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Influence of Parity and Lactation on Hip Fracture Risk

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Several studies indicate that parity and lactation are associated with modest, short-term bone loss, but the long-term effect on osteoporotic fracture risk is uncertain. The authors therefore analyzed data from a population-based case-control study among Swedish postmenopausal women aged 50–81 years between October 1993 and February 1995. Mailed questionnaires and telephone interviews were used to collect data on 1,328 incident cases with hip fracture and 3,312 randomly selected controls. In age-adjusted analyses, the risk of hip fracture among all women was reduced by 10% per child (95% confidence interval (CI): 5, 14). After multivariate adjustment including body mass index as a covariate, the risk reduction was 5% per child (95% CI: 0, 10). Oral contraceptive use modified the association of parity with hip fracture risk. Among never users of oral contraceptives, the risk of hip fracture was reduced by 8% per child (95% CI: 2, 13), whereas among ever users of oral contraceptives, the risk was in the opposite direction, with an increase in risk by 19% per child (95% CI: 0, 41). After parity was considered, there was no association of duration of lactation period with fracture risk. The authors conclude that parity is modestly associated with a reduced hip fracture risk among women who had not used oral contraceptives previously. *Am J Epidemiol* 2001;153:1166–72.

contraceptives, oral; hip fractures; lactation; parity

Pregnancy and lactation involve intense physiologic changes that may be important for bone. Both states cause pronounced changes in sex steroids and other hormones involved in calcium homeostasis (1, 2), and they also impose calcium losses that could reduce maternal bone mass (2). Indeed, there have been reports of reversible osteoporosis in association with pregnancy (3–5). On the other hand, bone loading under pregnancy and the sustained weight gain (1, 6, 7) that often occurs after delivery have the potential to increase bone mass. Calcium absorption becomes more efficient during pregnancy, a change that also tends to preserve maternal bone (2). Thus, pregnancy and lactation have the potential to be either beneficial or detrimental for bone mineral density.

Not surprising, the actual net long-term effect of parity and lactation on osteoporotic fracture risk is uncertain. Some studies of fracture risk (8) have addressed these issues, but they had limited power to ascertain moderate effects that might follow lactation and parity. We thus used data from a large, population-based case-control study to examine the joint influence of parity and lactation on hip fracture risk, the main osteoporotic fracture in developed countries.

MATERIALS AND METHODS

Cases

We endeavored to ascertain all fractures of the proximal femur that occurred between October 1993 and February 1995 among women resident in six counties in Sweden who were born after 1913. Using clinical records or operation registers in all 24 hospitals in the study area, we identified 2,597 possible incident cases (9, 10). We excluded those with a fracture due to malignancy ($n = 26$); high-energy trauma ($n = 4$); incorrect diagnosis ($n = 41$); old fracture ($n = 10$); blindness ($n = 5$); birth outside Sweden ($n = 202$); a diagnosis of severe alcoholic abuse, psychosis, or senile dementia ($n = 576$); or death within 3 months of the fracture ($n = 123$). All hospital records were scrutinized to confirm eligibility and ascertain the type of hip fracture and history of previous hip fracture. After exclusions, 1,610 eligible cases remained and were approached with a comprehensive questionnaire at a mean interval of 95 days (standard deviation, 23 days) after the fracture. The Swedish inpatient register identified 34 additional cases, who were also asked to complete the questionnaire.

Controls

Controls were native-born women randomly selected from the national, continuously updated population register

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Abbreviations: CI, confidential interval; HRT, hormone replacement therapy; PTH, parathyroid hormone.

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the month before the start of the study. Questionnaires were sent to controls on six occasions evenly distributed during the study period (October 1993 to February 1995). Potential controls aged 70–80 years were frequency matched (two controls:one case) to the expected hip fracture age distribution within county of residence. Controls aged 50–69 years were also randomly selected from the population register as part of a breast cancer study (11) being conducted at the same time with the same questionnaire. For these women, frequency matching to the expected number of breast cancer cases provided two to four times as many controls as hip fracture cases in each 5-year age group (50–69) and county of residence. Of the 4,872 candidate controls in the hip fracture analysis, 4,059 were eligible for the study, 610 were born outside of Sweden, 157 died before being approached, 44 were senile or psychotic, and two were blind.

