Prior oral contraception and postmenopausal fracture: a Women's Health Initiative observational cohort study

David Barad, M.D., M.S.,[a] *Charles Kooperberg, Ph.D.,*[b] *Jean Wactawski-Wende, Ph.D.,*[c] *James Liu, M.D.,*[d] *Susan L. Hendrix, D.O.,*[e] *and Nelson B. Watts, M.D.*[f]

[a] Albert Einstein College of Medicine, Bronx, New York; [b] Fred Hutchinson Cancer Research Center, Seattle, Washington; [c] University at Buffalo, Buffalo, New York; [d] University Hospitals of Cleveland, Cleveland, Ohio; [e] Wayne State University, Detroit, Michigan; and [f] University of Cincinnati College of Medicine, Cincinnati, Ohio

Objective: To test for the possible association of past oral contraceptive (OC) use and incident fracture after menopause.
Design: A prospective cohort of 93,725 postmenopausal women.
Setting: Forty Women's Health Initiative (WHI) clinical centers across the United States.
Patient(s): Ethnically diverse 93,725 volunteer postmenopausal women, 50 to 79 years old.
Intervention(s): None.
Main Outcome Measure(s): The main outcome was self-reported incident first fracture assessed prospectively by annual questionnaire.
Result(s): The adjusted relative hazard (HR) for fracture among past OC users was 1.07 (95% CI, 1.01–1.15). Among women without any postmenopausal hormone treatment, past OC use for ≤5 years led to an HR of 1.15 (95% CI, 1.04–1.27) and for past OC use >5 years led to an HR of 1.09 (95% CI, 0.97–1.23) compared with never users.
Conclusion(s): This study does not support the idea that past OC use protects against later fracture. (Fertil Steril® 2005;84:374–83. ©2005 by American Society for Reproductive Medicine.)

Key Words: Osteoporotic fracture, oral contraceptive metabolic effects, menopause, cohort study, Women's Health Initiative

Hormone treatment after menopause can preserve bone density and reduce the risk of fracture (1). However, evidence that premenopausal use of oral contraceptives (OC) has a positive effect on bone density is conflicting, and the association of OC with the risk of fracture after menopause remains unclear (2, 3).

Healthy women with normal ovarian estrogen production achieve peak bone mass by their third decade of life. Thereafter, bone resorption begins to outpace accumulation (4), resulting in slow but progressive loss of bone mineral content during later reproductive years (5, 6) and rapid loss after menopause. For young women, ovulatory disturbances that lower estrogen production can result in premature bone mineral loss (7–9) and increased risk of fracture (10, 11). Even among healthy young women, lower estradiol levels are associated with reduced bone mass (11–13). Among adult reproductive age women, OC use is associated with evidence of decreased bone turnover (14, 15).

Oral contraceptives have been reported to have beneficial effects (16–19) or no effect (20–23) on bone mineral density (BMD). For late reproductive age women who may already be estrogen deficient, OC use might increase estrogen exposure and help prevent bone loss (24). There is substantial evidence that OC use is associated with increased bone density among women over the age of 30 years (17–19, 25); however, there are few data concerning the effect of OC on bone density in younger women (22, 26).

Oral contraceptives suppress ovarian hormone production with synthetic estrogen and progestin that are different from endogenous hormones. This ovarian suppression could lead to decreased estrogen exposure, loss of bone mineral content, and increased risk of fractures in later life. Longitudinal studies have found decreased BMD in young women using depo-medroxyprogesterone acetate (Depo-Provera) contra-

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Reprint requests: David Barad, M.D., M.S., Obstetrics and Gynecology & Women's Health, Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, c/o 21 East 69th Street, New York, New York 10021 (FAX: 212-994-4499; E-mail: dbarad@whi.org).

