Original Article

The Effect of Long Term Use of Combined Pills and Depo-Provera on Bone Density Parameters

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Summary:

Background: Promotion of bone health is particularly important for young women at reproductive age group, as the critical years for building bone mass are from pre-adolescence to about age 30 years.

patients and Methods: This cross sectional study was performed on three groups, first group of 30 women who had used combined pills for more than 2 years, second group of 30 women who had used Depo-Provera for more than 2 years, last group contain 30 women who had used barrier method or they didn't use any contraceptive as a control group.Bone mineral density (BMD) of lumbar spine (L2-L4), right proximal femur was determined by dual energy x-ray absorptiometry in (femoral neck, greater trochanter, ward's triangle, and shaft of femur). Evaluation of serum calcium was performed.

Results: The results of three groups were compared to predict the influence of using hormonal contraceptive measures on bone mineral density. The study showed significant increase in BMD among women using combined pills, and decrease in BMD among women using Depo-Provera in all anatomical sites

Conclusions: The use of combined pills protects or increases BMD, while Depo-Provera diminishes BMD. In essence, improving BMD While using combined pills can be regarded as one of the benefits of this method.

Keywords: bone density, combined pills Depo-Provera.

Introduction:

The onset of vertebral bone mineral loss begins in the 20s, but over all change is small until menopause. Bone density in the femur peaks in the mid to late 20s and begins to decrease around age 30. In general, trabecular bone resorption and formation occur five times as fast as cortical bone, bone mass is more in black and obese women and less in white, Asian, thin and sedentary women. (1), (2) Several, but not all, studies suggest that exposure to combined oral contraceptives may preserve or even increase bone mineral density. In women exposed to combined pills , there is clinically significant higher bone mineral density which would be expected to reduce fracture risk. (3) Vertebral bone mineral density decreases by approximately 1% each year in premenopausal women; whereas the rates of loss may be less at the proximal femur and distal forearm. Pharmacologic doses of estrogen used to suppress ovulation may exert a positive influence on bone, preventing or slowing bone loss, particularly at sites rich in cancellous bone, which is more responsive to hormonal stimuli because of greater surface area.

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(3) Depot medroxyprogesterone acetate, currently the most extensively used of the injectable contraceptives, has been in use for approximately 30 years in more than 90 countries. (4), (5) the injectable contraceptive depot medroxyprogesterone inhibits pituitary gonadotropine secretion. Ovulation and ovarian estrogen production are suppressed, and women using Depo-provera for long periods are usually amenorrheic and have low plasma estradiol levels. (6), (7) Given that women are four times more likely than men to develop osteoporosis. New data shows that Depo-Provera usage decreases bone mineral density in women and an effect that appeared greater the longer the use. (7), (8) However the evidence also shows that when women stop using Depo-provera, the bone loss is at least partially reversed. (7), (8), (9) Long term users may develop decrease bone density, very low serum estradiol levels below 20 picogram-ml have occurred in some DMPA users. When the serum estradiol level falls below 30, confirmed by a second determination, women in some clinics are encouraged to take exogenous estrogen if they want to continue using DMPA as a contraceptive. (10) Pregnancy itself has not been shown to result in significant loss of bone density in studies of both animals and human beings. Sowers suggested that this might be a result of:

1. High estrogen levels known to increase osteoblastic activity.
2. Increased absorption of calcium in pregnancy.
3. Increased in body mass and its associated stress on the skeletal system. (11) All of these factors appear to override the transfer of 30 g of calcium to the fetus, mostly in the third trimester. This would be equivalent to 3-4 % loss of maternal skeleton if it were the only source of calcium. (12) Although the precise role of lactation on bone mass is currently under investigation, it is known that a 5% to 6 % transitory bone mass reduction occurs after 6 months of lactation. Furthermore, the complex and variable roles that estradiol, prolactin, and parathyroid-hormone-related protein play in bone metabolism during pregnancy and lactation. (11) Life style can have a beneficial effect on bone density. Diet and exercise are the two most important for strong and healthy bones. For young people, the low level of calcium intake can lead to lower bone mass. A common source of calcium is milk dairy product. Drinking one 8-ounce glass of milk provides 300 mg of calcium; adults need three times this amount of calcium daily. In addition to calcium, other minerals such as magnesium are important for bone health.(8) Adverse habits such as cigarette smoking or alcohol consumption are associated with an increased risk of osteoporosis, because of lower blood levels of estrogen in smokers. (2)

