used here in commenting on their publications. White's classification of preexisting diabetes in pregnancy was based on duration of diabetes and presence of diabetes complications, but it is rarely used since 2000.

Many of the epidemiologic studies of the relation of maternal diabetes factors to pregnancy or long-term outcomes reviewed in this chapter attempted to control for confounding variables. However, few of the data sets were used to analyze for interacting effects of comorbidities that are common in diabetes, yet often are not measured in retrospective or even prospective studies. Pioneering studies of comorbidity measures for use with administrative data showed that comorbidities, separated from the primary reason for hospitalization, had independent effects on outcomes, differing among separate patient groups (14). Comorbidity indexes have been validated for use in obstetric populations (15,16), for quantification of diabetes comorbidity risks across life (17), and assessment of comorbidity interrelatedness among patients with multiple chronic conditions (18). New morbidity and comorbidity measures based on International Classification of Diseases (ICD), Tenth Revision, groups were developed to be used to control for confounding (an example of outcome was death in hospital) (19). The challenge is to evaluate such approaches in future population-based studies of diabetes and pregnancy.

Some studies of epidemiologic data on pregestational diabetes in pregnancy used modeling to control for effects of possible confounders in a group of patients. The usual approach was to be able to state, for example, that there was an independent effect of average glycemic control on excess birth weight, with or without maternal obesity. These statements apply to outcomes for groups, and they have been used to guide current management. What is needed is individual information on risks, or probable benefit of certain treatments, taking into account individual patient characteristics and relevant comorbidities. The emerging hope is to use advanced epidemiologic and epigenetic data to provide information that will improve individual patient care, as well as to understand and "manage" large populations.

CONSIDERATIONS BEFORE PREGNANCY

PREVALENCE OF DIABETES IN WOMEN OF CHILDBEARING AGE

It is important to note the prevalence of type 1 and type 2 diabetes in women of childbearing age in the United States, because these women may become pregnant. The major types of surveys used since 2000 include those based on population sample blood testing (National Health and Nutrition Examination Survey [NHANES]), questionnaire/telephone surveys of women after giving birth (Pregnancy Risk Assessment Monitoring System [PRAMS]), telephone surveys of a population sample of women with diabetes by self-report (Behavioral Risk Factor Surveillance System [BRFSS]), and examination of medical records of youth (SEARCH for Diabetes in Youth study [SEARCH]).

In a new analysis conducted for *Diabetes in America*, among 1,338 women age 20–44 years in the NHANES 2005–2010, 2.6% had diagnosed diabetes, 2.0% had undiagnosed diabetes, and 22.8% had prediabetes based on blood sampling (A1c, fasting plasma glucose [FPG], or oral glucose tolerance test [OGTT] results). The prevalence of diagnosed diabetes varied from 2.3% to 3.5% in the three major racial/ethnic groups tested (Table 5.1). A published analysis including earlier data from the NHANES 1999–2010 showed that 10,491 nonpregnant women of reproductive age (15–44 years) reported no diabetes diagnosis; many of these women had A1c and/or fasting blood glucose (FBG) laboratory values available for analysis (20). Among 6,881 women with A1c values, 4.0% were "at risk of diabetes" with A1c 5.7%–6.4% (39–46 mmol/mol), and 30 women had A1c >6.5% (>48 mmol/mol; undiagnosed diabetes if confirmed). Among 4,352 women with FBG values, 11.2% were "at risk of diabetes" with FBG 100–125 mg/dL (5.55–6.94 mmol/L), and 28 women had FBG >125 mg/dL (undiagnosed diabetes if confirmed). (Risk estimates for undiagnosed diabetes were suppressed because minimum degrees of freedom for strata were not met.) Racial/ethnic groups were not analyzed in this data set, which included young women age 15–19 years but no OGTT values (20).

A separate analysis of NHANES data from 1999–2008 focused on the levels of dysglycemia (known diabetes; undiagnosed diabetes based on FPG ≥126 mg/dL [≥7.0 mmol/L] or A1c ≥6.5%; or prediabetes based on FPG 100–125 mg/dL or A1c 5.7%–6.4%) present in 7,162 nonpregnant women of childbearing

TABLE 5.1. Prevalence of Diagnosed Diabetes, Undiagnosed Diabetes, Prediabetes, and Normal Glucose Levels Among Women Age 20–44 Years, by Race/Ethnicity, U.S., 2005–2010

	PERCENT (STANDARD ERROR)			
RACE/ETHNICITY	Diagnosed Diabetes*	Undiagnosed Diabetes†	Prediabetes†	Normal Glucose Levels†
Total	2.6 (0.29)	2.0 (0.37)	22.8 (1.44)	72.6 (1.53)
Non-Hispanic white	2.3 (0.47)	1.8 (0.50)	19.9 (2.02)	76.0 (2.08)
Non-Hispanic black	3.5 (0.56)	[1]	25.7 (3.01)	69.3 (3.45)
All Hispanic	3.3 (0.61)	2.2 (0.57)	31.0 (2.82)	63.5 (3.11)
Mexican American	2.5 (0.57)	2.7 (0.79)	34.5 (3.32)	60.3 (3.48)
Other Hispanic	4.8 (1.28)	[1]	25.0 (4.67)	68.9 (5.07)
Other-multiracial	2.0 (0.93)	3.4 (1.40)	23.7 (6.19)	70.9 (7.16)

Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test.

* Diagnosed diabetes is self-reported.

† Undiagnosed diabetes is defined as A1c ≥6.5%, FPG ≥126 mg/dL, or OGTT ≥200 mg/dL; prediabetes is defined as A1c 5.7%–6.4%, FPG 100–125 mg/dL, or OGTT 140–<200 mg/dL; normal glucose levels are defined as A1c <5.7%, FPG <100 mg/dL, and OGTT <140 mg/dL.

[1] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

SOURCE: National Health and Nutrition Examination Surveys 2005–2010

age (15–49 years) (21). Any level of dysglycemia was present in 26.3% (95% confidence interval [CI] 22.3%–30.8%) of non-Hispanic black women (47% obesity), in 16.8% (95% CI 14.4%–19.6%) of non-Hispanic white women (28% obesity), and in 23.8% (95% CI 19.5%–28.7%) of Mexican American women (36% obesity). Analysis of adjusted prevalence risk ratios showed that the excess risk of dysglycemia for the black and Mexican American women was limited to those with body mass index (BMI) <30 kg/m^2. With obesity, similar high risks of dysglycemia were seen in all ethnic groups (21).

Another way to estimate the prevalence of diabetes in women most likely to become pregnant is to survey for preconception health status by self-report in women who gave birth to a liveborn infant. The PRAMS has been described elsewhere (22,23). The self-reported prevalence of diabetes before pregnancy (1.8%, 95% CI 1.6%–2.0%) in women interviewed after pregnancy in 2004 is given in Table 5.2, stratified by maternal age, race/ethnicity (prevalence range 1.2%–3.3%), and health insurance status before pregnancy (22). The variance in diabetes prevalence among 26 states was 0.9%–3.0% (average 1.8%, 95% CI 1.6%–2.0%), with highs at 2.7% in Georgia, 2.8% in Mississippi, 2.9% in North Carolina, 3.0% in Arkansas, and one outlier at 5.7% in West Virginia (22). An update of the PRAMS analysis for 2009 is given in Table 5.3 for 40,388 respondents in 29 reporting areas; 2.1% (95% CI 1.9%–2.4%) stated they were told of type 1 or type 2 diabetes before the most recent pregnancy (23). Stratification by age was slightly different in 2009 compared to 2004, and prevalence estimates varied by race/ethnicity in 2009 compared to 2004 (23).

The caveat is that the PRAMS assesses women who thought they had type 1 or type 2 diabetes (or "high sugar") before and during a recent pregnancy and does not survey nonpregnant women who might become pregnant. Since the total sample in 2004 and 2009 questioned all women in the participating states with a recent pregnancy, it is a way to estimate the prevalence of preexisting diabetes in women actually becoming pregnant. However, the PRAMS authors stated that "prevalence estimates of the risk indicators cannot be generalized to the entire population of reproductive-age women" (22). PRAMS 2009 data for the prevalence of hypertension 3 months before a recent pregnancy are also presented in Table 5.3 (23).

TABLE 5.2. Prevalence of Diabetes Before Pregnancy in Women Who Recently Gave Birth to a Liveborn Infant in One of 25 States or New York City, by Age, Race/Ethnicity, and Health Insurance Status, U.S., 2004

CHARACTERISTICS	PERCENT (95% CI)
Total	1.8 (1.6–2.0)
Age (years)	
<20	2.0 (1.3–2.7)
20–34	1.6 (1.4–1.8)
≥35	3.0 (2.3–3.7)
Race/ethnicity*	
Non-Hispanic white	1.2 (1.0–1.4)
Non-Hispanic black	3.3 (2.7–3.9)
Hispanic	2.6 (2.0–3.2)
Non-Hispanic other	1.8 (1.2–2.4)
Health insurance status before pregnancy	
Private	1.4 (1.2–1.6)
Medicaid	2.9 (2.0–3.8)
None	2.2 (1.8–2.6)

CI, confidence interval.
* Self-reported

SOURCE: Reference 22

TABLE 5.3. Weighted Prevalence Estimates of Women Age 18–44 Years Who Were Told of Diabetes or Hypertension Before Their Most Recent Pregnancy Yielding a Liveborn Infant or Who Were Ever Told by a Health Care Provider That They Had Diabetes or Hypertension, by Age and Race/Ethnicity, U.S., 2009

CHARACTERISTICS	PERCENT (95% CONFIDENCE INTERVAL)			
	Type 1 or Type 2 Diabetes Before Recent Pregnancy*	Told of Diabetes Outside Pregnancy†	Hypertension 3 Months Before Recent Pregnancy*	Told of Hypertension Outside Pregnancy†
Total	2.1 (1.9–2.4)	3.0 (2.7–3.2)	3.0 (2.6–3.4)	10.2 (9.8–10.6)
Age (years)				
18–24	1.8 (1.4–2.2)	1.0 (0.7–1.5)	2.5 (1.9–3.2)	4.7 (4.0–5.5)
25–34	2.0 (1.7–2.4)	2.4 (2.1–2.8)	2.7 (2.3–3.3)	8.5 (7.9–9.1)
35–44	3.4 (2.7–4.2)	4.5 (4.1–5.0)	5.3 (4.2–6.8)	14.7 (14.0–15.3)
Race/ethnicity				
White	2.0 (1.8–2.4)	2.3 (2.2–2.6)	2.5 (2.1–3.0)	9.3 (8.9–9.8)
Black	2.7 (2.2–3.5)	5.1 (4.2–6.2)	6.6 (5.3–8.1)	19.2 (17.5–20.9)
Hispanic	1.8 (1.3–2.4)	3.6 (2.9–4.5)	1.7 (1.1–2.8)	8.2 (7.3–9.2)
Other	3.1 (2.2–4.2)	3.3 (2.3–4.4)	2.8 (1.9–4.0)	7.9 (6.7–9.3)

* PRAMS, Pregnancy Risk Assessment Monitoring System 2009
† BRFSS, Behavioral Risk Factor Surveillance System 2009

SOURCE: Reference 23

The BRFSS, a state- and population-based telephone survey of noninstitutionalized adults administered by the Centers for Disease Control and Prevention (CDC), collected self-reports of being told of diabetes by a health care provider (excluding gestational diabetes) from 62,875 nonpregnant women of reproductive age 18–44 years from 51 reporting areas in 2009 (23). The weighted estimated prevalence of diabetes varied from 2.3% to 5.1% in four racial/ethnic groups and, among pooled groups, from 1.0% at age 18–24 years to 4.5% at age 35–44 years (Table 5.3). The total prevalence of diabetes among nonpregnant women of age 18–44 was 3.0% (95% CI 2.7%–3.2%) (23).

A BRFSS 2004 report showed that the prevalence of self-reported diabetes was 1.5% among 35,351 nonpregnant women of reproductive age (18–44 years) and 2.1% in the 3,288 women who reported intending pregnancy in less than 12 months (24). The prevalence of known diabetes was stable at 2.9% in a BRFSS analysis of 60,974 women of reproductive age in 2003, 75,346 women in 2007, and of 63,769 women in 2009 (95% CI 2.7%–3.2% for 2009) (25). Other important self-reported comorbidities were common in the total group for 2009 (weighted estimates and CI): asthma in 16.2% (95% CI 15.6%–16.7%), chronic high blood pressure (excluding only in pregnancy) in 10.1% (95% CI 9.7%–10.5%), and high cholesterol in 13.6% (95% CI 13.2%–14.1%) (25).

The 2002 National Survey for Family Growth revealed a self-reported prevalence of diabetes of 2.3% among 5,955 nonpregnant women age 20–44 years with recorded information on both diabetes status and BMI (23.6% of total group obese). Of 135 diabetic women, 80% were previously pregnant, 41.7% desired pregnancy, 38.8% used no contraception, and 36.3% reported they were surgically sterile (26).

The Medication Exposure in Pregnancy study sponsored by the U.S. Food and Drug Administration and conducted in 11 health maintenance organizations observed that 1.21% of insured women with 437,950 deliveries of a liveborn infant in 2001–2007 used any antidiabetic drug in the 4 months before pregnancy; 0.33% used insulin therapy alone. Medications were identified from the outpatient pharmacy dispensing data. Some of the metformin use (0.84% of total population) could have been for indications other than diabetes (27). A diagnosis code for type 1 or type 2 diabetes before pregnancy was present in 83.5% of the insulin-treated deliveries. The frequency of preconception insulin use was stable across the years 2001–2007, but percentages were greater by increasing maternal age: from 0.26% for age 12–24 years to 0.34% for age 25–39 years and 0.51% for age 40–50 years (27). The frequency of preconception insulin use was 0.33% in non-Hispanic whites, 0.32% in blacks/African Americans, 0.24% in Hispanic women, and 0.16% in Asian American women (27).

Thus, seven published population-based surveys (using different methods) of nonpregnant women of reproductive age conducted in the United States in 2001–2009 showed a range of prevalence of known diabetes of 1.2%–3.0% (higher in some racial/ethnic groups) (reference 23 includes two surveys) (22,23,24,25,26,27). The median prevalence was 2.1%. Basing diagnoses on blood tests in women without a history of diabetes, 1.8%–3.4% had undiagnosed diabetes in the NHANES 2005–2010, according to major racial/ethnic group (data prepared for *Diabetes in America*) (Table 5.1). All of these studies suggest the burden of diabetes in women who may become pregnant. The actual burden is influenced by the proportion of women who are fertile and sexually active without effective contraception and by the mostly unknown proportion of preconception diabetic women who have associated risk factors linked to poor outcomes (22,23): obesity, cigarette smoking, at-risk drinking, frequent mental distress (28), hypertension, and high cholesterol (25). Further analyses revealed inadequate levels of screening and intervention for hypertension and dyslipidemia among women of childbearing age (29) and that knowledge alone or a doctor's recommendation are not enough to modify the risk factors; "innovative programs and support systems are required to encourage women to adopt healthy behaviors throughout the childbearing years" (30).

It is also important to consider the prevalence rates of established diabetes in younger females who may become pregnant in the near future. SEARCH (31,32,33,34,35) is described in detail in Chapter 15 *Diabetes in Youth*; prevalences of type 1 and type 2 diabetes among females age 15–19 years by race/ethnicity in 2001 are shown in Table 5.4, and the annual incidence of diabetes in youth in 2002–2005 is shown in Table 5.5 (32,33,34,35). For the 71 African American and 45 Hispanic females age 15–19 years with type 2 diabetes, obesity was present in 73% and 77%, respectively (Table 5.5) (33,35).

By 2009, the prevalence of both types of diabetes had increased compared to 2001 in both sexes, in age groups 5–9, 10–14, and 15–19 years, and in black, Hispanic, and white youth (36). Among 3,458,974 youth surveyed in 2009, type 1

TABLE 5.4. Type 1 and Type 2 Diabetes Prevalence Among Females Age 15–19 Years, by Race/Ethnicity, SEARCH for Diabetes in Youth Study, 2001

RACE/ETHNICITY	DIABETES CASES (TYPE 1, TYPE 2)/ DENOMINATOR	PREVALENCE PER 1,000 (95% CI*)	
		Type 1 Diabetes	Type 2 Diabetes
Non-Hispanic white	788, 82 / 252,871	3.12 (2.91–3.34)	0.33 (0.26–0.40)
African American	101, 107 / 44,699	2.26 (1.86–2.75)	2.40 (1.99–2.90)
Hispanic	117, 55 / 71,743	1.64 (1.37–1.96)	0.77 (0.59–1.00)
Asian/Pacific Islander	42, 34 / 40,170	1.06 (0.78–1.43)	0.85 (0.61–1.19)

* Confidence intervals (CI) were calculated using an inverted score test from the binomial distribution.

SOURCE: References 32, 33, 34, and 35, copyright © 2009 American Diabetes Association, reprinted with permission from the American Diabetes Association. Supplementary tables available at PubMed site for each reference; use Full Text link to *Diabetes Care*. Accessed 13 December 2017

TABLE 5.5. Annual Incidence Rates of Type 1 and Type 2 Diabetes Among Females Age 15–19 Years, by Race/Ethnicity, SEARCH for Diabetes in Youth Study, 2002–2005

RACE/ETHNICITY	DIABETES CASES (TYPE 1, TYPE 2)/ DENOMINATOR	NUMBER OF NEW CASES (95% CI*) (PERCENT OBESE) PER 100,000 PER YEAR	
		Type 1 Diabetes	Type 2 Diabetes
Non-Hispanic white	150, 64 / 1,498,572	10.0 (8.5–11.8) (NA)	4.3 (3.4–5.5) (NA)
African American	34, 71 / 353,725	9.6 (6.8–13.4) (24)	20.1 (16.0–25.4) (73)
Hispanic	26, 45 / 355,210	7.4 (5.0–10.8) (14)	12.6 (9.4–16.9) (77)
Asian/Pacific Islander	14, 27 / 196,637	7.3 (4.4–12.2) (NA)	13.9 (9.6–20.2) (NA)

NA, not available.

* Confidence intervals (CI) were calculated using an inverted score test from the binomial distribution.

SOURCE: References 32, 33, and 34 for obesity data, copyright © 2009 American Diabetes Association, reprinted with permission from the American Diabetes Association. Incidence rates from supplementary tables available at PubMed site for each reference; use Full Text link to *Diabetes Care*. Accessed 13 December 2017

diabetes affected more youth (1.93/1,000) than did type 2 diabetes (0.24/1,000), although the proportion of type 2 diabetes reached 34.2%–37.6% in black, Hispanic, and Asian/Pacific Islander groups of 15–19-year-old youth of both sexes (37). Diabetes of all types in all age groups combined was somewhat more common in females (2.30/1,000) than males (2.16/1,000). Among 913,857 youth age 15–19 years (both sexes combined) surveyed in 2009, the prevalence of all types of diabetes reached 4.03/1,000 (95% CI 3.90–4.16) (37).

A summation of the SEARCH study published in 2014 noted that many youth with diabetes, especially those with type 2 diabetes, have very poor glycemic control and already have strong risk factors for chronic complications (38). This does not bode well for young diabetic women becoming pregnant. A special problem is the transition of young patients with type 1 diabetes from pediatric to adult care (38).

PRECONCEPTION CARE OF DIABETES AND CONTRACEPTION

Planning of Pregnancy

Counseling of the female adolescent or woman with type 1 or type 2 diabetes about risks of pregnancy associated with diabetes and its complications and the means of lowering risks is an important step of planning for pregnancy or its delay. Thorough clinical and laboratory evaluation of the patient is necessary, including assessment of mental health status and her support system. Until this is done and a safe level of glycemic control is established, provision of contraception is important (39,40). The details of the recommended preconception process for diabetic women have been published as official guidelines (40,41,42,43,44). The American Diabetes Association (ADA) recommends: "Starting at puberty, preconception counseling should be incorporated into routine diabetes care for all girls of childbearing potential. Family planning should be discussed and effective contraception should be prescribed and used until a woman is prepared and ready to become pregnant" (40).

There is information from the general population about optimal interpregnancy interval (pregnancy spacing) that should be considered in the counseling of parous diabetic women. Intervals that are less than 6–11 months (45,46,47,48) or longer than 24–60 months (depending on the study) (45,46,48,49) were associated with increased rates of neonatal mortality, morbidity, and major congenital malformations (50,51).

A common explanation for a short interval association is maternal depletion of nutrient stores, although the observed association might be due to residual familial confounding (49,52). Risk factors for the association also may be risk factors for adverse perinatal outcomes, such as socioeconomic status, relationship (marital or non-marital) status, high or low maternal weight, or poor glycemic control coupled with the stress of infant care (52). A few of the studies of interpregnancy interval included women with pregestational diabetes (47,48,51), but separate analyses were not done for this subgroup. Whether short interpregnancy interval in particular is causal for poor pregnancy outcomes remains controversial, and more studies need to be analyzed.

Women who had gestational diabetes form a special subset of childbearing women with a risk of developing type 2 diabetes before the next pregnancy (11,53,54,55). In a national U.S. retrospective analysis of insurance claims for women who delivered in 2006–2011, among 645,195 pregnancies that did not end in miscarriage (excluding unknown), 3.2% of 50,872 women with gestational diabetes progressed to type 2 diabetes within 3 months of delivery (54). The rate would be expected to increase dramatically over 5 years after delivery (53). Active follow-up after pregnancy of women who had gestational diabetes is poor in the United States (55,56,57) and elsewhere (58,59,60,61,62). Lifestyle interventions have been shown to prevent or delay the onset of type 2 diabetes in women who had gestational diabetes (63,64). This high-risk group should be targeted (53,60,61) for enhanced breastfeeding, contraception, behavior modifications (including appropriate weight loss), screening for diabetes in the years after pregnancy, and preconception management as needed.

Utilization of Preconception Care

Although preconception care of diabetic women is effective for the prevention of adverse outcomes (39,40,41) and such care should be coordinated with contraception, both preconception care and contraception continue to be underutilized among women with diabetes of reproductive age (65,66,67,68,69,70,71). Systematic reviews and meta-analyses of cohort studies conclude that preconception care of diabetes reduces the frequencies of major congenital malformations, preterm delivery, and perinatal mortality compared to outcomes in women who had no specific preconception care (71,72,73,74,75,76,77,78).

A 2001 meta-analysis (72) of preconception care of diabetic women included eight prospective and six retrospective cohort studies; major congenital anomalies were assessed by physical examination of liveborn and stillborn infants of 1,192 mothers who had received preconception care and 1,459 mothers who had not. The pooled rate of major malformations was lower among preconception care recipients (2.1%) than nonrecipients (6.5%) (relative risk [RR] 0.36, 95% CI 0.22–0.59, no heterogeneity present) (72). A 2012 meta-analysis included nine prospective cohort studies and four retrospective studies; the pooled rate of major malformations was 1.9% among 1,348 infants of diabetic women who received preconception care and 7.4% among 2,159 infants of diabetic women who did not (RR 0.25, 95% CI 0.16–0.37) (73). Modeling studies of preconception care also suggest beneficial impact (76,77,78) and cost savings (79,80,81) via risk reduction of major birth defects, preterm birth, and perinatal mortality.

Limitations of studies of preconception care of diabetes include the lack of randomized controlled trials (unethical to carry out), inconsistent inclusion of pregnancies terminated early due to major congenital malformations, lack of follow-up of infants for the first year of life for late detection of congenital anomalies, and exclusion of aneuploidy. Also important are differences in published definitions of pregnancy planning versus preconception advice or counseling versus intensified preconception care (71).

An important reason for low utilization of preconception care is the frequency of unintended pregnancies. The PRAMS reported that about half or more of pregnancies were unintended in women who stated they had diabetes before gestation (22,23). Surveys in the U.S. general population in 2006–2010 showed unintended pregnancy rates of 37.1% (82), 42.9% (83), and 51% (84). One survey of 21,161,000 births categorized the 37.1% unintended pregnancies as unwanted (13.8%, standard error [SE] 0.78), mistimed with birth occurring <2 years before the mother wanted to become pregnant (9.2%, SE 0.75), and mistimed with birth occurring ≥2 years before intended (14.0%, SE 0.93) (82). The authors examined the multiple stated reasons for not using contraception at conception among women who had an unintended birth, and 35.9% (SE 2.43) women agreed with the statement "did not think you could become pregnant" (82). Correlates of more unintended pregnancies in all the surveys were young maternal age, unmarried status, and lower income levels (82,83,84).

A retrospective PRAMS study (85) of self-reported behaviors conducted in 10 states in 2009–2010 determined that 1.5% (SE 0.1) of 23,386 women with recent pregnancies had prepregnancy diabetes and 52.6% (SE 4.0) of them said yes to the question: "Before you got pregnant with your new baby, did you talk with a doctor, nurse, or other health care worker to prepare for a healthy pregnancy and baby?" (85). This response was called positive for preconception care. No outcome data were presented.

An assessment by questionnaire of 236 diabetic women age 18–45 years in three managed care organizations in California, Indiana, and Michigan showed that 52% recalled that their current health care provider had mentioned the importance of good glucose control before pregnancy, and only 37% recalled family planning advice (86). No data were provided on measures of hyperglycemia or pregnancy outcome.

At a regional center in Ohio, utilization of preconception care for type 1 diabetes was 37% and the congenital malformation rate was low at 2.2% during a period 11–15 years after introduction of a well-advertised preconception program (87). Despite the information available in the region, utilization declined to 19.5% and the malformation rate rose to 3.7% when National Institutes of Health funding was discontinued and the program became less active (87).

The introduction of a systematic regional program of intensified use of preconception care of type 1 and type 2 diabetes in West Ireland resulted in a lower frequency of congenital malformations (major and minor) among live and stillbirths for 2010–2014 (2.0%) compared to 2005–2009 (5.9%; 2.6% in background population) (88). These results were obtained despite more obesity (43% vs. 29% with BMI >30 kg/m^2, p=0.002) in the later time period (88). In 2010–2014, there were significant increases in attendance at prepregnancy care (from 23% to 49%, p<0.001), use of folic acid (45% to 71%, p<0.001), and patients with first trimester A1c ≤6.5% (16% to 33%, p<0.001) (88). A separate analysis of pregnancy outcomes and costs associated with 149 diabetic women who participated in prepregnancy care in this regional program compared to 265 women who did not confirmed the better results, including lower rates of serious adverse outcomes in offspring of women with type 1 diabetes (1.8% vs. 11.4%, p=0.003), and that the program was cost-saving relative to the average cost of usual antenatal care and delivery (89).

In Ontario, Canada, a survey of 163 pregnant women with type 1 or type 2 diabetes in 2006–2008 showed that 47% reported "high pregnancy planning effort," coupled with attempts to optimize glycemic control in most of the planned pregnancies (90). The most important predictor of pregnancy planning was discussion with the physician (90). For 1996–2010, the survey was extended to the whole province (91). In this analysis, 93.8% of 13,278 women with preconception diabetes who later delivered were found to have a prepregnancy visit with a primary care physician within the 21- to 9-month window prior to the delivery date (91). When there were multiple visits, the great majority were to the same physician. What is unknown is how much pregnancy preparation occurred at those visits. The major malformation rate declined over those years from 7% for 1996–1997 to 5.5% for 2009–2010 (91), but it was unknown whether pregnancy terminations for malformations increased, as has been seen elsewhere.

Utilization rates of 27.6%–58.6% for women with unspecified preexisting or type 1 diabetes were published in 2003–2016 for preconception "advice, "care,"

"counseling," "guidance," or "planning plus folic acid" in European countries (Table 5.6) (89,92,93,94,95,96,97,98,99). There was one outlier at 84% for "planned the pregnancy" in the Netherlands (100). Lower rates of utilization of counseling plus management (24.0%–29.2%) were reported for women with type 2 diabetes before pregnancy (Table 5.6) (89,92,95,97,99). One survey reported 46.5% utilization of prepregnancy "advice" for 556 women with type 2 diabetes in a regional database in England (98); no outcome data on congenital malformations were reported.

A 2-year extension (101) of one survey (99) in Northern England found that attendance for preconception "care" by 1,753 women with type 1 diabetes actually declined over the years 1996 to 2010. Only 28.2% of all diabetic women had adequate periconception A1c (<7% [<53 mmol/mol]) (101). Another analysis of this population showed that the utilization of preconception care and level of periconception A1c did not improve

TABLE 5.6. Preconception Care of Diabetes in Population-Based or Multicenter Studies Reported Since 2000

REGION, YEARS (REF.)	POPULATION	NUMBER PDM PREGNANCIES BY TYPE OF DIABETES	PERCENT PRECARE*	DEFINITION OF PRECARE*	MAJOR CONGENITAL MALFORMATIONS, n (%)	
					Precare*	No Precare*
France, 2000–2001 (92)	12 centers	Type 1: 289 Type 2: 146	48.5 24.0	Information, management	1/140 (0.7) 1/35 (2.9)	12/149 (8.1)† 4/111 (3.6)†
Netherlands, 1999–2000 (100)	All hospitals	Type 1: 323‡	84	Planned the pregnancy	11/271 (4.1)	6/52 (11.5)
Denmark, 1993–1999 (93)	All hospitals	Type 1: 1,218§	58% of 1,153 women with information	Guidance	38/669 (5.7)§	55/549 (10.0)§
Scotland, 1998–1999, 2003–2004 (94)	All hospitals, prospective	Type 1: 423 (includes S/TAB)	50.4	Planned the pregnancy	28/213 (13.1)‖	55/210 (26.2)‖
Italy, 1999–2003 (95)	33 centers	Type 1: 504 Type 2: 164	43.9 29.1	Counseling, management	NR¶	NR¶
West Ireland, 2006–2014 (89)	All hospitals, prospective	Type 1: 269 Type 2: 145	41.3 26.2	Counseling, management	1/124 (0.8)# p=0.04	12/229 (5.2)#
East Anglia, England, 2006–2009 (96)	All hospitals, prospective	560 PDM deliveries**	27.6	Counseling, management	1/152 (0.7)†† 2/152 (1.3)††	23/408 (5.6)†† 32/408 (7.8)††
North England, 2001–2004 (97)‡‡	Regional database	Type 1: 418 Type 2: 119	48.4 31.1	Counseling	PDM pooled 14/240 (5.8)‡‡	PDM pooled 30/297 (10.1)‡‡ p=0.027
England, three regions, 2007–2008 (98)	Regional database	Type 1: 812 Type 2: 556	58.6 46.5	Advice§§	NR	NR
North England, 1996–2008 (99)‖‖	Regional database	Type 1: 1,314 Type 2: 363	44.4 29.2	"Care" undefined	PDM pooled 41/683 (6.0)‖‖	PDM pooled 79/985 (8.0)‖‖ unadjOR 1.37 (95% CI 0.92–2.02)
		Type 1: 1,314 Type 2: 363	32% folic acid 27% folic acid	Preconception folic acid	Folic acid 22/518 (4.2)‖‖	No folic acid 85/1,028 (8.3)‖‖

A1c, glycosylated hemoglobin; CI, confidence interval; NR, not reported; OR, odds ratio, adjusted (adj) or unadjusted (unadj); PDM, preexisting diabetes mellitus in pregnancy; S/TAB, spontaneous/therapeutic abortion; w, weeks gestation.

* Preconception care of diabetes for all specifications of preexisting diabetes

† In pooled type 1 and type 2 diabetes, four pregnancies were terminated for major congenital malformations, and eight perinatal deaths were associated with major malformations.

‡ Included multiple pregnancies and two pregnancy terminations for major congenital malformations and two for chromosomal abnormalities. Classified chromosomal abnormalities as major malformations. Database included 328 fetuses of ≥24 w or ≥500 g, plus the terminations.

§ Included deliveries ≥24 w (28 sets of twins) and three pregnancy terminations for severe malformations. Serious adverse outcomes included major and minor malformations detected in first week of life, plus perinatal mortality (26 stillbirths and 12 neonatal deaths in first week of life).

‖ Singleton pregnancies. Adverse outcomes included major malformations, perinatal mortality, miscarriages, and ectopic and molar pregnancies; rate of adverse outcomes was 5.9% (4/68) when contraception was discontinued after an optimal A1c level was achieved.

¶ Overall, 4.9% major congenital malformations in the diabetic women versus 0.86% for normal Italian pregnancies.

\# Percentages are based on the number of liveborn plus stillbirths as denominators, excluding 25 miscarriages in the prepregnancy care group and 36 in the no prepregnancy care group. Miscarriage defined as spontaneous pregnancy loss prior to 20 w. Apparently, there were no pregnancy terminations.

** Excluded 28 miscarriages defined as spontaneous termination of pregnancy before 24 w and one elective termination of pregnancy in the prepregnancy care group, and 71 miscarriages and 16 elective terminations of pregnancy in the group without prepregnancy care.

†† Denominators for serious adverse outcomes include deliveries after 20 w, plus nine early pregnancy terminations for congenital malformation in the no prepregnancy care group. In the latter group, there were six stillbirths and three neonatal deaths compared to only one stillbirth in the prepregnancy care group. Numerators represent malformations (top row) and serious adverse outcomes (bottom row), defined as malformation with or without termination of pregnancy, stillbirth, or neonatal death.

‡‡ Included singleton delivered pregnancies (excluded miscarriages and pregnancy terminations). Adverse pregnancy outcomes in women of both types of diabetes included major congenital malformations and perinatal deaths.

§§ Of 1,201 pregnancies with relevant data, 19.9% had "adequate pregnancy preparation, defined as preconception folic acid and first trimester A1c <7% (<53 mmol/mol). [overall] Serious adverse outcome rates (major malformation and perinatal mortality) were 55/1,000 and had not improved since 2002–2003."

‖‖ Included all singleton pregnancies resulting in live birth, stillbirth ≥24 w, late fetal loss (20–23 w), or termination of pregnancy following prenatal diagnosis of a fetal anomaly (any gestation). Denominators different for nonchromosomal congenital anomaly outcomes (pooled types of diabetes) due to cases with missing data. Adjusted relationship for use of folic acid (unadjOR 2.03, 95% CI 1.26–3.29) was not significant due to relation to periconception A1c (adjOR 1.30, 95% CI 1.18–1.43). Overall, relative risk of nonchromosomal major congenital anomalies was 7.2%; relative risk 3.8 (95% CI 3.2–4.5) for women with diabetes compared to pregnancies without diabetes (1.9% anomalies).

SOURCE: References are listed within the table.

in 220 second pregnancies, especially in those with adverse outcomes in the first pregnancy (102); the rate of major congenital anomalies was actually higher in second (9.5%) than first pregnancies (6.4%). Previous adverse outcome was not associated with preparation for the following pregnancy (102). In a survey of the largest health plan in Israel, despite a country-wide emphasis on the value of preconception care of diabetes, 49% of diabetic women becoming pregnant in 2008–2011 had a periconception A1c at the goal of <7.0%, only 45% used folic acid, and 13.9% continued the use of potentially teratogenic drugs in the first trimester (103).

In three regions of England, documented prepregnancy "advice" was provided to about half of 1,381 diabetic pregnancies in 2007–2008 (retrospective audit) (Table 5.6) (98). Only 19.9% of 1,201 pregnancies with first trimester glycemic control data were considered to be adequately prepared for pregnancy with both preconception folic acid use and first trimester A1c <7.0%. The only independent predictor of increased risk of serious adverse outcomes (major malformations or perinatal death) was first trimester glycemic control (adjusted odds ratio [OR] per 1% increase in A1c 1.38, 95% CI 1.21–1.57). The optimal A1c was considered to be <6.1% (<43 mmol/mol) during the first trimester to avoid adverse outcomes (98).

The A1c level of <6.1% is slightly lower than the statement by the ADA that "the quantity and consistency of data are convincing and support the recommendation to optimize glycemic control prior to conception, with A1c <6.5% associated with the lowest risk of congenital anomalies" (40). The official recommendation from the U.K. National Institute for Health and Care Excellence (NICE) is to try to achieve A1c <6.5% before pregnancy and to delay pregnancy if A1c exceeds 10% (86 mmol/mol) (42).

Evaluation of standardized A1c assays in normal pregnancy shows a decline of the reference ranges to 4.1%–4.5% (5th percentile; 21–26 mmol/mol) up to 5.7%–5.9% (95th percentile; 39–41 mmol/mol) by 14 weeks normal gestation (104,105,106). This may reflect the increased red cell turnover during pregnancy rather than ambient glycemia *per se*. Dutch (100) and Danish (105) investigators reported that first trimester standardized A1c levels >6.0%–7.0% (>42–53 mmol/mol) were linearly associated with serious adverse pregnancy outcomes.

Studies show that women with type 2 diabetes are less likely to use preconception care than women with type 1 diabetes (Table 5.6) (89,92,96,97,99,101,107). In a multicenter survey in West Ireland, 44% of 215 women with type 1 diabetes attended prepregnancy care and 65% used folic acid prior to pregnancy (presumably between 2007 and 2014) compared to 34% and 55% of 108 women with type 2 diabetes, respectively (108). It was notable that prepregnancy folic acid use was only 47% in 447 control women with type 1 diabetes and 43% in 213 controls with type 2 diabetes (108). A composite of major congenital malformations and stillbirths remained higher in fetuses of women with each type of diabetes compared to matched controls for each group (108). In the southeast region of Poland during 1999–2009, an intensive diabetes management program before pregnancy was utilized by 41.1% of 345 women with type 1 diabetes compared to 31.4% of 70 women with type 2 diabetes (109). Pregnancy planning produced significantly lower A1c levels in the first trimester for both groups, but the proportion of women achieving the goal was not provided (109).

The low utilization of preconception care in women with type 2 diabetes is problematic, because most studies report that these women have a similar excess risk of malformations related to hyperglycemia before and during organogenesis as women with type 1 diabetes (99,107,108, 109,110,111,112,113,114). In an analysis of 62,013 repetitive pregnancies in Utah, total congenital anomalies were not signficantly higher than controls (4.5%) in 458 women who developed mostly type 2 diabetes before the second pregnancy (6.3%) compared to 7.7% in 802 women with pregestational diabetes in the previous and current pregnancy (115). In a study of treatment of type 2 diabetes in youth in the United States, among 452 enrolled female participants, 46 (10.2%) had at least one pregnancy, despite reinforcement of the need for contraception (116). Of 39 liveborn infants, 8 (20.5%) had a major congenital anomaly (116).

Thus, the rising tide of type 2 diabetes in women of reproductive age contributes to the prevalence of birth defects, as does the global increase in type 1 diabetes. The fact that many cases of type 2 diabetes are unrecognized before pregnancy magnifies the problem. For this reason, medical organizations (42,117,118) recommend that some form of testing for hyperglycemia should be routinely included in early prenatal laboratory testing in populations with a high prevalence of diabetes.

Potential Confounders of the Relation of Preconception Glycemic Control to Major Malformations

Aside from preconception care and glycemic control, other possible predictors of congenital malformations include diabetic vascular disease (71,99), hypertension and its treatment (119,120,121,122,123,124), alcohol use and smoking cigarettes (125,126,127,128), and obesity (71,129,130,131,132,133,134). Ideal studies of diabetes, birth defects, and preconception management of hyperglycemia account for these possible risk factors.

Perhaps the strongest associations are with moderate-to-severe obesity and congenital heart defects (131,132,133,134). U.S. population-based, case-control studies examined the interaction between obesity and diabetes, showing obesity to be an independent risk factor (132,133,134). Whether obesity is additive with hyperglycemia needs further study in diabetic women (see the section *Major Congenital Malformations* for reference to epidemiologic studies of

possible diabetes-obesity gene interactions and malformations). Other studies found no modification by folic acid use of the association between obesity and congenital heart defects (133) or spina bifida, although it is expected that the combination of obesity and low folate intake is additive (135).

Investigators agree that finding associations of malformations with folic acid is more difficult to establish in the era of universal additives to grains in the United States and Canada. Studying the concept that use of multivitamin supplements containing folic acid will reduce rates of congenital anomalies in general (136) and diabetes-associated birth defects in particular (137,138) is limited by small numbers of women with preexisting diabetes and no measure of hyperglycemia in national case-control studies of birth defects (135,138). Within the limitations, the combination of maternal diabetes and low periconceptional intake (<400 mcg/day) of folic acid seemed to be associated with the highest risk (135,138). There are no randomized controlled trials of periconception use of folic acid in diabetic women.

Epidemiologic studies showing an influence of periconception nutrient intake (139,140,141,142) and subtle maternal metabolic changes (143,144) on an increased risk of specific congenital malformations in the general population should be applied to surveys of diabetic women. Preconception care of diabetes may improve maternal nutrient intake and contribute to its benefit, but experimental studies show a direct teratogenic effect of glucose on various malformations (145,146). Possible interactive effects of hyperglycemia and its molecular mechanisms, obesity, and intake of nutrients on congenital malformations should be investigated in diabetic women.

Few cohort studies of preconception care of diabetic women have included data on periconception use of multivitamins, folic acid, antioxidants, aspirin, or medications commonly used in diabetes (statins (147,148,149); angiotensin converting enzyme-inhibitors (150); angiotensin receptor blockers (151)). Fortunately, there is no strong evidence that aspirins, standard antihyperglycemic medications, or insulins, including analogues, are teratogenic (71,152). In sum, use of statins (153,154,155) and antihypertensive drugs during early pregnancy remains controversial (42,117,156,157,158,159,160), but the data reviewed do not seem to challenge current guidelines, suggesting caution.

Although no large studies have been conducted on structural birth defects associated with oral contraception that was continued during early unintended or unrecognized pregnancy in diabetic women, there are mostly reassuring general data from the National Birth Defects Prevention Study (161). This multisite, case-control study included mothers of 9,986 infants with 32 types of defects and 4,000 infants without birth defects. The only significant associations with oral contraceptive use during the first 3 months of pregnancy were for hypoplastic left heart syndrome (adjusted OR 2.3, 95% CI 1.3–4.3) and gastroschisis (adjusted OR 1.8, 95% CI 1.3–2.7). However, confounders such as undiagnosed diabetes, BMI, age, and lack of folate were incompletely adjusted for, and it is unclear whether the relatively low amounts of exogenous hormones were responsible for malformations. The authors also reviewed previous studies and concluded that women who use oral contraceptives during early pregnancy have no increased risk for most types of major congenital malformations (161).

Contraception for Diabetic Women

Given inadequate glycemic control and suboptimal nutrition in many diabetic women of reproductive age, effective use of contraception is important in preconception care. This concept needs to be emphasized in primary as well as diabetes specialist care, because survey research indicates that 37%–51% of all pregnancies are unplanned or unintended, including those in diabetic women (26,65,86). Despite promulgation of guidelines on use of contraceptive methods that are safe for diabetic women (162,163,164,165,166,167), utilization of contraception by diabetic women has been low compared to nondiabetic women, at all age ranges (65,66,67,68,69,70,168).

In a cohort of 452 female youth with type 2 diabetes enrolled in a multicenter randomized controlled trial of treatment options, with special attention paid to avoidance of pregnancy, 46 youth (10.2%) had 63 pregnancies (116). “Despite continued emphasis on adequate contraception, only 4.8% of the pregnant participants reported using contraception prior to pregnancy” (116). Pregnancy outcome was poor in 53 remaining pregnancies after excluding seven pregnancies that were electively terminated and three with no data. The rate of other pregnancy loss was 12 of 53 (22.6%), plus two stillbirths. Of 39 liveborn infants, 15.4% were delivered preterm, and 20.5% had a major congenital anomaly (116).

Using an analysis model based on outpatient visit data on nonpregnant women age 14–44 years collected in the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Care Survey for 1997–2000, investigators estimated an adjusted odds ratio of 0.42 (95% CI 0.21–0.82) for receipt of contraceptive counseling at ambulatory visits for diabetic women (918 visits) compared to nondiabetic women (22,064 visits) (66). Others analyzed the responses of 5,955 participants age 20–44 years in the 2002 National Survey for Family Growth to examine contraceptive practices among diabetic women and obese women (26). An unadjusted odds ratio of 2.61 (95% CI 1.22–5.58) was estimated for contraception *nonuse* in 75 diabetic women who were sexually active and not sterilized (vs. 4,394 controls) (26). After adjustment for eight relevant factors in the latter study (26), the odds ratio for contraception nonuse declined to 1.94 (95% CI 0.81–4.19).

Studies of barrier methods of contraception in diabetic women are limited. In the 2002 National Survey for Family Growth, barrier methods were used by 11.1% of 135 diabetic women and 15.8% of 5,820

controls; hormone-based methods were used by 15.3% of diabetic women and 26.4% of controls (26). Table 5.7 shows the proportion of 8,182 diabetic women in the age groups 15–24, 25–34, and 35–44 years receiving contraceptive counseling, prescriptions, or services in 2006–2007 in Northern California (68). Types of contraception are categorized in the table (excluding condoms). In the youngest and oldest age groups, more than 50% of diabetic women received no contraceptive prescriptions or counseling (68).

TABLE 5.7. Proportion of Nonpregnant Women With Diabetes Receiving Contraceptive Counseling, Prescriptions, or Services, or Not, Between January 2006 and June 2007, by Age, Kaiser Permanente Northern California Managed Care System

ACTIVITY	PERCENT			
		Age (Years)		
	Total (N=8,182)	15–24 (N=716)	25–34 (N=1,678)	35–44 (N=5,788)
Highly effective	20.6	1.5	14.0	24.8
Hysterectomy	5.5	0.1	1.4	7.4
Tubal and transcervical sterilization	9.4	0.6	5.8	11.6
Intrauterine method	5.6	0.8	6.7	5.8
Subdermal implant	0.05	0	0.1	0.03
Moderately effective	16.5	32.6	26.5	11.6
Injectable	3.1	5.5	3.9	2.6
Pill, patch, or ring	13.4	27.1	22.6	9.0
Less effective	0.6	1.3	1.1	0.4
Cervical caps, diaphragms	0.2	0	0.2	0.2
Emergency contraception	0.4	1.3	0.9	0.2
Counseling without prescriptions	10.3	13.3	16.9	8.0
No contraceptive prescriptions, no counseling	52.2	51.4	41.5	55.3

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The reasons for low utilization of contraception are complex (26,68,69,169,170, 171,172,173,174). There is a disconnect in the minds of many diabetic adolescents and women between no desire for pregnancy soon and the chance of an unintended or unplanned pregnancy (175). It is proposed that focusing on desire for pregnancy will better predict family planning practices and effective preconception care than "intendedness" of pregnancy (26,175,176), although this is yet to be demonstrated in diabetes populations. For example, a national BRFSS study of the lack of relation between intending pregnancy within 12 months and improving health-related behaviors in sexually active women age 18–44 years, included 530 women with self-reported diabetes, 69 (13%) of whom intended pregnancy within 1 year (177). However, no subanalysis was done to determine how many of this subgroup were smoking less tobacco, drinking less alcohol, using folic acid, or considering contraception in relation to glycemic control.

Regarding safety of contraceptive methods, use of preparations containing oral estrogens is not advised for diabetic women with vascular risk factors, including obesity and/or hypertension (162), due to increased risk of thromboembolism (178). A Danish historical cohort study of 1,626,158 female subjects included nonpregnant diabetic women age 15–49 years with no history of cardiovascular disease or cancer, who were followed for 15 years, during 1995–2009 (178). Use of hormonal contraception, clinical endpoints, and potential confounders were obtained from national registries. Medical risk factors were identified by the use of medications to treat those conditions (i.e., diabetes, heart arrhythmia, hypertension, and hyperlipidemia) (178). Study of the diabetic women yielded 123,264 person-years for analysis. In the diabetic group, there were 151 thrombotic strokes per 100,000 person-years (adjusted RR 2.73 compared to no exposure, 95% CI 2.32–3.22) and 129 myocardial infarctions per 100,000 person-years (adjusted RR 4.66, 95% CI 3.88–5.61) (178). The relative risks were adjusted for the other positive risk factors of hypertension, hyperlipidemia, and smoking. Among these, diabetes had the highest independent risk; no risk engine was developed for women with more than one risk factor (178).

In separate analyses of the total population, the number of person-years was fairly evenly distributed among seven age groups from 15–19 to 45–49 years, but the risks of both thrombotic stroke and myocardial infarction rose progressively with increasing age (178). Analysis of risk by type of contraceptive showed significant risk with combined oral contraceptive preparations, with increasing relative risk for myocardial infarction with increased doses of ethinyl estradiol ($p<0.001$ for trend), but no increased risk of arterial thrombosis with progestin-only pills. There was increased risk of thrombotic stroke with the vaginal ring (adjusted RR 2.49, 95% CI 1.41–4.41), but not for myocardial infarction. Use of the contraceptive patch had a small number of person-years (178).

Two earlier case-control studies found increased risk of ischemic stroke (179) and myocardial infarction (180) in diabetic women, and the latter study showed more increased risk of myocardial infarction in diabetic women exposed to oral contraception (180). The dilemma persists of a small absolute risk seen in a large population versus the responsibility for a potential risk in an individual patient. Potential length of exposure to a contraceptive method must also be considered. In a sample of 987 privately insured women of reproductive age in Pennsylvania who were sexually active but not intending pregnancy for 1 year, 130 women had a medical contraindication to estrogen-containing contraceptive use, including diabetes with complications (181). High use of combined hormonal contraceptives was reported among these women (39%). The authors concluded that "processes need to be improved to ensure that women with medical

contraindications to estrogen-containing contraception are being offered the safest and most effective methods, including long acting reversible contraceptives, such as intrauterine devices and the contraceptive implant" (181).

Regarding renal disease, the finding that oral contraception use was associated with microalbuminuria in nondiabetic women (182,183) was confirmed in a 20-year follow-up study of 114 women with type 1 diabetes in Denmark (184). None of the patients had microalbuminuria at baseline, but macroalbuminuria developed in 18% of 33 oral contraceptive users compared to 2% of 81 nonusers. After adjustment for known risk factors, oral contraception use remained a predictor for the development of macroalbuminuria (RR 8.90, 95% CI 1.79–44.4). The findings might be related to the well-known effect of oral contraceptives stimulating the renin-angiotensin-aldosterone system (184,185), but the association needs to be studied in large cohorts. Combined hormonal contraception with a transdermal patch did not stimulate the renin-angiotensin system in healthy premenopausal women, presumably related to lack of first-pass hepatic metabolism with the patch (185). This could be a fruitful area for research in diabetic women.

Regarding hormonal contraceptive use among women with known dyslipidemias, a systematic review of only three articles meeting inclusion criteria concluded that the limited data from poor-quality case-control or cohort studies suggested that such women may be at increased risk for myocardial infarction and may experience a minimally increased risk for cerebrovascular accidents or venous thromboembolism (186). Additional rigorous research is needed to assess true associations.

There are many factors potentially affecting contraceptive use in women with diabetes. A meta-analysis of seven North American clinical trials on the effect of obesity on the effectiveness of oral contraceptives in the general population suggested a 44% higher pregnancy rate during combined oral contraceptive use for obese women after adjusting for age and race (187). Studies also have examined the lack of use of contraception in women prescribed potentially teratogenic medications (188,189,190). The possible benefit of hormonal contraception to diabetic women, e.g., reduction of risk of some types of cancers, has not been well studied.

In summary, the focus of preconception care for diabetic women should be provision of effective and safe contraception (and multivitamins with folic acid) until all high-risk conditions are brought under control as well as possible (40), including hyperglycemia, hypertension, albuminuria/renal function, retinopathy, depression (53,191,192), eating disorders (193,194,195), gastropathy, and hyperlipidemia.

PREVALENCE OF PREEXISTING DIABETES DURING PREGNANCY

The true prevalence of preexisting diabetes (type 1 and type 2) during pregnancy cannot be obtained from an analysis of most birth or hospital records, since they usually do not include spontaneous and induced abortions prior to 20 weeks gestation (196). Further, until about 2000, birth certificates included gestational diabetes in the category of glucose intolerance during pregnancy. Even with "established diabetes" separated from "gestational diabetes" since 2003 (197), birth certificate data tend to underreport preexisting diabetes mellitus, whether used for prevalence or linkage to complications of pregnancy (198,199,200,201,202). Coding from hospital discharge data yields a higher sensitivity for preexisting or established diabetes in pregnancy, although it usually includes only deliveries beyond 20 weeks gestation (198,199,200,201,202) and may not include stillbirths. Linkage of birth and death certificates to hospital discharge data will improve the reporting of diabetes in pregnancy and its complications (198,200,202,203,204,205). However, it is recognized that clinical coding on hospital discharges may be incomplete (201).

Investigators have used birth certificates (196,206), integration of diabetes registries with pregnancy registries (206,207), audits of a regional perinatal database (206,207,208,209,210,211), regional (202,203,212,213,214) or national (215,216,217,218,219) delivery hospitalization records, primary care databases (220), insurance claims databases (54,221), or postpregnancy questionnaires/telephone interviews (22,23) to estimate changes in the prevalence of preexisting diabetes mellitus in pregnancy since the 1990s. Ontario, Canada, has a useful system that links "the delivering mother to her newborn where each record corresponds to a mother-child pair" (91). Hospital discharge records were then linked to a provincial diabetes database and to an outpatient health services database to obtain the data for a prominent study of prevalence, services, and outcomes (91). Analyses linking the California birth certificate registry to statewide hospital discharge data and death certificate data achieved similar results (203,204).

Large studies of diabetes prevalence (n/100 births) in pregnancy in the United States are summarized in Table 5.8 and for Canada in Table 5.9. The methods of data acquisition are presented in the footnotes to the tables. The age-adjusted prevalence of total preexisting diabetes mellitus in pregnancy in the 2000s ranged between 0.65% and 1.83% in the United States (206,207,213,216,217,218). The variance could be explained by differences in methods of data collection and in BMI, ethnic/racial mix, years of study, and region. All national studies found the highest prevalence of total preexisting diabetes in pregnancy in the South (including West Virginia) (54,216,217,218). Arizona, California, Hawaii, and Oregon are other regions with higher prevalence

TABLE 5.8. Increase in Prevalence in Pregnancy of Type 1 Diabetes, Type 2 Diabetes, or Total Preexisting Diabetes Mellitus, Population-Based Studies, United States, 1994–2014

REGION (REF.)	YEARS	NUMBER OF CASES	PERCENT (n/100) OF TOTAL BIRTHS		
			Total PDM (95% CI or SEM)	Type 1 Diabetes	Type 2 Diabetes
United States (217)*	1993 2009	NR 36,851	0.62 0.90 (0.83–0.98)		
United States (216)†	1994 1999 2004	217,777 for all years 1994–2004	0.33 0.47 0.75	0.24 0.31 0.33	0.09 0.16 0.42
United States (218)‡	2000 2010	13,217 18,168	0.65 0.89		
United States (54)§	2004–2011	11,261 births and miscarriages	1.34	0.13	1.21
California (213)‖	2001 2007	22,331 for all years 2001–2007	0.69 0.86		
Southern California (206)¶	1999 2002 2005	245 births 377 births 537 births	0.81 (0.02) 1.25 (0.02) 1.83 (0.03)		
Northern California (207)#	2000–2002 2006–2008 2012–2014	663 births 895 births 1,152 births	0.65 (0.60–0.71) 0.98 (0.92–1.04) 1.06 (1.00–1.13)	0.13 (0.11–0.16) 0.20 (0.18–0.23) 0.24 (0.21–0.27)	0.49 (0.45–0.54) 0.73 (0.68–0.79) 0.78 (0.73–0.83)

CI, confidence interval; DRG, Diabetes-Related Group; HCUP, Healthcare Cost and Utilization Project; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; NIS, National Inpatient Sample; NR, not reported; PDM, preexisting diabetes mellitus in pregnancy; PGDM, pregestational diabetes mellitus; SEM, standard error of the mean; w, weeks gestation.

* Age-standardized prevalence per 100 deliveries in the NIS, in states participating in the HCUP, women age 15–44 years; hospital delivery discharges were identified using DRG codes; PDM was identified using ICD-9-CM codes (648.0x).

† Age-specific rate per 100 deliveries in the NIS, hospital discharges, ICD-9 codes (250.xx). All results were weighted estimates representing the total number of delivery hospitalizations from 1994 to 2004 in the United States. Unspecified diabetes represented 3.6% of all discharge records with a code for diabetes compared to 7% for type 1 diabetes, 4.7% for type 2 diabetes, and 84.7% for gestational diabetes. The sampling frame for the NIS was different for 1994.

‡ Age-adjusted prevalence among deliveries in 19 states, Agency for Healthcare Research and Quality State Inpatient Databases, HCUP. Hospital delivery discharges were identified using DRG codes; PDM was identified using ICD-9-CM codes (648.0x, 250.xx, or 249.xx).

