Use of Depot Medroxyprogesterone Acetate and Fracture Risk

Christian Meier, Yolanda B. Brauchli, Susan S. Jick, Marius E. Kraenzlin, and Christoph R. Meier

Division of Endocrinology, Diabetes, and Metabolism (C.M., M.E.K.) and Hospital Pharmacy (C.R.M.), University Hospital Basel, CH-4031 Basel, Switzerland; Basel Pharmacoepidemiology Unit (Y.B.B., C.R.M.), Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, CH-4056 Basel, Switzerland; and Boston Collaborative Drug Surveillance Program (S.S.J., C.R.M.), Boston University School of Medicine, and Department of Epidemiology, School of Public Health, Boston University, Lexington, Massachusetts 02421

Context: Depot medroxyprogesterone acetate (DMPA), which has a high rate of use among teenagers in Europe and the United States, has been associated with impaired bone mineral acquisition during adolescence and accelerated bone loss in later life. Studies on the association between DMPA use and fracture risk are limited.

Objective: We aimed at evaluating the relationship between use of hormonal contraceptives, specifically DMPA, and fracture risk.

Design: We conducted a case-control analysis using the United Kingdom-based General Practice Research Database.

Setting and Participants: Participants were females aged 20–44 yr with an incident fracture diagnosis between 1995 and 2008.

Main Outcome Measures: Odds ratios (OR) with 95% confidence intervals (CI) of incident fracture in relation to exposure to DMPA or combined oral contraceptives were assessed. Adjustments were made for smoking, body mass index, and additional potential confounders.

Results: We identified 17,527 incident fracture cases and 70,130 control patients (DMPA exposure: 11 and 8%, respectively). Compared with nonuse, current use of one to two, three to nine, or 10 or more DMPA prescriptions yielded adjusted OR for fractures of 1.18 (95% CI = 0.93–1.49), 1.36 (95% CI = 1.15–1.60), and 1.54 (95% CI = 1.33–1.78), respectively. Fracture risk was highest after longer treatment duration (>2–3 yr), and there was no difference in patients below and above the age of 30 yr. For users of combined estrogen-containing oral contraceptives, the OR were around 1.

Conclusions: This population-based study suggests that use of DMPA is associated with a slightly increased risk of fractures. **(*J Clin Endocrinol Metab* 95: 4909–4916, 2010)**

Exposure to sex hormones during puberty plays an important role in the accrual of bone mass, and sustained production of estrogens is required for the maintenance of bone mass in adult women (1). Low estrogen levels are seen in women using depot medroxyprogesterone acetate (DMPA) for contraception, a long-acting progestin-only contraceptive, administered by 3-monthly im injection (2). DMPA is used by more than 9 million women worldwide and has a high usage in the United Kingdom and the United States (3). The contraceptive action of DMPA results from its suppression of gonadotropin secretion which in turn inhibits ovarian estradiol production

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Abbreviations: BMD, Bone mineral density; BMI, body mass index; CI, confidence interval; DMPA, depot medroxyprogesterone acetate; FPC, family planning clinic; GP, general practitioner; GPRD, General Practice Research Database; OR, odds ratio.

and prevents ovarian follicular maturation and ovulation. By one year of use, most women become amenorrheic (4), and there has been concern over potential negative effects on bone (5).

In contrast to estrogen-containing oral contraceptives, which do not appear to have negative effects on biochemical markers of bone turnover or bone mineral density (BMD) (6), use of DMPA has been associated with accelerated bone turnover (7–10) and with a decline in BMD (3, 7, 11–18). Cross-sectional studies have described BMD deficits ranging from 2.5–18% at the lumbar spine and from 2.2–17% at the proximal femur (18). Furthermore, longitudinal studies in adult women have demonstrated accelerated bone loss in new DMPA users (19–21) with loss at the lumbar spine of up to 5.8% after 2 yr (21).

