Past oral contraceptive use and angiographic coronary artery disease in postmenopausal women: data from the National Heart, Lung, and Blood Institute–sponsored Women's Ischemia Syndrome Evaluation

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Objective: To evaluate past oral contraceptive use and angiographic coronary artery disease in women.
Setting: Academic medical centers.
Patient(s): Six hundred seventy-two postmenopausal women enrolled in the Women's Ischemia Syndrome Evaluation (WISE) with coronary risk factors undergoing coronary angiography for suspected myocardial ischemia.
Intervention(s): Past oral contraceptive use, assessed by reproductive questionnaire.
Main Outcome Measure(s): Quantitative coronary artery disease, assessed by a core angiography laboratory.
Result(s): Past oral contraceptive use was associated with a lower mean coronary artery disease severity index score (mean ± SD: 11.8 ± 10.3 vs. 18.7 ± 17.3) compared with non–prior users, despite age adjustment. Past oral contraceptive use remained a significant independent negative predictor of coronary artery disease severity when adjusting for coronary risk factors, including age, diabetes mellitus, triglycerides, low-density lipoprotein cholesterol, smoking, aspirin use, and lipid-lowering medication (model $R^2 = 0.19$). The modeling indicated that past oral contraceptive use was associated with a 2.44 lower coronary artery disease severity score index. There was no apparent relationship between duration of past oral contraceptive use and the coronary artery disease severity index score.
Conclusion(s): Past oral contraceptive use is associated with less coronary artery disease, measured by quantitative coronary angiography, among postmenopausal women with suspected myocardial ischemia. These findings suggest that a prospective study should address the hypothesis that past oral contraceptive use during the premenopausal years might offer women protection from atherosclerotic coronary disease later in life. (Fertil Steril® 2006;85:1425–31. ©2006 by American Society for Reproductive Medicine.)

Key Words: Oral contraceptives, coronary artery disease, postmenopausal, atherosclerosis

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Women have a relatively lower age-adjusted risk of coronary artery disease compared with men (1), suggesting that endogenous reproductive hormones play a protective role against coronary artery disease. Animal models (2) and human epidemiological study (3) demonstrate that oophorectomy in the premenopause is a risk factor for accelerated coronary artery disease, though the role of other endogenous reproductive factors, such as menstrual cycling, pregnancy, and total estrogen (E) exposure in coronary artery disease has not been convincingly demonstrated (4).

Hormone therapy has been documented to play a protective role for atherosclerosis in animal models. Primate models using hormone therapy analogous to oral contraceptives in young animals have shown antiatherosclerotic effects (5), and epidemiological study in humans has suggested a protective effect for coronary artery disease in young hormone replacement therapy users after surgical oophorectomy (6), yet recent clinical trials in older postmenopausal women (7–10) have questioned the protective role of reproductive hormones in women. Although it is clear that concurrent oral contraceptive use causes an acute increase in myocardial infarction in patients with pre-existing risk factors (11, 12), insufficient prior data have existed with regard to past oral contraceptive use and subsequent atherosclerotic coronary artery disease, owing to the relatively prolonged onset of atherosclerosis over decades, combined with a relatively short population exposure time (oral contraceptives have only been available since the 1960s).

We undertook a detailed study to examine the relationship between past oral contraceptive use and angiographic coronary artery disease, measured by quantitative coronary angiography, in a large study of women undergoing coronary angiography.

MATERIALS AND METHODS

The Women's Ischemia Syndrome Evaluation (WISE) is a National Heart, Lung and Blood Institutes (NHLBI)-sponsored four-center study that aims to improve the diagnostic reliability of cardiovascular testing in the evaluation of ischemic heart disease in women. Women with chest pain symptoms or suspected ischemia undergo an initial evaluation that includes coronary angiography as well as collection of demographic, medical history, psychosocial, symptom, and physical activity data (13), as described previously (14). Blood for reproductive hormone determinations is drawn after an overnight fast in close proximity to the WISE testing.

Reproductive Status Questionnaire

The WISE reproductive status questionnaire has been validated to be an accurate assessment of menopausal status (14) and current hormone therapy use (15), using both a detailed questionnaire and validated steroid and protein assay methods for total E_2, bioavailable E_2, estrone, P, FSH, and LH (16). The WISE reproductive status questionnaire includes a detailed questionnaire that assesses history of menarche, date of last menstrual period, prior menstrual cycling patterns, prior reproductive events (pregnancy, hysterectomy, and oophorectomy), current and prior perimenopausal symptoms, and current and past oral contraceptive or hormone replacement therapy use.