§ Crude prevalence of preexisting type 1 or type 2 diabetes determined by ICD-9 codes (250.xx) prior to start date of pregnancy; patients with unclear diagnosis were excluded. Includes miscarriages up to 24 w and all births with claims to commercial insurance companies (Truven Health MarketScan database); 839,792 participants were enrolled >20 months prior to delivery date. Includes women age 18–45 years. Mothers linked to infants were identified by an ICD-9 birth code by a unique "family" identifier indicating enrollment under the same plan, relationship status of dependent, and year of child's birth. Miscarriage rate was higher with type 2 diabetes.

‖ Statewide delivery discharges using ICD-9-CM codes (648.0x) from the California Office of Statewide Health Planning and Development; age-adjusted prevalence of PGDM (n/100 births); ages 15–54 years included; subjects missing age or race/ethnicity data were excluded.

¶ Age-adjusted prevalence (n/100 births >19 w; SEM) of preexisting diabetes within the Kaiser Permanente Southern California system of hospitals. Data from diabetes and pregnancy database and birth certificates. Total 209,287 singleton pregnancies ending in livebirths or stillbirths in 1999–2005; repeat pregnancies included.

Age-adjusted prevalence (n/100 births; >19 w; 95% CI) of PGDM using perinatal and diabetes databases (99% sensitivity based on chart review validation), excluding gestational diabetes; deliveries beyond 19 w, in the Kaiser Permanente Northern California system of 13 hospitals. There were 5,222 PGDM births in 1996–2014 (type 1: 1,250; type 2: 3,972); 34 cases with unknown classification were excluded. There were 322,035 total deliveries in the time periods in the table. Unclassified type of diabetes was at 0.01% in each time epoch.

SOURCE: References are listed within the table.

(Nevada, New Mexico, and Texas were not reported) (206,207,218).

Two studies (207,216) included separate data on the rise in prevalence of both type 1 diabetes and type 2 diabetes in pregnancy over 14- and 10-year periods, respectively (Table 5.8). In an analysis based on hospital discharges in the National Inpatient Sample, the age-adjusted prevalence of type 1 diabetes in pregnancy rose from 0.24% in 1994 to 0.33% in 2004 and for type 2 diabetes the rise was from 0.09% in 1994 to 0.42% in 2004. However, there was a fairly high rate of unclassified cases in this study (Table 5.8) (216). In the KPNC system, the age-adjusted prevalence of type 1 diabetes in pregnancy rose from 0.13% in 2000–2002 to 0.24% in 2012–2014. The rise for type 2 diabetes was from 0.49% in 2000–2002 to 0.78% in 2012–2014 (Table 5.8). The rise in crude prevalence was similar (data not shown) (207). In a more detailed analysis of the same database, there was an apparent reduction in age-adjusted prevalence of type 1 diabetes in pregnancy in Northern California in 2012–2014 (0.24%, 95% CI 0.21%–0.27%) compared to 2009–2011 (0.29%, 95% CI 0.25%–0.32%) that contributed to an apparent leveling of the age-adjusted prevalence of overall pregestational diabetes mellitus after 2008 in that region (207). For the 1% of KPNC pregnant women who had preexisting diabetes identified at delivery in 2007–2011, 66.2% were obese compared to 53.4% in 1996–2000 (208).

In a retrospective claims analysis of a commercial insurance database from all regions of the United States in 2004–2011, the crude prevalence of type 2 diabetes in pregnancy was far higher (1.21%) than for type 1 diabetes in pregnancy (0.13%) (Table 5.8) (54). This is the only study in which miscarriages were included, with a higher rate for women with type 2 diabetes (25.2%). The relatively low rate of type 1 diabetes might be due to exclusion of some women from commercial insurance plans prior to 2010. In this analysis, there was a rise in the

TABLE 5.9. Prevalence in Pregnancy of Type 1 Diabetes, Type 2 Diabetes, or Total Preexisting Diabetes Mellitus, Population-Based Studies, Canada, 1996–2013

REGION (REF.)	YEARS	NUMBER OF BIRTHS	PERCENT (n/100) OF TOTAL BIRTHS		
			Total PDM	Type 1 Diabetes	Type 2 Diabetes
Canada (219)*	2002–2003	Total: >2.8 million live births	0.46	0.27	0.19
	2012–2013	>22 w or >500 g	0.75	0.28	0.47
Alberta, Canada (214)†	2005	Total: 41,166 births PDM: 292	0.74 (0.65–0.82)		
	2011	Total: 49,894 PDM: 407	0.83 (0.75–0.91)		
Ontario, Canada (91,212)‡	1996–1998	Total: 1,109,605 PDM: 13,278	0.81		
	1999–2001		1.01		
	2002–2003		1.22		
	2004–2006		1.41		
	2007–2009		1.51		
Ontario, Canada (210)§	2005–2006	Total deliveries: 120,604 Type 1 diabetes: 904 Type 2 diabetes: 516 ≥20 w		0.75	0.43

ICD-9/10, International Classification of Diseases, Ninth/Tenth Revision; PDM, preexisting diabetes mellitus in pregnancy; w, weeks gestation.

* National delivery discharge data (excluding Quebec); mother-infant records were linked; ICD-10 codes were used for type 1 and type 2 diabetes.

† Based on the Alberta Vital Statistics Birth File, all singleton and twin pregnancies that resulted in live births or stillbirths ≥20 w or ≥500 g were included. Women were identified as having PDM based on the Alberta Diabetes Database. Age-standardized rates (95% confidence interval).

‡ Used unique codes in the Canadian Institute for Health Information Discharge Abstract Database to link the delivering mother to her newborn where each record corresponds to a mother-child pair; women with pregestational diabetes were confirmed by diagnosis >280 days prior to the delivery date in the Ontario Diabetes Database, based on nonlaboratory administrative health claims.

§ Study included 3,188 women with gestational diabetes; delivery data were extracted from the Ontario Niday Perinatal Database with data entry by nursing staff at 72 hospitals with unique codes used; classification may be suspect because women with type 2 diabetes did not demonstrate an association with an increased risk of fetal macrosomia, congenital malformations (only 344 of 516 delivering women with type 2 diabetes had data on congenital malformations), or stillbirth.

SOURCE: References are listed within the table.

prevalence of type 2 diabetes in pregnancy from 2005 to 2009, with apparent stabilization in 2010 and 2011 (54).

The crude prevalence of undifferentiated preexisting diabetes in pregnancy rose from 0.81% in 1996–1998 to 1.51% in 2007–2009 in Ontario, Canada (Table 5.9) (91,212). Age-adjusted prevalence of pregestational diabetes was also 1.5% in 2010 (91). The age-standardized prevalence of pregestational diabetes was lower in Alberta, Canada, with a slight rise from 2005 (0.74%) to 2011 (0.83%) (Table 5.9) (214). In a national study of hospital discharges after all live births in Canada (excluding Quebec), the crude prevalence of type 1 diabetes remained the same between 2002–2003 and 2012–2013 (0.27% and 0.28%, respectively), but the prevalence of type 2 diabetes rose from 0.19% to 0.47% over the same years. The overall prevalence of preexisting diabetes in pregnancy in Canada (excluding Quebec) was 0.75% in 2012–2013 (Table 5.9) (219).

Statewide deliveries in California were analyzed in three separate studies, using ICD-9 codes. The frequency of deliveries of women with preexisting diabetes was 0.78% in 2006 (4,151 cases among 532,088 singleton, nonanomalous deliveries) (203) and 0.82% in 2001–2007 (of 29,089 cases among >3.5 million deliveries, excluding 6,758 due to missing age or race/ethnicity data, as well as ages <15 and ≥55 years) (213). A similar statewide analysis of 1,850,951 singleton, nonanomalous births between 24 and 42 weeks in California in 2005–2008 yielded 13,241 cases of preexisting diabetes mellitus for a crude prevalence of 0.72% (204). The higher prevalences (Tables 5.8 and 5.9) in Ontario, Canada (212), the Kaiser Permanente Southern California (KPSC) system (206), and KPNC (207) might be due to use of diabetes and pregnancy databases, in addition to birth certificates and hospital discharge data, or to population differences.

Based on all of these studies, one could expect about 1% of pregnant women to have preexisting diabetes during pregnancy in most regions of the United States.

As noted in the section *Prevalence of Diabetes in Women of Childbearing Age*, the PRAMS conducted postpregnancy interviews with women giving live birth and asked whether they had been told of diabetes before pregnancy. During 2004, 26 reporting areas collected data and achieved overall weighted response rates of >70%; these data represented 52% of all live births in the United States (22). The PRAMS did not distinguish between type 1 and type 2 diabetes. The overall prevalence of preconception diabetes was estimated to be 1.8% (95% CI 1.6%–2.0%) in women having live births. The prevalence of preconception diabetes in women grouped by age, race/ethnicity, and health insurance status is presented in Table 5.2 (22).

An updated PRAMS questionnaire and telephone survey of 40,388 postpregnancy respondents in 2009 revealed a preconception prevalence of type 1 or type 2 diabetes of 2.1% (95% CI 1.9%–2.4%) (23). The distribution of cases by maternal age and by race/ethnicity is given in Table 5.3. Some values seem to be increased compared to the PRAMS 2004 data. It is interesting that the frequency of preexisting diabetes was highest by self-report after pregnancy

than by other data acquisition methods used at the end of pregnancy.

An example of the increase in prevalence of pregestational diabetes in pregnancy between 1995 and 2012 in U.K. general practice (98% usage by the population) is provided by an analysis of 301,794 single pregnancies (one pregnancy randomly selected per woman) registered in The Health Improvement Network (THIN) primary care database (220). THIN is an electronic database representing 587 U.K. general practices, in which the physicians enter data, with added information from prescription codes, secondary referrals, and hospital discharges (220). Cases among pregnant women age >15 years were identified using diagnostic codes and prescriptions. The crude prevalence of type 1 diabetes increased from 0.16% to 0.41% between 1995 and 2012, a 162% increase over 17 years. For type 2 diabetes, the increase in prevalence was greater, from 0.23% in 1995 to 0.51% in 2008, then to 1.06% by 2012, an overall increase of 354%. The rate of type 2 diabetes increased sharply after 2008. The majority of women with both types of diabetes were overweight and of nonwhite ethnicity in assessments prior to pregnancy.

Another survey based on a regional perinatal database in the North of England found an increase in the crude prevalence (n/100) of pregnancies (births and miscarriages and early terminations) of women with pregestational diabetes from 0.31% in 1996–1998 to 0.37% in 1999–2001 and 0.47% in 2002–2004 (chi-square test for linear trend, p<0.0001) (209). There was a modest increase in type 1 diabetes from 0.29% in 1996–1998 to 0.33% in 1999–2001 and 0.35% in 2002–2004 (p=0.0244). There was a larger increase in type 2 diabetes from 0.02% in 1996–1998 to 0.04% in 1999–2001 and 0.12% in 2002–2004 (p<0.0001) (209).

Regarding variance by maternal age, in the analysis of delivery hospitalizations obtained from the National Inpatient Sample in 1994, 1999, and 2004, the rates of type 1 and type 2 increased in all age groups, with the highest prevalence rates of both types of diabetes in delivering women age ≥35 years (Table 5.10) (216). The authors could not rule out an improvement in reporting quality over time or increases in obesity "as partial explanations for the temporal increases" (216). Significant predictors of having a diabetes code at delivery included urban versus rural location (adjusted OR 1.40, 95% CI 1.31–1.51, for type 1 diabetes; adjusted OR 1.39, 95% CI 1.26–1.54, for type 2 diabetes), as well as Medicaid/Medicare versus other payment sources (adjusted OR 1.30, 95% CI 1.25–1.36, for type 1 diabetes; adjusted OR 1.94, 95% CI 1.81–2.08, for type 2 diabetes) (216). It was noted that studies of the performance of hospital discharge codes to identify diabetes in obstetric discharge data reported high positive predictive values (96%) and moderate sensitivity (64%) (197,198,199,200,201).

The number of cases at delivery and crude prevalence of preexisting diabetes mellitus by maternal age group in large U.S. surveys conducted during 1993–2010, as well as a new analysis of NVSS 2009 data conducted for *Diabetes in America*, are presented in Table 5.11 (12,23,215,217,218). In all studies from different years, the frequency of preexisting diabetes mellitus or of type 1 and type 2 diabetes increased by age. In the analysis of the National Inpatient Sample (delivery-related hospital discharges) for 2008–2010 (12,628,746 births), preexisting diabetes was coded in 0.9% of women who delivered age <35 years, in 2.1% of women age 35–44 years, and in 3.1% of women age ≥45 years (215). Among the 134,356 women with preexisting diabetes who delivered, 28.4% were age 35–44 years, and 0.55% were age ≥45 years. These rates are significantly higher than in nondiabetic women (215). The risks of many acute cardiac and pulmonary complications that threaten life increase significantly above age 35 years, and especially above age 45 years, although the absolute risks are low.

Table 5.12 presents preexisting diabetes prevalence data from southern (KPSC) (206) and northern (KPNC) California (208) by maternal age in different time periods (1999–2005 for KPSC; 1996–2011 for KPNC). In southern California, the biggest increase in prevalence during

TABLE 5.10. Number of Cases and Crude Prevalence of Type 1 or Type 2 Diabetes in Pregnancy, by Maternal Age, U.S. Hospital Discharges, 1994–2004

YEARS, MATERNAL AGE (YEARS)	TYPE 1 DIABETES		TYPE 2 DIABETES	
	Cases*	Percent	Cases*	Percent
1994–2004				
All ages	130,300		87,477	
15–24	32,813		14,026	
25–34	71,570		48,248	
≥35	25,917		25,203	
1994				
15–24		0.17		0.05
25–34		0.27		0.09
≥35		0.36		0.24
1999				
15–24		0.23		0.07
25–34		0.34		0.18
≥35		0.41		0.34
2004				
15–24		0.24		0.18
25–34		0.35		0.45
≥35		0.45		0.84

* Total of 43,121,708 hospital discharges estimated based on a national stratified sample of 8,724,814 delivery hospitalization discharge records; diabetes data include an estimated 65,095 records with unspecified diabetes codes and estimated 1,863,746 records with gestational diabetes codes (not listed here).

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TABLE 5.11. Number of Cases and Prevalence of Preexisting Diabetes Mellitus in Pregnancy by Maternal Age, U.S. National Studies, 1993–2010

YEARS (REF.)	MATERNAL AGE (YEARS)	NUMBER OF DELIVERIES		PERCENT (95% CI)
		Total	PDM	
2009 (12)*	All ages	2,689,578	17,784	0.66
	15–24	931,323	3,475	0.37
	25–29	763,190	4,599	0.60
	30–34	617,591	5,067	0.82
	≥35	377,474	4,643	1.23
2009 (23)†	All ages	40,388	848	2.1 (1.9–2.4)
	18–24			1.8 (1.4–2.2)
	25–34			2.0 (1.7–2.4)
	35–44			3.4 (2.7–4.2)
2009 (217)‡	All ages	4,097,012	36,851	0.90 (0.83–0.98)
	15–19	411,342	1,327	0.32 (0.28–0.38)
	20–24	993,554	5,469	0.55 (0.49–0.61)
	25–29	1,149,066	9,352	0.81 (0.74–0.89)
	30–34	953,452	10,811	1.13 (1.03–1.25)
	35–39	481,795	7,690	1.60 (1.42–1.80)
	40–44	107,804	2,203	2.04 (1.76–2.38)
2008–2010 (215)§	<35	10,768,536	95,515	0.89
	35–44	1,836,403	38,107	2.08
	≥45	23,807	734	3.08
2000–2010 (218)‖		NR	2000 / 2010	2000 / 2010
	All ages		13,217 / 18,168	0.65 / 0.89
	15–19			0.29 / 0.41
	20–24			0.44 / 0.56
	25–29			0.63 / 0.83
	30–34			0.78 / 1.06
	35–39			1.07 / 1.57
	40–44			1.55 / 2.14

CI, confidence interval; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; NIS, National Inpatient Sample; NR, not reported; PDM, preexisting diabetes mellitus in pregnancy.

* New analysis of National Vital Statistics System 2009 data for all ages conducted for *Diabetes in America, 3rd edition*.

† Estimated prevalence of women having a live birth who before their most recent pregnancy had ever been told by a health care provider that they had type 1 or type 2 diabetes; Pregnancy Risk Assessment Monitoring System (PRAMS), CDC; 29 reporting areas in 2009.

‡ Age-standardized prevalence, based on delivery-related hospital discharges in the NIS, Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality. Identification of PDM was based on ICD-9-CM codes (648.0x) for type 1 or type 2 diabetes or nongestational diabetes. Weighted prevalence estimates were based on the NIS sampling design.

§ Delivery-related hospital discharges in the NIS, Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality. Identification of PDM was based on ICD-9-CM codes (249.x, 250.x, 648.0x) for type 1 or type 2 diabetes or nongestational diabetes. Weighted crude prevalence estimates were based on the NIS sampling design.

‖ Estimates of prevalence of prepregnancy diabetes were age-standardized to the 2000 population of deliveries (n/100). Delivery-related hospital discharges for 19 states in the NIS, Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality. Identification of PDM was based on ICD-9-CM codes (648.0x, 250.xx, or 249.xx) for type 1 or type 2 diabetes or nongestational diabetes. Data were reported for each year from 2000 through 2010. Annual change is significant ($p<0.01$) for all states.

SOURCE: References are listed within the table.

1999–2005 seemed to be in the age groups 30–34 and 35–39 years; the prevalence at age ≥35 years also doubled during 1996–2000 to 2007–2011 in northern California (Table 5.12). These increases probably correlate with the greater increase in type 2 diabetes and obesity in older women. In an analysis of >3.5 million deliveries in California in 2001–2007 using hospital discharge data with complete information, prevalence of preexisting diabetes also varied with maternal age: 0.42% at age 20–24 years, 0.94% at age 30–34 years, and 2.41% at age 41–44 years (213).

One large national analysis of prevalence of preexisting diabetes and outcomes comes from South Korea (221), as an example of similar studies from Asia in the time frame of the reports from North America. All South Koreans use a national health insurance system, and an analysis of health claims in 2010–2012 showed 1,282,498 women age 15–49 years giving birth, of whom 32,207 were coded by ICD-10 as having preexisting diabetes (2.5%) (221). If there was more than one birth in the 3-year time period, only the first was counted. The high rate of diabetes did not change significantly in the years 2010, 2011, or 2012. Stratified by maternal age group, the rate of preexisting diabetes (10,072 cases) per 100 total deliveries (n=380,431) in South Korea in 2012 was 0.8 at age 15–20 years, 1.6 at age 21–30 years, 3.0 at age 31–40 years, and 6.6 at age 41–49 years (221).

Regarding disparities by race/ethnicity in the United States, data analyzed for *Diabetes in America* on the frequency of preexisting diabetes from birth certificates are presented in Table 5.13, according to maternal age grouping in each race/ethnicity category (NVSS) (12). In 2009, crude prevalences of preexisting diabetes mellitus in descending order were 1.72% in American Indians/Alaska Natives, 0.88% in non-Hispanic blacks, 0.66% in all Hispanics, 0.61% in Asians or Pacific Islanders, and 0.60% in non-Hispanic whites. Table 5.14 shows the distribution of preexisting diabetes by age group, race/ethnicity, and Hispanic origin (NVSS) (12). In comparison to these birth certificate data, much higher prevalences of preexisting diabetes were estimated for the three largest ethnic groups (2.7% for black, 1.8% for Hispanic, 2.0% for white) participating in the PRAMS 2009 postpregnancy survey (Table 5.3) (23).

More data on the prevalence of preexisting diabetes in pregnancy by race/ethnicity groups in United States regions are presented in Table 5.15. In an analysis of 3,556,567 deliveries in California in 2001–2007 using hospital discharge data, the age-adjusted prevalences of preexisting diabetes mellitus varied by ethnicity: 0.64% for Caucasian deliveries (reference rate), 1.23% for black (adjusted OR 1.65, 95% CI 1.56–1.76), 0.92% for Hispanic (adjusted OR 1.67, 95% CI 1.63–1.75), 0.66% for Asian/Pacific Islander (adjusted OR 1.0, 95% CI 0.94–1.05), and 1.65% for Native American (adjusted OR 2.35, 95% CI 1.82–3.04; data not shown in Table 5.15) (213).

Similar racial/ethnic prevalences of preexisting diabetes mellitus in pregnancy were reported in the PRAMS 2009 (29 reporting areas) (23) and the State Inpatient Databases (19 states pooled) in 2000 and 2010 (218) (Table 5.15). Lower frequencies of preexisting diabetes mellitus were found for non-Hispanic black pregnant women (0.5%) and non-Hispanic white pregnant women (0.3%) in Florida in 2004–2007 in an analysis using birth certificates linked to hospital discharge records; the authors discussed the reasons for low sensitivities and underestimation of prevalence (202). Much higher frequencies were seen in the southern California KPSC data for the same racial/ethnic groups as above in similar time periods (Table 5.15), probably reflecting the population of that seven-county region and the use of confidential health plan databases plus birth certificates (206). The age-adjusted prevalence of preexisting diabetes in each major ethnic group in the northern California KPNC data set of 322,035 women who delivered in 2000–2002, 2006–2008, and 2012–2014 is also presented in Table 5.15 (207). By 2012–2014, the highest rates for preexisting diabetes were seen in delivering non-Hispanic black women (1.41%) and Hispanic women (1.63%).

The age-adjusted prevalence of type 1 and type 2 diabetes separately in each major race-ethnicity group in the KPNC northern California data set of women (207) is presented in Table 5.16. The prevalence of both types of diabetes increased over time in all racial/ethnic groups, except for type 1 diabetes among 122,930 delivering Asian American women. The prevalence of type 2 diabetes greatly exceeded that for type 1 diabetes in each group and all time periods except in non-Hispanic whites, where the prevalence of type 1 diabetes became similar to that for type 2 diabetes by 2009–2011 and 2012–2014 (207).

Simulated estimates for the U.S. age-adjusted prevalence of preexisting diabetes in pregnancy for the years 1980, 1990, 2000, and 2008 were made for non-Hispanic blacks and non-Hispanic whites, using South Carolina birth certificate and hospital discharge data for 2004–2008 (205). Live births were recorded for women age 14–44 years. The data were adjusted for the U.S. population based on NHANES BMI estimates by age and race, as well as U.S. Census and National Center for Health Statistics natality and age distributions. The estimated prevalence of preexisting diabetes rose from 1.7% in non-Hispanic blacks in

TABLE 5.12. Number of Cases and Prevalence of Preexisting Diabetes in Pregnancy, by Maternal Age, California, 1996–2011

REGION (REF.)	YEARS	MATERNAL AGE (YEARS)	DELIVERIES		PERCENT
			Total	PDM	
Southern California (206)*	1999	All ages	32,089	245	0.76
		20–24			0.36
		25–29			0.59
		30–34			0.95
		35–39			1.39
	2001	All ages	29,980	315	1.05
		20–24			0.41
		25–29			0.85
		30–34			1.23
		35–39			1.87
	2003	All ages	29,598	451	1.52
		20–24			0.66
		25–29			1.19
		30–34			1.83
		35–39			2.61
	2005	All ages	28,231	537	1.90
		20–24			0.72
		25–29			1.29
		30–34			2.36
		35–39			3.43
Northern California (208)†	All years	All ages	540,591‡	4,080§	0.75
		15–24	123,017	436	0.35
		25–29	152,650	823	0.54
		30–34	157,145	1,339	0.85
		≥35	107,779	1,482	1.38
	1996–2000	All ages	156,326	801	0.51
		15–24	42,363	120	0.28
		25–29	44,363	187	0.42
		30–34	42,216	252	0.60
		≥35	27,384	242	0.88
	2001–2006	All ages	206,149	1,499	0.73
		15–24	47,188	178	0.38
		25–29	58,092	288	0.50
		30–34	59,726	486	0.81
		≥35	41,143	547	1.33
	2007–2011	All ages	178,116	1,780	1.00
		15–24	33,466	138	0.41
		25–29	50,195	348	0.69
		30–34	55,203	601	1.09
		≥35	39,252	693	1.77

Singleton deliveries of ≥20 weeks (liveborn and stillborn) in all Kaiser Permanente hospitals in southern or northern California. Cases were identified from clinical databases and birth certificates. ICD-9, International Classification of Diseases, Ninth Revision; PDM, preexisting diabetes mellitus in pregnancy.

* In the original report, all ages included brackets 13–19 years and ≥40 years, which are excluded here. Crude prevalence. Maternal age at delivery and race/ethnicity were obtained from birth certificate. Women were defined as having PDM if they met the criteria at least 270 days before delivery (ICD-9 hospital code, outpatient encounter code, glycosylated hemoglobin (A1c) >7.0%, prescription, excluded metformin with no other indicator, excluded cases with glyburide or insulin use only during pregnancy).

† Maternal age groups at delivery; maternal age obtained from electronic health records; crude prevalence.

‡ Does not include 4,096 deliveries (0.75%) in 1996–2006 with missing data.

§ Does not include 14 women with PDM (0.34%) in 1996–2006 with missing data; diabetes mellitus diagnosis before pregnancy obtained from the Kaiser Diabetes Registry.

SOURCE: References are listed within the table.

TABLE 5.13. Percent of Birth Certificates Listing Preexisting Diabetes in the Mother, by Maternal Age and Race/Ethnicity, U.S., 2009

MATERNAL RACE/ETHNICITY AND AGE (YEARS)	NUMBER OF BIRTHS		FREQUENCY OF PDM*
	Total	PDM	
Non-Hispanic white			
Total	1,398,578	8,360	0.60
15–19	102,232	297	0.29
20–29	736,322	3,737	0.51
30–39	521,623	3,897	0.75
40–44	38,259	429	1.12
Non-Hispanic black			
Total	351,907	3,114	0.88
15–19	55,895	160	0.29
20–29	200,077	1,287	0.64
30–39	88,446	1,455	1.65
40–44	7,489	212	2.83
Hispanic			
Total	759,940	4,999	0.66
15–19	105,702	187	0.18
20–29	414,897	1,992	0.48
30–39	222,711	2,478	1.11
40–44	16,630	342	2.06
Asian/Pacific Islander			
Total	160,087	980	0.61
15–19	3,308	5	†
20–29	61,633	259	0.42
30–39	88,409	634	0.72
40–44	6,737	82	1.22
American Indian/Alaska Native			
Total	19,208	331	1.72
15–19	3,167	10	†
20–29	11,280	140	1.24
30–39	4,447	165	3.71
40–44	314	16	†

Data include 28 states, New York City, and District of Columbia using the 2003 revised birth certificate. Data represent crude prevalence (cases/100 women). PDM, preexisting diabetes mellitus in pregnancy.

* Does not include spontaneous abortions or termination of pregnancy <20 weeks gestation.

† Frequency data are suppressed for <20 events.

SOURCE: National Vital Statistics System 2009 (Reference 12)

TABLE 5.14. Distribution of Maternal Age Among 17,672 Pregnant Women With Preexisting Diabetes, by Hispanic Origin and Race, U.S., 2009

RACE/ETHNICITY	PERCENT					
	Age (Years) of Mother					
	15–19 (n=658)	20–24 (n=2,804)	25–29 (n=4,573)	30–34 (n=5,033)	35–39 (n=3,530)	40–44 (n=1,074)
Total	3.7	15.8	25.9	28.5	20.0	6.1
Non-Hispanic white	3.6	17.0	27.8	28.7	17.8	5.1
Non-Hispanic black	5.2	17.2	24.0	26.8	20.0	6.8
All Hispanic	3.7	15.1	24.8	27.9	21.7	6.8
Mexican American	3.4	14.7	24.2	28.1	22.7	6.9
Puerto Rican	5.2	15.9	30.1	24.2	18.4	6.2
Cuban	3.8	12.3	21.7	35.8	19.8	6.6
Central or South American	1.2	12.7	21.7	33.7	22.4	8.3
Other Hispanic	6.4	18.4	26.7	24.1	18.3	6.1
Non-Hispanic other races	1.2	8.0	22.4	33.3	27.5	7.6

Data include 28 states, New York City, and District of Columbia using the 2003 revised birth certificate.

SOURCE: National Vital Statistics System 2009 (Reference 12)

1980 to 3.2% in 2008 and from 1.0% in non-Hispanic whites in 1980 to 1.9% in 2008 (205). Risk was assigned uniformly over time and varied only due to changes in the race/ethnicity-specific maternal age, BMI, and natality structure of the population. The authors concluded that increased maternal age and the obesity epidemic both contributed substantially to the increasing prevalence of preexisting diabetes in women delivering liveborn infants (205).

The KPSC, KPNC, statewide California, and national data sets did not include spontaneous abortions or pregnancy terminations <20 weeks gestation, so the true prevalence of preconception diabetes mellitus at the beginning of pregnancy cannot be estimated. *Large prospective studies of diabetic women from the preconception period forward are needed.* This effort might also have the effect of better linkage of general diabetes care to enhanced preconception management of diabetic women.

TABLE 5.15. Prevalence of Preexisting Diabetes Mellitus in Pregnancy, by Race/Ethnicity, U.S. Regions, 1996–2014

REGION, YEARS (REF.)	TOTAL	NUMBER WITH PDM	PERCENT (SEM OR 95% CI)				
			All	Non-Hispanic White	Non-Hispanic Black	Hispanic	Asian/ Pacific Islander
United States, 29 areas, 2009 (23)*	40,388	848	2.1 (1.9–2.4)	2.0 (1.8–2.4)	2.7 (2.1–3.5)	1.8 (1.3–2.4)	Other: 3.1 (2.2–4.2)
United States, 19 states (218)†							
2000	NR	13,217	0.65	0.56	1.01	0.74	0.59
2010	NR	18,168	0.89	0.72	1.27	0.94	0.73
California, 2001–2007 (213)‡	3,556,567	22,331‡	0.82‡	0.64 (n=6,791)	1.23 (n=1,478) OR 1.65§ (1.56–1.76)	0.92 (n=12,427) OR 1.67§ (1.63–1.75)	0.66 (n=1,574)
California, 2006 (203)‖	532,088	4,151	0.78	0.59	1.00	0.89	0.76
Southern California (206)¶							
2000	31,377	333	1.10 (0.02)	0.87 (0.02)	1.53 (0.03)	1.29 (0.02)	0.78 (0.02)
2005	28,231	537	1.83 (0.03)	1.38 (0.03)	2.77 (0.04)	1.95 (0.03)	1.73 (0.03)
Northern California (207)#							
1996–2014	655,428	5,222	0.80 (crude)				
2000–2002	102,060	663	0.65 (0.60–0.71)	0.57 (0.50–0.65)	1.24 (0.99–1.60)	0.81 (0.70–0.95)	0.45 (0.36–0.59)
2006–2008	109,200	895	0.98 (0.92–1.04)	0.77 (0.68–0.86)	1.59 (1.33–1.93)	1.26 (1.13–1.41)	0.87 (0.75–1.01)
2012–2014	110,775	1,152	1.06 (1.00–1.13)	0.80 (0.72–0.89)	1.41 (1.17–1.74)	1.63 (1.49–1.84)	0.96 (0.84–1.09)

CI, confidence interval; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; NR, not reported; OR, odds ratio; PDM, preexisting diabetes mellitus in pregnancy, including both type 1 diabetes and type 2 diabetes; SEM, standard error of the mean; w, weeks gestation.

* Estimated prevalence of women having a live birth who before their most recent pregnancy had ever been told by a health care provider that they had type 1 or type 2 diabetes; Pregnancy Risk Assessment Monitoring System (PRAMS), Centers for Disease Control and Prevention.

† Data from the Agency for Healthcare Research and Quality (AHRQ) State Inpatient Databases (SID) were used to identify maternal delivery hospital discharges involving PDM; 12 of 19 states with race/ethnicity data; age-standardized prevalence.

‡ Statewide delivery hospital discharges, age 15–55 years; demographic information and ICD-9-CM codes (648.0x for diabetes) for clinical diagnoses in the database of the California Office of Statewide Health Planning and Development. Not shown is a prevalence of 1.65% for 61 Native Americans (adjusted OR 2.35, 95% CI 1.82–3.04). Number with PDM is after exclusions for extremes of age or missing age or race/ethnicity data. Total crude prevalence is based on 29,089 cases of PDM before exclusions for extremes of age or missing age or race/ethnicity data.

§ Adjusted odds ratio of PDM versus Caucasian

‖ Statewide singleton nonanomalous births >20 w identified by linkage of birth certificates to hospital discharges (ICD-9 codes) and fetal death certificates (table does not include 126 cases of PDM among 14,953 births of "other" race/ethnicity groups); crude prevalence.

¶ Total delivery population 209,287 singleton deliveries ≥20 w (liveborn plus stillborn) in all Kaiser Permanente hospitals in southern California in 1999–2005, maternal age 13–58 years. Data obtained from clinical databases and birth certificates. Age-adjusted prevalence. Table does not include age-adjusted prevalence 0.35 in 2000 and 2.14 in 2005 for "other races," representing 1.5% of total delivery population 1999–2005. All increased prevalences over time highly significant ($p<0.0001$) by Poisson regression models.

All deliveries ≥20 w at 13 Kaiser Permanente delivery hospitals in northern California 1996–2014; PDM deliveries included 23.8% type 1 diabetes and 75.6% type 2 diabetes; 34 unclassified cases were excluded; clinically recognized diabetes mellitus before a pregnancy ascertained through the Kaiser Permanente Northern California Diabetes Registry; self-reported race/ethnicity obtained from the birth certificate; age-adjusted prevalence; in this data set, the category "All" includes 301 cases of overall pregestational diabetes classified as "Other" races or ethnicities and 58 cases with missing race/ethnicity data. In this data set, Asian means Asian American, and Pacific Islanders are in unlisted "Other" category.

SOURCE: References are listed within the table.

TABLE 5.16. Age-Adjusted Prevalence of Pregestational Type 1 and Type 2 Diabetes in Pregnancy, by Race/Ethnicity, Northern California, 1996–2014

TYPE OF DIABETES, YEARS	PERCENT (95% CONFIDENCE INTERVAL)			
	Non-Hispanic White	African American	Hispanic	Asian
Total deliveries	264,051	46,722	160,625	122,930
Type 1 (n, %)	716 (0.271)	119 (0.255)	241 (0.150)	109 (0.089)
1996–1999	0.17 (0.14–0.20)	0.23 (0.14–0.37)	0.08 (0.05–0.13)	0.11 (0.07–0.18)
2000–2002	0.17 (0.14–0.22)	0.26 (0.16–0.44)	0.09 (0.06–0.14)	0.04 (0.02–0.09)
2003–2005	0.24 (0.20–0.30)	0.38 (0.24–0.58)	0.17 (0.12–0.23)	0.11 (0.07–0.18)
2006–2008	0.28 (0.23–0.34)	0.24 (0.15–0.39)	0.16 (0.12–0.22)	0.10 (0.06–0.15)
2009–2011	0.37 (0.32–0.44)	0.37 (0.25–0.54)	0.26 (0.20–0.34)	0.13 (0.09–0.19)
2012–2014	0.36 (0.31–0.43)	0.27 (0.17–0.43)	0.16 (0.11–0.22)	0.09 (0.06–0.14)
Type 2 (n, %)	973 (0.368)	413 (0.884)	1,377 (0.857)	915 (0.744)
1996–1999	0.34 (0.29–0.39)	0.55 (0.41–0.75)	0.63 (0.54–0.75)	0.43 (0.34–0.55)
2000–2002	0.36 (0.31–0.43)	0.95 (0.72–1.25)	0.69 (0.58–0.81)	0.40 (0.31–0.52)
2003–2005	0.40 (0.34–0.47)	1.27 (0.99–1.61)	1.01 (0.88–1.16)	0.46 (0.37–0.58)
2006–2008	0.43 (0.37–0.50)	1.32 (1.07–1.62)	1.04 (0.92–1.18)	0.74 (0.62–0.87)
2009–2011	0.36 (0.31–0.43)	1.13 (0.91–1.41)	1.12 (0.99–1.26)	0.82 (0.71–0.96)
2012–2014	0.39 (0.33–0.45)	1.11 (0.88–1.39)	1.42 (1.26–1.59)	0.83 (0.71–0.95)

Data are derived from Kaiser Permanente Northern California and include deliveries at >19 weeks gestation. Race/ethnicity was self-reported on a birth certificate. Among 1,250 women with type 1 diabetes before pregnancy, 53 were categorized as "other," and 12 had no declared race/ethnicity. Among 3,972 women with type 2 diabetes before pregnancy, 248 were categorized as "other," and 46 had no declared race/ethnicity.

SOURCE: Reference 207

MATERNAL COMPLICATIONS BEFORE AND DURING PREGNANCY

MORTALITY AND SEVERE MATERNAL MORBIDITY

Maternal Mortality

In the United States, national maternal mortality assessment was enhanced by the addition of a pregnancy question (four checkboxes) to the U.S. standard death certificate in 2003 (222). WHO defines maternal death as the death of a woman during pregnancy or within 42 days after delivery when the cause is directly (obstetric complications) or indirectly related to pregnancy (preexisting disease or disease developing during pregnancy, aggravated by the physiologic effects of pregnancy). Deaths from accidental or incidental causes are excluded. In the United States, late maternal deaths are pregnancy-related deaths that occur from 43 days to 1 year after the end of pregnancy (222). Causes of death are coded according to ICD-10 since 1999, with reports filed in state vital statistics offices and subsequently compiled into the NVSS (222).

Investigators used these data from the 27 states and the District of Columbia that adopted the pregnancy question on death certificates to determine a rise in the maternal mortality ratio from 20.6 maternal deaths per 100,000 live births in 2008–2009 to 25.4 in 2013–2014 ($p<0.001$) (222). Maternal deaths are considered rare, but these ratios are much higher than in other developed countries. The rise was significant in non-Hispanic white women and, especially, in non-Hispanic black women, in women age ≥40 years (90.2% change), in women with all types of diabetes mellitus during pregnancy (80.3% change), in women with total indirect causes, and in women with late maternal causes. The maternal mortality ratios for diabetes mellitus in pregnancy were 0.5/100,000 in 2008–2009 and 1.0/100,000 in 2013–2014 (222). In 2013–2014, diabetes-related maternal deaths represented 3.7% of 907 total maternal deaths compared to 3.5% with preexisting hypertension and 8.7% with diseases of the circulatory system. Late maternal causes represented 246 additional maternal deaths (percentage with diabetes unknown). The investigators considered the potential effects of false-positive box checking on the reporting of maternal deaths (222).

Another current method to analyze maternal mortality in the United States is by using the CDC Pregnancy Mortality Surveillance System, to which 50 states, New York City, and the District of Columbia submit deidentified copies of death certificates for females age 12–55 years who died during or within 1 year of pregnancy from any cause; when available, linked birth or fetal death certificates are also sent (223). A pregnancy-related death is defined as the death of a woman during or within 1 year of pregnancy that was caused by a pregnancy complication, a chain of events initiated by pregnancy, or the aggravation of an unrelated condition by the physiologic effects of pregnancy. Coding for cause-of-death reporting is based on a system developed by the American College of Obstetricians and Gynecologists and the CDC Maternal Mortality Study Group. Of 2,009 pregnancy-related deaths in the United States in 2011–2013 (maternal mortality ratio 17.0 deaths/100,00 live births), deaths were most common in women age ≥35 years (especially ≥40 years) and non-Hispanic black women (223).

Of 1,743 women in whom the timing of death in relation to the end of pregnancy was known, 30.5% died before delivery, 16.8% on the day of delivery or pregnancy termination, 39.5% at 1–41 days postpartum, and 13.2% died on or after 42 days postpartum (223). Compared to previous years, deaths due to hemorrhage, hypertensive disorders of pregnancy, thrombotic pulmonary and amniotic fluid embolism, and anesthesia declined (sepsis was stable), but the percentage of deaths due to cardiovascular conditions, cardiomyopathy, cerebrovascular accidents, and other medical conditions (n=292) increased dramatically since 1990 (223). Maternal diabetes was not specified as a cause-of-death category, but 113 death or linked birth certificates had mention of diabetes mellitus (5.6% of total pregnancy-related deaths; 38 were in the other medical conditions category, representing 13% of that group), and 41 had mentions of gestational diabetes (personal communication from William Callaghan to JLK).

In the National Inpatient Sample of hospital discharge data for 2008–2010, of >12.6 million delivery admissions, maternal deaths at time of delivery were coded as DIED (215). The maternal death ratio was 6.3 per 100,000 deliveries for women age <35 years, 12.7 at age 35–44 years, and 58.8 at age ≥45 years (215); preexisting diabetes was present in 0.9% of women age <35 years, 2.1% of women age 35–44 years, and 3.1% of women age >45 years (215).

Analysis of the Nationwide Sample of Delivery Admissions for 1995–2008 by ICD-9 diagnostic and procedure codes (>56 million deliveries; 413,170 with pregestational diabetes; 0.73%) showed that maternal diabetes without chronic hypertension was associated with an increased risk of in-hospital mortality (OR 2.58, 95% CI 1.59–4.17, adjusted for multiple births, year of study, region, and age) (224). The adjusted odds ratio for pregestational diabetes with chronic hypertension was 6.02 (95% CI 2.71–13.40) (224).

The overall maternal mortality ratio in Finland in the 1980s was 4.7 per 100,000 (225). Among women with type 1 diabetes in Southern Finland during 1975–1997, there were five maternal deaths among 972 diabetic women (514/100,000; 100-fold increased rate) (225). Two deaths occurred in the first trimester with presumed hypoglycemia and one after a spontaneous abortion (ketoacidosis) (225). In an update of the Finnish experience with 519 consecutive pregnancies complicated by type 1 diabetes in 1999–2008, maternal mortality was not noted (226). Fatal events among mothers with type 1 diabetes were similar in the Netherlands in 1999 (100) and Italy in 1999–2003 (95). In these regional/national surveys (95,100,225), 25 maternal deaths occurred among 6,831 pregnancies complicated by preexisting diabetes, for a mortality ratio of 366 per 100,000 deliveries. Other reports of consecutive diabetic pregnancies during 1993–2004 in France (92), Denmark (93), and England (96) did not note maternal mortalities in a total of 2,330 diabetic women.

Accordingly, in other population-based surveys of diabetic pregnancies reported since 2000, no maternal deaths were recorded in three studies of a total of 2,186 patients with pregestational diabetes (Australia, Scotland, Ireland) (227,228,229). However, the Australian survey did not include pregnancies <20 weeks or after discharge from hospital (227). New analysis of KPNC data for *Diabetes in America* (208) found one maternal death recorded among 4,094 pregnancies ≥20 weeks gestation complicated by type 1 or type 2 diabetes in 1996–2011; the cause of death was pulmonary complications of anesthesia. Current estimates of the risk of maternal mortality in diabetic women in the United States will depend on national surveillance of the entire pregnancy and 42 days postpartum.

Stroke

In the National Inpatient Sample 2008–2010, the frequency of stroke occurring before or during delivery admissions was 0.03% for all women age <35 years and 0.05% for all women age 35–44 years (OR 1.87, 95% CI 1.74–2.01) (215). Regarding an association of diabetes with stroke in pregnancy, large population surveys in the United States (230) and Sweden (231) reported adjusted odds ratios of 2.5 (95% CI 1.3–4.6) and 1.7 (95% CI 0.7–3.7), respectively, for an association with maternal diabetes (including gestational diabetes). All types of diabetes in pregnancy (adjusted OR 26.8, 95% CI 3.2–∞), preeclampsia (adjusted OR 7.7, 95% CI 1.3–56), and history of migraine (adjusted OR 8.5, 95% CI 1.5–62.1) were independent risk factors for antenatal stroke (30 total cases) in the United Kingdom (nationwide Obstetric Surveillance System) (232). Overall, in this study, most cases occurred in the third trimester, and the case fatality rate was 50% for hemorrhagic stroke.

Analysis of the U.S. Nationwide Sample of Delivery Admissions for 1995–2008 based on ICD-9 diagnostic and procedure codes showed that pregestational diabetes without chronic hypertension (n=364,907) was independently associated with stroke/cerebrovascular complications (OR 1.85, 95% CI 1.41–2.44, adjusted for multiple births, year of study, insurance status, region, and age) (224). Pregestational diabetes with chronic hypertension (n=48,263) had an adjusted odds ratio for cerebrovascular complications of 7.14 (95% CI 4.90–10.40) (224). It was unclear how much of the diabetes-associated risk was associated with the significant confounders of preeclampsia and cesarean delivery (224).

Another analysis of the National Inpatient Sample for pregnancy hospitalizations in 1994–2011 based on ICD-9 diagnostic and procedure codes focused on hypertensive disorders of pregnancy and pregnancy-related strokes (233). Among 9,877 pregnancy hospitalizations with hypertensive disorders and stroke, 34.5% were classified as hemorrhagic, 34.5% as ischemic, and 31.0% as unspecified. Of the hemorrhagic strokes, 9.0% occurred in the antenatal period, 34.9% were associated with delivery, and 56.1% were recorded postpartum. Of the ischemic strokes, 24.6% were recorded at an

antenatal hospitalization, 40.9% at a delivery hospitalization, and 34.5% at a postpartum hospitalization (233).

In this study, *hemorrhagic stroke* was not associated with 222,485 cases of preexisting diabetes and a hospitalization with a hypertensive disorder of pregnancy (233). However, there were 190 cases of *ischemic stroke* among women with preexisting diabetes and a hospitalization with a hypertensive disorder of pregnancy, with an unadjusted odds ratio of 1.99 (95% CI 1.43–2.79) for the risk factor of diabetes compared to hypertensive disorder hospitalizations without diabetes (233). The crude absolute risk of ischemic stroke in diabetic women with hypertensive disorder hospitalizations was low, at 0.085% (233).

Myocardial Infarction

The National Inpatient Sample for 2000–2002 was queried for all pregnancy-related discharges. The case fatality rate was 5.1% for acute myocardial infarction (234). Using a multivariable logistic regression model, independent significant risk factors for pregnancy-related acute myocardial infarction were hypertension (adjusted OR 21.7, 95% CI 6.8–69.1), smoking (adjusted OR 8.4, 95% CI 5.4–12.9), diabetes (including gestational diabetes) (adjusted OR 3.6, 95% CI 1.5–8.3), and postpartum infection (adjusted OR 3.2, 95% CI 1.2–10.1) (234). In the National Inpatient Sample, of >12.6 million delivery admissions in 2008–2010, the rate of a history of myocardial infarction was 1 per 10,000 at maternal age <35 years, 6 per 10,000 at age 35–44 years, and 10 per 10,000 at age >45 years (215). Based on ICD-9 codes for myocardial infarction during the delivery admission, the rate was 0.2 per 10,000 at maternal age <35 years, 0.8 per 10,000 at age 35–44 years, and 5 per 10,000 at age ≥45 years. The rates of myocardial infarction were not specified for maternal medical complications, such as diabetes (215).

Diabetes mellitus was an identified risk factor for peripartum myocardial ischemia in the Canadian Hospital Morbidity database for 1970–1998 (235). In an analysis of maternal discharge records linked to death certificates in 1991–2000 in California, maternal mortality was 7.3% among women with acute myocardial infarction, and women with myocardial infarction had an increased odds of preexisting diabetes compared to women without myocardial infarction (OR 4.3, 95% CI 2.3–7.9). However, only 1 in 35,700 pregnancies was affected by an acute infarction (236).

Venous Thromboembolism

Venous thromboembolism (VTE), characterized by deep vein thrombosis (DVT) and/or pulmonary embolism (PE), is a leading cause of maternal death in the United States and developed countries (237). In the National Inpatient Sample for 2008–2010, there were 10,768,536 delivery-related discharges among women age <35 years, 1,836,403 discharges for women age 35–44 years, and 23,807 discharges for women age ≥45 years (215). Among these, the crude prevalence of DVT was 0.04% at age <35 years, 0.09% at age 35–44 years (OR 2.02, 95% CI 1.91–2.14), and 0.2% at age ≥45 years (OR 4.38, 95% CI 3.26–5.89). The crude prevalence of PE was 0.03% at age <35 years, 0.05% at age 35–44 years (OR 1.83, 95% CI 1.69–1.98), and 0.1% at age ≥45 years (OR 5.01, 95% CI 3.47–7.23). There was no analysis of VTE with pregestational diabetes, although the frequency of diabetes also increased with increasing age, as did hypertension (215).

Another analysis of pregnancy-related hospital discharges (antenatal, delivery, postnatal) in the National Inpatient Sample compared data from 2006–2009 to 1994–1997 (237). VTE diagnoses were identified by ICD-9 codes for DVT or PE. There was an upward trend in the frequency of PE with or without DVT in all pregnancy-related hospitalizations: 0.03% in 1994–1997 versus 0.07% in 2006–2009 ($p<0.001$), and the same trend was observed in antenatal, delivery, and postnatal hospitalizations. In 2006–2009, there were 12,371 cases of PE, representing 36.4% of all VTE diagnoses (237). These trends were accompanied by significant increases in the frequency of significant risk factors for VTE in multivariate analysis: anemia, obesity, heart disease, hypertension, preeclampsia, and all types of diabetes (delivery hospitalizations only for the last three risk factors). The adjusted odds ratio for diabetes (all types) as an independent risk factor for VTE was only 1.19 (95% CI 1.09–1.29). The authors speculated that increased used of computed tomographic pulmonary angiography could explain the increase in PE diagnoses (237).

By contrast, a substantially increased risk for VTE in the antepartum period up to birth for women with preexisting diabetes was observed in the THIN, a large medical practice-associated database in the United Kingdom (238). In 376,154 pregnancies resulting in livebirths or stillbirths in 1995–2009, age 15–44 years, there were eight events in the antepartum period among 4,022 women with preexisting diabetes (incidence rate ratio 3.54, 95% CI 1.13–11.0, adjusted for age, parity, BMI, mode of delivery, pregnancy length, obstetric hemorrhage, varicose veins, inflammatory bowel disease, cardiac disease, and smoking), but only four events in the 1 day to 12 week postpartum period (incidence rate ratio 0.69, 95% CI 0.25–1.85) (238).

In South Korea, the frequency of VTE identified by ICD-10 code during first pregnancies during the period 2010–2012 was 0.12% for 32,207 women with preexisting diabetes compared to 0.03% in 1,171,575 women with normal glucose tolerance (221). Using a multivariate model that adjusted for age, multiple pregnancy, hypertension prior to pregnancy, and delivery by cesarean section, preexisting diabetes was an independent risk factor for VTE (adjusted OR 3.31, 95% CI 2.35–4.64) (221).

In Sweden, a population-based study based on cross-linkage of national Inpatient and Birth Registers evaluated 1,003,489 deliveries during 1987–1995 to determine risk factors for PE, determined by ICD-9 codes (231). PE events occurred before or during the first 27 weeks

of pregnancy (148 cases), in the third trimester (29 cases), around delivery (34 cases), or from two days to six weeks after delivery (62 cases). Relative risks were modeled by use of Poisson regression. Pregestational diabetes and gestational diabetes were pooled. Among 273 cases of PE, eight were in diabetic women (crude RR 2.7, 95% CI 1.3–5.4), but the time period related to pregnancy was not stated (231). Other factors associated with PE on univariate analysis were maternal age ≥35 years (RR 1.6, 95% CI 1.1–2.2), parity ≥4 (RR 3.0, 95% CI 2.0–4.4), smoking (RR 1.4, 95% CI 1.1–1.9), severe preeclampsia (12 cases, RR 4.8, 95% CI 2.7–8.6), multiple birth (8 cases, RR 2.3, 95% CI 1.1–4.6), and cesarean delivery (92 cases, RR 3.8, 95% CI 2.0–4.9). With multivariate analysis, risks of PE were influenced by maternal age, parity, and smoking, with strong independent associations with preeclampsia, multiple birth, and cesarean section (although the majority of PE events occurred without preeclampsia or multiple birth). It was not stated whether the risk associated with diabetes became insignificant with multivariable analysis (231).

Sepsis

In the first population-based cohort study of the continuum of maternal sepsis severity in the United States, with 1,622,474 live births in California in 2005–2007, severe sepsis was recorded in 0.05% and septic shock in 0.003% (239). Among 113,211 pregnant women with preexisting diabetes, severe sepsis was recorded in 112 cases (0.10%), and septic shock was recorded in 11 cases (0.010%). Maternal diabetes (preexisting plus gestational diabetes) was independently associated with the risk of severe sepsis, including shock (adjusted for all factors studied, OR 1.47, 95% CI 1.04–2.09, p=0.014) (239). In the total population, severe sepsis/shock was the attributable cause of 11.5% of 122 maternal deaths. The maternal death frequency was 0.007% in 1,620,876 deliveries without sepsis, but was 1.770% in the group of 791 total cases of severe sepsis/shock (239). By contrast, severe infection was not more common in association with type 1 diabetes among 291,866 singleton deliveries in Finland in 2007–2011, regardless of route of delivery (240).

Using the National Inpatient Sample database for 1998–2008, investigators developed a study cohort of 5,338,995 women with hospital discharge delivery codes (241). Patients with sepsis were identified using ICD-9 codes 995.91 and 995.92; the rate of sepsis was 29.4 cases per 100,000 births (95% CI 28.0–30.9). The case fatality rate was 4.4% (95% CI 3.5%–5.6%). There was an unexplained increasing trend in incidence of maternal death by sepsis over a 6-year period between 2003 and 2008 (241). The likelihood of developing sepsis increased more than twofold in women with preexisting diabetes (adjusted OR 2.10, 95% CI 1.54–2.87). Other significant risk factors relevant to diabetes for the development of maternal sepsis included age >35 years, black race, smoking, cardiovascular disease, and delivery by cesarean section. Data on BMI were not available (241).

Less severe forms of maternal infection that might lead to sepsis have been sparsely analyzed in surveys of diabetes and pregnancy. For pregnancies that did not end in miscarriage in a national retrospective analysis of claims made to health insurance companies in 2005–2011, maternal complications coded as "infection" by ICD-9 were apparently more common in 6,665 women with type 2 diabetes (7.7%, RR 1.38, 95% CI 1.27–1.50) than in 586,875 nondiabetic controls (5.6%) (54). The rate of infection was 6.1% (nonsignificant [NS]) in 783 women with type 1 diabetes (54). Infection of the urinary tract using ICD-10 codes was recorded in 26% of claims from 32,207 women with preexisting diabetes in pregnancy (adjusted OR 1.32, 95% CI 1.28–1.35) made to the National Health Insurance System of South Korea in 2010–2012 compared to 21% in 1,171,575 pregnant women without diabetes (221). Pyelonephritis was recorded in 0.53% (adjusted OR 2.84, 95% CI 2.27–3.55) of 22,331 subjects with pregestational diabetes compared to 0.17% of subjects with gestational diabetes in the 2001–2007 California Health Discharge Database, using ICD-9 codes (213). Comparisons were not made to nondiabetic women.

Chorioamnionitis was recorded in 0.35% of 58,224 controls without diabetes in the previous or current pregnancy in Utah in 2002–2010, while it was recorded in 0.87% of 802 women with pregestational diabetes in the previous and current pregnancy (115). A test for effect size was not run due to sample size limitations. Puerperal sepsis was not more common in women with pregestational diabetes (0.12%, multivariate-adjusted OR 1.20, 95% CI 0.87–1.65) compared to 0.10% in national controls in South Korea in 2010–2012, using claims made to the National Health Insurance System based on ICD-10 codes (221). Postpartum wound infection was apparently less common in claims made for women with pregestational diabetes (2.57%, multivariate-adjusted OR 0.76, 95% CI 0.71–0.82) compared to women without diabetes (3.48%), despite a higher rate of cesarean delivery in the diabetic women (data not shown) (221).

Composite Severe Obstetric Morbidity

In order to provide more cases for analysis of risks associated with preexisting conditions and to better audit quality of maternal care, interest is increasing in measuring severe obstetric morbidity (221,227) or "near-miss" morbidity (242). In Australia, the measures for prespecified major maternal morbidity and mortality included acute renal failure, acute liver failure, disseminated intravascular coagulopathy, hysterectomy, procedures to stop bleeding, blood transfusion, shock, sepsis, admission to intensive care, or maternal death during the birth admission (227). Major morbidity was more common in 1,248 women with pregestational diabetes in 1998–2002 (7.9%, OR 3.17, 95% CI 2.56–3.92) than in 352,673 women not exposed to diabetes (2.6%). Admission to the intensive care unit (ICU) was 1.9% in pregestational diabetes mellitus (OR 9.08, 95% CI 5.89–13.89) compared to 0.2% in the controls, despite that antepartum hemorrhage (1.8%), placenta previa or

abruption (1.7%), and severe postpartum hemorrhage (0.8%) were similar in diabetic and control women (227).