Data collection

Data were collected through a mailed questionnaire that focused on reproductive history (ages at menarche and menopause, cycle length, cycle regularity, climacteric symptoms, parity, age at subsequent births, and duration of breastfeeding for each child) and use of exogenous sex hormones, including oral contraceptives and hormone replacement therapy (HRT). Information concerning pre- and postmenopausal estrogen use included the doses and types of preparations and the duration and dates of exposure. Identification of hormones was aided by picture charts of all preparations commonly used in Sweden during 1950–1995. We also requested information on anthropometric measures (current height and weight, weight 1 year previously, and weight at age 18 years), education, profession, dietary habits, alcohol consumption, cigarette smoking, and physical activity (at childhood, at ages 18 and 30 years, and in recent years). The women were also asked about medical history (stroke, diabetes mellitus, cardiovascular diseases, and inflammatory bowel diseases). Approximately 50 percent of the participants were approached by telephone for completion of missing information. Previous occupational activity, socioeconomic class, and marital status were available through matching to national census databases for 1980 and 1990.

Of those eligible, 1,328 cases (82.5 percent) and 3,312 controls (81.6 percent) answered the questionnaire; of these, 202 (15.2 percent) of the cases and 497 (15.0 percent) of the controls responded solely by telephone in a less extensive interview (omitting length and regularity of menstrual cycles at age 30 years, breastfeeding, menopausal symptoms, and alcohol consumption). Participants experiencing natural menses were classified as premenopausal (50 controls and one case) and were excluded from the analysis.

Data analysis

Parity was considered in categories of number of children (using nulliparas or primiparas as the reference category) or as a continuous variable in some analyses. For parous women, duration of breastfeeding was considered in four classes defined by the quartiles of either total duration or mean duration per child of breastfeeding among controls. Age at first pregnancy was categorized into five classes: 20 or less, 21–25, 26–30, 31–35, and more than 35 years. Smoking status and HRT use were defined as never, former, or current use. Oral contraceptive use was considered as ever versus never use. Body mass index was calculated as weight (kg)/height (m^2) and was categorized into quintiles among controls. Age was considered in six classes: 50–54, 55–59, 60–64, 65–69, 70–74, and 75–81 years.

Odds ratios and 95 percent confidence intervals computed by unconditional logistic regression were used as measures of association. Odds ratios changed only minimally after adjustment for height, weight (instead of body mass index), adult weight change, leisure time physical activity, education, history of stroke or diabetes mellitus, alcohol intake, coffee and milk consumption, age at menopause, climacteric symptoms, previous occupational activity, socioeconomic class, and marital status. Consequently, the multivariate analyses presented here included only the covariates age, body mass index, oral contraceptive use, HRT use, and smoking status. To account for possible differences between parous and nonparous women, we computed trends for parity both including and excluding nulliparous women. Interactions were considered through inclusion of product terms in the analysis by using likelihood ratio tests.

RESULTS

The characteristics of the study participants are summarized in table 1. Mean parity was slightly lower in cases than in controls (1.7 (standard deviation, 1.3) vs. 1.9 (standard deviation, 1.3)), and hip fracture risk decreased with increasing parity (table 2); the age-adjusted risk decreased by 10 percent (95 percent confidence interval (CI): 5, 14) per child. The odds ratios remained similar after further adjustment for oral contraceptive use, HRT use, and smoking in a multivariate model excluding body mass index. However, adiposity explained about half of the risk reduction associated with parity. The mean body mass index of the subjects increased by 0.44 kg/m^2 per child ($p < 0.0001$), and after further adjustment for body mass index, risk decreased by only 5 percent (95 percent CI: 0, 10) per child. Associations among parous women were less marked: There was only a weak association of parity with hip fracture risk after multivariate adjustment, including body mass index (reduction in risk per child, 2 percent, 95 percent CI: –5, 9).

