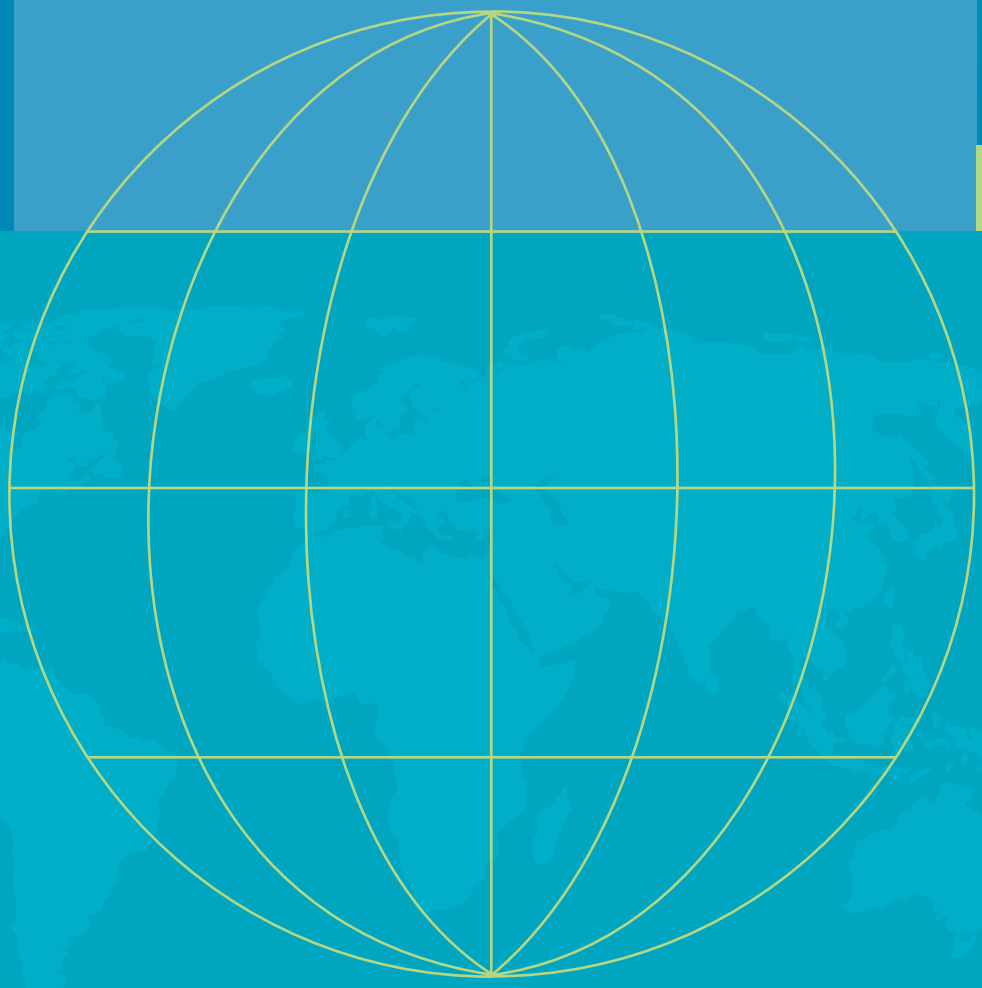
Technical consultation on the effects of hormonal contraception on bone health

Summary report
Geneva, Switzerland
20—21 June, 2005



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WHO/RHR/07.08

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ACRONYMS

BMD	Bone mineral density
BMI	Body mass index
CI	Confidence interval
COC	Combined oral contraceptive
DMPA	Depot medroxyprogesterone acetate
DXA	Dual energy X-ray absorptiometry
EE	Ethinyl estradiol
HT	Hormone therapy
IUD	Intrauterine device
NET-EN	Norethisterone enanthate (also named Norethindrone enantate)
OR	Odds ratio
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
USA	United States of America
WHO	World Health Organization

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Introduction

The Department of Reproductive Health and Research of the World Health Organization produces evidence-based guidance on contraceptive use. One of its guidelines, *Medical eligibility criteria for contraceptive use, Third edition, 2004*, provides recommendations on the use of various contraceptive methods by women and men with specific physical characteristics or with known pre-existing medical conditions. The Department carefully monitors the publication of new research evidence in order to keep these guidelines constantly up to date with the state of knowledge in the field.

In November 2004, the United States Food and Drug Administration and the United Kingdom Committee on the Safety of Medicines issued warnings on the use of the progestogen-only injectable contraceptive depot medroxyprogesterone acetate (DMPA). These warnings were based on their assessment of evidence of its effects on bone mineral density (BMD), including yet unpublished data issued by the Pfizer company. The company agreed to share its unpublished data with experts at WHO, and subsequently the Department updated its systematic review on Age and use of progestogen-only contraceptives [DMPA, norethisterone enanthate (NET-EN), progestogen-only pills, progestogen-only implants and levonorgestrel-releasing intrauterine device (IUD)] to include appraisal of all new evidence.

The Guidelines Steering Group is responsible for overseeing the update and maintenance of WHO's evidence-based guidelines in family planning. The group evaluated this systematic review and, together with the WHO Secretariat, issued a statement on the WHO website on DMPA and its effects on BMD. Through this appraisal process, the GSG and WHO Secretariat determined it necessary to convene a technical consultation to thoroughly evaluate the new evidence in light of prior evidence. In addition to a review of evidence on progestogen-only methods, it was also determined necessary to evaluate all evidence regarding the effects of combined hormonal contraceptives on BMD (combined oral contraceptives, combined injectable contraceptives, combined patch and combined ring).

A technical consultation on the effects of hormonal contraception on bone health was convened at WHO in Geneva, Switzerland, 20–21st June, 2005. The consultation brought together the GSG, other experts on hormonal contraception, and experts on bone health to evaluate all scientific evidence in this area. Along with the presentation of updated systematic reviews on age and use of hormonal contraceptives, which included evidence on the effects on BMD among different age groups, the participants were presented with data on the epidemiology of hormonal contraceptive use, bone health at different life stages, risk of fractures and related morbidity/mortality; risk factors for osteoporosis and fracture; and with unpublished data from a pharmaceutical manufacturer of DMPA. This report summarizes the material presented to participants during the consultation.