In West Ireland after 2007, the frequencies of antepartum hemorrhage >23 weeks gestation (1.0% and 0%) and postpartum hemorrhage (3.1% and 4.0%) were not significantly different in 191 pregnant women with type 1 diabetes and 99 women with type 2 diabetes, respectively, than in matched controls for each diabetic group (108). The rate of postpartum hemorrhage was 2.5% in a statewide study of 22,331 women with pregestational diabetes in California, using the 2002–2007 Health Discharge Database (213). The frequency of placental abruption was 1.6% in 761 women with type 1 diabetes enrolled in a multicenter study of the prevention of preeclampsia in the United Kingdom in 2003–2008 (243). A statewide study in California in 2006 used linked Vital Statistics Birth Certificate data with Patient Discharge data and Death Certificate data and the state Fetal Death File to identify cases of pregestational diabetes with (n=433) and without (n=3,718) chronic hypertension and morbidity (203). The ICD-9 coded rate of placental abruption was 0.8% in 522,377 controls, 1.4% in nonhypertensive diabetic women, and 1.9% in diabetic women with chronic hypertension ($p<0.001$ by chi-square analysis; adjusted OR 2.2, 95% CI 1.1–4.4 for the latter group) (203).

Finally, in the analysis of claims made to the South Korea National Health Insurance Review and Assessment Service database in 2010–2012, ICD-10-coded diagnoses of maternal morbidities were compared for 32,207 delivered women with preexisting diabetes with 1,171,575 delivered women without any form of diabetes (221). Only the first delivery was included if a woman had more than one. A delivery of twins counted as one delivery. The results showed that the rates of morbidities in controls compared to women with preexisting diabetes mellitus were: acute renal complication, 0.16% versus 0.65% (adjusted OR 3.53, 95% CI 3.05–4.10); liver disorder, 4.21% versus 19.31% (adjusted OR 5.01, 95% CI 4.87–5.16); premature separation of the placenta, 0.42% versus 0.64% (adjusted OR 1.28, 95% CI 1.11–1.47); placenta previa, 1.16% versus 1.89% (adjusted OR 1.39, 95% CI 1.28–1.51); antepartum hemorrhage, 2.39% versus 3.02% (adjusted OR 1.24, 1.16–1.32); and postpartum hemorrhage, 7.3% versus 6.0% (adjusted OR 0.80, 95% CI 0.76–0.83) (221). The multivariate-adjusted model adjusted for maternal age, multiple pregnancy, and preexisting hypertension. The authors did not discuss whether ascertainment bias (more complete coding or more claims made for high-risk pregnancies) could explain the modest increases in risk for mothers with preexisting diabetes mellitus (221).

The near-miss morbidity "occurs when a pregnant or recently postpartum woman survives a life-threatening event, either by chance or because of high-quality care" (242). Diabetes was evaluated as a contributing factor in near-miss maternal morbidity in an analysis of the National Inpatient Sample during 2003–2006 of 3,463,327 deliveries (242). The authors used an administrative data definition of end-organ injury associated with length of stay >99th percentile or discharge to a second medical facility. They identified all 4,550 cases of maternal near-miss morbidity or death from admissions for delivery. Approximately 1.3 per 1,000 (95% CI 1.3–1.4) admissions for delivery qualified as near-miss morbidity/mortality; diabetes, including gestational diabetes, was a comorbidity in 10.5% of the events compared to a diabetes rate of 5.5% in women without events (adjusted OR 1.18, 95% CI 1.05–1.33) (242). However, another analysis of the National Inpatient Sample, looking at severe obstetric morbidity in the United States in 1998–2005, found that "further adjustment for payer, multiple births, diabetes, and hypertension had little effect on any results" (244). The definition of diabetes included pregestational and gestational diabetes (244).

A register-based study of 292,253 singleton deliveries in Finland in 2007–2011 included 1,754 cases of insulin-dependent diabetes (240). The incidence per 1,000 deliveries of all severe maternal complications was 15.7 with diabetes compared to 23.3 with preeclampsia. An increased risk of life-threatening severe maternal complications was associated with diabetes in elective cesarean sections compared to vaginal delivery (adjusted OR 2.2, 95% CI 1.6–2.9) and in elective cesarean sections compared to attempted vaginal delivery (adjusted OR 1.5, 95% CI 1.2–1.8). There was a high rate of elective cesarean section (41.2%) in the diabetic women, regardless of obesity (240).

GLYCEMIC CONTROL COMPLICATIONS

Diabetic Ketoacidosis

It is difficult to find U.S. epidemiologic data on the frequency of DKA in pregnancy, although the fetal mortality is high (245). In an Italian national survey of 504 pregnant women with type 1 diabetes in 1999–2003, 27 ketoacidotic episodes were reported in 5.4% of patients; no episodes were reported in 164 women with type 2 diabetes (95). In a meta-analysis of five cohort studies with data on DKA in pregnant women with type 1 and type 2 diabetes, DKA was much less common in women with type 2 diabetes (OR 0.09, 95% CI 0.02–0.34) (110). The progressive increase in insulin resistance in pregnancy adds to the risk of DKA, especially with superimposed illness. During the 193 continuing pregnancies of women who were subjects in the DCCT, DKA was not reported (6). In a meta-analysis of four small randomized controlled trials comparing treatment with continuous subcutaneous insulin infusion (CSII) versus intensive conventional insulin therapy for pregnant women with type 1 diabetes, DKA was noted in 5 of 70 (7.1%) women in the former group versus none of 73 women in the latter group (NS) (246). The numbers were skewed by the occurrence of three cases of DKA in 16 women using CSII in one trial. Of note, insulin pumps have improved since these trials were concluded.

Hypoglycemia

Insulin-induced, inadvertent severe maternal hypoglycemia (<50–60 mg/dL [<2.78–3.33 mmol/L], requiring assistance of another person for recovery) (13) is well recognized as a limiting factor in intensified treatment of type 1 diabetes in pregnancy (247). The primary risk of acute hypoglycemia is to the mother rather than fetus (40). In the Italian national survey of 504 pregnant women with type 1 diabetes delivering in 1999–2003, 14.9% of patients had 75 severe hypoglycemic episodes; two episodes were reported in two women with type 2 diabetes (95). In a meta-analysis of five randomized controlled trials of insulin delivery methods in pregnant women with type 1 diabetes, "hypoglycemic spells" (undefined) were recorded in 22.3% of 94 women using CSII and 19.2% of 88 women using intensive insulin treatment with multiple injections daily (246).

In the DCCT, the frequency of severe hypoglycemia during 135 pregnancies was 17% (23 events) in women with type 1 diabetes who were in the original intensive therapy group compared to 19.8% (35 events) in 135 pregnancies in women who were in the original conventional treatment group (NS for frequency); women in the conventional treatment group were encouraged to practice intensive therapy during pregnancy (NS) (6). It is uncertain how many of the women in the original intensive therapy group really planned their pregnancies; 12.6% of 135 pregnancies resulted in nonmedical induced abortions in the first trimester compared to zero in 52 pregnancies in women who changed to intensive therapy before conception, and 12.0% of 83 pregnancies in women who did not (6). The mean level of A1c at conception was 7.4%±1.3% in women in the intensive therapy group compared to 6.9%±1.0% in those who changed to intensive therapy before conception and 8.8%±1.7% in those who did not (p=0.0001 for the two conventional therapy subgroups) (6). For the 52 pregnancies in women who changed from conventional to intensive therapy prior to pregnancy, the frequency of severe hypoglycemia during pregnancy was 6% with seven events compared to 12% with 28 events in 83 pregnancies in women who did not initiate intensive therapy before conception (p=0.043) (6).

In general, the "frequency distribution of severe hypoglycemia is very skewed, as 10% of the pregnant women account for 60% of all recorded events" (247). Severe hypoglycemia is most frequent in early pregnancy (247), and preconception care of diabetes may or may not decrease the risk (71,73). Risk factors for severe hypoglycemia in pregnancy are type 1 diabetes, a history of severe hypoglycemia in the year preceding pregnancy, impaired hypoglycemia awareness, long duration of diabetes, low A1c in early pregnancy, greatly fluctuating plasma glucose values (<70 mg/dL [<3.89 mmol/L] and >180 mg/dL [>10.00 mmol/L]), and excessive use of supplementary insulin injections between meals (247). In a meta-analysis of only three cohort studies with data on women with type 1 and type 2 diabetes, hypoglycemic coma seemed less common in women with type 2 diabetes (OR 0.17, 95% CI 0.03–1.11, p=0.06, heterogeneity 59.3%) (110).

DIABETIC RETINOPATHY

The DIEP reported the baseline prevalence of proliferative diabetic retinopathy (PDR) to be 9.7% in 155 women with type 1 diabetes in very early pregnancy (5). Retinal fundus photographs were obtained in these patients at the onset of pregnancy and at delivery or postpartum; 189 other participants with later registration of pregnancy did not have both sets of photographs (5). Among 32 women with mild nonproliferative diabetic retinopathy (NPDR) at baseline, two developed PDR by the end of pregnancy (6.3%). Of 31 patients with moderate NPDR at baseline, nine developed PDR by the end of pregnancy (29%) (5).

Women with elevated A1c at their first presentation (before conception or within 21 days of conception) were particularly at risk for progression (5). Twenty percent of women with a baseline A1c of 6.0%–7.0% had two-step progression in retinopathy; approximately 23% of women with a baseline A1c 7.1%–8.0% (54–64 mmol/mol) had a two-step progression in retinopathy; and approximately 40% of women with higher baseline A1c levels had progression in retinopathy. Since women with high baseline A1c had drops in A1c with institution of tight glycemic control, it was unclear whether the elevated initial level or the rapid improvement in glycemic control contributed to worsening of retinopathy, or if the changes persisted beyond the immediate postpartum period (5).

Risk factors examined for progression in pregnancy in this prospective study included initial A1c, gravidity, smoking, age, duration of diabetes, blood pressure, proteinuria, and baseline severity level of retinopathy (5). Using a stepwise multivariable logistic regression model, baseline moderate NPDR (OR 5.7, 95% CI 2.1–15.7) and initial A1c ≥6 standard deviations (SD) above the control mean (OR 2.7, 95% CI 1.1–7.2) remained independent predictors of progression. For development of PDR, duration of diabetes >15 years was also predictive (5).

In the DCCT, younger women with few complications were recruited for the trial (7). Therefore, only one of 180 women who became pregnant had PDR before gestation, but 4.5% had moderate NPDR, 16.7% had mild NPDR, and 33.3% had microaneurysms at baseline. Women in both DCCT treatment groups had statistically significant progression of NPDR over the course of their pregnancies. Within a year of pregnancy, progression was observed at 51% of visits while pregnant compared with 31% of visits while not pregnant (p<0.001) in the conventional treatment group and 31% of visits while pregnant compared with 23% while not pregnant (p<0.05) in the intensive treatment group. Subanalyses suggested that risk of progression peaked during the second trimester and persisted even at 6 months postpartum. During pregnancy, eight subjects in the prepregnancy conventional treatment group (n=86) and five subjects in the intensive treatment group (n=94) developed severe retinopathy changes (7). The rate of 13 of 179

(7.3%) is similar to that in the DIEP (11 of 140, 7.9%) (5).

Women in the prepregnancy conventional treatment group of the DCCT who had a greater A1c change (higher baseline A1c before conception) had increased risk of retinopathy with pregnancy (7), also similar to the DIEP (5). At the end of the DCCT (an average of 6.5 years later), pregnancy had no lasting effect on the prevalence of retinopathy; women who had had a pregnancy had similar risk of severe NPDR to women who had not had a pregnancy in the conventional treatment group (7.1% vs. 8.1%), as well as in the intensive treatment group (2.1% vs. 1.6%) (7).

The prevalence of retinopathy during pregnancy is influenced by the diagnostic system used. In a 2009 systematic review that included 13 U.S. and non-U.S. cohort studies, the prevalence of retinopathy (stage undefined) averaged 25.3% in pregnant women with type 1 diabetes and 6.2% in pregnant women with type 2 diabetes (110). The crude prevalence of diabetic retinopathy (nonproliferative and/or proliferative) identified during pregnancy is given in Table 5.17 for prospective population-based or multicenter studies reported since 2000 (89,92,93,95,99,107,113,208,248,249).

Investigators conducting a population-based study in West Ireland in 2006–2012 (250) investigated the frequency of patients having at least two retinal evaluations during pregnancy to check for progression as recommended in clinical guidelines (40,42,117,251). Among 208 pregnant women with type 1 diabetes in this survey, 64.4% had an adequate number of retinal evaluations compared to 51.5% of 99 pregnant women with type 2 diabetes (250). Among those with adequate evaluations, some progression of retinopathy was seen in 31.3% of pregnant women with type 1 diabetes and 11.8% of pregnant women with type 2 diabetes. Among the total of 48 diabetic women with progression, 66.7% had no retinopathy at baseline (26 of 32 progressed to background retinopathy only). Six of the 48 women with progression (12.5%; 3.2% of 185 women with appropriate screening) progressed to proliferative retinopathy and required laser therapy (250). Of nine women with maculopathy at baseline, three experienced a worsening and required laser therapy. Logistic regression analysis showed that higher systolic blood pressure at the first prenatal visit (OR 1.03, 95% CI 1.01–1.06) and greater drop in A1c between first and second trimesters of pregnancy (OR 2.05, 95% CI 1.09–3.87) significantly increased the odds of retinopathy progression (250).

Further support for the guidelines comes from analysis of results at a single referral center representing a large area of Denmark (252). The prevalence of diabetic retinopathy at the initial examination was 63% in 102 pregnant women with type 1 diabetes who had a second examination at 27 weeks gestation (nine with proliferative retinopathy and 16 with macular edema). Progression by the end of pregnancy was found in 28 of the total (27%, sight-threatening in six women) (252).

In the United States, the frequency of PDR in a group of 462 women with preexisting diabetes mellitus participating in a multicenter trial was 4.5% in the 1990s (248). In a new analysis of the KPNC population in 2007–2011 (1,780 women with preexisting diabetes mellitus, 64% type 2 diabetes), 2.0% of patients were coded as PDR by the end of pregnancy compared to 7.6% for NPDR (Table 5.17) (208). Other U.S. population-based data do not exist to evaluate the prevalence or progression of diabetic retinopathy (all stages) in pregnancy, based on appropriate examinations. Rates varied widely among other countries, perhaps reflecting different time periods and intensity of screening methods, as well as local variations in treatment and small study numbers (Table 5.17).

The effects of pregnancy on retinopathy have not been widely studied among women with type 2 diabetes (92,95,99,107,110,113,253). At the Danish regional center, the prevalence of diabetic retinopathy at the first examination was 16.25% in 80 pregnant women with type 2 diabetes who had a second evaluation (moderate nonproliferative in 5% of total, macular edema in 2.5%), and there was 14% progression by the end of pregnancy (11.6% if no retinopathy at baseline). No patient progressed to proliferation (253). The aggregate of patients with type 2 diabetes listed in Table 5.17 is 1,502 (88 with some degree of retinopathy, 5.9%) and 131 have been reported elsewhere (250,253). Due to the increasing incidence and prevalence of type 2 diabetes in youth, studies should be conducted in women with type 2 diabetes of childbearing age to assess the impact of preconception treatment regimens, the optimal target for preconception A1c, and the cost-effectiveness for retinal screening prior to and later in pregnancy.

Regarding long-term effects of pregnancy on diabetic retinopathy, the lack of effect in the DCCT was noted (7). The Pittsburgh Epidemiology of Diabetes Complications Study population consisted of participants with childhood-onset diabetes, presumed to be type 1 diabetes (254). Over the 4-year study period, the prevalence of PDR, defined as a history of laser therapy or a grade of >60, was similar between women who were parous (n=80) and nulliparous (n=80) at baseline (35% vs. 36%, respectively). The incidence of PDR between women who did (n=30) and did not (n=30) conceive over the study period was 25.0% versus 9.1% (p=0.58), respectively, a worrisome difference that was not statistically significant in part due to the small size of the cohort (254). The post-pregnancy findings are similar to those of a European cohort in which 425 reproductive-age women with type 1 diabetes were followed over a period of 6–8 years. The incidence of any retinopathy was similar between the 24% of women who delivered and those who did not (255). The findings of these population-based studies are similar to the lack of development of PDR requiring laser phototherapy over 5 years after pregnancy in a smaller cohort study in England (256).

TABLE 5.17. Crude Prevalence of Diabetic Microvascular Complications With Undifferentiated Preexisting Diabetes Mellitus, Type 1 Diabetes, or Type 2 Diabetes in Pregnancy, Population-Based or Multicenter Studies, 1988–2014

REGION, YEARS (REF.)	TOTAL BIRTHS TO DIABETIC WOMEN	TYPE OF DIABETES (n or %)	NUMBER OF CASES (PERCENT)	
			Diabetic Nephropathy*	Diabetic Retinopathy†
United States, 1990s (248)‡	462	PDM	86 (18.6)§	21 (4.5)‖
Northern California (208)¶				PDR / NPDR
2001–2006	1,506	PDM (60% type 2)	102 (6.8)#	38 (2.5) / 116 (7.7)
2007–2011	1,780	PDM Type 1 (619) Type 2 (1,137)	163 (9.2)# 86 (13.9)# 75 (6.6)#	36 (2.0) / 135 (7.6)
Nova Scotia, Canada, 1988–2002 (249)**	516	PDM	6 (1.2)§	16 (3.1)‖
France, 2000–2001 (92)††	435	Type 1 (289) Type 2 (146)	34 (11.8)‡‡ 7 (4.8)‡‡	99 (34.3) 4 (2.7)
Denmark, 1993–1999 (93)§§	1,215	Type 1	78 (6.4)§	83 (6.8)‖
Italy, 1999–2003 (95)‖‖	668¶¶	Type 1 (504) Type 2 (164)	6 (1.2)## 1 (0.6)##	106 (21.0)## 2 (1.2)##
East Anglia, England, 2006–2009 (107)	682¶¶	Type 1 (408) Type 2 (274)	9 (2.2)## 7 (2.6)##	119 (29.2)## 14 (5.1)##
North England, 1996–2008 (99)***	1,677	Type 1 (1,314) Type 2 (363)	57 (4.3)## 3 (0.8)##	263/1,255 (21.0)## 16/339 (4.7)##
West Ireland, 2006–2014 (89)†††	414¶¶	PDM	44 (10.6)##	166 (40.1)##
Japan 2003–2009 (113)‡‡‡	948	Type 1 (369) Type 2 (579)	34 (9.2)‡‡ 28 (4.8)‡‡	75 (20.3) 52 (9.0)

Table includes population-based or multicenter studies using prospectively entered data reported in 2000–2014. NPDR, nonproliferative diabetic retinopathy; PDM, preexisting diabetes mellitus in pregnancy, undifferentiated between type 1 diabetes and type 2 diabetes; PDR, proliferative diabetic retinopathy; w, weeks gestation.

* Nephropathy is defined as albuminuria or proteinuria at onset of care <20 w or before pregnancy. See additional footnotes for degree of albuminuria in each survey.

† Retinopathy was diagnosed by ophthalmologic exam during pregnancy and includes NPDR plus PDR.

‡ Multicenter study, with complete data from prospective observation of pregnancy outcomes among women with PDM (singleton pregnancies) who were enrolled at 13–26 w in a trial to compare low-dose aspirin with placebo for preeclampsia prevention (no effect). Authors also state that 86 women had proteinuria at baseline, so presumably 38 women had proteinuria between 20 and 26 w.

§ Nephropathy is defined as macroalbuminuria at onset of care <20 w.

‖ Retinopathy includes PDR alone.

¶ A. Ferrara and T. Peng, unpublished data from the Kaiser Permanente of Northern California system prepared for *Diabetes in America, 3rd edition*. Multicenter assessment of 3,286 pregnancies with diabetes prior to pregnancy, proceeding >19 w (includes 174 cases with dual coding for chronic hypertension and gestational hypertension). In 2007–2011, there were 24 cases with unclassified PDM (two with diabetic nephropathy). In 2007–2011, of the 163 cases of diabetic nephropathy, 27 were associated with chronic hypertension (16.6%), 37 with diabetic retinopathy (22.7%), and 27 with preeclampsia (16.6%).

Diabetic nephropathy code (includes persistent micro-macroalbuminuria) entered at any time in 2 years prior to pregnancy to avoid miscoding due to albuminuria developing during pregnancy.

** Data from perinatal database in Halifax, Nova Scotia, Canada; deliveries >19 w at 11 hospitals in the province; included women with type 1 or type 2 diabetes before pregnancy.

†† Multicenter survey of 12 tertiary multidisciplinary centers participating in the French Diabetes and Pregnancy Study Group; prospective data collection on all singleton pregnancies ≥22 w of women with type 1 and type 2 diabetes. Progression of retinopathy during pregnancy seen in 39 women with type 1 diabetes (39.4%). Onset of nephropathy seen during early pregnancy in five women with type 1 diabetes; onset of retinopathy seen in seven women with type 1 diabetes.

‡‡ Microalbuminuria plus macroalbuminuria at onset of care <20 w.

§§ Prospective multicenter study conducted in eight Danish centers treating pregnant women with type 1 diabetes; 1,215 pregnancies >23 w in 990 women.

‖‖ Prospective multicenter study in 33 centers participating in the Italian Diabetes and Pregnancy Study Group. Included all pregnancies in women with type 1 and type 2 diabetes; data recorded in the European Quality Indicators and Data Collection Database; chronic nephropathy and retinopathy assessed at booking; progression of nephropathy during pregnancy (3.4% in type 1 diabetes; 1.2% in type 2 diabetes) or retinopathy during pregnancy (5.1% in type 1 diabetes; 1.8% in type 2 diabetes) defined as a higher stage at the last evaluation than at baseline.

¶¶ Includes early pregnancy losses <20 w, spontaneous or induced.

Uncertain definitions of nephropathy or retinopathy in the article. Authors may have referred to another source for definition.

*** Northern Diabetes and Pregnancy Survey of all singleton pregnancies ≥24 w in women with PDM diagnosed at least 6 months before pregnancy (prevalence 0.42% in the total population of 401,149 pregnancies), plus late fetal loss at 20–23 w and termination of pregnancy following prenatal diagnosis of a fetal anomaly (any gestation). Text states nephropathy (undefined) was prepregnancy. Calculations for prepregnancy retinopathy (undefined) exclude 59 cases with missing data in the type 1 diabetes group and 24 cases in the type 2 diabetes group.

††† Prospective cohort study of 414 women with PDM (65% type 1 diabetes, 35% type 2 diabetes) attending antenatal centers along the Irish Atlantic Seaboard. The 414 pregnancies include 61 miscarriages <20 w. Definitions of nephropathy and retinopathy not stated.

‡‡‡ Retrospective 40-hospital survey throughout Japan, using prospective systematic database created by the Diabetes and Pregnancy Study Group of Japan. All patients received antidiabetic therapy prior to pregnancy. Pregnancies beyond 9 w included. Definitions of nephropathy and retinopathy not stated in the article, but additional information supplied by Dr. Takashi Sugiyama, personal communication to JLK; diabetic nephropathy included microalbuminuria and macroalbuminuria, and diabetic retinopathy included NPDR and PDR.

SOURCE: References are listed within the table.

DIABETIC NEUROPATHY

Population-based data on the prevalence of diabetic neuropathy during pregnancy are sparse. No population-based data are available on the progression of neuropathy during pregnancy. In a cohort of pregnant women with preexisting diabetes delivering in East Anglia, England, in 2006–2009, diabetic neuropathy was recorded in 2.7% of 408 women with type 1 diabetes and 0.7% of 274 women with type 2 diabetes (107). Similar percentages were obtained in a prospective survey of births to women with type 1 or type 2 diabetes recorded in North England in 1996–2008 (99). The frequency of prepregnancy neuropathy was 2.1% among 1,314 women with type

1 diabetes and none of 363 women with type 2 diabetes. The presence of neuropathy was not associated with the risk of major congenital anomalies, which is a marker for glycemic control before and in early pregnancy (99). In West Ireland, the frequency of neuropathy was recorded as 2.7% in 414 women during pregnancy with preexisting diabetes in 2006–2014 (89).

Regarding the risk of developing diabetic neuropathy after a pregnancy, the EURODIAB Prospective Complications Study followed 425 women with type 1 diabetes who were childless at baseline, for a mean of 7.3 years. The incidence of neuropathy was not significantly higher in the 102 women who gave birth during follow-up compared to 323 women who remained childless (255). In the Pittsburgh Epidemiology of Diabetes Complications Study conducted in 1986–1992, prevalence of diabetic neuropathy did not differ by parity at baseline (80 women of reproductive age with type 1 diabetes who had not been pregnant compared to 80 women who had been pregnant, 47% in both groups). Among women who delivered, the incidence of neuropathy increased over the 4-year study period compared to those who did not (30 women in each group, 41.7% vs. 4.8%, p<0.001) (254). The authors noted that the difference could be due to increased surveillance in pregnancy. Neuropathy was defined as the presence of two of the following three criteria: symptoms consistent with distal symmetrical polyneuropathy, decreased or absent tendon reflexes, or signs of sensory loss. Of note, the average A1c was approximately 10%, and the prevalence of neuropathy was similar to that of the overall cohort, suggesting that pregnancy did not lead to a greater overall frequency of the already high frequency of neuropathy, although it may have accelerated its course (254). This finding deserves further investigation.

DIABETIC NEPHROPATHY

In a systematic review of 10 cohort studies of diabetic pregnancy, the prevalence of micro/macroalbuminuria averaged 6.8% in women with type 1 diabetes and 2.9% in women with type 2 diabetes (110). Microalbuminuria is defined as 30–299 mg/24 hours in the absence of urinary tract infection, and macroalbuminuria as ≥300 mg/24 hours in early pregnancy (13,40). The crude prevalence of diabetic nephropathy at the onset of care in pregnancy in prospective population-based or multicenter studies reported since 2000 is given in Table 5.17, with varying definitions of nephropathy in the different studies.

The prevalence data are skewed for overall preexisting or type 1 diabetes with low values of 1.2%–6.4% reported for Nova Scotia, Canada (249), Italy (95), Denmark (93), East Anglia, England (107), and North England (99) compared to higher values of 9.2%–18.6% reported for multicenter studies in the United States (248), Northern California in 2007–2011 (208), France (92), West Ireland (89), and Japan (113). The higher frequencies in France (11.8%) (92), Japan (9.2%) (113), and Northern California in 2007–2011 (13.9%) (208) were associated with inclusion of micro/macroalbuminuria. The multicenter trial reported in the United States in 2000 tended to recruit higher risk women (10.3%) (248). Values of diabetic nephropathy for type 2 diabetes in pregnancy (range 0.6%–6.6%) were presented for Italy (95), North England (99), East Anglia, England (107), France (92), Japan (113), and Northern California in 2007–2011 (208). Microalbuminuria was included with macroalbuminuria for the pre- or early-pregnancy prevalence in type 2 diabetes in France (4.8%) (92), Japan (4.8%), and Northern California (6.6%) (Table 5.17).

Data from referral center-based series are skewed by a higher prevalence of overt nephropathy (257,258,259). These series are valuable in demonstrating the natural history of diabetic nephropathy under treatment during and after pregnancy (260,261), but national or regional community-based U.S. data are lacking to see what happens in the population. Almost all single-center cohort series reported in 2000–2012 consist of small numbers of patients (261). All authors find high rates of the comorbidities hypertension and retinopathy in pregnant diabetic women with chronic proteinuria, who have significantly increased perinatal morbidity and mortality compared to diabetic women without nephropathy (261).

The prevalence of microalbuminuria early in pregnancy was 10% in a population survey of 846 women with type 1 diabetes in Denmark performed in 1993–1999, in the absence of antihypertensive therapy (262). Early microalbuminuria was highly predictive of later preeclampsia (adjusted OR 4.0, 95% CI 2.2–7.2). In this Danish national survey, preeclampsia developed in 41% of type 1 diabetic women with baseline microalbuminuria compared to 12% in those with normoalbuminuria (p<0.001) (262). In a 2007–2012 series from eastern Denmark, the prevalence of diabetic nephropathy (macroalbuminuria or microalbuminuria in early pregnancy) was down to 2.5% in 445 women with type 1 diabetes and 2.3% in 220 women with type 2 diabetes (260). This may reflect the reduction in overall diabetic nephropathy with general intensified care in Denmark (263,264) and elsewhere (259), as well as increased use of antihypertensive therapy before and in early pregnancy (265,266).

Progression of nephropathy during pregnancy was 67.6% in France (micro/macroalbuminuria) (92) and only 2.8% in Italy (macroalbuminuria) (95). Among women with nephropathy at conception, pregnancy has been associated with an increase in proteinuria during pregnancy and with declines in renal function persisting postpartum in some, although not all, women (254,257,258,267). Pregnancy does not appear to worsen the course of nephropathy beyond its natural course, although study numbers are small. Newer data are lacking.

Women with minimal renal disease at baseline appear to have minimal declines in renal function over pregnancy. In the DCCT, where the majority of women had no albuminuria at baseline, incident microalbuminuria was statistically similar between women who conceived

versus those who did not, regardless of randomization arm, and a low incidence for macroalbuminuria was noted (<2% in all groups) (7). These results are similar to those of larger European studies, where no association was found between pregnancy and incident microalbuminuria after pregnancy (255) or a significant decline in glomerular filtration rate (267).

HYPERTENSIVE DISORDERS

After much confusion in prior literature (159), hypertensive disorders of pregnancy have been classified by the American College of Obstetricians and Gynecologists (158) and other organizations (268,269,270,271,272) as preeclampsia-eclampsia, chronic hypertension antedating pregnancy, chronic hypertension with superimposed preeclampsia, and gestational hypertension appearing after 20 weeks gestation (158). Preeclampsia can be superimposed on chronic hypertension or chronic renal disease. All forms are more common in pregnant women with preexisting diabetes compared to women without diabetes, and they contribute in a major way to poor pregnancy outcome. Elevated blood pressure is defined as >140 mmHg systolic or >90 mmHg diastolic in a pregnant woman sitting at rest, repeated at least once, 4–6 hours apart, and severe hypertension as systolic blood pressure >160 mmHg or diastolic blood pressure >110 mmHg (158,268,269,271,272). In the United Kingdom, hypertension in pregnancy is further graded as mild (140–149/90–99 mmHg) or moderate (150–159/100–109 mmHg), with implications for treatment (270).

Preeclampsia is defined as a syndrome of hypertension and new-onset proteinuria (defined as protein excretion ≥300 mg/24 hours, a urine protein:creatinine ratio of ≥0.3 mg/dL, or least precise, ≥1 positive protein on urine dipstick) after 20 weeks gestation in previously normotensive women in most of the diabetes surveys reviewed in this chapter (Table 5.18) (273). Proteinuria is best defined with automated measurement of repeated single samples (268,269,270,271,272). Unfortunately, some investigators depend on simple urine dipstick measures of >1+ for protein in the absence of urinary infection, which lacks sensitivity (158,270). After the studies cited in Table 5.18 were conducted, the definition of preeclampsia was expanded to include end-organ damage in the unusual absence of proteinuria, including decreased platelet count, increased transaminases, and elevated creatinine (158).

Gestational hypertension is defined as new-onset hypertension ≥20 weeks gestation in a woman with previously normal blood pressure, but without the proteinuria of *preeclampsia* or the other signs of organ damage (central nervous system, cardiorespiratory, hematological, renal, hepatic, fetoplacental) associated with severe preeclampsia (158,268,269,270,271,272). In some reports, gestational hypertension has been called "pregnancy-induced

TABLE 5.18. Prevalence of Hypertensive Disorders in Pregnant Women With Type 1 or Type 2 Diabetes in Pregnancy, Population-Based or Multicenter Studies, 1985–2013

REGION, YEARS (REF.)	TOTAL PDM, GESTATIONAL AGE	TYPE OF DIABETES	NUMBER OF CASES (PERCENT OF PREGNANCIES) VERSUS (PERCENT IN CONTROLS) AND EFFECT SIZE (95% CI)		
			Chronic Hypertension	Gestational Hypertension*	Preeclampsia
United States, 1990s (248)†	462	PDM	79 (17.1)		92 (19.9)‡
United States, 1995–2008 (224)§	413,170	PDM	48,263 (11.7)		
California, 2006 (203)‖	532,088 total births Controls: 522,377 PDM total: 4,151 PDM only: 3,718 CH only: 5,560 PDM+CH: 433	PDM	433 (10.4) vs. (1.06) p<0.001		490 (11.8)¶ vs. (2.7) p<0.001 PDM only: 353 (9.5) adjOR 3.4 (3.1–3.9) PDM+CH: 137 (31.7) adjOR 12.5 (10.0–15.5)
California, 2001–2007 (213)#	22,331 births >19 w	PDM	1,794 (8.0)		1,787 (8.0)‡ Mild: 1,182 (5.3) Severe: 568 (2.5) Eclampsia: 37 (0.2)
Northern California, 2001–2011 (208)**	3,112 births >19 w	PDM	454 (14.6)	212 (6.8)	369 (11.9)
Utah, 2002–2010 (115)††	802 births	PDM	56 (7.0) vs. (0.71) p<0.0001	35 (4.4) vs. (2.2) p<0.05	38 (4.7) vs. (1.6) p<0.0001
Ontario, Canada, 2005–2006 (210)‡‡	904 >19 w 516 >19 w	Type 1 Type 2		PIH included with PET and undefined	93 (10.3) adjOR 2.8 (2.2–3.5) 43 (8.4) adjOR 1.9 (1.3–2.7)

Table 5.18 continues on the next page.

TABLE 5.18. (continued)

REGION, YEARS (REF.)	TOTAL PDM, GESTATIONAL AGE	TYPE OF DIABETES	NUMBER OF CASES (PERCENT OF PREGNANCIES) VERSUS (PERCENT IN CONTROLS) AND EFFECT SIZE (95% CI)		
			Chronic Hypertension	Gestational Hypertension*	Preeclampsia
Ontario, Canada (212)§§ 1996 2001	 1,122 births 1,532 births	 PDM PDM			 40 (3.6)¶ vs. (1.0) 63 (4.1)¶ vs. (1.1)
Nova Scotia, Canada, 1988–2002 (249)‖‖	516 births	PDM	32 (6.2) vs. (0.9) adjRR 7.12 (5.07–10.0)	Mixed with PET	142 (27.5) vs. (9.1) adjRR 3.04 (2.64–3.50)
Alberta, Canada, 2005–2011 (214)¶¶	2,485 singletons 50 twin births	PDM	281 (11.1) vs. (1.7) adjOR 5.87 (5.16–6.67)		185 (7.4)¶ vs. (1.7) adjOR 3.38 (2.88–3.97)
New South Wales, Australia, 1998–2002 (227)##	1,248 births	PDM	69 (5.5) vs. (0.5) OR 14.2 (10.9–18.3)	112 (9.0) vs. (4.2) OR 2.74 (2.24–3.35)	172 (13.8) vs. (4.4) OR 3.97 (3.36–4.69)
Netherlands, 1999 (100)***	314	Type 1			40 (12.7)‡ vs. (1.05) RR 12.1 (9.0–16.1)
Denmark, 1993–1999 (93)†††	1,218 >24 w	Type 1	59 (4.8)		220 (18.1)‡ vs. (2.6) p<0.001
Italy, 1999–2003 (95)‡‡‡	613 subjects	Type 1: 469 Type 2: 144		65 (13.9) 15 (10.4)	22 (4.7) 5 (3.5)
Sweden, 1991–2003 (276)§§§	5,089 subjects	Type 1	107 (2.1) vs. (0.24) p<0.001	81 (1.6) vs. (0.87) adjOR 1.53 (1.18–1.99)	Mild: 494 (9.7) vs. (2.0) adjOR 4.30 (3.83–4.83) Severe: 219 (4.3) vs. (0.8) adjOR 4.47 (3.77–5.31)
Sweden, 1998–2007 (277)‖‖‖	Total: 3,457 BMI (kg/m²) <25: 1,644 25–29: 1,195 ≥30: 618	Type 1	92 (2.7) vs. (0.32) p<0.001		Total: 521 (15.1)‡ vs. (2.8) 222 (13.5)‡ vs. (2.1) adjOR 7.17 (6.04–8.50) 185 (15.5)‡ vs. (3.3) adjOR 9.9 (8.6–11.4) 114 (18.4)‡ vs. (5.8) adjOR 14.2 (11.5–17.5)
West Ireland, 2007–2013 (108)¶¶¶	290 births >23 w	Type 1: 191 Type 2: 99		43 (22.5) vs. (10) p=0.0003 24 (24.2) vs. (11) p=0.014	26 (13.6)‡ vs. (4.3) p=0.0003 9 (9.1)‡ vs. (8) p=1
North United Kingdom, 2003–2008 (243)###	761 enrolled <23 w	Type 1	112 (14.7)	83 (10.9)	127 (16.7)‡
Norway, 1985–2004 (278)[A]	1,307 births	Type 1			249 (19.1) vs. (3.6) adjOR 6.0 (5.2–6.9) 47% preterm
East Anglia, England, 2006–2009 (107)[B]	323 births 220 births	Type 1 Type 2			31 (9.6)¶ 14 (6.4)¶
Helsinki, Finland (226)[C] 1999–2003 2004–2008	 175 births 313 births	 Type 1 Type 1	 4 (2.3) 18 (5.8)	 24 (13.7) 38 (12.1)	 26 (14.9)‡ 53 (16.9)‡
Japan, 2003–2009 (113)[D]	948[E] >9 w 840[F] >19 w	Type 1: 330[F] Type 2: 510[F]	12/369 (3.25)[E] 50/579 (8.6)[E]	9 (2.7)[F] 10 (2.0)[F]	32 (9.7)[F] 70 (13.7)[F]
South Korea, 2010–2012 (221)[G]	32,207	PDM	2,118 (6.6) vs. (1.04) p<0.001	957 (3.0) vs. (1.0) adjOR 1.72 (1.60–1.85)	1,263 (3.9) vs. (1.1) adjOR 2.00 (1.87–2.13) Eclampsia: 51 (0.16) vs. (0.05) adjOR 1.53 (1.14–2.07)

Table includes population-based and multicenter studies reported in 2000–2015. AdjOR or adjRR, adjusted odds or risk ratios versus nondiabetic or general pregnancy population; BMI, body mass index; CH, chronic hypertension; CI, confidence interval; GH, gestational hypertension; HELLP, hemolysis, elevated liver enzymes, low platelet count; ICD-9/10, International Classification of Diseases, Ninth/Tenth Revision; NR, not reported; NS, not statistically significant; OR, odds ratio; PDM, preexisting diabetes mellitus in pregnancy, unclassified; PET, preeclamptic toxemia; PIH, pregnancy-induced hypertension; RR, relative risk; w, weeks gestation.

* GH or PIH defined as new resting blood pressure ≥140/90 mmHg in the second half of pregnancy, without proteinuria or other signs of organ damage.

Table 5.18 continues on the next page.

TABLE 5.18. (continued)

† Multicenter study, with complete data from prospective observation of pregnancy outcomes among women with PDM (singleton pregnancies) who were enrolled at 13–26 w in a trial to compare low-dose aspirin with placebo for preeclampsia prevention (no effect). Authors also state that 86 women had proteinuria at baseline, so presumably 38 women had proteinuria between 20 and 26 w.

‡ Preeclampsia defined as GH or PIH and proteinuria ≥0.3–0.5 g/day or >1+ on a urine dipstick in the second half of pregnancy.

§ Data obtained from the National Inpatient Sample of hospital discharges (20% stratified sample of all U.S. community hospitals). Analysis included all delivery hospitalizations of women age ≥15 years with complete data. Abortions and ectopic and molar pregnancies were excluded. Diagnoses based on ICD-9 codes. CH included cases with or without comorbidities.

‖ Normally formed singleton births in linked California Vital Statistics Birth Certificate Data, California Patient Discharge Data, Vital Statistics Discharge Data, and Vital Statistics Fetal Death File in 2006. 522,377 controls without diabetes or hypertension. Diagnoses based on ICD-9 codes. Multivariable logistic regression used to estimate odds ratios versus controls and respective 95% CIs associated with pregestational diabetes with or without CH, adjusted for maternal age, race/ethnicity, insurance type at delivery, education level, parity, obesity, and renal disease.

¶ Preeclampsia was undefined in the article.

Retrospective study using health discharge data for all deliveries in California during 2001–2007, based on dataset of the Office of Statewide Health Planning. Diagnosis based on ICD-9 codes. Subjects missing age or race/ethnicity data, as well as extremes of age (<15 and >55 years), were excluded.

** A. Ferrara and T. Peng, unpublished data from the Kaiser Permanente of Northern California multicenter system prepared for *Diabetes in America, 3rd edition*. Retrospective analysis of prospectively entered data in linked perinatal and diabetes databases. 62% type 2 diabetes, 66% BMI >30 kg/m^2; 174 cases with dual coding for CH and GH were omitted.

†† Singleton births; data collected retrospectively from electronic medical records of 20 hospitals in Utah; subjects were women with at least two consecutive pregnancies with PDM in both; data from last pregnancy. Only 75.8% of subjects were coded as using insulin during the index pregnancy. Tested for differences between 58,224 controls (women without any type of diabetes in the previous and current pregnancy) using Poisson regression models with robust variance estimators.

‡‡ Deliveries >19 w entered into the Ontario Niday Perinatal Database, a branch of the provincial Perinatal Surveillance System; 72 participating hospitals; data collected by nursing staff; diagnoses extracted by codes that are unique to the database. Excess risks of each birth outcome by diabetes subtype calculated by unconditional logistic regressions, adjusted by maternal age, region of residence, smoking, parity, attendance at first trimester visit, type of antenatal provider, but not maternal comorbidities.

§§ Data from Canadian Institute for Health Information hospital discharge abstracts database linked to Ontario Diabetes Database. Included all deliveries of diabetic women entered in the Ontario Diabetes Database >270 days prior to delivery, to be sure of PDM diagnosis. Total deliveries: 133,316 in 1996; 128,745 in 2001. Gestational diabetes possibly included in the control deliveries. Diagnoses based on ICD-9 codes 642.4–642.7. CH and GH omitted because hypertension during pregnancy without preeclampsia was not specified. Adjusted odds ratios omitted due to inordinately low frequency of preeclampsia in the control population.

‖‖ Data obtained from the Nova Scotia Atlee Perinatal Database, representing 11 maternity units throughout the province (50% of deliveries at the tertiary center in Halifax), using unique standardized clinical forms. Included all pregnancies reaching 20 w and 500 g at birth. PDM included women with type 1 diabetes, type 2 diabetes using insulin before pregnancy, and type 2 diabetes not using insulin before pregnancy (excluded gestational diabetes). PIH included preeclampsia. Controls were 150,589 singleton pregnancies of nondiabetic mothers. Outcomes reaching statistical significance on univariate analysis were entered into a backward conditional regression to obtain adjusted relative risk.

¶¶ Based on the Alberta Vital Statistics Birth File, included all live births or stillbirths at ≥20 w or ≥500 g at birth. Used the Alberta Diabetes Database registry to identify women with diabetes diagnosed before conception. Used the Alberta Hypertension Database registry to define preexisting hypertension, if hypertension was diagnosed before 20 w. Used the Hospital Abstract Database to obtain preeclampsia (included eclampsia). Controls were 306,576 births without any type of diabetes (311,673, including twin gestations for risk of CH). Used multinomial logistic regression to examine the association of diabetes in pregnancy with adverse outcomes, controlling for maternal characteristics. Adjusted for mother's age, First Nation status, parity, and CH for risk of PET (singletons only). Frequency of PET was 10% in twins in mothers with PDM versus 7.4% for singletons (NS). Denominator for CH is all deliveries; denominator for PET is singleton births only.

Used linked population databases to obtain all singleton births at >20 w or >400 g (n=370,703). ICD-10 codes used for diagnoses. Pregestational diabetes (type 1, 57%; type 2, 20%; unclassified, 23%) was underreported to the databases (sensitivities 50%–95.5%). Used chi-square contingency tables to compare PDM with no diabetes, with crude odds ratios and 95% CI.

*** Survey of all practitioners in the Netherlands to identify all births ≥24 w in women with type 1 diabetes; national data for comparison n=196,981.

††† Subject data from central registry of the Danish Diabetes Association. Background data from National Danish Patient Registry 1998–2000.

‡‡‡ Prospective multicenter study at 33 sites participating in the Italian Diabetes and Pregnancy Study Group of all pregnant women with type 1 or type 2 diabetes. Data recorded in the European Quality Indicators and Data Collection Aggregated Database. N excludes abortion <180 days of gestation.

§§§ Singleton births; study based on information prospectively entered into the Swedish Medical Birth Registry; before 2008, the registry only collected data from 28 w and did not register data on earlier fetal losses or induced abortions; diagnosis based on ICD-9 and ICD-10 codes; 97% of pregnant women had an ultrasound examination to determine gestational age; severe preeclampsia defined as diastolic blood pressure >110 mmHg or proteinuria >5 g/day, or both; multivariate analysis by logistic regression limited to mothers without missing BMI data; odds ratios adjusted for group differences in maternal age, BMI, parity, chronic hypertensive disorder, smoking habits, and ethnicity. Reference population n=1,260,207 controls.

‖‖‖‖ Singleton births; study based on information prospectively entered into the Swedish Medical Birth Registry; before 2008, the registry only collected data from 28 w and did not register data on earlier fetal losses or induced abortions; diagnosis based on ICD-9 and ICD-10 codes. BMI calculated based on maternal weight and height by recall. The reference population included 764,498 singleton pregnancies to mothers without a diagnosis of diabetes. Unconditional logistic regression used to explore associations between maternal type 1 diabetes and preeclampsia, with normal weight nondiabetic women as the reference category; adjusted for ethnicity, maternal age, height, parity, smoking first trimester, and CH.

¶¶¶ Retrospective case-control study using regional electronic database with prospective data collection; singleton births; comparison with matched controls by chi-square analysis; controls >12,000 women with normal glucose tolerance; cosine similarity matching for age, BMI, ethnic group, and parity with a customized nearest neighbors selection without replacement.

Data obtained from a randomized placebo-controlled trial of vitamins C and E (no effect) for prevention of preeclampsia in women with type 1 diabetes at 25 antenatal metabolic clinics in the U.K. Subjects included 112 women with CH (14.7%), 36 women with microalbuminuria (4.7%), and four women with macroalbuminuria (0.5%) at baseline.

A Linked two nationwide registries for subject and background data (n=1,161,092; preeclampsia defined as any preeclampsia registered in the Birth Registry, including proteinuria, eclampsia, and HELLP syndrome [and possibly PIH]); used logistic regression in SPSS to estimate odds ratios adjusted for maternal age, parity, ethnic origin, marital status, educational level, year of delivery, and sex of child. For the analysis of preterm deliveries, 15 diabetic women with preeclampsia were excluded due to no registered gestational age.

B Prospective cohort study of all singleton pregnancies in women with type 1 or type 2 diabetes in East Anglia, U.K. Pregnancies with miscarriage (n=99) or termination (n=25) at <24 w were excluded from this analysis. Pregestational diabetes defined as type 1 or type 2 diabetes diagnosed at least 12 months before pregnancy. CH was unrecorded, and preeclampsia was undefined.

C Retrospective analysis of 881 consecutive subjects with a singleton live birth at Helsinki University Central Hospital, the only referral center serving a population of 1.5 million; only last pregnancy analyzed if woman had more than one birth; for hypertension analyses, subjects with diabetic nephropathy were excluded.

D Retrospective 40-hospital study throughout Japan. Additional information supplied by Dr. Takashi Sugiyama, personal communication to JLK. Denominator of births different than in published paper due to exclusion of early fetal deaths (pregnancy losses) at 10–19 w (39 for type 1 diabetes, so 330 births >19 w and 328 liveborn infants; 69 for type 2 diabetes, so 510 births >19 w and 508 liveborn infants). Denominator for CH is births >9 w.

E 948 patients included at >9 w; 369 with type 1 diabetes and 579 with type 2 diabetes. There were 108 early pregnancy losses at 10–19 w; 39 in type 1 diabetes and 69 with type 2 diabetes. Chronic hypertension classified from 10 w.

F 840 patients included at >19 w. GH and preeclampsia classified from 20 w among 330 women with type 1 diabetes and 510 women with type 2 diabetes.

G Subject (age 15–49 years, only first delivery in the 3-year period analyzed) and control (n=1,171,575) data on deliveries obtained from Health Insurance Review and Assessment Service claims database; a delivery of twins counted as one delivery; diagnoses based on ICD-10 codes; used logistic regression analysis adjusted for maternal age, multiple pregnancy, and preexisting hypertension.

SOURCE: References are listed within the table.

hypertension" (PIH), but other authors have used PIH to denote preeclampsia as well, so use of the term PIH is discouraged.

Chronic hypertension has often been defined (158,268,269,270,271,272) as requiring antihypertensive therapy or recording of diagnostic ICD codes for hypertension prior to conception in studies of pregnancies with preexisting diabetes. Lacking preconception data, some organizations make the designation of chronic hypertension if elevated blood pressure is present in the first trimester or less than 20 weeks gestation (158,270,271,272). If no pre- or early-pregnancy information is available, then hypertension diagnosed during later pregnancy that persists longer than 12 weeks postpartum may be reclassified as chronic (158), but this information is not available at the time of coding at hospital discharge and leads to further confusion between gestational and chronic hypertension.

There is uncertainty about treatment for chronic blood pressure levels <160/110 mmHg in pregnancy (158,159,160,268, 269,270,271,272,274). A retrospective analysis (excluding pregnant women with preexisting diabetes) of a U.S. multicenter study of aspirin to prevent preeclampsia showed that mild chronic hypertension is associated with impaired pregnancy outcome with diastolic blood pressure levels >90 mmHg, regardless of aspirin treatment (275). There were increasing adverse outcomes per 5 mmHg rise in diastolic, but not systolic pressure, up to the exclusion level of ≥160/110 mmHg (275). A meta-analysis of U.S. studies of chronic hypertension in pregnancy found significantly increased relative risks of superimposed preeclampsia (RR 7.7, 95% CI 5.7–10.1) and perinatal death (RR 4.2, 95% CI 2.7–6.5) compared with U.S. general population incidences from the National Vital Statistics Report 2006 (273). Randomized trials of treatment are considered inadequate to date (160,274).

Regarding treatment of chronic hypertension in women with preexisting diabetes mellitus in pregnancy, most authors include them in the group of younger patients with "possible target organ disease," especially if there is evidence of macrovascular or microvascular disease. In this case, guidelines are inconsistent. Management is recommended to keep blood pressure levels <140/90 mmHg for "complicated chronic hypertension" in pregnancy (270) or at <140/90 mmHg "with comorbid conditions" (271,272). Guidelines suggest not lowering diastolic blood pressure <80 mmHg to reduce the chance of impaired fetal growth (40,270,271,272). However, as noted, randomized trials in pregnant diabetic women are lacking. Recommendations for blood pressure targets in pregnancy and safety of antihypertensive drugs in pregnancy are noted in the extensive and freely available U.K. (270) and Canadian (271,272) guidelines.

Prevalence of Chronic Hypertension in Pregnant Women With Preexisting Diabetes

In a new analysis of NVSS 2009 data for *Diabetes in America*, 13% of pregnant women with preexisting diabetes had prepregnancy hypertension. Among 413,170 deliveries of women with pregestational diabetes in the U.S. Nationwide Sample of Delivery Admissions for 1995–2008, 11.7% were coded as having chronic hypertension (224) (Table 5.18). There was a strong trend for increasing age-adjusted prevalence of chronic hypertension with pregestational diabetes among the total delivery sample from 1995–1996 to 2007–2008 (224).

Chronic hypertension is seen in pregnant women with either type 1 diabetes (range 2.1%–14.7%) (93,113,226,243,276,277) or undifferentiated pregestational diabetes (range 5.5%–17.1%) (115,203, 213,214,221,224,227,248,249) among population-based or multicenter studies reported since 2000, as well as in new analyses for *Diabetes in America* using KPNC data (208) (Table 5.18). Regions that reported rates of chronic hypertension >10% included the United States (224,248), Northern California (208), Alberta, Canada (214), and the northern United Kingdom (243). In eight studies with a nondiabetic control group, chronic hypertension was much more common in women with preexisting diabetes (115,203, 214,221,227,249,276,277) (Table 5.18; methods given in the footnotes). Only one report gave a frequency of chronic hypertension in pregnant women with type 2 diabetes: 8.6% in Japan (113) (Table 5.18).

Meta-analysis and systematic review of six smaller cohort studies providing original data on pregnancies in both type 1 and type 2 diabetes concluded that chronic hypertension is more common in women with type 2 diabetes (11.2%) than with type 1 diabetes (5.5%) (110). The relatively high rate of coding for chronic hypertension (14.6%) in the 3,112 women with preexisting diabetes giving birth >19 weeks in 2001–2011 in the KPNC multiethnic population is possibly due to the high proportion of women with type 2 diabetes (62%) and obesity (66%) (208) (Table 5.18).

An analysis of 532,088 birth and hospital records for 2006 in California (singleton, nonanomalous deliveries) revealed 4,151 cases of preexisting diabetes (0.78%), of whom 433 also had chronic hypertension (10.4%) (203). The combination of chronic hypertension with preexisting diabetes increased the risk of stillbirth (adjusted OR 2.3, 95% CI 0.9–6.3), preeclampsia at all gestational ages (adjusted OR 4.5, 95% CI 3.5–5.8), babies who were small for gestational age and sex (adjusted OR 2.2, 95% CI 1.5–3.1), preterm delivery <37 weeks gestation (adjusted OR 2.3, 95% CI 1.8–2.9), and reduced the risk of shoulder dystocia (adjusted OR 0.2, 95% CI 0.1–0.9) compared to diabetes without hypertension (203).

The combination of pregestational diabetes with chronic hypertension also increased the risk of maternal stroke/cerebrovascular complications, acute renal failure, pulmonary edema, in-hospital mortality, stillbirth, preterm delivery, and poor fetal growth (compared to no diabetes and no chronic hypertension, and compared to diabetes without chronic hypertension) in adjusted analyses of diagnostic and procedural ICD-9 codes

in delivering patients in the U.S. National Inpatient Sample for 1995–2008 (224). Assessment of the interaction of hypertension in diabetic pregnancy with such comorbidities as obesity, microalbuminuria, and hyperlipidemia is lacking.

Gestational Hypertension

Few population-based data sets show the prevalence of gestational hypertension in diabetic women in the United States. In a new analysis of NVSS 2009 data for *Diabetes in America*, 12.2% of pregnant women with preexisting diabetes had diagnostic codes for gestational hypertension and 13.0% had prepregnancy hypertension, although distinguishing between these conditions can be difficult. Gestational hypertension was recorded in 4.4% of pregnant diabetic women in a multicenter medical record study in Utah (115), and in 6.8% of 3,112 women with preexisting diabetes and gestations >19 weeks in the KPNC system in 2001–2011 in a new analysis for the *Diabetes in America* (208) (Table 5.18). In the latter analysis, 174 pregnancies were excluded due to dual coding for chronic and gestational hypertension.

The prevalence of gestational hypertension in women with preexisting diabetes varies widely in population-based international studies, from 2.7% in Japan (type 1 diabetes) (113) to 9.0% in Australia (pregestational diabetes) (227), 13.9% in Italy (type 1 diabetes) (95), and 22.5% in West Ireland (type 1 diabetes; 24% in type 2 diabetes) (108) (Table 5.18). Five surveys with control populations showed that gestational hypertension was significantly more common in women with pregestational diabetes (115,221,227) and type 1 diabetes (108,276) than in controls (Table 5.18). Studies of nondiabetic women suggest that gestational hypertension affects perinatal outcome, but there is insufficient evidence for the benefit or risk of antihypertensive treatment (158,268,269,270,271,272).

Preeclampsia

In a new analysis for *Diabetes in America*, among 3,112 women with preeexisting diabetes mellitus (62% type 2 diabetes, 66% obesity) delivering at >19 weeks gestation in the KPNC system in 2001–2011, the frequency of primary preeclampsia was 6.6%, and the frequency of preeclampsia superimposed on chronic hypertension was 4.4%; total preeclampsia was 11.0% (208) (Table 5.18). The rate might have been higher, because dual coding for chronic hypertension and gestational hypertension was excluded. Superimposed preeclampsia was recorded in 30.4% of diabetic women with chronic hypertension (208). The overall rate of preeclampsia was 19.9% in 462 women with preexisting diabetes participating in a U.S. multicenter trial conducted 20 years earlier (17.6% if no hypertension or proteinuria at baseline; 26.3% if both hypertension and proteinuria at baseline) (248) and the rate was similar to numbers in Denmark (93), Norway (278), and the region of Helsinki, Finland (226) for women with type 1 diabetes (Table 5.18).

