Gestational Diabetes and the Incidence of Type 2 Diabetes

A systematic review

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OBJECTIVE — To examine factors associated with variation in the risk for type 2 diabetes in women with prior gestational diabetes mellitus (GDM).

RESEARCH DESIGN AND METHODS — We conducted a systematic literature review of articles published between January 1965 and August 2001, in which subjects underwent testing for GDM and then testing for type 2 diabetes after delivery. We abstracted diagnostic criteria for GDM and type 2 diabetes, cumulative incidence of type 2 diabetes, and factors that predicted incidence of type 2 diabetes.

RESULTS — A total of 28 studies were examined. After the index pregnancy, the cumulative incidence of diabetes ranged from 2.6% to over 70% in studies that examined women 6 weeks postpartum to 28 years postpartum. Differences in rates of progression between ethnic groups was reduced by adjustment for various lengths of follow-up and testing rates, so that women appeared to progress to type 2 diabetes at similar rates after a diagnosis of GDM. Cumulative incidence of type 2 diabetes increased markedly in the first 5 years after delivery and appeared to plateau after 10 years. An elevated fasting glucose level during pregnancy was the risk factor most commonly associated with future risk of type 2 diabetes.

CONCLUSIONS — Conversion of GDM to type 2 diabetes varies with the length of follow-up and cohort retention. Adjustment for these differences reveals rapid increases in the cumulative incidence occurring in the first 5 years after delivery for different racial groups. Targeting women with elevated fasting glucose levels during pregnancy may prove to have the greatest effect for the effort required.

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estational diabetes mellitus (GDM), or impaired glucose intolerance first diagnosed during pregnancy (1), affects ~14% of pregnancies, or 135,000 women a year in the U.S., and is a risk factor for type 2 diabetes in the mother (2). The magnitude of the reported risk varies widely; it is unclear how much of the variation is explained by variations in ethnicity, length of follow-up,

selection criteria, and tests for GDM and type 2 diabetes (3–5). Understanding the basis of differences in risk could affect screening protocols for type 2 diabetes in women with a history of GDM and identify women with GDM who may be candidates for studies of preventive interventions of type 2 diabetes.

To examine the relative importance of several sources of variation on the risk of

ations in ethnicity, length of follow-up, several sources of variation on the risk of

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Abbreviations: GDM, gestational diabetes mellitus; NDDG, National Diabetes Data Group; OGTT, oral glucose tolerance test; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

type 2 diabetes in women with GDM, we performed a systematic review of the literature, examining the cumulative incidence of type 2 diabetes in women with GDM. We examined the study design, ethnicity, criteria for diagnosis of GDM and type 2 diabetes, length of follow-up, and other predictive factors. We hypothesized that much of the difference in the risk reported among studies could be explained by different lengths of follow-up, ethnic variation, and the diagnostic criteria used.

RESEARCH DESIGN AND

METHODS — We searched PubMed for studies published from 1965 to 2001 using the search strategy "gestational diabetes AND (type 2 diabetes OR noninsulin dependent diabetes)." The investigators reviewed these abstracts and then reviewed the articles that met selection criteria. We also reviewed the reference lists of review articles and consulted with experts to complete the data search.

Entry criteria for the studies included 1) specified criteria for diagnosis of GDM, 2) specified criteria for diagnosis of type 2 diabetes, and 3) the reported risk of type 2 diabetes in women with GDM. Studies that used an intravenous glucose tolerance test and studies that reported on similar study populations at a similar point in time were excluded. In these instances, only the study with the largest number of subjects was selected. If several reports on cumulative incidence were made on overlapping cohorts as they aged, all reports were included. No studies were excluded because of non-English language.

Information abstracted from each report included the study design, year of publication, population characteristics, diagnostic criteria for GDM and type 2 diabetes, exclusion criteria, number of subjects, length of follow-up, and cumulative incidence of type 2 diabetes (Table 1). When possible, we abstracted the percent of women with GDM tested for type 2 diabetes.