Whether DMPA influences fracture risk cannot be determined from existing literature because studies investigating the association between DMPA use and fracture risk are limited (6). A few case reports have suggested an association between DMPA use and fractures in adult women (22, 23), as did three observational studies (24–26). However, these studies had important limitations, such as low number of DMPA users or limited availability of potential confounders. Of note, bone loss occurring with DMPA use may be reversible with gain in BMD after discontinuation of DMPA (17, 19, 27). Therefore, the question remains whether past use of DMPA affects future fracture risk.

Given that use of DMPA is common and that its indication may expand due to its contraceptive efficacy and increasing use in women with bleeding disorders, it is important to learn more about potential deleterious effect of DMPA on skeletal health. In this large population-based study, we explored the association between use of DMPA or combined oral contraceptives and the risk of incident fracture.

Materials and Methods

We conducted a matched case-control analysis of the risk of having a first-time fracture in relation to current or previous use of DMPA, low-dose MPA alone, or estrogen containing oral contraceptives within the United Kingdom-based General Practice Research Database (GPRD).

Data source

Data were derived from the United Kingdom-based GPRD, which has been described previously (28, 29). Briefly, this database was established around 1987 and contains information on more than 5 million patients, of whom about 3 million are currently registered, and a cumulative follow-up time of more than 32 million person-years. The patients enrolled in the GPRD are representative of the United Kingdom with regard to age, sex, geographic distribution, and annual turnover rate. General practitioners (GP) have been trained to record medical information including demographic data, medical diagnoses, hospitalizations, deaths, and drug prescriptions using standard software and standard coding systems. The GP generate prescriptions directly with the computer, and this information is automatically transcribed into the computer record. It contains the name of the preparation, route of administration, dose, and number of tablets for each prescription. The recorded information on drug exposure and diagnoses has been validated and proven to be of high quality (30, 31). The GPRD has been the source of many observational studies, including research on fractures (32–35). Based on previous record reviews by ourselves (32) and others (35), we have determined that the diagnosis of fracture in the GPRD is very accurate, with a confirmed proportion of at least 90% after comparing computer-recorded diagnoses with hospital discharge letters and/or questionnaire information provided by GP. The study was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency database research.

Study population: case and control definition

We identified via Oxford Medical Information System and Read codes all females between 20 and 44 yr of age with a first-time fracture diagnosis (including vertebral and nonvertebral fractures) between 1995 and 2008. All fractures were clinically diagnosed. We excluded patients with less than 3 yr of active history in the database before the first-time diagnosis of fracture (index date), and we also excluded cases with a diagnosis of cancer, Paget's disease, osteoporosis, osteomalacia, alcoholism, HIV, or use of anti-osteoporotic drugs (*i.e.* bisphosphonates, teriparatide, calcitriol, and raloxifen) before the index date.

From the base population, we identified at random four control subjects per fracture case, matched on calendar time (same index date), age (same year of birth), sex, general practice, and years of history in the GPRD. We applied the same exclusion criteria to controls as to case patients.

Exposure to DMPA and other hormones

For each case and control, we assessed from the computer record the exposure history for DMPA, low-dose MPA alone, or combined oral contraceptives before the index date. Patients were classified as current users if the last prescription for a study drug of interest was recorded less than 180 d or as past users if it was recorded 180 or more days before the index date. We also classified users by duration of use before the index date, using the number of prescriptions as proxy (one to two, three to nine, or $\geq$10 for DMPA and for oral contraceptives, or one to two or three or more for MPA low dose), and we further combined duration and timing of use into one variable (*i.e.* we created user categories of current use of one to two, three to nine, or $\geq$10 prescriptions and past use of one to two, three to nine, or $\geq$10 prescriptions). For the main analysis, we created a model in which subsequent or concurrent use of various hormonal contraceptive drugs before the index date was possible, and we adjusted for such overlapping use in the multivariate model.

