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Effects of Hormonal Contraceptives on Bone Mineral Density

Barbara A. Cromer

Ohio State University, College of Medicine and Children's Hospital, Columbus, Ohio, USA

Abstract

The clinical research to date on the effects of 3 types of hormonal contraceptives, i.e. depot medroxyprogesterone acetate ('Depo-Provera'), levonorgestrel subdermal implants ('Norplant'), and oral contraceptives, on bone mineral density in premenopausal women is reviewed.

The large variance in results across studies for each method is in part due to differences in research design, techniques for measuring bone mineral density, age of the study participants and type of oral contraceptive preparation.

However, the balance of the evidence leans toward a positive effect of oral contraceptives on bone mineral density in women of all age. On the other hand, few observations have yet been published on the effects of the new progestin oral contraceptives on bone mineral density.

The few extant data suggest a positive impact of levonorgestrel subdermal implants on bone mineral density in women of all ages. Although the findings are preliminary, it appears that depot medroxyprogesterone acetate may exert a negative effect on bone mineral density. More specifically, caution should be exercised in prescribing long term depot medroxyprogesterone acetate (e.g. >5 years) especially in young adolescents (e.g. <16 years old) who may not have yet reached peak bone mass.

Osteoporosis is a major public health problem, with an increasing worldwide prevalence, in part reflecting a demographic shift toward an older population.[1] In addition to enormous healthcare costs, physical and social consequences to the individuals and their families can be devastating; hip fractures in the elderly carry up to a 20% mortality rate, and cause permanent disabilities in a large percentage of survivors.[2]

Recently, there has been some progress in pharmaceutical research towards producing a drug which can, at least partially, reverse osteoporosis. For example, raloxifene, a nonsteroidal benzothiophene, has been recently demonstrated to increase bone mineral density in postmenopausal women without apparent adverse effects on the endometrium or lipid levels.[3] However, the mainstay approach to the prevention of osteoporosis has been to prescribe estrogen therapy to women after the menopause, most commonly in combination with a progestogen. An additional approach to the prevention of osteoporosis is to maximise the peak bone mass (defined as the highest level of bone mineral density after linear growth and bone con-

solidation have ceased, usually in the third decade of life).[4] The level at which bone mass peaks is a critical predictor of the likelihood for osteoporosis in later life.[5]

A woman with a peak bone mass that is within the low, but 'normal' of the range, is likely to reach the critical threshold at which the basic architecture of the bone disintegrates long before a woman who has a peak bone mass in the upper end of the normal range. Also, it is important to remember that even small changes in bone mineral density may be of major clinical significance in the future. According to Kreipe and Forbes,[6] a permanent 10% decrease in bone mineral density is associated with a 2- to 3-fold increased risk of future fracture.

Adolescence is a crucial period in which bone mineral density should be optimised, thereby leading to a high peak bone mass. The vast majority of bone mass is accrued before the age of 20.[7-10] From the onset of puberty, at around the age of 11 years, until completion of puberty, at around the age of 15 years, total bone mineral density normally increases by 37%.[7] The majority of skeletal mass increase is caused by an increase in bone size associated with longitudinal growth; 15% of total adult height is achieved during this period of growth.[11] In a cross-sectional study by Matkovic et al.,[7] peak bone mass was reached at several anatomical sites by the of age of 18 years.

A myriad of factors affect bone mineral density in the premenopausal woman. Well documented negative predictors of bone mineral density include a family history of osteoporosis, smoking, lack of exercise, Caucasian ethnic background, poor intake of calcium, and low body fat, or any other source of estrogen deficiency.[1] Of this list, the genetic influence and estrogen levels are the 2 most powerful determinants of bone mineral density.

Several drugs have been demonstrated as having significant negative effects on bone mineral density, such as corticosteroids.[12] There have been some recent data that suggest there is a possible negative effect on bone mineral density by depot medroxyprogesterone acetate ('Depo-Provera') in older premenopausal women[13] and in adolescents[14] using the drug for contraception.

The purpose of this report is to review the clinical research salient to these findings and place them in context of the other commonly available forms of hormonal contraception, i.e. levonorgestrel implants ('Norplant') and oral contraceptives, in the premenopausal population.