Table 1—Studies of conversion from GDM to type 2 diabetes

Ethnicity	Exclusion criteria	GDM criteria*	Type 2 diabetes criteria*	GDM (n)	Length of follow-up [Mean or median (range)]	Percent tested for type 2 diabetes	Crude cumulative incidence of type 2 diabetes (%)	Reference
60% white		1979 NDDG	USPHS	615	6 months	76	6.6	14
40% other					28 years	?	49.9	4
Latina (assumed)		Local	Local	181	0–5 years	100	45.3	49
Irish		WHO	WHO	8	10	100	12.5	50
Pima		WHO	WHO	233	4–8	100	10	35
Mixed (assumed)		Local	WHO	447	1–12 years	39.1	11	36
73% white		1979 NDDG	WHO	86	3-12 months	100	26	31
17% Asian								
10% other								
Swedish		Local	Local	23	6 months to 3 years	100	26	51
65% white		1979 NDDG	1979NDDG	293	3-12 months	70	5	19
35% Latin, black								
German		Local	WHO	50	6 months	?	4	52
					1 year	?	18	
					8 year	?	46	
40% East Indian	Diabetes after	WHO	WHO	60	4.9 years (3.5-6.5)	38	62	53
40% black	delivery				,			
20% mixed								
Chinese	Normal post- partum OGTT	WHO	WHO	120	0–1 years	100	5	20
82% white		Carpenter	1979NDDG	103	6.6 weeks	100	2.6	22
6% black 6% Latin 6% other		1						
White East Asian East Indian		Local	WHO	1118	1–19 years	38	8–10 17 17	3
Swedish		WHO	MILO	1.45	2 4	61	3.4	24
			WHO	145	3–4 years	61		24
Danish		Local	WHO	241	6 years (2–11)	81	13.7	33
24% white 31% black 35% Latin 11% other		1979 NDDG	1979NDDG	274	6 months	72	18	30
				235	5 years	91	50	30
91% white 5% Latin 2% black		Carpenter	1979NDDG	350	0–10 years	100	6.9	23
2% Asian								
Zuni		1979 NDDG	1979NDDG	47	4.8 years (4–8)	100	30	29
Latina		1979 NDDG	1979NDDG	525	5–8 weeks	47	9	16
Latina	Abnormal Postpar- tum OGTT	1979 NDDG	1979NDDG	671	5–7 years	46	22	17
Navajo		1979 NDDG	WHO	111	6–11 years	71	42	28
Sioux		WHO	WHO	61	3 years (0–5)	81	70	54
? (Mixed)	Abnormal Postpar- tum OGTT	1979 NDDG	1979NDDG	68	1 year	49	18	34
		1080	1080		6 years	10-	36.8	
Latina Latina	Abnormal postpar-	1979 NDDG 1979 NDDG	1979NDDG WHO	179 77	4–6 weeks 15.4 months (11–26)	100 100	5.6 15	21 32
Chimana	tum OGTT	Local	WIIO	001	6	100	12	==
Chinese		Local	WHO	801	6 weeks	100	13	55

^{*1979} NDDG criteria for GDM are administration of a 100-g glucose load, and then at least two values equaling or exceeding the following cutoff points: fasting glucose, 100 mg/dl; 1-h glucose, 190 mg/dl; 2-h glucose, 165 mg/dl; 3-h glucose, 145 mg/dl. Carpenter and Coustan (27) criteria are administration of a 100-g glucose load, and then at least two values equaling or exceeding the following cutoff points: fasting glucose, 95 mg/dl; 1-h glucose, 180 mg/dl; 2-h glucose, 155 mg/dl; 3-h glucose, 140 mg/dl. WHO criteria for GDM are administration of a 75-g glucose load, and then at least one value equaling or exceeding the following cutoff points: fasting glucose, 140 mg/dl; 2-h glucose, 140 mg/dl. 1979 NDDG criteria for type 2 diabetes are a 75-g glucose load, and then at least two values equaling or exceeding the following cutoff points: fasting glucose, 140 mg/dl; 2-h glucose, 200 mg/dl. WHO criteria for type 2 diabetes are a 75-g glucose load, and then at least one value equaling or exceeding the following cutoff points: fasting glucose, 140 mg/dl; 2-h glucose, 200 mg/dl.