Results of other North American and international surveys are included in Table 5.18, with rates of preeclampsia ranging from 4.3% to 13.6% in women with type 1 diabetes (95,100,107,108,113,210,276), 3.5% to 13.7% in women with type 2 diabetes (95,107,108,113,210), and 3.6% to 13.8% in women with undifferentiated preexisting diabetes in pregnancy (115,203,212,213,214,221,227). In a large retrospective study of 532,088 singleton, nonanomalous births in California in 2006, preeclampsia occurred in 9.5% of 3,718 women with preexisting diabetes without chronic hypertension and in 31.7% of 433 women with both preexisting diabetes and chronic hypertension ($p<0.001$) (203). The effect size of preeclampsia in different gestational age brackets in preexisting diabetes with or without chronic hypertension versus women without disease was calculated in multivariable analysis (adjusted for age, race/ethnicity, insurance type, education level, parity, number of prenatal visits, obesity, and renal disease) (203). For women with preexisting diabetes alone, the adjusted odds ratio for preeclampsia <34 weeks was 1.6 (95% CI 1.1–2.4) compared to 8.9 (95% CI 5.1–15.6) in women with preexisting diabetes and chronic hypertension. Similar ratios of effect size were found for preeclampsia at 34–36 weeks and ≥37 weeks gestation (203).

Results of these studies did not always separate data for gestational hypertension. For 10 surveys of deliveries of diabetic women in Table 15.8 that did separate results for gestational hypertension, the frequencies of preeclampsia were <5% in three studies (95,115,221), 11.9%–14.0% in five studies (108,113,208,227,276), and 16.7% (243) and 16.9% (226) in two others. It is interesting that the rate of gestational hypertension was usually lower than the rate for preeclampsia, but gestational hypertension was much more frequent than preeclampsia in the reports from Italy (95) and West Ireland (108). In the 10-hospital assessment of secondary birth outcomes in Utah, the low rate of preeclampsia of 4.7% in women coded as having preexisting diabetes might be due to the exclusion of primiparity, a well-known risk factor for preeclampsia (115) (Table 5.18).

Of the surveys, nine studies included control nondiabetic or reference populations of total deliveries, and the crude relative risk or adjusted odds ratios for preeclampsia with type 1 diabetes or undifferentiated preexisting diabetes ranged from 2.8 to 3.4 in North America (203,210,214,249), from 4.3 to 12.1 in Europe (100,276,278), 4.0 in Australia (227), and 2.0 in South Korea (221) (Table 5.18). The methods for these comparisons are given in the footnotes to Table 5.18. Comparison of crude rates of preeclampsia were significantly higher in the diabetic women than controls in five other surveys (93,108,115,203,212) (Table 5.18). Three studies presented data for mild and severe preeclampsia or eclampsia: in California, in 2001–2007, 5.3% were recorded as mild preeclampsia, 2.5% as severe preeclampsia, and 0.2% as eclampsia (adjusted OR comparisons were made to gestational diabetes) (213); in Sweden, in 1991–2003, the adjusted odds ratios were 4.30 (95% CI 3.83–4.83) for mild preeclampsia and 4.47 (95% CI 3.77–5.31) for severe preeclampsia versus controls (276). The frequency of eclampsia was 0.2% in women with pregestational

diabetes in California (213) and 0.16% in South Korea (adjusted OR 1.53, 95% CI 1.14–2.07 vs. controls) (221) (Table 5.18).

Of 124 diabetic women in West Ireland who had preconception care and continuing pregnancies ≥20 weeks gestation, the frequency of preeclampsia was 10.5% compared to 12.2% (NS) in 229 diabetic women who registered for care during pregnancy (89). Of 161 KPNC mothers with diabetic nephropathy in 2007–2011 (defined by albuminuria prior to pregnancy), the frequency of superimposed preeclampsia was 16.8% (208). In four surveys comparing type 1 diabetes with type 2 diabetes in pregnancy (95,107,108,210), the frequency of preeclampsia was lower in type 2 diabetes in Canada or Europe (Table 5.18). In Japan, in 2003–2009, the frequencies of preeclampsia were 9.7% in 330 women with pregnancies proceeding >19 weeks gestation with type 1 diabetes and 13.7% in 510 women with type 2 diabetes (113). The majority of the preeclamptic women with type 2 diabetes in Japan had preceding chronic hypertension (113).

In a vastly larger group of women with preexisting diabetes in pregnancy in South Korea in 2010–2012, based on claims made to national health insurance, preeclampsia was recorded in only 3.9% of patients compared to 1.1% of controls (221). Chronic hypertension in diabetic pregnancy was coded more often in South Korea in women with undifferentiated preexisting diabetes (6.6%) (221) than in Japan for type 1 diabetes in pregnancy (3.25%), although chronic hypertension was recorded in 8.6% of women with type 2 diabetes in pregnancy in Japan (113) (Table 5.18).

Among classic risk factors for preeclampsia, including diabetes and chronic hypertension (279), there has been continuing evidence that poor glycemic control in early and later pregnancy increases the risk for preeclampsia (but not gestational hypertension) in diabetic women (262,280,281,282,283,284). Research on the mechanisms linking glycemia to preeclampsia should be productive in concert with investigation of the role of biomarker screening for prediction of severe preeclampsia, which has confirmed the excess risk of both early-onset (<34 weeks) (RR 5.2, 95% CI 2.9–9.2) and later-onset preeclampsia (RR 6.8, 95% CI 5.1–9.1) in women with pregestational diabetes (285).

Other research on possible prevention of preeclampsia has included diabetic women and is well reviewed in the freely available U.K. (270) and Canadian (271,272) guidelines on hypertensive disorders and pregnancy. Their recommendations are for prophylactic treatment of women with type 1 and type 2 diabetes with low-dose aspirin prior to 16 weeks gestation and the use of calcium supplementation in diabetic women with low calcium intake (270,272). These are management criteria to survey in future community or population-based epidemiologic studies of diabetes and pregnancy. Supplements with vitamins C and E did not reduce the frequency of preeclampsia in pregnant women with type 1 diabetes in multicenter placebo-controlled randomized trials (243,286).

FETAL COMPLICATIONS PRIOR TO DELIVERY

Definitions of and methodology for assessing gestational age, pregnancy losses, fetal deaths, and neonatal/infant deaths, as well as congenital anomalies/malformations or birth defects, have been highly variable in North America, as well as internationally. A consensus approach was published by the IADPSG (13). Gestational age is established by postmenstrual completed weeks, confirmed by ultrasound examination when possible (using ultrasound dates if >5 day discrepancy in the first trimester or >10 day discrepancy in the second trimester). Miscarriage is defined as pregnancy loss at <20 weeks. Stillbirth (fetal death) is delivery of an infant showing no signs of life at ≥20 weeks, if gestational age is known, or a weight ≥350 g, if the gestational age is not known. Late fetal death is at ≥28 weeks of gestation. Major congenital malformations include the ICD-10 codes Q00–Q99 (European Surveillance of Congenital Anomalies [EUROCAT] Guide). In addition, a major congenital abnormality requires medical or surgical treatment, has a serious adverse effect on health and development, or has significant cosmetic impact (13).

SPONTANEOUS ABORTION

Reliable data on spontaneous abortions (miscarriage; early fetal loss in some reports) require prospective evaluation from preconception to very early and later in gestation. The prospective DIEP five-center study conducted in 1980–1985 enrolled 386 women with type 1 diabetes before conception or by 21 days after conception (287). A caveat is that the willingness of diabetic subjects to enroll early for intensive glycemic monitoring meant that the DIEP did not represent the general population of women with type 1 diabetes. A major strength of the DIEP is that it is still the only prospective study that enrolled nondiabetic women as controls, also before or by 21 days after conception. Women may have been more carefully monitored as a result, with lower fetal loss rates than observed in other studies.

In the DIEP, the embryonic and early fetal loss rate <20 weeks gestation was 16.1% (62/386; including one ectopic pregnancy and one hydatidiform mole) in diabetic women compared to 16.2% (70/432; including three ectopic pregnancies) in nondiabetic controls (287). The proportion of the early pregnancy losses at 4–8 postmenstrual weeks gestation was 43.5% in diabetic women versus 52.4% in controls, 42.0% versus 37.1% at 9–12 weeks, and 14.5% versus 10% at 13–19 weeks. In the subgroup of diabetic women with poor glycemic control, the risk of pregnancy loss increased linearly with increasing glycohemoglobin levels (p=0.015). (287). In the total study group, multiple logistic regression identified only greater maternal age and nonwhite race as significant

demographic risk factors for spontaneous abortion. After adjustment for all demographic factors, the risk for spontaneous abortion remained equivalent in the diabetes and control groups.

Fasting and postprandial data from home blood glucose diaries in the DIEP confirmed the relation between elevated glucose and early pregnancy loss (287). Later analysis showed an increased risk of early fetal loss with low, as well as high, maternal glycoprotein levels (288). Considering clinical hypoglycemia, measurements <50 mg/dL "was no higher for any week in the first trimester (weeks 5 through 12) in the women who had spontaneous abortions than in those who delivered" (287). Although fasting beta-hydroxybutyrate levels were significantly higher at 6, 8, 10, and 12 weeks gestation in the diabetic than in the control women and correlated positively with fasting blood glucose, ketone levels were not increased in women suffering early fetal loss (289).

The relationship of rates of early fetal loss to measures of maternal hyperglycemia in early pregnancy was confirmed in early studies, with descriptions provided in a 1996 review (145). Another systematic review of four observational studies showed that miscarriage in type 1 and type 2 diabetes was associated with poor glycemic control (pooled OR 3.23, 95% CI 1.64–6.36) (290). In the DCCT, the rate of spontaneous abortion was 13.3% of 135 pregnancies in women with type 1 diabetes in the original intensive therapy group, 7.7% of 52 pregnancies in women who changed to intensive therapy before conception, and 12.0% of 83 pregnancies in women who did not (6). Mean A1c at conception was 7.4%±1.3%, 6.9%±1.0%, and 8.8%±1.7% in the three groups, respectively (6).

A data analysis of the outcomes of pregnancies complicated by type 1 or type 2 diabetes in the United Kingdom in the General Practice Research Database (GPRD) focused on early pregnancy losses (291). The database included 2,001 pregnancies with 669 early pregnancy losses in maternal type 1 diabetes (392 were spontaneous losses, 362 in the first trimester and 30 in the second trimester). During the pregnancies complicated by type 1 diabetes, 18.1% of pregnancies in the first trimester and 1.5% in the second trimester resulted in spontaneous abortions. During pregnancies complicated by type 2 diabetes (n=669), 19.0% of pregnancies in the first trimester and 2.1% of pregnancies in the second trimester resulted in spontaneous abortions. Induced pregnancy losses were recorded in 9.1% in the first trimester and 0.4% in the second trimester for type 1 diabetes compared to 10.3% in the first trimester and none in the second trimester for type 2 diabetes. First trimester pregnancy losses of unknown type were also recorded: 4.1% of all pregnancies for type 1 diabetes and 3.7% for type 2 diabetes (291). These rates in the GPRD are higher than previously anticipated, probably due to availability of primary care data. It is possible that poor outcomes were more likely to be reported to the database than routine outcomes.

The GPRD is useful due to inclusion of data on age, BMI, smoking status, duration of diabetes, and prescriptions for folic acid, antihyperglycemic medications, antihypertensives, and statins (291). Receiving folic acid prescriptions before pregnancy was infrequent in all groups in the GPRD, but no data were obtained on general multivitamin use (291). For type 1 diabetes, age >35 years, BMI >40 kg/m^2, and smoking were independent risk factors for early pregnancy losses, and specific prescription utilization was not. For type 2 diabetes, 31.4% of patients used only biguanides or other oral antihyperglycemic agents in the 3 months before pregnancy and the first trimester compared to 54.2% using insulin. The former group had higher pregnancy loss rates than the women using insulin, but data on A1c levels were insufficient to determine whether glycemic control was a factor (291).

Of 31 women with type 1 diabetes in this survey who were prescribed statins in the 3 months before pregnancy, 15 had pregnancy loss; of 35 women with type 2 diabetes presumably using statins before pregnancy, 16 had a pregnancy loss (291). In a subsequent report from the same group, in the GPRD, 281 pregnancies potentially exposed to statins just before or early in pregnancy were matched to 2,643 unexposed pregnancies; 48% of those exposed reported diabetes before pregnancy compared to 45% in the nonexposed (292). Spontaneous pregnancy loss occurred in 25.3% of all pregnancies exposed to a statin compared to 20.8% in those unexposed. Time to event analysis with exposure as a time-dependent covariate gave an adjusted hazard ratio (HR) of 1.64 (95% CI 1.10–2.46) of spontaneous pregnancy loss in the statin-exposed group (292). Stratifying by diagnosis gave a hazard ratio of 1.27 (95% CI 0.81–1.98) related to statin use for those with a diagnosis of diabetes versus 2.11 (95% CI 1.38–3.23) for those who did not have diabetes (292). This finding needs further investigation in diabetic women.

Although the major focus of prospective studies of preconception care of diabetes has been prevention of major congenital malformations (75), women participating in preconception care generally do not have increased rates of spontaneous abortion compared to DIEP controls (89,94,96,145,293,294).

Possible confounders of the relation between glycemic control and the risk of spontaneous abortion were evaluated in a sample of 191 pregnancies in women with type 1 diabetes in a regional center in Ohio (295). Early pregnancy smoking (OR 3.3, 95% CI 1.2–8.7) and caffeine consumption (OR 4.5, 95% CI 1.2–16.8) were associated with increased risk of spontaneous abortion when controlling for age, years since diagnosis of diabetes, previous spontaneous abortion, nephropathy, and retinopathy (295).

FETAL DEMISE (STILLBIRTH)

Unfortunately, investigators of the studies reviewed in this chapter have used different gestational age limits to determine the difference between spontaneous abortion (miscarriage; early fetal loss) and stillborn infants (20 weeks, 22 weeks, 24 weeks, 28 weeks, and even 32 weeks; the latter two

are holdovers from the past). Advances in perinatal care have progressively shifted limits of fetal viability to earlier gestational ages. Most data sets do not include data on spontaneous abortions, and many investigators are limited by historical parameters used in the creation of large public administrative databases.

As background, consider that National Center for Health Statistics fetal death and live birth data files showed U.S. population stillbirth rates for total pregnancies of at least 20 weeks gestation at 6.05 stillbirths per 1,000 deliveries in 2006 and 2012 (296). The total rates for non-Hispanic whites were 4.81 in 2006 and 4.91 in 2012; for non-Hispanic blacks, 10.73 in 2006 and 10.67 in 2012; for the Hispanic population, 5.29 in 2006 and 5.33 in 2012 (296). The authors computed gestational age-specific stillbirth rates at 20 weeks of gestation or greater. The percentage of total stillbirths was distributed as approximately 5% for each gestational age week from 23 weeks through 41 weeks, in contrast to the overwhelming proportion of live births at 37–41 weeks. "There was little change in the percent distribution of stillbirths by gestational age from 2006 to 2012. However, the percent distribution of live births by gestational age changed considerably: births at 34–38 weeks of gestation decreased by 10%–16%, and births at 39 weeks of gestation increased by 17%" (296).

The authors compared traditionally computed stillbirth rates (number of stillbirths at a given gestational age/number of live births plus stillbirths at that gestational age x 1,000) with prospective stillbirth rates by single weeks of gestation (number of stillbirths at a given gestational age/number of live births and stillbirths *at that gestational age or greater* x 1,000) (296). They concluded that the "prospective stillbirth rate is preferred for measuring stillbirth risk, because the denominator is the number of women who are pregnant, and thus at risk of stillbirth, at a given gestational age. In contrast, traditional stillbirth rates exhibit considerable volatility in the face of changes in the distribution of live births by gestational age" (296).

Among 94 women with type 1 diabetes randomized to intensive therapy in the DCCT prior to pregnancy in 1983–1993, intrauterine death occurred in five of 135 starting pregnancies (four at <20 weeks), or one of 96 pregnancies at ≥20 weeks (1.0%) (6). There was one stillbirth ≥20 weeks in 52 pregnancies of women randomized to conventional therapy but changed to intensive therapy before conception, and two in 83 pregnancies of women on conventional therapy changed to intensive therapy after pregnancy was diagnosed (6). In a landmark U.S. randomized trial of low-dose aspirin starting at 13–26 weeks gestation that included 462 women with unclassified preexisting diabetes, the stillbirth rate ≥20 weeks was 1.7% (four of eight prior to 26 weeks), and it was not affected by aspirin use (248).

A retrospective cohort study of prepregnancy risk factors compared 712 singleton antepartum stillbirths to 174,097 singleton live births at ≥23 weeks at 31 centers in the United States in 2002–2008 (297). The rate of maternal preexisting diabetes was 4.2% among 712 stillbirths compared to 1.5% among 174,097 livebirths ($p<0.0001$). The frequency of antepartum singleton stillbirth among 2,633 women with preexisting diabetes was 1.14% compared to 0.41% in the whole population (adjusted HR 2.7, 95% CI 1.8–3.9). Among many stillbirth risk factors undergoing multivariable analysis, the adjusted hazard ratios for preexisting diabetes were 3.5 (95% CI 2.0–6.1) in nulliparous births and 2.1 (95% CI 1.3–3.5) in multiparous births (297). Term stillbirth risk increased with preexisting diabetes (3.1/1,000), with chronic hypertension (1.7/1,000), with black race (1.8/1,000), and with maternal age ≥35 years (1.3/1,000)—all versus the reference rate of 0.8 per 1,000 in women with no risk factors (297).

In the National Inpatient Sample with 12,524,119 delivery records in 2008–2010, 0.41% of all sampled births in the United States had an ICD-9 code for stillbirth (298). The frequency of pregestational diabetes was 4.02% in 51,075 stillbirths compared to 1.03% in all live births ($p<0.0001$). The frequency of stillbirth was 1.57% among 130,970 women with preexisting diabetes in this study. Diabetes as an independent risk factor for stillbirth had a fully adjusted odds ratio of 3.21 (95% CI 3.06–3.38), with an adjusted odds ratio of 3.79 (95% CI 3.40–4.20) for diabetes with chronic hypertension (298).

A multisite population-based case-control study was conducted between 2006 and 2008 in 59 hospitals distributed throughout the United States by the Stillbirth Collaborative (299). Among 393 cases of stillbirth and 1,350 control deliveries, the adjusted odds ratio for risk of stillbirth independently associated with diabetes was 3.47 (95% CI 1.86–6.49). Limiting the analysis to nonanomalous singleton deliveries, which excluded 90 stillbirths, the adjusted odds ratio for diabetes as an independent risk factor for antepartum stillbirth was 3.83 (95% CI 1.93–7.60) (299). Similar risk ratios for the independent association of preexisting diabetes with stillbirth were found for New Jersey in 1997–2005 (adjusted RR 3.5, 95% CI 2.8–4.3) (300), for singleton pregnancies in Alberta, Canada, in 2005–2011 (adjusted OR 3.73, 95% CI 2.82–4.95) (214), and for the West Midlands region of England in 2009–2011 (frequency 1.4% vs. 0.4%; crude RR 3.7, 95% CI 2.0–6.9; adjusted RR 3.9, 95% CI 1.7–8.9; population attributable risk 2.0%) (301).

Population-based or multicenter surveys of birth outcomes of pregnancies with undifferentiated preexisting diabetes in the 1990s–2011 are shown in Table 5.19. The crude rates of stillbirth were 0.8%–2.1% in six studies in North America (203,208,213,214,248,249) and 0.5%–3.4% in other international studies (88,92,209,211,227,302) compared to 0.61%–3.1% in 17 surveys of women with type 1 diabetes (93,94,95,98,100,107,108, 113,114,210,229,243,276,278,303,304, 305,306), with variable inclusion of stillbirths starting at gestational ages 20–28 weeks (Table 5.20). Among five surveys of births to women with type 1 diabetes that included nondiabetic control populations, the range of adjusted risk for stillbirth was 2.3–5.0 (93,210,276,278,305) (see Table 5.20 for odds ratios or risk ratios, and the footnotes for methods of comparison). Maternal confounders or comorbidities

TABLE 5.19. Birth Outcomes With Undifferentiated Diabetes Diagnosed Before Pregnancy, Population-Based or Multicenter Studies, 1991–2014

REGION, YEARS (REF.)	TOTAL NUMBER OF BIRTHS, GESTATIONAL AGE OR WEIGHT	NUMBER OF CASES (PERCENT) VERSUS (PERCENT IN CONTROLS) AND EFFECT SIZE (95% CI)						
		Preterm (<37 Weeks Gestation)	Cesarean Section	Shoulder Dystocia (Percent of Vaginal Births)	Stillborn	Neonatal Death*	Perinatal Mortality*	Late Infant Death*
United States, 1991–1995 (248)†	462 >19 w	175 (37.9) <35 w: 75 (16.2)			8 (1.7)	3 (0.66)	11 (2.4)	
California, 2001–2007 (213)‡	22,331 >19 w	3,179 (14.2)	11,711 (52.4)	526 (4.95)	265 (1.2)			
California, 2006 (203)§	3,718 >19 w, no chronic hypertension	721 (19.4) vs. (9.3) adjOR 2.2 (2.1–2.4)		93 (2.5) vs. (1.1) adjOR 2.1 (1.7–2.7)	30 (0.8) vs. (0.3) adjOR 3.2 (2.1–5.0)			
Northern California, 2001–2011 (208)‖	3,286‖ >19 w 3,185 infants 3,157 liveborn	716 (21.8) <28 w: 22 (0.7) 28–33 w: 141 (4.3) 34–36 w: 553 (16.8)	1,924 (58.6)	128/1,362 (9.4)	28 (0.88)	24 (0.76)	52 (1.6)	6 (0.19)
Utah, 2002–2010 (115)¶	802 >19 w	156 (19.5) vs. (7.3) p<0.0001	295 (36.8) vs. (17.2) p<0.0001	26 (5.1) vs. (2.2) p<0.0001			9 (1.1) vs. (0.44)	
Nova Scotia, Canada, 1988–2002 (249)#	516 >19 w	143 (27.7) vs. (5.2) p<0.001	253 (49.0) vs. (19.5) p<0.001		5 (0.97) vs. (0.4) p=0.060	7 (1.37)	12 (2.3) vs. (0.6) p=0.004	1 (0.20)
Ontario, Canada, 1996–2009 (91,212)**	1996: 1,122 2001: 1,532 2009: 1,463** >19 w		411 (36.6) 535 (34.9) vs. (22.7) NR	43/711 (6.0) 64/997 (6.4) vs. (2.1) NR			10 (1.69)** 11 (1.3)** vs. (0.76) 27 (1.85)** vs. (0.77)	
Alberta, Canada, 2005–2011 (214)††	2,485 singleton births, 2,432 liveborn	125 (5.0)‡‡ 459 (18.5)§§	1,200 (48.3) adjOR 2.53 (2.33–2.74)	158 (12.3) adjOR 1.54 (1.31–1.81)	53 (2.1) adjOR 3.73 (2.82–4.95)	19 (0.8) adjOR 2.00 (1.27–3.17)	72 (2.90)	
Northern England, 1996–2008 (211)‖‖	1,548 >19 w, 1,502 liveborn	24–27 w: 15 (0.97) vs. (1.2) 28–36 w: 564 (36.4) vs. (7.3)			20–23 w: 5 (0.3) >23 w: 41 (2.65) RR 5.87 (4.3–8.0)	6 (0.40) RR 1.74 (0.8–3.9)	52 (3.36)	4 (0.27) RR 2.1 (0.8–5.6)
United Kingdom, 2002–2003 (302)¶¶	2,349 births ≥24 w, 2,290 liveborn	917 (38.7) 20–23 w: 16 (0.68) 24–27 w: 38 (1.60) 28–36 w: 863 (36.4)			59 (2.5) vs. (0.6) adjRR 4.7 (3.7–6.0) 24–36 w: 44 (1.9) ≥37 w: 15 (0.64)	19 (0.83) vs. (0.36) adjRR 2.6 (1.7–3.9) 24–36 w: 16 (0.7) ≥37 w: 3 (0.13)	75 (3.18) vs. (0.85) RR 3.8 (3.0–4.7)	
Northern England, 2002–2004 (209)##	428 >23 w, 420 livebirths				8 (1.9)	7 (1.7)	15 (3.5)	

Table 5.19 continues on the next page.

TABLE 5.19. (continued)

REGION, YEARS (REF.)	TOTAL NUMBER OF BIRTHS, GESTATIONAL AGE OR WEIGHT	NUMBER OF CASES (PERCENT) VERSUS (PERCENT IN CONTROLS) AND EFFECT SIZE (95% CI)						
		Preterm (<37 Weeks Gestation)	Cesarean Section	Shoulder Dystocia (Percent of Vaginal Births)	Stillborn	Neonatal Death*	Perinatal Mortality*	Late Infant Death*
Western Ireland, 2005–2014 (88)***	2005–2009: 187	60 (32.1) <34 w: 44	113 (60.4)	5 (6.8)	5 (2.7) vs. (0.49)	None in first week of life		
	2010–2014: 198	67 (33.8) <34 w: 42	130 (65.7)	3 (4.4)	1 (0.5) vs. (0.42)	None in first week of life		
France, 2000–2001 (92)†††	435 >21 w or ≥500 g	166 (38.2) <32 w: 21 (4.8) 32–36 w: 145 (33.4)	256 (58.9)	11 (6.1)	15 (3.4) Type 1: 12 Type 2: 3	4 (0.95) Type 1: 1 Type 2: 3		
Bavaria, Germany, 2001–2007 (318)‡‡‡	3,348 unknown gestational age	588 (17.6) vs. (8.7) OR 1.94 (1.8–2.1)			22 (0.66) vs. (0.35) OR 1.89 (1.2–2.9)	<8 days of life: 5 (0.15) OR 0.92 (0.4–2.2)		
New South Wales, Australia, 1998–2002 (227)§§§	1,248 singleton deliveries >20 w, 1,228 liveborn	240 (19.2) 20–27 w: 9 (0.7) OR 2.9 (1.4–5.8) 28–31 w: 24 (2.0) OR 4.7 (3.0–7.1) 32–36 w: 207 (16.6) OR 4.6 (3.9–5.3)	648 (51.9) Before labor: 415 (33.3) vs. (11.3) OR 4.8 (4.3–5.5) After labor: 233 (18.7) vs. (9.7) OR 3.2 (2.7–3.7)	27 (4.5) vs. (1.3) OR 3.5 (2.3–5.2)	20 (1.6) vs. (0.6) OR 2.9 (1.8–4.6)	5 (0.41) vs. (0.2) OR 1.78 (0.65–4.45)	25 (2.0)	
South Korea, 2010–2012 (221)‖‖‖	32,207	1,488 (4.62) vs. (2.04) adjOR 1.76 (1.67–1.87)	16,461 (51.1) vs. (35.9) p<0.0001	13 (0.08) vs. (0.03) adjOR 2.27 (1.29–3.99)				

Table includes prospective population-based and multicenter studies reported in 2000–2016. AdjOR, indicates odds ratio adjusted for multiple covariates; CH, chronic hypertension; CI, confidence interval; ICD-9/10-AM, International Classification of Diseases, Ninth/Tenth Revision, Australian Modification; NR, not reported; PDM, preexisting diabetes mellitus of pregnancy; PNM, perinatal mortality; PTD, preterm delivery; RR, rate ratio or relative risk (95% CI, significant) versus general maternity population adjusted for maternal age; w, weeks gestation.

* Unless otherwise defined in a footnote: neonatal death is defined as liveborn infants dying at 1–28 days after birth (percentage of liveborn infants); PNM is defined as the combination of stillbirths and neonatal deaths in births ≥20 w, or at varying gestational ages according to individual study; and late infant death is defined as liveborn infants dying at 29 days to 1 year of life.

† Multicenter randomized controlled trial of aspirin to prevent preeclampsia (no effect) with recruitment of 471 diabetic subjects at 13–26 w (excluded seven miscarriages and two cases with incomplete data). Diabetic women required insulin before pregnancy. Four stillbirths and one neonatal death occurred before 26 w.

‡ Retrospective study using health discharge data for all deliveries (age 15–54 years) during 2001–2007 (>3.5 million), California Office of Statewide Health Planning and Development; diagnoses by ICD-9 codes; multivariate analysis only versus gestational diabetes. Excluded subjects missing age or race/ethnicity data, as well as extremes of age (<15 and ≥55 years).

§ Normally formed singleton offspring delivered >19 w; data source California Vital Statistics Birth Certificate Data linked with the California Patient Discharge Data, as well as Vital Statistics Death Certificate Data and Vital Statistics Fetal Death File, in 2006; diagnoses by ICD-9 codes; 522,377 controls without diabetes or hypertension; multivariable logistic regression to estimate risks adjusted for maternal age, race/ethnicity, insurance type at delivery, education level, parity, obesity, and renal disease. PTD <37 w, PDM with CH, 35.5%, adjOR 4.9 (95% CI 4.0–6.0); PTD <32 w, PDM with CH, 10.1%, adjOR 7.6 (95% CI 5.1–11.2); stillbirth, PDM with CH, 2.2%, adjOR 7.1 (95% CI 3.1–16.2).

‖ A. Ferrara and T. Peng; unpublished data from multicenter analysis of births from 14 hospitals in Kaiser Permanente Northern California system, prepared for *Diabetes in America, 3rd edition*. Data sources were unique birth and diabetes registries with prospective data entry. N=3,286 for deliveries (denominator for PTD, cesarean section, and shoulder dystocia) is larger than N in Table 5.18 due to inclusion of 174 cases with dual coding for chronic and gestational hypertension here. For infants linked to mothers with PDM, n=3,185 (only one count if twins); denominator for stillbirth, neonatal death, and late neonatal death.

¶ Subjects with PDM in a previous and current pregnancy in a multicenter analysis. Singleton births; data collected retrospectively from electronic medical records of 20 hospitals in Utah; subjects here are women with at least two consecutive pregnancies with PDM in both, data from last pregnancy. Only 75.8% of subjects were coded as using insulin during the index pregnancy; 58,224 controls without diabetes in previous and current pregnancy. Tested for differences between subjects and controls using Poisson regression models with robust variance estimators.

Data on all births >19 w and ≥500 g at 11 maternity units throughout the province, obtained from Nova Scotia Atlee Perinatal Database. Diabetes ascertained at first prenatal visit as present before pregnancy. 150,589 nondiabetic controls. P values obtained from chi-square or Fisher's exact test as appropriate.

Table 5.19 continues on the next page.

TABLE 5.19. (continued)

** Data obtained from Canadian hospital discharge abstracts database linked to Ontario Diabetes Database. PDM diagnosis accepted if made >270 days before delivery. Deliveries for 1996 and 2001 obtained from reference 212. Denominators for PNM obtained from reference 91, supplementary tables 2 and 3: 591 PDM in 1996–1997; 845 PDM and 69,116 controls in 2002; 1,463 PDM and 90,187 controls in 2009.

†† Data sources were all singleton births in registry of the Alberta Vital Statistics Birth File, the Alberta Diabetes Database, a part of the Canadian National Diabetes Surveillance System (validated case definition of one hospitalization or outpatient visits in 2 years), the Alberta Hypertension Database, the Hospital Discharge Database, and the Ambulatory Care Classification System. Total of 306,576 controls without preexisting diabetes or gestational diabetes; multinomial logistic regression to examine risks with diabetes, adjusting for maternal age, parity, preexisting hypertension, and First Nations status.

‡‡ Preterm birth with labor induction

§§ Preterm birth with no labor induction

‖‖ Data source Northern Diabetes in Pregnancy Survey; singleton pregnancies; major congenital anomalies identified from the Northern Congenital Abnormality Survey excluded. Risks compared to 395,844 total births ≥20 w in women without preexisting diabetes obtained from the U.K. office for National Statistics; examined by a series of logit-linked generalized estimating equations. 22.1% type 2 diabetes. Rate of late miscarriage at 20–23 w in total population 0.2% (nonsignificant from PDM). Three of 41 stillbirths were intrapartum deaths in PDM versus 10.8% of all stillbirths in controls; relative risk for intrapartum fetal death associated with PDM 3.97 (95% CI 1.27–12.41), p=0.042 by Fisher's exact test.

¶¶ Study database obtained from 231 maternity units in England, Wales, and Northern Ireland by questionnaires and confidential inquiries into births; 2,349 PDM (27.6% type 2 diabetes) live and stillborn infants (41 multiple gestations) in March 2002 through February 2003, excluding five pregnancy terminations ≥24 w; data here taken from authors' Table 1 of gestational age distribution of fetuses delivered at ≥20 w. Article included 30 terminations of pregnancy <24 w for congenital anomaly, 14 late fetal losses at 20–23 w, and two neonatal deaths at 20–23 w. In this table, rates of stillbirths and neonatal deaths are given for each gestational age period and for total. Authors calculated relative risks include the terminations at 24–32 w and the stillbirths compared to PNM data from U.K. CEMACH 2002 death notifications (PNM there calculated as stillbirths >23 w plus neonatal deaths in first 7 days of life; PNM in table calculated as stillbirths >23 w plus neonatal deaths in first 28 days of life).

Data from the Northern Diabetic Pregnancy Survey, 14 maternity units, linked to the Northern Congenital Abnormality Survey and the Northern Perinatal Mortality Survey. Recorded total pregnancies in women with preexisting diabetes (26% type 2 diabetes) whose pregnancy ending in spontaneous loss (36 <13 w; 12 at 13–23 w), termination of pregnancy (n=2), or birth. Data here include births >23 w. Stillbirth defined as ≥24 w.

*** Multicenter study in the Irish Atlantic Seaboard. Of 445 pregnancies in the total time period, 38.7% were type 2 diabetes and 88% were Caucasian; here excluded 30 miscarriages in 2005 and 30 in 2010–2014.

††† Multicenter study in 12 perinatal centers participating in the French Diabetes and Pregnancy Study Group. Included women with type 1 (66%) and type 2 diabetes (34%). Prospectively recorded singleton births ≥22 w. Stillbirths defined as fetal death at ≥22 w or ≥500 g. Neonatal death within first 28 days of life. PNM 0.7% with preconception care and 8.1% without preconception care (p<0.005) among those with type 1 diabetes.

‡‡‡ Standard data set collected electronically from all Bavarian obstetric units and transferred to the central Office for Quality Assessment; stillbirth gestational age undefined; neonatal death defined as within first week of life. Controls were 737,013 births without diabetes; assessed crude odds ratios (95% CI) for risks.

§§§ All women and infant discharges after birth of liveborn or stillborn singletons at >20 w or >400 g birth weight in New South Wales in July 1998 through December 2002. Data obtained from linked Midwives Data Collection and the Inpatient Statistics Collection (both datasets suffer from underreporting; sensitivities 50%–95.5%). Diagnoses by ICD-10-AM codes (excluded 595 women with discordant diabetes coding). Preterm births are percentage of liveborn infants. Neonatal deaths are within the birth hospitalization. 352,673 controls without pregestational or gestational diabetes used in contingency tables to compare groups, for crude odds ratios (OR, 95% CI).

‖‖‖ Data source was maternal claims to the Health Insurance Review and Assessment Service database; subjects age 15–49 years; diagnoses by ICD-10 codes; only first of repeated deliveries in 3-year period counted; delivery of twins counted as one delivery; no lower gestational age given for deliveries; controls are 1,171,575 deliveries without preexisting or gestational diabetes; effect of diabetes estimated by logistic regression analysis adjusted for maternal age, multiple pregnancy, and preexisting hypertension; no neonatal data.

SOURCE: References are listed within the table.

TABLE 5.20. Birth Outcomes in Women With Type 1 Diabetes Diagnosed Before Pregnancy, Population-Based or Multicenter Studies, 1985–2013

REGION, YEARS (REF.)	TOTAL NUMBER OF BIRTHS, GESTATIONAL AGE OR WEIGHT	NUMBER OF CASES (PERCENT) VERSUS (PERCENT IN CONTROLS) AND EFFECT SIZE (95% CI)						
		Preterm (<37 Weeks Gestation)	Cesarean Section	Shoulder Dystocia (Percent of Vaginal Births)	Stillborn	Neonatal Death*	Perinatal Mortality*	Late Infant Death*
California, 2006 (114)†	563 >19 w	162 (28.8)	348 (61.8)	12/215 (5.6)	8 (1.42)			
Ontario, Canada, 2005–2006 (210)‡	904 >19 w	172 (19.0) vs. (8.4) adjOR 2.9 (2.4–3.5)	466 (51.6) vs. (27.6) adjOR 2.7 (2.3–3.1)	25 (5.7)‡ adjOR 2.5 (1.6–3.9)	10 (1.1) vs. (0.6) adjOR 2.3 (1.1–4.1)			
Northwest England, 1995–1999 (303)§	459				14 (3.0) vs. (0.51) p<0.001	7 (1.5) vs. (0.68) p=0.05	21 (4.6) vs. (0.85) p<0.001	
Scotland, 1998–1999 (304)‖	216 212 liveborn				4 (1.85)	2 (0.94)	6 (2.78)	1 (0.47)
Scotland, 1998–1999, 2003–2004 (94)¶	359 355 liveborn >23 w	127 (35.4)	238 (66.3)		4 (1.1)	3 in first week of life		
Northern United Kingdom, 2003–2008 (243)#	748 730 liveborn >20 w	278 (37.2) <28 w: 7 (0.94) <34 w: 71 (9.5)			18 (2.41)	5 (0.68)	23 (3.07)	
England, 2007–2008 (98)	793 >23 w	240 (29.8)**	497 (62.7)		12 (1.5)	6 (0.77)		

Table 5.20 continues on the next page.

TABLE 5.20. (continued)

REGION, YEARS (REF.)	TOTAL NUMBER OF BIRTHS, GESTATIONAL AGE OR WEIGHT	NUMBER OF CASES (PERCENT) VERSUS (PERCENT IN CONTROLS) AND EFFECT SIZE (95% CI)						
		Preterm (<37 Weeks Gestation)	Cesarean Section	Shoulder Dystocia (Percent of Vaginal Births)	Stillborn	Neonatal Death*	Perinatal Mortality*	Late Infant Death*
East Anglia, England, 2006–2009 (107)††	323 >23 w	120/322 (37.2)	205 (63.5)		5 (1.55)	3/318 (0.94)		
Dublin, Ireland, 1995–2006 (229)‡‡	511 >500 g	65 (12.7)	236 (46.2)		13 (2.54)	4 in first week of life		
West Ireland, 2007–2013 (108)§§	191 >23 w	60 (31.4) vs. (5.4) p=0.001	127 (66.5) vs. (31.1)	5/64 (7.8)	6 (3.1) vs. (0.4) p=0.027	0	6 (3.1)	
Netherlands, 1999–2000 (100)‖‖	314 pregnancies 324 infants 318 liveborn >23 w or >500 g	101 (32.2) RR 4.5 (3.8–5.3)	139 (44.3) RR 3.7 (3.2–4.2)	25/175 (14.3)	6 (1.9)	3 in first week of life		
Denmark, 1993–1999 (93)¶¶	1,215 pregnancies 1,243 infants 1,217 liveborn >23 w	507 (41.7) vs. (6.0) RR 7.0 (6.3–7.6)	680 (55.9) vs. (12.6) RR 4.4 (4.1–4.8)		26 (2.1) vs. (0.45) RR 4.7 (3.2–7.0)	12 in first week of life	38 (3.1) vs. (0.75) RR 4.1 (2.9–5.6)	
Italy, 1999–2003 (95)##	469 464 liveborn >180 days	176 (37.5)	342 (72.9)	7/127 (5.5)	5 (1.1) >26 w	1 (0.22)		
Sweden, 1991–2003 (276)***	5,089 5,020 liveborn	1,069 (21.0) vs. (5.1) adjOR 4.9 (4.5–5.3)	2,341 (46.0) vs. (12.0) adjOR 5.3 (5.0–5.7)	(13.7) vs. (0.2) adjOR 11.1 (8.2–14.9)	≥28 w: 69 (1.36) vs. (0.3) adjOR 3.3 (2.5–4.6)	(0.7) vs. (0.2) adjOR 2.7 (1.7–4.2)		
Sweden, 1998–2007 (307)†††	2,004 female 2,088 male infants ≥22 w	434 (21.7) vs. (4.7) 482 (23.1) vs. (5.2) M > F (NS)	992 (49.5) vs. (14.7) 1,096 (52.5) vs. (15.9) M > F (NS)		≥28 w: N and denominator uncertain	6 (0.3)††† vs. (0.03) 2 (0.1) vs. (0.05)	22 (1.1)††† vs. (0.4) 25 (1.2) vs. (0.4) different denominators?	14 (0.7)††† vs. (0.2) 8 (0.4) vs. (0.2) F > M (NS)
Flanders, Belgium, 2002–2004 (305)‡‡‡	354 pregnancies 361 infants 352 liveborn >23 w	98 (27.7) vs. (7.4) OR 4.8 (3.8–6.1)	184 (52.0) vs. (18.5) OR 4.6 (3.7–5.7)		9 (2.5) vs. (0.5) OR 5.0 (2.4–10.0)	2 (0.57) vs. (0.22) OR 2.6	11 (3.05) vs. (0.73) OR 4.28 (2.22–8.01)	2 (0.57) vs. (0.22) OR 2.5
Norway, 1985–2004 (278)§§§	1,307 1,280 liveborn ≥22 w or ≥500 g	316/1,199 (26.4) vs. (6.8) adjOR 5.0 (4.4–5.7)	498 (38.1) vs. (7.4)		27 (2.1) vs. (0.58) adjOR 3.8 (2.6–5.6)	6 (0.47) vs. (0.34) adjOR 1.5 (0.7–3.3) 5 of the deaths were early	32 (2.4) vs. (0.86) adjOR 3.1 (2.2–4.4)	7 (0.55) vs. (0.20) RR 2.75
Argentina, Canada, Europe, Israel, 2013 (306)‖‖‖	257 >22 w	63 (24.5)			2 (0.78)	1 in first week of life		
Japan, 2003–2009 (113)¶¶¶	330 328 liveborn >19 w	55 (16.7)	103 (31.2) 80 primary 23 repeat	5/227 (2.2)	2 (0.61)	2 (0.61) in first week of life	5 (1.52)	

Table includes prospective population-based and multicenter studies reported in 2000–2014. AdjOR, adjusted odds ratio versus background population; BMI, body mass index; CI, confidence interval; ICD-9/10, International Classification of Diseases, Ninth/Tenth Revision; IDM, infant of diabetic mother; NS, not significant; OR, odds ratio; PNM, perinatal mortality (definition varies per study); RR, relative risk (95% CI, significant) versus background population; w, weeks gestation.

* Unless otherwise defined in a footnote: neonatal death is defined as the number and percentage of liveborn infants dying at 1–28 days after birth; PNM is defined as the combination of stillbirths and neonatal death in births ≥20 w; late infant death is defined as liveborn infants dying at 29 days to 1 year of life.

† Retrospective cohort study based on all deliveries in California using birth certificates, death certificates, and hospital discharge data from the Department of Health; diagnoses based on ICD-9 codes

‡ Data source from the 2005–2006 fiscal year of the Ontario Niday Perinatal Database, a branch of the provincial Perinatal Surveillance System. Web-based data entry by 72 participating hospitals; diagnoses extracted by codes unique to the database, which included 873 singleton and 31 multiple gestations, and pregnancies with preexisting hypertension and nephropathy. Apparently, the rate of stillborn infants is based on the first of x infants from the multiple births, if any were stillborn. Excess risks of outcomes calculated by unconditional logistic regressions, using 115,996 pregnancies without maternal complications, including gestational diabetes, as controls; odds ratios were adjusted for maternal age, region of residence, smoking, parity, multiple birth, use of assisted reproductive technology, attendance at a first trimester visit, and

Table 5.20 continues on the next page.

TABLE 5.20. (continued)

type of antenatal provider. Shoulder dystocia rate is 25/438 vaginal deliveries; adjusted odds ratio for shoulder dystocia compares rates per total deliveries between type 1 diabetes and control populations.

§ Study cohort drawn from 10 maternity units in Cheshire, Lancashire, and Merseyside, England; diabetes database excludes 72 miscarriages and 16 terminations of pregnancy, but includes six twin gestations (all livebirths); study findings compared with regional background population data on all pregnancies published by the Office for National Statistics for the same time period. Gestational age limits for miscarriage and stillbirth undefined.

‖ A 1-year prospective audit of all pregnancies of women with type 1 diabetes prior to pregnancy, in Scotland's 22 consultant-led maternity units (including assessment during first year of infant life). Original data set of 273 pregnancies included 40 miscarriages and 20 induced abortions (seven due to congenital anomalies); the 213 pregnancies progressing to delivery of liveborn or stillborn infants included 210 singleton births and three twin births for 216 total infants.

¶ Results of two national audit periods of all pregnancies in women with preconception type 1 diabetes in Scotland. Women registered at first contact in pregnancy; data form sent to study center after conclusion of pregnancy. N for births excludes 54 miscarriages, two ectopic pregnancies, one molar pregnancy, (early loss rate 13.5%), 15 induced abortions, four twin gestations, and 10 pregnancies in the same woman. Gestational age limits for miscarriage and stillbirth undefined.

Multicenter analysis (25 antenatal metabolic clinics across Northern Ireland, Scotland, and northwest England), at 8–22 w, women with type 1 diabetes preceding pregnancy were enrolled in randomized controlled trial of vitamins C and E (no effect on preeclampsia); excludes eight miscarriages and six pregnancy terminations.

** Denominator includes both singleton and twin births (n=812).

†† All singleton pregnancies with type 1 diabetes diagnosed at least 12 months before pregnancy were enrolled at first antenatal visit at one of 10 regional maternity units participating in the East Anglia Diabetes and Pregnancy Study Group. Standardized data collection completed within 3 months of end of pregnancy. Miscarriage (n=53) or pregnancy termination (n=21) defined as <24 w (both excluded from N births). Denominator for preterm delivery is number with gestational age information. Of 205 cesarean deliveries, 109 were "emergency," and 96 were "planned."

‡‡ Retrospective multicenter study at three hospitals with diabetes and pregnancy units in Dublin, Ireland.

§§ Case control study (data recorded electronically and prospectively) among five multidisciplinary diabetes and pregnancy units at maternity centers in the Irish Atlantic Seaboard. Type 1 diabetes at least 6 months prior to pregnancy. Miscarriage defined as pregnancy loss before 24 w. Singleton pregnancies. Controls were selected from a group of >12,000 women screened negative for gestational diabetes, group-matched for maternal age, BMI, parity, and ethnic group to the group with type 1 diabetes, using cosine similarity matching with a customized nearest neighbor selection without replacement (447 matched controls for type 1 diabetes). N of cesarean sections provided by personal communication with author Lisa Owens.

‖‖ Data obtained by repeated questionnaires throughout pregnancy from all 118 Dutch hospitals having women with type 1 diabetes in antenatal care during April 1999 through March 2000, reported to the study coordinator. Excluded 23 women due to early spontaneous abortion, 16 due to diagnosis of type 2 diabetes, four terminations of pregnancy due to anomalies, four cases of late fetal loss <24 w, one maternal death at 17 w, and two lost to follow-up. Included fetuses of ≥24 w or ≥500 g; including eight twin pregnancies (one set terminated at 24 w for severe preeclampsia, counts as two stillbirths) and one triplet pregnancy, for 324 infants. Perinatal mortality defined here as intrauterine death at ≥24 w and death during the first 7 days of life. Compared outcomes with those in 196,981 pregnancies from the national 1998 Dutch Perinatal Database and with data from Statistics Netherlands for calculation of crude risk ratios (95% CI).

¶¶ During 1993–1999, all pregnancies with pregestational type 1 diabetes were prospectively reported to a central registry in the Danish Diabetes Association. Database included three terminations of pregnancy for congenital malformations <24 w and 28 twin gestations. Perinatal mortality defined as intrauterine deaths at ≥24 w and death during the first 7 days of life. Data on the background population based on 70,089 deliveries recorded by the Danish Health Board in 1995 were used for calculating crude risk ratios (95% CI). Perinatal mortality includes stillbirths >24 w; neonatal deaths within first week of life.

Italian maternity centers (n=33) participated in this prospective study as part of the Italian Diabetes and Pregnancy Study Group; all pregnant women with type 1 diabetes recruited; data entered into the European Quality Indicators and Data Collection Aggregated Database; 30 spontaneous abortions and five terminations of pregnancy <180 days gestation excluded. Stillbirth defined as ≥180 days gestation (~26 w). Neonatal death defined as before 28 days of life. Therefore, PNM rate is unique to this study and not given here.

*** Data from the Swedish Medical Birth Registry for 1991–2003, gestational age for inclusion of the 5,089 type 1 diabetic pregnancies is uncertain; diagnoses based on ICD-10 codes; number of multiple births uncertain; stillbirth defined as 28 w, so rate of fetal loss between 20 and 27 w is unknown; N=69 for stillbirth ≥28 w given in the text, and 58 occurred between 34 and 40 w; overall neonatal death within first 28 days of life; PNM defined as the combined rate of stillbirth ≥28 w and mortality within the first week of life in the article, so it is unique to this article and not presented in this table. The denominator for shoulder dystocia is uncertain: total births or vaginal deliveries, so calculation of N for shoulder dystocia is uncertain. Text gives the frequencies only, for diabetic and control women, and the effect size. Note: there are misprints in the authors' Table 3 in the publication. Perinatal mortality is printed as 20% in type 1 diabetes women and 4.8% in controls, but the text says "Perinatal mortality in type 1 diabetic pregnancies has decreased from 3.1% in 1982–1985 to 2.0% in the present study" (page 2008 of the article). Similarly, there is a misprint of 7.0% for neonatal deaths at 0–28 days in IDM and 2.2% in controls; the authors of this chapter believe the actual rates are 0.7% and 0.22%, respectively, values that are concordant with other published studies in the same time period. The denominator for neonatal deaths is uncertain: total births or liveborn infants. Therefore, the calculated N for neonatal deaths is uncertain. Controls were 954,292 mothers without type 1 diabetes in multivariate analyses for association of diabetes with outcomes by logistic regression, adjusted for maternal age, BMI, parity, chronic hypertension, smoking, and ethnicity. This study was not excluded from this review because it is the largest population-based survey of type 1 diabetic pregnancy published in 2000–2015.

††† Data from the Swedish Medical Birth Registry for 1998–2007, with inclusion of all singleton births ≥22 w; diagnoses based on ICD-10 codes and provided to registry on standardized forms at discharge from hospital after birth. Gestational age confirmed by ultrasound by midpregnancy. Divided analysis between female and male infants. "Information on live births includes all infants born after 22 completed weeks of gestation." Stillbirth defined as ≥28 w (so number of fetal losses between 22 and 28 w is unknown), and PNM as stillbirths plus neonatal deaths within first week of life (unique to this study). Authors' text and Table 2 ignore neonatal death in first week of life, and they present data on late neonatal death (8–28 days of life) and infant death within first year of life (methods unclear on follow-up of infants). We cannot separate neonatal deaths within 7 and 28 days of life, so we cannot calculate number of stillbirths from the PNM rate as presented in authors' Table 2. Denominators for neonatal and late infant deaths uncertain, as we cannot calculate number of liveborn infants. Comparisons made to 439,525 singleton births of female infants and 466,040 male infants born to mothers without diabetes with the chi-square test and Fisher's exact test.

‡‡‡ Retrospective analysis of the database of the Flanders Study Center for Perinatal Epidemiology. Diagnosis of type 1 diabetes as given by the treating physician. Included seven sets of twins. Authors present different numbers of preterm births in Table 2 (98 pregnancies) versus detailed Table 3, in which denominator seems to be delivered infants (including twins) (<37 w, 105/361 infants, 29.1%: <28 w, 5 infants, 1.4%; 28–33 w, 24 infants, 6.6%; 34–36 w, 76 infants, 21.1%); Early neonatal death defined as within 28 days of life, so late neonatal death stated by authors must be >28 days. 180,842 control infants used for crude odds ratio (95% CI) assessment.

§§§ All births in Norway 1985–2004 recorded in Medical Birth Register, linked with Norwegian Childhood Diabetes Registry to "ensure a valid diagnosis of type 1 diabetes," to Cause of Death Registry for data on infant deaths, and to Statistics Norway for information on maternal education and immigrant status. The study population from the Childhood Diabetes Registry includes approximately 33% of all births by women with type 1 diabetes in Norway during the study period. Births included if postmenstrual or ultrasound gestational age was ≥22 w, or birth weight ≥500 g. Multiple births uncertain. Neonatal death defined as within first 28 days of life, but perinatal mortality based on stillbirths plus deaths within first 7 days of life. Authors stated infant deaths as within first year of life, so 13 minus six neonatal deaths yields seven later deaths, but extent of follow-up to 1 year of life is uncertain. Controls were 1,161,092 births to mothers without type 1 diabetes; used in logistic regression in SPSS to estimate odds ratios with 95% confidence intervals, adjusted for maternal age, parity, educational level, ethnic origin, marital status, sex of infant, and year of delivery.

‖‖‖ Multicenter analysis, enrolled in randomized controlled trial of types of insulin, excludes congenital malformations and early fetal losses.

¶¶¶ Retrospective analysis of prospective data from 40 hospitals throughout Japan. Additional information provided by Dr. Takashi Sugiyama as personal communication to JLK. Denominator of births different than in published paper due to our exclusion of early fetal deaths (pregnancy losses) at 10–19 w (39 for type 1 diabetes, so 330 births >19 w and 328 liveborn infants). Shoulder dystocia is defined here clinically, with reference to the specific maneuvers used to release the fetal shoulders. PNM is defined here as stillbirths plus neonatal deaths in the first week of life.

SOURCE: References are listed within the table.

needing inclusion in multivariable analyses for risks of stillbirth in women with preexisting diabetes include race/ethnicity, maternal age, prepregnancy BMI ≥30 kg/m^2, weight loss, chronic hypertension, smoking, and alcohol use (297,298,299).

In eight surveys among women with type 2 diabetes, with data reported since 2000, the frequencies of stillbirth were 0.39%–2.1%, with acknowledged variation in the gestational age definition for live or stillbirths (95,98,107,108,113,114,210,309) (Table 5.21). In an analysis of 2,069 births to women with type 2 diabetes in California in 2002–2004, the rate of stillbirth was 4.2% if gestational weight gain was less than Institute of Medicine 2009 guidelines for BMI group, 1.7% if within guidelines, and 1.1% if above the guidelines (p<0.001) (308). However, with multivariable analysis to control for possible confounders, weight gain below or above guidelines did not significantly affect risk of stillbirth (308).

Within a large U.S. medical insurance claims database of inpatient, outpatient, and pharmacy benefits adjudicated or paid in 2005–2011, there were 783 pregnancies complicated by type 1 diabetes that did not end in miscarriage compared to 6,665 with type 2 diabetes (54). The frequency of stillbirth was only 0.4% in women with type 1 diabetes (RR 1.47, 95% CI 0.55–3.92 vs. controls) compared to 0.75% in women coded as type 2 diabetes (RR 2.51, 95% CI 1.94–3.26 vs. controls) (54). Cohort studies from Denmark suggested higher perinatal mortality in pregnancies complicated by type 2 diabetes compared to type 1 diabetes (111), whereas studies from the United Kingdom suggest similar risk of fetal death in type 2 diabetes compared to type 1 diabetes (112,211,302).

A nested case-control study using the GPRD in 1987–1997 reported stillbirth rates of 3.37% in 593 women with preexisting diabetes in pregnancy compared to 0.55% in 12,727 nondiabetic controls (310). In a cohort study from New Zealand, >75% of pregnancy losses in women with type 1 diabetes were due to congenital anomalies, whereas >75% of losses in women with type 2 diabetes were due to stillbirth (311).