1. Depot Medroxyprogesterone Acetate

The seminal work relating depot medroxyprogesterone acetate and bone mineral density was conducted by Cundy et al.[13] and published in 1991 (table I). In a cross-sectional design study, they compared bone mineral density in 30 users of depot medroxyprogesterone acetate (average age 42 years, minimum of 5 years of use) with that of 30 pre- and postmenopausal control individuals. Using the dual energy x-ray absorptiometry (DEXA) technique to measure bone mineral density, they found that depot medroxyprogesterone acetate users had a significantly reduced bone mineral density (mean difference 7.5% in the lumbar spine and 6.6% difference at the femoral neck) when compared with bone mineral density of premenopausal control individuals, but higher than that of postmenopausal control individuals. The mean estradiol level in the depot medroxyprogesterone acetate study participants was 81 pmol/L (range 35 to 400) which is low, consistent with the early follicular phase of the menstrual cycle.

In a prospective study by Naessen et al.,[15] 22 women (average age 33 years) were randomised to either depot medroxyprogesterone acetate or levonorgestrel subdermal implants. Single-photon absorptiometry (SPA) of the bone mineral density of the forearm was performed at baseline and after 6 months of treatment. Bone mineral density decreased by a mean of 0.41% in depot medroxyprogesterone acetate users and was interpreted as 'stable,' as this amount of loss would be consistent with the natural history of bone loss after peak bone mass, but before the menopause. No significant differences were found between estradiol levels from

Table I. Summary of studies evaluating bone mineral density (BMD) in depot medroxyprogesterone acetate (DMPA,'Depo-Provera') users

Study	Study design	Study sample	No. of participants	Method[a]	Site(s)[b]	Results[c]
Cundy et al.[13]	Cross-sectional	Pre- and postmenopausal women, control participants	30 per 3 groups	DEXA	Lumbar spine and femoral neck	↓ BMD in DMPA users *vs* that in control participants
Naessen et al.[15]	Randomised clinical trial	Premenopausal women	11 DMPA users, 11 levonorgestrel subdermal implant users	SPA	Forearm at baseline and 6 months	BMD 'stable'
Scholes et al.[16]	Longitudinal, cohort	Premenopausal women	166 DMPA users, 213 nonusers	DEXA	Lumbar spine	12- to 21-year-olds, BMD 12% ↓ in users *vs* that in nonusers
Cromer et al.[14]	Prospective	Adolescent girls	1 year: 15 DMPA users, 17 control participants; 2 years: 8 DMPA users, 4 control participants	DEXA	Lumbar spine at baseline, 1 year, 2 years	↓ BMD 1.53% in DMPA users *vs* ↑ 2.85% in control participants, after 1 year; ↓ BMD 3.12% in DMPA users *vs* ↑ 9.49% in control participants after 2 years
Taneepanichskul et al.[17,18]	Cross-sectional	Premenopausal women	50 DMPA users, 50 IUD users	DEXA	Distal radius	BMD no difference *vs* that in implant users

a Method used to measure bone mineral density.

b Anatomic site at which BMD is measured.

c Only statistically significant findings for DMPA are listed.

DEXA = dual x-ray absorptiometry; **IUD** = intrauterine contraceptive device; **SPA** = single photon absorptiometry; ↑ = increase; ↓ = decrease.

baseline to 6 months in the depot medroxyprogesterone acetate group.

Using a cohort design, Scholes and colleagues[16] studied bone mineral density at 6-month intervals in women between 18 and 39 years old who were either users (n = 166) or nonusers (n = 213) of depot medroxyprogesterone acetate. A significant age group–treatment interaction was found. The largest differences in bone mineral density were found between 18- to 21-year-old users and nonusers, with users in this age group having bone mineral densities on average 12% lower than the bone mineral density of nonusers of the same age. This is in contrast to findings in older women of all age groups which demonstrated a <3% difference in bone mineral density between users and nonusers. No estradiol levels were reported.[16]

