Bone and Hormonal Contraception: in different phases of reproductive life

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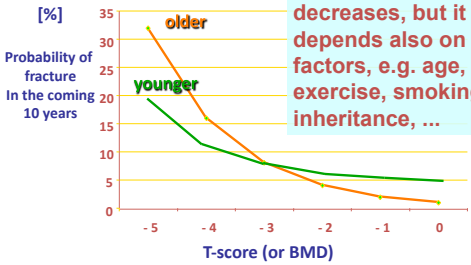
Bone metabolism during reproductive years

- Adolescence is a critical period for bone growth and mineralization.
- Starting 1 year before menarche, bone mineral density (BMD) increases by 2-10% per perimenarcheal year; most accumulation occurs between ages 12 and 14; 95% is reached by age 16-17 and BMD peaks around the age of 20-22 years. Peak bone mass is a predictor of osteoporosis.
- Bone mass is stable during adulthood, with a regular 0.3% turnover per year.
- Bone mass starts to decrease during the late perimenopause; this bone loss accelerates during the first post-menopausal years (2% loss per year at the spine, 1.5% loss per year at the hip) and tapers off over 10 years.

Effect or pregnancy and lactation on bone metabolism

- BMD decreases during pregnancy by 3-4% at the hip/pelvis and by 3-8% at the spine.
- BMD decreases further during lactation (4-8%). Return to baseline occurs within 12-18 months postpartum (varies with site).
- Yet: Multiparous women and those who breast-fed for long periods of time have a risk of fracture equal or less – depending on studies – to nulliparous women or to parous women who did not breast-feed or breastfed very little.

Bone mineral density and risk of fracture



Risk of fracture increases as the BMD decreases, but it depends also on other factors, e.g. age, BMI, exercise, smoking, inheritance, ...

Effects of estrogens and progestins on bone

Estrogens

- Estrogen receptors are expressed on osteoblasts and osteoclasts
  - ERα is preferentially expressed on cortical bone
  - ERβ is preferentially expressed on trabecular bone
- Estrogens suppress the formation of osteoclasts and inhibit bone resorption by osteoclasts
- Estrogens slow the rate of bone remodelling by attenuating the proliferation of osteoblasts

Progestins

- Progesterone nuclear receptors are present in osteoblasts and osteoclasts
- Progesterone seems to induce osteoblast differentiation and to have synergistic actions with estrogens
- Progestins will have different effects: progestational, androgenic, corticosteroidal, estrogenic

Combined methods

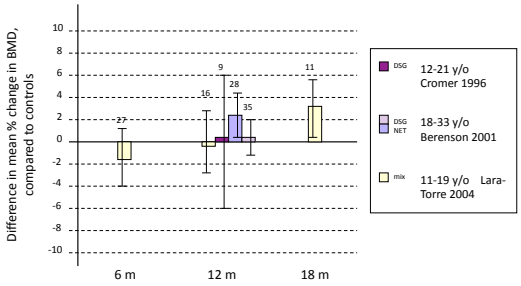
COC use and changes in BMD
Adult pre-menopausal women

- 8 RCTs comparing different preparations:
  - No difference in BMD between users, nor with non-randomized controls
  - Increase in markers of bone formation and reduction in markers of bone resorption, even for COCs containing 20 or 15 µg EE
- Findings supported by 25 non-randomized longitudinal studies with up to 3 years f/u

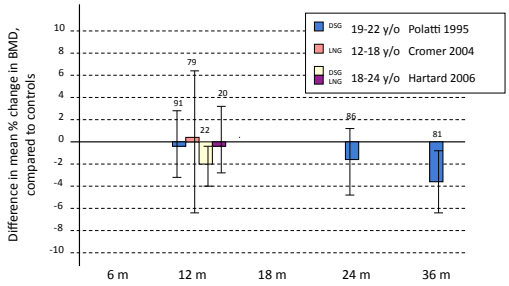
COC use and changes in BMD
Adult peri-menopausal women

