Inflammation Among Women With a History of Gestational Diabetes Mellitus and Diagnosed Diabetes in the Third National Health and Nutrition Examination Survey

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OBJECTIVE — We compared inflammatory markers among women with a history of gestational diabetes mellitus (hGDM), women with diagnosed diabetes, and unaffected women in a population-based sample.

RESEARCH DESIGN AND METHODS — We conducted cross-sectional analyses of 6,346 nonpregnant women in the Third National Health and Nutrition Examination Survey (1988–1994). Women were classified as having hGDM (n = 87), diagnosed diabetes (n = 244), or neither condition (n = 6,015). Inflammatory markers included ferritin, leukocyte count, and C-reactive protein levels.

RESULTS — After adjustment, women with diagnosed diabetes had the most marked differences in inflammatory markers compared with unaffected women. Differences between unaffected women and women with hGDM were minimal.

CONCLUSIONS — Women with diagnosed diabetes have less favorable inflammation profiles than unaffected women and greater ferritin levels than women with hGDM. After adjustment, women with hGDM who have not developed diagnosed diabetes have inflammation profiles similar to those of unaffected women.

Wmen with a history of gestational diabetes mellitus (hGDM) are at increased risk for future glucose intolerance, and this risk may be associated with inflammation (1–4). The association has not been examined in population-based studies and may not be robust after adjustment for BMI (1–4). Using data from the third National Health and Nutrition Examination Survey (NHANES III), a population-based cross-sectional study, we compared inflammatory markers among unaffected women versus women with hGDM and women with diagnosed diabetes.

RESEARCH DESIGN AND METHODS

The sampling strategy and data collection methods for NHANES III have been previously described (5). We excluded women who were currently pregnant, had missing data regarding pregnancy status, or had previous diabetes or hGDM diagnoses, for a total sample of 6,346 women. Women were classified as having diagnosed diabetes if they reported a diagnosis of diabetes outside of pregnancy, as having hGDM if they reported having a diagnosis of diabetes made only during pregnancy, and as unaffected if they did not have hGDM or diagnosed diabetes. Therefore, the categories of unaffected women (n = 6,015), women with hGDM (n = 87), and women with diagnosed diabetes (n = 244) were mutually exclusive. In NHANES III, undiagnosed diabetes was assessed in a subsample of nondiabetic individuals who were randomly assigned to a morning fasting examination.

Information on demographic and behavioral factors was collected by interview (5). The poverty index was calculated as the poverty-to-income ratio (6). Measurements of height, weight, and waist circumference were performed in a standardized manner. Leg length was calculated by subtracting sitting height from standing height (7). Measurement procedures for inflammatory markers for ferritin (8), leukocytes (9), and C-reactive protein (CRP) (6) in the NHANES III have been previously described.

Statistical analysis

All analyses accounted for the multistage, stratified, cluster-sampling design of NHANES III by using survey sample weights. We conducted tests for trend across unaffected women, women with hGDM, and women with diagnosed diabetes across exposure variables. We calculated predicted marginal probabilities and 95% CIs in multivariate models. In a sensitivity analysis, we excluded women who had fasting glucose ≥126 mg/dl and who were also classified as having hGDM or as unaffected, but results did not change. We restricted analyses to only parous women, but results did not change. Statistical analyses were conducted using SUDAAN 9.0 (Research Triangle Institute, Research Triangle Park, NC).

RESULTS — Women with diabetes were significantly older than women with hGDM and unaffected women (46 vs. 32 years, p < 0.01). After controlling for age, women with diagnosed diabetes had the highest mean CRP levels (5.9 vs. 1.6 mg/L, p = 0.0005), whereas women with hGDM had significantly higher mean ferritin levels (1,683 vs. 792 μg/L, p < 0.0005). Women with diagnosed diabetes had significantly lower mean CRP levels (2.6 vs. 5.5 mg/L, p < 0.0005) and higher mean ferritin levels (1,521 vs. 773 μg/L, p < 0.0005) compared with nonpregnant women.

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Table 1—Predicted probabilities (95% CIs) for inflammatory markers by categories for unaffected women, those with hGDM, and those with diagnosed diabetes

