Risk of IDDM in Children of Diabetic Mothers Decreases With Increasing Maternal Age at Pregnancy

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Offspring of women with insulin-dependent diabetes mellitus (IDDM) have a significantly lower risk of IDDM than the offspring of men with IDDM. Furthermore, a negative association of the risk of IDDM in the offspring with maternal age at delivery has been reported (4). This study tested the association with maternal age in an independent set of families (n = 103) in which the mother had at least one pregnancy before and after the onset of IDDM. In the 304 offspring, the mean ± SE risk of IDDM by age 20 was 6.0 ± 2.4% for those born at maternal ages <25 yr, whereas, the risk was significantly lower (0.7 ± 0.7%) for those born at older maternal ages (P = 0.03). These 304 offspring were combined with a sample of 1391 offspring previously reported for a multivariate analysis of other factors related to pregnancy (4). In the combined analysis, the risk of IDDM in offspring born at maternal ages >25 yr was one-fifth that for offspring born to younger mothers. The risk of IDDM in the offspring was not significantly related to birth order, mother's age at first pregnancy, or the interval between pregnancies for subsequent ones. The risk for the children born before the mother's onset of diabetes was higher than that for those exposed in utero to her diabetes, but the difference did not reach statistical significance. In conclusion, although genetic factors are important determinants of susceptibility to IDDM, exposure to maternal diabetes protects offspring from IDDM during the first 2 decades of life. Moreover, a child born to an IDDM mother >25 yr old has an even lower risk than a child born to that mother at a younger age. The combined result is that a child born to a >25-yr-old woman with IDDM has a very low risk of developing IDDM, almost as low as the children of nondiabetic parents. This has immediate practical implications for women with IDDM who are considering pregnancy and important implications for hypotheses regarding the mechanism that underlies the protective effect of exposure to maternal diabetes. *Diabetes* 40:1679–84, 1991

The frequent observation of discordant insulin-dependent diabetes mellitus (IDDM) in monozygous twins has drawn attention to the insufficiency of genetic factors alone to produce clinical disease (1). However, little progress has been made toward identifying specific environmental exposures that could provoke clinical manifestation of the genetic predisposition in one twin or prevent it in the other (2). For purposes of studying the respective roles of genes and environment, the offspring of diabetic probands are more readily available than identical twins. Such parent-offspring pairs share half a genome and provide an opportunity to examine environmental factors that influence manifestation of a predisposition to diabetes. Based on studies of the risk of IDDM in the offspring of a parent with IDDM, we have described a lower risk of IDDM in the children of mothers with IDDM than of fathers with IDDM (3,4), and similar findings have been reported by others (5,6). The lower risk cannot be explained by two classical mechanisms for producing a sex difference in transmission of a genetic trait, sex linkage and a lower liability threshold in one sex, because sons and daughters are equally affected.

Looking beyond the mode of inheritance for an explanation, we found no evidence that the lower IDDM risk for offspring of diabetic mothers can be attributed to selective loss of the susceptible phenotype in perinatal deaths or spontaneous abortions. There was no secular trend in the risk for offspring of diabetic mothers and no association with the age at diagnosis of the mother's diabetes, but there was a negative association with maternal age at delivery (4). Offspring born at maternal ages >25 yr had

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a significantly lower risk than those born at younger maternal ages.

This study tested this unforeseen association in an independent data set and explored whether the association might be stronger with other reproductive variables such as age at first birth, birth order, or interval between pregnancies.

RESEARCH DESIGN AND METHODS

During the years 1960–1979, 1127 women were registered in the Pregnancy Clinic of the Joslin Diabetes Center (Boston, MA) for one or more pregnancies. Of these women, 992 had IDDM, were white, and resided in New England. Mail questionnaires were sent regarding entire reproductive history (date and outcome of every pregnancy), vital status of each child, and diagnoses of diabetes and method of treatment among children and husbands. If no response was received after two mailings, the mother was called and the information sought by telephone interview.