The cumulative incidence and length of follow-up were reported in several ways. Most commonly, the reported incidence was only in the women who were retested, and length of follow-up was reported only as the range of follow-up years. Some authors attempted to account for various lengths of follow-up and incomplete retesting by performing lifetable analyses, or actuarial projections of how many women would have converted if all had been retested at the same length of follow-up. When available, these projections were abstracted.

We abstracted other risk factors associated with type 2 diabetes incidence, including maternal demographic risk factors (family history of type 2 diabetes, parity, and age) and anthropometric risk factors (prepregnancy and postpartum BMI, weight gain during pregnancy, blood pressure, and other serum results). Because of the variation in the statistical methods used, we also attempted to abstract the type of methods, but the order in which the variables were entered or other exclusion criteria were often not available.

RESULTS

Search for published data

Initial searches yielded 385 titles for studies that examined GDM and type 2 diabetes. By reviewing titles and abstracts, we excluded articles with no original data and articles that did not examine the conversion rate from GDM to type 2 diabetes. The vast majority of these articles reported on patients with type 2 diabetes with a history of GDM rather than on the incidence of type 2 diabetes in women with GDM. One early study was not included because it used clinical criteria for GDM and type 2 diabetes (6). Two studies were excluded because they used intravenous glucose tolerance tests (7,8) and three studies because they reported on populations similar to other studies included in the review (9-11). In these cases, the study that included the most participants was abstracted. In several instances, particularly with the Boston cohort, several reports on cumulative incidence were made on a cohort as it aged; in these instances, all reports were included (4,12-17).

Overall, 28 studies met inclusion criteria (Table 1). Subjects varied widely in ethnicity, length of follow-up, and criteria

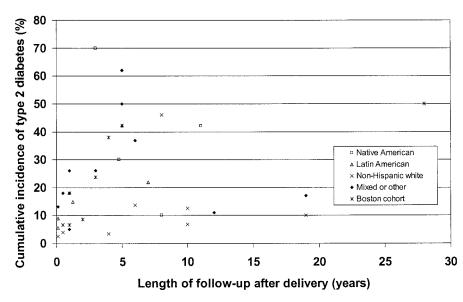


Figure 1—Crude cumulative incidence of type 2 diabetes by ethnicity and length of follow-up in all studies.

for GDM and type 2 diabetes (Table 1). The percent or characteristics of the pregnant population screened for GDM were not specified in the majority of the studies. Studies that defined a cohort of women with GDM and then examined progression had follow-up testing rates ranging from 38 to 100% (Table 1). It is unknown if women with GDM who were not tested for type 2 diabetes had higher or lower rates of type 2 diabetes.

Figure 1 illustrates cumulative incidences of type 2 diabetes by ethnicity and length of follow-up for all studies (Fig. 1).

If studies reported a crude and an adjusted cumulative incidence rate, the crude rate was plotted. The conversion rates to type 2 diabetes ranged from 2.6 to 70%, over a period from 6 weeks to 28 years postpartum. The majority of studies reported the cumulative incidence of type 2 diabetes. Few reported life-table analysis or survival analysis results. Studies that have shorter lengths of follow-up (18–21) or examine non-Hispanic white populations have the lowest cumulative incidence rates (22–24). However, the different criteria used for the diagnosis of

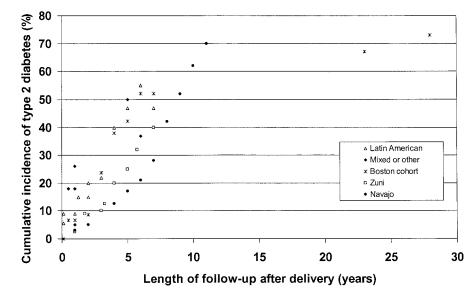


Figure 2—Cumulative incidence of type 2 diabetes by ethnicity and length of follow-up, adjusted for retention. Studies using local criteria or WHO criteria for GDM diagnosis are not illustrated.

the studies (Table 1) and the various length of follow-up within studies are not controlled in Fig. 1.

