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REVIEW

EFFECT OF ORAL CONTRACEPTIVES ON BONE MINERAL DENSITY

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Abstract

Contraceptives are widely used in our times and a lot of research has been conducted to clarify their impact on Bone Mineral Density. Combined Oral Contraceptives (COCs) may be detrimental to the BMD of adolescents. However, low-dose are more protective than ultra-low-dose COCs. When it comes to premenopause and perimenopause, COCs have no impact on BMD in women with good ovarian function and no estrogen deficiency. In women with impaired ovarian function, it seems that COCs have a positive influence on BMD. Progestin only-pills may not affect BMD, but further research is needed. Depot medroxyprogesterone acetate injection (DMPA) has a negative impact, especially in adolescents, which is duration related but evidence shows that BMD recovers after discontinuation. Levonorgestrel-releasing intrauterine system (LNG-IUS) has no impact on BMD.

Keywords: contraceptives, bone mineral density.

INTRODUCTION

Bone mineral density formation is the outcome of the influence of many factors. Diet, exercise, hormonal status, and calcium intake are some of the most important of them. We examine the effect of oral and some non-oral contraceptives on BMD. Their influence is classified in the hormonal status subunit, because they affect estrogen and progesterone levels, which have great importance on BMD.

A high percentage of women use contraception methods in order to avoid unintended pregnancies. It is a fact that abortion rates have been reduced, because of this new reality. Due to the wide use of contraception, we would like to search the bibliography and examine the impact of different contraception methods, with different dosages among the same methods and in different ages of women. In this way we aim to find the right contraception method for every stage of a woman's life concerning BMD and notice the gaps that are needed to be studied.

Types of Oral contraceptives

Oral contraceptives can be COCs or Progestin-only pills. COCs contain estrogen and progesterone and can be monophasic (same dose of both components in the active pills) or multiphasic (varying doses weekly of both or either component in the active pills). Also, they can be Low dose (35mcg or less estrogen) or Ultra-low dose (20mcg or less estrogen). The estrogen component can be Estradol, Ethinylestradiol, or Estetrol. The progesterone component can be first-generation progestin (Norethindrone acetate, Lynestrenol, Ethynodiol diacetate, Norethynodrel), second generation progestin (dl-Norgestrel, Levonorgestrel), third generation progestin (Norgestimate, Desogestrel, Gestodene) or Unclassified progestin (Drospirenone, Cyproterone acetate). Progesterone-only pills usually contain drospirenone (suppresses ovulation) 0.35 mg tablet/day for 28 days non stop or norethindrone (thickens cervical mucus, suppresses ovulation, decreasing the mid-cycle LH and FSH peaks and alters endometrium thickness) 4 mg tablet/day for 24 days and 4 hormone-free pills 1).

Bone Composition and BMD

Bone is a multifunctional system that provides a mechanical shield for support and security. Also bone is important in haemostasis and by new data aids in the function of endocrine glands. It is made up of an organic, a mineral part and bone cells.

The organic part (20-40% of the bone) contains approximately 90% type I collagen fibers, minor quantities of type III and V collagen and 10% non collagenous proteins such as proteoglycans, glycoproteins, osteocalcin and osteonectin. The levels

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of the glycoprotein alkaline phosphatase (ALP) when taken from a bone specific region can determine the activity of bone mineralization. Osteocalcin is indicated in osteoblasts and osteocytes and helps bind calcium and mineral deposition. It is an important marker of bone remodeling.

The mineral part (60-70% of the bone) contains calcium phosphate in the form of hydroxyapatite. Bone mineralization is the process of deposition of inorganic minerals on the organic matrix.

Osteoblasts, osteoclasts and osteocytes are the bone cells. Osteoblasts regulate mineralization and formulate the extracellular matrix. Osteoclasts are responsible for the resorption of the bone. Osteocytes are the mature osteoblasts. They are the 90-95% of bone cells and respond to mechanical strain in order to coordinate the bone remodeling (2).

Bone mineral density (BMD) is a way of measuring how many grams of calcium and other bone minerals are packed into a segment of bone.BMD reflects bone's strength and endurance. T-score is the most common scale used for BMD and it is expressed in standard deviations (SDs). BMD is normal when it's value is not lower than 1SD for normal. Osteopenia is defined as a value lower 1-2.5 SDs and osteoporosis as lower than 2.5 SDs (3).

