Parity and Carotid Artery Atherosclerosis in Elderly Women

The Rotterdam Study

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Background and Purpose—It has been postulated that physiological changes in the cardiovascular system, lipids, and glucose metabolism during pregnancy may increase subsequent risk of cardiovascular disease. Examination of the association between parity and risk factors for atherosclerosis may contribute information regarding possible mechanisms.

Methods—The relationship of parity with cardiovascular risk factors and the presence of carotid atherosclerosis was examined in the Rotterdam Study, a population-based study comprising 4878 women aged 55 years and older. Carotid atherosclerosis was assessed by ultrasonographic detection of plaques in the common carotid artery and bifurcation. Logistic regression models were used to compute odds ratios and 95% confidence intervals, adjusted for confounding factors.

Results—Parity was inversely associated with high-density lipoprotein cholesterol, and alcohol intake. Parity was positively associated with body mass index, total/HDL cholesterol ratio, insulin resistance, age at menopause, and socioeconomic status. Relative to nulliparous women, parous women had 36% (9% to 71%) greater risk of carotid atherosclerosis, rising to 64% in women with ≥4 children (19% to 127%). Adjustment for known cardiovascular risk factors, including insulin resistance and current lipid levels, did not diminish the magnitude of this association.

Conclusions—Data demonstrated that there is a positive association between parity and risk of carotid artery plaques in elderly women and, further, that high parity is associated with lower HDL cholesterol levels and higher glucose/insulin ratios long after childbearing has ceased. (Stroke. 2001;32:2259-2264.)

Key Words: atherosclerosis ■ cardiovascular diseases ■ lipids ■ parity ■ risk factors ■ women

The relationship between parity and risk of cardiovascular disease has been investigated in several studies. Increased parity was associated with increased risk of cardiovascular disease in some studies, whereas other studies have shown either no association or an increased risk associated with nulliparity. Although the evidence is conflicting, on balance the evidence favors the hypothesis that risk of cardiovascular disease increases with increasing parity.

Pregnancy is associated with structural and functional changes in the cardiovascular system. Changes in lipoprotein concentrations and insulin are of particular interest, given that lipid level (HDL cholesterol, triglycerides) and diabetes are much stronger risk factors for cardiovascular disease in women than in men. In addition, the adverse effect of pregnancy on lipid levels has been reported in 2 previous studies. Total cholesterol, LDL cholesterol, and triglycerides progressively increase during pregnancy. While triglycerides rapidly decrease during the postpartum period, total cholesterol and LDL may require much longer to return to baseline. Pregnancy has been shown to have an unfavorable effect on HDL, which peaks at mid-gestation and then falls to levels below baseline. Pregnancy is also associated with increased insulin levels, and this increase tends to persist after pregnancy. Changes in lipoprotein levels and glucose metabolism suggest a potential mechanism for the observed association between parity and cardiovascular disease.

The association between parity and coronary heart disease is difficult to study because of the long lag time between childbirth and the occurrence of coronary heart disease in women. Consequently, investigations of this association in relatively young women have been limited by a low incidence of cardiovascular disease. Atherosclerosis is present long before symptomatic coronary heart disease develops, and its presence in the carotid arteries has been shown to be a marker of generalized atherosclerosis throughout the body, including...
the large coronary arteries.\textsuperscript{16–18} Studying atherosclerosis rather than symptomatic cardiovascular disease should increase the power to detect the association of parity with cardiovascular disease.

We investigated the association between parity and the presence of carotid atherosclerosis in 2681 postmenopausal women, aged 55 to 99 years, who participated in the Rotterdam Study.

Subjects and Methods

Study Population

The Rotterdam Study is a population-based prospective cohort study among 7983 men and women aged \( \geq 55 \) years, living on Ommoord, a suburb of Rotterdam, the Netherlands. The rationale and design of the Rotterdam Study have been described previously.\textsuperscript{19} Briefly, the Rotterdam Study is designed to investigate the prevalence, incidence, and determinants of cardiovascular, neurological, locomotor, and ophthalmological disease in the elderly. Baseline measurements were carried out from March 1990 to July 1993. The overall response rate was 78%.

Measurements

Trained research assistants interviewed the participants in their homes. Information on current health status, medical history, medication use, and smoking status was obtained by computerized questionnaire. The computerized interview also included questions on parity and socioeconomic status: education, occupation of the head of household, and household income in 13 predefined categories. Equivalent household income was defined as the midpoint of each income category divided by the number of persons living on that income raised to the power 0.36.\textsuperscript{20}

The home interview was followed by 2 visits to the research center. Height and weight were measured while subjects wore indoor clothes without shoes. Body mass index (BMI) was calculated as weight divided by height squared. A random zero sphygmomanometer was used to measure blood pressure. The average of 2 consecutive measurements was used to calculate the diastolic and systolic pressures. Hypertension was defined as systolic pressure \( \geq 160 \) mm Hg, or diastolic pressure \( \geq 95 \) mm Hg, or use of antihypertensive medication.