On the last day of the consultation, participants developed concrete recommendations on the use of hormonal contraceptives, taking into consideration any potential effects on bone health. These recommendations appear on the WHO web site (http://www.who.int/reproductive-health/family_planning/bone_health.html) and at the end of this report. The recommendations have also been published in the *WHO Weekly Epidemiological Record* (http://www.who.int/wer/2005/wer8035/en/index.html).

Review of evidence

Epidemiology of hormonal contraception and pregnancy-related risks

Dr Laneta Dorflinger (Family Health International, Research Triangle Park, USA) gave a presentation on global estimates of maternal mortality and patterns of modern contraceptive method use, and focused on progestin-only injectables, namely depot medroxyprogesterone acetate (DMPA) and norethisterone enanthate (NET-EN). Worldwide use of DMPA is far greater than that of NET-EN. At the time of the consultation, DMPA was registered in more than 100 countries.

DMPA is a highly effective, private, and convenient method of contraception that is not dependent upon daily or coitally-related actions. Injections of 150 mg depot medroxyprogesterone acetate are given every three months. Side effects of DMPA include menstrual disruption, amenorrhoea, weight gain, and a delayed return to fertility. Bleeding irregularities experienced by users are believed to be the main reason for the relatively high discontinuation rates among DMPA users. Nevertheless, surveys do report that approximately 50% of users who discontinue using DMPA re-initiate this method at a later time. *(1)*

Assessing whether the health risks associated with injectable contraceptive use are greater than risks associated with using other contraceptive methods (or whether other contraceptive methods are available), necessitates a balanced discussion of the possibility that a woman might experience pregnancy-related morbidity or mortality. According to WHO/UNFPA/UNICEF estimates, *(2)* in 2000 there were 529 000 maternal deaths in the world, and more than 99% of these deaths occurred in developing countries. Although in absolute numbers slightly more maternal deaths were reported from Asia, both the maternal mortality ratio and the lifetime risk of maternal death were far greater in Africa, particularly in countries located in Sub-Saharan Africa, where the maternal mortality ratio is estimated to be 920 maternal deaths per 100 000 live births. In contrast, maternal mortality ratios are estimated to be 520 maternal deaths per 100 000 live births in South-Central Asia and 20 in developed regions. Lifetime risk of maternal death is estimated to be 1-in-16 in Sub-Saharan Africa, 1-in-94 in Asia, 1-in-160 in Latin America and the Caribbean, and 1-in-2800 in developed countries.

Maternal mortality is influenced by many factors including the probability of becoming pregnant and the risk of death while pregnant. Since the probability of pregnancy is associated with the availability of contraceptives and whether or not they are used effectively, estimates of contraceptive prevalence and patterns of use were reviewed. Estimates from six Southeast Asian and Sub-Saharan African countries with high rates of maternal mortality show low prevalence of contraception and high levels of unmet contraceptive need. *(3)*

According to the United Nations World Contraceptive Use report, *(3)* approximately 3% of married women between 15 and 49 years of age used injectables in 2000. Of the 30.3 million women using injectables around the world, nearly 29 million lived in developing countries. Within the developing world, Africa had the highest proportion of women reporting injectable use of contraceptives (20%) compared with Asia or Latin America (5.3% and 5.5%, respectively). According to sales data, one DMPA manufacturer estimates that 100 million women use the product worldwide, and use is highest among young women and women over 35 years.

Comparisons of country-specific data show Indonesia reporting the highest percentage of injectable use (27.8%) as well as the greatest number of users (11.2 million women). Other countries with high proportions of injectable users include South Africa (23.2%), Namibia (18.7%), Thailand (17.5%), and Malawi (16.4%). In the five countries with the highest number of women using injectables (Bangladesh, Indonesia, Kenya, South Africa, and Thailand), within age groups, injectable use is proportionally highest among younger women. More than 60% of currently married women 15–24 years of age who use a modern contraceptive method, use injectables. Nevertheless, these countries continue to experience high rates of teenage pregnancy and motherhood with more than 25% of women

who are 18 years old having had a baby or being pregnant. (*1, 4*–7) Finally, survey data from Indonesia show an increased use of modern contraceptive methods between 1987 and 2003, which is largely attributable to a greater use of injectables. *(8)*

Thus, limiting the use of DMPA would reduce contraceptive options in a way that may be critical for women from Southeast Asia and Sub-Saharan Africa. Younger women may be especially vulnerable as their options for contraceptives may be more limited compared with older married women, and the need for highly effective contraception could be more acute due to sociocultural pressures. In addition, if women must switch to another method, contraceptive options vary depending upon whether they intend to space their pregnancies or limit their fertility. Options for women wanting to space their pregnancies include pills, condoms, implants and IUDs, while options to limit their fertility include IUDs, implants, and sterilization (female or male). Given these scenarios, limiting the use of DMPA may exacerbate unmet contraceptive need in some areas.

The challenge for policy-makers and programme managers lies with balancing the clinical significance and importance of bone loss due to DMPA use, with bone loss that may occur at other periods during a woman's reproductive years (i.e. due to pregnancy and/or lactation) and with the use of perhaps less effective methods of contraception leading to possible risky unwanted pregnancy and maternal mortality.

Bone health in adolescents and adults

Dr René Rizzoli (University Hospital, Geneva, Switzerland) gave an overview on bone health during a woman's lifespan, with a focus on the relation between BMD and future fracture risk. In addition, the epidemiology of bone health, methods to measure bone density, and the interpretation of bone measurements were discussed.

By age 50, the lifetime risk of a fragility fracture for a woman at any bone site is 46%, which is more than two times greater than a man's risk (22%) according to population-based data from Sweden. *(9)* Bone fractures are associated with morbidity, loss of independence (or increase of dependence), and mortality. Morbidity due to vertebral fractures includes pain, loss of height, deformity, reductions in pulmonary function, and a diminished quality of life. *(10)* A Geneva study recorded 3.2% of hip fracture patients died within 16 days following hospital discharge and 23.8% died within one year of their discharge. *(11)* According to a five-year cohort study, the age-standardized mortality ratio from an osteoporotic fracture of the proximal femur is 2.2 for women and 3.2 for men. *(12, 13)* Further, it is estimated that hip fractures reduce the life expectancy of women and men by 5.8 and 5.9 years, respectively. *(13)*

Bone fractures are complications of mechanical overload (falls) to the skeletal system or mechanical incompetence of the skeletal system (osteoporosis), or both. Low peak bone mass, sex hormone deficiency, age, and nutrition insufficiency contribute to the development of osteoporosis. Osteoporosis manifests as skeletal fragility and measuring of bone mass (or BMD) is used to diagnose the disease.