Timing of Stillbirth With Preexisting Diabetes

In a population of >1.1 million deliveries from Norway in 1985–2004 (278), the adjusted odds ratio for stillbirth ≥22 weeks gestation in type 1 diabetes (n=1,307; 27 stillbirths; frequency 2.7%) compared to the background population was 3.8 (95% CI 2.6–5.6). The excess risk persisted in 1999–2004 (278). The adjusted odds ratio was 4.0 (95% CI 2.1–7.5) for births at ≥37 weeks gestation among deliveries with stated gestational age (adjusted OR 5.8, 95% CI 3.1–10.9, without adjustment for gestational age). However, the excess risk for preterm diabetic stillbirths was not significant (adjusted OR 1.1, 95% CI 0.6–2.0) (278). In other studies of preexisting diabetes mellitus that stratified by gestational age in the United Kingdom (211,283), spontaneous fetal demise at 20–25 weeks gestation represented 18%–50% of the total stillbirths in women with preexisting type 1 or type 2 diabetes, and 18%–22% of stillbirths occurred at 24–27 weeks compared to 34%–56% at 34–41 weeks (211,283). The rate of fetal loss at 20–23 weeks gestation rises considerably if pregnancy terminations for major congenital anomalies are included (283).

Surveys of stillbirths related to gestational age at occurrence in large general populations show a U-shaped curve in the percentage of stillbirths, with and without diabetes, with elevated proportions at 20–23 weeks and again rising at approximately 34 weeks (297,300,312,313). However, since the proportion of total deliveries increases with advancing gestational age, the absolute rate of fetal death goes down with gestational age, while the relative risk of stillbirth with diabetes compared to nondiabetic populations remains elevated at all gestational age groupings in most studies (211,278,302,312,314,315).

Causes of Fetal Demise With Preexisting Diabetes

In later pregnancy, increasing A1c values are associated with increased risk of fetal loss, as also predicted by periconception A1c levels (211,306,316). Maternal-fetal hyperglycemia is associated with fetal hypoxemia and acidosis (40). Major congenital anomalies are linked to fetal deaths in pregnancies with preexisting diabetes (302,317). Most studies of stillbirth in the general population focus on nonanomalous fetuses. Comorbidities associated with stillbirth in maternal diabetes include maternal ketoacidosis, fetal growth restriction with or without maternal vascular disease, hypertension, preeclampsia, placental abruption, and possibly fetal macrosomia (100,211,248,302,314,318,319). Confounders include maternal age, obesity, race/ethnicity, education level, previous early or late pregnancy loss, smoking, and substandard antenatal care (297,299,301,313,318). A large population-based cohort study of pregestational diabetes (4,092 type 1 diabetes, 412 type 2 diabetes) in Sweden in 1998–2007 found that male infants were not more likely to suffer fetal demise than female infants with either type of maternal diabetes (307).

Diabetes has been noted as a significant risk factor in both placental and nonplacental causes of death and with and without fetal growth restriction (320). In one U.S. case-control study of stillbirth and known risk factors, diabetes and hypertension did not totally explain the association of obesity with stillbirth (299). In a population-based case-control study by the Stillbirth Collaborative Research Group in the United States, the increased risk for stillbirth associated with diabetes (adjusted OR 2.58, 95% CI 1.43–4.67) persisted after adjustment for significant life events and across family characteristic groups (321).

TABLE 5.21. Birth Outcomes in Women With Type 2 Diabetes Diagnosed Before Pregnancy, Population-Based or Multicenter Studies, 1990–2013

REGION, YEARS (REF.)	TOTAL NUMBER OF BIRTHS, GESTATIONAL AGE	NUMBER OF CASES (PERCENT) VERSUS (PERCENT IN CONTROLS) AND EFFECT SIZE (95% CI)						
		Preterm (<37 Weeks Gestation)	Cesarean Section	Shoulder Dystocia (Percent of Vaginal Births)	Stillborn	Neonatal Death*	Perinatal Mortality*	Late Infant Death*
California, 2006 (114)†	2,224 >19 w	414 (18.6)	1,276 (57.4)	38/948 (4.0)	27 (1.2)			
Ontario, Canada, 2005–2006 (210)‡	516 >19 w	72 (14.0) vs. (8.4) adjOR 1.85 (1.38–2.49)	196 (38.0) vs. (27.6) adjOR 1.60 (1.31–1.94)	6/320 (1.9)	3 (0.58) vs. (0.6) adjOR 0.42 (0.02–1.88)			
West Midlands, England, 1990–2002 (309)§	163 singleton births >23 w; 161 liveborn	44 (27.0)	95 (58.3)		2 (1.2) vs. (0.6) p=0.47	3 (1.9)§ vs. (0.53) p=0.21	5 (3.1)	2 (1.2) vs. (0.22) p=0.24
East Anglia, England, 2006–2009 (107)‖	220 >23 w	38/217 (17.5)	113 (51.4)		2 (0.90)	0		
England, 2007–2008 (98)¶	543 >23 w	93 (17.1)	306 (56.4)		11 (2.1)	4/532 (0.75)		
West Ireland, 2007–2013 (108)#	99 >23 w	24 (24.2) vs. (8.5) p=0.001	57 (57.6)	1/42 (2.4)	2 (2.02)	0	2 (2.02)	
Italy, 1999–2003 (95)**	144 >180 days	48 (33.6)	100 (69.3)	2/44 (4.5)	3 (2.1)	3/141 (2.1)		
Sweden, 1998–2007 (307)††	208 female	56 (26.9) vs. (4.7)	84 (40.4) vs. (14.7)			0††	2 (1.0)†† vs. (0.4)	0†† vs. (0.2)
	204 male ≥22 w	55 (27.0) vs. (5.2)	86 (42.2) vs. (15.9)			1††	3 (1.5)†† vs. (0.4)	2 (1.0)†† vs. (0.2)
Japan, 2003–2009 (113)‡‡	510 >19 w	102 (20.0)	202 (39.6)	15/308 (4.9)	2 (0.39)	3 (0.59) in first week of life	5 (0.98)	

Table includes prospective population-based and multicenter studies reported in 2000–2014. AdjOR, adjusted odds ratio (significant 95% CI) versus background population; CI, confidence interval; PNM, perinatal mortality, varied definitions according to study; w, weeks gestation.

* Unless otherwise defined in a footnote: neonatal death is defined as the number and percentage of liveborn infants dying at 1–28 days after birth; PNM is defined as the combination of stillbirths and neonatal death in births ≥20 w; late infant death is defined as liveborn infants dying at 29 days to 1 year of life.

† Retrospective cohort study based on all deliveries in California using birth certificates, death certificates, and hospital discharge data from the Department of Health; diagnoses based on ICD-9 codes.

‡ Data source from the 2005–2006 fiscal year of the Ontario Niday Perinatal Database, a branch of the provincial Perinatal Surveillance System. Web-based data entry by 72 participating hospitals; diagnoses extracted by codes unique to the database, which included 500 singleton and 16 multiple gestations, and pregnancies with preexisting hypertension and nephropathy. Apparently, the stillborn outcomes were calculated based on the first of x infants of the multiple births. Excess risks of outcomes calculated by unconditional logistic regressions, using 115,996 pregnancies without maternal complications, including gestational diabetes, as controls; odds ratios were adjusted for maternal age, region of residence, smoking, parity, multiple birth, use of assisted reproductive technology, attendance at a first trimester visit, and type of antenatal provider.

§ Retrospective multicenter study of five maternity units; data transferred to central database; subjects were 55% Indo-Asian, 26% Caucasian, and 19% Afro-Caribbean; 16 miscarriages and three terminations of pregnancy were excluded; of the 95 cesarean deliveries, 54 were emergency (21 during induction of labor), and 41 were elective. Text says two early (first week) and one late (8–28 days) neonatal death, plus two postnatal infant deaths. Discrepancy noted between table 1 versus table 2 on the number of neonatal deaths; two of three neonatal deaths and both late infant deaths were due to congenital anomalies; their PNM rate has different denominator and is undefined, so not compared with reference population. Mortality comparisons were made with regional data published by the Office of National Statistics using z-scores.

‖ All singleton pregnancies with type 2 diabetes diagnosed at least 12 months before pregnancy were enrolled at first antenatal visit at one of 10 regional maternity units participating in the East Anglia Diabetes and Pregnancy Study Group. Standardized data collection completed within 3 months of end of pregnancy. Miscarriage (n=46) or pregnancy termination (n=4) defined as <24 w (both excluded from N births). Denominator for preterm delivery is number with gestational age information. Of 113 cesarean deliveries, 58 were "emergency," and 55 were "planned."

¶ Combined data from three regional U.K. pregnancy audits to yield 556 women with type 2 diabetes for analysis; 543 pregnancies with data >23 w.

Retrospective case-control study using regional electronic database with prospective data collection; five maternity units on the Irish Atlantic seaboard; comparison with matched controls by chi-square analysis; controls were selected from >12,000 women with normal glucose tolerance; cosine similarity matching for age, BMI, ethnic group, and parity with a customized nearest neighbors selection without replacement (213 matched controls for type 2 diabetes).

** Italian maternity centers (n=33) participated in this prospective study as part of the Italian Diabetes and Pregnancy Study Group; all pregnant women with type 2 diabetes recruited; data entered into the European Quality Indicators and Data Collection Aggregated Database; 17 spontaneous abortions and three terminations of pregnancy <180 days gestation excluded. Stillbirth defined as ≥180 days gestation (~26 w). Neonatal death defined as before 28 days of life. Therefore, PNM rate is unique to this study and not given here.

†† Data from the Swedish Medical Birth Registry for 1998–2007, with inclusion of all singleton births ≥22 w; diagnoses were based on ICD-10 codes and provided to the registry on standardized forms at discharge from hospital after birth. Gestational age was confirmed by ultrasound by mid-pregnancy. Divided analysis between female and male infants. "Information on live births includes all infants born after 22 completed weeks of gestation." Stillbirth defined as ≥28 w, so number of fetal deaths between 22 and 27 w inclusive is unknown. Authors' text and table 2 ignore neonatal death in first week of life (they include those deaths in their definition of PNM), and they present data on late neonatal death (8–28 days of life) and infant death within the first year of life (methods unclear on follow-up of infants). The authors of this chapter cannot discriminate between unknown number of stillbirths and early neonatal deaths to make up two perinatal deaths in females and three in males by their definitions. Comparisons were made to 439,525 singleton births of female infants and 466,040 male infants born to mothers without diabetes with the chi-square test and Fisher's exact test.

‡‡ Retrospective analysis of prospective data collected from 40 hospitals throughout Japan. Additional information provided by Dr. Takashi Sugiyama as personal communication to JLK. Denominator of births is different than in published paper due to exclusion of early fetal deaths (pregnancy losses) at 10–19 w (69 for type 2 diabetes, so 510 births >19 w and 508 liveborn infants). Of the 202 cesarean deliveries, 165 were primary and 37 were repeat. Authors' PNM definition is stillbirths ≥20 w (n=2) plus neonatal deaths (n=3) in first week of life.

SOURCE: References are listed within the table.

COMPLICATIONS OF DELIVERY

PRETERM DELIVERY

Preterm delivery at <37 completed weeks gestation is a major determinant of infant mortality, morbidity, and long-term development of the child. Early preterm birth is before 32 weeks gestation (13). In a large U.S. multicenter clinical trial of low-dose aspirin use starting at 12–26 weeks gestation, 461 women with preexisting diabetes more frequently delivered preterm compared to 2,738 women without diabetes (38% vs. 14% at <37 weeks; 16.3% vs. 6.1% at <35 weeks) (248,322). Both medically indicated or planned preterm delivery (21.9% vs. 3.4% at <37 weeks; 7.4% vs. 1.6% at <35 weeks) and spontaneous preterm delivery (16.1% vs. 10.5% at <37 weeks; 8.9% vs. 4.5% at <35 weeks) were more common in diabetic women. The most common reason for indicated preterm delivery with diabetes was preeclampsia (38%). Small-for-gestational age (SGA) babies were also common in indicated preterm deliveries in the diabetic women. Aspirin had no effect on these outcomes (248,322). So-called "late preterm" deliveries at 34–36 weeks continue to be a clinically significant problem in the United States (323), and this is exacerbated with maternal diabetes.

Population-based surveys since 2000 of pregnant women with unclassified preexisting diabetes in North America reported rates of delivery <37 weeks gestation to be 14.2%–27.7% of births (115,203,208,213,214,249), with one outlier at 37.9% in the 1990s (248) (Table 5.19). The same variation occurred in international studies (88,92,211,221,227,302,318) (Table 5.19) and in both U.S. and international studies for type 1 diabetes (93,94,95,98,100, 107,108,113,114,210,229,243,276,278, 305,306,307) (Table 5.20) and type 2 diabetes (95,98,107,108,113,114,210, 307,309) (Table 5.21). Despite this wide distribution of the frequency of preterm delivery among the population-based or multicenter studies of birth outcomes in diabetic women, the rates were considerably higher than in control populations in the seven studies with comparative data for unclassified preexisting diabetes (115,203,211,221,227,249,318) (Table 5.19) and for such studies of pregnant women with type 1 or type 2 diabetes (93,108,210,276,278,305,307) (Tables 5.20 and 5.21). The methodology of the studies is given in the footnotes.

Rates of preterm delivery were lower for type 2 diabetes (Table 5.21) than type 1 diabetes (Table 5.20) in studies in England (98,107), West Ireland (108) and Ontario, Canada (210), but not in California (114), Italy (95), or Sweden (307). In type 1 diabetes (Table 5.20) and in studies that did not distinguish between types of preexisting diabetes (Table 5.19), rates of preterm delivery were lower in data collected in 2001–2011 than in the 1990s but were still well in excess of controls (methods of comparison given in footnotes to the tables). The lower rates may be due to improved control of blood glucose and blood pressure and less apprehension about carrying diabetic pregnancies to full term.

Several studies categorized preterm delivery into gestational age groups in women with preexisting diabetes in pregnancy. Rates of very preterm delivery <28 weeks gestation ranged from 0.7% to 2.4% in four surveys (208,211,243,302). Using a cutoff of <32 weeks gestation, preterm delivery rates of 2.3% (276), 2.7% (227), 2.8% (208), 3.4% (278), 4.8% (226), and 4.8% (92) were observed; still significantly higher than reference populations. In a California statewide survey, the rates of preterm delivery at <32 weeks were 3.1% in pregestational diabetes without chronic hypertension and 10.1% with diabetes and chronic hypertension compared to 1.6% in nondiabetic, nonhypertensive controls (p<0.001) (203). In a new analysis for *Diabetes in America*, the distribution of gestational age at birth in liveborn infants of 17,784 mothers with preexisting diabetes is shown in Table 5.22 using data from the NVSS 2009. NVSS comprised data from 28 states, New York City, and the District of Columbia using the 2003 revision of the birth certificate (12). In this analysis, 24.7% of births were preterm, 4.24% were <32 weeks gestation, and 1.54% were <28 weeks.

Indications for preterm delivery in women with preexisting diabetes include preeclampsia and fetal testing suggesting stress, which are more common among diabetic women, although these outcomes do not explain the higher spontaneous preterm labor and delivery rates. These findings were consistent with older analyses of population-based birth certificate data (324). Some population surveys divided preterm delivery rates into indicated versus spontaneous in women with pregestational diabetes and controls. Of these, indicated preterm delivery was recorded in 5.0% of births to women with preexisting diabetes versus 1.6% in controls in Alberta, Canada (adjusted OR 3.8, 95% CI 3.2–4.6) (214); in 7.9% versus 1.5% in Utah (p<0.0001) (115); and in 15.4% versus 2.2% in Norway (OR 2.9, 95% CI 2.3–3.7) (278). Spontaneous preterm delivery was recorded in 10.5% of births to women with preexisting diabetes versus 5.1% in controls in Utah (p<0.0001) (115), in 10.9% versus 4.6% in Norway (no statistical test) (278), and in 18.5% versus 5.5% in Alberta (adjusted OR 4.2, 95% CI 3.8–4.7) (214).

Preterm birth in diabetic women is sometimes associated with polyhydramnios or

TABLE 5.22. Distribution of Gestational Age at Birth in Liveborn Infants of 17,784 Mothers With Preexisting Diabetes Mellitus in Pregnancy, U.S., 2009

GESTATIONAL AGE (WEEKS)	PERCENT
<20	0.04
20–27	1.5
28–31	2.7
32–33	3.4
34–36	17.1
37–38	36.5
39	21.2
40	9.4
41	4.0
≥42	4.1

Data include 28 states, Washington, DC, and New York City using the 2003 revised birth certificate.

SOURCE: National Vital Statistics System 2009 (Reference 12)

preterm premature rupture of membranes (325), but these data are not often recorded in more recent surveys. Only one multicenter study reported preterm premature rupture of membranes: 7.2% in 749 women with type 1 diabetes, as well as 7.5% polyhydramnios and 37.2% preterm delivery (243). Polyhydramnios was reported since 2000 in three other multicenter studies (108,309) or population surveys (115) of pregnant women with preexisting diabetes. Frequencies of 2.0% were found in women with pregestational diabetes in the previous and current pregnancy in Utah (vs. 0.53% of nondiabetic women, p<0.0001) (115) and 11.5% for type 1 diabetes (vs. 1.8% of matched controls) and 7.1% for type 2 diabetes (vs. 5.6% of matched controls) in births >23 weeks gestation in the Irish Atlantic seaboard (108). A1c values throughout pregnancy were significantly higher in type 1 diabetic women with polyhydramnios than in type 2 diabetic women with the condition (p=0.01) (108). Polyhydramnios defined as a maximum pool depth of 10 cm by ultrasound occurred in 9.3% of 182 women with type 2 diabetes compared to 3% of nondiabetic women in the West Midlands of England in 1990–2002 (309). Polyhydramnios was not examined in reference to preterm birth in this study, and fetal macrosomia was not associated with polyhydramnios. However, an infant death was more likely to occur in type 2 diabetic women with polyhydramnios compared to those without (17.6% vs. 2.7%, p<0.01) (309).

Improved glycemic control of women with preexisting diabetes may decrease the indicated and spontaneous preterm birth rates, since early and midpregnancy A1c levels predict increase in risk of spontaneous and indicated preterm delivery (262,283,284,306,316). Male fetal sex was not a significant risk factor for preterm birth in pregnancies complicated by either type 1 diabetes, type 2 diabetes, or gestational diabetes in a large survey in Sweden in 1998–2007, in contrast to significant male bias in births at <32 weeks and at 32–36 weeks gestation in the reference population (307).

CESAREAN DELIVERIES

Whether elective cesarean section should be performed in diabetic and other women to minimize the chance of birth trauma remains a burning question (326). In a new analysis conducted for *Diabetes in America*, using NVSS data from 2009 (12), the prevalence of cesarean sections was 56.5% among women with preexisting diabetes, and the rate of instrumental vaginal delivery was low, at 3.0% of the total or 6.9% of vaginal deliveries (Table 5.23). In an analysis of New York City birth certificate data from 1999–2001, there was excess risk of primary cesarean delivery in women with chronic diabetes compared to women without diabetes (adjusted OR 2.37, 95% CI 2.05–2.75), and the excess risk was present in all racial/ethnic groups examined (324).

In the population-based surveys of pregnant women with preexisting diabetes in North America listed in Tables 5.19, 5.20, and 5.21, the cesarean section rates were 36.8%–61.8% (undifferentiated preexisting diabetes in pregnancy, type 1 diabetes, type 2 diabetes) (114,115,208,210,213,214,249), with similar rates in other countries (88,92,93, 94,95,98,100,107,113,221,227,229, 276,278,305). Cesarean section rates were >50% in five of nine North American data sets and 51.1%–72.9% in 14 of the 20 international data sets (Tables 5.19, 5.20, and 5.21). The high rates were seen for both type 1 and type 2 diabetes in some (95,98,107,108,114), but not all (113,210,307), surveys (Tables 5.20 and 5.21).

For population-based data sets including diabetic women and control populations, the crude or adjusted effect sizes for cesarean delivery in diabetes ranged from adjusted odds ratios of 1.6 (95% CI 1.3–1.9) for type 2 diabetes and 2.7 (95% CI 2.3–3.1) for type 1 diabetes in Ontario, Canada (210); adjusted odds ratio 2.5 (95% CI 2.3–2.7) for undifferentiated preexisting diabetes in Alberta, Canada (214); relative risk 3.7 (95% CI 3.2–4.2) for type 1 diabetes in the Netherlands (100); relative risk 4.4 (95% CI 4.1–4.8) for type 1 diabetes in Denmark (93); odds ratio 4.6 (95% CI 3.7–5.7) for type 1 diabetes in Belgium (305); adjusted odds ratio 5.3 (95% CI 5.0–5.7) for type 1 diabetes in Sweden (276); and odds ratio 6.2 (95% CI 4.5–8.6) for preexisting diabetes in South Carolina (327). Even after adjustment for indications for cesarean delivery, including prior cesarean delivery, preeclampsia, and fetal macrosomia, and for other risk factors such as maternal and gestational age, diabetes was a significant predictor of cesarean delivery—a finding supported by another report based on birth certificates (324). Women with preexisting diabetes mellitus more frequently fail attempts at vaginal delivery after cesarean section than do nondiabetic women (38% vs. 24%) (328), with higher failure rates corresponding to more severe diabetes (329).

TABLE 5.23. Distribution of Birth Weight and Route and Method of Delivery for Gestational Age >37 Weeks Among Women With Preexisting Diabetes Mellitus in Pregnancy, U.S., 2009

BIRTH DATA	PERCENT
Route and method of delivery	
Spontaneous	40.5
Forceps	0.8
Vacuum	2.2
Cesarean	56.5
Birth weight (g)	
500–<1,000	0.02
1,000–<1,500	0.1
1,500–<2,000	0.6
2,000–<2,500	3.3
2,500–<3,000	14.9
3,000–<3,500	33.0
3,500–<4,000	29.3
4,000–<4,500	12.8
4,500–<5,000	4.6
≥5,000	1.4

Data include 28 states, Washington, DC, and New York City using the 2003 revised birth certificate. Missing values for route and method of delivery, n=10. Missing values for birth weight, n=9.

SOURCE: National Vital Statistics System 2009 (Reference 12)

NEONATAL COMPLICATIONS IN INFANTS OF MOTHERS WITH PREEXISTING DIABETES

Admissions to a neonatal intensive care unit (NICU) for a variety of reasons are much more common for infants of mothers with pregestational diabetes than controls, adding greatly to medical costs. With undifferentiated preexisting diabetes, 48.9% of 454 liveborn infants were admitted to NICU among diabetic mothers participating in a multicenter randomized controlled trial of aspirin use to prevent preeclampsia in 1991–1995, but reported in 2000 (no effect). The rate was 70.4% if the mother had diabetic vascular disease (248). In a separate analysis of this trial, for deliveries of liveborn infants of diabetic mothers at <37 weeks, the rates of admission to NICU were 69.2% for indicated preterm deliveries and 74.6% for spontaneous deliveries (322). Analysis of a multicenter study in Utah in 2002–2010 showed 20.6% of 802 infants of women with preexisting diabetes in the current and previous pregnancy were admitted to NICU compared to 7.6% of controls ($p<0.0001$) (115).

In a population-based study in Alberta, Canada, in 2005–2011, NICU admission occurred in 32.4% of liveborn infants of diabetic mothers versus 16.4% of infants of mothers with gestational diabetes and 10.8% of controls (adjusted OR 3.81, 95% CI 3.49–4.16 for preexisting diabetes vs. controls). The rate of admission to NICU was 72.9% in 50 twin deliveries of mothers with preexisting diabetes (214). In West Ireland in 2010–2014, 44% of infants of mothers with type 1 and type 2 diabetes (mixed) received neonatal intensive care (88). Multicenter studies of mothers with type 2 diabetes showed NICU admission rates of 42.2% in the West Midlands of England (309), 39.2% in West Ireland (108), and 39.6% in Japan (113).

Lower rates of NICU admission were reported in Australia in 1998–2002 for 1,228 liveborn infants of mothers with pregestational diabetes (10.4% vs. 2.1% in controls, OR 5.45, 95% CI 4.51–6.58) (227) and in East Anglia, England, in 2006–2009 (9.8% of 317 liveborn infants of mothers with type 1 diabetes and 5.0% of 218 liveborn infants of mothers with type 2 diabetes) (107). These rates of NICU admission may be affected by strategies of triage of infants to transitional observational or special care units (107). There was a trend for admission to NICU for infants of mothers with type 1 diabetes in Finland from 25.3% in 1999–2003 to 18.0% in 2004–2008 (226).

NEONATAL, PERINATAL, AND INFANT MORTALITY

In the United States, all live births, regardless of gestational age, are to be reported as vital record events (330). Infant deaths involve reporting both live birth and death certificates, which also include demographic and clinical information that could support cause-of-death determination. A live birth that results in death within the first 364 days of life is defined as an infant death, further subdivided as early neonatal (<7 days), late neonatal (7–27 days), neonatal (<28 days), or postneonatal (28–364 days) (13,330). The last subcategory is important because intensive neonatal care often produces survivors >28 days when the initial problem was a perinatal event or process. Perinatal mortality comprises the combination of fetal and neonatal deaths <28 days of life, assuming that similar factors are associated with these losses (13,330). Surveys that exclude pregnancies with congenital malformations in the infants will have lower fetal and infant death rates, so they are not comparable to standard surveys of pregnancy outcome.

Studies with variable definitions of neonatal mortality and perinatal mortality from Europe are included here because few North American population-based studies of pregestational diabetes provide neonatal data. Information on neonatal mortality was available in four reports (208,214,248,249) with large data sets collected since 2000 in the United States and Canada and not available in seven surveys (91,114,115,203,210,212,213) (Tables 5.19, 5.20, and 5.21). The frequency of neonatal death among liveborn infants of mothers with undifferentiated preexisting diabetes was <1.0% in three surveys in North America (208,214,248), with one outlier at 1.37% in a rural province with data collected in 1988–2002 (249) (Table 5.19). Excess risk of neonatal mortality compared to nondiabetic pregnancies could be calculated in only one study with an adjusted odds ratio of 2.0 (95% CI 1.27–3.17) in Alberta, Canada (214).

In Europe, in 1996–2008, four surveys of pregnancies complicated by preexisting diabetes of unclassified type had neonatal mortality rates of 0.40% in Northern England in 1996–2008 (211), 1.7% in Northern England in 2002–2004 (209), 0.83% in the United Kingdom in 2002–2003 (302), and 0.95% in France in 2000–2001 (92). Crude relative risk was calculated in one study from the United Kingdom at 1.74 (95% CI 0.8–3.9) (211). Two other studies defined neonatal death as within the first week of life with the following rates: zero in West Ireland in 2005–2014 (88) and 0.15% in Bavaria, Germany, in 2001–2007 (318). The Australian survey presented a neonatal death in hospital rate of 0.4% for infants of mothers with pregestational diabetes versus 0.2% in controls in 1998–2002 (OR 1.78, 95% CI 0.65–4.45) (227). These data are presented in Table 5.19, with methods in the footnotes.

Of 17 European population-based surveys or multicenter studies of pregnancies complicated by type 1 diabetes conducted in 1993–2013 (Table 5.20), among liveborn infants, eight reported neonatal mortality rates of 0.47%–0.96% (98,107, 243,276,278,302,304,305), and there were two outliers with rates of 0.22% in a multicenter study in Italy in 1999–2003 (95) and 1.5% in Northwest England in 1995–1999 (303) (see footnotes to Table 5.20 regarding references 276 and 307). Three surveys presented the effect size for neonatal death compared to control populations: adjusted odds ratio 2.7 (95% CI 1.7–4.2) for Sweden in 1991–2003 (276); odds ratio 2.6 in Belgium in 2002–2004 (305); and adjusted odds ratio 1.5 (95% CI 0.7–3.3) in Norway in 1985–2004 (278). Methods are shown in the footnotes to Table 5.20. Five studies had data

only for the first week of neonatal life (93,94,100,229,306), as well as one multicenter study in Japan (113). No neonatal deaths were reported in a study of 191 women with type 1 diabetes in West Ireland in 2007–2013, but the length of follow-up of infants was undefined (108).

Only six population-based or multicenter analyses had data on mothers with type 2 diabetes (Table 5.21); none was conducted in North America. Zero neonatal deaths among 218 liveborn infants were reported in East Anglia, England, in 2006–2009 (107), and there were no infant deaths up to 1 year of life in 208 female infants of mothers with type 2 diabetes and two in 204 male infants (1.0%) in a national survey in Sweden in 1998–2007 (307). The crude neonatal death rates with type 2 diabetes were 0.75% (98), 0.95% (302), 1.9% (309), and 2.1% (95) over the past decade in Europe. In the West Midlands of England (309), the rate of 1.86% contrasted with 0.53% for the background population (p=0.21). The rate in a multicenter study in Japan was 0.59% for infants dying in the first week of life (113).

Perinatal mortality rates (n/100; defined as fetal death ≥20 gestational weeks and neonatal deaths <29 days) have declined to 1.1% in Utah (115), 1.3% in Ontario, Canada (212), and 1.6% in Northern California (208) compared to 2.3% in Nova Scotia, Canada, in 1988–2002 (249), 2.4% in a multicenter study in the United States in the 1990s (248), and 2.9% in Alberta, Canada, in 2005–2011 (214) (Table 5.19). Surveys from Europe with deliveries since 2000 reported perinatal mortality rates of 3.05% to 3.5% in the United Kingdom (209,243,302), West Ireland (108), and Flanders, Belgium (305), and 2.02% for infants of type 2 diabetic mothers in West Ireland (108) (Tables 5.19, 5.20, and 5.21). Studies with definitions of stillbirth as >27 weeks were excluded. Effect sizes were relative risks of 3.8 (95% CI 3.0–4.7) in the United Kingdom (for type 1 and type 2 diabetes combined) (302) and 4.1 (95% CI 2.9–5.6) in Denmark (93), adjusted odds ratio 3.1 (95% CI 2.2–4.4) in Norway (278), and odds ratio 4.28 (95% CI 2.22–8.01) in Flanders, Belgium (305), in studies of type 1 diabetes with reference populations (deliveries 1985–2004; see footnotes to Tables 5.19 and 5.20 for methods of comparison). Many studies have linked poor glycemic control in early and continuing pregnancy with increased perinatal mortality (290,316,317,331).

Population-based surveys of the frequency of postneonatal (late infant) death, i.e., from 29 days to 1 year of life in infants of diabetic mothers (unclassified or type 1 diabetes) show rates of 0.20% to 0.57% in relatively small studies (211,249,304,305) (Tables 5.19 and 5.20) compared to 0.19% among 3,157 liveborn infants in Northern California (208), 0.7% among 2,004 female infants and 0.4% among 2,088 male infants in Sweden (307), and 0.55% among 1,280 liveborn infants in Norway (278). Effect sizes were odds ratio 2.5 (305) and relative risks 2.1 (95% CI 0.8–5.6) (211) and 2.75 (278) in three studies with reference populations. In two studies of infants of mothers with type 2 diabetes, postneonatal death rates were 1.0% in male infants in Sweden (vs. 0.2% in controls) (307) and 1.2% in the West Midlands of England (vs. 0.2% in the background population) (309).

In the only large population-based study of the effect of fetal sex on pregnancy outcomes with maternal diabetes, there was no significant male bias in perinatal mortality (fetal death at ≥28 weeks or within the first week of life) in 4,092 births with type 1 diabetes in 1998–2007 nor in late neonatal deaths or infant deaths in the first year (307). The findings were the same in 8,602 pregnancies with gestational diabetes, in contrast with a significant male bias in late neonatal deaths in the reference population of 905,565 births (307).

CONDITION AT BIRTH AND SEQUELAE

Due to the previous high perinatal mortality with maternal diabetes, for decades there has been anxiety about the condition of the baby at birth. Poor condition has been described as "fetal distress," "fetal jeopardy," "depressed," and "birth asphyxia." In the DCCT, among 191 liveborn infants of mothers with type 1 diabetes, the state of consciousness of the newborn was described as normal (89.5%), hyperalert (1.1%), lethargic (7.3%), comatose (0.5%), and unknown (1.6%) (6). Definitions at birth range from fetal distress defined as "whenever vacuum extraction or cesarean section was performed as a result of suspected or manifest fetal hypoxia," which was coded as present in 14% of 5,089 infants of mothers with type 1 diabetes delivered in Sweden in 1991–2003 (276), to fetal distress undefined in 13.6% of 464 infants of mothers with type 1 diabetes and 4.3% of 141 infants of mothers with type 2 diabetes delivered in Italy in 1999–2003 (95).

Use of Apgar scores to mark depression at birth has been quite variable in studies of infants of diabetic mothers. In a new analysis for *Diabetes in America,* NVSS data based on birth certificates from 2009 (12) were used to assess the distribution of 5-minute Apgar scores according to route and method of delivery in newborns of women with preexisting diabetes, including a subgroup with chronic hypertension. Apgar scores <7 were recorded in 3.7% of spontaneous vaginal deliveries, in 5.4% of forceps vaginal deliveries, in 4.5% of vacuum vaginal deliveries, and in 5.1% of cesarean deliveries. Apgar scores <7 were recorded in 6.6% of births to diabetic women with preexisting hypertension. Five-minute Apgar scores <4 were recorded in less than 2.4% in any category of delivery (Table 5.24).

Apgar scores were used as follows in other population-based studies: 5-minute Apgar score <7 in 3.1% and <4 in 0.8% of 5,020 liveborn infants of mothers with type 1 diabetes in Sweden (adjusted OR 2.39, 95% CI 1.64–3.51 for Apgar score <4 vs. controls) (276); 5-minute Apgar score <7 in 5.0% of 318 liveborn infants of mothers with type 1 diabetes in the Netherlands (100); 5-minute Apgar score <4 in 0.7% of 1,228 liveborn infants of mothers with diabetes in Australia (crude OR 2.83, 95% CI 1.37–5.62 compared to infants of mothers without diabetes) (227); and

TABLE 5.24. Route and Method of Delivery by 5-Minute Apgar Score in Newborns of Women With Preexisting Diabetes Mellitus in Pregnancy, U.S., 2009

DELIVERY METHOD AND MATERNAL COMORBIDITY	PERCENT			
	Apgar Score			
	0–3	4–6	7–8	9–10
Route and method of delivery				
Spontaneous	1.5	2.2	16.8	79.5
Forceps	2.3	3.1	22.5	72.1
Vacuum	1.1	3.4	21.5	74.0
Cesarean	1.3	3.8	21.0	73.9
Comorbidities				
Preexisting hypertension	2.1	4.5	21.7	71.7

Data include 28 states, Washington, DC, and New York City using the 2003 revised birth certificate.

SOURCE: National Vital Statistics System 2009 (Reference 12)

5-minute Apgar score <3 in 1.8% of 904 infants of mothers with type 1 diabetes (adjusted OR 2.48, 95% CI 1.44–4.00 compared to nondiabetic controls) and 1.4% of 516 infants of mothers with type 2 diabetes (adjusted OR [NS] compared to nondiabetic controls) in Ontario, Canada (210). In the Helsinki region of Finland (226), umbilical artery pH <7.15 was used as a marker of condition at birth, found in 5.9% of 188 liveborn infants of mothers with type 1 diabetes in 1999–2003 and 15.1% of 324 liveborn infants of mothers with type 1 diabetes in 2004–2008. "In logistic regression analysis, nulliparity, in addition to poor glycemic control, was associated with the risk of [umbilical artery] pH <7.15 and low Apgar score at birth" (226).

While neonatal encephalopathy (NE) is uncommon (2–5 per 1,000 live births), it is an important cause of neonatal death, and up to 30% of infants with NE exhibit significant long-term neurodevelopmental disability (332). Maternal diabetes is also associated with risk of neonatal seizures or NE via neonatal hypoglycemia (333,334) and perhaps by hypocalcemia or hyperbilirubinemia. Hypoglycemia is associated with adverse neurodevelopmental outcomes in all infants at risk for NE (335,336). A European case-control study compared characteristics of 27 singleton term infants who developed NE (0.09%) in 1993–2003 with those of 100 randomly selected controls; maternal diabetes was one of the antenatal risk factors related to occurrence of NE (337).

NE rates are not often collected or stated in population-based or multicenter studies of preexisting diabetes mellitus. Of seven reports with detailed neonatal morbidity data, the multicenter survey in Italy reported neonatal asphyxia in 9.3% of 464 liveborn infants of mothers with type 1 diabetes and 8.5% of 141 liveborn infants of mothers with type 2 diabetes, but it was not clear how long after birth the clinical evaluation was made or what criteria were used (95). Data from a large Swedish birth registry from 1998–2007 with infants born alive at 32–43 weeks gestation (SGA babies excluded) showed two cases of NE among 1,783 appropriate-for-gestational age (AGA) infants of mothers with type 1 diabetes and two cases among 1,734 large-for-gestational age (LGA) infants of mothers with type 1 diabetes (338).

Neonatal seizures in term infants are a subset of NE (332). Preexisting diabetes mellitus was an independent risk factor for term neonatal seizures (adjusted OR 4.32, 95% CI 1.62–6.59 compared to infants of mothers without diabetes) in a case-control study using the Colorado Birth Certificate Registry (333). Neonatal seizures were recorded in 0.56% of 1,783 AGA infants of mothers with type 1 diabetes and 0.35% of 1,734 LGA infants of mothers with type 1 diabetes in a large Swedish birth registry for liveborn infants at 32–43 weeks gestation in 1998–2007 (SGA babies excluded) (338).

Cerebral palsy (CP) is a major concern for infants with NE (332). In a case-control study in Sweden in 1984–1998, type 1 diabetes was associated with CP (OR 2.1, 95% CI 1.4–3.1) to a greater degree than was preeclampsia (OR 1.5, 95% CI 1.3–2.4) (339) compared to controls without diabetes or preeclampsia. Other large data sets, CP registries, or systematic reviews have stated maternal diabetes was not a risk factor for CP in offspring, without defining the type of diabetes (340), or diabetes was not mentioned in the analysis. In a study using the Canadian Cerebral Palsy Registry, among 155 term-born children with CP following NE, seven were infants of insulin-dependent diabetic mothers (4.5%) (341). Overall, 12 CP cases were associated with shoulder dystocia (7.7%), and four of those were infants of mothers with gestational diabetes (341). This suggests the possibility of a link among maternal diabetes, difficult delivery, NE, and CP.

FETAL GROWTH AND SIZE AT BIRTH

Due to restricted numbers of deliveries earlier in pregnancy (although in greater proportion than in nondiabetic women), it is not certain that populations of fetuses of diabetic mothers in early gestational age groups are bigger or smaller than controls (277,305). *Fetal macrosomia in utero* is common with type 1 or type 2 diabetes after 26 weeks gestation (305,342,343,344) and is predicted by elevated maternal A1c (283,284,345,346,347,348), obesity (343,344,349), and excess gestational weight gain—the latter relationship noted especially in the absence of obesity (308,348).

The usual method to define fetal growth restriction is by the proportion of SGA infants at birth (and small for sex and/or racial/ethnic group; SGA is <10th percentile birth weight in a reference population) and to define excess fetal size or mass by the proportion of LGA infants at birth (and large for sex and/or racial/ethnic group; LGA is >90th percentile birth weight in a reference population) (13). Other methods of assessment are discussed below. However, the denominators used to determine rates of SGA and LGA vary in different studies. Use of percentage of

total births beyond a defined gestational age reflects the fact that some stillborn infants are obviously too small or too large (especially if estimated by ultrasonography prior to demise). Use of percentage of liveborn infants reflects the fact that not all stillborn infants are weighed and that *in utero* fetal mass can change after demise.

Table 5.23 shows the distribution of birth weights among women with preexisting diabetes in U.S. states using the 2003 revised birth certificate, in a new analysis of NVSS 2009 data for *Diabetes in America* (12). Birth weights were at 4,000–4,499 g in 12.8% of deliveries >37 weeks gestation, at 4,500–4,999 g in 4.6%, and ≥5,000 g in 1.4%. Thus, 18.8% of term births had fetal macrosomia defined by birth weight ≥4,000 g. The data set does not account for infants born at <38 weeks who were large-for-gestational age and sex (LGA) on growth charts. Table 5.25 shows the distribution of birth weight >4,000 g among women with preexisting diabetes by gestational weight gain from the NVSS 2009 (12). The prevalence of birth weight >4,000 g increased by gestational weight gain, from 10.4% with gain of <11 lb to 29.1% with gain of >40 lb. The interaction with glycemic control is not available in this data set.

In the largest data set examining the relationship of maternal BMI to fetal overgrowth in infants of type 1 diabetic mothers in the Swedish Medical Birth Registry for 1998–2007, the adjusted odds ratios for LGA babies were 1.18 (95% CI 1.01–1.38) for 1,195 overweight mothers (BMI 25–29.9 kg/m^2; 50% LGA) and 1.21 (95% CI 1.00–1.47) for 618 obese mothers (BMI ≥30 kg/m^2; 51% LGA) compared to 1,644 diabetic mothers with normal BMI 18.5–24.9 kg/m^2 (47% LGA) (277). The modest effect was adjusted for maternal age, height, parity, smoking, chronic hypertension, and Nordic origin (yes/no). BMI values were obtained from maternal recall of height and prepregnancy weight. No information about glycemic control or gestational weight gain was available.

A stronger effect of maternal BMI was seen in the 764,498 control mothers without diabetes, where glycemic control was not an issue: 8.2% LGA with maternal BMI 18.5–24.9 kg/m^2 (reference value), 13% LGA with BMI 25–29.9 kg/m^2 (adjusted OR 1.76, 95% CI 1.73–1.79), and 18% LGA with BMI ≥30 kg/m^2 (adjusted OR 2.60, 95% CI 2.55–2.66) (277). The likelihood ratio test was used for potential interaction between maternal BMI categories and type 1 diabetes for the risk of LGA. Then, the adjusted odds ratios for LGA with maternal diabetes compared to controls stratified on prepregnancy BMI were 10.72 (95% CI 9.56–12.01) with BMI 18.5–24.9 kg/m^2, 13.55 (95% CI 12.23–15.02) with BMI 25–29.9 kg/m^2, and 13.26 (95% CI 11.27–15.59) with BMI ≥30 kg/m^2 (interaction p<0.001) (277).

Great variations in size at birth are associated with short-term and long-term morbidity (350,351,352), especially in infants of diabetic mothers (353). But there is nonconformity in the definitions of the normal limits of birth weight, adiposity and body composition, and length and head circumference for gestational age (too small; too large) that are used in the general population.

Most authors of the population-based or multicenter studies of preexisting diabetes listed in Tables 5.26 and 5.27 used birth weight <10th percentile for gestational age and sex for SGA and birth weight >90th percentile for gestational age and sex for LGA, using population-based birth weight percentiles relevant to their geographic area (88,93,108,113,115, 203,208,214,226,227,248,277,308, 309,322). Newborn macrosomia has also (113,115,208,248,308,309) or only (95,114) been categorized as ≥4,000 g or also as ≥4,500 g (88,93,107,108,208,309) in these studies (Tables 5.26 and 5.27; references 206 and 215 were excluded due to unclear definitions). One set of authors also used <2.5th or <3rd percentile or >95th–97.5th percentile for a more stringent definition of severe SGA or marked LGA (226). Another way to look at the shifted population distribution of birth weights with maternal diabetes is to use birthweight *z*-scores (<2.0 SD units, <2.3th percentile; >2.0 SD units, >97.7th percentile) (226).

TABLE 5.25. Birth Weight >4,000 g Among 17,784 Women With Preexisting Diabetes Mellitus in Pregnancy, by Maternal Weight Gain, U.S., 2009

GESTATIONAL WEIGHT GAIN (LBS)	PERCENT
Total	16.1
<11	10.4
11–20	14.9
21–30	22.5
31–40	23.1
41–98	29.1

Data include 28 states, Washington, DC, and New York City using the 2003 revised birth certificate.

SOURCE: National Vital Statistics System 2009 (Reference 12)

The IADPSG-proposed codification of definitions of pregnancy outcomes with maternal diabetes accepts LGA as ≥90th percentile for gestational age or macrosomia as birth weight ≥4,000 g (13). Comparing the two outcome measures, in a regional study of 350,311 singleton births in England in 1988–1997, macrosomia was a better predictor of obstetrical morbidity than was LGA (350). Nested in the study were 1,072 cases of preexisting diabetes, which was a much stronger predictor of LGA (OR 6.97, 95% CI 5.96–8.16) than of birth weight >4,000 g (OR 1.81, 95% CI 1.50–2.19), probably due to LGA being present in early deliveries with diabetes, before the fetus reaches >4,000 g. The effect size of maternal obesity was equivalent at predicting LGA (OR 1.97, 95% CI 1.88–2.06) or macrosomia (OR 2.08, 95% CI 1.99–2.17) (350). An analysis with similar results was made in 2,432 live births to women with preexisting diabetes (30.2% LGA, adjusted OR 3.94, 95% CI 3.61–4.31; 11.3% macrosomia >4,200 g, adjusted OR 2.11, 95% CI 1.86–2.40) compared to 304,696 singleton live births to women

TABLE 5.26. Neonatal Outcomes for Pregnancies in Women With Undifferentiated Preexisting Diabetes Mellitus in Pregnancy, Population-Based or Multicenter Studies, 1991–2014

REGION, YEARS (REF.)	TOTAL NUMBER OR LIVEBORN INFANTS OF DIABETIC MOTHERS	NUMBER OF CASES (PERCENT) VERSUS (PERCENT IN CONTROLS) AND EFFECT SIZE (95% CI)					
		Birth Trauma*	Small-For-Gestational Age	Large-for-Gestational Age	Respiratory Distress Syndrome and/or TTN	Neonatal Hypoglycemia	Hyperbilirubinemia Phototherapy
United States, 1991–1995 (248)†	454‡		22 (4.8)‡	159 (35.0)‡ >4,000 g: 71 (15.6)‡	NR NICU care: 48.9%‡		
United States, 1991–1995 (322)†	454‡		<35 w: 4/61 (6.6) <37 w: 15/161 (9.3)		RDS <35 w: 24/58 (41.4) RDS <37 w: 41/156 (26.3)		
California, 2006 (203)§	PDM alone: 3,718‖ PDM with CH: 433‖		361 (9.7)‖ adjOR 1.0 (1.0–1.2) 79 (18.2)‖ adjOR 2.2 (1.6–3.0)	301 (8.1)‖ adjOR 3.4 (3.0–3.8) 26 (6.0)‖ adjOR 1.8 (1.2–2.7)			
California, 2001–2007 (213)¶	22,331‖		391 (1.75)‖	1,657 (7.42)‖			
Northern California, 2007–2011 (208)#	1,730‖ 1,712‡	44 (2.6)‡	119 (6.9)‖	560 (32.4)‖ ≥4,000 g: 374 (21.6)‖ ≥4,500 g: 119 (6.9)‖	150 (8.8)‡ <37 w: 104 (6.1)‡ ≥37 w: 46 (2.7)‡	32 (1.9)‡	352 (20.6)‡
Utah, 2002–2010 (115)**	802 singleton births‖	9 (1.1)‖ vs. (0.84)	34 (4.3)‖ vs. (5.8)	193 (24.2)‖ vs. (9.2) p≤0.0001 >4,000 g: 104 (13.0)‖ vs. (7.4) p≤0.0001	70 (8.7)‖ vs. (3.2) p≤0.0001	18 (2.2)‖ vs. (1.9)	All types of jaundice: 239 (29.8)‖ vs. (19.0) p≤0.0001
Alberta, Canada, 2005–2011 (214)††	2,432 singleton births‡		161 (6.6)‡ vs. (10.3) adjOR 0.65 (0.55–0.76)	734 (30.2)‡ vs. (9.1) adjOR 3.94 (3.61–4.31) >4,200 g: 276 (11.3)‡ vs. (5.2) adjOR 2.11 (1.86–2.40)	NR NICU care: 788 (32.4)‡ vs. (10.8) adjOR 3.81 (3.49–4.16)		
West Ireland, 2005–2014 (88)‡‡	2005–2009: 187‖ 182‡ 2010–2014: 198‖ 197‡		14 (7.5)‖ 14 (7.1)‖	46 (24.6)‖ >4,500 g: 12 57 (28.8)‖ >4,500 g: 15	NR NICU care: 105 (57.7)‡ NR NICU care: 100 (50.8)‡	33 (18.1)‡ 27 (13.7)‡	
New South Wales, Australia, 1998–2002 (227)§§	1,228‡	46 (3.75)‡ vs. (2.9) crOR 1.31 (0.96–1.78)	77 (6.3)‡ vs. (9.8) crOR 0.93 (0.73–1.20)	430 (35.0)‡ vs. (10.4) crOR 4.91 (4.28–5.63)	NR NICU care: 128 (10.4)‡ vs. (2.1) crOR 5.45 (4.51–6.58)	587 (47.8)‡ vs. (1.6) crOR 56.8 (50.5–63.8)	

Table includes prospective population-based and multicenter studies reported in 2000–2014. Neonatal is defined as 1–28 days of life. AdjOR, adjusted odds ratio (95% CI); CH, chronic hypertension; CI, confidence interval; crOR, crude odds ratio; ICD-9/10, International Classification of Diseases, Ninth/Tenth Revision; LGA, large-for-gestational age, ≥90th percentile for age (and sex); NICU, neonatal intensive care unit; NR, not reported; PDM, preexisting diabetes mellitus in pregnancy, undifferentiated; RDS, respiratory distress syndrome; SGA, small-for-gestational age, <10th percentile for age (and sex); TTN, transient tachypnea of the newborn; w, weeks gestation.

* Undefined birth trauma

Table 5.26 continues on the next page.

TABLE 5.26. (continued)

† Multicenter: References 248 and 322 are aspects of the same prospective multicenter randomized controlled trial of low-dose aspirin use in pregnancy to prevent preeclampsia; aspirin without effect. Diabetic women required insulin before pregnancy; included 55 diabetic women with CH; singleton births, excluded congenital anomalies; recruited at 13–26 w. Numbers from reference 322 exclude cases with missing data. Reference 322 also showed three cases of neonatal intraventricular hemorrhage among 34 spontaneous preterm deliveries at <35 w.

‡ Denominators are all liveborn infants.

§ Includes normally formed singleton infants recorded in the California Vital Statistics Birth Certificate Database linked with the California Patient Discharge Database. Women with PDM and CH identified by ICD-9 codes. Multivariable logistic regression used to determine estimated effect size versus women without disease, adjusted for maternal age, race/ethnicity, insurance type at delivery, education level, parity, number of prenatal visits, obesity, and renal disease.

‖ Denominators are total deliveries.

¶ Statewide hospital delivery discharges with complete data; subjects missing age or race/ethnicity data as well as extremes of age (<15 and ≥55 years) were excluded. Diagnoses based on ICD-9 codes. "Poor fetal growth" and "excess fetal growth" were undefined in the report. No prevalences given in article for infants of nondiabetic women, only for women with gestational diabetes.

A. Ferrara and T. Peng, unpublished data from the Kaiser Permanente of Northern California system of 10 maternity hospitals, prepared for *Diabetes in America, 3rd edition.* Included number of infant records linked to maternal records. SGA and LGA if having <10th and ≥90th centiles, respectively, of the race-specific cutpoints for birth weight. Neonatal hypoglycemia (ICD-9 775.6) was treated in NICU. Hyperbilirubinemia if meeting the American Academy of Pediatrics guidelines to treat with phototherapy based upon the bilirubin level, time after birth, and several risk factors (i.e., gestational age, Coombs testing).

** Retrospective multicenter analysis of electronic medical records of 20 hospitals. Included here preexisting diabetes ICD-9 codes in the previous and current index pregnancy (type 1 diabetes 103, type 2 diabetes 118, unknown 581; 75.8% used insulin, 11.4% oral agents, 12.8% diet). Number of liveborn versus stillborn infants unknown, so denominator for all outcomes here is total deliveries. Relative risks compared to population of 58,224 births to women without any type of diabetes in the previous and current index pregnancy; assessed by Poisson regression models with robust variance estimators. ICD-9 code 769 used for respiratory distress syndrome: a condition of the newborn marked by dyspnea with cyanosis, heralded by such prodromal signs as dilatation of the alae nasi, expiratory grunt, and retraction of the suprasternal notch or costal margins. ICD-9 code 775.6 used for listing of neonatal hypoglycemia. Jaundice based on ICD-9 codes 774.6 for unspecified fetal and neonatal jaundice and 774.2 for neonatal jaundice associated with preterm delivery.

†† Here included all singleton pregnancies that resulted in delivery of live births ≥20 w, based on the Alberta Vital Statistics Birth File. Clinical diagnoses based on ICD-10 codes, linking the Alberta Diabetes Database, the Notice of Birth database, the Hospital Abstract Database and Ambulatory Care Classification System, and the Hospital Discharge Database. Here, denominator of livebirths in PDM includes unknown number of cases in which data for SGA and LGA were not available; 176 cases were unavailable in total population, including PDM, gestational diabetes, and controls. Used multinomial logistic regression to examine the association of PDM with adverse outcomes, controlling for maternal characteristics; 306,576 pregnancies without any type of diabetes.

‡‡ All hospitals in regional diabetes and pregnancy program in the Irish Atlantic seaboard; 39% type 2 diabetes. Births >23 w. Denominators for SGA and LGA include five stillbirths in period 1 and one stillbirth in period 2. Neonatal hypoglycemia stated for liveborn infants, but undefined.

§§ Data obtained from linkage of two New South Wales Department of Health computerized datasets: the Midwives Data Collection and the Inpatient Statistics Collection, covering all births of >20 w or >400 g birth weight. Used ICD-10 diagnostic and procedure codes. Contingency tables were used to compare groups (352,673 pregnancies without diabetes). Neonatal hypoglycemia is ICD-10 P70.4.

SOURCE: References are listed within the table.

TABLE 5.27. Neonatal Outcomes for Pregnancies in Women With Type 1 Diabetes or Type 2 Diabetes, Population-Based or Multicenter Studies, 1990–2013

REGION, YEARS (REF.)	TOTAL NUMBER OR LIVEBORN INFANTS BY TYPE OF MATERNAL DIABETES	NUMBER OF CASES (PERCENT OF TOTAL DELIVERIES* OR LIVEBORN†) VERSUS (PERCENT IN CONTROLS‡) AND EFFECT SIZE (95% CI)					
		Birth Trauma Percent of Liveborn (All† or Vaginal§ Deliveries)	Small-for-Gestational Age or <2,500 g	Large-for-Gestational Age	Respiratory Distress Syndrome and/or TTN†	Neonatal Hypoglycemia†	Hyperbilirubinemia Phototherapy†
California, 2002–2004 (308)‖	Type 2: 2,042* 1,999† >36 w		97 (4.75)*	525 (25.7)* ≥4,000 g: 371 (18.2)*			
California, 2006 (114)¶	Type 1: 563* 555† Type 2: 2,224* 2,197†		62 (11.0)* 285 (12.8)*	>4,000 g: 66 (11.7)* 272 (12.2)*	36 (6.5) 49 (2.2)		145 (26.1) 496 (22.6)
West Midlands, England, 1990–2002 (309)#	Type 2: 163* 161†		17 (10.4)*	52 (31.9)* >4,000 g: 15 (9.2)* >4,500 g: 6 (3.7)*	NR NICU care: 68 (42.2)		
West Ireland, 2007–2013 (108)**	Type 1: 191* 185† Type 2: 99* 97† >23 w		12 (6.3)* vs. (6.5) 6 (6.1)* vs. (6.5)	52 (27.2)* 22 (22.2)* >4,500 g: Type 1: 14 (7.3)* Type 2: 9 (9.1)*	NR NR NICU care: Type 1: 102 (55.1) Type 2: 38 (39.2)	43 (23.2) 7 (7.2)	13 (7.0) 9 (9.3)

Table 5.27 continues on the next page.

