The effect of past use of oral contraceptives on bone mineral density, biochemical markers and muscle strength in healthy pre- and post-menopausal women: a cross-sectional study

Fadoua Allali¹,²,³, Laila El Mansouri¹², Fatima zohra Abourazzak¹², Linda Ichchou¹², Hamza KHazzani¹², Loubna Bennani¹², Redouane Abouqal³ and Najia Hajjaj-Hassouni.¹,²,³

1 Department of Rheumatology, El Ayachi University-Hospital, Sale, Morocco.
2 LIRPOS : Laboratory of information and research on bone diseases
3 Laboratory of Biostatistical, Clinical Research and Epidemiology (LBRCE). Faculty of Medicine and Pharmacy, Rabat, Morocco

Author's email address:
Fadoua ALLALI : fadouaallali@yahoo.fr
Redouane ABOUQAL : abouqal@invivo.edu
Najia HAJJAJ-HASSOUNI : n.hajjaj@medramo.ac.ma
Laila EL MANSOURI : la_mansouri1@yahoo.fr
Fatima Ezzahra ABOURAZZAK : f.abourazzak@yahoo.fr
Linda ICHCHOU : ilinda19@yahoo.fr
Hamza KHAZZANI : hamzakhazzani@yahoo.fr
Loubna BENNANI : loubnabannani29@yahoo.fr

Correspondence and requests for reprints: Prof Fadoua Allali,
Department of Rheumatology (Pr N.Hajjaj-Hassouni), El Ayachi University Hospital, Salé, Morocco.
Tel: 0021261181824
Fax: 0021237782653
e-mail: fadouaallali@yahoo.fr
ABSTRACT

Background: It has been suggested that use of the oral contraceptive pill by women confers protection against osteoporosis later in life. However, cross-sectional studies of bone density among pill users have yielded discrepant results. Methods: A cross-sectional design was used to compare bone mineral density, biochemical markers (osteocalcin, C-terminal cross-linking telopeptide of type I collagen) and three physical performance measures (timed get-up-and-go test, five-times-sit-to-stand test, and 8-feet speed walk) between past oral contraceptive users and never users. We recruited pre- and post-menopausal women (24 to 86 years) including 210 with at least two years of previous oral contraceptive use and 200 never users. Results: Bone mineral density and biochemical markers were similar for past users and never users. However, subgroup analyses for pre-menopausal women showed differences between past users and never users in osteocalcin (15.5 ± 7ng/mL vs. 21.6 ± 9 ng/mL; p =0.003) and C-terminal cross-linking telopeptide of type I collagen (0.30 ± 0.1 ng/mL vs. 0.41 ± 0.2 ng/mL; p = 0.025). This difference persisted after adjustment for age, body mass index, age at menarche and number of pregnancies. There were no differences in bone biochemical markers between past users and never users for post-menopausal women. Past users showed significantly better physical performance compared to never users. Women who had used oral contraceptives for ten or more years had significantly better physical performance. Conclusions: This study demonstrated 1) no significant differences in bone mineral density between past users and never users, 2) decreased bone turnover in pre-menopausal past users, and 3) better physical performance for those with ten or more years of oral contraceptive use.
BACKGROUND

Osteoporosis following menopause is a major health problem that is associated with a high incidence of spine and hip fractures. It is well recognized that chronic hypo-estrogenic states increase bone turnover and lead to decreased bone mineral density (BMD), important risks for fracture. Post-menopausal bone loss can be prevented or reduced by hormonal replacement therapy.

Considerable controversy exists, however, as to whether oral contraceptives (OCs) improve bone mineral density. Studies provide conflicting results regarding the effect of OCs on BMD, with some showing protection [1-4], and others no protection [5, 6]. A review by Kuohung [7] reported no consensus regarding the effects of OCs on BMD and bone metabolism.