Bone mineral density can be measured using single or dual energy X-ray absorptiometry (DXA), ultrasound, computer tomography, or radiography. Currently, DXA is the most frequently reported means of measurement in the literature and it has received the most attention with respect to validation and technical development. DXA assesses the bone mineral content of the skeleton (or specific site), which is then divided by the area of the site measured to derive the BMD value. Because BMD values for healthy young adults are approximately normal, individual BMD values are expressed in relation to a young reference distribution using standard deviation (SD) units or a t-score for diagnostic purposes. *(14)* Studies of hormonal contraception and BMD frequently use a z-score, where the z-score expresses the difference in BMD among contraceptive users and non-users. In this context, the z-score represents the number of standard deviations the mean BMD in the contraceptive users is above or below the mean BMD of the non-users. *(15)* BMD measurements can be affected by fluid retention, weight gain, and altered composition of tissues (due to water retention). Thus, during pregnancy and lactation, the accuracy of BMD measurements can be problematic. In addition, DXA is not 100% accurate for measuring gross changes in BMD, since changes in fat due to drugs or changes in hormonal status can affect results. This is also problematic for persons using anabolic steroids.

Across different anatomical measurement sites, one SD decrease in BMD represents a 40–60% increased relative risk of fracture at any site. *(16)*

The WHO standard definition for osteoporosis is 2.5 SD below the mean BMD value of a healthy population. *(17)*

Accelerated increase in bone mass begins during pre-adolescence and accelerates during adolescence. Both girls and boys experience large amounts of bone accrual between 10 and 20 years of age. *(18)* The period of greatest bone mass accrual occurs over an approximately 3-year period for girls, whereas boys have a slightly extended period of bone accrual (4 years). Both sexes achieve peak bone mass by 20 years of age. Data are unavailable to address whether early age of menarche leads to a shorter time period to achieve peak bone mass.

Bone mineral density is largely affected by heredity factors (60–70%), but other factors including sex hormones, nutrition, and mechanical forces determine BMD as well. During puberty, circulating estrogens in females serve to increase insulin-like growth factors which promote the longitudinal growth of bones, and estrogens lower bone turnover or resorption, leading to greater bone cortical thickness and stronger bones. Thus estrogen deficiency during puberty affects both bone growth and the attainment of peak bone mass. In addition, there may be periods when bone is more susceptible to environmental factors. Exercise prior to puberty may confer residual benefits in adult BMD; *(19, 20)* however, this has not been observed among oligo-amenorrheic long distance runners. *(21)*

According to a review of studies investigating the effect of maternity on BMD, significant decrements in BMD at the hip/pelvis (-2 to -5%) and at the spine (-1 to -4.5%) occur during pregnancy. *(22)* During six months lactation, BMD at the hip and spine remained significantly lower compared with baseline BMD. Following pregnancy, regardless of lactation or length of lactation, gains in BMD at 12 months postpartum occur. BMD exceeded baseline values for the spine, whereas BMD at the femoral neck had not reached baseline at 12 months postpartum.

Eight studies *(23–30)* in this review examined whether BMD varies by parity status. Five studies *(23, 24, 26–28)* found parous women had significantly higher BMD at the hip compared with nulliparous women, and six studies *(23, 24, 26–29)* reported significantly higher BMD at the spine among parous women compared with nulliparous women. In addition, ten studies *(31–40)* compared the risk of fracture at various anatomical sites among parous and nulliparous women. Three studies *(36, 39, 40)* reported parity ≥ 1 conferred a statistically significant protective effect against sustaining a hip fracture compared with nulliparous women, whereas two studies *(33, 35)* found parity ≥ 1 was protective, but not statistically significant. Two studies *(34, 37)* found the risk of sustaining a fracture at any site was significantly protective among women with parity ≥ 1 or parity ≥ 2, compared with nulliparous women. Finally, increasing parity was not protective against sustaining a fracture at the vertebrae, hip, or hip and forearm in three studies. *(31, 32, 38)*

In conclusion, a 5% loss of BMD occurs during pregnancy and 6-months lactation, however, BMD recovers by 12 months. Women with multiple pregnancies or prolonged lactation have BMD similar to or higher than women with no or few pregnancies. Women with multiple pregnancies or prolonged lactation have a fracture risk similar to or lower than women with no or few children and women who do not lactate or do so for a short duration.

Osteoporosis: risk factors for osteoporosis and fracture

A presentation on risk factors associated with bone fracture and osteoporosis was provided by Dr John Kanis (University of Sheffield, United Kingdom). The strength of the evidence, with respect to the consistency and quality of the epidemiological studies comprising the body of evidence, was also discussed.

The internationally accepted definition of osteoporosis states that osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. *(17)* Globally, the average age for osteoporosis is 75 years, and the average for persons living in developed countries is 80 years. Determinants of osteoporotic fracture include the risk of falling, the force of impact and the strength of bone. Bone strength relies on geometry of the bone, BMD, and bone quality.

Numerous risk factors for osteoporotic fracture are reported in the literature; however, the consistency of the directionality of their effects vary and few risk factors have been validated by studies that are reproducible, display a dose response effect, and

include appropriate study populations. *(14)* From methodologically sound studies, nutritional and lifestyle factors that consistently increase the risk of osteoporotic fractures include: cigarette smoking, excessive alcohol consumption, and long-term immobility. In contrast, low calcium intake, low vitamin D intake, high caffeine consumption, and low levels of physical exercise are inconsistently associated with increasing osteoporotic fracture risk.

Diseases and conditions known to consistently increase fracture risk identified by rigorously designed studies include: rheumatoid arthritis, prior fracture, stroke, visual impairment, and having an organ transplant. The increased risk associated with inflammatory bowel disease, thyroid disease, gastric surgery, and Parkinson's disease is consistent, but the evidence base for these factors comes from less rigorously designed studies. The evidence for risk associated with using anticoagulants or statins remains inconsistent.