Completed questionnaires were obtained for 752 women (76%). Questionnaires for the other 240 were not completed because 110 were deceased, 59 refused, and 71 could not be traced. Women who reported a spouse with diabetes (n = 16) were excluded.

Among the remaining 736 women, 103 completed one or more pregnancy before the onset of IDDM and for that reason were excluded from an earlier report of this study (4). Demonstration in this group of families that the association of maternal age at delivery with risk of IDDM in the offspring is similar to that in the previous study would be independent confirmation of the association and would increase the sample size for examination of the association in detail.

For most of the 103 women, the pregnancies that preceded the onset of IDDM were nondiabetic pregnancies, but a few women had gestational diabetes or non-insulin-dependent diabetes mellitus (NIDDM) during a pregnancy. Eleven had IDDM onset during the second pregnancy, 8 during the third pregnancy, and 1 each during the sixth, seventh, and ninth pregnancies. The others (n = 81) had IDDM onset between pregnancies. All 103 women eventually had a clinical diagnosis of IDDM, and most presented in a manner consistent with that diagnosis from the outset. When the onset coincided with a pregnancy, a diagnosis of gestational diabetes was entertained, thus some women discontinued insulin for a period after parturition. Only those who resumed their requirement for daily insulin injections within 1 yr were considered insulin dependent. Median age at onset of IDDM was 26 yr (range 16–39 yr).

The 103 women reported 463 pregnancies. Six ended in therapeutic abortion, 99 in spontaneous abortion, 37 in stillbirth, and 17 in neonatal death. There were 168 children born before the mother's onset of IDDM that survived the neonatal period, and 124 have been followed beyond 20 yr of age. Six developed IDDM before 20 yr and 1 at 21 yr. Another 136 surviving children were born after the mother's onset of IDDM, and 56 have been followed beyond 20 yr of age. One child developed IDDM at age 14. There is one pair of siblings among the eight cases of IDDM.

In the previous report (4), the other 633 questionnaire respondents (whose onset of diabetes preceded their first pregnancy) were combined with a similar group of 106 women whose pregnancies occurred before 1960 and who had responded to an earlier questionnaire (3). The median age at onset of diabetes for the combined group of 739 women was 12 yr (range 1–35 yr), and 86% of them had the onset before age 20 yr. Regardless of age of onset, all had a clinical presentation typical of IDDM, and IDDM persisted at the time of follow-up. Altogether, they reported 2132 pregnancies. Eighty ended in therapeutic abortion, 450 in spontaneous abortion, 115 in stillbirth, and 96 in neonatal death. There were 1391 offspring who survived the neonatal period, and IDDM developed in 20 of them before age 20 yr. Among 420 offspring followed beyond age 20 yr, IDDM has developed in 1 at age 23 yr. There is one pair of siblings among these 21 cases of IDDM.

Verification of the information on the questionnaires was described previously (4). To assess factors influencing the risk of IDDM in the offspring, actuarial methods (7), log-rank tests (8), and Cox regression models (9) were used. Calculation of confidence intervals (CIs) for differences in actuarial estimates of net risk was based on a modification of a method suitable for small numbers of events (10).

To investigate alternatives to maternal age per se as the basis for the higher risk in the offspring of the younger mothers, the two data sets were combined in a single analysis with a Cox regression model. Alternative hypotheses were represented in the model by indicator variables for young maternal age at delivery (<25 yr of age), for having a mother of young age at first pregnancy (1st pregnancy before age 23 yr was chosen because it gave a satisfactory split of the children born before maternal age 25 yr), and for birth order (2nd order, and 3rd or more).

RESULTS

Because the evidence of a maternal age association in the previous report was found in a multivariate logistic analysis but was not described, presentation of the findings in the additional set of 103 families will be prefaced by a descriptive summary of the maternal age association in the larger study.