- 4 RCTs comparing different preparations with calcium supplements:
  - 2-3% increase in BMD among users of pills containing 20 or 30 µg EE, compared to a decrease in calcium users
- 2 prospective cohort studies find stable BMDs among pill users, while users of non-hormonal methods lost 6% BMD over 3 years

Prospective studies in adolescents and young women using pills ≥ 30 µg EE

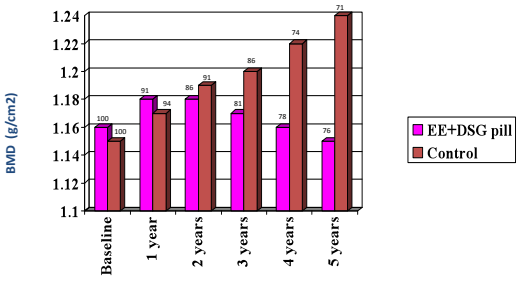


Prospective studies in adolescents and young women using pills ≤ 30 µg EE



Variation in spinal BMD among 200 girls aged 19-22 years over 5 years: 100 COC users (20 µg EE + 100 µg DSG) and 100 controls

(Polatti et al 1995)



COC use by adolescents

- No RCT
- With pills containing 30-35 µg EE, BMD increases at a rate similar to controls
- With pills containing <30 µg EE, BMD does not seem to change significantly, while control subjects experience a steady increase in BMD. Most significant among younger groups
- Does the use of pills containing <30 µg EE, prevent adolescents to reach their peak bone mass and thus affect their risk of osteoporosis later in life ?

COC use and fracture risk

- 3 prospective cohort studies:
  - 20% increased risk of fracture in ever-users but further analysis in a sub-group with longer f/u showed no increase except if 10 years or more since use *Cooper et al, 1993*
  - Highly significant trend of increased risk with increased duration of use (highest after 8 years); 30% increased risk with recent use (<1 year) *Vessey et al, 1998*
  - no increased risk in post-menopausal women compared to never-users *Barad et al, 2005*
  - ➢ BUT limitations in duration of follow-up post-menopause and in monitoring of possible confounding variables (smoking and alcohol)
- 5 case-control retrospective studies and 2 cross-sectional studies provide conflicting results
- No data on pills with <30 µg EE

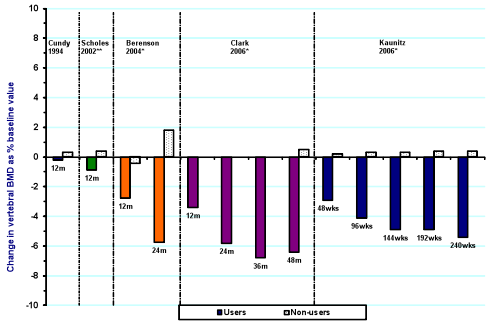
Other combined methods

- Monthly injectables:
  - 1 prospective study over 2 years, Mesigyna (49 users) vs Cu IUD (99 users), 38-50 y/o
  - 1 cross-sectional study of Mesigyna (33 users) vs Cyclofem (64 users) vs Cu IUD (97 users), 20-45 y/o
    - → No significant difference in BMD at the lumbar spine between the groups
- Nuvaring (15 µg EE + 120 µg DSG)
  Evra patch (20 µg EE + 150 µg norelgestromin) :
  - 1 prospective study of ring over 2 years (144 users),18-35 y/o: Increase in spine and hip BMD in controls, no change among users, <1 SD, without clinical significance
  - 1 RCT ring vs patch over 1 year, 20 users in each group + 20 controls, 23-54 y/o:
    no difference in spinal BMD

Progestogen-only methods

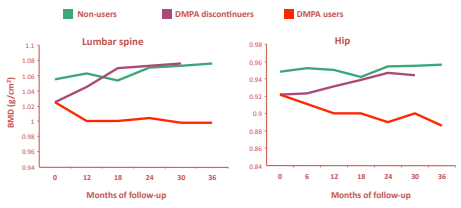
1. DMPA

Longitudinal studies of BMD changes at the level of lumbar spine among adult DMPA users