Several factors related to hormonal status that have been shown to consistently increase the risk of fracture include: young age at menopause and use of hormone therapy (HT). Evidence is inconsistent with respect to age at menarche, infertility, parity, and use of contraceptives. Other risk factors include age, female sex, family history, low body mass index (BMI) (defined as weight in kg/height in metres squared), low BMD, and Asian or Caucasian origin.

Data across countries show great heterogeneity in the lifetime risk of hip fracture among women at age 50: risk of hip fracture varies from less than 1% in Turkey to more than 25% in Sweden. Globally, BMD standardized for age, height, and weight at the spine and femoral neck differs as well. Further, studies show marked country variations in the prevalence of osteoporosis, particularly with increasing age. For example, the estimated prevalence of osteoporosis among 80-year-old women ranges from approximately 30% in Hiroshima, Japan to 50% in Rochester, USA. These variations are difficult to explain according to the prevalence of risk factors. Some areas with the highest risk of fracture, such as northern Europe, are also locations where the prevalence of protective factors such as calcium intake, are also high.

In conclusion, there are relatively few well-validated risk factors for osteoporotic fracture, and known risk factors explain only a small part of the global pattern of disease.

The effects of combined hormonal contraceptives on bone

Dr Anna Glasier (Lothian Family Planning Service, United Kingdom) presented results from a systematic review of evidence published in peer reviewed journals from 1966 through March 2005 on the effects of combined hormonal contraception on bone health. The review included 45 cross-sectional studies, 23 prospective studies, and two case series of BMD outcomes and nine studies of fracture outcome. Attention was drawn to common limitations across these studies, such as variations in measurement technologies, types of comparison groups, duration of pill use, and pill formulations. Many studies contained few participants.

Current combined oral contraceptive (COC) use

Four cohort and two cross-sectional studies reported on adolescent or young adult populations. Results from one cohort study showed BMD in combined oral contraceptive (COC) (20µg ethinyl estradiol (EE)/100µg desogestrel) users did not change significantly over five years of follow-up, whereas non-users gained 7.8% BMD ($p<0.01$). *(41)* Moreover, differences between COC users and non-users were significant at three years and continued to widen through the fourth and fifth year of follow-up. In contrast, differences in BMD between COC users and non-users were not significant in other cohort *(42–44)* or cross-sectional studies of adolescents or young adults. *(45, 46)*

Eleven prospective studies, 34 cross-sectional studies, and two case series were conducted among premenopausal adult women. Two methodologically sound cohort studies *(47, 48)* found BMD at the spine, hip, and whole body did not differ between COC (≤35µg EE) users and non-users over one or three years follow-up. Another cohort study reported significant differences in BMD loss at 24 months among women using a COC containing desogestrel (30 µg EE/150 µg desogestrel) compared with non-users, but no differences were detected between users of a COC containing norethisterone and controls. *(49, 50)* A cohort study of women with stress-related oligo-amenorrhoea observed significant gains in BMD among women who took COCs containing 30 µg EE (+2.4%) or 20µg EE (+2.5%) compared with controls (-1.1%) over 12 months follow-up. *(51)*

Evidence on current COC use and BMD among peri- or post-menopausal women was evaluated by one randomized controlled trial (RCT), five cohort studies and six cross-sectional studies. Results from the RCT of postmenopausal women who were assigned to COCs (30 µg EE/150 µg desogestrel, n=40) or HT were highlighted. *(52)* Both groups experienced significant gains in BMD at five sites (spine, trochanter, inter-trochanter, Ward's triangle, and proximal femur), and women treated with COCs also had significantly increased BMD at the femoral neck, which was not observed in the HT group. When the sample was further divided into low and normal BMD groups according to baseline BMD values, *(53)* the investigators found that COC therapy was significantly more effective than HT at increasing the spinal BMD of women in the low BMD group ($p<0.05$).

Past COC use

Sixteen cross-sectional studies and one cross-sectional analysis from a cohort study assessed the relationship between BMD and prior use of COCs among postmenopausal populations. *(54–70)* Overall, there is no evidence that BMD at the spine, hip, forearm, or whole body was affected by COC use; although z-scores were significantly higher among COC past-users compared with never users in two studies and significantly lower in two other studies.

Other combined hormonal methods

Evidence on the use of other combined hormonal contraceptives among premenopausal women and BMD was available from a randomized trial of a monthly combined injectable contraceptive (Mesigyna®) *(71)* and a prospective study of a combined contraceptive vaginal ring (NuvaRing®). *(72)* No changes in spinal BMD were recorded over two years follow-up among CIC users compared with women using a copper IUD. *(71)* While BMD at the spine or femoral neck did not change significantly among vaginal ring users over 24 months and significantly increased among non-users, the estimates were not adjusted for age, parity, or prior COC use, which were differentially distributed between vaginal ring users and non-users. *(72)*

Fracture

Nine studies investigated the association between risk of fracture and COC use, with mixed results. Evidence from two large prospective studies was highlighted. According to the first study, COC ever-users were more likely to have a fracture than never-users (relative risk [RR]=1.2, 95% CI=1.08–1.34) after adjusting for smoking, social class, age and parity. *(73)* The second study, however, reported a reduced risk of hip fracture among ever-users of COCs compared with never-users (odds ratio [OR]=0.75, 95% CI=0.59–0.96), adjusting for age, HT use, parity, and body mass index (BMI) (kg/m^2). *(74)* There were no exclusive users of low-dose COCs in the study population. Additional protective effects were noted among ever-users of high-dose COCs (adjusted OR=0.56, 95% CI=0.42–0.75) and women who started using COCs after age 39 (adjusted OR=0.69 for all COCs, adjusted OR=0.61 for high-dose COCs). In a separate analysis of the same data, the authors reported significant effect modification by COC use on the association between parity and hip fracture, fracture risk was reduced by 8% per child among never-users but increased 19% per child among ever-users of COCs. *(36)*

Based upon the evidence reviewed, the effect of current COC use on BMD varies with age at the time of use and a woman's estrogenic state. Studies do not find that past use of COCs has an effect on BMD when compared with never using COCs. Finally, data on COC use and risk of fracture are inconsistent and no data are available for current COC formulations.