Offspring of women with IDDM diagnosed before first pregnancy (n = 1391). Overall, the risk of IDDM by age 20 yr (net cumulative incidence rate) was 2.1 ± 0.5%; however, it was significantly higher for offspring born before maternal age 25 yr than for those born at an older maternal age (P = 0.02). For offspring born at maternal ages <25 yr (n = 458), it was 3.6 ± 1.1%, whereas for those born at older maternal ages (n = 933), it was 1.1 ± 0.4%, a difference of 2.5% (Fig. 1). The 95% CI for the difference was 1–6%. We examined the offspring risk according to maternal age at delivery in 5-yr age-groups and found no significant difference other than that produced by the dichotomy at maternal age 25 yr at delivery.

TABLE 1
Net cumulative risk of IDDM by age 20 yr in children of women with IDDM according to study group, maternal diabetes status during pregnancy, and maternal age at delivery

Maternal diabetes status	Maternal age at delivery (yr) 15–24 Risk (%)	95% CI	25–42 Risk (%)	95% CI
Onset of maternal IDDM after 1st pregnancy				
Birth before mother's IDDM	7.2	3.3–14.8 (6 of 88*)	0	0–4.5 (0 of 80*)
Birth after mother's IDDM	0	0–16.8 (0 of 20)	1.4	0.2–7.5 (1 of 116)
Onset of maternal IDDM before 1st pregnancy				
Birth after mother's IDDM	3.6	2.0–6.4 (12 of 458)	1.1	0.6–2.2 (8 of 933)

IDDM, insulin-dependent diabtes mellitus; CI, confidence interval. *n* given in parentheses.
*Number of children affected with IDDM and number of children under follow-up.

Offspring born at maternal ages <20 or >35 yr were too few to assess their risk of IDDM separately.

In contrast, the risk of IDDM in the offspring did not vary significantly according to birth order regardless of whether birth order was based on live births, stillbirths together with live births, or all pregnancies. When maternal age and birth order were taken into account jointly, the maternal age association persisted, and there was still no significant birth order effect.

Offspring of women with their first pregnancy before onset of IDDM (*n* = 304). Overall, the cumulative incidence of IDDM by age 20 yr was 2.7 ± 1.0%, similar to the overall rate of 2.1% in the preceding group of offspring. Moreover, a very similar and statistically significant association with maternal age at delivery was found ($P = 0.03$). The cumulative risk by age 20 yr for offspring born before maternal age 25 yr ($n = 108$) was 6.0 ± 2.4%, whereas, it was only 0.7 ± 0.7% for those born at older maternal ages ($n = 196$), a difference of 5.3% (Fig. 2). The 95% CI for the difference was 2.1–12.9%. As before, there was no significant effect of birth order.

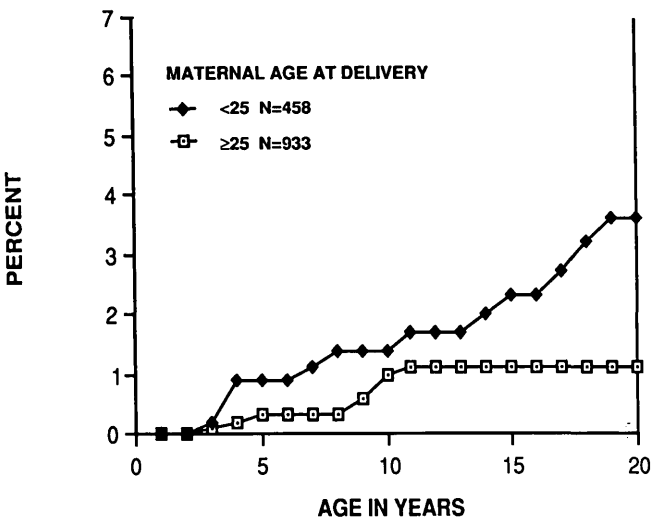

FIG. 1. Net cumulative risk of insulin-dependent diabetes mellitus by age 20 yr in offspring of women with insulin-dependent diabetes mellitus before their 1st pregnancy according to maternal age (yr) at delivery.