Mean age at first pregnancy was similar in cases and controls (table 1) and had no association with hip fracture risk, even after comparison of women who bore their first child during their teen years and those who first gave birth after age 35 years (data not shown). The spacing of births also did not substantially affect fracture risk. Among multiparous women, the odds ratio for the risk of hip fracture was 1.13 (95 percent CI: 0.93, 1.36) for those with two births within 2 years in comparison with women with longer intervals between all births. We found no interaction between body mass index and parity for fracture risk; the risk by parity was

TABLE 1. Descriptive characteristics of the participants and number of subjects who provided information, Sweden, 1993–1995

Characteristics	No. of cases/ no. of controls	Cases	Controls
		Mean (SD*)	
Age (years)			
At first pregnancy	1,327/3,262	26.2 (5.0)	25.6 (4.9)
At menopause	1,317/3,251	49.8 (3.9)	49.6 (4.0
At time of study	1,327/3,262	72.5 (6.8)	70.5 (7.7)
Parity	1,319/3,257	1.7 (1.3)	1.9 (1.3)
Duration of breastfeeding among parous women (months)	715/1,947	10.9 (8.9)	11.5 (8.9)
Weight (kg)	1,308/3,233	61.0 (11.1)	66.8 (11.8)
Weight at age 18 years (kg)	808/2,207	56.7 (7.6)	55.4 (7.6)
Adult weight change (kg)	803/2,195	4.3 (10.8)	11.0 (11.6)
Height (cm)	1,307/3,235	164.1 (6.6)	163.3 (5.9)
Body mass index (kg/m^2)	1,294/3,216	22.2 (3.8)	24.6 (4.2)
		%	
Ever use of oral contraceptives	130/562	11.6	19.1
Ever use of HRT*	120/456	9.0	14.0
Parity			
Nulliparous	274/518	20.6	15.9
1	312/665	23.5	20.4
2	399/1,123	30.1	34.4
≥3	334/951	25.2	29.2
Smoking status			
Never	719/1,872	54.3	60.7
Former	260/619	19.6	20.0
Current	345/595	26.1	19.3

* SD, standard deviation; HRT, hormone replacement therapy, i.e., medium-potency estrogens such as estradiol compounds or conjugated estrogens.

similar among those with a low body mass index and those with a high body mass index.

Long total duration of breastfeeding was associated with a reduction in risk (table 3), but this association disappeared after adjustment for parity, body mass index, and use of exogenous estrogens. There were no substantial risk differences in analyses that considered mean duration of breastfeeding per child (quartiles 0–2, 3–4, 5–6, and 7 months per child or more) (data not shown). Long duration of breastfeeding also had no substantial association with hip fracture risk among those with their first pregnancy as a teenager or among those with their first pregnancy after age 30 years. The relative risk estimates for lactation and parity were similar for cervical and trochanteric hip fracture (data not shown).

The risk reduction with parity was similar among never and ever users of HRT and among heavier and lighter women (data not shown), but oral contraceptive use modified the effect of parity (table 4). Among never users of oral contraceptives, the risk of hip fracture was reduced by 7 percent per child (95 percent CI: –1, 14). However, among ever users, the effect was in the opposite direction: an increase in risk of 18 percent per child (95 percent CI: –4, 46). The p value for interaction was less than 0.01 among all women and less than 0.05 among parous women. The differences in risk were most pronounced among women who had four or more children (table 4). The increase in risk with parity was most evident among women who used oral contraceptives after age 30 years; in this group, there was a 33 percent increase in risk per child (95 percent CI: 3, 71 percent). In analyses that omitted women who had taken only modern, low-dose oral contraceptives, progestogen only, or unknown preparations, the results remained similar (data not shown).