Statistical analysis

We conducted conditional logistic regression analyses using the SAS statistical software (version 9.1; SAS Institute, Cary, NC). We displayed relative risk estimates as odds ratios (OR) with 95% confidence intervals (CI). We adjusted OR for the

potential confounders age, sex, general practice, calendar time, and years of recorded history in the database by matching, and for smoking status (non, current, ex, or unknown) and body mass index (BMI) (<18.5, 18.5–24.9, 25.0–29.9, and ≥30 kg/m^2, or unknown) in the multivariate model. The risk estimates were further adjusted for a recorded history of asthma, epilepsy, use of β-blockers, proton pump inhibitors, and anticonvulsants [all combined by timing (current means <90 d before index date; past means thereafter) and duration (one to nine or ≥10 prescriptions)]; systemic corticosteroids, benzodiazepines, and serotonin reuptake inhibitors [all combined by timing (current menas <90 d before index date; past means thereafter) and duration (one to four or five or more prescriptions)]; and progestins (same classification as for DMPA).

Potential confounding by a number of other variables was further tested in univariate analyses with the log likelihood ratio test, but they were not included in the final model because they did not materially change the main effect measure.

To evaluate whether missing information on exposure to DPMA obtained by women from family planning clinics (FPC) would materially affect our results, we conducted a number of sensitivity analyses. First we excluded women from the analysis who may have received DPMA exclusively via FPC. We compared longer-term DPMA use with short-term DPMA use and assessed the relative fracture risk; thus, this analysis was restricted to women who used DMPA obtained through the GP. It is still possible that the short-term user group also contained some women who were actually long-term DMPA users, if for example most DMPA use was issued by a FPC and the GP noted only one prescription in the record. To evaluate this possibility, we classified women with only one recorded DMPA prescription in a separate group in another analysis. Then we conducted another analysis in a subgroup of women who most likely received all of their DMPA prescriptions from the GP by excluding all women who had any evidence in their records of attending a FPC. Because we were mainly interested in low-trauma fractures, we also conducted another sensitivity analysis in women who did not have any evidence for an accident recorded before the index date. Although we excluded patients with alcohol abuse from our study, we explored the impact of social alcohol consumption on the relative fracture risk. We categorized patients into current, former, or no alcohol consumption (or unknown), and we stratified those with recorded current alcohol consumption into fewer than eight, eight to 14, 15–42, 43–63, 64 or more, or unknown number of units per week. Because nonusers of contraceptives may be different from users, we compared exclusive DMPA users with exclusive users of other hormonal contraceptives instead of nonusers of DMPA. Finally, we restricted our analysis to patients who had a fracture potentially related to osteoporosis, *i.e.* to patients with spine, hip, wrist, or humerus fractures.

Results

We identified 17,527 female case patients with an incident fracture diagnosis and 70,130 matched control women. The mean number of years for cases and controls before the index date was around 9 yr. Table 1 shows the type of clinically diagnosed fractures.

The age distribution and the prevalence of relevant comorbidities of cases and controls are displayed in Table 2.

TABLE 1. Type of fractures

Fracture site	No. (n = 17,527)	%
Spine	285	1.6
Hip, femur, patella	355	2.0
Hip	62	0.3
Femur, patella	293	1.7
Lower leg	2808	16.0
Foot (including toes)	4234	24.2
Toes	2072	11.8
Calcaneus	100	0.6
Clavicle	496	2.8
Humerus, elbow	1020	5.8
Forearm (including wrist)	2859	16.3
Hand (including fingers)	4261	24.3
Fingers	1911	10.9
Rib	789	4.5
Not specified	420	2.4
Osteoporotic fractures (spine, hip, wrist, humerus)	1936	11.0