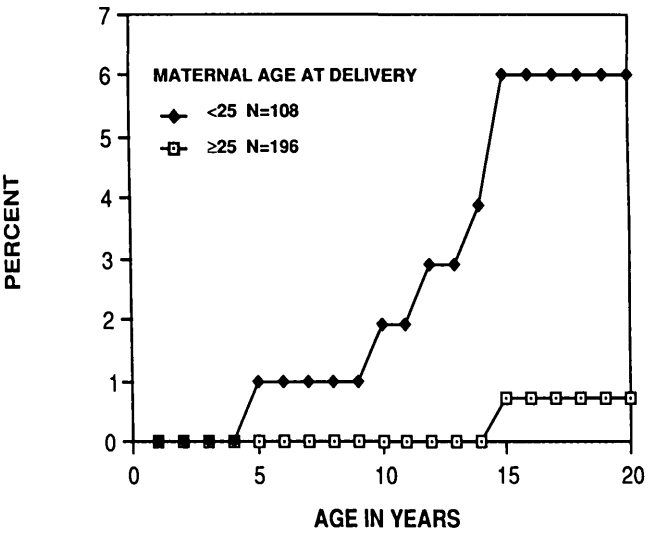

FIG. 2. Net cumulative risk of insulin-dependent diabetes mellitus by age 20 yr in offspring of women who had ≥1 pregnancy before onset of insulin-dependent diabetes mellitus according to maternal age (yr) at delivery.

In this group of families, it is possible to compare the risk of IDDM in the offspring born before their mother's clinical onset of IDDM with the risk in the offspring exposed to their mother's IDDM in utero. This comparison, stratified by maternal age, is presented in Table 1 together with the corresponding cumulative incidence rates for the offspring of the group of mothers with IDDM before their first pregnancy. The cumulative risk for the 88 offspring born at maternal ages <25 yr and before the mother's onset of IDDM was 7.2 ± 2.8%, whereas, there were no cases of IDDM among the 20 offspring born after the onset of maternal IDDM but before a maternal age of 25 yr. If the risk for these 20 offspring was 3.6% (the same as for offspring of mothers with IDDM before their first pregnancy), less than one case would be expected, thus, the absence of any cases was likely due to the small sample size. Therefore, the data for offspring born at maternal ages <25 yr suggest that the risk for offspring not exposed to maternal IDDM in utero might be twice that for offspring born after their mother's onset of IDDM, although the difference is not statistically significant with the available sample sizes. The data for offspring born at maternal ages >25 yr suggest that the cumulative risk of IDDM was very low regardless of whether the offspring were exposed in utero to overt diabetes.

Combined analysis. Instead of maternal age per se, some other factor correlated with it might be more closely

TABLE 2
Cox regression analysis of determinants of risk of IDDM in children of women with IDDM

Characteristic	Children (*n*)	Relative hazard	χ^2	*P*
Maternal age at delivery (yr)				
15–24	566			
25–42	1129	.20	8.42 (1df)	<0.005
Maternal age at 1st pregnancy (yr)				
15–22	625	1		
23–40	1070	1.01	0.01 (1df)	>0.90
Birth order†				
1	697	1		
2	553	1.55		
≥3	445	1.82	3.23 (2df)	<0.20
Birth after mother's onset of IDDM				
Yes	1527	1		
No	168	1.67	0.66 (1df)	<0.50
Age at onset of IDDM in mother (yr)				
0–19	1199	1		
20–35	496	.90	0.04 (1df)	>0.80