Participants came to the research center throughout the day. Blood was drawn by venepuncture, and subjects not using antidiabetic medications received a glucose drink of 75 g of glucose. Two hours later, a second blood sample was obtained. Postload glucose levels were measured by the glucose hexokinase method and postload insulin levels by radioimmunoassay (Medgenix Diagnostics), as described previously.\textsuperscript{21} Diabetes was defined as a random or postload blood glucose level \( >11.0 \) mmol/L and/or use of antidiabetic drugs (oral or insulin). Insulin resistance was assessed by calculating the 2-hour postload insulin/glucose ratio.\textsuperscript{22}

Total serum cholesterol was determined by an automated enzymatic procedure in a nonfasting blood sample.\textsuperscript{23} HDL cholesterol was measured after precipitation of the non-HDL fraction with phosphotungstic acid/magnesium. All cholesterol measurements were carried out in the laboratory of the Department of Epidemiology and Biostatistics (Erasmus University Medical School), which participated in the Dutch National Cholesterol Standardization Program. The Dutch National Cholesterol Standardization Program is based on the program of the Centers for Disease Control, Lipid Standardization Laboratory, in Atlanta, Ga.

Carotid atherosclerosis was assessed by carotid duplex scan ultrasonographic investigation of the carotid arteries, with use of a 7.5 MHz linear array transducer (ATL, Ultramark IV). The common and internal carotid arteries and the carotid bifurcation of the left and right sides were evaluated online for the presence (yes/no) of atherosclerotic lesions on both the near and the far wall of the carotid artery. Plaques were defined as focal widening relative to adjacent segments, with protrusions into the lumen, either composed only of calcified deposits or a combination of calcifications and noncalcified material. No attempt was made to quantify the size or extent of the lesions. Carotid atherosclerosis was defined as the presence of plaques at 1 or more sites.

The procedure for measurement of intima-media thickness (IMT) has been previously described.\textsuperscript{24} Briefly, the interfaces of the far and near wall of the distal common carotid artery are marked offline over a length of 10 mm with a cursor. The beginning of the dilatation of the distal common carotid artery served as a reference point for the start of the measurement. This method permits the determinations of mean as well as maximal values for IMT. The average of the IMT of each of 3 frozen images was calculated. For each subject, the mean IMT of the far and near wall of both the left and right side was computed. In addition, the maximal thickness (highest value of the 4 measures) was computed. Reproducibility studies have been performed between paired measurements of sonographers, readers, and visits. The mean differences (SD) in far-wall IMT of the common carotid artery were \(-0.005\) mm (0.09), 0.060 mm (0.05) and \(-0.033\) mm (0.12), respectively.\textsuperscript{25}

Ultrasonographic scans of the carotid arteries were conducted on 3569 (83\%) of the 4274 women who visited the research center. Online measurements of carotid plaques were not performed until October 1, 1991; as a result, online measurements were available in only 2313 subjects.

Offline measurements of carotid plaques were available for an additional random sample of 368 women, resulting in a total of 2681 women with plaque measurements available. IMT readings were obtained in a random sample of 934 women.

Subjects with incomplete data for the variables of interest, eg, parity (9), hypertension (1), smoking (51), socioeconomic status (13), lipids (36), BMI (43), and insulin/glucose ratio (391), were excluded from the analysis (544 exclusions in total).

Statistical Analyses

ANCOVA was used to compare means of continuous variables, adjusted for age. For lipid measures and postload insulin/glucose ratio, additional adjustment was made for BMI. Categorical variables were tested for differences by using the \( \chi^2 \) test and \( \chi^2 \) test for trend. Logistic regression analysis was used to estimate odds ratios and 95% confidence intervals. The dependent variable was the presence or absence of carotid plaques. The independent variable of interest was parity. In the multivariate model, adjustments were made for the following variables: total cholesterol, HDL cholesterol, total/HDL cholesterol ratio, hypertension, systolic and diastolic blood pressure, diabetes, age, hormone replacement therapy, age at menopause, socioeconomic status, BMI, waist-to-hip ratio, and smoking status (never, current, former). To ensure adequate numbers in all categories, parity was divided into 4 groups: no children, 1 child, 2 or 3 children, 4 or more children. Four levels of education were defined. The lowest category comprised women with only primary-level education, and the highest level included women with higher vocational training or university education. Four levels of occupational status were defined on the basis of the occupation of the head of the household: professional, administrative/managerial, skilled, and unskilled labor occupations.