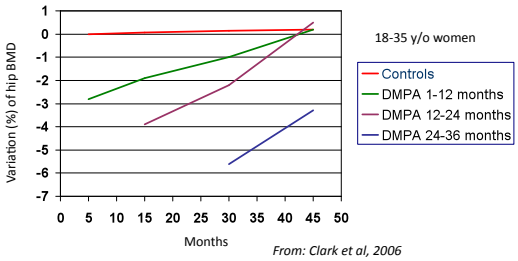
Note: same findings with DMPA IM (150 mg) and DMPA SC (104 mg)

Variations in bone mineral density among 182 DMPA users and 258 non-users, 18-39 y/o



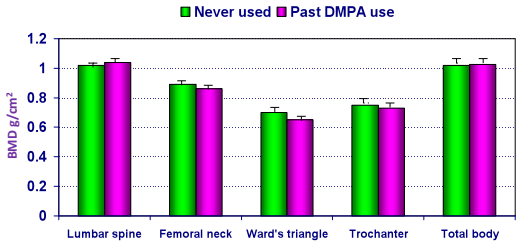
Source: Scholes et al, 2002

Variation of hip BMD, after discontinuation of DMPA use



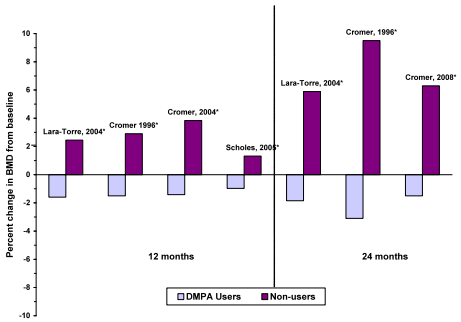
From: Clark et al, 2006
Similar observations by Harel et al, 2010 among 12-18 y/o adolescents

Bone mineral density among 60 y/o women: 312 never users of DMPA and 34 ever users of DMPA

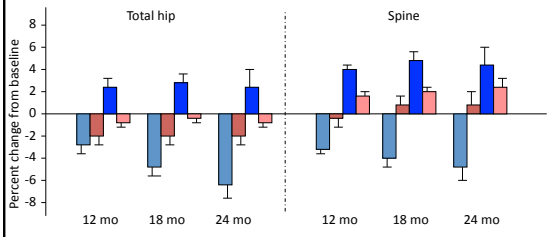


Orr-Walker et al, 1998

Longitudinal studies of DMPA use among adolescents

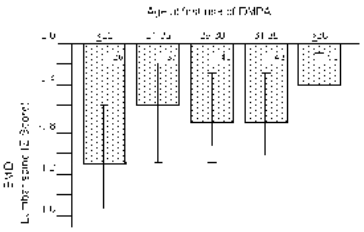


BMD changes in 14-18 y/o adolescents during DMPA use or following discontinuation



From: Scholes et al, 2005

Lumbar spine BMD of 200 current DMPA users who used DMPA for 2-26 years, grouped by age at first use, and compared to 350 controls



Source: Cundy et al, 1998

5 studies on DMPA and risk of fracture

- 2 case-control studies
  - ➢ In one study, OR associated with ever use of DMPA was 1.44 (1.01 – 2.06)

    Higher among women > 50 y/o: OR 2.25 (1.14 – 4.42)
    with regular use: OR 1.94 (1.09 – 3.45)
    use > 4 years: OR 2.16 (1.32 – 3.53)

    Low number of DMPA users
    Limited information on potential confounding factors

    Vestergaard et al, 2008
  - ➢ In a second study based on the UK GPRD, trend with duration of use:

    1-2 injections: OR 1.17 (1.07 – 1.29)
    3-9 injections: OR 1.23 (1.11 – 1.36)
    ≥10 injections: OR 1.30 (1.09 – 1.55)

    Increase in risk not significant for osteoporotic fractures
    Nutritional status, parity, education could not be controlled for.