TABLE 5.27. (continued)

REGION, YEARS (REF.)	TOTAL NUMBER OR LIVEBORN INFANTS BY TYPE OF MATERNAL DIABETES	NUMBER OF CASES (PERCENT OF TOTAL DELIVERIES* OR LIVEBORN†) VERSUS (PERCENT IN CONTROLS‡) AND EFFECT SIZE (95% CI)					
		Birth Trauma Percent of Liveborn (All† or Vaginal§ Deliveries)	Small-for-Gestational Age or <2,500 g	Large-for-Gestational Age	Respiratory Distress Syndrome and/or TTN†	Neonatal Hypoglycemia†	Hyperbilirubinemia Phototherapy†
Netherlands, 1999 (100)††	Type 1: 324 births* 318† >23 w or >500 g	5/175 (2.9)§		146 (45.1)* crRR4.5 (4.0–5.1)	RDS: 17 (5.3) TTN: 22 (6.9)	141 (44.3)	82 (25.8)
Denmark, 1993–1999 (93)‡‡	Type 1: 1,243* births 1,217† >23 w			761 (61.2)* ≥4,500 g: 97 (7.8)* vs. (3.4) cRR 2.3 (1.9–2.9)	RDS: 202 (16.6)		215 (17.7)
Italy, 1999–2003 (95)§§	Type 1: 469* 464† Type 2: 144* 141† >179 days	8 (1.7)† 2 (1.4)†		>4,000 g: 62 (13.2)* 17 (11.8)*	7 (1.5) 5 (3.5)	77 (16.6) 28 (19.9)	105 (22.6) 22 (15.6)
Sweden, 1991–2003 (276)‖‖	Type 1: 5,089* 5,020† >27 w	Erb's palsy: 56 (2.1)§ vs. (0.25) adjOR 6.7 (4.8–9.3)	117 (2.3)* vs. (2.5) adjOR 0.7 (0.6–0.9)	1,578 (31)* vs. (3.6) adjOR 11.4 (10.6–12.4)	RDS: (1.0) vs. (0.2) adjOR 4.7 (2.2–9.8) TTN: (9.5) vs. (2.6) adjOR 3.4 (3.0–3.9)		
Sweden, 1998–2007 (277)¶¶	Type 1 (18% obese) singleton: 3,457* >27 w		109 (3.2)* vs. (10) p<0.001	1,694 (49)* vs. (11) p<0.001			
Sweden, 1998–2007 (307)##	Type 1 singleton Total: 4,092* Female: 2,004 Male: 2,088 Type 2 singleton Total: 412* Female: 208 Male: 204 >22 w				RDS: 82 (2.0)* 30 (1.5) vs. (0.4) p<0.001 52 (2.5) vs. (0.5) p<0.001 5 (1.2)* 2 (1.0) vs. (0.4) p<0.001 3 (1.5) vs. (0.5) p<0.001 TTN: 157 (3.8)* 64 (3.2) vs. (0.7) p<0.001 92 (4.4) vs. (1.1) p<0.001 12 (2.9)* 5 (2.4) vs. (0.7) p<0.001 7 (3.4) vs. (1.1) p<0.001	403 (9.85)* vs. (1.3) 188 (9.4) vs. (0.97) 215 (10.3) vs. (1.6) 27 (6.55)* vs. (1.3) 12 (5.8) vs. (0.97) 15 (7.4) vs. (1.6)	
Helsinki, Finland, 1999–2008 (226)***	Type 1 singleton: 519† 1999–2003: 190 2004–2008: 329		6 (3.2)† 6/328 (1.8)†	101 (53.2)† 171/328 (52.1)†	NICU care: (25.3) (18.0)	108 (56.8) 157/327 (48.0)	

Table 5.27 continues on the next page.

TABLE 5.27. (continued)

REGION, YEARS (REF.)	TOTAL NUMBER OR LIVEBORN INFANTS BY TYPE OF MATERNAL DIABETES	NUMBER OF CASES (PERCENT OF TOTAL DELIVERIES* OR LIVEBORN†) VERSUS (PERCENT IN CONTROLS‡) AND EFFECT SIZE (95% CI)					
		Birth Trauma Percent of Liveborn (All† or Vaginal§ Deliveries)	Small-for-Gestational Age or <2,500 g	Large-for-Gestational Age	Respiratory Distress Syndrome and/or TTN†	Neonatal Hypoglycemia†	Hyper-bilirubinemia Phototherapy†
Sweden, 1998–2007 (338)†††	Type 1: 3,517† >31 w	85 (4.8)§		1,734 (49.3)†	RDS: 29 (0.8) TTN: 114 (3.2)	349 (9.9)	216 (6.1)
	AGA: 1,783	24/1,032 (2.3)§		PTD: (30.4)	RDS: 12 (0.7) TTN: 39 (2.2)	163 (9.1)	81 (4.5)
	LGA: 1,734	61/741 (8.2)§ p<0.001		PTD: (44.3) p<0.01	RDS: 17 (1.0) TTN: 75 (4.3) p<0.001 for TTN	186 (10.7)	135 (7.8) p<0.001
Japan, 2003–2009 (113)‡‡‡	Type 1: 330* 328†	1/227 (0.44)§	43 (13.0)*	112 (33.9)*	34 (10.4)	45 (13.7)	56 (17.1)
	Type 2: 510* 508† >19 w	2/308 (0.65)§	91 (17.8)*	190 (37.3)* >4,000 g: Type 1: 17 (5.2)* Type 2: 29 (5.7)*	62 (12.2)	78 (15.4)	89 (17.5)

Table includes prospective population-based and multicenter studies reported in 2000–2015. Neonatal is defined as 1–28 days of life. Conversions for glucose values are provided in *Diabetes in America Appendix 1*. AdjOR, adjusted odds ratio; AGA, appropriate birth weight for gestational age and sex; BMI, body mass index; CI, confidence interval; cRR, crude relative risk; LGA, large birth weight for gestational age and sex (>90th percentile); NICU, neonatal intensive care unit; NR, not reported; PTD, preterm delivery; RDS, respiratory distress syndrome; SD, standard deviation; SGA, small birth weight for gestational age and sex (<10th percentile); TTN, transient tachypnea of the newborn; w, weeks gestation.

* Denominators are total deliveries.

† Denominators are all liveborn infants.

‡ All studies compared to controls, except Denmark 1993–1999 (reference 93), which is compared to a reference population for fetal macrosomia.

§ Denominators are vaginal deliveries.

‖ Retrospective cohort study of all women with type 2 diabetes who were cared for in the statewide Sweet Success California Diabetes and Pregnancy Program from 2001 through 2004. Included singletons with complete data, mothers overweight and obese only; excluded anomalies and preterm deliveries; included 14% with gestational diabetes diagnosed <14 w. Data excluded outcomes of 241 women who lost weight during pregnancy. 537 women with type 2 diabetes who gained less than Institute of Medicine guidelines had significant increase in stillbirths than other weight gain groups (p<0.001). Women with type 2 diabetes who gained in excess of Institute of Medicine guidelines had significant increase in macrosomic infants (p<0.001).

¶ Data based on California Birth, Death, and Discharge records. Hyperbilirubinemia listed as jaundice. RDS also undefined, but frequency also lower at term in type 2 diabetes (0.39%) than type 1 diabetes (2.0%, p<0.002).

Retrospective multicenter study of five maternity units with multidisciplinary diabetes and pregnancy programs; data transferred to central database; subjects 55% Indo-Asian, 26% Caucasian, and 19% Afro-Carribean; 16 miscarriages and three terminations of pregnancy excluded.

** Retrospective case-control study using regional electronic database with prospective data collection; five maternity units with multidisciplinary diabetes and pregnancy programs on the Irish Atlantic seaboard; type 1 and type 2 diabetes diagnosed more than 6 months prior to index pregnancy. Comparison with matched controls by chi-square analysis; controls selected from >12,000 women with normal glucose tolerance; cosine similarity matching for age, BMI, ethnic group, and parity with a customized nearest neighbors selection without replacement (447 matched controls for type 1 diabetes and 213 for type 2 diabetes). Neonatal hypoglycemia and hyperbilirubinemia undefined.

†† Repeated questionnaire survey throughout pregnancy of 364 patients with type 1 diabetes in 118 hospitals from April 1, 1999 through March 2000. Excluded 23 women due to early spontaneous abortion, 16 due to diagnosis of type 2 diabetes, four terminations of pregnancy due to anomalies, four cases of late fetal loss <24 w, one maternal death at 17 w, and two lost to follow-up; includes eight twin pregnancies and one triplet pregnancy. Compared maternal and perinatal outcomes with national data from the 1998 Dutch perinatal database and with data from Statistics Netherlands; calculated crude relative risks and associated 95% confidence intervals. Defined macrosomia as birth weight >90th centile corrected for gestational age, sex, and parity; fetal growth chart based on the 1998 Dutch perinatal database (including 181,000 deliveries). Defined infant RDS and TTN according to X-ray and clinical findings. Defined neonatal hypoglycemia as <36 mg/dL (<2.0 mmol/L) and hyperbilirubinemia as infant needing phototherapy for jaundice.

‡‡ Nationwide prospective multicenter study in eight centers; information collected after each delivery by one to three caregivers per center and reported to a central registry. Included repeat (n=228) and twin (n=28) pregnancies ≥24 w; excluded earlier fetal losses. Macrosomia defined as birth weight >90th centile for a Danish standard population or as ≥4,500 g (compared to background population of 70,089). Respiratory distress defined as need for continuous positive airway pressure for >1 hour after delivery; hyperbilirubinemia defined as needing phototherapy.

§§ Multicenter prospective study in 33 units participating in the Italian Diabetes and Pregnancy Study Group; recruited all pregnant women with type 1 and type 2 diabetes at booking; data recorded in the European Quality Indicators and Data Collection Aggregated Database (excluded 30 spontaneous abortions <180 days gestation in women with type 1 diabetes and 17 with type 2 diabetes; excluded five pregnancy terminations in women with type 1 diabetes and three with type 2 diabetes). RDS given as hyaline membrane disease. Neonatal hypoglycemia and hyperbilirubinemia undefined.

‖‖ Prospective population-based study based on information from the Swedish Medical Birth Registry in 1991–2003. ICD-9 and ICD-10 codes used for clinical diagnoses in mothers and infants. Stillbirths defined as singleton births >27 w. Denominators uncertain for cells. Authors' table 3 shows 1.5% of 5,089 births were stillborn (n=76), but text says 69 stillbirths. Birth trauma is brachial plexus injury in vaginally delivered infants. LGA (≥97.5 percentiles) and SGA (≤2.5 percentiles) defined as birth weights >2 SD above or below the mean for normal fetal growth according to Swedish reference data. RDS and TTN defined by authors' reference to another publication. Logistic regression used to evaluate any association between maternal type 1 diabetes and outcomes. Multivariate analyses limited to 954,292 mothers with prepregnancy BMI data. Odds ratios adjusted for group differences in maternal age, BMI, parity, chronic hypertensive disorder, smoking habits, and ethnicity.

¶¶ Prospective population-based study (two reports, references 277 and 307) based on information from the Swedish Medical Birth Registry in 1998–2007. Included singleton births from 28 w (those with missing data excluded), so no data on earlier fetal losses or induced abortions. Maternal and neonatal diagnoses based on ICD-10 codes; ICD-9 codes also included to be sure that no patients were missed. Percentiles for birth weight were based on all liveborn, singleton infants, without major malformations, born to 764,498 mothers without a diagnosis of diabetes, adjusted for sex and gestational age. Rate of LGA did not differ significantly whether mothers with type 1 diabetes were of appropriate weight by usual BMI standards, overweight, or obese (underweight mothers excluded) (reference 277).

Table 5.27 continues on the next page.

TABLE 5.27. (continued)

In the second report (reference 307), the text says liveborn infants ≥22 w were included, but no fetal deaths at 22–27 w. The study cohort was divided into 4,092 singleton births to mothers with type 1 diabetes (2,004 female infants, 2,088 male infants) and 412 singleton births to women with type 2 diabetes (208 female infants, 204 male infants). Stillbirths and early neonatal deaths at 0–6 days of life were combined for perinatal mortality in the report, so the number of liveborn infants as denominator for RDS, TTN, and neonatal hypoglycemia cannot be stated in this table. Neonatal hypoglycemia was defined as plasma glucose <2.6 mM recorded after 6 hours of life. In this report, the reference population consisted of 439,525 female infants and 466,040 male infants. Univariable analyses of dichotomous data were carried out with the chi-square test and Fisher's exact test. P values versus controls. Test results not shown in table were significantly increased rates of RDS and TTN in male infants versus female infants of type 1 diabetic mothers (both p<0.05), but not with maternal type 2 diabetes.

*** Analyzed the obstetric records of 519 consecutive type 1 diabetic patients with a singleton live birth between 1999 and 2008 at Helsinki University Central Hospital (serves a regional population of 1.5 million). LGA was defined as >90th percentile using a Finnish standard population standardized for sex and gestational age birthweight z score >1.28 SD units). Birth weights below -2.0 SD were defined as small-for-dates (<-2.3th percentile) and above 2 SD (birth weight z score; >97.7th percentile) were defined as macrosomia (not in table). In 1999–2003, 32.1% >97.7th percentile; in 2004–2008, 33.5% >97.7th percentile. Neonatal hypoglycemia was defined as a plasma glucose level <2.6 mmol/L during the first day of life.

††† Data from Swedish Medical Birth Registry (excluded pregnancies <28 w, but this analysis excluded births <32 w). Included singleton live births; excluded all stillbirths and infants with major congenital anomalies (4.2%) or born SGA (3.6%), multiple births (2.8%), and those with missing data (4.6%). Birth trauma includes Erb's palsy and fracture of clavicle in vaginal deliveries (conflicting number of vaginal deliveries in authors' tables 1 and 2; table 2 used for this report). AGA (appropriate for gestational age and sex) defined as between 10th and 90th centiles. LGA defined as a birth weight >90th centile according to gestational age and sex. RDS and TTN defined by ICD-10 codes (not given). Neonatal hypoglycemia defined as blood glucose <2.6 mmol/L after 6 hours postnatally. Hyperbilirubinemia defined as requiring phototherapy or exchange transfusion.

‡‡‡ Retrospective analysis of prospective data collected from 40 hospitals throughout Japan. Additional information provided by Takashi Sugiyama as personal communication to JLK. Denominator of liveborn infants different than in published paper due to exclusion of early fetal deaths (pregnancy losses) at 10–19 w (39 for type 1 diabetes, 60 for type 2 diabetes) in this table. Birth trauma defined as brachial plexus paralysis. Respiratory disorder undefined. Neonatal hypoglycemia defined as blood glucose <1.94 mmol/L (<35 mg/dL). Hyperbilirubinemia defined as requiring phototherapy.

SOURCE: References are listed within the table.

without diabetes in 2005–2011 in Alberta, Canada (see footnotes to Table 5.26 for methods of comparison) (214).

Small-for-Gestational Age With Maternal Diabetes

The use of customized birth weight charts (adjusted for gestational age, infant sex, maternal ethnicity, parity, and BMI between 20 and 30 kg/m^2) (13) may or may not categorize more women with diabetes as having infants with pathologic growth (354). A population-based study encompassing three regions of England in 2007–2008 used customized birth weight percentiles and found that SGA <10th percentile was seen in 6.8% of 793 cases of maternal type 1 diabetes compared to 12.9% of 543 cases of maternal type 2 diabetes (p<0.0005); no comparison was made to standard population birth weight percentiles (98).

In the North American population-based and multicenter studies listed in Tables 5.26 and 5.27, using standard birth weight charts, SGA was identified in 4.3%–9.7% of total deliveries or liveborn infants (as defined in the tables) in five studies in North America of pregnant women with undifferentiated preexisting diabetes (115,203,208,214,248) (excluding one outlier of 1.8% (213)); in 11.0% in one survey of women with type 1 diabetes in California (114); and in 4.75% (308) and 12.8% (114) in two California surveys of women with type 2 diabetes. Similar results were reported in England (309), West Ireland (88,108), and Australia (227), with lower values in Sweden (276,277) and slightly higher values in Japan (113) (Tables 5.26 and 5.27). These prevalences were not adjusted for such maternal factors as hypertension, inadequate gestational weight gain, or current smoking. In a statewide survey of births to women with diabetes and/or hypertension in California in 2006 (203), the frequency of SGA was 9.7% with maternal pregestational diabetes alone, 18.2% with both diabetes and chronic hypertension, and 10.1% in controls (adjusted OR 2.2, 95% CI 1.6–3.0 for the interaction vs. controls) (203).

In studies that included a reference population, the effect sizes of pregestational diabetes on SGA prevalence were adjusted odds ratio 0.65 (95% CI 0.55–0.76) for 2,342 infants of diabetic mothers in Alberta, Canada (214) and adjusted odds ratio 0.7 (95% CI 0.6–0.9) for 5,020 infants of diabetic mothers in Sweden (276). In another Swedish analysis, SGA was recorded in 3.2% of 3,457 infants of diabetic mothers in Sweden versus 10% in 764,498 nondiabetic controls (p<0.001) (277). Methods of comparison are given in footnotes to Tables 5.26 and 5.27. The tendency to fetal macrosomia with maternal diabetes (shift to higher birth weights) (355) may result in a lowered percentage of birth weights below the standard 10th percentile for gestational age (<7% in 8 of 15 studies), which is the definition of SGA (13). Whether customized percentiles would change the identification rate in a meaningful way remains to be seen, and prospective trials are needed.

Large-for-Gestational Age With Maternal Diabetes

LGA or birth weight >4,000 g was much more common in the infants of the diabetic women in the population-based or multicenter studies listed in Tables 5.26 and 5.27. That is, more common compared to rates of SGA and more frequent in these studies in comparison to nondiabetic populations (214). In North America, rates of LGA were 24.2%–35.0% (115,208,214,248,308) except for two unlikely outliers of 7.4% (213) and 8.1% (203) for diabetes using a statewide database in California (Tables 5.26 and 5.27). Birth weight ≥4,000 g was recorded in 11.7%–21.6% of North American infants of diabetic mothers (114,115,208,248,308) (vs. 7.4% in controls in Utah (115)) and >4,200 g in 11.3% in Alberta, Canada (vs. 5.2% in controls) (214). The large KPNC study recorded 7.0% of infants of diabetic mothers as ≥4,500 g at birth (208) compared to 6.0% in the NVSS sample of diabetic women in 2009 (Table 5.23) (12).

In 10 listed data sets from other countries (93,100,108,113,226,227,276, 277,309,338), the frequency of LGA in liveborn infants was 22.2%–61.2% whether mothers had type 1 diabetes,

type 2 diabetes, or undifferentiated preexisting diabetes in pregnancy. The rate was >40% in one-half of the studies (93,100,226,277,338) (Tables 5.26 and 5.27). Rates of birth weight >4,500 g were recorded in 7.8% of infants of type 1 diabetic women in Denmark (93) and 7.3% in West Ireland (108); for infants of type 2 diabetic mothers, rates of birth weight >4,500 g were 3.7% in England (309) and 9.1% in West Ireland (108). Achieving a fetal LGA rate <30% in a population of diabetic women is considered a marker for improved control of hyperglycemia and excess weight gain (108,115,308), as long as it is not achieved by iatrogenic prematurity or increased rates of SGA. Despite improved preconception care and glycemic control in West Ireland in 2010–2014 compared to 2005–2009, the rate of LGA increased somewhat from 25% to 29% (Table 5.26), perhaps related to significant increases in maternal obesity and gestational weight gain (88).

For surveys that included controls, the effect sizes on risk of LGA with maternal diabetes were adjusted odds ratios 3.4 (95% CI 3.0–3.8) in California (203), 3.94 (95% CI 3.61–4.31) in Alberta, Canada (214), and 11.4 (95% CI 10.6–12.4) in Sweden (276), and odds ratio 4.91 (95% CI 4.28–5.63) in Australia (227). Adjusted odds ratios were 1.78 (95% CI 1.47–2.14) for birth weight >4,000 g with type 1 diabetes in Ontario, Canada (210) and 2.11 (95% CI 1.86–2.40) for birth weight >4,200 g with pregestational diabetes in Alberta, Canada (214). The methods used for comparison are given in the footnotes to Tables 5.26 and 5.27.

Newborn macrosomia is associated with increased neonatal and long-term morbidities in infants of diabetic mothers (353,356). In the national audit of pregnant women with type 1 diabetes in the Netherlands in 1999–2000, macrosomia was associated with more shoulder dystocia and neonatal hypoglycemia (100,345). In the Swedish national study of births to women with type 1 diabetes in 1998–2007, composite morbidity, fetal distress coding, Apgar score <7 at 5 minutes, Erb's palsy, clavicular fracture, acute respiratory disorder, and hyperbilirubinemia were significantly more common in the LGA infants (but not neonatal hypoglycemia; shoulder dystocia was not coded) (277). What is uncertain is how much of the morbidity relates to antepartum versus intrapartum processes.

The increasing proportions of LGA births over time in the general population seem to be related to increases in maternal BMI, especially between pregnancies (357). However, improved glycemic control by nutrition therapy (and its correlates) is known to reduce the rates of LGA in women with mild diabetes, independently of maternal size (358,359). In untreated women with mild gestational glucose intolerance, increased levels of maternal BMI at baseline have been associated with increased birth weight z-score and neonatal fat mass, independent of maternal glucose tolerance test levels (360).

Another measure of fetal overgrowth or adiposity used in some studies of diabetes and pregnancy is ponderal index (PI; birth weight in grams per length in centimeters) (277). Investigators of the Swedish Medical Birth Registry incorporated PI >90th percentile with birth weight >90th percentile to define neonatal overweight in 3,457 infants of type 1 diabetic mothers and 764,498 controls (277). In this study, neonatal overweight was recorded in 21% of infants of diabetic mothers with maternal BMI 18.5–24.9 kg/m^2 versus 3% in controls (adjusted OR 8.40, 95% CI 7.32–9.64), in 24% with maternal BMI 25–29.9 kg/m^2 versus 5% in controls (adjusted OR 9.86, 95% CI 8.76–11.11), and in 27% with maternal BMI >30 kg/m^2 versus 8% in controls (adjusted OR 11.29, 95% CI 9.42–13.53) (p<0.016 for trend in infants of diabetic mothers) (277). The method used for comparison is given in the footnote to Table 5.27.

In a subsequent rigorous assessment of 3,517 infants born to mothers with type 1 diabetes in the Swedish Birth Registry in 1998–2007, 45.6% of the 1,734 LGA infants had a PI >90th percentile (weight for length) according to gestational age and sex in comparison to the reference population (874,620 liveborn singleton infants) (338). Except for fetal distress and Apgar scores <7 at 1 minute, there was no significant difference in the risk of adverse outcome between proportionate and disproportionate LGA infants of diabetic mothers born preterm or at term, including birth trauma (338). As noted above, in this study, LGA infants compared to AGA infants of type 1 diabetic mothers had significantly more neonatal morbidities, including birth trauma (8.8% vs. 2.5% of vaginally born infants, p<0.001) (338). Although disproportionate LGA infants had fewer vaginal deliveries (35% vs. 49%, NS), this potential bias disappeared in an adjustment analysis. This implies that high birth weight is the most important risk factor for birth trauma (338). This result seems to contradict a prior report from a regional center in Ohio, in which asymmetric growth (predicted by enlargement of the fetal abdomen on two prenatal ultrasound examinations in 35 patients with type 1 diabetes) correlated with increased rates of neonatal hypoglycemia and hyperbilirubinemia; however, there was no assessment of shoulder dystocia or birth trauma (356).

VAGINAL DELIVERY WITH SHOULDER DYSTOCIA AND BIRTH TRAUMA

Fetal macrosomia near term and at term certainly increases the risk of shoulder dystocia in deliveries of diabetic mothers (361,362,363,364,365). The comorbidity of maternal obesity may also contribute. In population-based or multicenter surveys reported since 2000 and listed in Tables 5.19, 5.20, and 5.21, rates of shoulder dystocia in vaginal deliveries of diabetic women in North America were 1.9% (210) and 2.5% (203) in two data sets and 4.0%–6.4% in five data sets (114,115,210,212,213), plus 9.4% in Northern California (208) and 12.3% in Alberta, Canada (214), in all types of diabetes. The adjusted odds ratios versus controls estimated in two large studies in North America were 2.1 (95% CI 1.7–2.7) in California (203) and 1.54 (95% CI 1.31–1.81) in Alberta, Canada (214), as well as 2.5 (95% CI 1.6–3.9) for 438 vaginal births to women with type 1 diabetes in

Ontario, Canada (210). The methods used for comparison are given in the footnotes to Tables 5.19, 5.20, and 5.21.

Shoulder dystocia rates among vaginal deliveries varied from 5.5% to 6.1% in two studies (92,95) and 7.8% to 14.3% in three other studies in Europe (100,108,276), as well as 4.5% in Australia (227) and 2.2% for type 1 diabetes in Japan (113) (227 vaginal births; 31.2% cesarean delivery rate). Rates for type 2 diabetes were 2.4% in West Ireland (108), 4.5% in Italy (95), and 4.9% in Japan (113) (Table 5.21). An outlier is the analysis based on claims made to a national insurance registry in South Korea, which recorded only 13 cases of shoulder dystocia among 15,746 vaginal deliveries of women with preexisting diabetes (221).

Table 5.28 presents the frequency or excess risk of shoulder dystocia according to birth weight in diabetic and nondiabetic women in three large data sets devoted to the issue (methods of comparison given in footnotes to the table): California (361), Norway (363), and Sweden (364). In California, there were 175,886 vaginal births in 1992 at >300 hospitals; birth certificate records were linked with hospital discharge records for mother and for infant (361). The rates of shoulder dystocia increased dramatically with increasing birth weight, and at each birth weight category >3,749 g, the rate was higher in diabetic women (Table 5.28). Assisted delivery (adjusted OR 1.94, p=0.0001) and induction of labor (adjusted OR 1.27, p=0.0001) also increased the risk of shoulder dystocia in each birth weight category. Hispanic patients were significantly less likely to have a birth complicated by shoulder dystocia (adjusted OR 0.84, p=0.0001) (361).

In an analysis of the national Norwegian registry of all births in 1967–2009, the rates and risks of shoulder dystocia were analyzed by birth weight group among vaginal deliveries >31 weeks gestation (363). For 11,188 diabetic women, the rate of shoulder dystocia rose considerably once the level of fetal macrosomia was reached (≥4,000 g) (Table 5.28). In the diabetic women, the crude odds ratios (with reference to birth weights of 3,000–3,499 g) increased to 13.78 (95% CI 8.10–23.42) at birth weights of 4,000–4,499 g and to 34.13 (95% CI 19.82–58.71) at birth weights of 4,500–4,999 g (363). Shoulder dystocia also varied with gestational age in diabetic mothers: 2.2% for vaginal deliveries at 32–35 weeks (adjusted OR 2.9, 95% CI 1.5–5.5) and 5.1% at 36–37 weeks (adjusted OR 2.7, 95% CI 2.0–3.6). The rate did not increase at 38–39 weeks, probably due to practices of earlier deliveries or delivery by cesarean section (363).

In a national population-based study of Swedish patients conducted in 1987–1996, using the Medical Birth Registry and ICD-9 codes, 1,397 patients with shoulder dystocia (0.13%) were identified, of whom 78 women had diabetes (5.6%

TABLE 5.28. Rates of Shoulder Dystocia by Birth Weight and Odds Ratios With Diabetes During Births to Diabetic and Nondiabetic Women in Selected Regions

REGION, YEARS (REF.)	NUMBER OF BIRTHS	BIRTH WEIGHT (g)	PERCENT SHOULDER DYSTOCIA		ODDS RATIO (95% CI) FOR SHOULDER DYSTOCIA WITH DIABETES*
			Diabetes*	No Diabetes	Total
California, 1992 (361)†	175,886 vaginal births of singleton infants >3,500 g		Unassisted / assisted‡ births		adjOR 1.70 for birth weight >3,500 g
		3,750–3,999	5.8 / 8.9	2.0 / 4.0	
		4,000–4,249	8.4 / 12.2	5.2 / 8.6	
		4,250–4,499	12.3 / 16.7	9.1 / 12.9	
		4,500–4,749	19.9 / 27.3	14.3 / 23.0	
		4,750–4,999	23.5 / 34.8	21.1 / 29.0	
Norway, 1967–2009 (363)§	Diabetes: 11,188		All vaginal births		adjOR 2.23 (2.0–2.5)
		3,500–3,999	2.2	0.4	
		4,000–4,499	7.0	1.8	
	No diabetes: 2,003,768	4,500–4,999	15.7	5.8	
		≥5,000	31.8	15.1	
Sweden, 1987–1996 (364)‖	1,076,545; 1,397 shoulder dystocia cases, 78 with diabetes	3,500–3,999			5.90 (3.5–10.1)
		4,000–4,499			3.81 (2.7–5.4)
		4,500–4,999			2.40 (1.6–3.6)
		5,000–5,499			1.79 (0.96–3.4)

CI, confidence interval; OR, odds ratios were adjusted (adj) for birth weight and operative delivery.

* Includes International Classification of Diseases, Ninth Revision, (ICD-9) codes for preexisting and gestational diabetes.

† Linked birth certificate records with hospital discharge records, statewide in California. Uncertain whether diabetes included gestational diabetes. Logistic regression was used to evaluate the effect of diabetes on risk for shoulder dystocia; adjusted for parity, ethnicity, Medicaid insurance, birth weight 4,000–4,500 g, birth weight >4,500 g, and assisted delivery. Confidence intervals were not presented in the article.

‡ Vacuum- or forceps-assisted births

§ National population-based Norwegian Medical Birth Registry study. Vaginal deliveries of singleton infants in cephalic presentation 32–42 weeks gestation were included; those with missing gestational age or birth weight were excluded. Gestational age was determined by postmenstrual dates in 1967–1998 and by routine ultrasonography in 1999–2009. Logistic regression was used to estimate the effect of diabetes on shoulder dystocia, adjusting for maternal age, parity, period of delivery, birthweight, induction of labor, use of epidural analgesia at delivery, prolonged labor, and assisted delivery (forceps or vacuum).

‖ All singleton deliveries at ≥2,000 g birth weight. Used information stored in the Medical Birth Registry of Sweden. Diagnoses were determined by ICD-9 codes. Odds ratios were calculated with 95% confidence intervals, based on the normal approximation of the Poisson distribution. Risks may decrease with higher birth weights in the diabetic group due to common use of primary cesarean section with predicted fetal macrosomia compared to nondiabetic women.

SOURCE: References are listed within the table.

of shoulder dystocia cases) (364). There was considerable variation in the rate of recorded shoulder dystocia among the 63 delivery units throughout the country, possibly reflecting difficulties in definition of shoulder dystocia or experience in handling high-risk pregnancies. Possibly more severe cases of shoulder dystocia were reported, since the frequency of brachial plexus palsy (BPP) was high at 26.3% (364). Shoulder dystocia was related to short maternal stature: 140–159 cm, 0.19%; 160–169 cm, 0.14%; 170–179 cm, 0.09%; 180–195 cm, 0.04%. Overall, shoulder dystocia was more likely with maternal diabetes in all birth weight groups in the range 3,500–4,999 g (Table 5.28). The authors noted that the greatest comparative likelihood of shoulder dystocia with diabetes was at birth weight 3,500–3,999 g and that when extreme macrosomia >5,000 g occurred, the association with diabetes was no longer significant, perhaps due to planned cesarean sections. The authors also found that infant mortality among infants delivered with shoulder dystocia was higher with maternal diabetes (6.4%) than without maternal diabetes (0.9%) (prelabor intrauterine death excluded) (364).

Most investigators agree that antepartum ultrasonic prediction of fetal weight related to risk of shoulder dystocia has been difficult (365,366). Other investigators have looked for disproportion in fetal size by ultrasonic means related to shoulder dystocia: increased fetal abdominal circumference (AC) (367,368,369) and increased ratio of AC to head circumference (HC) (370,371,372,373). These methods have not been applied in epidemiologic studies of diabetic pregnant women.

The denominator used to establish rates of birth trauma varies among studies. Use of percentage of total liveborn infants reflects the fact that a small proportion of injured infants are delivered by cesarean section. However, many investigators use percentage of liveborn infants delivered vaginally.

BPP (367,374,375,376,377,378) and various other birth injuries have increased risk in infants of mothers with all types of diabetes compared to control infants (367,379,380,381,382,383), a fact which may contribute to the high cesarean section rates for diabetic mothers listed in Tables 5.19, 5.20, and 5.21. In an analysis of all births to 1,094,298 women in California in 1994–1995, 1,611 (0.15%) had the diagnosis of BPP recorded (379). There was a significant association with diabetes (gestational diabetes and preexisting diabetes in pregnancy combined) of crude odds ratio 1.9 (95% CI 1.7–2.1). Among the diabetic women (number not given), the apparent frequencies of BPP were 0.6% for normal vaginal delivery of infants at birth weight 3,500–4,500 g and 1.1% for assisted vaginal delivery. At birth weights >4,500 g, the apparent frequency of BPP was 3.7% for normal spontaneous delivery of infants of diabetic mothers compared to 7.8% for assisted vaginal delivery (379).

A population-based retrospective analysis of all deliveries in the Swedish Medical Birth Registry found that the adjusted odds ratio for the effect of maternal diabetes (both manifest and pregnancy-induced) on BPP was 2.4 (95% CI 1.7–3.5). Other strong predictors were birth weight of >4,500 g (adjusted OR 8.7, 95% CI 7.9–9.6) and operative vaginal delivery (adjusted OR 3.4, 95% CI 3.1–3.8) (380). In a regional study in Norway covering 1991–2000, BPP was diagnosed in 0.3% of 30,574 liveborn children who survived >12 months compared to 1.8% of 227 infants of diabetic mothers ($p<0.005$); the four cases of BPP were transient (382).

There is a strong link between shoulder dystocia at delivery in large infants and BPP (374,375,376,379,380,381,382). The nationwide mean and standard error of the incidence of neonatal BPP in the United States was at least 1.51±0.02 cases per 1,000 live births in 1997, 2000, and 2003 combined (376). In multivariate analysis, shoulder dystocia had a 100 times greater risk for BPP, birth weight >4,500 g had a 14 times greater risk for BPP, and forceps delivery had a nine times greater risk for injury (376).

Among 524 cases of shoulder dystocia analyzed in San Francisco, California, in 1976–2001, the frequency of BPP was 6.5% (381). Although shoulder dystocia was more frequent in women diagnosed with preexisting diabetes (7.0%) or gestational diabetes (3.9%) compared to pregnancies without diabetes (1.7%) ($p=0.001$), only gestational diabetes had significant effect size or risk of BPP (adjusted OR 4.54, 95% CI 1.40–14.7) (381). Other significant risk factors for BPP in the setting of shoulder dystocia were maternal BMI ≥26 kg/m^2 (adjusted OR 4.79, 95% CI 1.53–15.0), birth weight >4,000 g (adjusted OR 2.53, 95% CI 1.09–5.85), second stage of labor ≥3 hours (adjusted OR 3.05, 95% CI 1.07–8.65), vacuum-assisted delivery (adjusted OR 3.24, 95% CI 1.37–7.67), and occiput posterior position at delivery (adjusted OR 10.43, 95% CI 3.03–35.9). There was no analysis of possible interactions among these risk factors (381).

The same authors then conducted a retrospective cohort study of term singleton births complicated by shoulder dystocia in 1997–2006 in all of California (383). During the 10-year period, 62,762 deliveries were complicated by shoulder dystocia, with 3,168 reports of BPP (5.0%). Among 5,426 cases of shoulder dystocia in diabetic women (both gestational diabetes and preexisting diabetes in pregnancy), there were 497 cases of BPP (9.2%) versus 4.7% of births in women without diabetes. The frequency of BPP according to birth weight intervals was graphed for maternal diabetes: ~7% of shoulder dystocia cases at 3,500–3,999 g, ~9.5% at 4,000–4,599 g, ~14.5% at 4,500–4,999 g, and ~19.5% at birth weight >5,000 g (383). Among all cases of shoulder dystocia, the effect size of diabetes on BPP was adjusted odds ratio 1.77 (95% CI 1.58–2.00). Other significant risk factors for BPP were African American race (adjusted OR 2.39, 95% CI 2.05–2.78), birth weight 4,000–4,999 g (adjusted OR 2.95, 95% CI 2.48–3.50), birth weight 4,500–4,999 g

(adjusted OR 5.35, 95% CI 4.45–6.43), birth weight ≥5,000 g (adjusted OR 9.36, 95% CI 7.32–11.98), and operative vaginal delivery (adjusted OR 1.67, 95% CI 1.52–1.84) (383).

In a Medical Birth Registry study of pregnancy outcomes for women with type 1 diabetes in Sweden in 1998–2007 (1,773 singleton, normally formed liveborn infants of diabetic mothers delivered vaginally at 32–43 weeks), rates of birth trauma were compared among AGA infants (24/1,032 [2.3%]) and LGA infants (61/741 [8.2%], p<0.001) (338). There was no significant difference in the frequency of birth trauma between proportionate LGA and disproportionate LGA infants with elevated PI (weight/height >90th percentile) (338). Among the 24 cases of birth trauma in the AGA infants delivered vaginally, seven suffered BPP (0.68% of vaginal births) and 20 had clavicle fracture (1.94%) (note overlap); among 61 cases of birth trauma in the LGA group, 30 infants had BPP (4.05%) and 37 had a fractured clavicle (4.99%) (p<0.001 for both types of trauma, comparing AGA to LGA infants) (338). The differences in birth trauma between AGA and LGA held after adjustment for maternal BMI and height. Cesarean delivery rates were 42% for AGA, 51% for proportionate LGA, and 65% for disproportionate LGA (338).

In the population-based surveys or multicenter studies of infants of women with preexisting diabetes listed in Tables 5.26 and 5.27, the rates of birth trauma (BPP and/or fractures) were 2.1% and 2.9% of vaginal deliveries (100,276) and 1.4%–3.75% of all liveborn infants of diabetic mothers (95,208,227). Japan had relatively low risks of shoulder dystocia (3.74%) and BPP (0.56%) in vaginal deliveries of women with type 1 or type 2 diabetes in 2003–2009, as well as low rates of cesarean section (36.5%), but BPP occurred in three of 20 cases of shoulder dystocia (113) (Tables 5.20, 5.21, and 5.27).

The question remains of the likelihood of permanence of BPP in long-term follow-up studies of affected children (377,378,384,385), of which there are few with maternal diabetes as a factor (382,386). One prominent investigator of the long-term outcomes of infants with BPP noted that "the proportion of injuries that remain permanent is significantly lower among studies conducted by obstetricians (13%, 10%–17%, 55/419) than pediatricians and orthopedic surgeons (51%, 43%–58%, 86/170) (p<0.0001)" (377). In Los Angeles, California, a retrospective case-control analysis from computer-stored databases identified 49 children with permanent BPP (≥1 year) associated with shoulder dystocia and compared them with an equal number with transient BPP from a shoulder dystocia database (386). Transient BPP cases had a higher incidence of diabetes (either insulin-dependent or non-insulin-dependent) than those with permanent BPP (34.7% vs. 10.2%, OR 4.68, 95% CI 1.42–16.32) (386).

In one county in Sweden, in 1981–1989, about 50% of all cases of BPP had impairment at age 15 months, and 22% had severe impairment (378). In a later analysis in the same part of Sweden, 114 children born between 1999 and 2001 were diagnosed with obstetric BPP (0.29% of 38,749 deliveries); of 98 children with BPP followed to age 18 months, the frequency of persistent palsy up to age 18 months was 18.4% (385). Another study in western Sweden reported 16% of children with BPP had residual functional deficits at age 18 months, and downward traction with substantial force at delivery of the head was applied in all of these 18 cases (375). In a regional study in Norway, of 91 newborns with BPP at 24 hours after birth, at follow-up at 3 months to 3 years, 76 cases were transient (84%), and 15 were permanent (382). All four cases in infants of diabetic mothers were transient BPP. The main predictor of permanent BPP was the difficulty with delivery and associated newborn hypoxia. BPP can also occur without shoulder dystocia (382). Although high birth weight is a risk factor for shoulder dystocia and for BPP, it is not necessarily so for permanence of BPP (377,378,382). It is unknown whether infant neurologic injury that occurs in the setting of maternal hyperglycemia is less likely to resolve (383).

The use of "early" induction of labor or "later" cesarean delivery to prevent birth injury in infants of diabetic women remains controversial (326,387,388). A multicenter randomized controlled trial of induction of labor (n=407) versus expectant management (n=411) was conducted in Europe in women with singleton fetuses whose estimated fetal weight exceeded the 95th percentile by 37–38 completed weeks gestation (389). Induction of labor significantly reduced the risk of shoulder dystocia or associated morbidity (n=8) compared with expectant management (n=25) (RR 0.32, 95% CI 0.15–0.71) (389). No cases of brachial plexus injury, intracranial hemorrhage, or perinatal death were recorded. Rates of cesarean delivery and neonatal morbidity did not differ significantly between the groups (389). These results echo those of an earlier randomized controlled trial in Los Angeles in insulin-treated pregnant women at term (85% gestational diabetes) (390) and two observational comparative studies done in San Antonio (391) and Israel (392) in women with gestational diabetes. Similar randomized controlled trials are lacking in women with type 1 or type 2 diabetes.

MAJOR CONGENITAL MALFORMATIONS

The increased risk of major congenital malformations associated with poor glycemic control of type 1 and type 2 diabetes is well established (71,72,73,74). This relationship, other possible risk factors, and the role of preconception care of diabetes continued into early pregnancy are discussed in the section *Preconception Care of Diabetes and Contraception*.

For major congenital malformations, most authors of diabetes surveys use the definition of nonchromosomal, nonsyndromic major malformations (single or multiple in same infant) that cause death or seriously affect the health of the child (13). The use of genetic investigations and investigation of gene-environment interactions to

characterize fetal losses or malformations has not been standardized (393,394,395) and has been hardly applied to the study of diabetic pregnancies. Investigations of maternal-fetal gene interactions associated with glucose homeostasis and obesity metabolism (396,397) and nutrient intake (139,140,141,142) should be adapted to epidemiologic studies of infants and diabetic mothers.

The denominator used to establish rates of congenital malformations varies among studies. Ideally, the denominator should be all pregnancies from their onset through 1-year follow-up of the infant after birth. It is difficult to determine malformations in spontaneous abortions and pregnancy terminations, unless diagnosis was predicted by ultrasonography prior to the pregnancy loss. Most studies of malformations in infants of diabetic mothers do not account for abortions, whether spontaneous, elective, or indicated. Use of percent total births beyond a defined gestational age accounts for the fact that congenital malformations can be predicted or diagnosed in stillborn infants, but many investigators have used percentage of liveborn infants, diagnosed in surviving or dying infants within a stated range of neonatal (within 1 week or within the first 28 days of life) or postneonatal life (within the first year).

In an early population-based case-control study based in Atlanta, Georgia, the relative risk for major malformations among infants of mothers with type 1 diabetes was 7.9 (95% CI 1.9–33.5) for 1968–1980 (398). In this study, the relative risks for major central nervous system and cardiovascular system defects were 15.5 (95% CI 3.3–73.8) and 18.0 (95% CI 3.9–82.5), respectively. A case-control analysis using linked birth-hospital discharge records in Washington State in 1987–2007 found increased risk of congenital urinary tract anomalies with maternal preexisting diabetes (OR 3.46, 95% CI 2.17–5.54) (399). A population-based case-control study in Manitoba, Canada, confirmed a significant association of maternal pregestational diabetes (adjusted OR 1.67, 95% CI 1.14–2.46) with congenital anomalies of the kidney and urinary tract in children between 1996–1997 and 2009–2010 (400).

A large U.S. multicenter case-control study of malformations conducted in 1997–2003 yielded 283 major malformations in infants of mothers with type 1 or type 2 diabetes and 12,747 in women without preexisting diabetes, but including gestational diabetes (660 major malformations) (National Birth Defects Prevention Study) (401). The study included terminations of pregnancy. Adjusted odds ratios for women with pregestational diabetes versus 4,895 control subjects for all isolated and multiple defects were 3.17 (95% CI 2.20–4.99) and 8.62 (95% CI 5.27–14.10), respectively. Models were adjusted for maternal age, race/ethnicity, entry into prenatal care, BMI, study center, and household income (401). The study also revealed pregestational diabetes-associated adjusted odds ratios of 2.34 (95% CI 1.44–3.81) for isolated noncardiac defects and 7.80 (95% CI 4.66–13.05) for noncardiac multiple defects. The exposure odds were especially high for bilateral renal agenesis/hypoplasia (OR 11.91, 95% CI 3.10–45.72), hydrocephaly (OR 8.80, 95% CI 3.39–22.84), and for anorectal atresia (OR 4.70, 95% CI 1.55–14.26) (401).

The pregestational diabetes-associated adjusted odds ratio for isolated cardiac malformations was 4.64 (95% CI 2.87–7.51) and was 10.77 (95% CI 6.23–18.62) for multiple anomalies with cardiac defects (401). The exposure odds were especially high for atrial ventricular septal defect (VSD; OR 12.36, 95% CI 3.68–41.49), right ventricular outflow tract associations (OR 9.61, 95% CI 3.53–26.15), total anomalous pulmonary venous return (OR 7.12, 95% CI 1.99–25.42), atrial septal defect (ASD) secundum (OR 8.47, 95% CI 4.37–16.42), VSD plus ASD (OR 5.83, 95% CI 2.48–13.70), and for tetralogy of Fallot (OR 4.89, 95% CI 2.18–10.95) (401). Analyses explored the independent and joint effects of prepregnancy BMI and preexisting diabetes and showed that the association between preexisting diabetes and "birth defects is consistent, irrespective of maternal BMI, for both isolated and multiple defects" (401). The preexisting diabetes-associated exposure adjusted odds ratios for all major malformations were 3.50 (95% CI 1.68–7.30) for diabetic women of average weight, 5.44 (95% CI 1.97–15.05) for overweight diabetic women, and 5.28 (95% CI 2.76–10.10) for obese diabetic women. The study had no information on measures of glycemic control (401).

The overall rates of major malformations in surveys of pregnancies complicated by preexisting diabetes reported since 2000 in Canada were 9.4% for liveborn infants of mothers with type 1 diabetes (adjusted OR 2.38, 95% CI 2.20–2.57) and 9.3% (adjusted OR 2.31, 95% CI 2.16–2.47) for type 2 diabetes in 2002–2013 (219), 9.1% of births for preexisting diabetes (adjusted OR 3.10, 95% CI 2.28–4.22) in Nova Scotia in 1988–2002 (249), and 3.5% of births for type 1 diabetes (adjusted OR 1.71, 95% CI 1.03–2.82) in Ontario in 2005 (210) (Table 5.29). The details of these studies are given in the footnotes to Table 5.29. None of these studies included terminations of pregnancy for birth defects.

The national U.S. survey of insurance health claims in 2006–2011 (liveborn infants ≥24 weeks) reported diabetes-associated relative risks of 1.92 (95% CI 1.50–2.47) for all major malformations in type 1 diabetes and 1.84 (95% CI 1.68–2.01) in type 2 diabetes (54). Subjects needed to have continuous health plan enrollment ≥21 months before and 3 months after the birth. The relatively high rate of major congenital malformations in this survey (11.4% for 482 cases of type 1 diabetes, 10.9% for 4,166 cases of type 2 diabetes, and 5.9% for 353,599 controls) may be related to exclusion of a large amount of records from all groups due to unknown outcomes and a greater propensity of women to submit health insurance claims with complicated pregnancies (54).

More surveys of women with preexisting diabetes have been reported in Europe since 2000. These studies are presented on the background of analysis of the

TABLE 5.29. Types and Prevalence of Major Congenital Malformations (Nonchromosomal, Unless Noted) in Infants of Women With Undifferentiated Preexisting Diabetes Mellitus in Pregnancy, Type 1 Diabetes, or Type 2 Diabetes, Population-Based Surveys in North America, 1993–2013

REGION, YEARS (REF.)	NUMBER OF PDM BY TYPE OF DIABETES, GESTATIONAL AGE	GROUPS OF TYPES OF MALFORMATIONS NUMBER OF CASES (PERCENT OF INFANTS) VERSUS (PERCENT IN CONTROLS) AND EFFECT SIZE (95% CI)					
		Major Congenital Anomalies	Cardiovascular*	Central Nervous System or Neural	Musculoskeletal System	Digestive System	Urogenital
United States, 2005–2011 (54)†	Type 1: 482‡	55 (11.4)‡ cRR 1.92 (1.50–2.47)	Cardiac 38 (7.9) cRR 2.61 (1.93–3.55) Circulatory 17 (3.5) cRR 2.35 (1.47–3.75)	1 (0.2) cRR 1.25 (0.18–8.90)	1 (0.2) cRR 0.31 (0.04–2.19)	Alimentary 1 (0.2) cRR 0.68 (0.10–4.79) Digestive NR	Genital 4 (0.8) cRR 1.71 (0.64–4.55) Urinary 3 (0.6) cRR 0.98 (0.32–3.02)
	Type 2: 4,166‡	454 (10.9)‡ cRR 1.84 (1.68–2.01)	Cardiac 272 (6.5) cRR 2.17 (1.93–2.43) Circulatory 172 (4.1) cRR 2.75 (2.37–3.19)	13 (0.3) cRR 1.89 (1.09–3.27)	31 (0.7) cRR 1.11 (0.78–1.58)	Alimentary 16 (0.4) cRR 1.25 (0.76–2.05) Digestive 11 (0.3) cRR 2.19 (1.21–3.98)	Genital 24 (0.6) cRR 1.19 (0.80–1.78) Urinary 28 (0.7) cRR 1.05 (0.73–1.53)
	Liveborn ≥24 w						
Nova Scotia, Canada, 1988–2002 (249)§	PDM: 516 Singleton pregnancies >19 w	47 (9.1) vs. (3.1) adjOR 3.10 (2.28–4.22)	25 (4.8) vs. (0.8) RR 6.4 (4.3–9.4)	7 (1.4) vs. (0.2) RR 7.4 (3.5–15.7)	14 (2.7) vs. (1.1) RR 2.5 (1.5–4.3)	Ear, nose, throat 5 (1.0) vs. (0.2) RR 4.0 (1.7–9.5)	Genitourinary 3 (0.6) vs. (0.4) RR 1.3 (0.4–4.1)
	1988–1995: 256	21 (8.2) vs. (3.0)					Hypospadias 6 (1.2) vs. (0.4) RR 2.8 (1.3–6.2)
	1996–2002: 260	26 (10.0) vs. (3.1)					
Ontario, Canada, 2005–2006 (210)‖	Type 1: 904	32 (3.5) vs. (1.9) adjOR 1.71 (1.03–2.82)	4	2	4	2	1
	Type 2: 516	9 (1.7) adjOR 1.0 (0.41–2.43)	2	0	0	0	0
	All deliveries ≥20 w						
Canada, 2002–2013 (219)¶	Type 1#	(9.37) vs. (4.17) adjOR 2.38 (2.20–2.57)	(4.74) vs. (0.75) adjOR 6.55 (5.89–7.29)	(0.53) vs. (0.15) adjOR 3.48 (3.55–4.76)	(1.76) vs. (1.78) adjOR 0.99 (0.84–1.18)	(0.47) vs. (0.16) adjOR 3.06 (2.20–4.25)	(2.07) vs. (1.09) adjOR 1.92 (1.64–2.45)
	Type 2#	(9.33) adjOR 2.31 (2.16–2.47)	(4.12) adjOR 5.35 (4.83–5.89)	(0.59) adjOR 3.85 (2.97–4.99)	(2.60) adjOR 1.49 (1.32–1.69)	(0.40) adjOR 2.41 (2.76–3.29)	(2.03) adjOR 1.85 (1.61–2.13)
	Liveborn ≥22 w or ≥500 g						

Table includes population-based studies reported in 2000–2015. Numbers in rows do not add up to total malformations due to types of malformation uncharted here. AdjOR, adjusted odds ratio; CI, confidence interval; cRR, crude or unadjusted relative risk; ICD-9/10, International Classification of Diseases, Ninth/Tenth Revision; NR, not reported; PDM, preexisting diabetes mellitus in pregnancy, undifferentiated; RR, relative risk; w, weeks gestation.

* Includes major circulatory malformations.

† Retrospective claims analysis from a national market scan database; participants age 18–45 years with ascertainable preexisting type 1 or type 2 diabetes status (yes/no) from ICD-9 codes, with continuous health plan enrollment >20 months before and at least 3 months after birth. Excluded miscarriages up to 24 w. Multiple pregnancies included. Controls were 353,599 births with no diabetes, included for nonadjusted comparisons. ICD-9 codes used to define major malformations, based on insurance claims filed within at least 3 months after birth. Many incomplete records excluded in diabetic and control groups due to no indication of outcomes (may increase the apparent rate of malformations, including in the control population [5.9%]).

‡ Rates of major malformations and denominators may be biased due to exclusion of 298 liveborn records from women with type 1 diabetes and 2,449 liveborn records from women with type 2 diabetes, due to unknown outcomes (also excluded 231,531 nondiabetic controls with unknown outcomes).

Table 5.29 continues on the next page.

TABLE 5.29. (continued)

§ Population-based study using the Nova Scotia Atlee Perinatal Database (11 maternity units throughout the province; 96% white population) which included 150,589 infants of nondiabetic mothers as controls and excluded multiple pregnancies, gestational diabetes, and infants whose gestational ages or birth weights were unknown. The authors did not have access to data concerning pregnancies resulting in loss or termination before 20 w, even if associated with major malformations. Major congenital anomaly was defined as lethal, life-shortening, life-threatening, required major surgery, or affecting in a significant way the quality of life. The definition included chromosomal abnormalities. Infant death followed up to 1 year of life, but it was unclear when diagnoses of major anomalies were made. Many infants were counted more than once in the rows due to multiple anomalies in same infant. The category musculoskeletal anomaly included three cases of caudal regression (RR 219). The category central nervous system included one case of spina bifida (RR 17). Odds ratio was adjusted for maternal age and smoking. Outcomes reaching statistical significance on univariate analysis were entered into a backward conditional regression to obtain adjusted relative risks.

‖ Data source from the 2005–2006 fiscal year of the administrative Ontario Niday Perinatal Database, a branch of the provincial Perinatal Surveillance System Web-based data entry by 72 participating hospitals; diagnoses extracted by codes unique to the database, which included singleton and multiple gestations and pregnancies with preexisting hypertension and nephropathy. Gestational age of anomalies undefined, including length of follow-up of infant; percentage in authors' table 2 would indicate n=32 for type 1 diabetes, but table 3 shows only 15 cases, including one of trisomy 21; text referring to that table indicates exclusion of cases of spontaneous or therapeutic terminations of pregnancy (<20 w) that occurred as a result of a congenital malformation. Excess risks of outcomes calculated by unconditional logistic regressions, using 115,996 pregnancies without maternal complications (including gestational diabetes) as controls; odds ratios adjusted for maternal age, region of residence, smoking, parity, multiple birth, use of assisted reproductive technology, attendance at a first trimester visit, and type of antenatal provider.

¶ Liveborn infants (n=2,839,680) in the national Discharge Abstract Database (excluding Quebec). Information previously validated. Mother-newborn records linked. Type 1 or type 2 diabetes and congenital malformations were determined by ICD-10 codes.

N of diabetes or malformation cases was not given in report, but prevalence of type 1 diabetes was 0.27% in 2002–2003 and 0.28% in 2012–2013. Prevalence of type 2 diabetes increased from 0.19% in 2002–2003 to 0.47% in 2012–2013 (p<0.0001). Adjusted odds ratios with 95% confidence intervals were estimated for the association between prepregnancy diabetes and congenital anomalies, using multivariate logistic regression, adjusting for maternal age, parity, and the year of delivery. Etiological contribution of PDM to overall congenital malformations increased between 2002–2003 and 2012–2013: the annual population attributable risk percentage rose from 0.6% (95% CI 0.4%–0.8%) in 2002–2003 to 1.2% (95% CI 0.9%–1.4%) in 2012–2013, because the prevalence of PDM increased, while the relation between PDM and congenital malformations rose only slightly.

SOURCE: References are listed within the table.

prevalence of congenital anomalies in all births in 22 countries in Europe during 2003–2007 (402). EUROCAT is a network of population-based registers, with a common protocol and data quality review (402). In the general population, the prevalence of major congenital anomalies was 2.4%; of these, 17.6% of cases were terminations of pregnancy following prenatal diagnosis, 2.0% were stillbirths or fetal deaths from 20 weeks gestation, 80% were livebirths, and 2.5% of livebirths with congenital anomaly died in the first week of life (402). The prevalence of chromosomal anomalies was relatively low (0.36% of all births), but they contributed heavily to 48% of terminations for major malformations and to 28% of fetal deaths with congenital anomaly from 20 weeks gestation. For the 85% of major anomalies that were coded as nonchromosomal, congenital heart defects were the most common (0.65% of all births), followed by limb defects (0.38% of all births), anomalies of the urinary system (0.31% of all births), and nervous system defects (0.23% of all births) (402).

In the surveys of diabetic pregnancies in Europe, the rates of major malformations were widely distributed (Table 5.30): 7.2%–9.5% for mothers with undefined preexisting diabetes or type 1 diabetes in three surveys (99,303,403), 4.0%–6.0% in six others (92,93,94,95,302,304,404), and as low as 2.2% in a multicenter study in Dublin (229) and 3.0% in a population-based study in North Italy (405). In South Australia, in 1986–2000, the overall rate of malformations in fetuses of women with preexisting diabetes was 10.1% compared to 5.1% in the reference population (includes some minor anomalies; adjusted RR 1.91, 95% CI 1.58–2.31; children followed to age 5 years) (406). The assessment of malformation rates seen in Tables 5.29 and 5.30 is influenced by whether investigators included late spontaneous abortions, pregnancy terminations, and stillborn infants with malformations (study details in the footnotes to the tables), as well as the length of follow-up of liveborn infants to 1 year of life or more (99,406).