In a study of bone mineral density in adolescent depot medroxyprogesterone acetate users, Cromer et al.[14] compared bone mineral density changes prospectively, using the DEXA technique, over 2 years in girls younger than 18 years old who were receiving 3 different forms of hormonal contraception: oral contraceptives, depot medroxyprogesterone acetate or levonorgestrel subdermal implants, or no hormonal treatment (control group). Over each of the 2 years of assessment, bone mineral density decreased on average by 1.5% in the girls receiving depot medroxyprogesterone acetate. This finding was in marked contrast to an average increase in bone mineral density in the oral contraceptive, levonorgestrel subdermal implant and control groups of 2.7% after the first year and an average 6.7% increase in the levonorgestrel subdermal implant and control groups after the second year (figures 1 and 2), totalling a 12.4% difference between the depot medroxyprogesterone acetate and the other groups after 2 years of treatment. The significant differences persisted after controlling for a variety of potentially confounding variables.

The observation of an association between depot medroxyprogesterone acetate use and bone mineral density is not universal. In 2 related articles, Taneepanichskul et al.[17,18] compared bone mineral density, in a cross-sectional sample of 50 women (average age 32.5 years) receiving depot

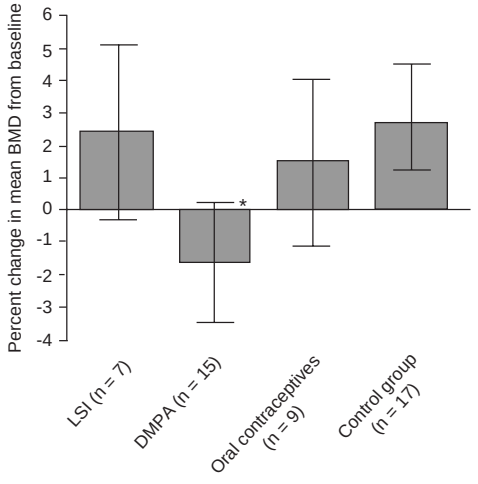

Fig. 1. Percent change in mean bone mineral density (BMD) 1 year after initiation of hormonal contraception. Error bars represent half the confidence interval of the Tukey test (reproduced from Cromer et al.[14] with permission). **DMPA** = depot medroxyprogesterone acetate; **LSI** = levonorgestrel subdermal implants; * F = 3.87, p < 0.02 (percent change in DMPA users versus the control group).

medroxyprogesterone acetate, with bone mineral density in intrauterine contraceptive device (IUD) users and levonorgestrel subdermal implant users. Employing DEXA measurements of the distal radius, they found no significant differences between the contraceptive groups in bone mineral density. However, they did find significantly lower estradiol levels among depot medroxyprogesterone acetate users compared with those in implant or IUD users.

The finding that depot medroxyprogesterone acetate may have a negative impact on bone metabolism, particularly in younger women, appears to result from low circulating levels of estrogen which, in turn, results from suppression of gonadotrophin production in the pituitary gland. An interesting contrast is the positive effect on bone metabolism of progestins, including medroxyprogesterone acetate, in postmenopausal women.[19]

Several possible explanations have been offered for this apparent contradiction. First, progestin effects may predilect for cortical (e.g. radius), rather than trabecular (e.g. spine) bone;[20] thus, anatomical sites of measurement may affect bone mineral density results. Secondly, different progestins have different anabolic potential resulting in different impacts on bone. For example, progestins derived from the 19-norsteroid family (e.g. norethisterone) have higher anabolic potency than medroxyprogesterone acetate (derived from the 21-norsteroid family) and may account for a differential effect on bone. Thirdly, progestins are thought to compete with glucocorticoids at cell receptor sites; if the latter compounds are high, then treatment with progestins would exert a positive effect by displacing glucocorticoids, which are known to have a negative impact on bone.[12] Finally, and most importantly, is the role of estrogen. There may be inherent differences in endogenous estrogen levels derived from adrenal androgens in postmenopausal