Of the 17,527 fracture cases and their 70,130 controls, 1913 (11%) and 5715 (8%), respectively, had some DMPA use recorded. The OR of developing a fracture in association with current use of one to two, three to nine, or 10 or more DMPA prescriptions, compared with nonuse of DMPA and adjusted for BMI, smoking, comorbidities and comedication, were 1.18 (95% CI = 0.93–1.49), 1.36 (95% CI = 1.15–1.60), and 1.54 (95% CI = 1.33–1.78), respectively. The adjusted OR of developing a fracture for past use of one to two, three to nine, or 10 or more DMPA prescriptions were 1.17 (95% CI = 1.07–1.29), 1.23 (95% CI = 1.11–1.36), and 1.30 (95% CI = 1.09–1.55), respectively (Table 3). We additionally used a different cutoff for past use (*i.e.* ≥720 d), and the OR for current and past use of DMPA were 1.03 (95% CI = 0.88–1.22), 1.38 (95% CI = 1.22–1.55), and 1.52 (95% CI = 1.34–1.72) for current use and 1.24 (95% CI = 1.11–1.37), 1.17 (95% CI = 1.03–1.32), and 1.17 (95% CI = 0.92–1.49) for past use, for the various levels of exposure duration.

We then stratified the group of current DMPA users of 10 or more DMPA prescriptions by age and fracture type. An increased fracture risk in association with current DMPA use was seen in patients below and above the age of 30 yr. For patients above 30 yr of age, past use of 10 or more DMPA prescriptions also yielded an increased relative risk. The risk of all types of fractures tended to be increased with current long-term exposure to DMPA (Table 4).

Low-dose MPA (data not shown) and estrogen-containing hormonal contraceptives did not affect the relative fracture risk (Table 3).

As mentioned above, we conducted a number of sensitivity analyses. In the analyses that we conducted to reduce potential exposure misclassification, we found OR

TABLE 2. Characteristics of case patients with fractures and matched controls

Variable	No. of cases (n = 17,527)	%	No. of controls (n = 70,130)	%	OR adjusted[a] (95% CI)
Age group (yr)[b]					
20–29	5745	32.8	22,959	32.6	
30–39	7533	43.0	30,165	43.0	
40–44	4249	24.2	17,006	24.3	
Smoking status					
Nonsmoker	8532	48.7	37,479	53.4	Reference
Current smoker	5336	30.4	17,888	25.5	1.25 (1.20–1.30)
Ex-smoker	1841	10.5	6870	9.8	1.13 (1.07–1.20)
Unknown	1818	10.4	7893	11.3	1.00 (0.92–1.07)
BMI (kg/m^2)					
12–18.4	511	2.9	2165	3.1	0.96 (0.87–1.07)
18.5–24.9	7513	42.9	31,976	45.6	Reference
25–29.9	3526	20.1	13,113	18.7	1.13 (1.08–1.18)
30–60	2582	14.7	8757	12.5	1.20 (1.14–1.27)
Unknown	3395	19.4	14,119	20.1	1.05 (1.00–1.11)
Comorbidities					
Asthma	3234	18.5	10,500	15.0	1.16 (1.11–1.22)
Epilepsy	416	2.4	1109	1.6	1.16 (0.99–1.35)

[a] Adjusted for all covariates listed in the table plus use of β-blockers, proton pump inhibitors, systemic corticosteroids, benzodiazepines, serotonin reuptake inhibitors, and anticonvulsants.

[b] Matching variables.

around 1.25 regardless of the definition of short-term use (patients with one to two DMPA prescriptions, or patients with one or two to three DMPA prescriptions separated). In women who had no FPC attendance recorded, the OR for current use of 10 or more DMPA prescriptions, as compared with nonuse, was 1.58 (95% CI = 1.36–1.83). The OR for current users of 10 or more DMPA prescriptions *vs.* nonusers was 1.59 (95% CI = 1.36–1.85) in an analysis restricted to cases without any evidence for an accident-related fracture before the index date.

Compared with patients who consumed no alcohol, increasing use of alcohol was associated with an increasing

TABLE 3. Exposure to DMPA and other hormonal contraceptives and relative risk of fracture