Patient and methods:

Cross-sectional study was conducted at family planning clinic in Baghdad teaching hospital and Al-Elwayia maternity teaching hospital from October 2004 to October 2005. The cases studied were 30 women between the age 25-35 years, who had used combined oral contraceptive pills, Microgynon, (ethinyloestradiol 0.03mg, levonorgestrel 0.15 mg) daily for 24 months or more, and another 30 women also between the age 25-35 years who had used Depo-Provera, 3 monthly for 24 months or more as contraception. A control group consisted of thirty women their age between 25-35 years, women where new attendants to family planning clinic, and had never used hormonal contraceptives, or those who depended on mechanical contraception. Body height was measured to the nearest 0.5cm with the patient in the erect position without shoes. Body weight with the indoor clothing, but without shoes, was measured to the nearest 1 kg Body mass index was calculated (by dividing the weight of the participant) in kilograms per square of height in meter. Serum calcium level estimated by taking blood sample without tourniquet, and put it in a test tube without anticoagulant and then centrifuged for 10 minutes. The serum was separated and by using colorimetric device in comparison with a control, the color of the serum directly correlated with the amount of the ion. Bone mineral densities were measured by DEXA scanner (the device manufactured by lunar medical equipments), by scanning lumbar spine at L2-L4, bone mineral density of the right proximal femur were determined by dual energy x-ray absorptiometry in four regions:

1. Femoral neck, defined as a rectangular band positional transcervically to avoid the greater trochanter and adjacent pelvic bone.
2. The greater trochanter, demarked distally by the femoral midline and medially by the femoral neck.
3. Ward's triangle, defined as a square of 1x1cm with the lowest density within the proximal femur which is generated by the device.
4. Shaft of femur

The bone mineral density (BMD) is expressed by g/cm^2 which is the absolute measurement of BMD of the region measured.

BMD compared with age and sex matched controls is the (Z-scores)

BMD compared with young adult sex matched controls is the (T-scores)

In this study, the T scores which can predict the future risk of pathological fracture Statistical analyses were computer assisted using ANOVA test. Frequency distribution for selected variables was done first. The statistical significance of difference in mean of an outcome is continuous. Normally distributed variables were assessed by independent samples T-test. P value of <0.05 was considered statistically significant.

Results:

As shown in table 1, three groups (control, Depo-Provera users, and combined pills users) had a comparable age, BMI, age of menarche, parity, lactation period , duration of contraception use and serum calcium level as there is no statistically significant difference among the three groups and the only difference is the type of contraceptinused used .

The bone mineral density was measured in five different areas of the femur, and lumbar spine. It shows the bone density measures in 30 control women, 30 Depo-Provera users, and 30 combined pills users and comparisons among them which result in:

1) As shown in figure 1, there is significant increment of mean BMD in the lumbar spine among combined pills users versus control and Depo-Provera users respectively (1.29 ± 0.08 g/cm^2 vs. $0.96 \pm 0.07 g/cm^2$ and $0.87 \pm 0.02 g/cm^2$).

2) A statistically significant ($p<0.01$) higher mean BMD of neck of femur among combined pills users (1.35 ± 0.09 g/cm^2), than those who had used Depo-Provera ($0.82 \pm 0.06 g/cm^2$), and control group ($0.91 \pm 0.07 g/cm^2$). As shown in figure 2.

3) Wards' triangle in combined pills users ($1.40 \pm 0.04 g/cm^2$) had significant elevation of mean BMD than control group (0.90 ± 0.05) and those who had

used Depo-Provera (0.80 ±0.06g/cm^2).As found in figure 3.

4)In greater trochanter, mean BMD of combined pills users (1.37 ±0.01g/cm^2), mean BMD of control (0.91±0.01g/cm^2), and of Depo-Provera (0.81 ±0.04 g/cm^2), both combined pills users and control group were statistically different (g/cm^2) from Depo-Provera users. As shown in figure 4.