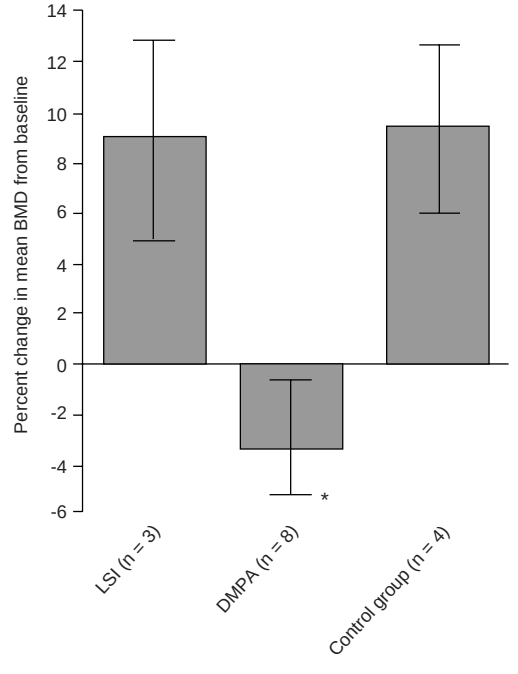

Fig. 2. Percent change in mean bone mineral density (BMD) 2 years after initiation of contraception. Error bars pictured represent half the confidence interval of the Tukey test (reproduced from Cromer et al.,[14] with permission). **DMPA** = depot medroxyprogesterone acetate; **LSI** = levonorgestrel subdermal implants; * F = 20.56, p < 0.0001 (percent change in DMPA users versus LSI and control groups).

women. In premenopausal women, estrogen insufficiency induced by depot medroxyprogesterone acetate may override any potential positive effect from a progestin,[21] particularly in the adolescent still undergoing active skeletal mineralisation.

2. Levonorgestrel Subdermal Implants ('Norplant')

The first report of bone mineral density in women receiving levonorgestrel subdermal implants was made by Naessen et al.,[15] whose methodology is described in section 1 (table II). Over 6 months of observation in a small group of adult women, bone mineral density increased on average by 2.94% from baseline in the levonorgestrel subdermal implant group, compared with essentially no difference in the depot medroxyprogesterone acetate group. Estradiol levels increased significantly from a mean 192 pmol/L to 389 pmol/L in the levonorgestrel subdermal implant group. Additional bone markers obtained were consistent with increased bone formation.

In the study of adolescents by Cromer et al.,[14] bone mineral density increased on average by 2.5% over the first year and on average by 6.3% in the second year, totalling on average 9.8% over 2 years. The findings for the untreated control group were almost identical. No estradiol levels were obtained.

In a previous metabolic study of levonorgestrel subdermal implants, Brache et al.[22] measured estradiol levels twice a week for 5 weeks in 88 adult women. They found that the levels clustered into 3 distinct profiles. About a third of the sample had low estradiol levels,) a third had cyclical fluctuations within the normal range, and a third had high, sustained levels of estradiol.

Thus, a majority of women receiving levonorgestrel subdermal implants would be expected to have normal or elevated estradiol levels, resulting in higher bone mineral density. One explanation is that the levonorgestrel subdermal implant exerts a lower level effect on the pituitary gland than depot medroxyprogesterone acetate so there is more gonadotropin release and therefore, more activity at the ovary and more estrogen production. Many women, especially after the first year of implant treatment, will have escape ovulation, indicating intermittent high levels of estrogen. Because of additional mechanisms of contraceptive action (e.g. thinned endometrial lining, thickened cervical plug), however, the efficacy of levonorgestrel subdermal implants is still very high and comparable to that of depot medroxyprogesterone acetate.

3. Oral Contraceptives

The studies conducted thus far on the effects of oral contraceptives on bone mineral density have produced mixed results (table III). Contributing to the conflicting findings are the differing types and strengths of the oral contraceptives studied. For example, the earliest studies in this area were ex-

Table II. Summary of previous studies examining bone mineral density (BMD) in levonorgestrel subdermal implant (LSI, 'Norplant') users