Because we were interested in evaluating relatively long-term associations between past premenopausal use of oral contraceptives and angiographic coronary artery disease, only postmenopausal women were included in the current analysis. Among the WISE women without a history of hysterectomy or oophorectomy, the mean age at the last menstrual cycle was 49.1 years in nonsmokers, compared with 47.7 years in smokers, thus we imputed these menopausal ages for cessation of ovarian cycling in women with a hysterectomy (with and without unilateral oophorectomy).

Measurement of Coronary Artery Disease

Coronary angiography was assessed by a core laboratory used in previous NHLBI-sponsored multicenter trials that have included angiographic outcomes (17). Measurements included quantitative assessment of the presence, severity, and complexity of epicardial coronary artery disease, with previously published methods. For the purposes of these analyses, coronary artery disease was defined as $\geq$70% luminal diameter stenosis in at least one epicardial coronary artery. A continuous coronary artery disease severity score was used to estimate the coronary artery atherosclerosis severity and was calculated with previously validated methods (17).

Because of the strong relationship between age and coronary artery disease and between age and past oral contraceptive use, all *P* values were adjusted for age. For comparing women with and without angiographic coronary artery disease, unadjusted means $\pm$ SDs or frequencies (%) were listed and age-adjusted *P* values obtained by logistic regression. Stepwise linear regression was used to model the coronary artery disease severity index as a function of past oral contraceptive use and other coronary risk factors. A *P* value of $\leq$.05 was considered statistically significant. Because many variables had skewed distributions, log transformations were attempted for both the dependent and independent variables. All analyses were performed with commercial software (SAS 8.2; SAS Institute, Cary, NC).

RESULTS

The demographic data and clinical profile for the 672 postmenopausal women with complete past oral contraceptive use history and coronary angiography results are shown in Table 1. By definition, all women were postmenopausal, and most had at least one cardiac risk factor. Representation of minorities was 18% and included African Americans, Asians, Hispanics, and American Indians. Overall, 39% reported prior oral contraceptive use.

TABLE 1

Demographic and clinical variables.

Variable	Value
Age (y), mean ± SD	62 ± 10
Race (% white)	82
Hypertension (%)	62
Diabetes mellitus (%)	26
Current smoking (%)	18
Lipid-lowering rx (%)	32
Current postmenopausal HT use (%)	44
Past OC use (%)	39
(If yes) Years of OC use, mean ± SD	4.5 ± 5.3
Coronary artery disease (% ≥1 coronary ≥70%)	26
Coronary artery severity score, mean ± SD	16.0 ± 15.3

Note: N = 672. HT = hormone therapy; rx = therapy; OC = oral contraceptive.

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TABLE 2

Reproductive variables, past oral contraceptive use, and coronary artery disease.

Variable	No CAD (n = 498)	CAD (≥70%) (n = 174)	*P*
Age (y)	61 ± 9	66 ± 9	<.0001
Menarche age (y)	12.6 ± 1.8	12.8 ± 1.8	.61
Regular periods	80	84	.63
No. of live births	2.9 ± 1.9	3.2 ± 2.2	.25
No. of miscarriages	0.7 ± 1.3	0.7 ± 1.6	.92
Menopausal age[a] (y)	44 ± 8	46 ± 8	.20
Prior oral contraceptive use	44	26	.06

Note: Values are mean ± SD or %. All *P* values are age-adjusted. CAD = coronary artery disease.

[a] Menopausal age includes natural and surgical menopause.

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Reproductive Variables, Oral Contraceptive Use, and Angiographic Coronary Artery Disease

Women in the no coronary artery disease group (n = 498) were younger compared with those in the coronary artery disease group (n = 174). Nevertheless, there were no significant differences between the two groups in term of age of menarche or menopause, number of live births, or miscarriages (Table 2), though there was a trend toward greater prior oral contraceptive use in the no coronary artery disease group (44% vs. 26%, age-adjusted P=.06). Women with prior oral contraceptive use reported a history of irregular menstrual cycles more frequently compared with women without prior oral contraceptive use (25% vs. 21%, P=.055 after adjusting for age, respectively). Past oral contraceptive use was associated with a significantly lower coronary severity score compared with no prior oral contraceptive use (mean ± SD: 11.8 ± 10.3 vs. 18.7 ± 17.3, P=.002) (Fig. 1).