Exposure, no. of prescriptions	No. of cases (n = 17,527)	%	No. of controls (n = 70,130)	%	Unadjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)
DMPA						
Nonuse	15,614	89.1	64,415	91.9	Reference	Reference
Current						
1–2	93	0.5	305	0.4	1.27 (1.01–1.61)	1.18 (0.93–1.49)
3–9	209	1.2	573	0.8	1.52 (1.30–1.79)	1.36 (1.15–1.60)
≥10	280	1.6	710	1.0	1.67 (1.45–1.92)	1.54 (1.33–1.78)
Past						
1–2	620	3.5	1985	2.8	1.31 (1.19–1.44)	1.17 (1.07–1.29)
3–9	529	3.0	1609	2.3	1.38 (1.25–1.53)	1.23 (1.11–1.36)
≥10	182	1.0	533	0.8	1.45 (1.22–1.72)	1.30 (1.09–1.55)
Hormonal contraception (estrogen-containing)						
Nonuse	6591	37.6	26,578	37.9	Reference	Reference
Current						
1–2	215	1.2	871	1.2	0.99 (0.85–1.16)	1.01 (0.87–1.18)
3–9	1136	6.5	4696	6.7	0.98 (0.91–1.05)	1.01 (0.94–1.09)
≥10	2327	13.3	9073	12.9	1.04 (0.98–1.10)	1.09 (1.03–1.16)
Past						
1–2	1972	11.3	7820	11.2	1.02 (0.96–1.08)	1.00 (0.95–1.07)
3–9	3178	18.1	12,787	18.2	1.01 (0.96–1.06)	0.99 (0.94–1.04)
≥10	2108	12.0	8305	11.8	1.03 (0.97–1.10)	1.03 (0.97–1.10)

[a] Adjusted for age, general practice, calendar time, and history in the database by matching.

[b] Adjusted for BMI, smoking, asthma, epilepsy, use of progestins (single preparations), MPA low dose, β-blockers, proton pump inhibitors, systemic corticosteroids, benzodiazepines, serotonin reuptake inhibitors, anticonvulsants, and contraceptive not under investigation.

TABLE 4. Use of DPMA and relative risk of fracture, stratified by fracture type and age[a]

Characteristics	Cases		Controls		OR	95% CI	*P* value
	n	%	n	%			
Current use of ≥10 DMPA prescriptions by type of fracture							
Spine	5	1.8	12	1.1	1.88	0.58–6.06	0.2922
Hip, femur, patella	5	1.4	15	1.1	1.36	0.45–4.11	0.5819
Hip	0	0.0	3	1.2	NA	NA	NA
Femur, patella	5	1.7	12	1.0	1.77	0.56–5.56	0.3274
Lower leg	44	1.6	107	1.0	1.56	1.08–2.27	0.0185
Foot	67	1.6	165	1.0	1.62	1.20–2.18	0.0015
Calcaneus	1	1.0	3	0.8	1.22	0.07–20.79	0.8913
Toes	31	1.5	82	1.0	1.53	0.99–2.37	0.0543
Forearm	42	1.5	125	1.1	1.35	0.94–1.93	0.1068
Clavicle	7	1.4	25	1.3	1.19	0.49–2.91	0.7035
Hand	77	1.8	182	1.1	1.55	1.17–2.05	0.0022
Fingers	28	1.5	81	1.1	1.28	0.81–2.01	0.2936
Humerus, elbow	19	1.9	48	1.2	1.56	0.89–2.74	0.1237
Rib	12	1.5	26	0.8	1.95	0.89–4.28	0.0950
Osteoporotic fractures (spine, hip, wrist, humerus)	31	1.6	87	1.1	1.49	0.97–2.28	0.0671
Current and past use of ≥10 DMPA prescriptions by age (yr)							
<30, current use	100	1.7	258	1.1	1.54	1.21–1.96	0.0005
30–44, current use	180	1.5	452	1.0	1.56	1.31–1.87	<0.0001
<30, past use	43	0.8	169	0.7	0.97	0.69–1.37	0.8553
30–44, past use	139	1.2	364	0.8	1.46	1.19–1.79	0.0002

NA, Not applicable.

