Parity and the Association With Diabetes in Older Women

Angela G. Fowler-Brown, MD1
Ian H. de Boer, MD2
Janet M. Catov, PhD1
Mercedes R. Carnethon, PhD4

OBJECTIVE — To examine the relationship of parity with diabetes and markers of glucose homeostasis in older women.

RESEARCH DESIGN AND METHODS — We used data from the female participants in the Cardiovascular Health Study, a longitudinal cohort of adults aged ≥65 years. These data included an assessment of parity (baseline) and fasting serum levels of glucose, insulin, and medication use (baseline and follow-up). We estimated both the cross-sectional relationship of parity with baseline diabetes and the relationship of parity with incident diabetes.

RESULTS — In unadjusted analyses, women with grand multiparity (≥5 live births) had a higher prevalence of diabetes at baseline compared with those with fewer births and with nulliparous women (25 vs. 12 vs. 15%; P < 0.001). In regression models controlling for age and race, grand multiparity was associated with increased prevalence of diabetes (prevalence ratio 1.57 [95% CI 1.20–2.06]), with addition of demographic and clinical factors to the model, the association was attenuated (1.33 [1.00–1.77]). In final models that included body anthropometrics, the association was no longer significant (1.21 [0.86–1.49]). In those without diabetes at baseline, parity was not associated with incident diabetes or with fasting glucose; however, there was a modest association of parity with fasting insulin and homeostasis assessment model of insulin resistance.

CONCLUSIONS — Grand multiparity is associated with diabetes in elderly women in cross-sectional analyses. This relationship seems to be confounded and/or mediated by variation in body weight and sociodemographic factors by parity status. In older nondiabetic women, higher parity does not pose an ongoing risk of developing diabetes.

Diabetes Care 33:1778–1782, 2010

Pregnancy is a time-limited condition; however, there is evidence that child-bearing could have a long-term impact on the health of women. The dramatic alterations in physiology and metabolism associated with the state of pregnancy have sparked questions about the association of child-bearing with the subsequent risk of conditions such as diabetes.

Pregnancy induces a state of insulin resistance in a woman’s peripheral tissues. In susceptible nondiabetic women, insulin resistance may be severe enough to cause gestational diabetes mellitus. It is generally assumed that pregnancy-associated insulin resistance resolves after parturition, but subtle metabolic changes could persist, leading to increased risk for diabetes in the future.

Researchers examining the relationship between parity and risk of diabetes have come to discordant conclusions. Some studies have suggested a link between higher parity and increased risk of future diabetes (1–5). However, other studies have demonstrated no increased risk of diabetes associated with child-bearing (1.6). In the face of conflicting data, some researchers have suggested that the relationship of increased parity with higher diabetes risk that is observed in some studies is confounded or mediated by other factors, such as body weight and socioeconomic status (6).

The aim of our study was to examine the relationship between parity and diabetes in older women, who have the highest prevalence of diabetes. We hypothesized that higher parity was positively associated with the prevalence of diabetes in older women. We studied the influence of potential confounding variables, such as education, race, and alcohol intake, on our hypothesized association between parity and diabetes as well as possible mediators of the association, such as BMI and waist circumference. Finally, we tested the influence of parity on biochemical markers of glucose homeostasis, such as fasting serum glucose and insulin levels, and the homeostasis model assessment of insulin resistance (HOMA-IR) in those without diabetes.

RESEARCH DESIGN AND METHODS — The Cardiovascular Health Study (CHS) is a National Institutes of Health National Heart, Lung, and Blood Institute–funded, population-based longitudinal study of adults aged ≥65 years (7). (A full list of principal CHS investigators and institutions can be found at http://www.chs-nhlbi.org/pi.htm.) The main objective of the study was to study the onset and course of coronary heart disease and stroke. Participants were sampled from Medicare eligibility lists in four U.S. communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. CHS initially recruited 5,201 men and women in 1989–1990. Subsequently, an additional 687 black women were recruited in 1992–1993. Participants underwent extensive physical and labo-
Table 1—Baseline characteristics of women enrolled in CHS