The most commonly used criteria for the diagnosis of GDM include World Health Organization (WHO) criteria (25), 1979 National Diabetes Data Group (NDDG) criteria (26), and the Carpenter and Coustan revisions (27) (Table 1). The most common criteria used for the diagnosis of type 2 diabetes are NDDG criteria (26) and WHO criteria (25) (Table 1).

Incidence of type 2 diabetes

To further facilitate comparison between studies, we excluded studies that did not use the 1979 NDDG criteria for GDM (Fig. 2). We then plotted actuarial projections of the cumulative incidence of type 2 diabetes if these were reported by the authors (4,12,14,17,28-30); this adjustment would account for variable testing rates and lengths of follow-up between and within the studies. Figure 2 shows less marked differences among ethnic groups. Once diagnosed with GDM, women appeared to progress to type 2 diabetes at more similar rates. Cumulative incidence increased markedly in the first 5 years, and then appeared to increase more slowly after 10 years. The studies of mixed populations by Metzger et al. (30) and Farrell et al. (31), which have higher cumulative incidences than the Boston cohort at comparable times, did not exclude women with symptomatic diabetes from the diagnosis of GDM. As O'Sullivan (14) noted, this factor could explain their higher rates compared with the Boston cohort, which excluded women with diabetes symptoms confirmed by an abnormal oral glucose tolerance test (OGTT) or hyperglycemia (with or without symptoms) of 300 mg/dl on two or more occasions. Exclusion criteria would be expected to have a relatively greater influence on conversion rates soon after delivery by excluding women who might have had preexisting diabetes before pregnancy. The cohort of Farrell et al. (31) also used WHO criteria for the diagnosis of type 2 diabetes. WHO criteria are more sensitive and are expected to yield higher rates than NDDG criteria (12).

With adjustment for dropouts and length of follow-up in Fig. 2, studies of Latin populations appear to have similar cumulative incidences to the Boston cohort. The slightly lower rate of progression to type 2 diabetes may be explained

by different exclusion criteria. In studies of Latin women in Southern California, only those with normal OGTTs were followed for longer than 6 weeks. This approach would lead to lower cumulative incidences of type 2 diabetes in the remainder of the women (16,17,32). In Native American women, adjustment for rates and length of follow-up also yields cumulative incidences more similar to the Boston cohort (28,29), although it is possible that the conversion rate was slightly lower. Diminished cohort retention might be expected to have a larger impact further out from delivery; therefore, adjustment for this variable is particularly important for the studies that report on women years after delivery. For instance, in the Navajo cohort, retesting did not occur regularly, and the life-table figures also contain women who presented clinically with type 2 diabetes. For this reason, Steinhart and colleagues (28) note that the curve of diabetes onset should probably be shifted to the left (Fig. 2).

No studies reporting on only white patients used 1979 NDDG criteria for GDM diagnosis because the majority of these studies were performed outside the U.S. and used local criteria. Examination of non-Hispanic white patients diagnosed with GDM by WHO criteria also identified low rates of type 2 diabetes, although this finding could be due to the less restrictive WHO criteria.

In summary, adjustment for retesting rates and length of follow-up markedly reduced the differences between studies. The remaining differences between studies could be explained by differences in cohort definitions rather than ethnicity, although it is impossible to know this for certain without a comparison between ethnic groups within the same study.

Other risk factors for type 2 diabetes

Several investigators used univariate and multivariate analysis to identify factors associated with conversion to type 2 diabetes. The variables examined varied widely among studies. Although many studies used stepwise logistic regression, it was usually not specified how variables were selected or how the model was constructed, and the significance of the variables could heavily depend on the order in which they were entered. Not surprisingly, the significance of particular risk factors varied among studies.