[a] Adjusted for age, general practice, calendar time, and history in the database by matching and for BMI, smoking, asthma, epilepsy, use of progestins (single preparations), MPA low dose, β-blockers, proton pump inhibitors, systemic corticosteroids, benzodiazepines, serotonin reuptake inhibitors, anticonvulsants, and other oral contraceptives.

risk of fracture. The OR of developing a fracture for patients who consumed fewer than eight, eight to 14, 15–42, 43–63, or 64 or more units per week were 1.07 (95% CI = 1.02–1.14), 1.29 (95% CI = 1.20–1.39), 1.62 (95% CI = 1.46–1.79), 1.81 (95% CI = 1.11–2.96), and 2.41 (95% CI = 1.19–4.85), respectively. However, adjustment for alcohol consumption did not change the association between DMPA use and fracture.

A direct comparison of users of 10 or more prescriptions of DMPA with users of 10 or more prescriptions of other hormonal contraceptives yielded an OR of 1.46 (95% CI = 1.15–1.85). Finally, when we considered only patients with fractures potentially related to osteoporosis (n = 1936), the OR for users of 10 or more prescriptions of DMPA to develop a fracture was 1.49 (95% CI = 0.97–2.28) compared with nonusers of DMPA.

Discussion

Cross-sectional (3, 7, 11–18) and longitudinal (19–21) studies have indicated that the use of DMPA may have adverse effects on bone metabolism, resulting in impaired bone mineral acquisition during adolescence and accelerated bone loss in adult life. The findings of this large, population-based case-control analysis provide further evidence that current or past use of DMPA may be associated with an increased risk of fractures in women between the age of 20 and the perimenopausal period. The relative fracture risk was mainly increased for women with current exposure of more than 2–3 yr. We also observed a slightly increased risk after past exposure of 10 or more DMPA prescriptions, mainly in women above the age of 30. When we used another cutoff for past exposure to DMPA (*i.e.* ≥720 d instead of ≥180 d), the increased risk for past exposure to DMPA largely disappeared, which may indicate that the effect of DMPA on fracture risk may be reversible after some time after stopping the medication. The fracture risk was independent of BMI, smoking habits, comorbidities, and comedication including use of other contraceptives and hormonal treatments.

Data on the association between DMPA use and fracture risk are limited. In a survey of administrative records of medications and fractures in 6773 women with developmental disabilities, DMPA use was related to fractures

(OR = 2.4; 95% CI = 1.3–4.4) (24). Lappe *et al.* (25) found an increased risk of stress fractures among non-Hispanic White female army recruits with a history of DMPA use who were completing basic training (relative risk = 1.7; 95% CI = 1.0–2.9; $P = 0.04$). Of note, these reports are not necessarily representative of the entire female population, because women with developmental disorders may be more likely to have epilepsy-related fractures (36), and stress fractures are a greater hazard for army recruits than for the general population. Recently, the authors of a Danish case-control study reported an increased risk of fractures in DMPA users compared with nonusers (OR = 1.44; 95% CI = 1.01–2.06); however, the interpretation of the study findings is limited due to a low number of DMPA users and limited availability of potential confounders (26). In our study involving a larger group of exposed women (8.7%), we observed an increasing relative fracture risk associated with increasing DMPA exposure duration, with the highest risk in users of 10 or more recorded DMPA prescriptions corresponding to more than 2–3 yr, independent of the timing of exposure.

When we stratified the results by age (<30 and ≥ 30 yr), the association between current use and fracture risk was seen in both age strata. Past use was associated with an increased fracture risk only in women between 30 and 44 yr of age but not in younger women. These findings remain unclear specifically because duration of DMPA exposure in both age strata has been similar. One might hypothesize that despite the fact that discontinuation of DMPA use may restore bone loss (17, 19, 27), this process may take longer in women of more advanced age.