There were fewer datasets for infants of mothers with type 2 diabetes: 2.1% major malformations in a multicenter study in Italy (95), 4.3% in the United Kingdom (302), 5.5% in North England (99), and 9.9% in the West Midlands of England (309). In Japan in 2003–2009, major congenital malformations were found in 4.6% of 367 liveborn infants of mothers with type 1 diabetes compared to 4.1% in 577 infants of mothers with type 2 diabetes (113). Of the surveys including nondiabetic women, the effect sizes for major malformations were relative risk 1.5 in Dublin, Ireland (229), relative risk 1.7 (95% CI 1.3–2.2) in Denmark (93), adjusted relative risk 1.91 (95% CI 1.58–2.31 in South Australia (406), adjusted odds ratio 2.04 (95% CI 1.60–2.59) in Norway (404), adjusted prevalence odds ratio 2.1 (95% CI 1.5–3.1) in Hungary, and relative risk 3.8 (95% CI 3.2–4.5) in North England (99) (Table 5.30).

Table 5.30 also shows the effect sizes of risk for groups of types of major malformations associated with maternal diabetes compared to controls in Europe and Australia. As in a large data set from Canada (excluding Quebec) (219) and one from Nova Scotia, Canada (249) (Table 5.29), significantly elevated relative risks or adjusted odds ratios were seen for cardiovascular system (99,302,404,405,406,407), central nervous system or neural (99,302,406), musculoskeletal (99,405), digestive system (99), and urogenital malformations (99,405,406,407) (Table 5.30).

Other studies provided the frequency of each of the type-groups of malformations in a reference population without a test for effect size (303,309,403). Some of these studies also show increased rates for cardiovascular system (303,309,403), urogenital (303), orofacial clefts (218,403), and limb malformations (99,403,405,406). The few studies that consider them show that multiple nonsyndromic malformations in the same infant are significantly more common in the setting of maternal

TABLE 5.30. Types and Prevalence of Major Congenital Malformations (Nonchromosomal, Except as Noted) in Infants of Women With Undifferentiated Preexisting Diabetes in Pregnancy, Type 1 Diabetes, or Type 2 Diabetes, Population-Based or Multicenter Studies in Europe and Australia, 1993–2013

REGION, YEARS (REF.)	NUMBER OF PDM BY TYPE OF DIABETES, GESTATIONAL AGE	GROUPS OF TYPES OF MALFORMATIONS NUMBER OF CASES (PERCENT OF INFANTS) VERSUS (PERCENT IN CONTROLS OR REFERENCE POPULATION) AND EFFECT SIZE (95% CI)						
		Major Congenital Malformation	Cardiac*†	Central Nervous System or Neural*	Musculo-skeletal System*	Digestive System*	Urogenital*	Multiple Anomalies*
Northwest England, 1995–1999 (303)‡	Type 1: 547 from first trimester 72 miscarriages 16 terminations 14 stillbirths 451 live births (6 pairs of twins)	48 (8.78) vs. (2.42) 2 4 4 38	15 (3.2) vs. (0.075)				Renal: 10 (2.15) vs. (0.06)	
United Kingdom, 2002 (302)§	Type 1: 1,706 Type 2: 650 from first trimester	81 (4.7) 28 (4.3) Total adjPR 2.2 (1.8–2.6) 4.6% of all PDM	33 (1.9) 9 (1.4) Total adjPR 3.4 (2.5–4.6)	11 (0.6) 4 (0.6) Total adjPR 2.7 (1.5–4.4)	15 (0.9) 4 (0.6) Total adjPR 1.4 (0.8–2.1)	1 (0.06) 2 (0.3) Total adjPR 0.8 (0.2–2.5)	9 (0.5) 1 (0.15) Total adjPR 1.2 (0.6–2.2)	Total 23/109; 21.1% of PDM with anomalies
West Midlands, England, 1990–2002 (309)‖	Type 2: 182 from first trimester 16 miscarriages 3 terminations 2 stillbirths 161 live births	18 (9.9) vs. (0.85) 1 2 15	8 (4.8) vs. (0.075)					
North England, 1996–2008 (99)¶	PDM: 1,677 (Type 2: 363)	120 (7.2) vs. (1.9) RR 3.8 (3.2–4.5) Type 1: 100 (7.7) Type 2: 20 (5.5)	44 (2.6) vs. (0.7) RR 3.6 (2.7–4.8)	16 (1.0) vs. (0.2) RR 5.0 (3.0–8.1)	3 (0.2) vs. (0.014) RR 13.0 (4.1–41.5)	10 (0.6) vs. (0.1) RR 5.7 (3.0–10.6)	Urinary: 12 (0.7) vs. (0.2) RR 2.9 (1.7–5.2)	9 (0.5) vs. (0.1) RR 4.9 (2.5–9.4)
Scotland, 1998 (304)#	Type 1: 276 fetuses 236 from first trimester	11 (4.0)	4	3	1	1		
Scotland, 1998–1999, 2003–2004 (94)**	Type 1: 423 359 ≥24 w	17 (4.6) 7 terminations 10 births ≥24 w	7	3	2	2	1	1/17
Dublin, Ireland, 1995–2006 (229)††	Type 1: 511 ≥24 w	11 (2.2) RR 1.5	6	3			1	
Netherlands, 1999 (100)‡‡	Type 1: 328 324 infants >24 w 4 terminations for anomaly	18 (5.5)	8	3			4	
Denmark, 1993–1999 (93)§§	Type 1: 1,246 births ≥24 w 3 terminations	61 (4.9) vs. (2.8) RR 1.7 (1.3–2.2)	14	2	6		4	

Table 5.30 continues on the next page.

TABLE 5.30. (continued)

REGION, YEARS (REF.)	NUMBER OF PDM BY TYPE OF DIABETES, GESTATIONAL AGE	GROUPS OF TYPES OF MALFORMATIONS NUMBER OF CASES (PERCENT OF INFANTS) VERSUS (PERCENT IN CONTROLS OR REFERENCE POPULATION) AND EFFECT SIZE (95% CI)						
		Major Congenital Malformation	Cardiac*†	Central Nervous System or Neural*	Musculo-skeletal System*	Digestive System*	Urogenital*	Multiple Anomalies*
Sweden, 1987–1997 (403)‖‖	PDM: 3,864	369 (9.5) vs. (3.7) in Med Birth Registry	133 (3.44) vs. (1.05)	8 (0.21) vs. (0.2)	45 (1.16)	70 (1.81)	27	22 (0.57) vs. (0.26)
Norway, 1999–2004 (404)¶¶	Type 1: 1,583 >11 w	91 (5.7) vs. (2.9) adjOR 2.04 (1.60–2.59)	51 adjOR 3.5 (2.7–4.7)	4	10	2	8	7/91
Hungary, 1980–1996 (407)##	case-control study	63 PDM in 22,843 cases; 50 PDM in 38,151 controls adjPOR 2.1 (1.5–3.1)	20 adjPOR 3.4 (2.0–5.7)	Neural tube: 3 adjPOR 1.9 (0.6–6.2)			Renal dysgenesis: 2 adjPOR 14.8 (3.5–62.1) Obstructive: 3 adjPOR 4.3 (1.3–13.9)	9 adjPOR 5.0 (2.4–10.2)
Italy, 1999–2003 (95)***	Type 1: 469 Type 2: 144 >180 days	28 (6.0) 3 (2.1)	11 2	3 0		4 0	8 0	
North Italy, 1997–2010 (405)†††	PDM: 2,269 cohort and case-control study; uncertain gestational age	68 (3.0) vs. (1.68)	23 (1.01) vs. (0.53) adjPR 1.93 (1.19–3.13)	0 vs. (0.04)	18 (0.8) vs. (0.3) adjPR 2.35 (1.33–4.12)	4 (0.18) vs. (0.17)	13 (0.57) vs. (0.29) adjPR 1.97 (1.03–3.76)	8 (0.35) vs. (0.19) adjPR 1.88 (0.83–4.26)
South Australia, 1986–2000 (406)‡‡‡	PDM: 946 >19 w	96 (10.1) vs. (5.1) adjRR 1.91 (1.58–2.31)	23 (2.4) vs. (0.9) RR 2.84 (1.89–4.26)	3 (0.3) vs. (0.1) RR 3.16 (1.02–9.85)	18 (1.9) vs. (1.4) RR 1.34 (0.85–2.12)	4 (0.4) vs. (0.4)	30 (3.2) vs. (1.4) RR 2.34 (1.64–3.33)	

Table includes population-based or multicenter studies reported in 2000–2015. "Multiple" indicates in the context of other abnormalities. AdjOR, adjusted odds ratio; adjPOR, adjusted prevalence odds ratio; adjPR, adjusted prevalence ratio; BMI, body mass index; EUROCAT, European Surveillance of Congenital Anomalies; ICD-9/10, International Classification of Diseases, Ninth/Tenth Revision; IDM, infant of diabetic mother; PDM, preexisting diabetes mellitus in pregnancy, undifferentiated; RR, unadjusted or adjusted relative risk; w, weeks gestation.

* Number represents specific congenital malformations among all major malformations. Numbers in rows do not add up to total malformations due to other types of malformations uncharted here or to infants with multiple malformations counted more than once.

† Includes major circulatory malformations.

‡ Multicenter, including 10 maternity units in Cheshire, Lancashire, and Merseyside. Congenital malformations were classified according to EUROCAT criteria. Among liveborn male IDM, the malformation rate was 9.05% (95% CI 5.36%–12.74%) compared with female liveborn IDM at 7.76% (95% CI 4.22%–11.31%). Reference population was all births as detected by the congenital anomaly survey of Merseyside and Cheshire. Rates of cardiovascular and renal abnormalities expressed as percentage of live births plus stillbirths (n=465) and comparisons made with the national reported rates (Office of Population Census and Surveys: *1990 Congenital Malformation Statistics*).

§ National population-based pregnancy cohort from 231 maternity units in England, Wales, and Northern Ireland. Coded confirmed (by postmortem findings, genetic results, or correspondence) major anomalies according to the classification system used by EUROCAT (6 of 109 offspring with anomalies were chromosomal; offspring included fetal losses after 20 w and terminations of pregnancy at any gestational age). Calculated the congenital anomaly rate as the number of offspring with one or more major anomalies divided by the number of livebirths and stillbirths. Urogenital anomalies here are of the internal urogenital system. 65% of all anomalies diagnosed antenatally. Compared the numbers of observed major anomalies with expected numbers based on age-specific rates for 2002 reported to EUROCAT, adjusted for the maternal age distribution in this study. Used the Poisson distribution to obtain the exact 95% confidence intervals for the prevalence ratios.

‖ Multicenter, from five maternity units in a defined area of the West Midlands. Includes miscarriages, terminations of pregnancy <20 w, live births, and stillbirths. Congenital abnormalities undefined. One miscarriage with Klinefelter syndrome; includes two terminations for diaphragmatic hernia and for severe neural tube defect. Of 15 liveborn IDM with malformations, two had neonatal deaths due to congenital heart disease, and two had post-neonatal deaths due to congenital heart disease or osteogenesis imperfecta. Total recorded pregnancy loss rate due to congenital anomalies in 182 type 2 diabetic women was 3.85%. Reference population was national data published by the Office for National Statistics.

¶ The Northern Diabetes in Pregnancy Survey recorded data on all singleton pregnancies in 1996–2008 resulting in live birth, stillbirth ≥24 w, late fetal loss at 20–23 w, and terminations of pregnancy for fetal anomaly at any gestational age. Included women with diabetes diagnosed at least 6 months prior to the index pregnancy, and excluded gestational diabetes. Diabetes and pregnancy registry data were linked to data on congenital anomalies diagnosed up to age 12 years in the registry of the Northern Congenital Anomaly Survey. Major congenital anomalies were coded according to ICD-10 and categorized using EUROCAT criteria by group (the system affected), subtype (the individual disorder), syndrome (patterns of anomalies arising from a single cause, e.g., genetic), skeletal dysplasias (syndromes of skeletal development), sequences (patterns of anomalies arising from a prior anomaly or a mechanical factor), associations (recognized patterns of anomalies of unknown cause), and chromosomal anomalies (see authors' table 3). Cases were classified as multiple anomalies if they had two or more unrelated anomalies across separate organ systems. Individuals with several anomalies from the same organ system were included in that group but not classified by subtype. A congenital anomaly was classified as isolated if it occurred alone or if all coexisting anomalies were commonly associated secondary anomalies. Only isolated or multiple nonchromosomal malformations are included in the table above. Among the other categories, only the sequence group (caudal dysplasia sequence, sirenomelia, and partial urorectal septum malformation sequence; RR 12.0, 95% CI 5.6–25.6) and the laterality syndrome (RR 57, CI 23–139) were highly associated with maternal diabetes. Chromosomal anomalies recorded in 0.54% of diabetic women, similar to controls. Pregnancy terminations occurred in 18% of diabetic pregnancies affected by anomalies. Elevated A1c progressively predicted risk of malformation, which was also increased with diabetic nephropathy. Control population data (women without diabetes in the same region and years; n=399,472) on live and stillbirths, late fetal losses,

Table 5.30 continues on the next page.

TABLE 5.30. (continued)

and pregnancy terminations were obtained from the U.K. Office for National Statistics. Prevalence rates of congenital anomaly by group were compared by calculating the relative risk, and 95% confidence intervals for prevalence rates were calculated using exact methods. Heterogeneity of relative risks between anomaly groups was examined using Cochran's Q test.

\# A 1-year audit of type 1 diabetes in Scotland in April 1998 through March 1999, including pregnancies ending in miscarriage (n=40), in termination (n=20, including n=6 for antenatally detected fetal anomalies), stillbirth (n=4), and liveborn infants, including three sets of twins (n=212).

** Combines data from national audits in April 1998 through March 1999 and April 2003 through March 2004. Here excluded cases of twins; repeat pregnancies in the same woman; miscarriages; induced abortions, except for seven because of detection of fetal anomaly; and two author-listed cases of Patau syndrome and trisomy 21.

†† Data from three university hospitals covering the Dublin metro area, including 142,498 control nondiabetic pregnancies.

‡‡ Repeated questionnaire survey throughout pregnancy of 364 patients with type 1 diabetes in 118 hospitals from April 1, 1999 through March 2000. Excluded 23 women due to early spontaneous abortion, 16 due to diagnosis of type 2 diabetes, four cases of late fetal loss <24 w, one maternal death at 17 w, and two lost to follow-up; includes eight twin pregnancies and one triplet pregnancy. Classified a malformation as major (n=18) if it was fatal, potentially life-threatening, likely to lead to serious handicap or a major cosmetic defect, required major surgery, or was a chromosomal abnormality (n=4). Compared maternal and perinatal outcomes with national data from the 1998 Dutch perinatal database and with data from Statistics Netherlands. Text states that major anomaly rate in pregnancies with type 1 diabetes was three times the national rate.

§§ Nationwide prospective multicenter study in eight centers; information collected after each delivery by one to three caregivers per center and reported to a central registry. Included repeat (n=228) and twin (n=28) pregnancies ≥24 w; excluded earlier fetal losses. Women entering the study were all considered to have type 1 diabetes by their caretakers and used insulin treatment before conception. Congenital malformations assessed during postbirth hospital stay only, except for three pregnancy terminations <24 w for severe malformations. Malformations in the study sample and the background population (n=70,089) include major and minor malformations, but in the background population, congenital malformations were reported to a central registry after the first year of life. Both factors would contribute to a lower rate of malformations reported in this survey of diabetic women. Uncertain if chromosomal abnormalities were included. Major malformations defined as those responsible for death, causing a significant future handicap, or requiring major surgery. Major malformations (n=32) represented 52.5% of those in the study sample.

‖‖ Data from Swedish Medical Birth Registry, Registry of Congenital Malformations, and the Hospital Discharge Registry combined. Use of the latter registries showed 26% (n=97) underreporting of congenital malformations in IDM to the Medical Birth Registry. All registries used for the national reference population. Gestational age for inclusion in registry not given. Congenital malformations identified by specific ICD-9 codes, with length of infant follow-up not reported. Total malformations number and percentage represents "any congenital malformation", including four with chromosomal anomaly, three with diaphragmatic hernia, three with spleen malformation, 19 with orofacial clefts (0.49% of IDM vs. 0.21% of reference population), and with a number of less severe malformations listed in report, but not shown in the types in this table. Groups of types of major malformations are constructed from authors' original table 1.

¶¶ Combined data from Medical Birth Registry (ICD-10 diagnoses made by physicians before infant left the nursery, including infants transferred to a neonatal ICU and neonatal deaths, and for stillbirths and terminations of pregnancy after 12 w because of antenatally diagnosed anomalies) and from the Norwegian Diabetes Registry to be sure all pregnancies with type 1 diabetes were included (96.8% of all cases of type 1 diabetes were in the Medical Birth Registry). Excluded anomalies categorized as minor in accordance with the EUROCAT system, but included three cases of chromosomal malformation and 10 cases of isolated patent ductus arteriosus at term birth (see authors' table 5). Background population (n=349,378) taken from the Medical Birth Registry for 1999–2004. Odds ratios were adjusted for maternal age, parity, gender of infant, maternal education, maternal smoking in pregnancy, European origin of mother, and year of birth.

Pregestational insulin-treated diabetes ascertained by questionnaire (requested information on underlying maternal diseases, drugs used, and pregnancy complications by gestational month) sent to all parents of cases and controls; nonrespondents visited by regional district nurses (5% of case mothers refused to participate). Maternal antenatal logbooks were available for 88% of cases and 94% of controls. Hungarian Congenital Abnormality Registry (compulsory for all physicians in Hungary) comprises cases, including malformed fetuses after termination of pregnancy due to antenatal diagnosis of fetal defects, stillborn fetuses, and liveborn infants diagnosed with congenital abnormalities in the first year of life. Autopsy data included. Excluded mild abnormalities and syndromes of known origin, like chromosomal disorders. Controls were two newborns without congenital abnormalities for each case, selected from the National Birth Registry of the Central Statistical Office, matched according to sex, birth week, and district of parent's residence. Used unconditional logistic regression to adjust for potential confounding from maternal age, birth order, and use of antiepileptic and antipsychotic drugs.

*** Multicenter, with referral centers throughout Italy. Study fostered by the Italian Diabetes and Pregnancy Study Group. Congenital malformations undefined. Original data set included 30 spontaneous abortions in the type 1 diabetes group and 17 in the type 2 diabetes group, excluded here. Unknown whether any of the 31 malformations were among the eight pregnancies with induced abortions (five with type 1 diabetes, three with type 2 diabetes) that were excluded from the n in this table.

††† Population-based cohort and case-control study in the Northern Italy Emilia-Romagna region. Linked maternal and newborn hospital discharge records with birth certificates and the Region Birth Defects Registry. Singleton liveborn and stillborn infants and repeat pregnancies included. Diagnoses based on ICD-9 codes and anomalies according to EUROCAT. Authors state that severe cardiovascular and nervous system anomalies were missing because they have no data on spontaneous abortions and terminations of pregnancy due to malformations. Of the congenital anomalies in IDM, five were chromosomal anomalies; of the 202 congenital anomalies in controls, 10 were chromosomal anomalies (adjPR 2.35, 95% CI 0.80–6.86); all excluded here. This table excludes three cases of polydactyly/syndactyly in the diabetes group and 13 in the control group. Multiple malformations were nonsyndromic. Authors identified only 18% of the total diabetic population as type 1 and only 20.7% as type 2, based on an incomplete prescription database, so data are included as total pregestational diabetes here. Controls were 10,648 births to nondiabetic women, used for adjusted odds ratio (95% CI) for total congenital anomalies, adjusting for maternal age and area of residence, hospital and year of delivery, education, and smoking habits. No data on maternal BMI or maternal medications that were possibly teratogenic. For the adjusted prevalence ratios, authors matched each birth to a diabetic woman with five randomly selected births to nondiabetic women and used a conditional logistic model that controlled for the matching factors of maternal age, province of residence, year, and hospital of delivery.

‡‡‡ South Australian Birth Defects Register receives notifications of congenital anomalies up to a child's fifth birthday. Congenital anomalies coded by ICD-9, British Pediatric Association Perinatal Supplement. The Register excluded most minor anomalies, unless they were disfiguring or required treatment. Multiple anomalies in same infant not discussed. Chromosomal, hematologic, metabolic, and respiratory anomalies were included in the reference population but were not recorded in the group with PDM. Birth defects data were linked to data of the Pregnancy Outcomes Statistics Unit of the South Australian Department of Health. Pregestational diabetes examined separately from gestational diabetes. Includes stillbirths ≥400 g or ≥20 w, singleton livebirths, but not pregnancy terminations. The comparatively high rate of anomalies in the total population (5.1%) and the sample with pregestational diabetes (10.1%) suggests that some minor malformations and all chromosomal abnormalities were included, as well as infants counted twice due to multiple anomalies. Reference population was all births (n=282,260) in the district in 1986–2000. Relative risk for all anomalies in PDM versus reference population was adjusted for maternal age, ethnicity, place of birth, and year of birth. Musculoskeletal defects include one abdominal wall defect and five limb reduction defects (RR 9.22, 95% CI 3.79–22.40). Orofacial clefts (n=2) were included in digestive category.

SOURCE: References are listed within the table.

diabetes (99,403,407), with one exception (405) (Table 5.30). The details of the methods of these studies are provided in the footnotes to Tables 5.29 and 5.30.

A population-based case-control study in Hungary (births in 1980–1996) included malformations in terminations of pregnancy, stillbirths, and liveborn infants up to 1 year of life; autopsies were usually done for stillbirths and infant deaths (407). The strongest association of risk for types of malformations with maternal diabetes included renal agenesis (prevalence odds ratio [POR] 14.8), obstructive congenital abnormalities of the urinary tract (POR 4.3), cardiovascular congenital abnormalities (POR 3.4), and multiple congenital abnormalities in the same infant (POR 5.0) (407).

Another large case-control study of nonchromosomal anomalies examined data from 18 population-based EUROCAT registries of congenital anomalies in 1990–2005 (669 pregestational diabetes cases and 92,976 nondiabetes cases) (408). There were significantly increased odds ratios associated with pregestational diabetes for anencephaly, encephalocele, omphalocele, bilateral renal agenesis,

subgroups of congenital heart defects, and multiple congenital anomalies in the same infant (present in 13.6% of 669 cases in the diabetes group and 6.1% of 92,976 cases in the nondiabetic group). The odds ratio for caudal regression sequence was very high (26.4, 95% CI 9.0–77.6), but only 17% of all caudal regression cases resulted from a pregnancy with pregestational diabetes (408).

Despite early suggestions of *fetal sex-associated risk* (409,410), major malformations were not significantly more common in male versus female infants of women with type 1 diabetes in large surveys from Norway (404) and Sweden (307), with the proviso that the latter studies do not include data on terminations of pregnancy or fetal deaths before 28 weeks gestation. Perhaps the teratogenic effects of the uncontrolled diabetic state obscure (411) the small, but significant, fetal sex-associated risks of some congenital malformations found in liveborn infants in the general population (male excess in some anomalies, female excess in others) (307,404,412,413,414,415,416,417).

Regarding possible effects on the final sex ratio, it is of interest that early male embryos are slightly more likely to be abnormal (418), but that female fetuses are slightly more likely to be lost at 6–20 weeks gestation, and male fetuses are slightly more likely to expire at 28–35 weeks (418). This study of the human sex ratio is the largest and most comprehensive performed as of 2014 (418), and the article considers the discrepancies in prior studies (419). The great majority of pregnancy losses occur by 20 weeks. Perhaps this biology biases the slight overrepresentation of males among liveborn and stillborn infants with some congenital malformations in the general population (genital, urinary, musculoskeletal, digestive, orofacial clefts) (417). Nervous system defects (413), including neural tube defects (412,413,414,415,416), and limb defects (417) seem to be more common in female than male liveborn infants in some, but not all, studies. Interestingly, multiple malformations in the same infant in the general population were less common in males in one study (413) and more common in two others (416,417). The role of fetal survival has long been considered important in selection bias of studies of human teratogens (420), including diabetic embryopathy (421).

Major malformations with deformations and chromosomal abnormalities remain the leading cause of infant death in the United States (20.6%), followed by disorders related to short gestation and low birth weight (17.4%) (422). Malformations compete with early preterm delivery as an initiating cause for death in infants of mothers with diabetes (93,278,302). Table 5.31 shows the percentage of neonatal deaths with any birth defects in infants of mothers with diabetes, grouped by maternal age and race/ethnicity. The data are from the NVSS 2007 (accessed for *Diabetes in America*). Malformations contribute to

TABLE 5.31. Percent of Neonatal Deaths With Any Birth Defects Among Women With Preexisting Diabetes Mellitus in Pregnancy, by Maternal Age and Race/Ethnicity, U.S., 2007

MATERNAL RACE/ETHNICITY AND AGE (YEARS)	NUMBER OF DEATHS*	DEATHS WITH BIRTH DEFECTS	
		Number	Percent†
Total	116	10	8.6
15–19	3	0	0
20–24	19	0	0
25–29	35	2	5.8
30–34	25	2	8.0
35–39	24	5	21.4
40–44	10	1	9.8
Non-Hispanic white			
Total	45	4	8.9
15–19	1	0	0
20–24	7	0	0
25–29	16	0	0
30–34	9	2	22.3
35–39	11	2	18.0
40–44	1	0	0
Non-Hispanic black			
Total	44	4	9.1
15–19	1	0	0
20–24	12	0	0
25–29	9	2	22.0
30–34	10	0	0
35–39	7	2	29.8
40–44	5	0	0
All Hispanic			
Total	25	2	8.0
15–19	1	0	0
20–24	0	0	0
25–29	9	0	0
30–34	5	0	0
35–39	6	1	17.6
40–44	4	1	24.5
Asian/Pacific Islander			
Total	1	0	0
American Indian/Alaska Native			
Total	0	0	0

Data include states using the 2003 revised birth certificate. Neonatal is defined as 0–27 days of life. Birth defects include anencephaly, meningomyelocele/spina bifida, cyanotic congenital heart disease, congenital diaphragmatic hernia, omphalocele, gastroschisis, limb reduction defect, cleft lip with or without cleft palate, cleft palate alone, Down syndrome, suspected chromosomal disorder, and hypospadias.

* Data with missing information on age deleted from totals.

† The percent of deaths with birth defects is a weighted estimate that corrects for biases in the percent of records linked by major characteristics.

SOURCE: National Vital Statistics System 2007

the high cost of care of infants of diabetic mothers (77,78,79,80,81) and to lifelong disability. Since malformations are related to poor glycemic control and occur early in pregnancy (71,290), the intensified preconception care mentioned in the section *Preconception Care of Diabetes and Contraception* is essential in prevention (71,72,73,74).

Few population-based data are available on the *prenatal detection of major malformations* in pregnancies complicated by type 1 or type 2 diabetes, so information depends on data from regional centers. Shortened crown-rump length ("early fetal growth delay") in the first trimester does not seem to predict risk of major malformations in the setting of diabetes (346,423,424). Increased fetal nuchal translucency by late first trimester scanning may suggest increased risk that a major malformation is present, especially in conjunction with A1c >8.3% (>67 mmol/mol; sensitivity 70.6%, specificity 77.4%, positive predictive value 16.2%, negative predictive value 97.7%) (425). The antenatal detection rate of noncardiac malformations by midpregnancy ultrasound scanning varied from 30% to 70% in women with preexisting diabetes (426,427,428,429). The antenatal detection rate of congenital anomalies was reduced by maternal BMI >30–40 kg/m^2 (429,430,431). This presents a clinical challenge, since there may be an association between obesity and noncardiac and cardiac major malformations in women with preexisting diabetes (432). Twin pregnancy in diabetic women increases the rate of perinatal morbidity (433), including an increased rate of major malformations in twin versus singleton gestations (434,435) (e.g., adjusted rate ratio 3.51, 95% CI 1.31–9.40) (435).

Congenital Heart Defects

Congenital heart defects are among the most important malformations in infants of mothers with diabetes in terms of mortality, morbidity, and long-term costs (81,434,436,437,438). All large population data sets show an increased risk of congenital heart defects with maternal preexisting diabetes, both type 1 and type 2 diabetes, with both isolated and multiple cardiovascular defects, that often occur with malformations of other body parts (~30%) (54,99,219,249,302,303, 309,405,406,436,437,438) (Tables 5.29 and 5.30; methods of comparison to controls are given in the footnotes).

In a study of all mother-infant pairs in Canada (excluding Quebec) in 2002–2010, maternal diabetes was a solid risk factor for congenital heart defects in both type 1 diabetes (adjusted OR 4.65, 95% CI 4.13–5.24) and type 2 diabetes (adjusted OR 4.12, 95% CI 3.69–4.60) (434). The risk of congenital heart defects in infants of diabetic women is independent of other contributing factors, such as age, parity, obesity, and smoking (434,436). The risk is strongly and linearly related to poor glycemic control at the beginning of pregnancy (99,105,145,290,316,437). Diabetes-related comorbidities that may add to risk of major cardiovascular malformations include hypertension (adjusted OR 1.81, 95% CI 1.61–2.03) and thyroid disease (adjusted OR 1.45, 95% CI 1.26–1.67) (434), plus diabetic nephropathy (adjusted OR 2.5, 95% CI 1.1–5.3) (99).

Almost all severe types of congenital heart defects are increased in infants of mothers with diabetes, especially heterotaxia, conotruncal defects, transposition of the great vessels, atrioventricular septal defect, anomalous pulmonary venous return, left and right ventricular outflow obstruction, and complex defects, as well as large isolated septal defects (401,434,436,437,438).

In one large population-based case-control analysis of cardiovascular malformations conducted in 1981–1989, most types of malformation with excess risk in infants of mothers with diabetes were in the developmental category of cardiovascular malformations occurring early in organogenesis (laterality and cardiac looping defects, outflow tract anomalies, atrioventricular septal defects) (436). In this Baltimore-Washington Infant Study, the case mortality rate was more than doubled in infants with cardiovascular malformations born to diabetic mothers (39%) compared with infants with cardiovascular malformations of nondiabetic mothers (17.8%). The leading causes of death among infants with cardiovascular malformations were heart failure (47.8%), surgical complications (34.8%), and infections (13.0%), with little difference in causes between infants of mothers with diabetes and control cases. Additional characteristics of deceased case infants born to mothers with preexisting diabetes mellitus were the presence of extracardiac anomalies in 43.0%, birth <37 weeks gestation in 47%, and SGA in 19% (436).

THE CONTRIBUTION OF THE PLACENTA

It is difficult to find population-based data on the characteristics of the placenta (even size or weight) (439,440) in births to women with preexisting diabetes. This lack is glaring in view of multiple single-center studies and reviews since 2000 on placental histologic changes with diabetes (441,442,443,444,445,446), the contribution of the placenta to glucose utilization and transport (447) and production and transfer of other nutrients, metabolites, and signaling cytokines (448,449,450, 451,452,453,454,455), plus changes in gene expression (456,457,458,459,460, 461,462,463,464,465) that could well contribute to fetal growth and development (466) and to perinatal and long-term morbidities in the setting of maternal diabetes (467,468,469). In addition to placental sampling (470,471), measures of umbilical components have provided important data (472,473,474,475). Only selected articles published since 2008 are cited here. There is need for measures that can be adapted to epidemiologic studies (476,477).

OTHER NEONATAL MORBIDITY ASSOCIATED WITH MATERNAL DIABETES

Respiratory Distress

Definitions of neonatal respiratory distress in infants of diabetic mothers have varied or were not defined in the multicenter or population-based reports discussed below. The IADPSG-proposed definition of respiratory distress of the neonate states:

"respiratory difficulties requiring any positive pressure ventilation ≥24 h that occurs beyond the first 10 min of the resuscitation period, and/or given surfactant within 72 h after birth" (13). Some authors did not distinguish this more severe illness from the usually milder distress known as transient tachypnea of the newborn (TTN). The IADPSG definition of TTN states: "lung disorder resulting from delayed resorption and clearance of fetal alveolar fluid, with onset usually at the time of birth and within 2 h after delivery with tachypnea being the most prominent clinical feature. Characteristic findings on chest radiograph support the diagnosis and help to rule out other conditions. Symptoms usually last for 12–24 h, and as long as 72 h in severe cases. Infants may require some form of positive pressure support in the first 24–48 h of life +/- supplemental oxygen" (13).

Historically, hyaline membrane disease or respiratory distress syndrome (RDS) due to pulmonary surfactant deficiency was a major cause of death of infants of mothers with diabetes (1). Among mothers with type 1 diabetes in the DCCT who gave birth during 1983–1993, respiratory distress (undefined) was reported in 36 of 191 liveborn infants (18.8%) (6). All subjects received intensive diabetes care during pregnancy. There was no difference in frequency of neonatal respiratory distress whether or not the mother had intensive therapy before conception. Rates of preeclampsia and preterm birth were not stated, except to note they were not different in women in the original study groups (6).

The rate of respiratory distress recorded in liveborn infants of women with pregestational diabetes who participated in a randomized controlled trial of low-dose aspirin use to prevent preeclampsia in 1991–1995 in North America was 24 of 90 infants (27%) with indicated deliveries at <37 weeks gestation and 17 of 66 (26%) spontaneous deliveries at <37 weeks (322). For deliveries at <35 weeks, the rates were 44.0% in 25 indicated and 39.4% in 33 spontaneous deliveries (322). The authors noted that the number of preterm deliveries was greater in their Table II on preterm birth than in their Table III on neonatal outcomes after preterm delivery, due to inclusion of stillbirths, miscarriages, and neonatal missing data in their Table II (322). The overall rate of RDS of 9% assumes no cases were seen at >36 weeks. Maternal aspirin use did not affect preterm birth or RDS (322).

Respiratory distress frequency was reported to be 6.5% (114), 8.7% (115), and 8.8% (208) in three population-based surveys of pregnancies of mothers with pregestational (115,208) or type 1 diabetes (114) reported since 2000 in North America (Tables 5.26 and 5.27). In the survey of 1,712 liveborn infants matched to diabetic mothers in Northern California in 2007–2011, the frequencies of RDS plus TTN per gestational age group were 69.8% of infants delivered at 24–34 weeks, 15.4% of infants delivered at 34–36 weeks, and 3.44% of infants delivered at ≥37 weeks (208). It was gratifying to see the overall rates of respiratory distress decline from 13.5% in 1996–2000 to 10.2% in 2001–2006 and to 8.8% in 2007–2011 in the KPNC database (208). For infants of women with type 2 diabetes in California, the rate of RDS was 2.2% in 2,197 liveborn infants (114) (Table 5.27). Four North American surveys did not present data on respiratory distress in the infants (203,213,214,308).

In European population-based surveys or multicenter studies of women with preexisting diabetes with data (Table 5.27), the reported rates of RDS in infants of mothers with type 1 diabetes were 0.8% in Sweden (338), 1.0% in Sweden (276), 2.0% in Sweden (307), and 1.5% in Italy (95) compared to 5.3% in the Netherlands (100) and 16.6% in Denmark (93). The Swedish (276,338) and Dutch (100) studies presented separate data on TTN, and perhaps the milder cases of respiratory distress were included in the coding in Denmark. In Japan, in 2003–2009, the rates of respiratory distress were reported to be 10.4% in 328 liveborn infants of women with type 1 diabetes and 12.2% in 508 infants of mothers with type 2 diabetes (113).

The large study using the Medical Birth Register in Sweden for 1998–2007 showed that neonatal respiratory disorders were more common in male than female infants of mothers with type 1 diabetes (n=4,092, adjusted OR 1.50, 95% CI 1.12–2.02), but there was no sex difference for respiratory disorders in 412 infants of mothers with type 2 diabetes (307). For the male infants of mothers with either type of diabetes, there was no increased risk of (a) preterm birth at <32 weeks or at 32–37 weeks, (b) neonatal hypoglycemia, (c) major congenital malformations, or (d) perinatal mortality, although the first three categories, plus respiratory disorders and late neonatal and infant deaths, were significantly more common in the 466,040 male infants in the reference population compared to reference female infants (307).

Hypertrophic Cardiomyopathy

Another possible cause of cardiorespiratory difficulties in infants of mothers with diabetes is hypertrophic cardiomyopathy. The prevalence may be >12% of infants of mothers with diabetes, depending on the frequency of fetal macrosomia and of newborn screening with echocardiography (478). Population-based data on hypertrophic cardiomyopathy in infants of mothers with diabetes are difficult to find. Its frequency was 5% in 324 infants of mothers with type 1 diabetes in the Netherlands in 1999–2000, based on clinical diagnosis (100). In the Baltimore-Washington Infant case-control study conducted in 1981–1989, maternal diabetes was strongly associated with neonatal cardiomyopathy (OR 15.1, 95% CI 5.5–41.3) (436).

Polycythemia

Neonatal polycythemia and secondary hyperviscosity syndrome have been identified in infants of mothers with diabetes (479,480,481,482). IADPSG defines polycythemia in a term infant as hematocrit in a peripheral venous sample >65% or hemoglobin >22 g/dL (13). Despite its importance, data on polycythemia in

infants of mothers with diabetes are scant (479,480,481,482). In the 40-center study fostered by the Japanese Diabetes and Pregnancy Study Group in 2003–2009, the recorded frequencies of neonatal polycythemia were 2.1% of 328 liveborn infants of mothers with type 1 diabetes delivered at ≥20 weeks gestation and 2.4% of 508 liveborn infants of mothers with type 2 diabetes (113).

METABOLIC PROBLEMS IN INFANTS OF DIABETIC MOTHERS

The categories of metabolic complications in infants of mothers with diabetes (483,484) described in this section are commonly used but demonstrate the complex interactions that characterize infant physiology. These metabolic problems are important because they require expensive neonatal care and they may be linked to developmental problems in children.

Neonatal Hypoglycemia

Neonatal hypoglycemia remains common in the first day of life in infants of diabetic mothers (485,486,487), but there is not wide agreement on its definition (488,489,490) nor on the proper method of glucose measurement in the newborn (484). Correlates of hypoglycemia in infants of diabetic mothers are poor maternal glycemic control, fetal hyperinsulinemia, large or small size of the fetus, and late preterm birth (485,487), but in one prospective study including 202 infants of diabetic mothers, 37% of newborn infants of diabetic mothers with hypoglycemia were of appropriate size and born at term (486). Of 133 hypoglycemic episodes in the infants of diabetic mothers in this study, 52% occurred in the first 6 hours of life, 83% occurred in the first 24 hours, and 17% were recurrent at 24–48 hours (486). It is important to note "a disconnect" (491) between neonatal glucose values and the nonspecific symptoms of neonatal hypoglycemia (492). "Acute symptoms and long-term neurologic sequelae occur within a continuum of low plasma glucose values of varied duration and severity" (492).

The IADPSG-proposed codification of pregnancy outcomes for diabetic women (13) defines neonatal hypoglycemia as a plasma glucose value <40 mg/dL (<2.22 mmol/L), based on the 10th percentile of more than 17,000 neonatal values at 1–4 hours of life in the global Hyperglycemia and Adverse Pregnancy Outcome Study (493), which is described in Chapter 4. Others state that "the validity of statistical definitions of neonatal hypoglycemia has been appropriately criticized" and that neonatal glucose should be evaluated with regard to long-term outcomes (492).

A retrospective population-based study of 1,395 newborn-student pairs in Arkansas showed that transient hypoglycemia levels of <35, <40, and <45 mg/dL (<1.94, <2.22, and <2.50 mmol/L) were associated with lower literacy achievement test scores at age 10 years (adjusted OR 0.49, 95% CI 0.28–0.83, adjusted OR 0.43, 95% CI 0.28–0.67, adjusted OR 0.62, 95% CI 0.45–0.85, respectively), while controlling for gestational age group, race, sex, multifetal gestation, insurance status, maternal educational level and socio-economic status, and gravidity (494). Infants with prolonged hypoglycemia, congenital anomalies, or chromosomal abnormalities were excluded from the study. Similar associations were found with the levels of transient newborn hypoglycemia and mathematics achievement test scores (494).

A New Zealand 2-year follow-up study of 148 children with neonatal hypoglycemia (<47 mg/dL [<2.61 mmol/L]) in the first 48 hours of life found that 32% had mild neurosensory impairment and 3.8% had moderate-severe impairment on cognitive, language, or motor scores (495). The infants had been enrolled in a randomized controlled trial of oral dextrose gel to treat the hypoglycemia, which had no effect on the 2-year outcomes (495).

However, another analysis of a somewhat larger sample of 404 New Zealand infants at risk for hypoglycemia, revealed that 216 had blood glucose levels <47 mg/dL and were treated with any combination of additional feeding, buccal dextrose gel, or intravenous dextrose to maintain blood glucose >47 mg/dL for 24–48 hours on frequent monitoring (496). Of the total group, 161 were infants of diabetic mothers, and 49.7% of them had blood glucose levels <47 mg/dL. Infants who were followed for 2 years showed that hypoglycemia, as defined and treated as above, was not associated with the risk of neurosensory impairment or processing difficulty (496). Follow-up data were not presented separately for the infants of diabetic mothers. Of note, the 5th quintile of all infants with the highest blood glucose levels on treatment during the first 48 hours (>70 mg/dL) did have significantly more neuroimpairment at age 2 years (496).

The American Academy of Pediatrics (AAP) published a guideline in 2011 for the screening and management of neonatal hypoglycemia in late-preterm infants and term infants at risk, who are those "born to mothers with diabetes, small for gestational age, or large for gestational age" (491). The guide was intended to provide adequate screening and treatment for infants who need it, to avoid cerebral energy deficiency, without creating a huge barrier to initiation of successful breastfeeding, which is also important for long-term health. It is known that successful breastfeeding at discharge from hospital is strongly dependent on breastfeeding at the first feed in diabetic women (497). The AAP protocol should be reviewed because it is apparent that prenatal diabetes and pediatric management teams must work in concert to reduce the frequency of neonatal hypoglycemia and NICU admissions and provide for optimal long-term health and development of the child. In 2015, recommendations from the Pediatric Endocrine Society focused on the evaluation and management of *persistent* hypoglycemia in neonates, infants, and children. The Society agreed that infants of diabetic mothers are among the neonates at increased risk for hypoglycemia and require glucose screening (498).

In the analysis of subjects with type 1 diabetes who became pregnant during the DCCT in 1983–1993, neonatal hypoglycemia was defined as blood glucose

<40 mg/dL within 72 hours after birth. Neonatal hypoglycemia was recorded in 39.6% of infants of mothers who were on intensive diabetes management at conception and 35.9% of infants of mothers who changed to intensive treatment after pregnancy was diagnosed (6).

Only three population-based surveys or multicenter studies (115,208,227) of pregnancies complicated by undifferentiated preexisting diabetes reported since 2000 presented data on neonatal hypoglycemia (Table 5.26). In a multicenter study including the previous and current pregnancy of multiparous women in Utah in 2002–2010, among 802 infants of mothers with pregestational diabetes in both pregnancies, the rate of neonatal hypoglycemia was only 2.2% (ICD-9 code 775.6) compared to 1.9% in 58,224 control infants (115). In the new analysis for *Diabetes in America,* of 1,712 liveborn infants to mothers with type 1 or type 2 diabetes in the KPNC system in 2007–2011, the frequency of neonatal hypoglycemia defined as needing treatment in the NICU was only 1.9% (208). This result is similar to the rates of 2.0% in 555 liveborn infants of mothers with type 1 diabetes and 1.3% in 2,197 infants of mothers with type 2 diabetes in a statewide California survey in 2006 (114). In these latter cases, neonatal hypoglycemia was defined as needing intravenous glucose therapy for the newborn infant (114). The rate of neonatal hypoglycemia was 47.8% (ICD-10 code P70.4) among 1,228 liveborn infants of diabetic mothers in New South Wales, Australia, in 1998–2002 compared to 1.6% of infants of 352,673 control pregnancies without any kind of diabetes (227). The difference may be rigorous screening of infants of diabetic mothers and use of a statistical definition versus testing of symptomatic infants of nondiabetic mothers. Of the infants of mothers with diabetes, 35% were LGA (vs. 10.4% of controls), and 80.8% were born at ≥37 weeks gestation (vs. 94.8% of controls) (227).

Regarding infants of women with type 1 diabetes in international multicenter studies reported since 2000 (Table 5.27), the rates of neonatal hypoglycemia in 1998–2013 were 16.6%, 23.2%, and 13.7% in multicenter studies in Italy (95), West Ireland (108), and Japan (113), respectively. Of two reports using the Swedish Medical Birth Registry for 1998–2007, rates of neonatal hypoglycemia in infants of mothers with type 1 diabetes were coded as 9.85% in one study (307) and as 9.9% in the other (338). Hypoglycemia was defined as <2.6 mM recorded after 6 hours of life in both analyses. In the latter study, hypoglycemia >6 hours was 9.1% in AGA infants and 10.7% in LGA infants (338). Neonatal hypoglycemia at 0–6 hours was recorded in 11.2% of AGA infants and 12.7% of LGA infants (338). For some reason, rates were much higher in infants of women with type 1 diabetes in the national survey in the Netherlands in 1999 (44.3% at <36 mg/dL [<2.00 mmol/L]) (100) and in the Helsinki area of Finland in 1999–2003 at 56.8% and in 2004–2008 at 48.0% (<47 mg/dL) (226).

Rates of neonatal hypoglycemia for infants of women with type 2 diabetes in these international studies were 7.2% in West Ireland (p=0.004 vs. controls) (108), 6.55% in Sweden (1.3% in 905,565 controls) (307), 15.4% in Japan (113), and 19.9% in Italy (95) (Table 5.27).

In the Swedish Medical Birth Register for 1998–2007, neonatal hypoglycemia was not significantly more frequent in 2,088 male infants of women with type 1 diabetes (10.3%) versus 2,004 female infants (9.4%) (307). In 412 infants of women with type 2 diabetes in this study, the rate of neonatal hypoglycemia was 5.8% in female infants and 7.4% in male infants (NS). These rates compared to 0.97% in 439,525 female infants in the reference group versus 1.6% in 466,040 male infants in the reference group (p<0.001 for males vs. females). In the reference group, male infants were more likely to be born at 32–36 weeks gestation (4.4%) than female infants (4.0%, p<0.001).

The variation in "prevalence" in these studies denotes the problem with the definition of neonatal hypoglycemia by a glucose measurement in the infant of the diabetic mother (13,491,492) or by the treatment applied to the baby (114,208). Small studies have shown that prevention of the need for aggressive treatment of neonatal hypoglycemia may depend on control of the maternal glucose during delivery in previously well-controlled women (499,500), early feeding of colostrum or formula to the newborn (501,502,503,504,505), or administration of buccal dextrose gel to the infant with glucose <47 mg/dL (506).

In an analysis of 147 LGA infants of women with preexisting diabetes delivered ≥34 weeks at Ohio State University in 2008–2011 (malformations excluded), a triage system was applied in the delivery room, with 43 asymptomatic infants referred to the Well Baby Nursery (WBN), and 104 infants transferred to the NICU (53% for respiratory disorder, 27% for "prevention of hypoglycemia," 19% for prematurity, 1 for asphyxia) (507). The WBN infants were screened for hypoglycemia by the first hour of life and prior to first feeding. Of the 43 WBN infants, 18 (42%) had blood glucose episodes <40 mg/dL in the first 48 hours of life (10 on single occurrence), and most episodes were corrected by feeding. Of the 104 NICU infants, 48 (46%) developed hypoglycemia, possibly reflecting illness or later feeding (507). The authors concluded that safe triage of asymptomatic LGA infants of diabetic mothers from the delivery room to the WBN can be accomplished in the majority of cases (507).

None of the population-based surveys of births to diabetic women reviewed here linked their neonatal outcome data to long-term development and health of the children. The challenge for future research is to account for the interaction among

neonatal complications in infants of diabetic mothers and the confounders that also may influence long-term outcomes.

Hypocalcemia and Hypomagnesemia

For babies of mothers with type 1 diabetes who participated in the DCCT, the frequency of hypocalcemia was 4.5% among 134 liveborn infants born to women who were in the intensive control group prior to conception compared to 2.1% of 57 liveborn infants born to women with type 1 diabetes who began intensive diabetes management after diagnosis of pregnancy (6). In another study, lower umbilical cord calcium concentration and earlier gestational age were the best independent predictors of the lowest neonatal serum calcium level in a prospective study of 186 infants of mothers with diabetes (508). Studies at the same leading institution showed that neonatal hypocalcemia in infants of diabetic mothers also correlated with neonatal hypomagnesemia (480) and maternal glucose control in a randomized trial (509). The consensus panel on clinical and laboratory definitions of the IADPSG proposed in 2015 to define neonatal hypocalcemia as total plasma calcium below 2.2–2.5 mmol/L (13).

In the population-based or multicenter studies of pregnancies complicated by type 1 diabetes and reported since 2000, the frequency of hypocalcemia in Italy in 1999–2003 was 8.2% of 464 liveborn infants of mothers with type 1 diabetes and 6.4% of 141 liveborn infants of women with type 2 diabetes (95). The rate of hypocalcemia (undefined) was 0.9% among 328 liveborn infants of mothers with type 1 diabetes in a multicenter study in Japan compared to 2.6% among 508 liveborn infants of mothers with type 2 diabetes delivered in 2003–2009 (statistical test not done) (113). Neonatal hypocalcemia and hypomagnesemia were not recorded in the other population-based surveys or multicenter studies that provided some data on infants of women with preexisting diabetes mellitus during pregnancy.

Hyperbilirubinemia and Jaundice

Hyperbilirubinemia has been observed more frequently in infants of mothers with diabetes than in control infants at any gestational age (510). The IADPSG proposal for codifications of pregnancy outcomes with maternal diabetes suggests an operational definition: use of phototherapy or exchange transfusion for the infant (13). The AAP published guidelines (2004; updated 2009) to treat infants born at ≥35 weeks gestation with phototherapy based upon the bilirubin level, time after birth, and several risk factors (i.e., gestational age, Coombs test) (511,512,513).

The U.S. Preventive Services Task Force (USPSTF) concluded that the evidence was insufficient up to 2009 to assess the balance of benefits and harms of screening for hyperbilirubinemia to prevent rare chronic bilirubin encephalopathy (514,515). The USPSTF found inadequate evidence that treating elevated bilirubin levels in term or near-term (≥35 weeks) infants to prevent severe hyperbilirubinemia resulted in the prevention of the rare chronic bilirubin encephalopathy. The Task Force stated that potential harms of phototherapy included interruption of breastfeeding and disruption of the maternal-infant relationship (514,515), already problems for infants of diabetic mothers. Subsequent pediatric studies of risk factors to enhance indications for phototherapy do not include maternal diabetes.

Transcutaneous bilirubin estimates are often used for screening for clinical neonatal hyperbilirubinemia (512,513). The goal of therapy is to "reduce the incidence of severe hyperbilirubinemia and bilirubin encephalopathy (kernicterus) while minimizing the risks of unintended harm, such as maternal anxiety, decreased breastfeeding, and unnecessary costs and treatment" (511). The guideline includes a systematic assessment of the infant before discharge. Thus, it is assumed that assessment of the rates of hyperbilirubinemia for infants of diabetic mothers reviewed here depended on discharge diagnoses, if not on the use of phototherapy or exchange transfusion. What is usually unknown is the rate of readmission of infants of diabetic mothers to the hospital for treatment.

Studies of hyperbilirubinemia in babies of women with preexisting diabetes mellitus used different definitions (see footnotes to Tables 5.26 and 5.27). For infants of women with preexisting diabetes mellitus of mixed types in the previous and current pregnancy, the rate of all types of jaundice was 29.8% in Utah in 2002–2010 compared to 19.0% in 58,224 control pregnancies ($p \leq 0.0001$) (115). In a survey based on State of California birth, death, and hospital discharge records for 2006, neonatal hyperbilirubinemia was listed in 26.1% of 555 liveborn infants of mothers with type 1 diabetes and 22.6% of 2,197 infants of mothers with type 2 diabetes (114). In the new analyses for *Diabetes in America* from the KPNC system in 2007–2011 (208), based on phototherapy ever in chart review findings and treated according to AAP guidelines, the rate of neonatal hyperbilirubinemia was 20.6% among 1,712 infants of mothers with undifferentiated preexisting diabetes in Northern California. The frequency of hyperbilirubinemia in infants of diabetic mothers in the KPNC system was 15.0% in 1996–2000 and 15.3% in 2001–2006, compared to the rate of 20.6% in 2007–2011 (208). The use of phototherapy nearly doubled for all infants in the KPNC system after 2001–2006 (after the 2004 AAP guidelines were adopted) (208).

For liveborn infants of women with type 1 diabetes in international population-based studies reported since 2000, the rates of neonatal hyperbilirubinemia were 17.1% in Japan (113), 17.7% in Denmark (93), 22.6% in Italy (95), and 25.8% in the Netherlands (100) compared to 6.1% requiring phototherapy or exchange transfusion in Sweden (4.5% if AGA, 7.8% if LGA) (338) and 7.0% in West Ireland (108) (Table 5.27). For infants of mothers with type 2 diabetes, the rates were 15.6% in Italy (95) and 17.5% in Japan (113) compared to 9.3% in West Ireland (vs. 4.7% in controls) (108) (Table 5.27).

EPIDEMIOLOGIC STUDIES OF METHODS OF MANAGEMENT OF DIABETES IN PREGNANCY

Population-based or multicenter studies linking poor maternal glycemic control (marked by elevated A1c or blood glucose levels independent of other contributing factors) with excess risks of spontaneous abortion (94,96,287,288,293,294), major congenital malformations (94,96, 99,105,107,262,316), fetal macrosomia (107,283,284,306,347,348,516,517), preeclampsia (262,280,281,282,283,284), preterm birth (262,283,284,306,316), adverse neonatal outcomes (283,284, 509), and perinatal mortality (105,107,211, 306,316,317) have been cited at appropriate places in the text. A systematic review of observational studies prior to 2006 of poor A1c control and adverse pregnancy outcomes in type 1 and type 2 diabetes was published (290). Population-based or multicenter studies published since 2006 continue to show the same significant relationships (107,211,228,262, 280,281,282,283,284,306,316,331,347, 348,518,519).

Due to ethical restraints in women with preconception diabetes, there are no large randomized trials comparing intensified glycemic control to "standard" care before or during pregnancy, with the exception of secondary analyses of the DCCT (6,7) and important trials that established benefit of glycemic control in women with mild gestational diabetes (358,359). In the DCCT, women with type 1 diabetes in the standard care group who became pregnant were switched to intensive care as soon as possible, often before conception, if pregnancy was planned (6,7). Observational cohort studies and reviews comparing pregnancy outcomes of diabetic women who participated in preconception care with those who did not participate are discussed in the section *Utilization of Preconception Care*. The weight of the evidence is that intensified care of diabetes before pregnancy and continued during pregnancy will significantly reduce the frequencies of spontaneous abortion, major congenital malformations, preeclampsia, preterm birth, and perinatal mortality in a cost-effective manner, without causing great harm. The mostly unmet challenge is to achieve these results on a community-wide basis (76,80,86,87,88,90,94,96).

All clinical guidelines advise pregnant diabetic women to achieve the best glycemic control possible without significant maternal hypoglycemia before and during pregnancy (42,43,44,117,520,521,522). ADA-recommended A1c targets are <6.5% in early and later pregnancy, but the target may be relaxed to <7% if necessary to prevent hypoglycemia (117). "As A1c represents an integrated measure of glucose, it may not fully capture postprandial hyperglycemia, which drives macrosomia" (117). Therefore, A1c measurements are considered secondary to glucose monitoring during pregnancy (42,43,117,522). "Given the alteration in red blood cell kinetics during pregnancy and physiologic changes in glycemic parameters, A1c levels may need to be monitored more frequently than usual (e.g., monthly)" (117).

There is some evidence that measurement of maternal serum glycated albumin provides an additional aggregate marker for glycemia in pregnancy (523,524), not affected by maternal iron deficiency, as is A1c (525), but affected by late gestational age, maternal proteinuria, and maternal obesity (526,527,528). Measurement of glycated albumin may be a better marker for fetal/neonatal glycemia compared to A1c in umbilical cord or neonatal blood (529,530). Glycated albumin has not yet been used in epidemiologic studies of diabetic pregnant women and their infants.