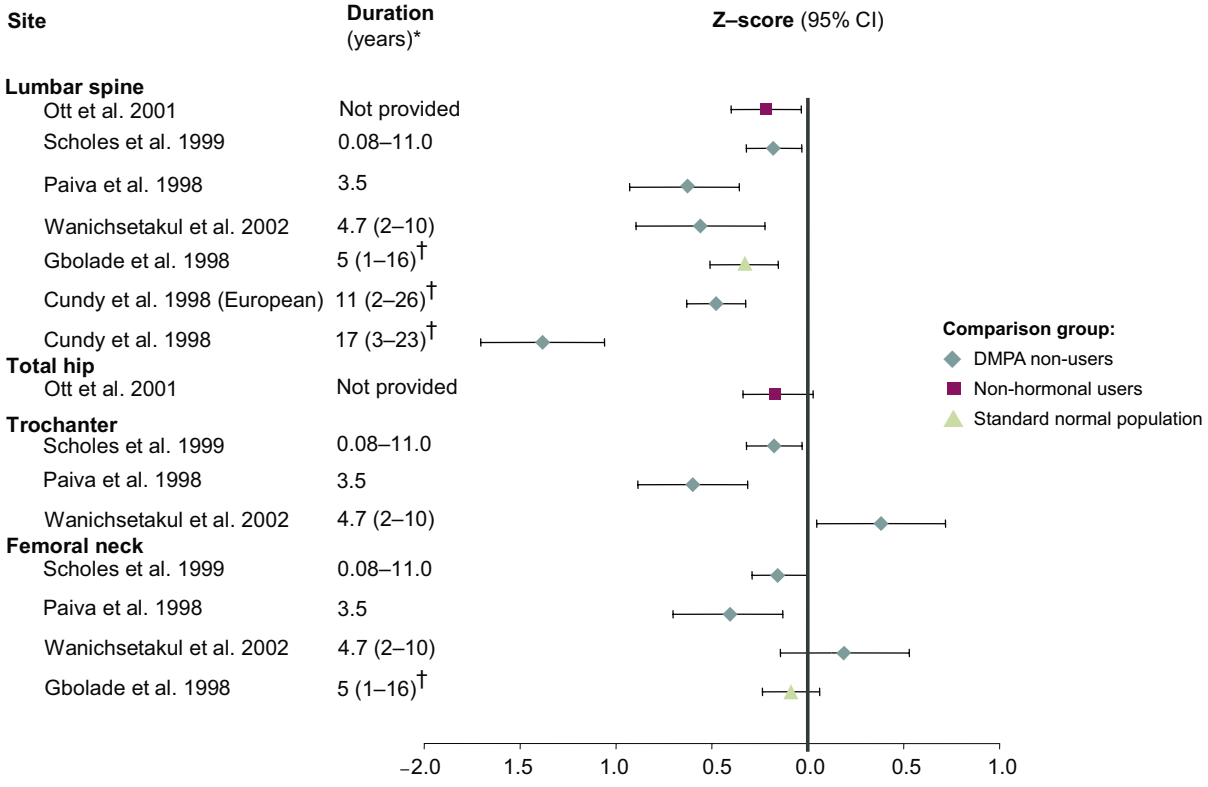
The effects of progestogen-only contraceptive use on bone mineral density and fracture risk

Dr Kathryn Curtis (Centers for Disease Control and Prevention, USA) presented a systematic review of published evidence from 1966 through May 2005 on the impact of using progestogen-only contraceptive methods on BMD and risk of fracture. The review addressed three questions: 1) do progestogen-only contraceptive users have an increased risk of current or future fracture compared with non-users? 2) do current progestogen-only users have different BMD levels than non-users? and 3) do former progestogen-only contraceptive users have different BMD levels than non-users?

Fracture

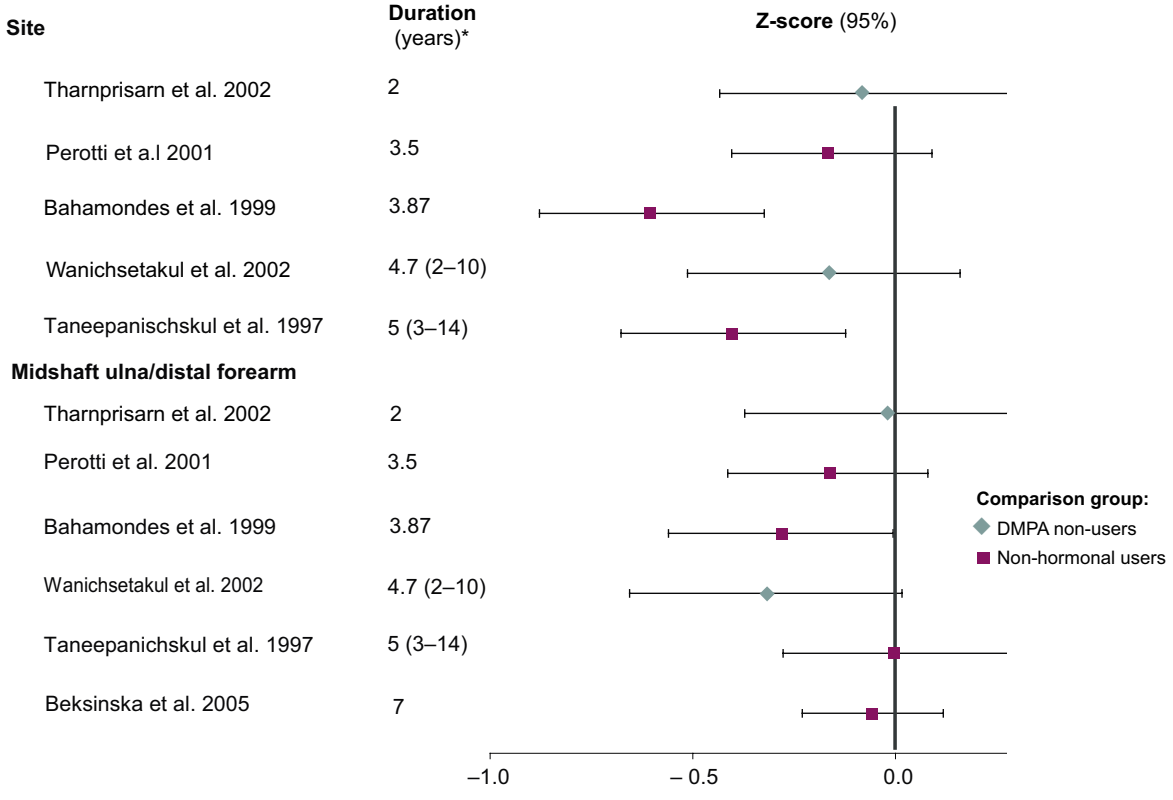
Evidence on fracture outcome was available from one cohort study of United States Army recruits aged 16–35 years, during eight weeks of basic training, who were currently using DMPA (n=169) or a non-hormonal method (n=2629). (*75*) Among DMPA users, the crude RR of stress fracture was 1.71 (95% CI=1.01–2.90), however, the estimate