|                      | Total          | Nulliparous     | 1–2 live births | 3–4 live births | ≥5 live births |
|----------------------|----------------|-----------------|-----------------|-----------------|---------------|
| Age (years)          | 72.5 ± 5.4     | 73.7 ± 5.9      | 72.9 ± 5.9      | 71.2 ± 4.7      | 71.8 ± 5.3    |
| Black race           | 500 (15.6)     | 118 (20.8)      | 197 (13.6)      | 97 (10.9)       | 88 (28.2)     |
| Less than high school education | 921 (28.7) | 161 (28.4)      | 383 (26.5)      | 222 (25.0)      | 155 (49.7)    |
| Current smoking      | 404 (12.6)     | 73 (12.9)       | 184 (12.7)      | 112 (12.6)      | 35 (11.2)     |
| Alcohol abstinence   | 1,791 (55.8)   | 317 (55.8)      | 788 (54.6)      | 464 (52.3)      | 222 (71.2)    |
| BMI (kg/m²)          | 26.8 ± 5.3     | 26.6 ± 5.4      | 26.4 ± 5.2      | 27.0 ± 5.2      | 28.5 ± 5.5    |
| Waist circumference (cm) | 92.0 ± 14.4   | 92.0 ± 14.7     | 90.9 ± 14.2     | 92.3 ± 13.7     | 96.8 ± 15.5   |
| Height (cm)          | 158.8 ± 6.2    | 158.4 ± 6.7     | 158.5 ± 6.2     | 159.5 ± 5.9     | 159.1 ± 6.4   |
| BMI age 50 years (kg/m²) | 25.3 ± 3.0    | 25.3 ± 3.1      | 25.1 ± 3.0      | 25.2 ± 3.0      | 26.2 ± 3.1    |
| C-reactive protein (mg/l) | 4.8 ± 7.6     | 5.0 ± 8.0       | 4.7 ± 7.0       | 4.7 ± 8.5       | 5.1 ± 6.9     |
| Diabetes             | 440 (14.0)     | 86 (15.1)       | 175 (12.1)      | 111 (12.5)      | 78 (25.0)     |

Data are means ± SD or n (%).

Diabetes was defined as the first use of diabetes medications or by a criterion of fasting blood glucose of ≥126 mg/dl during the follow-up years for which fasting blood glucose was available. Participants were followed for incident diabetes outcome through 2007. Insulin resistance was estimated at baseline using HOMA-IR, calculated by the following formula: HOMA-IR = fasting serum insulin (microunits per milliliter) × fasting plasma glucose (millimoles per liter)/22.5.

Statistical analysis

We used descriptive statistics to characterize participant's demographic characteristics at baseline. To examine the relationship between parity and prevalent diabetes, we estimated the prevalence ratios using generalized linear models with a log-link and Poisson distribution (10). Models using a binomial link yielded similar point estimates and confidence intervals but did not converge in all cases. To examine the association between parity and incident diabetes in those without diabetes at baseline, we used Cox proportional hazard models to estimate hazard risk ratios related to parity.

For both the incident and prevalent diabetes outcomes, we examined the relationship between parity and outcomes in multivariable sequentially adjusted models. Initial multivariable models controlled for age and race. The next models controlled for several possible confounders including age, race, income (three categories), education (more than high school, high school, or less than high school), marital status (married, single, widowed, or divorced), height (centimeters) smoking (current, never, or former), study site, and alcohol intake (user/abstainer). Our final models contained all of the previously listed potential confounders and in addition controlled for body anthropometrics as potential mediators (baseline BMI [calculated from measured weight and height], and measured waist circumference, and self-report of BMI at age 50 years; because of missing data, age 50 years BMI was imputed from age, race, and baseline BMI in 128 women). In these final models, we examined the degree of mediation using the SAS mediate macro (11).

We also conducted multivariable linear regression analyses to examine whether parity was associated with baseline fasting serum glucose, insulin levels, and HOMA-IR only among those without diabetes at baseline. Because insulin and HOMA-IR were, as expected, right-skewed, both were log-transformed to improve normality.