When we stratified by fracture type, we observed increased fracture risks for longer DMPA users particularly for nonvertebral fractures, specifically lower extremity fractures (mainly foot fractures) and hand and humerus fractures. There was also a tendency toward increased fracture risks for other types of fractures. Although the types of fractures that we included in our analysis were mainly low-trauma fractures, we additionally restricted our analysis to patients who did not have any evidence for an accident in their records before the index date and found an OR that was closely similar to the overall relative risk. Nevertheless, because fractures observed in women between 20 and 44 yr of age were not typically related to metabolic bone disease, we cannot rule out severe trauma as a proximal cause for some fractures. Whether these fractures are the result of DMPA-associated increased bone turnover remains contentious. Finally, we ran an analysis restricted to patients with fractures potentially related to osteoporosis; the adjusted OR for users of 10 or more DMPA prescriptions was 1.49 (95% CI = 0.97–2.28) compared with nonusers of DMPA.

As depicted in Table 2, we observed an increased fracture risk in women with a BMI above 25 kg/m^2. However, in a former analysis in which we had included also women above the age of 50, we observed an increased fracture risk for patients with a BMI below 18.5 kg/m^2, whereas for patients with a BMI above 25 kg/m^2, there was a slightly decreased fracture risk (data not shown). For patients below the age of 50 (or below the age of 45, as in our study population), this could not be observed. Our findings are in line with a recent metaanalysis evaluating BMI as a predictor of fracture risk (37), which reported that the gradient of risk per unit of BMI increased with advancing age, predominantly after 55 yr of age, without adjustment for BMD.

Several studies investigated the effect of combined oral contraceptives on BMD, but none included fractures as an outcome. Combined oral contraceptives do not appear to affect bone mass or bone turnover as a result of maintained estrogen exposure (6, 38). In accordance with these data, we did not observe an effect on fracture risk in women with current or past use of estrogen-containing oral contraceptives. A direct comparison of women using 10 or more DMPA prescriptions with users of combined oral contraceptives yielded an adjusted OR of 1.46 (95% CI = 1.15–1.85).

In the United Kingdom, FPC can also prescribe hormonal contraceptives to women, which may lead to exposure misclassification in the GPRD. If exposure is missed at random (*i.e.* about the same proportion is affected in cases and controls), the estimated OR would tend toward the null. According to a report of the Office for National Statistics in the United Kingdom, more than 82% of the women who used Family Planning Services had also seen their own GP or a practice nurse. Furthermore, a large proportion of women who attended FPC were below the age of 20 yr, and we did not include this age group in our analysis (39). The authors of a previous GPRD-based study explored use of hormonal contraception among diabetic women and concluded that recording of hormonal methods was at a high level when compared with official United Kingdom statistics; there was evidence only for low recording of nonhormonal contraceptive methods (40). However, to further address the issue of exposure misclassification in our study population, we conducted a number of sensitivity analyses that all resulted in similar findings of a slightly increased OR of around 1.25.

Aside from potential exposure misclassification, additional potential limitations of our study need to be discussed. First, we cannot exclude the possibility that a small proportion of fractures may have been missed or misclassified. Systematic radiographic screenings to identify

asymptomatic vertebral deformities and fractures are not available; consequently, the number of vertebral fractures may be underestimated. Second, it is possible that certain demographic or lifestyle factors, such as socioeconomic status, dietary habits, and physical activity, are associated with fracture risk and with use of DMPA and that we did not fully control for potential confounding by such parameters. This is of special interest because it has been reported that DMPA users are less likely to be educated beyond 16 yr and more likely to have a low calcium intake and to become pregnant at a younger age and more frequently than their peers, all of which may have an effect on bone health (15, 20–21, 41). To control for socioeconomic status as much as possible, case patients and controls were matched on general practice. Furthermore, we compared DMPA users of longer duration with short-term DMPA users, which yielded an increased fracture risk with long exposure duration of DMPA, which would not be expected if the increased fracture risk was due only to residual confounding by socioeconomic or lifestyle factors.

In summary, this large population-based case-control study provides additional evidence that the use of DMPA of approximately 2 or more years may slightly increase the risk of fractures.

Acknowledgments

Address all correspondence and requests for reprints to: Christoph R. Meier, Ph.D., M.Sc., Basel Pharmacoepidemiology Unit, Hospital Pharmacy, University Hospital Basel, Spitalstrasse 26, CH-4031 Basel, Switzerland. E-mail: meierch@uhbs.ch.

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