Likelihood ratio χ^2 for a comparison of the model that includes all 5 characteristics compared to the null model was 14.58 on 6 df, $P < 0.025$. χ^2 for each characteristic is a likelihood ratio χ^2 for a comparison of the full model to the reduced model, which omits that characteristic. Birth order data include stillbirths. IDDM, insulin-dependent diabetes mellitus; df, degrees of freedom.

linked to the risk of IDDM in the offspring. Besides birth order, possible variables to be considered are young age at first pregnancy and aspects of the interval between pregnancies. To investigate these alternatives, the two data sets were combined in a single analysis with a Cox regression model (Table 2). The alternatives were represented in the model by indicator variables for young maternal age at delivery, young age at first pregnancy, and birth order. Furthermore, two diabetes variables were included. One variable indicated that the mother did not have IDDM at the time of delivery. This would test whether the diabetic state versus a predisposition to diabetes affects the risk in the offspring differently. The second variable, an indicator for age at onset of maternal diabetes, was included to test the possibility that such onset ages might represent a different type of diabetes. If true, they would be less likely to transmit a genetic predisposition to a juvenile onset of IDDM, and this variable might detect a lower risk of IDDM in their children.

This multivariate approach confirmed the main finding of the previous analysis. A young maternal age at delivery is strongly related to an offspring's risk of IDDM, but a young age at the mother's first pregnancy has no effect (Table 2). There was a positive but not statistically significant association between risk of diabetes and birth order. Because an association with birth order might reflect an effect of short intervals between pregnancies, an alternative model was fitted that replaced birth order (2nd, and 3rd or more) with intervals between pregnancies (<2 vs. >2 yr). The estimated effect for short pregnancy interval was not statistically significant, and the rest of the model was essentially unchanged. The last two results of this analysis relate to aspects of the mother's diabetes. The risk of IDDM for children born before the mother's onset of diabetes was 67% higher than those born after onset, which is consistent with the findings in Table 1, but the difference does not reach statistical significance. The risk for offspring of women whose onset of diabetes was after age 20 yr was almost identical to that for offspring of women who had juvenile onset of diabetes. This is exactly the result expected if the women with late onset of IDDM represent the same disease as those with young onset.

DISCUSSION

Our previous studies of children of a father or mother with IDDM showed that exposure to maternal diabetes protects offspring from IDDM during the first 2 decades of life (3,4). Evidence from other types of studies support our findings (5,6). This study indicates that a child born to a mother >25 yr old has an even lower risk of IDDM than a child born to that mother at a younger age. The combined result is that a child born to a woman >25 yr old with IDDM has a very low risk of developing IDDM, almost as low as children of nondiabetic women (11).

There are immediate practical implications of our findings. Unlike the sex of the affected parent, maternal age can be a matter of choice and therefore might be influenced by counseling. One-third of the children of IDDM mothers in this study were born at maternal ages <25 yr. If all were born at older maternal ages, there would have been half as many diabetic offspring. For the individual woman with IDDM, however, the benefit of a reduced risk of IDDM for her offspring must be balanced against the increased chance that she will have developed a serious complication of diabetes before age 25 yr. If there is evidence of incipient nephropathy, for example, the benefit of postponed pregnancy may not outweigh the increased risk of a complicated pregnancy.

The implications apply only to the offspring of women with IDDM. There has been no investigation of the determinants of risk of IDDM in offspring of fathers with IDDM, and the effects of maternal characteristics in these pregnancies might be nonexistent or quite different from those of diabetic pregnancies. There is indirect evidence that the latter might be the case. An increased risk for children born at older maternal age has been reported where neither the mother nor father has diabetes (12,13). Because offspring of diabetic men are not exposed to maternal diabetes in utero, we hypothesize that their risk might vary more like the offspring of nondiabetic parents than that of diabetic mothers.

These epidemiological findings must reflect biological mechanisms that underlie clinical manifestations of disease susceptibility (14), thus, they can aid in discriminating which of several potential mechanisms involved in the pathogenesis of diabetes are most likely to account for these observations. There are three possible mechanisms that seem to be the best candidates.