All analyses were conducted with SAS statistical software (version 9.2).

RESULTS — Baseline characteristics of our sample are presented in Table 1. The baseline age of our sample was 72.5 years. Those with grand multiparity (≥5 livebirths) were more likely to be black, have larger BMI and waist circumferences at baseline, more likely to abstain from alcohol, and less likely to have graduated from high school. In unadjusted analyses, diabetes was considerably more prevalent in women with grand multiparity (25%) compared with those with fewer livebirths (12%) and with those who were nulliparous (15%; P < 0.001).
**Parity and diabetes**

Table 2—Multivariable models of parity and prevalent diabetes

| Model 1:         | Model 2:   | Model 3: all potential confounders and anthropometrics† |
|------------------|------------|-------------------------------------------------------|
| age and race     | potential confounders* | potential confounders and anthropometrics† |
| All              | 1.0        | 1.0                                                   |
| Nulliparous      | 1.0        | 1.0                                                   |
| 1–2 live births  | 0.85 (0.67–1.08) | 0.85 (0.66–1.09) | 0.87 (0.65–1.06) |
| 3–4 live births  | 0.91 (0.70–1.19) | 0.90 (0.68–1.18) | 0.88 (0.63–1.08) |
| ≥5 live births   | 1.57 (1.20–2.06) | 1.33 (1.00–1.77) | 1.21 (0.86–1.49) |
| Blacks           |            |                                                       |
| Nulliparous      | 1.0        | 1.0                                                   |
| 1–2 live births  | 0.78 (0.51–1.18) | 0.81 (0.54–1.23) | 0.86 (0.58–1.29) |
| 3–4 live births  | 0.93 (0.58–1.49) | 0.91 (0.56–1.50) | 1.02 (0.64–1.64) |
| ≥5 live births   | 1.64 (1.10–2.45) | 1.54 (1.02–2.32) | 1.43 (0.98–2.10) |
| Whites           |            |                                                       |
| Nulliparous      | 1.0        | 1.0                                                   |
| 1–2 live births  | 0.88 (0.66–1.18) | 0.86 (0.62–1.19) | 0.88 (0.64–1.20) |
| 3–4 live births  | 0.92 (0.67–1.26) | 0.89 (0.63–1.26) | 0.84 (0.60–1.18) |
| ≥5 live births   | 1.50 (1.03–2.17) | 1.20 (0.81–1.78) | 1.06 (0.72–1.57) |

Data are prevalence ratio (95% CI). Generalized linear models with a log-link and Poisson distribution are shown. *Model 2: age, race, marital status (4), income (3), education (3), height (in centimeters), alcohol yes/no, clinic (4), and smoking (3). †Model 3: also for BMI, BMI at age 50 years, and waist circumference.

**Parity and prevalent diabetes**

In regression models controlling for age and race, we observed a nearly 60% increase in prevalent diabetes associated with grand multiparity compared with women who were nulliparous (Table 2). Lesser degrees of parity were not associated with prevalent diabetes. After addition of demographic and clinical factors (including measures of socioeconomic status) to the model, the observed increase in prevalent diabetes associated with grand multiparity was reduced to 33% but remained statistically significant. In a final model that controlled for body anthropometrics, the prevalence of diabetes associated with grand multiparity was 21% higher than that for the referent nulliparous group and no longer significant. The degree of attenuation was somewhat less if we adjusted only for BMI recalled from age 50 years rather than measured BMI also (prevalence ratio 1.27 [95% CI, 0.96–1.68]), consistent with a greater degree of measurement error in recalled BMI. Comparing generalized estimating equation models with and without adjustment for anthropometrics, these factors explained 44% ([2–86%]; P = 0.04) of the adjusted association of grand multiparity with prevalent diabetes.