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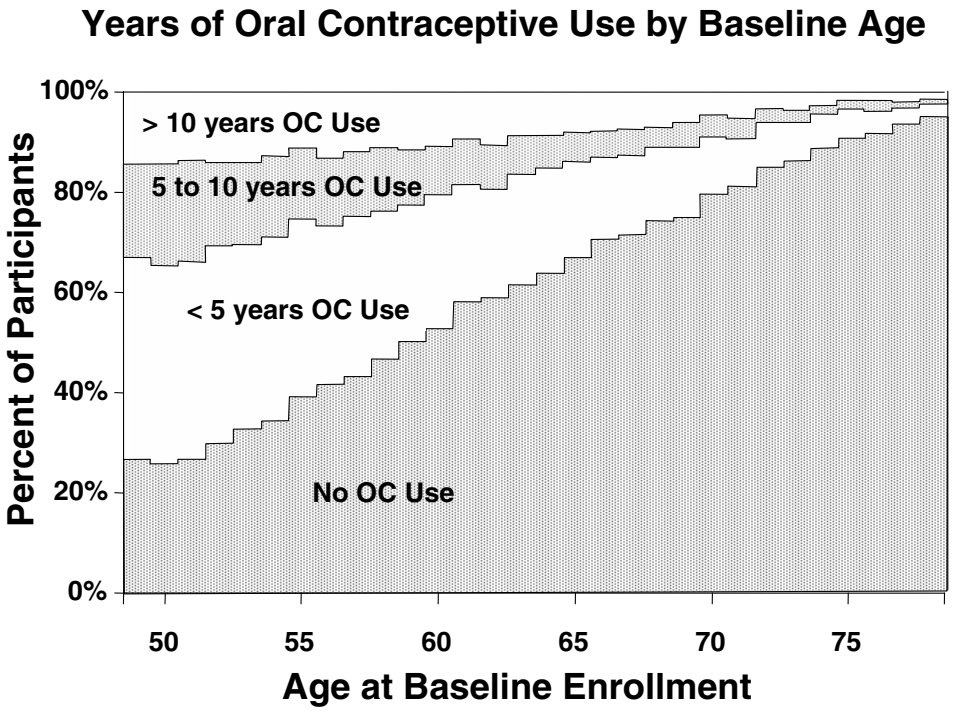
FIGURE 1

Cross-sectional depiction of percent of participants by categories of past contraceptive use by baseline age. The prevalence and duration of self-reported past use of oral contraceptives became progressively less with advancing baseline age.



Barad. Oral contraceptive and fracture. Fertil Steril 2005.

ception (27, 28) or ultra-low dose OC (29); however, BMD appears to recover after stopping contraceptive use.

We examined the association of self-reported past OC use and the first occurrence of fracture in a prospective cohort of postmenopausal women to investigate how premenopausal OC use may be associated with the incidence of fracture after menopause.

MATERIALS AND METHODS

Study Population

The Women's Heath Initiative (WHI) is a multicenter study of U.S. women composed of a set of four partly overlapping clinical trials and an observational study (OS). The OS is a prospective cohort study designed to assess the impact of biological, lifestyle, biochemical, and genetic factors on the risk of heart disease, cancer, osteoporosis, fracture, and other major health events.

Women aged 50 to 79 years were recruited to the WHI at 40 clinical centers in the United States, mostly through mass mailings to age-eligible women. A detailed description of the WHI design is reported elsewhere (30). Women were either directly recruited to the OS or were offered OS enrollment because they were ineligible or unwilling to participate in the clinical trials. Exclusions for enrollment in the OS were participation in a clinical trial, less than 3 years predicted survival, alcohol or drug dependency, mental illness, dementia, or other inability to participate in the study. This analysis is of participants who enrolled in the OS between September 1994 and February 1997.

Fracture occurrence in women participants was ascertained annually after enrollment through February 28, 2000, with a mean follow-up time of 2.5 years. Of the 93,725 participants recruited into the observational study, 2,428 were excluded because no outcome data were available. In an effort to decrease confounding factors, we excluded 59 participants (7 fractures) who had a history of bone cancer, 2,338 participants (162 fractures) who reported use of bisphosphonates at baseline, and 7,953 (641 fractures) with missing information on key covariates. The remaining cohort consisted of 80,947 observational study participants. In these, 4,674 reported an incident fracture during the prospective follow-up period.

Each investigator obtained approval from their institutional review boards. Each of the participants signed written informed consent to participate in the WHI observational study.