When evaluated only among prior oral contraceptive users, there was no correlation between the coronary artery disease severity index and duration of past oral contraceptive use (r_s = .002, P=.98). Among the prior users, 116 (44%) reported a total duration of use >3 years, 81 (31%) reported a total duration of use >6 years, and 56 (21%) reported a total duration of use >9 years. With a threshold of a duration of use of >3 years, duration of past oral contraceptive use was not associated with coronary severity score (P=.88). Analysis with the other duration thresholds also failed to demonstrate a relationship. The results did not substantially differ when women with an imputed menopausal age were not included. There were no differences in the coronary artery disease severity score when stratified by the other reproductive variables.

Predictors of Angiographic Coronary Artery Disease Severity Index

We next explored potential confounding variables that might explain this protective association between past oral contra-

FIGURE 1

Coronary artery severity score, assessed by quantitative coronary angiography (17), stratified by reported prior oral contraceptive use.

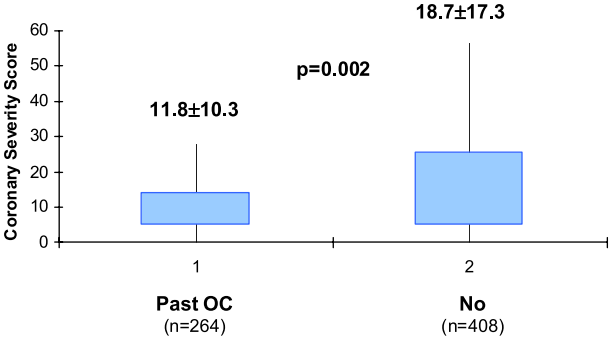

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TABLE 3

Variables significantly associated with past oral Contraceptive use.

Variable	No OC (n = 408)	Prior OC (n = 264)	P
Age	66 ± 9	57 ± 8	<.0001
White	78	88	.0001
Married	53	68	.01
Waist circumference	37.0 ± 7.8	36.6 ± 6.7	.04
No. of live births	2.9 ± 2.0	3.1 ± 2.0	.003
Never pregnant	10	5	.01
Current HT	37	56	.02
Ever HT	51	71	.01
Hx PCO (self-reported)	3	10	.002
Tubal ligation	14	34	.005
Estradiol (pg/mL)	21 ± 20	30 ± 28	.0005
FSH (mIU/mL)	44 ± 22	38 ± 22	.006
Total cholesterol (mg/dL)	192 ± 43	205 ± 45	.01
HDL cholesterol (mg/dL)	53 ± 12	57 ± 14	.0006
Depression	18	34	.009
Migraine headaches	15	32	.003
Antidepressants	13	26	.004
Lipid-lowering rx	38	24	.02
Vitamins C, E, A	27	30	.03

Note: Values are mean ± SD or %. Additional "not significant" variables (after adjusting for age) included education, job status, activity level (measured by a validated physical activity questionnaire [14]), private health care insurance status, self-rated environmental stress, body mass index, metabolic syndrome (defined by NCEP ATP III criteria), blood pressure, history of hypertension, diabetes mellitus, smoking, prior coronary artery disease, other comorbid conditions and medications, bilateral oophorectomy, hysterectomy, other hormones, other lipids. All *P* values are age-adjusted. Hx = history; PCO = polycystic ovary; HDL = high-density lipoprotein; NCEP ATP = National Cholesterol Education Program Adult Treatment Panel.

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ceptive use and coronary artery disease. The women with past oral contraceptive use differed from the women not reporting use in a number of variables (Table 3), including several variables with a beneficial (lower age, higher high-density lipoprotein cholesterol) and multiple variables with adverse (higher cholesterol, lower statin medication use, higher frequency of ethnicity, and higher medical comorbidity) relationships to atherosclerosis. Using stepwise linear regression, we assessed the angiographic coronary artery disease severity score, a measure of atherosclerosis, with demographic variables, including race, education, and occupation, traditional coronary risk factors, prior oral contraceptive and other medication use, and core laboratory blood lipoprotein determinations. Past oral contraceptive use remained a significant independent negative predictor of coronary artery disease severity score ($P=.04$) when adjusted for the significant coronary risk factors, including age, diabetes mellitus, triglycerides, low-density lipoprotein cholesterol, smoking, aspirin use, and lipid-lowering medication (Table 4).