ANCOVA, adjusted for the same covariates used in the multivariate logistic regression analysis, was used to evaluate the association between parity and mean or maximum IMT.

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc), version 7.5. All probability values are 2-sided, and \( P<0.05 \) was chosen as the cutoff for statistical significance.

Results

Parity in this population ranged from 0 to 16 children. Nulliparous women (968) constituted 21.5% of the population. The distribution of known cardiovascular risk factors with parity is illustrated in Table 1. Age decreased with increasing parity. Age at menopause, BMI, and waist-to-hip
ratio increased with increasing parity. Blood pressure and prevalence of hypertension did not vary with parity. There was a significant trend toward lower HDL levels and higher total/HDL cholesterol ratios with increasing parity. Additional adjustment for BMI, smoking, and socioeconomic status did not alter this association. There was also a significant trend toward higher 2-hour postload insulin/glucose ratios with increasing parity ($P < 0.003$), which remained significant after adjustment for socioeconomic status and smoking. However, after adjustment for BMI and waist-to-hip ratio, the difference in insulin/glucose ratio across parity groups decreased somewhat ($P = 0.087$ and $0.057$, respectively). Alcohol consumption decreased with increasing parity, while the prevalence of diabetes mellitus did not show any association with parity. The prevalence of current smokers and former smokers was lowest in women with $\geq 4$ children. Socioeconomic status, measured by education, occupational status, and mean equivalent household income decreased with increasing parity. Although this trend was statistically significant for education and occupational status, it did not reach statistical significance for mean equivalent household income.

Logistic regression analysis of the association between parity and carotid artery atherosclerosis yielded an age-adjusted OR of $1.05$ (95% CI $1.00$ to $1.11$) per live birth. Additional adjustment for lipid levels and glucose metabolism (insulin, insulin/glucose ratio) did not alter the magnitude of the association (OR $1.06$, 95% CI $1.01$ to $1.12$). The multivariate adjusted model included age at baseline, smoking status (current, former, never), socioeconomic status (education level), hypertension, diastolic and systolic blood pressures, BMI, lipid levels (total and HDL cholesterol), and insulin/glucose ratio. The results in Table 2 indicate that for every live birth, risk of carotid artery plaques increased by $10\%$ (95% CI $4\%$ to $17\%$). Parous women have a $36\%$ greater risk of carotid artery plaques relative to nulliparous women (95% CI $9\%$ to $71\%$).
Because lower parity was associated with higher levels of education, income, and occupational status, all 3 measures of socioeconomic status were tested to determine whether 1 or more of the measures altered the observed association between parity and carotid artery plaques. Of the 3 measures, education level showed the strongest association with parity. Nevertheless, when adjusted for age, it was not a significant predictor of outcome, nor did it modify the observed association between parity and carotid artery plaques.

For the random sample of 934 women, IMT measurements by parity group are presented in Table 3. There was a trend to increased mean and maximum IMT with increased parity, which remained significant after adjustment for covariates ($P=0.005, P=0.001$, respectively).

**Discussion**

Our analysis indicates that risk for carotid artery atherosclerosis is 36% higher in parous than nulliparous women and increases to 64% in women with $\geq 4$ children. The IMT results in a smaller group of randomly selected women corroborate this finding by demonstrating greater mean and maximum IMT measures in multiparous women. In addition, we have demonstrated that parity is inversely associated with HDL cholesterol and positively associated with the total/HDL cholesterol ratio and postload insulin/glucose ratio.

Before interpreting these results, several issues need to be addressed. Because the Rotterdam Study is a large cohort study in an elderly population, there is a possibility of survival bias. Women had to survive until $\geq 55$ years of age to enter our study. If parity were indeed associated with carotid artery atherosclerosis, complications such as fatal stroke in parous women would bias our results by underestimating the associations.

The distribution of several known risk factors—smoking, socioeconomic status, alcohol intake, and BMI—varied by parity level. These factors are, therefore, potential confounders or intermediates of the association between parity and carotid artery atherosclerosis. Although we controlled for these factors in our analysis, residual confounding, due to imprecise measurement of the confounders, may still be present. In addition, measurements taken at baseline (mean age 72 years) may not reflect exposure levels during childbearing years. In addition to measurement error of the covariates, measurement error of the outcome variable must be considered. However, the presence or absence of carotid artery plaques is unlikely to be subject to much error. Duplex imaging is an accurate and sensitive method for noninvasive detection of atherosclerotic plaques in the carotid artery. 