There are relatively few cross-sectional studies of OC use and BMD in pre-menopausal women. The Canadian Multicenter Osteoporosis Study showed lower spine and trochanter BMD values in pre-menopausal past OC users compared to never users [8]. In contrast, a large study of pre-menopausal Finnish women showed that OC users had improved age-adjusted dual-energy X-ray absorptiometry (DXA) scores compared to non-users [9]. These conflicting findings may have been due to differences in study duration, oestrogen and progestin dosages, and anatomic sites evaluated in the studies.

Previous research examining the influence of oral contraceptives on muscle function has been limited. Sarwar et al. [10] demonstrated changes in muscle strength, relaxation and fatigability during menstruation, but these changes were unaffected by oral contraceptive use. Elliott et al. [11] have also suggested that oral contraceptive use does not significantly affect muscle strength.
We conducted a cross-sectional study of pre- and post-menopausal women to assess BMD, biochemical markers and physical performance differences between past users and never users of OCs.

METHODS

Design and subjects

We conducted a cross-sectional study of 210 past users of combined estrogen and progesterone OCs and 200 never users. All past users had used OCs for at least two years and had discontinued OCs at least six months prior to the study.

Women were recruited through advertisements at local hospitals in Rabat, Morocco. Informed consent was obtained from all patients and the study was approved by the ethics committee of our university hospital. We excluded patients with a history of (1) using medications known to influence bone metabolism within the past two years (e.g. vitamin D, calcium, corticosteroids, bisphosphonates and hormone replacement therapy); (2) musculoskeletal, thyroid, parathyroid, adrenal, hepatic, or renal disease; (3) malignancy; or (4) hysterectomy.

Data collection and measurements

Each patient completed a questionnaire to assess demographic characteristics and reproductive and menstrual history. Reproductive history included age at menarche, number of pregnancies, duration of lactation and age at menopause. Oral contraceptive use was documented by the age at first use, and the name and type of each preparation used with its duration of use.

Bone mineral density measurements

Lumbar spine, trochanter, femoral neck and total hip BMD were measured by DXA (Lunar Prodigy densitometer). Daily quality control was performed using Lunar Phantom...
measurements, which showed stable results during the study. The Lunar Phantom showed a precision of 0.08 expressed as the coefficient of variation (CV) in percent. Both T and Z scores were obtained. T-scores were calculated using the manufacturer's European reference population range because no Moroccan reference ranges were available.

**Biochemical measurements**

Morning fasting blood and random urine samples were obtained to measure serum calcium, phosphorus, albumin, creatinine, 25-hydroxy vitamin D, osteocalcin, and C-terminal cross-linking telopeptide of type I collagen (CTX). Serum calcium, phosphorus, albumin, and creatinine were measured by automated standard laboratory methods. Serum 25-hydroxy vitamin D was measured by chemiluminescence (Liaison, Diasorin). The intra- and inter-assay CVs were 5% and 11%, respectively (normal range: 20 to 60 ng/mL). Osteocalcin and CTX were measured by immunochemoluminometric assay (Elecsys, Roche Diagnostics, Mannheim, Germany). Intra- and inter-assay variances were 5% and 7%, respectively (normal ranges: 15 to 46 ng/mL for osteocalcin and 0.3 ng/mL to 0.6 ng/mL for CTX).

**Physical performance measures**

Three measures were used to assess physical performance: timed get up and go test (TGUG), five-times-sit-to-stand test (FTSST) and 8-feet speed walk (FSW). Time was measured by stopwatch and rounded to the nearest hundredth of a second.

*Timed get up and go test:* In this test, the patient rises from a chair, walks 3 meters, turns around, returns to the chair, and sits down. The patient was instructed to: "Sit with your back against the chair and your arms on the arm rests. On the word ‘go,’ stand upright, then walk at your normal pace to the line on the floor, turn around, return to the chair, and sit down." The
stopwatch was started on the word `go' and stopped when the patient returned to the starting position.