Figure 1a. Cross-sectional studies of adult DMPA users (spine and hip sites)



*Mean and/or range
(except where median is indicated) †

Figure 1b. Cross-sectional studies of adult DMPA users (forearm sites)



*Mean and/or range

was no longer significant when adjusted for baseline heel bone density. Information on baseline heel density and other baseline characteristics were not reported in the article.

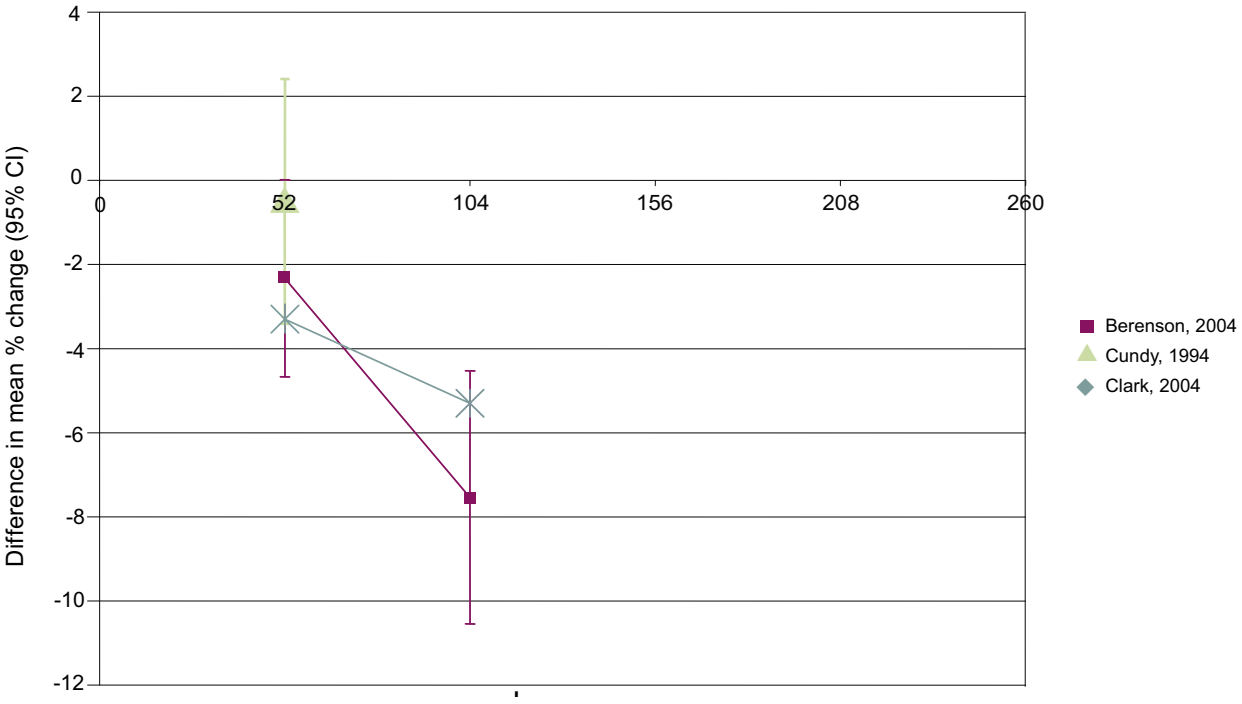
Current DMPA use

Information on current DMPA use and BMD was available from 15 cross-sectional studies of adult women (*76–90*) and two cross-sectional studies of adolescents. *(78, 91)* Cross-sectional studies showed that current DMPA use generally was associated with lower BMD; however, DMPA users had mean BMD values generally within -0.5 standard deviation of the mean BMD among non-users (i.e. z-score <-0.5). (*76–90*) The range in z-score values for the hip, spine, and forearm are illustrated in Figure 1a and Figure 1b.

Seven longitudinal studies investigated the effect on BMD of current DMPA use among adult women; three of them are shown in Figure 2. *(50, 92–97)* The net deficit in BMD in DMPA users compared with non-users ranged from 0.5% to 3.5% *(44, 69, 70)* at one year and 5.7% to 7.5% *(44, 69)* at two years. Two studies examining estrogen supplementation among DMPA users found that at 12 months, treated DMPA users lost less BMD than users who received supplementation (0.03% versus 0.2%); (*95*) and at 24 months, treated users experienced a 1.0% gain in BMD compared with a -2.6% loss among untreated users. (*94*)

Six longitudinal studies of adolescents investigated DMPA use and BMD. *(42–44, 98, 100)* Over one or two years follow-up, significant declines in BMD at the spine, hip, femoral neck, and whole body among DMPA initiators or continuers were recorded compared with non-user groups. Mean per cent differences between users and non-users were -2.29% to -12.61% for the spine, -1.62% for the hip, -4.5% for the femoral neck, and -0.15% for the whole body. Further, new users lost more bone than continuing users and mean changes in BMD decreased with increasing DMPA cumulative use. In a study of teenagers using DMPA who also received 24 months of estradiol cypionate supplementation, significant gains in BMD at the spine and femoral neck were observed in treated users compared with non-treated users. (*100*)

Figure 2. Spine BMD, difference in mean % change from baseline, DMPA vs control in adults in 3 studies