    Meier et al, 2010

- 3 cohort studies:
  - ➢ In one prospective study of BMD in women age 25-35, fractures were reported as adverse events. New DMPA users compared to controls during 5 years of treatment and 2 years post-tx.

    No difference in fracture risk.

    No adjustment for confounding factors. *Kaunitz et al, 2006*
  - ➢ In one retrospective study, DMPA users compared to COC users.

    Rate ratio adjusted for age was 1.44 (1.38 – 1.50) for all fractures; no significant difference for axial fractures.

    Risk greater for those who received 1-7 injections than for those who received 8 or more. *Kaunitz et al, 2010*
  - ➢ In one retrospective study of the same data set:

    DMPA users have a higher risk of fracture than comparison group, before contraception is initiated. This risk does not increase with DMPA use.

    Lanza et al, 2013

Progestogen-only methods

2. Other Progestogen-only Methods

Other progestin-only methods

- Norplant /Jadelle:
  5 longitudinal studies and 5 cross-sectional studies: mixed results, minimal BMD changes without clinical significance
- Implanon:
  1 longitudinal study, comparison with Jadelle over 3 years,
  1 longitudinal study, comparison with IUD over 2 years:
  → no difference between the groups in each case
  1 cross-sectional study: compared to controls, no difference at spine or femur; lower BMD at distal radius and ulna
- Mirena:
  1 cross-sectional study: no difference with Cu IUD users
- Norethisterone enanthate:
  1 longitudinal study (490 adolescents: no difference in radius BMD between DMPA, pill or non-hormonal method users, but decrease in NET-EN group) and 1 cross-sectional study (decrease in BMD compared to controls, similar to DMPA, with return to baseline after discontinuation)

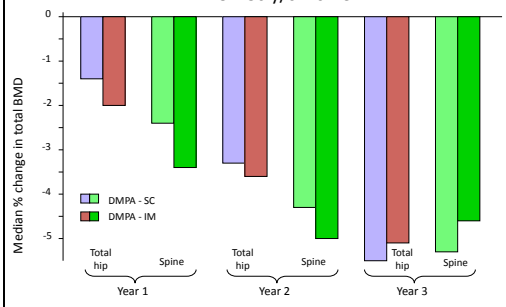
Use of progestins during lactation

- No RCT
- A few small studies suggest that use of progestins during lactation does not worsen the loss of BMD. Some suggest that it might stabilize bone loss.
- Limitations: small sample size, mix of methods, length of f/u, lack of control for confounding factors, etc

Conclusions

- Use of DMPA induces a significant decrease in BMD, which is reversible
- DMPA users may have an increased risk of fractures
- Among adolescents, use of DMPA and of COCs containing < 30 µg EE may prevent them to reach their peak bone mass, putting them at risk of osteoporotic fractures later in life.
- Use of DMPA (and ultra low-dose pills ?) by adolescents beyond 2 years should carefully assess risks and benefits for the individual user.

Comparison of DMPA-SC with DMPA-IM: Median % change in BMD from baseline
18 – 36 y/o women



Source: Kaunitz et al 2009

Key evidence gaps (1)

1. What are the effects of hormonal contraceptive use on fracture risk later in life in populations in both developing and developed countries?
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. How do other risk factors for osteoporosis influence the effect of DMPA on BMD and fracture risk?
5. How does DMPA use affect BMD in lactating women?
6. What are the long-term effects of pregnancy and lactation on BMD and fracture risk?

Summary regarding pre-menopausal women

- Use of DMPA induces a decrease in BMD during the first 2 years (5 to 7% for lumbar spine), which then stabilizes and remains within 1 SD of baseline.
- Upon discontinuation, BMD returns to baseline over a period of 18-24 months, depending on the length of DMPA use, more slowly at the hip than at the lumbar spine.
- No difference was observed between DMPA IM (150 mg) and DMPA SC (104 mg) in terms of their effect on bone metabolism.