|                | No GDM or diabetes | hGDM | Diagnosed diabetes | R²  |
|----------------|--------------------|------|-------------------|-----|
| **Ferritin (ng/ml)** |                    |      |                   |     |
| Model 1*       | 66.3 (62.2–70.4)   | 72.7 (55.0–90.3)† | 120.3 (96.4–144.2) | 0.08 |
| Model 2†       | 66.4 (62.1–70.7)   | 68.0 (50.2–85.9) | 112.8 (88.5–137.1) | 0.10 |
| Model 3‡       | 63.4 (59.8–67.1)   | 61.3 (44.7–77.9) | 108.4 (86.9–129.9) | 0.09 |
| Model 4§       | 63.5 (60.0–67.1)   | 61.3 (44.1–78.6) | 106.5 (85.6–127.4) | 0.09 |
| **Leukocyte count (cells/ml)** |            |      |                   |     |
| Model 1*       | 7.2 (7.1–7.4)      | 7.5 (6.7–8.4) | 8.5 (7.1–8.9) | 0.11 |
| Model 2†       | 7.2 (7.1–7.4)      | 7.4 (6.5–8.3) | 8.1 (7.8–8.4) | 0.16 |
| Model 3‡       | 7.2 (7.1–7.3)      | 7.3 (6.5–8.1) | 8.0 (7.7–8.3) | 0.16 |
| Model 4§       | 7.2 (7.1–7.3)      | 7.3 (6.4–8.1) | 8.0 (7.7–8.4) | 0.16 |
| **CRP (mg/l)**  |                    |      |                   |     |
| Model 1*       | 0.4 (0.4–0.5)      | 0.5 (0.2–0.7) | 0.8 (0.5–1.1) | 0.03 |
| Model 2†       | 0.4 (0.4–0.5)      | 0.4 (0.2–0.6) | 0.7 (0.4–1.0) | 0.10 |
| Model 3‡       | 0.4 (0.4–0.4)      | 0.4 (0.2–0.6) | 0.7 (0.4–0.9) | 0.12 |
| Model 4§       | 0.4 (0.4–0.4)      | 0.4 (0.2–0.6) | 0.7 (0.4–1.0) | 0.14 |

*Model 1 adjusted for age, race, family history of diabetes, parity, smoking, and alcohol consumption. †Model 2 adjusted for model 1 variables in addition to waist circumference. ‡Model 3 adjusted for model 1 and model 2 variables in addition to leg length. §Model 4 adjusted for model 1, model 2, and model 3 variables in addition to poverty index ratio. |Significant differences vs. women with diagnosed diabetes at P < 0.05.

and 36 years, respectively; P < 0.0001) and more often reported non-Hispanic black ethnicity (P < 0.0001), a family history of diabetes (P < 0.0001), the least favorable poverty-to-income ratio (P = 0.0036), the fewest number of alcoholic beverages per day (P < 0.0001), and the greatest waist circumference (P < 0.0001). Waist circumference increased across unaffected women, women with hGDM, and women with diabetes from 85.9 to 92.4 to 103.2 cm, respectively (P < 0.0001). Few women were nulliparous; all of the women in the hGDM and diabetic groups and >91% of unaffected women had at least one delivery. Women with diabetes had the highest ferritin measurements compared with women with hGDM and unaffected women (135.1 vs. 59.4 and 62.7 ng/ml, respectively; P < 0.0001), the highest leukocyte counts (8.4 vs. 8.0 and 7.2 cells/ml, respectively; P < 0.0001), and the highest CRP levels (0.88 vs. 0.51 and 0.40 mg/l, respectively; P = 0.0012).

When we adjusted for patient covariates, the most striking differences were seen between women with diabetes and unaffected women. After adjustment for demographic and behavioral factors (Table 1, model 1), women with diabetes had greater ferritin, leukocyte, and CRP measurements than unaffected women. After further adjustment for waist circumference (Table 1, model 2), women with diabetes had greater inflammatory marker levels than unaffected women, but the differences in CRP were no longer significant. As in unadjusted analyses, we observed no significant differences in inflammatory markers between unaffected women and women with hGDM. Women with hGDM had lower inflammatory markers than women with diabetes, but the differences were statistically significant only for ferritin, not for CRP or leukocyte counts.

**CONCLUSIONS** — This population-based cross-sectional study suggests that differences in inflammatory markers are greatest between women with diagnosed diabetes and unaffected women. Ferritin levels distinguished women with diabetes from unaffected women and women with hGDM before and after adjustment for other risk factors, but ferritin did not differ significantly between unaffected women and women with hGDM.

Our findings are consistent with results from previous studies of women with hGDM versus unaffected women that have not shown robust associations after adjustment of BMI or other markers of adiposity (1–4). Our findings are also consistent with studies that compared unaffected women and women with diabetes that found more robust associations (10).

This study has several limitations. NHANES III was cross-sectional and may not reflect disease progression in individuals. It is possible that the relationship between inflammation and hGDM would have been stronger had we been able to distinguish which women would go on to develop diabetes and if we were able to adjust for time since delivery. It is also possible that examination of other markers with greater discrimination would have shown an association. There may have been unmeasured confounding with other inflammatory conditions not included in our analysis. Finally, the number of women with hGDM was greater than in most other reports, though still small, leading us to report group differences only when the 95% CIs were mutually exclusive.

In conclusion, the differences in inflammatory markers between women with hGDM and unaffected women were much smaller than those between women with diabetes and unaffected women. Prospective longitudinal studies using inflammatory markers with greater discrimination may elucidate how inflammation progresses in women who develop GDM and then diabetes after delivery.

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