The ADA *Standards of Medical Care—2018* states that: "fasting and postprandial monitoring of blood glucose is recommended to achieve metabolic control in pregnant women with diabetes. Preprandial testing is also recommended for women with preexisting diabetes using insulin pumps or basal-bolus therapy, so that premeal rapid-acting insulin dosage can be adjusted. Postprandial monitoring is associated with better glycemic control and lower risk of preeclampsia. There are no adequately powered randomized trials comparing different fasting and postmeal glycemic targets in diabetes in pregnancy" (40).

Two randomized trials compared postprandial with preprandial blood glucose monitoring in pregnant women with diabetes, with benefits accruing to the former (531,532). Optimal timing of single postprandial blood glucose tests seems to be 60–90 minutes after beginning the meal, based on continuous blood glucose monitoring studies in diabetic pregnant women (533,534).

The ADA (40), the American College of Obstetricians and Gynecologists (520,521), the Canadian Diabetes Association (43,522), and NICE in the United Kingdom (42) suggest specific blood glucose targets for women with pregestational diabetes: fasting <90–95 mg/dL (<5.00–5.27 mmol/L), 1-hour postprandial <130–140 mg/dL (<7.22–7.77 mmol/L), and 2-hours postprandial <115–120 mg/dL (<6.38–6.66 mmol/L). Epidemiologic studies are needed to determine adherence to and effectiveness of these guidelines in populations of diabetic pregnant women.

The elements of diabetes care needed to achieve excellent glycemic control for pregnancy were established in observational cohort studies at regional centers of excellence and have been reviewed (1,42). These elements include patient self-participation in intensified care, self-monitoring of glucose (531,532,533,534,535,536, 537,538) and food intake, nutritional guidance (42,537,538), appropriate physical activity (537,538,539), optimal use of insulin regimens (244,306,537,538), and psychological support (538). Unfortunately, population-based data are lacking on the application of elements of diabetes care in the United States since 2000.

An example is studies confirming the effects of high gestational weight gain in diabetic women on risks of excess fetal growth and high birth weight scores, independent of maternal BMI and glycemic control (540,541,542). In general obstetric populations, prospective studies showed that gestational weight gain below the

2009 Institute of Medicine recommendations adjusted for maternal BMI was independently associated with low fetal growth (543), but gestational weight gain above the recommended amount was associated with a 46% increase in the odds of having an overweight/obese child at age 2–5 years (adjusted OR 1.46, 95% CI 1.17–1.83) after controlling for multiple confounding variables (544).

Large studies of nutritional intake and physical activity in pregnancy have focused on prevention of gestational diabetes (545,546,547,548) or follow-up of gestational diabetes to reduce the risk of progression to type 2 diabetes before the next pregnancy (63,64, 549,550,551,552,553,554,555,556, 557). The latter studies include the importance of postpartum weight loss (554,558) and of duration and intensity of lactation to long-term maternal health (559,560,561,562,563,564,565).

HEALTH RISKS IN CHILDREN OF MOTHERS WITH DIABETES BEFORE AND DURING PREGNANCY

In 1954 and 1961, Jorgen Pedersen hypothesized that fetal exposure to hyperglycemia, especially with fetal hyperinsulinemia and macrosomia, led to permanent fetal changes, including an increased risk of developing type 2 diabetes and obesity in later life (566,567). The concept of fetal overnutrition and hyperinsulinemia *in utero* was confirmed (568,569) and expanded to include other energy sources, including free fatty acids and triglycerides (570), plus multiple biochemical processes and epigenetic expressions. One example is the link between alteration in genome-wide DNA methylation in adult offspring of mothers with type 1 diabetes during the index pregnancy and offspring kidney dysfunction (571). Other studies in general populations led to the concept of fetal-placental-infant origins of adult disease, including diabetes (572,573,574,575,576,577,578,579, 580), with the added role of early childhood growth in determining outcomes (581,582,583,584). In this rapidly developing field of inquiry, this section focuses on the offspring of diabetic women.

DEVELOPMENT OF DIABETES IN CHILDREN AND ADULT OFFSPRING OF DIABETIC MOTHERS

The genetic risks for development of both types of diabetes in offspring of parents with diabetes are well known and discussed in Chapter 12 *Genetics of Type 1 Diabetes* and Chapter 14 *Genetics of Type 2 Diabetes*. The hypothesis of *in utero* influences has been supported by observations in the Pima Indian population, which found increased risk of diabetes among children whose mothers had diabetes (585,586), and a large cohort study that also suggested that exposure to maternal diabetes *in utero* was a risk factor independent of obesity (587,588).

Other large datasets confirming the hypothesis for development of type 2 diabetes, obesity, and related metabolic changes include the Framingham Offspring Study (paternal diabetes also a risk factor) (589), LGA infants of mothers with gestational diabetes in Rhode Island (590), offspring of mothers with gestational diabetes who were in the 1959–1965 National Collaborative Perinatal Project (591), offspring of mothers with gestational diabetes in the Pacific Northwest and Hawaii (592), and offspring of women with gestational diabetes and type 1 diabetes in Denmark (593,594). Thus, the larger infant size and attendant perinatal complications characterizing diabetic offspring continue their influence past infancy into childhood, later youth, and adulthood. The estimates of maternal diabetes for diabetes risk in the offspring and implications for the prevalence of diabetes in youth are discussed in greater detail in Chapter 13 *Risk Factors for Type 2 Diabetes* and Chapter 15.

BREASTFEEDING, INFANT FEEDING, AND HEALTH OF OFFSPRING OF DIABETIC MOTHERS

Based on reviews of abundant evidence of the benefits of successful breastfeeding to infant and child health (including less obesity and diabetes) (595), in 2012, the AAP concluded that infant nutrition should be considered a public health issue and not only a lifestyle choice (596). "National campaigns to prevent obesity begin with breastfeeding support" (596). The AAP reaffirmed its strong recommendation of exclusive breastfeeding for 6 months, followed by continued breastfeeding as complementary foods rich in iron and other micronutrients are introduced at about age 6 months, with continuation of breastfeeding for 1 year or longer as mutually desired by mother and infant. Thus, breastfeeding is the normative standard for healthy infant nutrition (596).

Of particular importance to infants of diabetic mothers, the AAP recommended (a) direct skin-to-skin contact with mothers immediately after delivery until the first feeding is accomplished and encouraged throughout the postpartum period and (b) delay in routine procedures (weighing, measuring, bathing, blood tests, vaccines, and eye prophylaxis) until after the first feeding is completed (596). Exclusive breastfeeding is "safe" for the prevention of neonatal hypoglycemia in most cases (597) and need not contribute to high rates of neonatal jaundice (598). Studies published since the AAP report continue to support the beneficial importance of early infant nutrition (599,600,601) to long-term outcomes, including child and later obesity (602,603,604,605,606,607,608), diabetes (609,610,611,612,613,614,615), and the infant-child microbiome (616).

Controversy was ignited by initial reports that first-week breast-milk (volume determined by daily weights of infants of diabetic mothers at a regional center in East Germany) of mothers with type 1 diabetes was associated with increased childhood obesity (retrospective analysis) (617,618). In the Netherlands, in 2002, a retrospective survey of 141 mothers with type 1 diabetes who delivered 2–3 years earlier showed no significant difference between breast-, formula-, and

mixed-fed infants (by maternal recollection) in weight and BMI at age 1 year (619). These studies were controverted by larger, mostly prospective studies which found that duration and intensity of breastfeeding by diabetic women was independently associated with less childhood overweight (602,620,621,622) and adiposity (623). Indeed, some studies suggested that the relationship of maternal diabetes to child obesity was influenced by lack of breastfeeding (620,621,623).

The group in Berlin agreed that increased weight gain during the first 4 months of life was a strong, independent risk factor for childhood overweight in 152 offspring of women with type 1 diabetes (624). In general, formula-fed infants with rapid weight gain in the first week of life have increased risk of later obesity (625). Breastfeeding ≥6 months is known to produce less childhood BMI growth velocity than formula feeding in children both exposed (n=89–94) and unexposed (n=379–399) to diabetes *in utero* (621,622). In these studies, the low neonatal breastfeeding group included ~33% of diabetic women who exclusively or mostly formula-fed their infants (622). Long-term studies concluded that low breastfeeding and high infancy weight gain in general is associated with childhood and adult obesity (604,605,626,627,628). The complexity of predictors of childhood obesity (gender, birth weight, maternal prepregnancy BMI, paternal BMI, maternal smoking in pregnancy, in addition to breastfeeding status) (628) may need to include maternal carbohydrate and sugar intakes during pregnancy (629), fetal macrosomia at birth (630), as well as the total infant feeding patterns over the first year of life (631). It is difficult to account for all possible confounders in epidemiologic analyses, but randomized controlled trials of breastfeeding versus formula feeding are considered unethical, due to the unquestioned beneficial impact of breastfeeding on infant health, such as reduced infections (595,596).

Intensity and duration of breastfeeding was also associated with lower rates of later type 2 diabetes in indigenous Native American populations, which included nursing mothers with diabetes (632,633). A quantitative analysis of seven studies confirmed that subjects who were breastfed had a lower risk of type 2 diabetes later in life (estimates pooled by using fixed-effect models; adjusted OR 0.61, 95% CI 0.44–0.85) (634). In the SEARCH Case-Control Study, breastfeeding (ever versus never) was associated with significantly less type 2 diabetes in youth age 10–21 years after adjusting for 12 potential confounders (adjusted OR 0.43, 95% CI 0.19–0.99) (635). There was possible mediation through current childhood weight status. Youth with type 2 diabetes in African American, Hispanic, and non-Hispanic white groups all had lower rates of being breastfed in infancy (significant only in the larger Hispanic and non-Hispanic white groups) (635).

Data on breastfeeding were rarely included in the surveys of diabetic pregnancies listed in Tables 5.26 and 5.27. Despite all available evidence of the benefits of breastfeeding, women with diabetes continue to have lower rates of initiation and continuation of lactation in other studies (497,636,637,638,639,640) than do women in reference populations. Factors delaying breastfeeding as the first feed are the major determinant of breastfeeding on discharge in diabetic women (497). A host of factors influence the success of exclusive breastfeeding over the first 6 months (637,639,640, 641,642,643,644,645), but success is not unattainable (639,640,646). Some hoped that hydrolyzation of standard cow's formula at early weaning during the first 4 months of life would reduce later beta cell autoimmunity in children of mothers with type 1 diabetes, but that was proved not to be the case (647), so continued exclusive breastfeeding should be encouraged by mothers with type 1 diabetes. Multifaceted support (600,601,642,643,648) must be given to improve the rates of successful breastfeeding in all diabetic women.

OBESITY, THE METABOLIC SYNDROME, AND HEALTH IN OFFSPRING OF DIABETIC MOTHERS

Investigators question whether pregnancy blood glucose concentrations (very limited data points) in nondiabetic (649,650,651,652) or mild diabetes status independently correlate with measures of childhood overweight/obesity at age 2–7 years (653,654,655,656,657,658,659, 660,661,662,663). There is need to account for other influences on child obesity, such as early pregnancy nutrition (664,665), maternal BMI and gestational weight gain (651,652,653,657,666, 667,668,669), female or male infant traits in excess birth weight and later adiposity (670,671,672,673,674,675), and infancy feeding and weight gain (629,630,631,637). The trialists of treatment of mild gestational diabetes have conducted short-term follow-up studies of offspring (676,677,678), but they were underpowered to detect differences in child obesity according to maternal treatment of glucose levels (675). What may be most important to study are other markers of health or future disease, such as the metabolic syndrome in the offspring of diabetic mothers (590,679,680,681,682,683).

Offspring of mothers with type 1 or type 2 diabetes during the pregnancies usually showed more obesity and adiposity than reference populations (620,657,681,684,685,686). There were also increases in markers for cardiometabolic disease in the children (681,687), youth (666,686), and adult offspring (594,688,689) of diabetic mothers. However, mothers with type 1 diabetes and adequate glycemic control (group mean A1c 6.2% [44 mmol/mol]) in a nationwide study in the Netherlands had offspring age 6–8 years with no higher prevalence of overweight (unless macrosomic at birth) (690) and no greater frequency of components of the metabolic syndrome than controls (691).

A large prospective combined clinical and register-based cohort follow-up study (13–21 years) was conducted in 1,326

offspring of women with type 1 diabetes in Denmark, with results compared to 131,884 controls (692). Overall mortality (HR 2.10, 95% CI 1.33–3.30, significant only up to age 1 year) and incidence of hospital admissions (12 diagnostic categories) up to age 15 years (incidence rate ratio 1.45, 95% CI 1.38–1.53) were significantly increased among the index children, and the incidence of hospital admissions was related to maternal A1c before and during early pregnancy (692).

MENTAL AND PSYCHOMOTOR DEVELOPMENT OF CHILDREN OF DIABETIC MOTHERS

Studies reported in 1991–2001 (693, 694,695,696,697,698,699,700) of impaired intelligence, memory, fine and gross motor function, emotion processing, and higher rates of inattention and/or hyperactivity in children of diabetic mothers, and their correlation with poor maternal metabolic control have been reviewed (701). Continuing studies extend investigation of neural correlates to ages 3–4 (702) and 10 years (703).

More recently, in a population-based cohort study up to age 24 months in upstate New York, children of mothers with pregestational diabetes took longer to achieve motor milestones than nonexposed children, independent of maternal obesity, gestational age, or birthweight (704). Minor deviances in infant motor development (low tone symptoms) may be associated with an increase in delays in nonverbal cognitive function at age 2.5 years in general studies (705), and with poor other mental functions at age 6–9 years, but not nonverbal intelligence or language comprehension (706). A confounder in such testing may be delivery at the earlier end of the so-called normal gestational age range 37–41 weeks (707,708), which can certainly be an issue in infants of diabetic mothers. The extent of breastfeeding may also be a factor in determining developmental delay (709).

Follow-up of 40 children age 6–12 years of women with type 1 diabetes in England showed no difference in overall full-scale IQ compared to U.K. normative data, but there was poorer working memory (710). A Danish population-based cohort study of 282 Danish male offspring of mothers with diabetes born between 1976 and 1984 compared to population-based control subjects up to military conscription revealed a slightly higher army rejection rate and similar group mean cognitive scores (711), but in a subset with available lab values, there was an inverse relation of maternal A1c (711) and fasting blood glucose levels >180 mg/dL (712) with the validated intelligence test. Among 357,768 Swedish males, lower intellectual performance at military conscription was associated with being born SGA at term, or with shorter length, and smaller head circumference at any gestational age, all independent of maternal, socioeconomic, or familial factors. Maternal diabetes was not considered in this study (713,714).

Another Danish follow-up study of 158 adult offspring of women with type 1 diabetes compared to a matched reference group found lower global cognitive scores in the subjects, but the difference was insignificant when adjusted for psychosocial confounders, and there was no association with maternal glycemia during pregnancy (715). Delivery <34 weeks gestation predicted lower cognitive scores, and the authors reasoned that this could explain a previous association with poorly controlled diabetic mothers (715).

Large epidemiologic surveys reported lower school marks in Swedish 16-year-old offspring of diabetic women (716), a consistent negative association between maternal A1c levels >7.4% in pregnancy and primary school grades in Denmark (717), and lower cognition and educational attainment in children (ages 4, 8, or 16 years) of women with type 1 diabetes in southwest England (Avon Longitudinal study), even with adjustment for many potential confounders (718). Additional analysis of the Avon study confirmed that 8-year-old offspring of mothers with existing diabetes, gestational diabetes, or glycosuria twice during pregnancy exhibited a lower IQ score than children born to nondiabetic mothers (mean difference -3.5, 95% CI -5.6 to -1.5, p=0.001), with adjustment for child's age and sex, maternal age at delivery, gestational age, birthweight, and duration of breastfeeding (719). The authors were suspicious of a likely causal link between fetal exposure to glucose and the children's IQ scores, because there were mixed results for the association of maternal genetic variants for fasting glucose and type 2 diabetes with lower or higher child IQ test results (719). Results may have been diluted by inclusion of women with gestational diabetes (720), and certainly glycosuria, which may occur in nondiabetic pregnancy.

A study linked national registers in Sweden to explore associations between maternal pregnancy diabetes and male offspring educational achievement at age 16 years, as well as IQ at the mandatory military conscription examination at age 18 years (721). Among nonsiblings, maternal diabetes was significantly associated with slightly lower offspring cognitive ability, even after adjustment for maternal age at birth, parity, education, early pregnancy BMI, offspring birth year, gestational age, and birth weight. But since no such association was found within sibships, the authors concluded that the relation of maternal diabetes to offspring cognitive outcomes "is likely explained by shared familial characteristics and not by an intrauterine mechanism" (721).

Systematic reviews of studies of the possible effects of maternal prenatal distress and poor nutrition (722) or maternal diabetes (723) on neurocognitive development in offspring point out the difficulties of determining the impact of these states on later health and well-being. One important confounder in these studies of the results of diabetes in pregnancy is likely to be maternal-placental-fetal-infant iron, copper, triiodothyronine, selenium, and zinc status (724,725,726,727,728,729, 730,731,732) and their interrelated homeostatic mechanisms in the brain.

Increased risks of schizophrenia (733) and autism in offspring have also been linked to maternal diabetes (734,735) or gestational diabetes (736) in the index pregnancies. Research will continue on the possible influences of *in utero* state, maternal diabetes and its comorbidities, and pregnancy complications and infant characteristics on the long-term development of neurologic and psychological function.

LIST OF ABBREVIATIONS

A1c. . . . . .glycosylated hemoglobin
AAP . . . . . .American Academy of Pediatrics
AC . . . . . .abdominal circumference
ADA . . . . . .American Diabetes Association
AGA . . . . . .appropriate-for-gestational age
ASD . . . . . .atrial septal defect
BMI . . . . . .body mass index
BPP . . . . . .brachial plexus palsy
BRFSS. . . . . .Behavioral Risk Factor Surveillance System
CDC. . . . . .Centers for Disease Control and Prevention
CI. . . . . .confidence interval
CP . . . . . .cerebral palsy
CSII . . . . . .continuous subcutaneous insulin infusion
DCCT. . . . . .Diabetes Control and Complications Trial
DIEP. . . . . .Diabetes in Early Pregnancy study
DKA. . . . . .diabetic ketoacidosis
DVT . . . . . .deep vein thrombosis
EUROCAT . . . .European Surveillance of Congenital Anomalies
FBG . . . . . .fasting blood glucose
FPG . . . . . .fasting plasma glucose
GPRD. . . . . .General Practice Research Database
HC . . . . . .head circumference
HR . . . . . .hazard ratio
IADPSG . . . . . .International Association of Diabetes and Pregnancy Study Groups
IBP. . . . . .insulin before pregnancy
ICD-9/10 . . . . .International Classification of Diseases, Ninth/Tenth Revision
IDM1/IDM2 . . .infants of type 1/2 diabetic mothers
IQ. . . . . .intelligence quotient
KPNC. . . . . .Kaiser Permanente Northern California
KPSC. . . . . .Kaiser Permanente Southern California
LGA . . . . . .large-for-gestational age
NE . . . . . .neonatal encephalopathy
NHANES . . . . .National Health and Nutrition Examination Survey
NICE . . . . . .U.K. National Institute for Health and Care Excellence
NICU . . . . . .neonatal intensive care unit
NPDR. . . . . .non-proliferative diabetic retinopathy
NS . . . . . .nonsignificant
NVSS. . . . . .National Vital Statistics System
OGTT. . . . . .oral glucose tolerance test
OR . . . . . .odds ratio
PAR . . . . . .population attributable risk
PDR. . . . . .proliferative diabetic retinopathy
PE . . . . . .pulmonary embolism
PI. . . . . .ponderal index
PIH. . . . . .pregnancy-induced hypertension
POR. . . . . .prevalence odds ratio
PRAMS . . . . . .Pregnancy Risk Assessment Monitoring System
RDS . . . . . .respiratory distress syndrome
RR . . . . . .relative risk
SD . . . . . .standard deviation
SE . . . . . .standard error
SEARCH . . . . .SEARCH for Diabetes in Youth Study
SGA . . . . . .small-for-gestational age
THIN. . . . . .The Health Improvement Network
TTN . . . . . .transient tachypnea of the newborn
USPSTF . . . . . .United States Preventive Services Task Force
VSD . . . . . .ventricular septal defect
VTE . . . . . .venous thromboembolism
WBN . . . . . .Well Baby Nursery

CONVERSIONS

Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*.

DUALITY OF INTEREST

Drs. Kitzmiller, Ferrara, Cissell, and Kim and Ms. Peng reported no conflicts of interest.

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APPENDIX 5.1.

This appendix lists selected additional multicenter and regional/national population-based studies published from January 2016 to July 2017. References are listed in same order as topics in the text of Chapter 5 *Preexisting Diabetes and Pregnancy*. Commentary is provided by the lead author of the text.

PRECONCEPTION CARE OF DIABETES

Holmes VA, Hamill LL, Alderdice FA, Spence M, Harper R, Patterson CC, Loughridge S, McKenna S, Gough A, McCance DR; Women with Diabetes Project Team: Effect of implementation of a preconception counselling resource for women with diabetes: a population based study. *Prim Care Diabetes* 11:37–45, 2017

Diabetic women viewing a preconception counselling DVD had significantly improved pregnancy planning indicators. Women with type 2 diabetes were difficult to reach.

Rubio JA, Ontanon M, Perea V, Megia A; Grupo Espanol de Diabetes y Embarazo: Health care of pregnant women with diabetes in Spain: approach using a questionnaire. [Article in English, Spanish] *Endocrinol Nutr* 63:113–120, 2016

Responding centers (n=87) accounted for only 39% of births in 2013; 53 centers identified as pregnancy and diabetes units, and 87% of these had preconception clinics.

Nwolise CH, Carey N, Shawe J: Preconception care education for women with diabetes: a systematic review of conventional and digital health interventions. *J Med Internet Res* 18:e291, 2016, Nov 8 [Epub] doi: 10.2196/jmir.5615

Searched for quantitative studies of preconception care education published from 2003 to June 2016; reviewed 12 studies. All studies showed a positive effect on pregnancy outcomes.

Wotherspoon AC, Young IS, Patterson CC, McCance DR, Holmes VA: Diabetes and Preeclampsia Intervention Trial (DAPIT) Study Group: Effect of pregnancy planning on maternal and neonatal outcomes in women with type 1 diabetes. *Diabet Med* 34:1303–1308, 2017

Only 64% of 455 type 1 diabetic women who considered their pregnancy as planned received actual prepregnancy counselling. Of 747 diabetic women, 39% considered their pregnancy unplanned; they had higher A1c levels throughout pregnancy and their infants were more likely to be SGA and to be admitted to the NICU, with a longer stay in hospital.

Egan AM, Galjaard S, Maresh MJ, Loeken MR, Napoli A, Anastasiou E, Noctor E, de Valk HW, van Poppel M, Todd M, Smith V, Devane D, Dunne FP: A core outcome set for studies evaluating the effectiveness of prepregnancy care for women with pregestational diabetes. *Diabetologia* 60:1190–1196, 2017

European panelists agreed on nine measures of pregnancy preparation, six neonatal outcomes, and two maternal outcomes to be used in future studies of preconception care of diabetic women.

Frayne DJ, Verbiest S, Chelmow D, Clarke H, Dunlop A, Hosmer J, Menard MK, Moos MK, Ramos D, Stuebe A, Zephyrin L: Health care system measures to advance preconception wellness: consensus recommendations of the Clinical Workgroup of the National Preconception Health and Health Care Initiative. *Obstet Gynecol* 127:863–872, 2016

Monitoring nine preconception wellness measures in the United States will establish benchmarks and allow for comparison within and among regions, health care systems, and communities to drive improvements.

PREVALENCE OF DIABETES IN PREGNANCY

Haghighat N, Hu M, Laurent O, Chung J, Nguyen P, Wu J: Comparison of birth certificates and hospital-based birth data on pregnancy complications in Los Angeles and Orange County, California. *BMC Pregnancy Childbirth* 16:93, 2016 Apr 27 [Epub] doi: 10.1186/s12884-016-0885-0

Diabetes was underreported in birth certificate data (1.97%) compared to a hospital system perinatal research database (5.56%). Underreporting was significantly higher among Hispanic women compared to non-Hispanic white women and among all women with public insurance.

Robledo CA, Yeung EH, Mendola P, Sundaram R, Boghossian NS, Bell EM, Druschel C: Examining the prevalence rates of preexisting maternal medical conditions and pregnancy complications by source: evidence to inform maternal and child research. *Matern Child Health J* 21:852–862, 2017

Ascertained diagnoses of preexisting diabetes and chronic hypertension according to birth certificates, maternal self-report 4 months postpartum, and a mandated New York statewide hospital reporting system for discharge codes.

Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, Imperatore G, Linder B, Marcovina S, Pettitt DJ, Pihoker C, Saydah S, Wagenknecht L; SEARCH for Diabetes in Youth Study: Incidence trends of type 1 and type 2 diabetes among youths, 2002–2012. *N Engl J Med* 376:1419–1429, 2017

Ascertained cases of type 1 diabetes (age 0–19 years) and type 2 diabetes (age 10–19 years) at five study centers in the United States for the period 2002–2012; denominators (4.9 million youths annually) obtained from the U.S. Census or health plan member counts; after adjustment for age, sex, and race or ethnic group, the relative annual increase in the incidence of type 1 diabetes was 1.8% (21.7 cases per 100,000 youths per year in 2011–2012) and 4.8% for type 2 diabetes (12.5 cases per 100,000 youths in 2011–2012).

Coton SJ, Nazareth I, Petersen I: A cohort study of trends in the prevalence of pregestational diabetes in pregnancy recorded in UK general practice between 1995 and 2012. *BMJ Open* 6:e009494, 2016 Jan 25 [Epub] doi: 10.1136/bmjopen-2015-009494

Prevalence of type 1 diabetes in pregnancy increased from 0.16% in 1995 to 0.41% in 2015; prevalence of type 2 diabetes increased from 0.23% in 1995 to 1.06% in 2012.

Fadl HE, Simmons D: Trends in diabetes in pregnancy in Sweden 1998–2012. *BMJ Open Diabetes Res Care* 4:e000221, 2016 Aug 11 [Epub] doi: 10.1136/bmjdrc-2016-000221

Using Swedish national medical birth registry data (84% to 76.5% Nordic origin), over the 15-year period, type 1 diabetes increased by 33.2% (prevalence 0.38% in 1998–2000 and 0.47% in 2010–2012; stable since 2004) and type 2 diabetes by 111% (prevalence 0.03% in 1998–2000 and 0.10% in 2010–2012; steady increase), adjusted for maternal BMI, ethnicity, and age in a logistic regression model.

MATERNAL COMPLICATIONS

Persson M, Cnattingius S, Wikstrom AK, Johansson S: Maternal overweight and obesity and risk of preeclampsia in women with type 1 diabetes or type 2 diabetes. *Diabetologia* 59:2099–2105, 2016

Among 1,532,682 singleton births in Sweden in 1997–2012, 0.46% of mothers were registered as type 1 diabetes and 0.06% as type 2 diabetes. Preeclampsia was diagnosed in

15.6% of pregnant women with type 1 diabetes and 9.7% with type 2 diabetes compared to 2.8% of nondiabetic controls; preeclampsia was severe in 5.6% of women with type 1 diabetes, 3.2% with type 2 diabetes, and 0.9% of nondiabetic controls.

Morrison FJ, Movassaghian M, Seely EW, Curran A, Shubina M, Morton-Eggleston E, Zera CA, Ecker JL, Brown FM, Turchin A: Fetal outcomes after diabetic ketoacidosis during pregnancy. *Diabetes Care* 40:e77–e79, 2017, Jul [Epub] doi: 10.2337/dc17-0186

In a multicenter study in Boston, Massachusetts, between 1995 and 2015, there were 77 DKA events in 64 pregnancies; fetal demise occurred at the time of or within one week of the event in 9.4% and eventual preterm delivery in 46.3%.

BIRTH OUTCOMES

Murphy HR, Bell R, Cartwright C, Curnow P, Maresh M, Morgan M, Sylvester C, Young B, Lewis-Barned N: Improved pregnancy outcomes in women with type 1 and type 2 diabetes but substantial clinic-to-clinic variations: a prospective nationwide study. *Diabetologia* 60:1668–1677, 2017

Cohort included 3,036 pregnant women from 155 maternity clinics in England and Wales in 2015 (46% type 2 diabetes). Preterm delivery: 39.7% in type 1 diabetes and 21.7% in type 2 diabetes. LGA infants: 46.4% of type 1 diabetes and 23.9% of type 2 diabetes. Congenital anomaly: 4.6% in type 1 diabetes and 3.5% in type 2 diabetes. Stillbirth: 1.1% in type 1 diabetes and 1.05% in type 2 diabetes. Neonatal death: 0.8% in type 1 diabetes and 1.1% in type 2 diabetes.

Allen AJ, Snowden JM, Lau B, Cheng Y, Caughey AB: Type-2 diabetes mellitus: does prenatal care affect outcomes? *J Matern Fetal Neonatal Med* 31:93–97, 2017

Based on vital statistics data linked to birth certificates in California from 1997–2006, women with pregestational type 2 diabetes who presented for care at the time of delivery (no prenatal care) had an 11.3% risk of stillbirth compared to 0.9% in those who presented in the first trimester.

Strom-Roum EM, Tanbo TG, Eskild A: The associations of maternal body mass index with birthweight and placental weight. Does maternal diabetes matter? A population study of 106 191 pregnancies. *Acta Obstet Gynecol Scand* 95:1162–1170, 2016

Based on data in the Medical Birth Registry of Norway from 2009–2012, mean birthweight and placental weight were significantly higher in pregnancies of type 1 diabetic women compared to pregnancies without diabetes, but there was no influence of maternal BMI on birthweight or placental weight in type 1 diabetes (as there was in nondiabetic women or gestational diabetes).

Abell SK, Boyle JA, de Courten B, Knight M, Ranasinha S, Regan J, Soldatos G, Wallace EM, Zoungas S, Teede HJ: Contemporary type 1 diabetes pregnancy outcomes: impact of obesity and glycemic control. *Med J Aust* 205:162–167, 2016

Analyzed all singleton births ≥20 weeks of women with type 1 diabetes in a specialist diabetes and maternity care network in the region of Victoria, Australia, for 2010–2013 compared to 27,075 control pregnancies. Significant adjusted odds ratios >4.0 for diabetic risk were found for increased rates of preterm delivery, fetal macrosomia, shoulder dystocia, perinatal death, and neonatal hypoglycemia and jaundice.

CONGENITAL MALFORMATIONS

Persson M, Cnattingius S, Villamor E, Soderling J, Pasternak B, Stephansson O, Neovius M: Risk of major congenital malformations in relation to maternal overweight and obesity severity: cohort study of 1.2 million singletons. *BMJ* 357:j2563, 2017 Jun 14 [Epub] doi: 10.1136/bmj.j2563

Analyzed liveborn singleton infants without chromosomal aberrations or syndromes born ≥22 weeks in Sweden from 2001 to 2014; 3.5% of offspring had any major congenital malformation (43,550 events); 46% were congenital heart defects. Overall, major malformations were more likely in boys than girls (adjusted OR 1.46, 95% CI 1.43–1.49), especially for genital, urinary tract, and limb malformations; congenital heart defects were reported in 1.67% of girls and 1.56% of boys. There was a limited stepwise association of risk with increasing maternal BMI (in both fetal sexes), with number of cigarettes smoked per day, but not with increasing maternal age. The major adjusted effects of increasing maternal BMI ≥30 kg/m^2 were seen for congenital heart defects, nervous system defects, orofacial clefts, digestive system defects in boys, and genital organs. Sensitivity analysis excluding 2,860 events associated with maternal pregestational diabetes mellitus (6.6% of total events) did not change the results.

Agha MM, Glazier RH, Moineddin R, Booth G: Congenital abnormalities in newborns of women with pregestational diabetes: a time-trend analysis, 1994 to 2009. *Birth Defects Res A Clin Mol Teratol* 106:831–839, 2016

Surveyed all liveborns and their mothers in Ontario, Canada; the prevalence of births among diabetic mothers increased by almost 200% during the study period. In their children, the prevalence for all anomalies combined was 47% higher and for various cardiac and central nervous system anomalies up to a threefold to fivefold higher rate than in those born to nondiabetic mothers. The rate of birth defects in both groups declined after folate food fortification in 1999, but the excess risk associated with maternal pregestational diabetes mellitus remained.

Feldkamp ML, Carey JC, Byrne JL, Krikov S, Botto LD: Etiology and clinical presentation of birth defects: population based study. *BMJ* 357:j2249, 2017 May 30 [Epub] doi: 10.1136/bmj.j2249

Reviewed 5,504 cases of birth defects among 270,878 births (prevalence 2.03%) in Utah in 2005–2009. Only 20.2% could have a definite cause assigned: chromosomal or genetic conditions in 19.1% of total cases, conjoined or acardiac twinning in 0.29%, and poorly controlled pregestational diabetes mellitus in 0.6%. In the latter group, 75% of cases had ≥2 major anomalies in the same fetus (vs. 15.7% in total nondiabetic group) with a 28% fetal loss rate (stillbirths and terminations of pregnancy) with multiple anomalies in maternal diabetes versus a 15.1% fetal loss rate with multiple major anomalies without maternal diabetes.

Oyen N, Diaz LJ, Leirgul E, Boyd HA, Priest J, Mathiesen ER, Quertermous T, Wohlfahrt J, Melbye M: Prepregnancy diabetes and offspring risk of congenital heart disease: a nationwide cohort study. *Circulation* 133:2243–2253, 2016

In a Danish national cohort from 1978–2011, 0.36% of infants were exposed to maternal pregestational diabetes mellitus; the prevalence of congenital heart disease in them was 3.18% in comparison with a baseline rate of 0.80% (adjusted RR 4.00, 95% CI 3.51–4.53). The association was not modified by year of birth, maternal age at diabetes onset, or duration or type of diabetes. All specific congenital heart defect phenotypes were associated with maternal pregestational diabetes mellitus (RR range 2.74–13.8).

Leirgul E, Brodwall K, Greve G, Vollset SE, Holmstrom H, Tell GS, Oyen N: Maternal diabetes, birth weight, and neonatal risk of congenital heart defects in Norway, 1994–2009. *Obstet Gynecol* 128:1116–1125, 2016

Of 914,427 live births, stillbirths, and terminated pregnancies, 0.61% were complicated by maternal pregestational diabetes mellitus. In the latter group, the prevalence of offspring

with cardiac defects was 3.44% versus 1.14% without diabetes (adjusted RR 2.92, 95% CI 2.54–3.36). The associated risk did not change during the study period. Within the pregestational diabetes mellitus group, the prevalence of congenital heart defects in very macrosomic infants (birth weight >3 SDs above the reference mean) was 5.61% compared to 2.48% in the nonmacrosomic group (adjusted RR 2.23, 95% CI 1.39–3.59).

Chou HH, Chiou MJ, Liang FW, Chen LH, Lu TH, Li CY: Association of maternal chronic disease with risk of congenital heart disease in offspring. *CMAJ* 188:E438–E446, 2016

Of 1,387,650 live births ≥22 weeks in Taiwan in 2004–2010, using several registration datasets, the prevalence of congenital heart defect diagnosed in infancy was 1.69%; the risk was greater with type 1 diabetes (adjusted OR 2.32, 95% CI 1.66–3.25, PAR [population attributable risk] 0.04%), with type 2 diabetes (adjusted OR 2.85, 95% CI 2.60–3.12, PAR 1.45%), and with chronic hypertension (adjusted OR 1.87, 95% CI 1.69–2.07, PAR 0.71%). In the total birth cohort, significant risks for congenital heart defect were recorded for stepwise increasing maternal age ≥30 years (no data on BMI), smoking (adjusted OR 2.46, 95% CI 1.69–3.58), but not for male infant sex (adjusted OR 1.02, 95% CI 0.99–1.05).

Groen In't Woud S, Renkema KY, Schreuder MF, Wijers CH, van der Zanden LF, Knoers NV, Feitz WF, Bongers EM, Roeleveld N, van Rooij IA: Maternal risk factors involved in specific congenital anomalies of the kidney and urinary tract: a case-control study. *Birth Defects Res A Clin Mol Teratol* 106:596–603, 2016

Case (562)-control (2,139) study using a multicenter databank; diabetes during pregnancy increased risk of posterior urethral valves (OR 2.6, 95% CI 1.1–5.9). Use of folic acid supplements only was associated with risk for duplex collecting systems (OR 1.8, 95% CI 1.0–3.4) and vesicoureteral reflux (OR 1.8, 95% CI 1.1–2.9); use of multivitamins reduced the risk of overall congenital anomalies of the kidney and urinary tract (OR 0.5, 95% CI 0.2–1.0).

Fisher SC, Van Zutphen AR, Werler MM, Lin AE, Romitti PA, Druschel CM, Browne ML; National Birth Defects Prevention Study: Maternal antihypertensive medication use and congenital heart defects: updated results from the National Birth Defects Prevention Study. *Hypertension* 69:798–805, 2017

Included singleton births 2004–2011, excluded pregestational diabetes mellitus; 10,625 congenital heart defect cases and 11,137 nonmalformed controls; controlled for maternal age, BMI, race/ethnicity, first trimester cigarette smoking, and study site; compared 164 case mothers and 102 control mothers who reported antihypertensive use for their chronic hypertension during the month before conception through the third month of pregnancy. The study found increased risk of four congenital heart defect phenotypes regardless of antihypertensive class reported: coarctation of the aorta (adjusted OR 2.50, 95% CI 1.52–4.11), pulmonary valve stenosis (adjusted OR 2.19, 95% CI 1.44–3.34), perimembranous ventricular septal defect (adjusted OR 1.90, 95% CI 1.09–3.31), and secundum atrial septal defect (adjusted OR 1.94, 95% CI 1.36–2.79). The strongest risk was seen for mothers using beta-blockers or renin-angiotensin system blockers. The authors could not completely rule out confounding by underlying disease characteristics. The study did not account for terminations of pregnancy.

Bateman BT, Patorno E, Desai RJ, Seely EW, Mogun H, Dejene SZ, Fischer MA, Friedman AM, Hernandez-Diaz S, Huybrechts KF: Angiotensin-converting enzyme inhibitors and the risk of congenital malformations. *Obstet Gynecol* 129:174–184, 2017

Used a cohort of 1,333,624 completed pregnancies linked to liveborn neonates derived from Medicaid claims from 2000 to 2010; 0.31% were exposed to angiotensin-converting enzyme (ACE) inhibitors during the first trimester. The prevalence of overall malformations in the exposed infants was 5.9% compared with 3.3% in the unexposed (crude RR 1.82, 95% CI 1.61–2.06), of cardiac malformations 3.4% compared with 1.2% (crude RR 2.95, 95% CI 2.50–3.47), and of central nervous system malformations 0.27% compared with 0.18% (crude RR 1.46, 95% CI 0.81–2.64). After restricting the exposed and unexposed cohorts to pregnancies with chronic hypertension and accounting for potential confounders (maternal demographics, medical conditions, exposure to other medications, measures of health care utilization), there was no significant increase in the risk for any of the outcomes assessed. The study did not account for terminations of pregnancy.

NEONATAL COMPLICATIONS

Boghossian NS, Hansen NI, Bell EF, Brumbaugh JE, Stoll BJ, Laptook AR, Shankaran S, Wyckoff MH, Colaizy TT, Das A, Higgins RD; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network: Outcomes of extremely preterm infants born to insulin-dependent diabetic mothers. *Pediatrics* 137:e20153424, 2016

U.S. multicenter study of 312 infants of multiethnic mothers using insulin before pregnancy (IBP), delivered at 22–28 weeks and cared for at one of 24 NIH Neonatal Research Network hospitals in 2006–2011; outcomes were compared to 10,245 controls without maternal diabetes. Birth weight extremes for gestational age and sex (Olsen norms) were 10% LGA (NS) and 18% SGA (NS); 5% major birth defects (NS); 15% Apgar score ≤3 at 5 minutes (NS). Rates of morbidities in-hospital in 286 IBP infants surviving >12 hours included 20.6% death before discharge (NS); 99% respiratory distress syndrome (NS); 36% need for supplemental oxygen use at 36 weeks postmenstrual age (NS); 16% severe intraventricular hemorrhage (NS); 3% periventricular leukomalacia (NS); 15% necrotizing enterocolitis (vs. 11%; adjusted RR 1.55, 95% CI 1.17–2.05); and 35% late-onset sepsis after 3 days (vs. 28%; adjusted RR 1.26, 95% CI 1.07–1.48). Of 189 IBP infants eligible for follow-up at age 18–22 months, there were 37% total deaths between birth and age 18–22 months (NS vs. 38% of 6,598 infants eligible for follow-up). Of 109 IBP offspring examined at age 18–22 months, 19% had neurodevelopmental impairment (NS vs. 16% of 3,608 controls). There were no data on maternal glycemic control.

Cnattingius S, Lindam A, Persson M: Risks of asphyxia-related neonatal complications in offspring of mothers with type 1 or type 2 diabetes: the impact of maternal overweight and obesity. *Diabetologia* 60:1244–1251, 2017

Population-based study using prospectively collected data on live singleton births of nonmalformed infants from several nationwide Swedish registries for 1997–2011; 5,941 infants of mothers with type 1 diabetes (IDM1), 711 infants of mothers with type 2 diabetes (IDM2), compared to 1,337,099 infants of mothers without any type of diabetes (controls). Maternal characteristics were: BMI ≥30 kg/m^2 in 17.5% of women with type 1 diabetes, 55.5% of women with type 2 diabetes, and 10.7% in controls (excluding women with missing data); smoking in 10.2% of type 1 diabetes, 11.7% of type 2 diabetes, and 9.4% of controls; chronic hypertension in 4.2% of type 1 diabetes, 7.5% of type 2 diabetes, and 0.6% of controls; preeclampsia in 14.2% of type 1 diabetes, 7.6% of type 2 diabetes, and 2.7% in controls; delivery by cesarean section in 50.7% of type 1 diabetes, 42.6% of type 2 diabetes, and 15.1% of controls.

Neonatal characteristics were: delivery at <32 weeks in 1.8% of IDM1, 2.0% of IDM2, and 0.6% of controls; delivery at 32–36 weeks in 17.9% of IDM1, 11.0% of IDM2, and 3.9% of controls; birth weight <third percentile for gestational age in 1.0% of IDM1, 1.3% of IDM2, and 1.5% of controls; birth weight >97th percentile for gestational age in 33.3% of IDM1, 19.8% of IDM2, and 3.4% of controls; Apgar score 0–6

at 5 minutes in 2.6% of IDM1 (adjusted OR 2.67 compared to controls, 95% CI 2.23–3.20), 2.1% of IDM2 (NS), and 0.9% of controls; and combined convulsions/hypoxic-ischemic encephalopathy in 1.0% of IDM1 (adjusted OR 3.40 compared to controls, 95% CI 2.58–4.48), in 1.3% of IDM2 (adjusted OR 2.54 compared to controls, 95% CI 1.13–5.69), and 0.3% of controls. There was some relation of risk of low Apgar score and neonatal convulsions to increasing maternal BMI in IDM1 and certainly in controls, but the increased rates of the complications in IDM1 remained greater than controls at each maternal BMI grouping. There were no data on maternal glycemic control.

DIABETES MANAGEMENT: MATERNAL FOLLOW-UP

Asbjornsdottir B, Akueson CE, Ronneby H, Rytter A, Andersen JR, Damm P, Mathiesen ER: The influence of carbohydrate consumption on glycemic control in pregnant women with type 1 diabetes. *Diabetes Res Clin Pract* 127:97–104, 2017

Regional study of 80 women with type 1 diabetes who recorded dietary intake for at least 2 days before the first antenatal visit in the Copenhagen, Denmark, area. A1c was positively associated with the quantity of carbohydrate consumed, regardless of type of insulin treatment; 45% of the women used carbohydrate counting daily and had somewhat lower A1c than in those who did not record daily (p=0.01).

Chico A, Herranz L, Corcoy R, Ramirez O, Goya MM, Bellart J, Gonzalez-Romero S, Codina M, Sanchez P, Cortazar A, Acosta D, Picon MJ, Rubio JA, Megia A, Sancho MA, Balsells M, Sola E, Gonzalez NL, Lopez-Lopez J; GEDE (Group of Diabetes and Pregnancy of the Spanish Diabetes Association): Glycemic control and maternal and fetal outcomes in pregnant women with type 1 diabetes according to the type of basal insulin. *Eur J Obstet Gynecol Reprod Biol* 206:84–91, 2016

Retrospective cohort study of 1,534 pregnancies at 18 Spanish tertiary hospitals; basal insulin most commonly used was NPH in 51.7% (reference), followed by glargine in 23.2% and CSII in 21.1% (4% missing data). Multiple logistic regression analysis showed that CSII was independently associated with higher A1c in all trimesters and higher rates of miscarriage, preterm birth, and neonatal hypoglycemia; glargine use was related to a higher risk of preterm birth and an SGA infant. Randomized controlled trials are underway elsewhere.

Egan AM, Carmody L, Kirwan B, Dunne FP; Atlantic DIP Collaborators: Care of women with diabetes before, during and after pregnancy: time for a new approach? *Diabet Med* 34:846–850, 2017

In a multicenter study in West Ireland, 247 women with type 1 diabetes and 137 women with type 2 diabetes were evaluated before, during, and after pregnancy; 20% were lost to 1-year follow-up from clinical care. Average A1c had returned to preconception level for both diabetes groups, and there was no improvement in other measures of diabetes control. Attendees for prepregnancy care (44.9% of type 1 diabetes and 27.7% of type 2 diabetes) maintained superior glycemic control throughout the study and were more likely to be receiving specialist care postpartum.

BREASTFEEDING AND OFFSPRING

Bartick MC, Schwarz EB, Green BD, Jegier BJ, Reinhold AG, Colaizy TT, Bogen DL, Schaefer AJ, Stuebe AM: Suboptimal breastfeeding in the United States: maternal and pediatric health outcomes and costs. *Matern Child Nutr* 13:e12366, 2017 Jan [Epub] doi: 10.1111/mcn.12366

Modeled a hypothetical cohort of U.S. women followed from age 15 to 70 years and their children from birth to age 20 years, using Monte Carlo simulations based on current literature on the associations between breastfeeding and health outcomes for nine pediatric and five maternal diseases. For every 597 women who optimally breastfeed, one maternal death (including myocardial infarction, breast cancer, or diabetes) or child death (including sudden infant death syndrome or necrotizing enterocolitis) is prevented.

Nucci AM, Virtanen SM, Sorkio S, Barlund S, Cuthbertson D, Uusitalo U, Lawson ML, Salonen M, Berseth CL, Ormisson A, Lehtonen E, Savilahti E, Becker DJ, Dupre J, Krischer JP, Knip M, Akerblom HK; TRIGR Investigators: Regional differences in milk and complementary feeding patterns in infants participating in an international nutritional type 1 diabetes prevention trial. *Matern Child Nutr* 13:e12354, 2017 Jul [Epub] doi: 10.1111/mcn.12354

Among newborn infants with a first degree relative with type 1 diabetes and increased HLA-conferred susceptibility to type 1 diabetes distributed in four regions of Europe, two of North America, plus Australia, a lower proportion of infants born to mothers with than without type 1 diabetes were breastfed until age 6 months in all regions (range 51%–60% vs. 70%–80%). Maternal diabetes status was associated with breastfeeding and other milk feeding patterns similarly across regions but was unrelated to the introduction of complementary foods, which did vary by region overall, largely inconsistent with guidelines.

Lund-Blix NA, Dydensborg Sander S, Stordal K, Nybo Andersen AM, Ronningen KS, Joner G, Skrivarhaug T, Nijolstad PR, Husby S, Stene LC: Infant feeding and risk of type 1 diabetes in two large Scandinavian birth cohorts. *Diabetes Care* 40:920–927, 2017

Analyzed data from 155,392 children participating in Norwegian and Danish studies; parents reported infant dietary practices at ages 6 and 18 months. Children who were never breastfed had a twofold increased risk of type 1 diabetes at follow-up compared with those who were breastfed (HR 2.29, 95% CI 1.14–4.61). The incidence of type 1 diabetes was independent of duration of full or partial breastfeeding.

Uusitalo U, Liu X, Lang J, Aronsson CA, Hummel S, Butterworth M, Lernmark A, Rewers M, Hagopian W, She JX, Simell O, Toppari J, Ziegler AG, Akolkar B, Krischer J, Norris JM, Virtanen SM; TEDDY Study Group: Association of early exposure to probiotics and islet autoimmunity in the TEDDY Study. *JAMA Pediatr* 170:20–28, 2016

Ongoing prospective cohort follow-up study of 7,473 infants with high-risk HLA (human leukocyte antigen)-DR genotypes at three U.S. and three European centers to determine persistent islet autoimmunity. In children with the DR3/4 genotype, early (age 0–27 days), but not later, supplementation with varied probiotics by parental report (mainly in Europe; from dietary supplements in Finland and probiotic infant formulas in Germany) was associated with decreased risk of later islet autoimmunity when adjusting for duration of exclusive breastfeeding and many other factors (HR 0.40, 95% CI 0.21–0.74) and strongly associated with diarrhea and antibiotic use in the first year of life.

Krischer JP, Lynch KF, Lernmark A, Hagopian WA, Rewers MJ, She JX, Toppari J, Ziegler AG, Akolkar B; TEDDY Study Group: Genetic and environmental interactions modify the risk of diabetes-related autoimmunity by 6 years of age: the TEDDY Study. *Diabetes Care* 40:1194–1202, 2017

Infants with HLA-DR high-risk genotypes were prospectively followed for diabetes-related autoantibodies. The persisting GAD (glutamic acid decarboxylase) antibody was associated with only father as the diabetic proband and infant weight at age 12 months; mother as the diabetic proband was not a significant risk factor.

Hummel S, Beyerlein A, Tamura R, Uusitalo U, Andren Aronsson C, Yang J, Riikonen A, Lernmark A, Rewers MJ, Hagopian WA, She JX, Simell OG, Toppari J, Ziegler AG, Akolkar

B, Krischer JP, Virtanen SM, Norris JM; TEDDY Study Group: First infant formula type and risk of islet autoimmunity in the Environmental Determinants of Diabetes in the Young (TEDDY) Study. *Diabetes Care* 40:398–404, 2017

Confirms an earlier analysis that islet autoimmunity is not reduced and may be increased by using hydrolyzed compared with nonhydrolyzed cow's milk-based infant formula as the first formula in infants at increased genetic risk for type 1 diabetes.

Halipchuk J, Temple B, Dart A, Martin D, Sellers EA: Prenatal, obstetric and perinatal factors associated with the development of childhood-onset type 2 diabetes. *Can J Diabetes* 42:71–77, 2018

Retrospective matched case (270)-control (1,341) study using Manitoba, Canada, administrative data. Low maternal income (OR 6.67, 95% CI 3.01–14.79) and exposure to maternal pregestational diabetes mellitus (nearly sixfold) increased the risk of childhood-onset type 2 diabetes, and breastfeeding reduced the risk (OR 0.52, 95% CI 0.36–0.74).

Martens PJ, Shafer LA, Dean HJ, Sellers EA, Yamamoto J, Ludwig S, Heaman M, Phillips-Beck W, Prior HJ, Morris M, McGavock J, Dart AB, Shen GX: Breastfeeding initiation associated with reduced incidence of diabetes in mothers and offspring. *Obstet Gynecol* 128:1095–1104, 2016

Retrospective database study of 334,533 deliveries (1987–2011) in Manitoba, Canada, with up to 24 years of follow-up for diabetes; initiation of breastfeeding before hospital discharge recorded. Breastfeeding initiation was associated with reduced risk of later-developed diabetes in non-First Nations mothers (HR 0.73, 95% CI 0.68–0.79) and in First Nation mothers (HR 0.89, 95% CI 0.81–0.98) and was associated with reduced risk of youth-onset type 2 diabetes in all offspring.

Forster DA, Moorhead AM, Jacobs SE, Davis PG, Walker SP, McEgan KM, Opie GF, Donath SM, Gold L, McNamara C, Aylward A, East C, Ford R, Amir LH: Advising women with diabetes in pregnancy to express breastmilk in late pregnancy (Diabetes and Antenatal Milk Expressing [DAME]): a multicentre, unblinded, randomised controlled trial. *Lancet* 389:2204–2213, 2017

In a method-safety trial, analyzed results in Australia from 317 women with preexisting or gestational diabetes randomized to milk expressing twice per day from 36 weeks gestation and 315 diabetic women in the standard care group. The proportion of infants admitted to the NICU did not differ between groups (15% with antenatal expressing vs. 14% with standard care). Adverse events were three cases of need for respiratory support in the antenatal expressing group and three cases of moderate to severe encephalopathy in the standard care group.

Stuart B, Panico L: Early-childhood BMI trajectories: evidence from a prospective, nationally representative British cohort study. *Nutr Diabetes* 2016 Mar 7 [Epub] doi: 10.1038/nutd.2016.6

Millennium Cohort Study, sample drawn from 9,699 infants born in the United Kingdom from September 2000 to January 2002 with complete information on child's weight and height at ages 3, 5, 7 and 11 years. By age 11 years, 20% of the sample was overweight and 5.0% obese in boys and 5.7% in girls. Obese trajectory diverges by age 3 years and accelerates after age 5 years and more after age 7 years. In multinomial logistic regression of socioeconomic and early-life factors by latent trajectory for the obese group, the significant weighted relative risk ratios were 1.33* for not breastfed, 1.96† for smoking during pregnancy, 2.16* for high birth weight, 1.94* for low parental education, 0.45* for high parental education, 0.73* for sex (child is male), and 0.36† for ethnicity (child is white). Early-life factors may be crucial in setting up lifelong BMI trajectories.
* $p<0.05$
† $p<0.001$

Martin RM, Kramer MS, Patel R, Rifas-Shiman SL, Thompson J, Yang S, Vilchuck K, Bogdanovich N, Hameza M, Tilling L, Oken E: Effects of promoting long-term, exclusive breastfeeding on adolescent adiposity, blood pressure, and growth trajectories: a secondary analysis of a randomized clinical trial. *JAMA Pediatr* 171:e170698, 2017 Jul 3 [Epub] doi: 10.1001/jamapediatrics.2017.0698

Units in Belarus (31 maternity hospitals and their associated outpatient polyclinics) were randomized in the 1990s (a time of economic crisis) to a control arm with standard breastfeeding practices already in effect (8,178 children) and to an intervention arm based on the Baby-Friendly Hospital Initiative (8,864 children). Weight gain and BMI gain were significantly less in children at intervention units at age 3–12 months, and for weight gain but not for BMI gain thereafter at ages 8.5–14.5 and 14.5–19.9 years; 4%–5% were obese at age 16 years. All participants at least initiated breastfeeding, and the study did not include a formula-feeding arm. "The intention to treat analysis likely underestimates the magnitude of effect of breastfeeding exclusivity and duration, owing to overlap in breastfeeding between the randomized groups: many intervention mothers did not exclusively breastfeed for 3 or 6 months, and some control mothers did." "Higher-than-expected breastfeeding duration was observed in the control group, which may have been owing to deteriorating economic conditions in Belarus during the trial and the higher cost of formula."

Papoutsou S, Savva SC, Hunsberger M, Jilani H, Michels N, Ahrens W, Tornaritis M, Veidebaum T, Molnar D, Siani A, Moreno LA, Hadjigeorgiou G; IDEFICS Consortium: Timing of solid food introduction and association with later childhood overweight and obesity: the IDEFICS Study. *Matern Child Nutr* 14:e12471, 2018, Jan [Epub] doi: 10.1111/mcn.12471

Cross-sectional data from 10,808 children age 2–9 years residing in eight European countries in 2007–2008. Late solid food introduction (age ≥7 months) was associated with an increased prevalence of later childhood overweight/obesity among exclusively breastfed children (OR 1.38, 95% CI 1.01–1.88). Children who were introduced to solids right after 6 months of exclusive breastfeeding and continued to receive breast milk (≥12 months) were less likely to become overweight/obese (OR 0.67, 95% CI 0.51–0.88) compared to children who did not continue to receive breast milk. Early solid food introduction (age <4 months) was associated with a lower prevalence of overweight/obesity among children who ceased exclusive breastfeeding earlier than 4 months (OR 0.63, 95% CI 0.47–0.84). Recall bias was an important limitation.