We observed similar associations between parity and prevalent diabetes in blacks and whites (Table 2). Although the association of grand multiparity with prevalent diabetes was numerically stronger in blacks, interaction terms of race and parity were not statistically significant. We did not observe any significant variation in the association of parity with prevalent diabetes among the first in a population-based cohort of older women, helps to elucidate the relationship of parity with diabetes among younger women. We found that grand multiparity (≥5 live births) was associated with higher risk of prevalent diabetes in analyses controlling for age and race. This association was attenuated but continued to be statistically significant after adjustment for demographic and clinical factors. When anthropometric measures were added to the models, the magnitude of association was further attenuated and became statistically insignificant. Thus, the association of grand multiparity with increased prevalence of diabetes seems to be confounded or mediated, in large part, by variation in sociodemographic factors and higher body weight associated with grand multiparity. Lesser degrees of parity were not associated with prevalence of diabetes in older women. Further, we did not observe any significant variation in the association of parity and metabolic markers

Unadjusted analysis suggested a modest trend toward increased fasting insulin and HOMA-IR associated with grandmultiparity, whereas fasting glucose was not significantly associated with parity (Table 4). In multivariable models, controlling for age, race, marital status, income, education, height, alcohol use, clinic site, and smoking, we again observed no association with fasting glucose but a trend toward increased insulin and HOMA-IR with higher categories of parity (P_trend = 0.01 for insulin and 0.02 for HOMA-IR).

In analyses stratified by race, there was no interaction between parity and race and fasting glucose (P = 0.3). Intermediate degrees of parity appeared to have a greater impact on insulin and HOMA-IR in black women than in white women, whereas the reverse was true for grandmultiparity (Table 4). Interaction terms of parity (defined categorically) and race were statistically significant in the adjusted models with log(insulin) and log(HOMA-IR) as the outcome (P = 0.02 for both). When we tested the interaction specifically between race and grandmultiparity, the P values for effect modification by race were 0.90, 0.06, and 0.09 for glucose, log(insulin), and log(HOMA-IR), respectively. The apparent differences by race in the relationship of parity with insulin resistance were not markedly different in analyses that further adjusted for anthropometrics (data not shown).

**Conclusions**—Our study, among the first in a population-based cohort of older women, helps to elucidate the relationship of parity with diabetes among older women. We found that grand multiparity (≥5 live births) was associated with higher risk of prevalent diabetes in analyses controlling for age and race. This association was attenuated but continued to be statistically significant after adjustment for demographic and clinical factors. When anthropometric measures were added to the models, the magnitude of association was further attenuated and became statistically insignificant. Thus, the association of grand multiparity with increased prevalence of diabetes seems to be confounded or mediated, in large part, by variation in sociodemographic factors and higher body weight associated with grand multiparity. Lesser degrees of parity were not associated with prevalence of diabetes in older women. Further, we did not observe any significant variation in the association of parity...
Table 4—Parity and metabolic markers among those without diabetes

| Unadjusted baseline measures of metabolic markers by parity | Fasting glucose (mg/dL) | Log(fasting insulin) (mU/L) | Log(HOMA-IR) |
|-----------------------------------------------------------|-------------------------|----------------------------|--------------|
| Nulliparous                                                | 98.9 ± 10.1             | 2.5 ± 0.4                  | 1.1 ± 0.5    |
| 1–2 live births                                            | 98.4 ± 9.9              | 2.5 ± 0.5                  | 1.1 ± 0.5    |
| 3–4 live births                                            | 98.5 ± 9.4              | 2.5 ± 0.5                  | 1.1 ± 0.5    |
| ≥5 live births                                             | 99.4 ± 10.7             | 2.6 ± 0.5                  | 1.2 ± 0.5    |