The increasing fracture risk with parity among oral contraceptive users was concentrated among women with long

TABLE 2. Parity and the risk of hip fracture, Sweden, 1993–1995

	No. of cases	No. of controls	Age-adjusted analysis		Multivariate analysis*	
			OR†	95% CI†	OR	95% CI
Parity						
No. of children						
0	274	518	1.00	Reference	1.00	Reference
1	312	665	0.88	0.72, 1.07	0.90	0.73, 1.12
2	399	1,123	0.69	0.57, 0.83	0.75	0.62, 0.91
≥3	334	951	0.67	0.55, 0.81	0.80	0.66, 0.98
Per child			0.90	0.86, 0.95	0.95	0.90, 1.00
Among parous women						
No. of children						
1	312	665	1.00	Reference	1.00	Reference
2	399	1,123	0.79	0.66, 0.94	0.82	0.68, 0.99
≥3	334	951	0.76	0.63, 0.91	0.87	0.72, 1.06
Per child			0.92	0.86, 0.99	0.98	0.91, 1.05

* Adjusted for age (≤54, 55–59, 60–64, 65–69, 70–74, and ≥75 years), hormone replacement therapy (never, former, and current use), oral contraceptive use (never and ever use), and body mass index (by quintiles).
† OR, odds ratio; CI, confidence interval.

TABLE 3. Lactation and the risk of hip fracture among parous women, Sweden, 1993–1995

	No. of cases	No. of controls	Age-adjusted analysis		Multivariate analysis*	
			OR†	95% CI†	OR	95% CI
Breastfeeding (total months)						
1–5	150	390	1.00	Reference	1.00	Reference
6–10	199	568	0.83	0.66, 1.05	0.87	0.68, 1.11
11–16	154	420	0.84	0.65, 1.08	0.86	0.66, 1.12
>16	161	470	0.76	0.60, 0.98	0.86	0.67, 1.12
Per 3 months			0.96	0.94, 0.99	0.98	0.95, 1.01
Breastfeeding, also adjusted for parity‡						
1–5	150	390	1.00	Reference	1.00	Reference
6–10	199	568	0.86	0.68, 1.09	0.90	0.70, 1.15
11–16	154	420	0.94	0.71, 1.23	0.95	0.72, 1.26
>16	161	470	0.92	0.68, 1.23	1.01	0.75, 1.38
Per 3 months			0.98	0.95, 1.02	1.00	0.96, 1.04
Trend per 3 months of breastfeeding, by age at first pregnancy (years)‡						
<20	43	147	0.99	0.89, 1.10	1.05	0.92, 1.19
20–30	545	1,507	0.97	0.93, 1.00	0.98	0.94, 1.02
>30	125	290	0.95	0.66, 1.05	0.96	0.86, 1.08

* Adjusted for age (≤54, 55–59, 60–64, 65–69, 70–74, and ≥75 years), hormone replacement therapy (never, former, and current use), oral contraceptive use (never and ever use), and body mass index (by quintiles).
† OR, odds ratio; CI, confidence interval.
‡ By number of children (1, 2, and ≥3).

duration of lactation. Mothers who had ever used oral contraceptives and who had breastfed their children for less than the median of 5 months per child had an odds ratio of 0.95 (95 percent CI: 0.70, 1.30) per child, an association similar to that among women who never took oral contraceptives. Ever users of oral contraceptives with longer mean duration of breastfeeding, however, had an odds ratio of 1.36 (95 percent CI: 0.91, 2.01) per child. The p value for interaction was 0.15. Among oral contraceptive users with a long mean duration of breastfeeding, the increasing risk with parity was further concentrated among women who had ever used oral contraceptives within 3 years after any birth (data not shown).