5)Mean BMD of shaft of femur in combined pills users (1.92 ±0.14g/cm^2) which are significantly higher than mean BMD of Depo-Provera users (0.83 ±0.04g/cm^2) and control group (0.96 ±0.01g/cm2).

Table 1: shows the epidemiological characteristics of the 3 study groups as assessed by ANOVA test

Characteristics	Control Group (N=30)	Co pills users group (N=30)	Depot users Group (N=30)	F value	P value
Age (Years)	30.6±2.3	30.1±2.7	30.8±1.4	0.726	NS
BMI (kg/m^2)	25.9±1.3	25.8±1.6	26.6±1.3	2.456	NS
Menarche age(years)	12.4±1.1	12.5±1.1	12.0±0.8	1.851	NS
Parity(Mean)	2.6±0.5	2.7±0.5	2.6±0.4	0.28	NS
Total lactation period (Month)	19.9±2.5	18.9±3.7	19.3±2.9	0.778	NS
Duration of hormonal contraception usage (Months)	Nil	27.6±2.9	25.8±2.3	7.97	NS
Serum Calcium (mmol/L)	2.1±0.5	2.2±0.6	1.8±0.5	2.433	NS

NS non significant

Table: 2 shows the bone mineral densities measured at different anatomical sites among the study groups as assessed by ANOVA test

Bone Mineral density (g/ cm^2)	Control Group (N=30)	Co pills users group (N=30)	Depot users Group (N=30)	F value	P value
Lumbar spine	0.96±0.07	1.29±0.08	0.87±0.02	186.5	P<0.01
Neck of femur	0.91±0.07	1.35±0.09	0.82±0.06	21.14	P<0.01
Ward's triangle	0.90±0.05	1.40±0.04	0.80±0.06	36.49	P<0.01
Greater trochanter	0.91±0.01	1.37±0.01	0.81±0.04	146.8	P<0.01
Shaft of femur	0.96±0.01	1.92±0.14	0.83±0.04	5.74	P<0.01

Significant if P<0.05

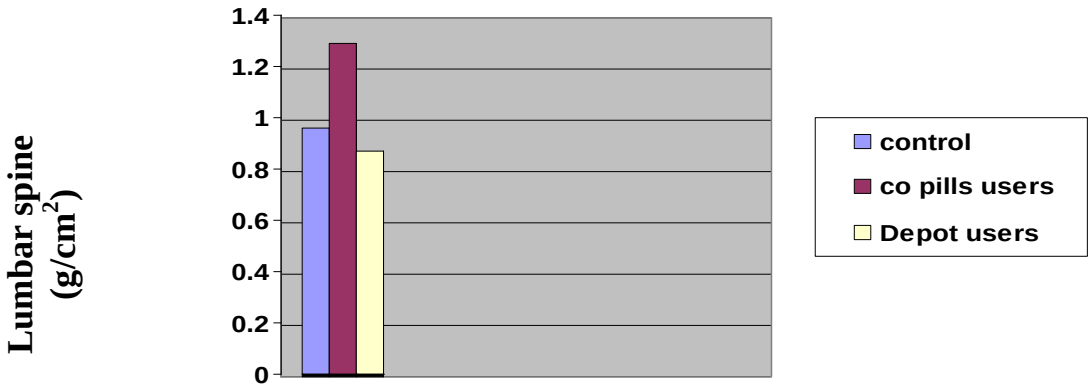

Figure (1) shows the BMD in lumbar spine of three groups of study.