*Five-times-sit-to-stand test:* Patients were asked to stand up and sit down five times as quickly as possible without the use of their hands. They were timed from their initial seated position to the final standing position at the end of the fifth stand.

*8-feet (2.4 m) speed walk:* Patients were instructed to walk as fast as possible for 8 feet (2.4 m). Patients wore the footwear they normally used. The distance was marked on the floor with red tape and the participant stood just behind the starting line before the test. A digital stopwatch was used to measure the time between the start of walking and when the first foot crossed the finish line.

**Statistical analysis**

For statistical analysis, we used the Student’s *t*-test for matched samples and the *Khi-2 test* to analyze qualitative variables. Descriptive statistics are presented as means and standard deviations (SDs) for continuous variables. Factors significantly associated with biochemical markers, BMD or physical performance measures were tested by multiple linear regression analysis to eliminate potentially confounding factors (age, body mass index (BMI), number of pregnancies, age at menarche, 25-hydroxy vitamin D, and total calcium intake). All analyses were performed using SPSS, version 10.0 for Windows. Results with *p* values less than 0.05 were considered statistically significant.

**RESULTS**

Table 1 shows demographic characteristics, reproductive and menstrual history variables we summarize the distribution for past users and never users. The mean duration of OC use was 7.7 ± 6 years (range 2 to 30 years). Past users were younger compared to never users
(54.3 ± 7.7 years vs. 57.2 ± 11.2 years; p = 0.003). The groups had similar BMIs, daily calcium intake and age at menarche. Before and after adjustment for covariates, pre- and post-menopausal past users did not differ significantly with respect to mean BMD of the lumbar spine, trochanter, femoral neck or total femur (Table 1). Duration of OC exposure (less than 2-4 years; 4 to 6 years; greater than 6 years) did not affect these findings (results not shown).

Biochemical markers were similar for past users and never users: osteocalcin (21.4 ± 10 ng/mL vs. 23.9 ± 14 ng/mL ; p= 0.1) and CTX (0.42 ± 0.2 ng/mL vs. 0.46 ± 0.2 ng/mL; p= 0.1) (Table 1). However, pre-menopausal past users had significantly lower levels of osteocalcin (15.5 ± 7 ng/mL vs. 21.6 ± 9 ng/mL; p= 0.003) and CTX ( 0.30 ± 0.1 ng/mL vs. 0.41 ± 0.2 ng/mL; p= 0.025) compared to pre-menopausal never users. This difference persisted after adjustment for age, BMI, age at menarche and number of pregnancies (Table 2).

**Association between oral contraceptive use and physical performance**

Figure 1 shows the mean duration for three physical performance measures by history of OC use. Past users had significantly better physical performance compared to never users. This difference persisted after adjusting for age.

The crude and adjusted mean differences for the TGUG, the 8 FSW and the FTSST by quartile OC duration are shown in Table 3. The never user group was used as a reference. Women with a past OC use of ten or more years showed significantly faster TGUG tests in the crude analysis (p = 0.002). This association remained after controlling for age, menopausal status and 25-hydroxy vitamin D level (p = 0.027). Similar results were observed with the FTSST. In adjusted analyses, patients with ten or more years of past use were 1.84 s quicker in the TGUG (p < .005) and 1.9 s quicker in the FTSST (p < 0.005) compared to never users. There was also an association between past OC use of ten or more years and
faster 8 FSW tests (p < .005), but this association was not significant after adjustment for age, menopausal status, and 25-hydroxy vitamin D level (p < .005).

**DISCUSSION**

The findings of this cross-sectional study of pre- and post-menopausal women suggest no significant differences in BMD between past users and never users of OCs. These results add to the body of literature that includes reports of no impact of OCs on BMD [5, 7, 12, 13] and reports of positive associations between BMD and OCs [1-4]. The apparently divergent findings from previous studies may be due to diverse age ranges, study durations, and OC dosages used.