Study	Study design	Study sample	No. of participants	Method[a]	Site(s)[b]	Results[c]
Naessen et al.[15]	Randomised clinical trial	Premenopausal women	11 DMPA, 11 LSI	SPA	Forearm at baseline and 6 months	↑ BMD 2.94% from baseline
Cromer et al.[14]	Prospective	Adolescent girls	1 year: 7 LSI users, 17 control participants; 2 years: 3 LSI users, 4 control participants	DEXA	Lumbar spine at baseline, 1 year and 2 years	BMD ↑ 2.5% after 1 year, totalling 9.8% after 2 years, similar to changes in control participants
Taneepanichskul et al.[17,18]	Cross-sectional	Premenopausal women	50 LSI users, 50 IUD users	DEXA	Distal radius	No difference between DMPA and LSI users

a Method used to measure bone mineral density.

b Anatomic site at which BMD is measured.

c Only statistically significant findings for LSI are listed.

DEXA = dual x-ray absorptiometry; **DMPA** = depot medroxyprogesterone acetate; **SPA** = single photon absorptiometry; ↑ = increase.

Table III. Summary of previous studies examining bone mineral density (BMD) in oral contraceptive (OC) users

Study	Study design	OC estrogen content	Study sample	No. of participants	Method[a]	Site(s)[b]	Results[c]
Goldsmith & Johnston[23]	Cross-sectional	High dose estrogen (100μg vs 50-80μg EE)	Pre- and postmenopausal women	2135	'Photon absorption method'	Distal radius	Women <30 years old using high estrogen pill more likely to be in the 'high mineralisation' group
Shargil[24]	Prospective	30-40μg EE *vs* placebo	Perimenopausal women	100 OC users *vs* 100 nonusers	Radio-densitometry	Spine and hands	OC group lost no BMD *vs* control participants losing 6% over 3 years
Lindsay et al.[25]	Retrospective	Unknown	Premenopausal women	Total of 101 in 2 studies	DPA; SPA	Lumbar spine; midshaft radius	BMD ↑ 1% per year of use
Hreshchyshyn et al.[26]	Cross-sectional	Unknown	Pre- and postmenopausal women	151 with normal BMD at lumbar spine plus 201 with normal BMD at femoral neck	DPA	Lumbar spine	No difference between women with <1 year of past OC use *vs* no OC use
Lloyd et al.[27]	Cross-sectional	50μg mestranol	Premenopausal women	25 (11 >5 years OC use, 14 no OC use) premenopausal women, 25 matched control participants	CT scan	Lumbar spine	No difference in BMD between OC users and nonusers
Kleerekoper et al.[28]	Cross-sectional	Unknown	76% post- and 24% premenopausal women	2297	DPA	Lumbar spine, distal radius	0.78 odds ratio for past use *vs* no use of OC
Rodin et al.[29]	Cross-sectional	30-40μg EE	Premenopausal women	45 OC users *vs* 40 nonusers	DPA	Multiple sites	No relationship between BMD and OC use
Mazess & Barden[5]	Prospective	Unknown	Premenopausal women	300 with variable history of OC use	SPA or DPA	Radius, lumbar spine, femoral neck	No effect of OCs on BMD
Kritz-Silverstein & Barrett-Connor[30]	Retrospective	Unknown	Postmenopausal women	239 with variable history of OC use	DEXA	Lumbar spine, femoral neck	↑ BMD with past OC use >5 years *vs* BMD in nonusers
Recker et al.[4]	Prospective	Unknown	Young women	156 with variable history of OC use	SPA or DPA	Lumbar spine, forearm, total body	OC use correlated with changes in total body bone mass but not individual sites
Cromer et al.[14]	Prospective	30μg EE	Adolescent OC users *vs* control participants	9 OC users, 17 control participants	DEXA	Lumbar spine after 1 year	No difference between BMD changes in OC users *vs* implant users, and control participants

a Method used to measure bone mineral density.

b Anatomic site at which BMD is measured.

c Only statistically significant findings for OCs are listed.