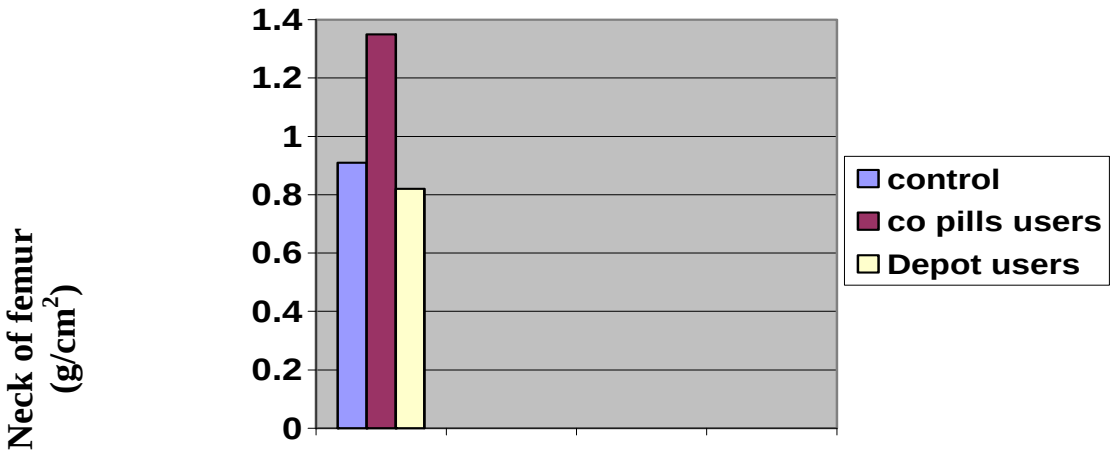

Figure (2) shows the BMD in neck of femur in the three groups of study.

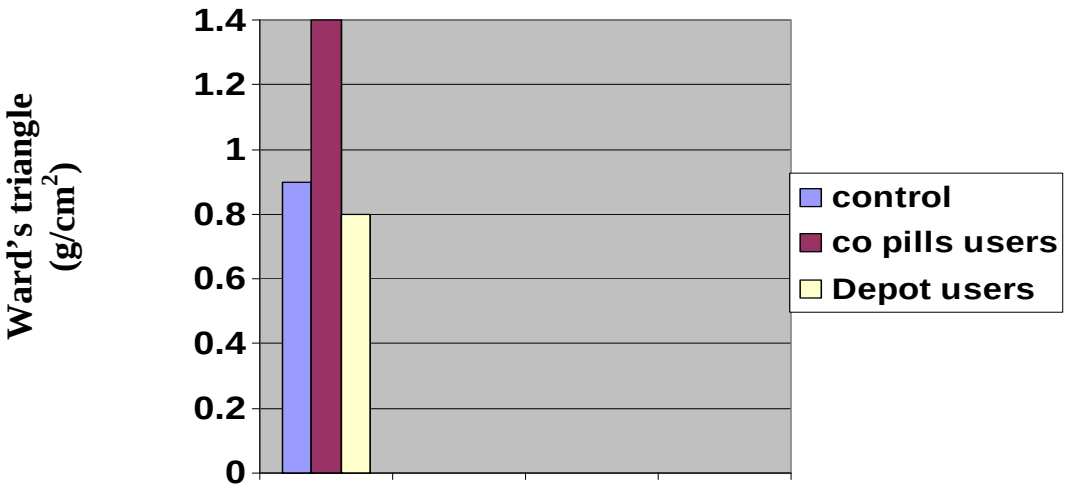

Figure (3) shows the BMD in ward's triangle among the three groups of the study.

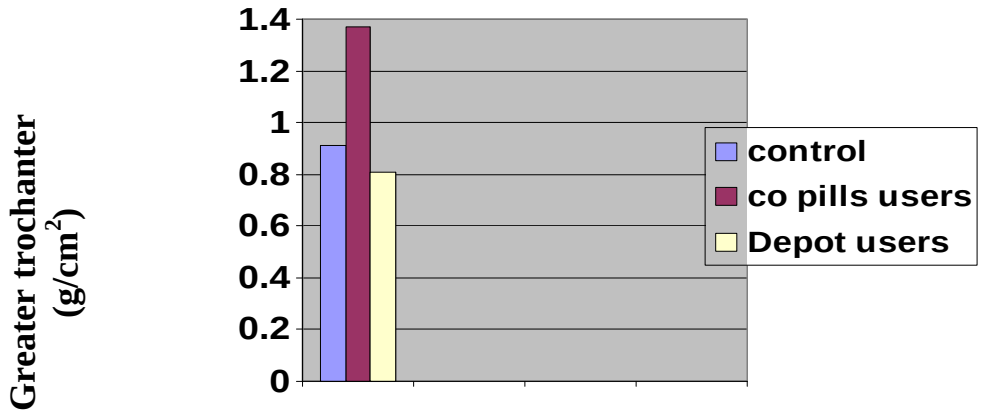

Figure (4) shows the BMD in greater trochanter in the three groups

Discussion:

Osteoporosis and the fractures accompanying low bone density are a major public health. Although prevention efforts to date have emphasized on minimizing postmenopausal bone loss, factors influencing the attainment and maintenance of peak bone mass at younger age also affect the future risk of fractures. (13) The increasing age of the female's population will result in a substantial increase in morbidity and mortality as a result of complications from fractures caused by osteoporosis. This is predominantly a condition of women and is exacerbated by loss of estrogen that occurs during the perimenopausal and menopausal periods. (13) BMD is affected by many like parity, lactation, and period of hormonal contraceptive usage, exercise, and type of diet. Nevertheless in this study there were no statistical differences regarding those factors as shown in table 1 and this suggest that the differences in BMD among the three groups is attributed to the type of contraception used. The co pills are safe method for contraception and effective. It is one of the most extensively studied medications ever prescribed. The overall risks and benefits of co pills suggest that it may be appropriate to make them available without a prescription. (14) Hormonal contraceptives are used by numerous women very often throughout a prolonged period of time and more frequently early in life, within the first reproductive years. The close relationship between estrogen metabolism and bone turnover raises the question of the potential bone impact of oral contraceptives containing low dose of ethinyl-oestradiol. (14) In this study BMD measurement done without obstacles because it was inexpensive(0.3 $), non invasive (low dose radiation 0.05 RAD) especially we exclude pregnancy and perform it after the cycle immediately completed, and short time of scanning (less than 10 minutes).Yet some patients refuse to do it.

In this study we found that women using combined pills had higher BMD measures and T-scores at all anatomical sites measured above. This agrees with:

- Pasco et al, (3) 2000, found that positive association had reported between oral contraceptive use and bone mineral density at the lumbar spine, distal radius, proximal femur, and the whole body.

It disagrees with:

- Mais et at, (15) 1993, reported a no significant trend for higher bone mineral density associated with the use of low-dose oral contraceptives.

A small sample size and a short period of exposure may have limited the ability to detect small differences in this study.

We observed that use of DMPA for 24 months or more has an adverse effect on BMD, compared with combined pills users. In general, women who used DMPA experienced loss in BMD, and T-scores in all anatomical sites measured in this study compared with those not using hormonal contraception and good gain among combined pills users, this explained by significantly lower estrogen levels in DMPA users, than users of nonhormonal contraception, and it could be related to the exogenous glucocorticoid-like effect of DMPA. (16)

The result of our study goes with finding of:

- Berenson et al, (16) the study performed on 155 women, the patients chose their method for contraception, DMPA, combined pills, and nonhormonal contraceptives. This study shows DMPA has an adverse effect on BMD in lumbar spine, in comparison with combined pills or nonhormonal methods, when used for 12 months.
- Cundy et al, (6) 1998, found that women (after age 21 years) using long-term DMPA contraception have significantly reduced bone density.
- Petitti et al, (1) 2000, in his study 2474 women were participating over 3 years. For combined pill use, adjusted mean BMD was significantly higher in short-term, current users compared with women who never used hormonal contraceptives. For DMPA, adjusted mean BMD in mid shaft ulna and distal radius was statistically significantly lower in short-term users compared with those who never used hormonal contraceptives. This study suggests that hormonal contraceptive use by young adults is associated with small changes in BMD that occur after initiation of use.
- Gbolade et al, (14) 1998, found that DMPA users with more than one year had over all bone density of the lumbar spine that was significantly lower than the population mean for women in reproductive age.
- Cromer et al, (17) 1996, reported that only among adolescents who used DMPA, vertebral bone density decreased from baseline density, whereas for measures of oral contraceptives it increased. This raises concern about the effects of this agent on bone density in younger adolescents, who are building bones at higher rates.

This study disagrees with:

- Virutamasen et al, (18) 1994, found no statistically significant difference in radiographic measures of bone density between DMPA users and the comparison group, this may be due to different race or number of patients .

Conclusion:

Women who had used DMPA experienced loss in BMD, while those who had used combined pills had a significant gain in BMD.

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