Horsman et al. [14] reported that post-menopausal women taking 15 to 25 µg of estrogen daily experienced no bone loss, whereas those taking greater than 25 µg daily demonstrated net bone mass gain. Thus, improved bone mineralization among low-dose OC users is biologically plausible. Furthermore, conflicting findings may reflect differences in duration of OC use. Berenson et al. [15] reported that long-term oral contraceptive use increased bone mass. This finding was supported by other studies showing that using high-dose OCs for ten or more years provided the greatest protection against low BMD [16, 17]. However, Petitti [12] reported that OCs provide short-term BMD increases that are reversible. The mechanism by which hormonally-mediated BMD loss may be reversed is unclear. In this study, we did not know the dosages of OCs used. But since the 1960s, when some of the women in our study had used contraception, the estrogen content of OCs has always been ≤50 µg ethinyl estradiol. Furthermore, longer duration of OC use did not affect BMD in this study.

To date, relatively few cross-sectional studies of OC use and BMD have focused on pre-menopausal women. The relationship between OCs, bone mineral density and
osteoporotic fracture risk remains controversial because past OC users are also more likely to use post-menopausal hormone replacement therapy. Furthermore, some reviews suggest a negative association between OC use and BMD, but the reasons for this are unclear.

Our finding of decreased bone turnover in OC users is consistent with previous cross-sectional and prospective studies of biochemical markers. Garnero et al. [18] examined several biochemical markers, including BSAP and DPD in a cross-sectional comparison of users and non-users [18]. When compared to non-users, biochemical markers in OC users decreased 15–24% and bone resorption decreased 17–28%. Utilizing a prospective design, Karlsson et al. [19] reported a 50% decrease in osteocalcin in OC users after three months. In our study, bone turnover markers (osteocalcin and CTX) were decreased in pre-menopausal past users compared to never users; there was no change in post-menopausal women.

The effects of OC use on muscle mass and performance have been less well investigated. Exogenous, synthetic reproductive hormones (in particular hormone replacement therapy) have been shown to increase muscle strength [20, 21]. Therefore, strength might have been expected to increase as a result of oral contraceptive administration. However, there are conflicting data regarding the effect of OC on physical performance, which may reflect differences in estrogen and progestin formulations. OC use has been shown to decrease, maintain, or have no effect on a variety of strength measures [22-25]. In the present study, patients who used oral contraceptives for ten or more years had better physical performance measures compared to never users. Adjustments for major possible confounders did not affect these results. However, the impact of OCs on physical performance should be viewed with caution. We are unaware of any literature supporting these findings, and the study did not control for the presence or degree of osteoarthritis.

Our study has some limitations. First, the cross-sectional design relied on information about past use, and data was obtained from patient recall without medical record
confirmation. Secondly, although the overall sample size was adequate, the small number of pre-menopausal women may have reduced our power to detect small differences in BMD.

However, this study does have several strengths. First, the study evaluated a large number of patients. Second, we evaluated three criteria: 1) bone mineral density, 2) biochemical markers of bone turnover, and 3) physical performance using several validated instruments. Finally, all variables were analyzed in pre- and post-menopausal women from Morocco, a population where little research has been done on this topic.

In conclusion, this cross-sectional study of pre- and post-menopausal women showed no significant differences in BMD between OC past users and never users, decreased bone turnover in OC pre-menopausal past users, and better physical performance in patients with ten or more years of past OC use. Future research should investigate the effect of oral contraceptives on other strength and performance measures (such as muscle fatigability and endurance) as well as various health measures so that specific recommendations can be made for oral contraceptive users.
COMETING INTERESTS

The authors declare that they have no competing interests for this study.

ACKNOWLEDGEMENTS

This work was supported by grants from the University Mohammed V, Souissi, Rabat-Morocco.

The University Hospital Center of Rabat- Morocco supported the bone mineral density measures.