Fasting glucose levels from OGTTs

administered during pregnancy was the factor most often examined. Fasting glucose level on OGTTs was predictive in the majority of studies (16,17,20,22,23, 28,33,34), except for those that also included more specific measures of β -cell function (30,32). Although 1- and 2-h glucose levels were studied less often than fasting glucose levels, these were also associated with future type 2 diabetes, even in studies that did examine β -cell function (20,22,30,32,35). Area under the OGTT curve was associated with type 2 diabetes in two studies (17,28) but not others (24,32), which again may reflect simultaneous control for other variables in these studies. In the remainder of cases that examined prepartum OGTT values, OGTT predicted type 2 diabetes either by using mean glucose levels or by incorporating the OGTT values in an unspecified manner (3,24,33,36). Several investigators attempted to use insulin measures or insulin secretion rates to predict type 2 diabetes. Not surprisingly, those who did examine fasting insulin or insulin area under the curve found an association (24,33) unless a more specific measure of B-cell function was used (30,32). Therefore, glucose tolerance during pregnancy, particularly fasting glucose, was the factor most commonly associated with type 2 diabetes.

Investigators usually adjusted for fasting glucose as a continuous variable; therefore, a particular threshold value was difficult to identify. Steinhart et al. (28) found that a fasting glucose >106 mg/dl was associated with an 11-fold increased risk for future diabetes compared with fasting glucose levels <106 mg/dl. Other investigators compared the highest quartile of fasting glucose with the lowest quartile, although the quartile cutoffs were not always specified (17,33). Catalano et al. (22) found that women with normal follow-up OGTTs had an average of 97 ± 13 mg/dl compared with women with diabetes, who had an average of 137 ± 25 mg/dl. Similarly, Kjos et al. (16) found that women with normal follow-up OGTTs had an average fasting glucose of 101 ± 2 mg/dl and women with diabetes had a fasting glucose of 144 ± 5 mg/dl. Other studies found smaller differences and greater SDs between women with and without diabetes with average fasting glucose. This finding may reflect the local criteria used to diagnose GDM (3) and the grouping of women with impaired glucose tolerance together with women with diabetes (20).

Attempts to identify maternal risk factors such as BMI, maternal age, previous history of GDM, family history of diabetes, and parity yielded mixed results. Of these predictors, pre- and postpartum BMI were the most commonly examined. Several studies found an association between prepregnancy BMI or BMI measurements averaged over pregnancy and type 2 diabetes without adjusting for other factors (22,24,28) and after adjusting for other maternal factors (17,20, 23,24,30,34), but other studies did not (32,33). There was no apparent difference between these two groups of studies in ethnicity, length of follow-up, or other variables included in multivariate models. Postpartum BMI was associated with type 2 diabetes risk in several studies (3,28,34,36) in univariate analysis but not in others in multivariate analysis (17,20,23,30,32-34). Weight gain during pregnancy or since pregnancy was not associated with type 2 diabetes in multivariate analysis (23,32,34).

Maternal age at time of diagnosis was not associated in univariate analyses (17, 22,24,28,34), with the exception of an Australian series (3,36), but was not associated in multivariate analyses (16, 17,20,24,30,32,34). Prior history of GDM was associated with type 2 diabetes in univariate analysis (3,28,36) but not in multivariate analysis (17), perhaps because women with a history of GDM also had higher glucose levels during pregnancy. Family history of type 2 diabetes was also not associated with type 2 diabetes in univariate (17,22,36) or multivariate analysis (17,20,23,30,33), with one exception (3). Parity was associated in two studies without adjustment (28,33) and one study with adjustment for other variables (3) but not in others (17,20, 30,33,34). The reasons for this difference in findings are unclear, but the study that found an association after adjustment only found an association if the woman had a history of five or more pregnancies

The use of insulin during pregnancy heavily depends on provider and patient treatment preferences and the success of other lifestyle interventions, which may explain why insulin use was associated in some studies (3,20,22) but not in others (23,28). Similarly, gestational age at diagnosis of GDM may depend on the screen-

ing protocols in place at a particular site, which may explain why gestational age was associated in four studies (16,17, 22,24) but not in others (20,33,34). When examined, breast-feeding (17, 22,32), blood pressure (17,32,34), triglyceride level (17,34), and fetal complications (17,28) were not associated with risk of type 2 diabetes in multivariate analyses.

