Chromosomal Anomalies among the Offspring of Women with Gestational Diabetes

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A limited body of data over the past 35 years has suggested that autoimmunity may be responsible for some cases of aneuploidy. The role of diabetes mellitus in the etiology of chromosomal anomalies has been infrequently studied. This study was designed to compare the prevalence of chromosome abnormalities among the offspring of women with gestational diabetes and the offspring of women without it. The authors used data from 7,332 women who underwent amniocentesis in a prospective study of pregnancy outcome (1984–1988) and examined the prevalence of autosomal and sex chromosome defects associated with gestational diabetes. Among the offspring of 231 women with gestational diabetes, the crude prevalence of chromosomal defects was twice as high as that seen in the offspring of 7,101 women without gestational diabetes. These anomalies were predominantly numeric sex chromosome defects. After adjusting for potential confounding by maternal age, body mass index, education, and first-trimester exposures in multiple logistic regression analysis, the authors found that women with gestational diabetes were 7.7 times as likely (95% confidence interval: 2.8, 21.1) to have an infant with a numeric sex chromosome defect as those without gestational diabetes. These results support the theory that some women who develop gestational diabetes may have underlying biochemical changes that induce nondisjunction and the development of chromosomal defects.

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Rates of gestational diabetes mellitus have risen in recent years (1). This rise may be, in part, a consequence of the increased prevalence of obesity (2), as well as the tendency for women to be older at the time of their first pregnancy (3). Gestational diabetes is characterized by reduced insulin sensitivity and reduced pancreatic insulin output in response to a given glucose load (4). Clinically, it is defined simply as carbohydrate intolerance that has its onset or initial detection during pregnancy (1, 5). Gestational diabetes is most often manifest in later pregnancy (after 24 weeks) in response to naturally occurring hormonal changes (6). Its significance as a clinical entity is still debated, as is the need for routine screening for the disorder (1, 7). Recent studies, including at least one physician survey, have also highlighted widely variable clinical practices associated with gestational diabetes (8, 9).

For some women, gestational diabetes is a precursor to type I diabetes mellitus, while for others, it is a marker for increased risk of subsequent type II diabetes (10, 11). Thus, gestational diabetes is a heterogeneous disease with different etiologic pathways and variable pathophysiology. For some women with gestational diabetes, there may be metabolic disturbances or other abnormalities present before clinical detection of the condition, and these early abnormalities could affect fetal development (12–16).

The effect of diabetes mellitus, especially gestational diabetes, on the number of fetal chromosomes is a complex issue. Since the diagnosis of gestational diabetes necessarily postdates the development of the fetal chromosome complement, gestational diabetes might best be considered a marker for some underlying metabolic or physiologic anomaly in the mother. There is now convincing evidence that the presence of islet cell antibodies in women with gestational diabetes (17, 18) and the presence of antibodies to glutamic acid decarboxylase in both healthy women and women with gestational diabetes (19–22) are strong predictors of subsequent development of type I diabetes. Other work has shown that specific human leukocyte antigens, particularly DR3, predispose women to the development of these diabetes-associated autoantibodies and later-onset type I diabetes (11, 23–25). Thus, at least a subset of women may have autoimmune disorders that predate the clinical presentation of gestational diabetes.

In 1964, Fialkow first hypothesized that autoimmunity may be responsible for some cases of aneuploidy (26). He later showed an increased frequency of thyroid autoimmunity among mothers of children with Down’s syndrome (27). Other work conducted around that time supported the
notion that autoimmunity, perhaps from infectious agents or other causes, may predispose to nondisjunction (28). In recent years, animal studies have lent further support to the hypothesis that something associated with diabetes mellitus, such as associations of nucleolar organizing regions, may be responsible for numeric chromosome anomalies due to nondisjunction (29, 30).

There have been few human studies of the effect of diabetes mellitus or gestational diabetes on the risk of chromosomal anomalies, although a limited body of data suggests that there is an increased risk of Down’s syndrome among women with either preexisting diabetes or gestational diabetes (31, 32). As early as the 1960s, it was shown that adults with Klinefelter’s syndrome, Turner’s syndrome, and Down’s syndrome had higher rates of endocrine dysfunction and thus much higher risks of developing diabetes mellitus as adults (33–38). Therefore, it is possible that these apparent bidirectional associations between endocrine dysfunction and chromosome abnormalities have common autoimmune pathways.