REFERENCES


FIGURE LEGENDS

Figure 1: Comparison of mean duration of the three physical performance tests.
# TABLES

**Table 1**: Demographic and anthropometric characteristics of Ocs users and nonusers

<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients n=410</th>
<th>Pre-menopausal women n=92</th>
<th>Post menopausal women n=318</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OC users</strong></td>
<td><strong>Nonusers</strong></td>
<td><strong>OC users</strong></td>
<td><strong>Nonusers</strong></td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.3 ± 7.7</td>
<td>57.2 ± 11.2*</td>
<td>45±5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28 ± 4.5</td>
<td>28.5 ± 4.8</td>
<td>28.8±3.9</td>
</tr>
<tr>
<td>Age at menarche (years)</td>
<td>12.7 ± 1.8</td>
<td>12.6 ± 1.6</td>
<td>13.1±1.6</td>
</tr>
<tr>
<td>Number of pregnancies</td>
<td>4.4 ± 2.2</td>
<td>4.2 ± 3.5</td>
<td>3.6±1.8</td>
</tr>
<tr>
<td>Breast feeding duration (months)</td>
<td>29.9 ± 42.7</td>
<td>30 ± 42.9</td>
<td>17.5±21.9</td>
</tr>
<tr>
<td>Age of menopause (years)</td>
<td>46.5 ± 9.4</td>
<td>47 ± 6.8</td>
<td>-</td>
</tr>
<tr>
<td>Daily calcium intake (mg/j)</td>
<td>695 ± 229</td>
<td>688 ± 226</td>
<td>730±258</td>
</tr>
<tr>
<td>Lumbar spine (g/cm²)</td>
<td>1.01 ± 0.17</td>
<td>0.99 ± 0.19</td>
<td>1.14±0.13</td>
</tr>
<tr>
<td>Femoral neck (g/cm²)</td>
<td>0.88 ± 0.13</td>
<td>0.88 ± 0.15</td>
<td>1±0.13</td>
</tr>
<tr>
<td>Ward's triangle (g/cm²)</td>
<td>0.72 ± 0.16</td>
<td>0.71 ± 0.17</td>
<td>0.86±0.13</td>
</tr>
<tr>
<td>Trochanter (g/cm²)</td>
<td>0.72 ± 0.12</td>
<td>0.71 ± 0.14</td>
<td>0.82±0.1</td>
</tr>
<tr>
<td>Total femur (g/cm²)</td>
<td>0.93± 0.14</td>
<td>0.91± 0.15</td>
<td>1.06±0.1</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>96.4± 5.2</td>
<td>97 ± 4.8</td>
<td>95.4± 6.1</td>
</tr>
<tr>
<td>Phosphatus (mg/dl)</td>
<td>36.1± 4.9</td>
<td>35.5± 5</td>
<td>34.56± 5.13</td>
</tr>
<tr>
<td>25 OH Vitamin D</td>
<td>18.8 ±8.1</td>
<td>17.4± 7.9</td>
<td>20.2± 7.4</td>
</tr>
<tr>
<td>Osteocalcin (ng/ml)</td>
<td>21.4 ± 10</td>
<td>23.9 ± 14</td>
<td>15.5 ± 7.5</td>
</tr>
<tr>
<td>CTX (ng/ml)</td>
<td>0.42 ± 0.2</td>
<td>0.46 ± 0.21</td>
<td>0.30 ± 0.11</td>
</tr>
</tbody>
</table>

*Significantly different from Oral contraception users. p<0.005
Table 2: Relationship between oral contraception use and biochemical bone markers in linear regression analysis

<table>
<thead>
<tr>
<th></th>
<th>CTX</th>
<th>Osteocalcin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>P</td>
</tr>
<tr>
<td>Age</td>
<td>0.15±0.23</td>
<td>0.5</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.18±0.31</td>
<td>0.5</td>
</tr>
<tr>
<td>Age at menarche</td>
<td>0.91±0.80</td>
<td>0.2</td>
</tr>
<tr>
<td>Number of pregnancies</td>
<td>0.33±0.68</td>
<td>0.6</td>
</tr>
<tr>
<td>Oral Contraception</td>
<td>-7.71±2.80</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 3: Relationship between physical test and oral contraception duration use.