Note: The points on this graph represent the mean % difference in the non-users

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The effect of current DMPA use among older women on BMD was examined by two cross-sectional studies *(87, 90)* and one follow-up study. *(101)* According to one study, BMD among older DMPA users did not significantly differ from a reference population; however, two other studies reported significantly lower mean BMD at the lumbar spine, femoral neck, trochanter, and Ward's triangle among users compared with never users at baseline *(87)* and after three years follow-up. *(101)*

Past DMPA use

Among adult women, two cross-sectional studies examined the impact of past use of DMPA on BMD recovery. *(83, 102)* BMD of former DMPA users did not significantly differ compared with non-users across five anatomical sites (lumbar spine, femoral neck, Ward's triangle, trochanter, total body) and mean BMD did not correlate with duration of DMPA use, age at initiation of DMPA, age at discontinuation of DMPA, or time between discontinuation and menopause. *(79)* The second study found no differences between former DMPA users and non-users when assessing forearm BMD. *(60)*

Three longitudinal studies examined recovery of BMD after discontinuation of DMPA use in adults *(93, 97, 103)* and one longitudinal study followed BMD recovery among adolescent girls who discontinued DMPA use. *(99)* Two studies *(93,97)* showed adult DMPA discontinuers gained bone at the spine, hip, and femoral neck throughout two or more years follow-up at rates greater than non-users, regardless of duration of DMPA use. Recovery of hip BMD occurred more slowly than spinal BMD. The third adult study *(103)* examined women who had reached menopause. Statistically significant gains in spinal and hip BMD among former DMPA users (who initiated hormone therapy during three years follow-up) compared with DMPA discontinuers (not using HT and controls who had never used DMPA and were not using HT) were reported. Among adolescents who discontinued using DMPA, *(99)* recovery of spine, hip and whole body BMD occurred throughout two years of follow-up. Moreover, at 12 months follow-up, adjusted mean BMD values for discontinuers were at least as high as those of non-users at all sites and at all subsequent follow-up periods.

Other progestogen-only contraceptive methods

Two reports of one cross-sectional study and five longitudinal studies of current users ofprogestogen-only implants (primarily Norplant®, but one study of Implanon®) showed either no significant difference in BMD or increases in BMD compared with non-users. *(42, 85, 96, 104–107)* Nevertheless, one cross-sectional study found that mean BMD at the mid-shaft of the ulna was lower among exclusive users of Norplant compared with non-hormonal users. This difference was statistically significant, however; it was within one standard deviation of the mean of the non-users. *(83)* The only study of NET-EN also found no difference in cross-sectional analysis between NET-EN users and non-hormonal users. *(77)* The only study of progestogen-only pill use evaluated breastfeeding women and found that pill users lost less bone than non-users. *(108)*

Various limitations of the studies included in the systematic review were discussed. Principally, there is a lack of evidence concerning the main outcome of interest: fracture. Attention was drawn to the urgent need for globally representative information on the impact of DMPA use on bone health, as well as the limited availability of evidence on other progestogen-only contraceptives. Most studies, particularly studies of adolescents, experienced high rates of loss to follow-up and many studies were conducted over relatively short time periods. Further, the potential for bias to explain many study results cannot be ruled out, because few studies adjusted for potential confounders, and several studies allowed participants to self-select their method of contraception.

Depot medroxyprogesterone acetate use and bone mineral density in young women

Dr Delia Scholes (Group Health Cooperative, USA) presented results from two cohort studies conducted among young women (1994–1998) and

adolescents (1998–2003) using DMPA. These are published studies and were therefore included in the preceding systematic review of progestogen-only contraceptives. Accordingly, the presentation offered more complete information collected from the adolescent cohort study, including some unpublished data.

The adolescent cohort study comprised 80 DMPA users and 90 non-users aged 14 through 18 years, who were followed for a minimum of 24 and a maximum of 36 months. *(99)* At baseline, no significant differences in bone mineral density, as measured by DXA, were observed between DMPA users and non-users. However, significantly more DMPA users currently smoked and had been pregnant previously compared with non-users, and mean daily calcium intake was significantly lower among DMPA users compared with non-users. Among DMPA users, a greater proportion of older girls (17–18 years) reported having had two or more injections, than younger girls (14–16 years).

To compare changes in BMD and adjust for baseline and time varying covariates, mean changes in BMD (in g/cm^2) were computed at 6-monthly intervals using repeated measures models and expressed as annualized (average annual) percentage change. Follow-up data were available for 84% of adolescents at 12 months, 82% at 18 months, and 78% at 24 months. During 24 months follow up, DMPA users lost an average of 1.81% BMD annually at the hip compared with a loss of 0.19% BMD among non-users. At the spine, a loss of 0.97% BMD occurred among DMPA users compared with a 1.32% gain among non-users.

To evaluate whether recovery of BMD following DMPA discontinuation occurs, 61 adolescent participants were followed who discontinued DMPA use during the cohort study. The mean period of follow-up for discontinuers was 14 months (range: 1–36 months). Use of DMPA among discontinuers ranged from 3 to 62 months. Adjusting for baseline and time varying covariates, DMPA discontinuers experienced average six-monthly gains in BMD of 0.0058 g/cm^2 at the hip and 0.0133 g/cm^2 at the spine (p=0.004 for difference in BMD change in non-users). These changes correspond to mean annualized BMD gains of 1.34% and 2.86%, respectively, and were statistically significant relative to the comparison group of girls who were non-DMPA users. Among discontinuers aged 14–16 years, similar findings were reported. Younger discontinuers experienced mean adjusted 6-monthly gains of 0.0043 g/cm^2 at the hip, and 0.0131 g/cm^2 at the spine, whereas non-users in this age group had gains of 0.0010 g/cm^2 and 0.0086 g/cm^2, respectively and DMPA users had losses of 0.0077 g/cm^2 at the hip and 0.0042 g/cm^2 at the spine.

Depot medroxyprogesterone acetate: results of recent studies on bone mineral density from a manufacturer of DMPA

Following presentations of published data on DMPA use and bone health, representatives from the Pfizer Company, Inc. shared confidential data on DMPA obtained from two cohort studies. Accordingly, participants signed a statement by which they agreed to respect the confidentiality of the data. These data were considered, however, during the deliberations along with data from other presentations.