The goal of the current study was to compare the prevalence of chromosome abnormalities among the offspring of women with gestational diabetes with that seen in the offspring of women without gestational diabetes.

**MATERIALS AND METHODS**

Between October 1984 and June 1987, 24,559 US women (primarily from New England) were invited to participate in a prospective study of pregnancy outcome. The women had completed their first trimester of pregnancy at the time of referral to the study and had undergone either a maternal serum α-fetoprotein screening test or amniocentesis. Details on recruitment have been previously published (39). In this analysis, we included only those women who underwent amniocentesis in the second trimester for examination of fetal chromosomes (n = 7,368). The women were followed through pregnancy termination; those with livebirths were followed for 1 year after parturition.

Nurse interviewers completed a pregnancy history survey by telephone between weeks 15 and 20 of pregnancy (before the woman obtained amniocentesis results) to ascertain detailed information on exposures incurred prior to pregnancy and during the first trimester. Information on past or current diabetes mellitus or gestational diabetes, based on standard diagnostic criteria used in each physician’s clinical practice, was collected during the interview. Each woman was also asked about medication usage during the first 8 weeks of pregnancy, including the use of insulin and oral diabetes medications. The interviewer asked the woman for the exact name of each drug used, how long she had been taking it, when she had first started taking it, and whether its use had been discontinued or changed during pregnancy. Among the 7,368 women who underwent amniocentesis, there were 14 women with type I diabetes mellitus and 22 women with type II diabetes mellitus. Since there were too few cases of type I or type II diabetes for us to draw any meaningful conclusions regarding risk of chromosomal defects, we excluded these women, which left a final study population of 7,332 women. (There were no chromosomal aberrations among the 36 excluded women with type I or type II diabetes mellitus.)

We used data from both the pregnancy history and an outcome questionnaire sent to the delivering obstetriciangynecologist around the expected time of delivery to classify each woman as having or not having gestational diabetes. Women with a history of previous gestational diabetes were included in the exposure group. Those who developed diabetes at any time during pregnancy, regardless of their need for exogenous insulin and regardless of whether the diabetes resolved during the postpartum period, were classified as having gestational diabetes (5). (There were insufficient numbers of women with insulin-requiring gestational diabetes for us to analyze them separately.) There were 231 women with a diagnosis of gestational diabetes among the 7,332 participants who underwent amniocentesis. Of these, 59 had a history of previous gestational diabetes, while 172 had gestational diabetes in the current pregnancy only.

The presence of chromosomal anomalies was determined by the Center for Human Genetics at Boston University School of Medicine on the basis of the amniocentesis results. Chromosomal abnormalities were coded using the 6-Digit Code List for Reportable Congenital Anomalies published by the Centers for Disease Control and Prevention (40). At least two independent coders who were blinded to the subject’s exposure information carried out the coding. Inherited chromosomal defects were excluded. We classified all noninherited defects of autosomes or sex chromosomes according to whether the defects were structural or numeric in nature.

**Statistical analysis**

We first calculated the prevalence of autosomal and sex chromosome defects according to the presence of gestational diabetes. We then calculated crude prevalence ratios and Mantel-Haenszel exact 95 percent confidence intervals for the effects of gestational diabetes on the risk of each type of chromosomal defect (41). Potentially confounding variables that were included in the multivariable models were selected on the basis of a known or purported association with diabetes mellitus (including gestational diabetes) or chromosomal defects. We used multiple logistic regression analysis to adjust for the potentially confounding effects of maternal age (<35 years vs. ≥35 years), body mass index (weight (kg)/height (m)2) before conception, education (any college vs. no college), history of thyroid disease (yes/no), and first-trimester cigarette smoking (yes/no) and alcohol drinking (number of drinks per day).

**RESULTS**

Seventy-one percent of the women with gestational diabetes were aged 35 years or older, as compared with 63.8 percent of women without gestational diabetes (table 1). Women with gestational diabetes had a higher prepregnancy body mass index (26.4 percent had a body mass index ≥27) than women without gestational diabetes (10.6 percent).
Women with gestational diabetes were also less likely to smoke (10.8 percent vs. 15.2 percent) and had a slightly higher prevalence of thyroid disease, but they were otherwise similar to women without gestational diabetes.