| Multivariable models of metabolic markers by parity*       | Fasting glucose | Fasting insulin | HOMA-IR |
|------------------------------------------------------------|----------------|----------------|---------|
| All races                                                  |                |                |         |
| Nulliparous                                                | Referent       | Referent       | Referent|
| 1–2 live births                                            | -0.6 (0.6)     | 0.01 (0.03)    | 0.00 (0.03) |
| 3–4 live births                                            | -0.3 (0.6)     | 0.05 (0.03)    | 0.04 (0.03) |
| ≥5 live births                                             | 0.2 (0.8)      | 0.06 (0.04)    | 0.07 (0.04) |
| Blacks                                                     |                |                |         |
| Nulliparous                                                | Referent       | Referent       | Referent|
| 1–2 live births                                            | 1.7 (1.5)      | 0.15 (0.07)    | 0.17 (0.08) |
| 3–4 live births                                            | 0.2 (1.8)      | 0.10 (0.09)    | 0.10 (0.10) |
| ≥5 live births                                             | 1.3 (2.1)      | 0.03 (0.10)    | 0.04 (0.11) |
| Whites                                                     |                |                |         |
| Nulliparous                                                | Referent       | Referent       | Referent|
| 1–2 live births                                            | -1.0 (0.6)     | -0.02 (0.03)   | -0.03 (0.03) |
| 3–4 live births                                            | -0.5 (0.7)     | 0.03 (0.03)    | 0.02 (0.03) |
| ≥5 live births                                             | -0.1 (0.9)     | 0.07 (0.04)    | 0.07 (0.05) |

Data are means ± SD or β coefficient (SEM). *Multivariable linear regression: models include age, race, marital status (4), income (3), education (3), height (in centimeters), alcohol yes/no, clinic (4), and smoking (3).

parity with diabetes between blacks and whites.

On the other hand, among women who remained free of diabetes into older age, parity was not associated with incident diabetes nor with fasting glucose among those free of diabetes. However, there was a statistically significant, albeit weak in magnitude, association of parity with increased risk of diabetes for example, Selvin et al. (5) examined a cohort of middle-aged black and white women and found that those who had borne ≥5 children had twice the risk of incident diabetes in unadjusted analyses (hazard ratio [HR] 2.10 [95% CI 1.73–2.53]). In their study, the increased risk of diabetes was attenuated but persisted after adjustment for factors including socioeconomic factors and anthropometrics (adjusted HR 1.27 [1.02–1.57]). Consistent with our findings, an earlier study examining the relationship between parity and glucose homeostasis in middle-aged to older women found that after adjustment for covariates, each pregnancy was associated with increased fasting insulin and decreased insulin sensitivity that was not explained by obesity and body composition measures (12). This study suggested that changes in insulin sensitivity related to parity persist many years after childbearing.

However, other studies have not shown similar effects. For example, Manson et al. (6) examined a cohort of >120,000 registered nurses, aged 30–55 years at baseline. Similar to our findings, their unadjusted analyses suggested that women with high parity (defined in their study as ≥6 live births) had a 50% higher risk of incident diabetes over 12 years of follow-up. However, after adjustment for age and BMI, they observed no significant relationship between parity and incident diabetes. Their results are concordant with ours in connecting high levels of parity with diabetes in middle age and in the finding that the effects of high parity are largely related to the impact on midlife weight. Together, ours and the previous study emphasize the importance of weight management targeted to multiparous women.

Our study has several strengths, including analysis of a large biracial sample. We also had standardized measures of several potential confounding and mediating variables, including directly measured weight and waist circumference, allowing us to examine the mechanism of association of our relationship of interest. However, there are several limitations to be considered. First, some information that may have been helpful in the interpretation of the results, such as history of gestational diabetes mellitus, was not available. Next, our results may not be generalizable to other races and ethnicities, such as Native Americans and Asians (13,14), and we may have had limited power to detect differences between blacks and whites. In addition, we had a limited number of cases of incident diabetes, particularly among grand multiparous women, 25% of whom already had diabetes at baseline, limiting our power to detect a small effect of grand multiparity on incident diabetes. Finally, because our analysis examines the relationship between a relatively early life exposure with outcomes much later in life, our results may be influenced by survivor bias. Accordingly, selective survival of women into older age may result in an attenuated measured association of parity with later diabetes outcomes.