In addition, we tested the potential confounders race, history of hypertension, body mass index, waist/hip ratio, family history of premature coronary disease, Beck depression index, self-reported stress, anticoagulant medication use, Framingham global risk estimate, history of dyslipidemia, psychoactive medication, antihypertensive medication, comorbid conditions, the metabolic syndrome, systolic and diastolic blood pressure, fasting glucose, functional status, education, marital status, income, creatinine, and high-sensitivity C-reactive protein. None of these variables were independent predictors of coronary artery disease severity, nor did their addition to the model affect the relationship between prior oral contraceptive use and the coronary severity score. The β of

TABLE 4

Significant predictors of coronary artery disease severity: *final linear regression model.*

Variable	β	SE	P
Past oral contraceptive use	−2.44	1.20	.04
Age	0.30	0.06	<.0001
Diabetes	4.61	1.25	.0003
Triglycerides (log)	2.31	0.94	.01
LDL cholesterol	0.04	0.01	.006
Aspirin use last week	4.36	1.14	.0001
Current smoker	3.62	1.48	.01
Lipid lowering rx	4.02	1.21	.0009

Note: $R^2 = 0.19$. The variables of age, race, hypertension, diabetes mellitus, body mass index, waist-hip ratio, current smoking, family history of premature coronary artery disease, blood lipoprotein levels, Beck depression, environmental stress, aspirin use, and anticoagulant use were evaluated in the multivariate model. Race, hypertension, body mass index, waist/hip ratio, family history, HDL cholesterol, total cholesterol, Beck depression, stress, and anticoagulant use were not independently associated with coronary artery disease severity. Also evaluated and not significant were NCEP ATP III risk score, psychoactive medications, antihypertensive medications, other chronic diseases, and metabolic syndrome. LDL = low-density lipoprotein.

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−2.44 indicates that past oral contraceptive use was associated with an approximately 2.5 lower coronary artery disease severity score. When we included postmenopausal hormone use into the model, the past oral contraceptive use predictive *P* value declined to .08, whereas other variables remained significant. There was a significant relationship between past oral contraceptive use and hormone therapy use, such that among women who had used oral contraceptives, 71% also used postmenopausal hormone therapy (odds ratio 2.38 [1.7–3.3], $P < .0001$ compared with non–past oral contraceptive users).

We explored whether limited statistical power might explain our failure to find a relationship between past oral contraceptive use duration and angiographic coronary artery disease severity. With 116 women using oral contraceptives for >3 years and 146 for ≤3 years and an SD in the coronary artery severity score of 10.4, if the coronary artery disease severity score is 11.5 in one group, we could detect a severity score in the second group of at least 15.2 with 80% power and a score of 15.7 with 90% power. Because the coronary artery severity score was 11.8 in the women with past oral contraceptive use and 18.7 among those without past oral contraceptive use, we believe that statistical power was not a problem in detecting a threshold of a 3-year duration effect. If a duration of >3 years (e.g., >6–9 years) is biologically relevant, we might have been limited in statistical power to test this duration hypothesis.

DISCUSSION

To our knowledge, our findings represent the first observation linking a detailed characterization of past oral contraceptive use with an accurate core laboratory assessment of angiographic coronary artery disease in postmenopausal women. We found that past use of oral contraceptives in the premenopause was associated with less subsequent coronary artery disease in the postmenopause, despite adjustment for age and cardiac risk factors. Past use of oral contraceptives demonstrated a significant relationship to coronary artery disease severity, a measure of atherosclerotic burden. These data are consistent with prior animal work demonstrating that oral contraceptive therapy has antiatherosclerotic effects in oophorectomized young female monkeys (2).

Insufficient prior data have existed with regard to past oral contraceptive use and atherosclerotic coronary artery disease, owing to the relatively prolonged onset of atherosclerosis over decades, combined with a relatively short recent population exposure time to oral contraceptives. Stampfer et al. (18) demonstrated a lower relative risk for major coronary disease of 0.8 (95% confidence interval [CI] 0.6–1.0) among the past users of oral contraceptives in 119,061 population-based women followed for 8 years compared with non-users. Although this result suggested protection, there were relatively few coronary events in this population with an estimated mean age of 63 years, and this analysis has not been updated. Similar results have been found in studies evaluating cardiac events (19) and coronary angiography (20). The present study results are consistent with this finding and provide mechanistic support to the concept that protection against postmenopausal cardiovascular events by past premenopausal oral contraceptive use is mediated by an antiatherosclerotic effect, as measured in our women with coronary angiography. A quantitative meta-analysis, however, of 13 studies included in the Stampfer work provided an estimated relative risk associated with past oral contraceptive use of 1.01 (95% CI 0.91–1.13), resulting in their conclusion that past oral contraceptive use had little or no impact on subsequent cardiovascular disease (21). Additional work in this area is needed to resolve these data uncertainties and should be increasingly feasible, given the large numbers of "baby boom" generation women entering menopause who had the opportunity to take oral contraceptives.