Work by previous authors supports the use of this measure as a proxy for generalized atherosclerosis. Plaque measurements were available for only 75% of women who visited the research center. However, the missing plaque data resulted from logistic problems and is, therefore, considered random.

Exposure information obtained through self-report can be susceptible to systematic error. Parity data in the Rotterdam Study was obtained by self-report. However, there is no apparent reason why women with ultrasonographic evidence of carotid artery plaques should report parity differently from those without evidence of plaques.

This is the first study to evaluate the association between parity and carotid artery atherosclerosis. Most previous studies, which have focused on the association between parity and symptomatic coronary heart disease, have yielded contradictory results. Studies by Beral and Ness et al also examined the association between parity and cerebrovascular disease. Again, the results were conflicting; Beral observed a higher cerebrovascular mortality rate in parous compared with nulliparous women, while Ness et al did not find an association.

A recent study, using data from the first National Health and Nutrition Examination Survey (1971 to 1975), was designed to examine the effect of parity on subsequent risk of stroke. After adjusting for stroke risk factors, women with $\geq 6$ pregnancies had 30% greater risk of stroke compared with nulliparous women (95% CI 0.9 to 1.9).

The demonstration of an inverse relationship between HDL cholesterol levels and parity in the Rotterdam Study is consistent with results in 2 other studies in which the relationship between parity and lipoproteins has been examined. Both studies identified significantly lower HDL cholesterol levels in parous women than nulliparous women at 1 and 2 years after childbirth. The study by van Stiphout also demonstrated that lower levels of HDL persisted up to 6 years after childbirth. Our data are the first to provide evidence that lower HDL levels following pregnancy persist for decades after childbearing has ceased.

High circulating levels of insulin have been associated with the development of CVD in some studies but not in others. Our results demonstrate that insulin resistance, as measured by the 2-hour postload insulin/glucose ratio,...
creases with increased parity. However, following adjustment for BMI or waist-hip-ratio, the mean ratio in the nulliparous group increased to 8.7, whereas the ratio in the highest parity group decreased to 9.5 (P for trend=0.087). This suggests that part of the difference in insulin/glucose levels was due to differences in BMI across parity levels. This concurs with the suggestion that the observed association is mediated by obesity or postpregnancy alterations in the distribution of body fat, as measured by waist-to-hip ratio.33 Our results are in contrast to those from an earlier study by Kritz-Silverstein,34 which concluded that the association between increased insulin resistance and increased parity was independent of BMI and WHR.

Given the association of parity with an atherogenic lipid profile and insulin resistance, it is reasonable to speculate that lipids and/or insulin resistance might mediate the observed association between parity and carotid artery atherosclerosis. However, adjustment for lipid levels and insulin/glucose ratio did not alter the magnitude of the association, nor did adjustment for other cardiovascular risk factors. This finding is in contrast to results obtained by Qureshi et al,28 in which there was attenuation of the magnitude of the association between parity and stroke after adjustment for risk factor levels. In the study by Qureshi et al, however, heart disease was included as one of the covariates in the adjusted model. It is also important to note that our study relied on single measurements of serum cholesterol and insulin resistance taken at baseline. These measurements will not be representative of lifelong lipid and insulin levels and certainly will not capture any changes in these levels that occurred more proximal to the pregnancies.

Several authors have speculated that the association between parity and cardiovascular disease may be mediated by socioeconomic status. The Rotterdam Study demonstrates the expected association of lower parity with higher levels of education, income, and occupational status. In a univariate model, socioeconomic status was also a significant predictor of risk or carotid artery atherosclerosis. However, after adjustment for age and other risk factors, socioeconomic status was not an independent predictor, and its inclusion in the final model did not alter the odds ratio for the association between parity and carotid atherosclerosis.

It remains unclear how the association between parity and risk for carotid artery atherosclerosis is mediated. Because the magnitude of the association was modest, further exploration of this relationship will be important to exclude the possibility that parity is merely a marker for unmeasured confounders that account for the elevated risk of carotid artery atherosclerosis in parous women.

In conclusion, data from the Rotterdam Study demonstrate a positive association between parity and risk of carotid artery plaques in elderly women. The Rotterdam Study confirms earlier findings associating parity with adverse effects on lipid and glucose metabolism and extends these observations by noting that higher parity is associated with an atherogenic profile—lower HDL cholesterol levels and higher glucose/insulin ratios—many years after childbearing has ceased.

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