CT = computerised tomography; **DEXA** = dual x-ray absorptiometry; **DPA** = dual photon absorptiometry; **EE** = ethinylestradiol; **SPA** = single photon absorptiometry; ↑ = increase; ↓ = decrease.

amining oral contraceptives containing much higher amounts of estrogen than are contained in currently available preparations. However, an even larger issue is the almost universal use of cross-sectional design studies. Because of the combination of relatively large interindividual variability in bone mineral density, coupled with small absolute changes from medication effects in bone mineral density over time, the likelihood of finding statistically significant differences between treated individuals and control individuals, is reduced. Thus, the optimal research design is prospective, with multiple measurements in the same individuals over time, so that each study participant serves as her own 'control'. In addition, with cross-sectional designs, extra attention must be directed to controlling for confounding influences on bone mineral density, as variables like exercise and smoking may not exist equally between oral contraceptive users and non–oral contraceptive users. These same criticisms also been apply to cross-sectional studies of the long term progestin treatment.[31]

Another issue is the different techniques which have been used to measure bone mineral density in the various studies. The first studies on oral contraceptives in the 1970s used a photon absorption method to measure the density of cortical bone at the radius.[23] However, most studies in the 1980s used SPA or double photon absorptiometry (DPA) to measure bone mineral density. Current research with hormonal contraceptives uses the DEXA technique of measuring bone mineral density of trabecular bone at the lumbar vertebrae.

The only certain conclusion that can be safely drawn from previous studies in this area is that oral contraceptives do not have a detrimental effect on bone.[32] Whether or not there is a true positive effect is a matter of debate. Even though multiple earlier studies examining calcium metabolism in oral contraceptive users had been performed, the first salient study utilising a more direct measure of bone mineral density was published by Goldsmith and Johnston[23] in 1975. The design was cross-sectional and involved over 2000 women, of whom 41% were <40 years old and 72% were receiving a high dose estrogen pill containing 100μg of mestranol (with norethindrone). They found that women <30 years old and with a current or past history (during third decade of life only) of using the high dose estrogen pill were significantly more likely to be in the 'high' mineralisation group than all women using a lower dose mestranol pill (50 to 80μg of mestranol) or, interestingly, a pill containing any amount of ethinylestradiol.

Four salient studies conducted in the 1980s will be now be discussed, 2 of 4 of which demonstrated a positive impact of oral contraceptives on bone mineral density. In one of the few prospective studies, Shargil[24] examined bone mineral density in 41- to 49-year-old, perimenopausal (still menstruating but with climacteric symptoms) women randomised to receive either a low dose ethinylestradiol 30 to 40μg pill combined with levonorgestrel, or to a placebo, for 3 years. While the control group lost about 6% of bone mineral density over the 3 years, the oral contraceptive–treated group lost, on the average, no bone mineral density.

Lindsay et al.[25] found a positive effect of oral contraception on bone mineral density in a report of 2 separate studies of premenopausal women receiving ethinylestradiol 30 to 50μg plus norgestrel. Using DPA of the lumbar vertebrae, the authors found in the first study that a past use of oral contraceptives was associated with about a 1% increase in bone mineral density per year of use. In the second study, they found that premenopausal women with a long term exposure to oral contraceptives (mean exposure time was 8 years) had bone mineral density an average of 12% higher than women without a history of oral contraceptive use.

Also using DPA in a cross-sectional design study, Hreshchyshyn et al.[26] examined bone mineral density at the lumbar vertebrae and femoral neck in over 300 adult women of all ages. Bone mineral content (measured in g/cm^2) was compared between women with a history of >1 year of past oral contraceptive use and those with no history of oral contraceptive use. No significant rela-

tionships were found between bone mineral content and past or current oral contraceptive use.

Finally, Lloyd and colleagues[27] conducted a cross-sectional evaluation of bone mineral density in closely matched premenopausal 30-year-old women using computerised tomography of the lumbar vertebrae. Eleven women had used oral contraceptives for at least 5 years and bone mineral density of this group was compared with that of 14 women with a history of no oral contraceptive use. No significant differences in bone mineral density were found. Notably, power analysis indicated that a 15% difference in bone mineral density between the groups was needed to enable a true difference to be found in such a small sample.