TABLE 4. Risk of hip fracture by parity, stratified by oral contraceptive use, Sweden, 1993–1995

	No. of cases	No. of controls	Age-adjusted analysis		Multivariate analysis*	
			OR†	95% CI†	OR	95% CI
Never users of oral contraceptives						
Parity (no. of children)						
0	210	392	1.00	Reference	1.00	Reference
1	238	502	0.88	0.70, 1.10	0.92	0.72, 1.16
2	306	792	0.72	0.58, 0.89	0.77	0.61, 0.96
3	157	426	0.69	0.54, 0.88	0.78	0.60, 1.01
4	52	167	0.58	0.41, 0.83	0.67	0.46, 0.97
≥5	28	93	0.55	0.35, 0.86	0.75	0.47, 1.20
Per child			0.88	0.83, 0.93	0.92	0.87, 0.98
Among parous women (no. of children)						
1	238	502	1.00	Reference	1.00	Reference
2	306	792	0.81	0.66, 1.00	0.83	0.67, 1.02
3	157	426	0.78	0.61, 0.99	0.84	0.66, 1.08
4	52	167	0.66	0.46, 0.93	0.72	0.50, 1.03
≥5	28	93	0.62	0.39, 0.97	0.80	0.51, 1.29
Per child			0.89	0.82, 0.96	0.93	0.86, 1.01
Ever users of oral contraceptives						
Parity (no. of children)						
0	11	59	1.00	Reference	1.00	Reference
1	23	90	1.34	0.60, 2.98	1.46	0.64, 3.34
2	50	231	1.18	0.57, 2.42	1.40	0.67, 2.96
3	23	133	0.93	0.42, 2.04	1.31	0.58, 2.97
4	18	36	2.52	1.06, 6.01	2.78	1.13, 6.87
≥5	5	12	2.03	0.58, 7.03	2.96	0.80, 10.91
Per child			1.11	0.94, 1.32	1.19	1.00, 1.41
Among parous women (no. of children)						
1	23	90	1.00	Reference	1.00	Reference
2	50	231	0.88	0.50, 1.54	0.96	0.54, 1.70
3	23	133	0.70	0.37, 1.33	0.89	0.46, 1.74
4	18	36	1.89	0.90, 3.97	1.91	0.88, 4.13
≥5	5	12	1.53	0.48, 4.89	2.07	0.61, 7.00
Per child			1.12	0.91, 1.38	1.18	0.96, 1.46

* Adjusted for age (≤54, 55–59, 60–64, 65–69, 70–74, and ≥75 years), hormone replacement therapy (never, former, and current use), and body mass index (by quintiles).

† OR, odds ratio; CI, confidence interval.

DISCUSSION

In this large, population-based case-control study, we found that increasing parity was associated with a modest reduction in risk of hip fracture, an effect due at least in part to the association of parity with body weight. Unexpectedly, we found that, among oral contraceptive users, multiparity was associated with an increased risk of hip fracture. Duration of lactation was not associated with risk after parity was taken into account.

During each pregnancy, maternal bone mineral is reduced by about 3 percent in the absence of adaptational processes (2). These counterbalancing processes lead to more efficient calcium absorption and reduce maternal loss of bone mineral. The adaptation is probably partly mediated by higher circulating levels of 1,25 dihydroxyvitamin D during pregnancy (2), but changes in parathyroid hormone (PTH), growth hormone, prolactin, and estrogen may also contribute to a more efficient calcium conservation (2). Furthermore, increased body weight during and after pregnancy would tend to increase bone density, especially of the lower extremities, by mechanical loading. Perhaps reflecting these countervailing forces, studies that have examined the net amount of bone lost during pregnancy have been inconsistent (2).

Two major studies have tried to evaluate the long-term effect of parity on bone density. A large, cross-sectional

British study reported a protective effect of parity on bone. The lowest bone density values at the spine and neck were observed in nulliparous women, intermediate values were seen in primiparas, and the highest values in women with two or more children (12). These differences were partially attenuated after control for body mass index. In contrast, reproductive history was not associated with bone density in an American study after control for age and obesity (13).

Research regarding parity and fracture risk has also been conflicting (8). High parity was related to a reduced hip fracture risk in two studies (14, 15), even after adjustment for body mass index, but most investigators have found no association (16–20). The two positive studies used nulliparous women as the reference group, a technique that would distort the association if nulliparity is a reflection of a hormonal environment that inhibits both pregnancy and bone formation (2). Indeed, in our study, the trends in risk were less pronounced when the analyses was restricted to parous women.