Table 2 shows the prevalence of chromosomal defects per 1,000 pregnancies among the offspring of women with and without gestational diabetes. Of the 7,332 women who underwent amniocentesis, 159 had an infant with a chromosome anomaly. The total prevalence of chromosomal defects was twice as high among the offspring of the 231 women with gestational diabetes (43.3 per 1,000) as among the offspring of women without gestational diabetes (21.0 per 1,000). The proportions of pregnancies resulting in an autosomal defect were similar for mothers with and without gestational diabetes (17.3 and 17.7 per 1,000 pregnancies, respectively), whereas anomalies of sex chromosomes were seen much more frequently than expected among the offspring of mothers with gestational diabetes (26.0 per 1,000 pregnancies vs. 3.2 per 1,000 pregnancies). All but one of the defects of sex chromosomes in the offspring of women with gestational diabetes were due to nondisjunction—namely, there were three cases of Klinefelter’s syndrome (XXY) and two cases of triple X syndrome (XXX).

The adjusted prevalence ratio estimates for the effect of gestational diabetes on risk of chromosomal aberrations are given in Table 3. The adjusted prevalence ratios indicate that there was no confounding of these effects by maternal age, body mass index, education, history of thyroid disease, or first-trimester cigarette or alcohol use. Overall, the offspring of women with gestational diabetes were 2.1 times as likely (prevalence ratio = 2.1, 95 percent confidence interval: 1.1, 4.0) to have a chromosomal defect as the offspring of women without gestational diabetes. There was no excess risk of autosomal defects associated with gestational diabetes. Finally, we examined the effect of gestational diabetes on the risk of sex chromosome anomalies specifically related to nondisjunction. Women with gestational diabetes were 7.7 times as likely (95 percent confidence interval: 2.8, 21.1) to have an infant with a numeric sex chromosome defect as women without gestational diabetes.

**DISCUSSION**

The offspring of women with gestational diabetes in this cohort were substantially more likely to have an anomaly of sex chromosomes due to nondisjunction, particularly Klinefelter’s syndrome and triple X defects, than were offspring of women without gestational diabetes. The number of cases of these specific defects in this study population was small, but the strength of the association was compelling. It has been estimated that the occurrence of Klinefelter’s syndrome ranges from 1.0 to 1.6 per 1,000 liveborn males (or approximately 0.5–0.8 per 1,000 total births) (42). In our cohort, the occurrence at the time of amniocentesis was 1.6 per 1,000 pregnancies. However, women with gestational diabetes had an occurrence rate 10 times higher than that seen among women without gestational diabetes (13.0 vs. 1.3 per 1,000 pregnancies). Triple X syndrome has been estimated to occur in approximately 1.1 per 1,000 female livebirths (or about 0.5 per 1,000 total births) (43). In our cohort, the prevalence of this outcome at the time of amniocentesis was 0.7 per 1,000 pregnancies. The two cases of triple X syndrome among 231 women with gestational diabetes (a prevalence of 8.7 per 1,000 pregnancies) was more than 20 times that seen among the women without gestational diabetes (0.4 per 1,000 pregnancies).

We were particularly concerned about the possibility of confounding by maternal age. Among the four age categories (<25, 25–34, 35–39, and ≥40 years), we found that chromosomal defects were, as expected, most frequent in the oldest women (28.9, 20.5, 20.5, and 35.1 per 1,000 pregnancies in the four age groups, respectively), although the youngest women had a higher risk than women in the two middle age categories. It is notable that the defects in the offspring of the youngest women were disproportionately due to anomalies of sex chromosomes, while those in offspring of the oldest women were predominantly autosomal. Specifically, four of the seven chromosomal defects (57 percent) in the offspring of women under 25 years of age were anomalies of sex chromosomes, while only two of the 16 defects (13 percent) in the oldest women were defects of that type. We modeled maternal age as a continuous variable (with first- and second-order terms) and as a categorical variable (<35 years vs. ≥35 years); the results from all mod-
els were virtually identical. Thus, confounding by maternal age is not an explanation for the excess risk of chromosomal defects associated with gestational diabetes that we found in this study.