Previously, we hypothesized that the low risk of IDDM

in the offspring of diabetic mothers might be due to immunologic mechanisms analogous to those involved in the induction of immune tolerance to foreign tissue grafts in mice before birth (4). If some characteristic of a diabetic mother triggers β-cell antigen presentation in utero, the impact might be induction of nonresponsiveness to that antigen (16,17). An attempt to mimic such a process in a rodent model of IDDM has been reported (18). Pharmacological stimulation of neonatal β-cells resulted in reduced incidence of diabetes in these stimulated animals. The investigators' hypothesis is that β-cell stimulation elicits presentation of antigen during the period when neonatal tolerance could be induced. For this hypothesis to be a plausible explanation for the observations in human IDDM, it must be elaborated further to account for the variability of the process at different maternal ages.

Another candidate mechanism for the maternal protective effect revolves around the genes of HLA class II region on the short arm of chromosome 6 that have been implicated in the development of IDDM (19,20). Selection against fetuses bearing HLA haplotypes that include diabetes-susceptibility genes in mothers with IDDM has been suggested as a mechanism for the lower incidence of IDDM in children of diabetic women (21). Therefore, the observed maternal age association might arise through increasing efficiency of the selective process at higher maternal age. Although this mechanism has not been investigated directly, we have shown previously that variation in the frequency of recognized fetal and neonatal losses is not correlated with the risk of IDDM in the surviving offspring (4).

The pattern of transmission of IDDM in families, that is different diabetes risks for the children of IDDM mothers compared with children of IDDM fathers but equal risks for sons and daughters in each case, is consistent with the concept of genomic imprinting (22). This term refers to the differential expression of genetic material at either a chromosomal or allelic level, depending on whether the genetic material has come from the father or mother. The actual mechanism involved in the imprinting phenomenon is unknown, thus, it is difficult to design a test of this hypothesis, but if it can be shown that imprinting varies with parental age, the attractiveness of this hypothesis would be greatly increased.

As with other diseases that have genetic determinants, there remains the possibility that diabetes in some families is primarily determined by genetic factors, whereas environmental factors may play a larger role in others. Moreover, there may be heterogeneity within both the genetic and environmental determinants of IDDM. Specifically, the modifying effects of exposure to maternal diabetes in utero may be quite different, depending on which genetic determinants are in the fetus. There is no better illustration of this type of interaction than the contrast between the findings of this study and the reported effects of fetal exposure to maternal diabetes in Pima Indians. That population has a very high prevalence of NIDDM even among young people, and there is a very strong association with maternal diabetes (23). In the age-group 20–24 yr, the prevalence of NIDDM is 1.4% among children of nondiabetic mothers, whereas, it is 8.6% among children of mothers who were nondiabetic during pregnancy but developed NIDDM later. Among children who were exposed to diabetes in utero, however, the prevalence of NIDDM by age 20–24 yr jumps to 45%. These findings suggest that the intrauterine environment is an important determinant of the development of NIDDM and that its effect is in addition to effects of genetic factors. The mechanisms by which exposure to maternal diabetes increases the risk of NIDDM in young Pima Indians are unknown.

In summary, this study demonstrates that maternal age (presumably a marker of changes in the intrauterine environment) interacts with genetic determinants of IDDM in a manner that reduces the offsprings' risk of developing IDDM before age 20 yr. Several issues remain to be studied, such as whether this protection persists through adulthood and whether heterogeneity exists among families with regard to this interaction between genes and intrauterine environment. Furthermore, to determine whether these interactions occur only in a diabetic milieu, the risk of IDDM in the children of fathers with IDDM needs to be investigated for a modifying effect of the nondiabetic mother's age (or other characteristics). Finally, regarding data from Pima families, there is a possibility that, although exposure to maternal IDDM protects the offspring from IDDM, it increases the risk of NIDDM later in life.

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