During lactation with a daily milk production of 600–1,000 ml, an average of 200 mg of calcium is lost each day (2, 21). In the absence of compensatory mechanisms, this would entail about a 5 percent loss of mineral at the hip after 6 months of full lactation. Several studies (2) have found that there are short-term losses of bone mass during lactation, which are, however, restored after weaning and the return of normal menses.

After taking parity into account, we found no association between duration of breastfeeding and hip fracture risk. Other studies also suggest that breastfeeding has little independent impact on this risk (15, 16, 18, 19). In one study (22), breastfeeding was found to reduce hip fracture risk, but parity was not considered in that analysis.

Calcium intake could theoretically modify an association between lactation and fracture risk, so that the relatively high dietary intake of calcium among Swedish women (23) may have masked an association that would be evident among women with lower calcium intake. However, calcium supplementation does not prevent short-term bone losses during lactation (21), and differences in regular calciotrophic hormone levels such as vitamin D and PTH seem not to be related to maternal bone mineral loss or to increased bone turnover during lactation (24). Increased PTH-related peptide could be a mechanism that provides adequate calcium to infants and thus induces maternal bone loss (23, 25, 26). These losses, observed in longitudinal studies, are generally recovered after weaning (27, 28). This could explain why no net losses of bone with lactation are observed in cross-sectional studies (2) and also why we found no influence of breastfeeding on hip fracture risk.

Our finding that oral contraceptive use modifies the association between parity and hip fracture risk is novel. The increase in risk with high parity among ever users of oral contraceptives was predominantly seen among those who had reported a long period of breastfeeding—approximately 5 months or more per child—and who were probably those with the greatest bone loss before weaning. This effect modification could be due either to chance or to a previously unrecognized interference of oral contraceptive use with bone regrowth after weaning in the 1–2 years postpartum. Weaning is normally associated with increases in serum PTH, renal conservation of calcium, and increased intestinal calcium absorption (29–31), changes that counterbalance the short-term losses of bone associated with gestation and lactation. Estrogens can affect secretion of PTH and also modulate its peripheral effects (32, 33). The effect of supraphysiologic serum levels of estrogen and progestin from oral contraceptive use could potentially influence calcium homeostasis after weaning, although, to our knowledge, this has not previously been investigated.

Even though our findings regarding parity and oral contraceptive use are biologically plausible, they should be interpreted with caution, since they were based on post hoc analyses of small subgroups, with broad confidence intervals around the odds ratios. Some of the participants had missing data for oral contraceptive use, and our results could have been affected unpredictably by this nonresponse. However, the mean age of cases and controls who did not respond to the oral contraceptive question was 75 years at the time of study. The older women in our study would have been in their late forties at the time of introduction of oral contraceptives in Sweden and so were unlikely to have used these drugs. We therefore believe that the impact of this missing information on our results is modest.

Major strengths of our study are its population-based design, the large sample size, and the high response rate. In addition, the detailed questionnaire allowed us to consider the influence of many covariates. However, all of the information included was self-reported, and actual measures of exposure would have reduced misclassification. Reproductive factors are, however, probably reliably reported (34) and presumably were not differentially recalled by cases and controls; thus, any misclassification should have led to an underestimate of true associations. Oral contraceptive use in our sample included partaking of various compounds, although the majority had taken medium- or high-dose combined preparations not commonly prescribed today, typically a daily dose of 50 μg or more of ethinylestradiol or its equivalent. We did not have sufficient power to examine the influence of modern, low-dose oral contraceptives on fracture risk with parity. The study design enabled us only to investigate reports from survivors, i.e., cases and controls who were deceased at the time we sent the questionnaires could not be included. The impact of this possible survival bias is uncertain.

Despite these possible limitations, we conclude that higher parity is modestly associated with a reduced hip fracture risk, and this risk reduction seems partially attributable to weight gain with parity. The reduction in risk with parity, however, seems to be mitigated by exogenous sex steroid use as oral contraceptives. Overall, lactation is not associated with hip fracture risk.

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