In summary, grand multiparity, but not lesser degrees of parity, is associated with prevalent diabetes in elderly women. Much of the higher prevalence of diabetes associated with past child-bearing seems to be mediated (or confounded) by the heavier BMI associated with grand multiparity. This finding presents an opportunity for education and intervention related to weight control among grand multiparous women to reduce diabetes prevalence. In nondiabetic women who have reached older age, higher parity is not associated with increased risk of developing diabetes but tended to be associated with small increases in fasting insulin and HOMA-IR. Additional longitudinal studies designed specifically to
study the long-term medical effects of child-bearing should be conducted. Future studies should include multiple longitudinal measures of diabetes related factors over time to better understand the interplay of risk factors over time.

Acknowledgments—This research was supported by the National Institute on Aging (grant AG-023629). Additional support was provided through the National Institute on Aging (grants R01 AG-15928, R01-AG-20098, and AG-027058), the National Heart, Lung and Blood Institute (grant R01-HL-075366), and the University of Pittsburgh Claude D. Pepper Older Americans Independence Center (grant P30-AH-024827). C.H.S. was supported by the National Heart, Lung and Blood Institute (contract N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01-HC-15103, N01-HC-55222, N01-HC-75150, and N01-HC-45133 and grant U01-HL-080295) with additional contribution from the National Institute of Neurological Disorders and Stroke.

No potential conflicts of interest relevant to this article were reported.

References
1. Gunderson EP, Lewis CE, Tsai AL, Chiang V, Carnethon M, Quesenberry CP Jr, Sidney S. A 20-year prospective study of childbearing and incidence of diabetes in young women, controlling for glycemia before conception: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Diabetes 2007;56:2990–2996
2. Beral V. Long term effects of childbearing on health. J Epidemiol Community Health 1985;39:343–346
3. Green A, Beral V, Moser K. Mortality in women in relation to their childbearing history. BMJ 1988;297:391–395
4. Ness RB, Harris T, Cobb J, Flegal KM, Kelsey JL, Balanger A, Stunkard AJ, D'Agostino RB. Number of pregnancies and the subsequent risk of cardiovascular disease. N Engl J Med 1993;328:1528–1533
5. Nicholson WK, Asao K, Brancati F, Coresh J, Pankow JS, Powe NR. Parity and risk of type 2 diabetes: the Atherosclerosis Risk in Communities Study. Diabetes Care 2006;29:2349–2354
6. Manson JE, Rimm EB, Colditz GA, Stampfer MJ, Willett WC, Arky RA, Rosner B, Hennekens CH, Speizer FE. Parity and incidence of non-insulin-dependent diabetes mellitus. Am J Med 1992;93:13–18
7. Fried LP, Borhani NO, Enright P, Furbeg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A, et al. The Cardiovascular Health Study: design and rationale. Ann Epidemiol 1991;1:263–276
8. Psaty BM, Lee M, Savage PJ, Rutan GH, German PS, Lyles M. Assessing the use of medications in the elderly: methods and initial experience in the Cardiovascular Health Study. The Cardiovascular Health Study Collaborative Research Group. J Clin Epidemiol 1992;45:683–692
9. Cushman M, Cornell ES, Howard PR, Bovill EG, Tracy RP. Laboratory methods and quality assurance in the Cardiovascular Health Study. Clin Chem 1995;41:264–270
10. Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. Am J Epidemiol 2005;162:199–200
11. Hertzmark E, Pazars M, Spiegelman D. The SAS MEDIATE macro. [article online], 2009. Available from http://www.hsph.harvard.edu/faculty/spiegelman/mediate/mediate.pdf. Accessed 21 September 2009
12. Kritz-Silverstein D, Barrett-Connor E, Wingard DL, Friedlander NJ. Relation of pregnancy history to insulin levels in older, nondiabetic women. Am J Epidemiol 1994;140:375–382
13. Hanley AJ, McKeown-Eyssen G, Harris SB, Hegele RA, Wolever TM, Kwan J, Zinman B. Association of parity with risk of type 2 diabetes and related metabolic disorders. Diabetes Care 2002;25:690–695
14. Charles MA, Pettitt DJ, McCance DR, Hanson RL, Bennett PH, Knowler WC. Gravidity, obesity, and non-insulin-dependent diabetes among Pima Indian women. Am J Med 1994;97:250–255