We were unable to detect a relationship between duration of oral contraceptive use and coronary artery disease severity among the past users. This lack of dose–response association questions the biological validity of our findings and raises the possibility that the beneficial relationship might be due to factors associated with past oral contraceptive use rather than a physiological effect of the oral contraceptive. We might have been underpowered to adequately test for a dose–response relationship, because of the relatively few (n = 56; 21%) women who had taken them for more than a total of 9 years, possibly owing to a limited availability of oral contraceptives for this age group of women during their reproductive years. Also, because oral contraceptives vary with regard to their dosages of E and progestin, if the relationship was related to a dose × duration exposure, we might have failed to detect a relationship because we did not have the dosage information.

Although we were unable to demonstrate group differences in socioeconomic status, education, or health care access, we cannot exclude an unknown and therefore unmeasured health variable that might be the true atherosclerotic protective factor. Notably, however, the majority of group differences between the past oral contraceptive users and non-users that could have conceivably played a role were present in the wrong direction (e.g., the prior oral contraceptive users had generally a greater cardiovascular risk factor burden despite their younger age). Nevertheless, future prospective study is needed to answer this question of causality vs. association.

Women with past oral contraception use also reported more frequent use of postmenopausal hormone therapy, and inclusion of postmenopausal hormone therapy as a variable in our regression model reduced the significance of negative association between prior oral contraception use and angiographic coronary artery disease. We did not use the postmenopausal hormone variable in our final model because randomized clinical trials do not demonstrate benefit from postmenopausal hormone therapy on angiographic coronary disease (8, 10) and because of the observed significant relationship between past oral contraceptive and postmenopausal hormone therapy, possibly due to a common willing-

ness to use or access to hormone preparations. Furthermore, our results are consistent with prior primate data, whereby premenopausal oral contraceptive exposure produced significantly less subsequent atherosclerosis in the postmenopausal monkeys, an effect that was independent of postmenopausal hormone therapy administration (22). Future prospective study is needed, however, to confirm and clarify our findings in humans.

The putative protective effect of oral contraceptive use for atherosclerosis could potentially involve a variety of hormonal mechanisms. Estrogen has been documented to have a number of antiatherosclerotic properties (23), and the dose of ethinyl E_2 in oral contraceptives produces higher blood levels that ovarian-related E levels. Oral contraceptives could also ensure adequate E levels in women with ovulatory dysfunction. Prior work demonstrates that up to 33% of premenopausal women have ovulatory dysfunction that increases osteoporosis risk (24), and recent work from the Nurses Health Study has documented a positive association between history of irregular menstrual cycling and coronary artery disease events (25). Oral contraceptives also suppress ovarian androgens and raise sex hormone-binding globulin levels, thus changing the free fraction of all circulating androgens. Finally, oral contraceptives seem to blunt the neuroendocrine stress response in primates, which might also offer indirect protection from atherosclerosis (26).

The current study results are limited by the cross-sectional design that precludes determination of causality. Our study results might also be limited by historical reporting inaccuracies (recall bias) and/or insufficient power to detect relationships. Our results could be confounded by a healthy user bias that we were unable to document, despite the many health variables measured in the WISE. Additionally, survival bias in the case of patients who used oral contraceptives but who died from atherosclerotic disease could be contributing to our results. Finally, these results are limited to the population of women with suspected ischemia undergoing coronary angiography and might not be applicable to a more general population of women.

Recent negative trials of postmenopausal hormone replacement therapy (7–10) have called into question the E–coronary artery disease protection hypothesis and have questioned the validity of prior animal model data (5, 22–24), as well as prior epidemiological study data suggesting that young women might benefit from exogenous hormone therapy after oophorectomy (3). We believe that our present study results support the hypothesis that E provided in the past to young women in the form of oral contraceptives might provide subsequent protection from atherosclerosis that results in coronary artery disease later in life. Clearly, further work with exogenous hormone therapy including both basic science and animal work is needed, as well as further human pathophysiological work and clinical trials in a variety of populations of women.

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