<table>
<thead>
<tr>
<th></th>
<th>Crude OR</th>
<th>Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timed get-up-and-go test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never user</td>
<td>0 (reference)</td>
<td>0 (reference)</td>
</tr>
<tr>
<td>OC use &lt;3 y</td>
<td>-1.39 (-3.31, 0.62)</td>
<td>-0.89 (-2.7, 0.9)</td>
</tr>
<tr>
<td>OC use for 3-6 y</td>
<td>0.04 (-2.13, 2.22)</td>
<td>-0.45 (-2.5, 1.6)</td>
</tr>
<tr>
<td>OC 6-10 years</td>
<td>0.42 (-1.98, 2.83)</td>
<td>-0.32 (-2.5, 1.8)</td>
</tr>
<tr>
<td>OC&gt;10 years</td>
<td>-2.52 (-4.15, -0.93)*</td>
<td>-1.84 (-3.2, -0.47)</td>
</tr>
<tr>
<td><strong>Five-times-sit-to-stand test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never user</td>
<td>0 (reference)</td>
<td>0 (reference)</td>
</tr>
<tr>
<td>OC&lt;3 years</td>
<td>-1.39 (-3.30, 0.50)</td>
<td>-1.62 (-4.0, 0.7)</td>
</tr>
<tr>
<td>OC 3-6 years</td>
<td>0.41 (-1.67, 2.49)</td>
<td>0.79 (-1.8, 3.4)</td>
</tr>
<tr>
<td>OC 6-10 years</td>
<td>-0.54 (-2.84, 1.87)</td>
<td>0.34 (-2.4, 3.1)</td>
</tr>
<tr>
<td>OC&gt;10 years</td>
<td>-1.56 (-3.10, -0.04)*</td>
<td>-1.9 (-3.6, -0.17)</td>
</tr>
<tr>
<td><strong>8-feet (2.4 meters) speed walk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never user</td>
<td>0 (reference)</td>
<td>0 (reference)</td>
</tr>
<tr>
<td>OC&lt;3 years</td>
<td>-0.42 (-1.21, 0.37)</td>
<td>0.07 (-0.7, 0.9)</td>
</tr>
<tr>
<td>OC 3-6 years</td>
<td>-0.21 (-1.07, 0.65)</td>
<td>-0.59 (-1.5, 0.3)</td>
</tr>
<tr>
<td>OC 6-10 years</td>
<td>-0.014 (-0.97, 0.94)</td>
<td>-0.3 (-1.3, 0.7)</td>
</tr>
<tr>
<td>OC&gt;10 years</td>
<td>-0.85 (-1.50, -0.22)*</td>
<td>-0.22 (-1.3, -0.7)</td>
</tr>
</tbody>
</table>

Multiple regression analysis: adjustment on age, menopausal status and 25 OH Vit D.
Figure 1: Comparison of mean duration of the three physical performance tests according to OC use.
Figure 1

The bar chart shows the physical performance time (in minutes) for different activities: TGT, FTST, FWST. The chart compares oral contraception users (open bars) and never users (solid bars).
Additional files provided with this submission:

Additional file 1: payment.doc, 19K
http://www.biomedcentral.com/imedia/1454058833227757/supp1.doc
Additional file 2: cover lettre laila.doc, 26K
http://www.biomedcentral.com/imedia/9878904092615890/supp2.doc
Additional file 3: comment 2.doc, 37K
http://www.biomedcentral.com/imedia/4941823292507986/supp3.doc
Additional file 4: comment 1.doc, 55K
http://www.biomedcentral.com/imedia/1848446874250799/supp4.doc