Summary regarding adolescent girls

- Adolescent girls who use DMPA experience a decrease in BMD during the first 2 years of use (-2 to -3% at the level of the lumbar spine) which then stabilises, while those who do not use hormonal contraception gain 6-10% BMD.
- Upon discontinuation, adolescent girls regain BMD at a rate faster than the natural rate of controls, but it is not known whether they will reach their potential peak bone mass and whether they are at increased risk for osteoporotic fracture later in life.

Summary regarding perimenopausal women

- Perimenopausal women who discontinue DMPA before the menopause can recover their BMD.
- Those who discontinue DMPA at menopause do not experience the rapid bone loss observed in non-users.
- Post-menopausal women who used DMPA in the past have a BMD similar to never users of DMPA.

November 2004:
Black Box Warning for DMPA
US FDA and UK MHRA

FDA U.S. Food and Drug Administration

FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA

FDA Talk Paper

T04-60
November 17, 2004

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

Black Box Warning Added Concerning Long-Term Use of Depo-Provera Contraceptive Injection

The Food and Drug Administration (FDA) announced today that a "black box" warning, highlighting prolonged use may result in the loss of bone density, will be added to the labeling of Depo-Provera Contraceptive Injection, an established injectable drug approved for use in women to prevent pregnancy.

Although Depo-Provera Contraceptive Injection has been used for decades for birth control throughout the world and remains a safe and effective contraceptive, FDA and Pfizer, the drug's manufacturer, are taking this action to ensure that physicians and patients have access to this important information.

USFDA Medwatch (October 2010)

- Women who use DMPA may lose significant BMD. Bone loss is greater with increasing duration of use and may not be completely reversible.
- It is unknown if DMPA use during adolescence or early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.
- DMPA should not be used long-term (> 2 years) unless other contraceptive methods are considered inadequate.

UK Faculty of Sexual and Reproductive Healthcare Clinical Guidance (June 2009)

- In women <18 y/o, DMPA may be used as first-line contraception after all options have been discussed and considered unsuitable or unacceptable.
- A re-evaluation of the risks and benefits of treatment for all women should be carried out every 2 years in those who wish to continue use.
- For women with significant lifestyle and/or medical risk factors for osteoporosis, other methods of contraception should be considered.
- **Women should be informed that DMPA use is associated with a small bone loss, which is usually recovered after discontinuation. (Grade B)**

WHO Statement on DMPA and bone health (July 2006)

World Health Organization

1. There should be no restriction on the use of DMPA, including no restriction on duration of use, among women aged 18 to 45 years who are otherwise eligible to use the method.
2. Among adolescents (menarche to <18 years) and women over 45 years, 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.

World Health Organization

UNDP – UNFPA – WHO – World Bank Special Programme of Research, Development and Research Training in Human Reproduction

WHO STATEMENT
ON HORMONAL CONTRACEPTION AND BONE HEALTH
July 2005

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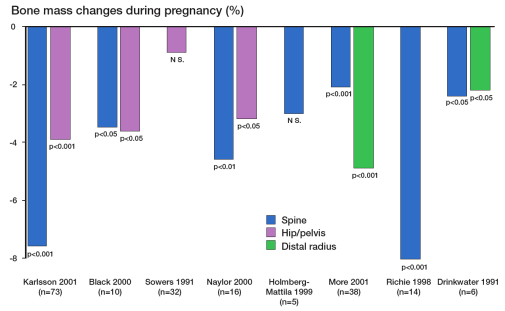
3. Recommendations regarding DMPA use also pertain to use of NET-EN.
4. There should be no restriction on the use of other progestogen-only contraceptive methods among women otherwise eligible to use these methods, including no restrictions on duration of use.
5. There should be no restriction on the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

Bone mineral density during pregnancy

Karlsson et al, 2005



Bone mineral density during lactation

Karlsson et al, 2005