CONCLUSIONS— As expected, in this systematic review, we found that the cumulative incidence of type 2 diabetes varied widely among studies. The differences were largely explained by various lengths of follow-up and retention rates among studies. Diagnostic criteria and selection of the initial population with GDM also contributed to the variation. Once diagnosed with GDM, women from mixed or nonwhite cohorts seemed to progress to type 2 diabetes at similar rates. The progression to type 2 diabetes increased steeply within the first 5 years after delivery, and then appeared to plateau. It is possible that cohorts of women of predominantly white ethnicity also progressed to diabetes at a similar rate, but this comparison was difficult to make because of the relatively few studies of this population that used comparable diagnostic criteria for GDM. Elevated fasting glucose levels obtained during pregnancy predicted type 2 diabetes, except when more specific measures of pancreatic β-cell function were concurrently examined, but other risk factors generally had inconsistent or little predictive value after adjustment for other variables, especially glucose. This observation suggests that once women have elevated fasting glucose levels during pregnancy, their course of insulin resistance then progresses at a similar rate; ethnicity may be important in determining susceptibility to initial elevation in glucose levels.

Our review does not support the use of different screening algorithms for type 2 diabetes in women with a history of GDM by ethnicity or other risk factors aside from markedly increased fasting glucose levels during pregnancy. The fact that these women have already been identified as high risk for type 2 diabetes by their diagnosis of GDM appears to be a significant predictor. Recommendations for postpartum screening should account for the time elapsed from the index pregnancy and perhaps the criteria used for

patient selection. Because women with the highest glucose levels during pregnancy seemed to have the highest future risk of type 2 diabetes, it may be possible to stratify risk further based on this variable.

Debate regarding GDM screening has primarily focused on the benefit to the fetus (37-41). Consequently, several organizations have not endorsed universal screening for GDM and therefore have not addressed risk for type 2 diabetes in these women (42). However, now that intervention in patients with impaired glucose tolerance has been demonstrated to delay the onset of type 2 diabetes, it is possible that screening for GDM will be used for its value of identifying mothers at higher risk for type 2 diabetes. Individuals at high risk for developing type 2 diabetes, specifically those with impaired glucose tolerance, have been shown to benefit from lifestyle and pharmacological interventions, at least in the short term (43–45). These results have not yet been extrapolated to women with GDM, who may have normal glucose tolerance testing postpartum. However, if women with GDM have insulin resistance that is unmasked by the stress of pregnancy, such interventions may prove beneficial in this population. To date, no trials have specifically intervened in women with GDM or a history of GDM to prevent diabetes, except one that examined troglitazone and was subsequently discontinued because of the drug-induced hepatotoxicity reported in other populations (46).

More exact quantification of risk factor magnitude and specific recommendations for type 2 diabetes testing criteria were not possible because we could not combine studies in a formal metaregression analysis. We could not combine studies because of the variations noted earlier, most importantly because the populations tested for GDM and type 2 diabetes were not necessarily selected at random. Also prohibiting combination of studies was the fact that several different tests for GDM and type 2 diabetes were used, possibly leading to different incidence estimates. Our review is also limited by examination of published studies only, although it is unlikely that an additional study would detract from our conclusions given the heterogeneity of the other studies already included.

Testing and preventive intervention in women with GDM are complicated by issues of discontinuity of care in young women, partially due to the loss to follow-up after delivery, mothers' underestimates of their risk of type 2 diabetes (47), and difficulties of implementation of exercise and diet in women with small children (48). Therefore, unique strategies to prevent diabetes in the generally older groups of patients with impaired glucose tolerance may be required in this population.

Current American Diabetes Association guidelines recommend that women with GDM undergo postpartum glucose testing at 6-8 weeks and every 3 years thereafter (1). Our review indicates that women with higher fasting glucose levels during pregnancy and after delivery may warrant more frequent testing and that lower-risk women may require less frequent testing. Further analysis of rates of conversion by ethnicity between studies could clarify the role of ethnicity in determining the rate of progression. Future research should examine the applicability of preventive strategies in the unique post-GDM population and, in particular, address the barriers that these mothers face in access to health care and lifestyle interventions. In the meantime, all women with GDM should be encouraged to engage in preventive behaviors such as increased physical activity, healthy diets, and maintenance of a normal body weight.

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