Two studies conducted in the 1990s had similar designs. Both were cross-sectional in design and involved measurements of bone mineral density at multiple anatomical sites using SPA or DPA, mostly in postmenopausal women and examined the relationship between bone mineral density and past history of oral contraceptive use. In the study by Kleerekoper et al.,[28] past oral contraceptive use was protective of bone mineral density, even after controlling for several confounding variables (including anatomical site). The odds ratio for estimating the relative risk of past oral contraceptive use versus no past use and being assigned to the lowest quartile of bone mineral density versus the other 3 quartiles was 0.78 [95% confidence interval (CI) 0.63 to 0.98]. The odds ratio for duration of oral contraceptive use was also significant, ranging from 0.52 (95% CI 0.27 to 1) for <2 years of use and 0.23 (0.07 to 0.73) for >10 years use.

In the other study, Kritz-Silverstein and Barrett-Connor[30] found a significant positive relationship between past oral contraceptive use of >5 years and bone mineral density at the lumbar spine and femoral neck but not the distal radius. This finding may not be surprising, as the former sites are composed of trabecular bone and, thus, are more sensitive to fluctuations in bone metabolism than the mixed and trabecular cortical bone at the radius.

In a third cross-sectional study, the bone mineral density in 45 premenopausal women who were current users of oral contraceptives for at least 2 years was compared with the bone mineral density in 40 women with no history of oral contraceptive use and in 17 women with a distant history of oral contraceptive use. Average age ranged from 23.7 to 26.7 years across the groups. DPA of multiple anatomical sites was used as the outcome measure and the oral contraceptives used contained ethinylestradiol 30 to 40 μg/pill and levonorgestrel or norethisterone. No significant association was found between bone mineral density and oral contraceptive use at any site, nor was there any relationship found between duration of oral contraceptive use and bone mineral density.[29]

Two prospective studies conducted in the 1990s both lend support for the positive effects of oral contraceptives on bone mineral density. Recker et al.[4] obtained bone mineral density measurements, using SPA or DPA, in a longitudinal fashion from college students for up to 5 years. The ongoing use of oral contraceptives was significantly correlated with change in the total body bone mass, but not with the changes seen at the individual anatomical sites.

In the second study (described in section 1) Cromer et al.[14] obtained bone mineral density measurements from a small group of adolescent oral contraceptive users (the oral contraceptive contained ethinylestradiol 30μg and desogestrel 0.15mg) and compared the findings after 1 year with those in depot medroxyprogesterone acetate and levonorgestrel subdermal implants users. Bone mineral density increased in similar fashion among oral contraceptive users and control individuals, suggesting that the hormonal milieu provided exogenously in oral contraceptives is adequate for bone growth and consolidation during this developmental period. This is the only study to date which examined the effect on bone mineral density of the new-progestin pills and which contain low dose estrogen and 1 of the following 3 progestins: desogestrel, norgestimate or gestodene. The balance of the data to date from the studies described above leans toward a positive effect of oral contraceptives on bone mineral density.

4. Clinical Research Implications

From the studies summarised, it would appear that levonorgestrel subdermal implants or oral contraceptives could be used in women of all ages without a detrimental effect on bone mineral density. Clearly, however, more research is indicated involving studies with prospective designs and with particular focus on evaluating oral contraceptives containing the new progestins and their relationship to bone mineral density. Further studies are also needed in adolescent levonorgestrel subdermal implant users, as the data that are available to date, indicating its protective effect during the crucial developmental period, are based on a small number of patients.

The implications of the findings to date on depot medroxyprogesterone acetate and bone mineral density are more complicated. In adult premenopausal women past their peak bone mass, the effects may not be significant unless use is long term i.e. >5 years. Also, there may be substantial recovery of bone mineral density after cessation of treatment with depot medroxyprogesterone acetate.[33] The issue of recovery, and the degree of recovery, particularly in the younger age group also needs further investigation. From a clinical management standpoint, because of concern regarding bone mineral density loss in young women (especially those younger than 16 years) with multiple risk factors, these patients may need to have bone mineral density measurements done prior to initiation of depot medroxyprogesterone therapy and at 1 to 2 years after treatment, or should use another form of contraception.

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Correspondence and reprints: Dr *Barbara A. Cromer*, Section of Adolescent Health, Children's Hospital, 700 Children's Drive G3-X, Columbus, Ohio 43205-2696, USA.
E-mail: cromerb@paediatrics.ohio-state.edu