One possible limitation of the current study is the fact that the analyses were carried out in a subset of 7,368 women undergoing routine second-trimester amniocentesis. Since we did not collect blood specimens from newborns, we were unable to determine the prevalence of chromosomal anomalies in the full cohort of 24,559 women. However, since referral for amniocentesis was unrelated to the occurrence of gestational diabetes, as the onset of gestational diabetes generally postdated the amniocentesis referral, it is very unlikely that the use of this amniocentesis cohort would have biased the results of these analyses in some way. In addition, the persons who carried out the analysis of fetal chromosomes were blinded with respect to the existence of maternal illnesses or complications such as gestational diabetes, making it even less likely that the gestational diabetes-related prevalence of sex chromosome anomalies found in this cohort is biased.

Gestational diabetes cannot be considered a risk factor for the occurrence of numeric chromosome defects, since nondisjunction occurs around the time of conception, thus preceding the development of gestational diabetes. However, gestational diabetes could be considered a marker for other preexisting factors, such as autoimmunity, that may induce nondisjunction and the development of chromosome anomalies. Offspring of both women and men with diabetes mellitus have been shown to develop autoantibodies to islet cells, insulin, and glutamic acid decarboxylase very early in life (43, 44). Children with higher numbers of circulating autoantibodies have a higher risk of subsequent diabetes mellitus than those without such antibodies or with fewer antibodies (45, 46). Women with circulating autoantibodies are at higher risk for development of insulin-requiring gestational diabetes as well as type I diabetes mellitus (17–22, 47). Since these autoantibodies may be present before gestational diabetes is clinically apparent, it is possible that their presence could have an adverse effect on first- or second-phase meiotic divisions.


<table>
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<tr>
<th></th>
<th>No. among all pregnancies (n = 7,332)</th>
<th>No gestational diabetes mellitus (n = 7,101)</th>
<th>Gestational diabetes mellitus (n = 231)</th>
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<tr>
<td></td>
<td>No.</td>
<td>Prevalence *</td>
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<tr>
<td>Any chromosomal defect</td>
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<td>21.0</td>
<td>149</td>
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<tr>
<td>Autosomes</td>
<td>130</td>
<td>17.7</td>
<td>126</td>
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<tr>
<td>Sex chromosomes</td>
<td>29</td>
<td>3.2</td>
<td>23</td>
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<tr>
<td>Individual defects</td>
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<td></td>
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<tr>
<td>Total defects†</td>
<td>164</td>
<td>21.7</td>
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<tr>
<td>Autosomes</td>
<td>135</td>
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<tr>
<td>Trisomy 21</td>
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<td>3</td>
</tr>
<tr>
<td>Structural anomaly</td>
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<td>6.6</td>
<td>47</td>
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<tr>
<td>Sex chromosomes</td>
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<td>23</td>
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<tr>
<td>Triple X syndrome (47, XXX)‡</td>
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<td>3</td>
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<td>0.3</td>
<td>2</td>
</tr>
<tr>
<td>Structural anomaly</td>
<td>3</td>
<td>0.3</td>
<td>2</td>
</tr>
</tbody>
</table>

* Per 1,000 pregnancies.
† The offspring of five women had two separate chromosomal defects (a total of 164 defects among the offspring of 159 women).
‡ Includes cases with mosaicism.

### TABLE 3. Risk of chromosomal defects among offspring of women with gestational diabetes mellitus as compared with offspring of women without gestational diabetes mellitus, 1984–1988

<table>
<thead>
<tr>
<th></th>
<th>Crude analysis</th>
<th>Adjusted analysis*</th>
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<tr>
<td></td>
<td>PR†</td>
<td>95% CI†</td>
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<td>2.1</td>
<td>1.1, 4.1</td>
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<tr>
<td>Autosomal defects</td>
<td>0.98</td>
<td>0.36, 2.7</td>
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<tr>
<td>Numeric sex chromosome defects‡</td>
<td>7.5</td>
<td>2.8, 20.0</td>
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</table>

* Adjusted for maternal age, body mass index, education, history of thyroid disease, and first-trimester smoking and alcohol use.
† PR, prevalence ratio; CI, confidence interval.
‡ Excludes structural sex chromosome defects.
Gestational diabetes is an increasingly common complication of pregnancy, yet a number of recent studies show that there is no current consensus regarding its clinical significance or treatment. Additional research evaluating and quantifying the effects of potential metabolic derangements underlying gestational diabetes in the development of fetal chromosome anomalies is needed. Such research would help to guide choices for prenatal diagnosis among these women.

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REFERENCES


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