Conclusions

Steroid hormonal contraceptives, including oral contraceptives, injectables and implants, are highly effective and widely used. These contraceptives have important health benefits, including contraceptive and non-contraceptive benefits, and some health risks. For most women, the health benefits of use clearly exceed the health risks. Questions have been raised regarding the association between use of one particular hormonal contraceptive, depot medroxyprogesterone acetate (DMPA), and the risk of bone loss. In response, WHO convened a consultation in Geneva, Switzerland, 20–21 June 2005, to assess current evidence on the relationship between the use of steroid hormonal contraceptives and bone health.

Bone health may be influenced by many factors including pregnancy, breastfeeding and use of hormonal contraceptives. The principal clinical outcome of interest with regard to bone health is the occurrence of fracture. Bone mineral density (BMD) measurements are commonly used to assess fracture risk, but the accuracy of measurements can be influenced by changes in body composition, including changes in lean body mass and fat. Furthermore, fracture risk is related to many factors, BMD being only one of them. The relationship between decrease in BMD and increase in fracture risk has been best studied in postmenopausal women, among whom the risk of any fracture increases approximately 1.5-fold for each standard deviation (SD) decrease in BMD.

There is little information on the impact of BMD changes in young age groups on fracture risk later in life.

Combined methods of contraception

The use of current formulations of combined oral contraceptives (COC) may have some small effects on BMD that are unlikely to be of clinical significance. Adolescent COC users may gain less BMD compared with adolescent non-users while perimenopausal users generally have increased BMD compared with perimenopausal non-users. A number of studies have investigated the risk of fracture among postmenopausal women in relation to past use of COCs, but the findings are inconsistent. Data for other combined hormonal contraceptives are scarce.

Progestogen-only methods of contraception

With regard to progestogen-only methods, data on levonorgestrel implants suggest no adverse effect on BMD. Other low-dose progestogen-only contraceptives such as pills, other implants and the levonorgestrel-releasing intrauterine device do not appear to have an effect on BMD, although data for these methods are limited.

The use of DMPA for contraception produces a hypo-estrogenic state in women; some studies have shown that this is associated with a decrease in BMD. The weight of data indicates that DMPA use reduces BMD in women who have attained peak bone mass, and impairs the acquisition of bone mineral among those who have not yet attained peak bone mass. The magnitude of effect on BMD is similar across a variety of studies. Cross-sectional studies show lower BMD in longer-term DMPA users by approximately 0.5 SD at hip and spine compared with non-users. In longitudinal studies, adults (≥ 18 years) and adolescents (menarche to < 18 years) both lost around 5–7% (approximately 0.5 SD) of BMD at the same sites, after two years of continuous use of DMPA. The rate of loss appeared to decrease over time.

When DMPA use is discontinued, BMD increases again in women, regardless of age, except for those who have reached menopause. Among adults, BMD values appear to return to those of comparable non-DMPA users over a period of two to three years. It is not clear whether the loss in BMD among adolescent users of DMPA prevents attainment of potential peak bone mass. There remains a concern that older women who reach the menopause while still using DMPA may no longer have the opportunity to regain BMD before entering the period of bone loss normally associated with the postmenopause.

Absolute fracture risk is low during the reproductive years, and insufficient data exist to assess whether DMPA use modifies this risk. There are also insufficient data to assess whether DMPA use during the reproductive years affects the risk of fracture in future postmenopausal life. Since the effect on BMD is largely reversible, any lifetime increase in fracture risk is likely to be small.

Data regarding the use of the other progestogen-only injectable contraceptive, norethisterone-enanthate (NET-EN), are insufficient to determine whether there is any effect of NET-EN on bone health. In the absence of evidence, the concerns regarding DMPA and bone health also apply to NET-EN.

DMPA is a highly effective and widely available method of contraception, which plays an important role in the contraceptive method mix. This is particularly so in regions with a high unmet need for contraception and where maternal morbidity and mortality are high. Any decisions regarding choice of a contraceptive method should also consider this fact.

WHO will continue to monitor research in this area and will review these recommendations as and when new evidence becomes available. WHO also encourages relevant research in this area to fill key evidence gaps.

Recommendations

With regard to bone metabolism:

- There should be no restriction on the use of DMPA, including no restriction on duration of use, among women aged 18 to 45 who are otherwise eligible to use the method.
- Among adolescents (menarche to <18) and women over 45, the advantages of using DMPA generally outweigh the theoretical safety concerns regarding fracture risk. Since data are insufficient to determine if this is the case with long-term use among these age groups, the overall risks and benefits for continuing use of the method should be reconsidered over time with the individual user.

- Recommendations regarding DMPA use also pertain to use of NET-EN.
- There should be no restriction on the use of other progestogen-only contraceptive methods among women otherwise eligible to use these methods, including no restrictions on duration of use.
- There should be no restriction on the use of combined hormonal contraceptive methods among women who are otherwise eligible to use these methods, including no restrictions on duration of use.

Key evidence gaps

1. What are the effects of hormonal contraceptive use on fracture risk later in life in both developing and developed country populations?
2. Do very young women who use DMPA fully recover BMD to their potential after discontinuation? Is this dependent upon duration of use?
3. Do adolescents who use DMPA attain their potential peak bone mass, and is this dependent upon duration of use?
4. Do women who have used DMPA during the perimenopause have lower BMD in post-menopausal years, compared to women who never used DMPA ? What is the impact of these changes on fracture risk?
5. How do other risk factors for osteoporosis influence the effect of DMPA on BMD and fracture risk?
6. How does DMPA use affect BMD in lactating women?
7. What are the long-term effects of pregnancy and lactation on BMD and fracture risk?
8. What is the incidence of fracture in developing country populations?
9. What are the patterns of DMPA use among women in different settings?
10. With regard to the attainment of peak bone mass, is the use of ultra-low-dose COCs (≤ 20 µg EE) as appropriate for adolescents as pills containing 30–35 µg EE?
11. Are there differences in the way DMPA and NET-EN affect bone metabolism?

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Annex

Technical consultation on the effects of hormonal contraception on bone health

Salle A, World Health Organization
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