Estrogen Effects on Bone

Estrogens affect BMD in different direct and indirect ways and some of them are not known yet. They are the major regulator of bone metabolism and their deficiency increases bone resorption. The rate of formation cannot counterbalance this situation, so we result in bone loss. Estrogens inhibit the bone resorption in multiple ways. The reduced osteocytes apoptosis leads to minimizing the activation of bone remodeling. In order to maintain bone formation they affect osteoblasts by three mechanisms. They reduce osteoblast apoptosis, oxidative stress and NF-kB activity. Additionally, estrogens increase osteoblast apoptosis, modulates osteoblast-osteocyte and T-cell regulation of osteoclasts and decreases their RANKL-induced differentiation leading to low bone resorption. Estrogen efficiency block osteoblast synthesis of pro-osteoclastic cytokines such as IL-1, IL-6,IL-7. IL-6 reinforces bone resorption. Also, estrogens may directly antagonize IL-6 receptors. Finally, estrogens influence TNF. All these pathways lead to bone maintenance and low bone remodeling, resorption and loss (4,5).

Estrogen Receptor Subtype alpha (ERa) and beta (ERβ) on Bone

ERα and ERβ are nuclear receptors that regulate many processes in the whole body. Their impact on almost all tissues has been used in therapy of breast, prostate, colorectal, lung cancers, cardiovascular diseases, neuropathies, obesity and menopause symptoms. ERα is mostly found in mammary gland, uterus, ovary's thecal cells, bones, testes, epididymis, prostate's stroma and liver. ERα has a more prominent role in bone homeostasis. ERβ is mostly found in prostate's epithelium, bladder, ovary's granulose cells, colon, immune system. ERβ counteracts the cell hyperproliferation in breast and uterus. Both ERα and ERβ are found in adipose tissue, cardiovascular and central nervous system.

Estradiol and HRT increase the breast cancer, endometrial cancer and thromboembolism risk, because they activate ERα and ERβ. SERMS selectively target some of these receptors but perfect balance has not been achieved yet. This balance would be a situation where a factor would selectively target the receptor of interest in one tissue as an agonist or an antagonist and at the same time would not affect the other tissues. Another problem with these receptors is that they have different expression among tissues and among different stages of the same cancer.

Bones are mainly affected by ERα but they also express ERβ. In order to face postmenopause osteoporosis, estrogen based therapy (HRT) is given. On the other hand through ERα, breast and uterus cancer risk is increased. Also, HRT increases the risk of heart diseases and strokes (6).

The role of ERα and ERβ in bone biology is needed to be further elucidated. It is known that E2 activates ERα via inducing the transcription of FasL (Fas Ligand). MMP3 cleaves FasL from cell surface and FasL induces osteoclast apoptosis. ERα and ERβ have been detected in osteoclasts, osteocytes and osteoblasts. It is interesting that, in a patient with a mutation on ERα has been noticed incomplete epiphyseal closure and low bone mineral density. ERβ function has not been fully explained but it seems that this receptor antagonizes ERα effects (7).

Progestogen Effects on Bones

Progestogens have different influence on glucocorticoid, androgen or mineralocorticoid receptors due to their group. Progestins can be pregnanes, gonanes or estranges but the studies have not detected statistically significant differences in BMD between groups. P.Hadji *et al.* (4) suggest that POPs (progestin-

only contraceptives) when used and lead to estradiol serum levels 30-50 pg/mL or higher, bone loss isn't seem to be accelerated and when DMPA (Depot medroxyprogesterone acetate) is used and lead estradiol serum levels 20-30 pg/mL, progesterone is harmful and should be avoided. Also, P.Hadji *et al.* (4) gather the information of different studies about serum estradiol levels due to the progestogen used.

It is interesting to cite here different E2 levels that were detected after treatment with different progestogens:

- Dienogest 37 pg/mL
- Levonorgestrel 120 pg/mL
- Etonogestrel 90 pg/mL
- DMPA 26.6-35.1 pg/mL
- Drospirenone 48.7 pg/mL
- Desogestrel 54.4 pg/mL

Adolescence and Young women

When it comes to greater BMD and bone health, it is known that the best way to manage it, is the maximum acquisition of peak BMD (8). These procedure happens at higher tempo during adolescence 1 year before menarche and 3 years after. Plenty of factors interfere, such as diet, calcium intake, exercise and hormone status. Hormone status is affected by oral contraceptives (OCs) that establish new hormone levels and suppress the endogenous estradiol and hypothalamic-pituitary-ovarian axis. OCs are commonly used during adolescence and post-adolescence and their demand is increasing.

Zinglar *et al.* (8) in their review conclude that COCs containing 20-30μg of ethinyl estradiol prevent the acquisition of peak BMD but limited data exist about 35 μg COCs and progestin only contraceptives on adolescents and young adults. Lina Warholm *et al.* (9) report in their review that few studies indicate that COCs have negative impact on BMD and expresses the need for more studies. Barbara A Cromer *et al.* (10) mention that there is a difference between low dose (30-40 μg EE) and ultra low dose (20 μg EE) in the acquisition of optimal peak BMD in young women. Low dose seem to be more protective than ultra low-dose OCs but other factors and cessation of contraceptive method have also important role in the long-term BMD. Also Cibula *et al.* (11) in their RCT on adolescents note that BMD of Lumbar Spine during adolescence may be interfered especially when ultra low does COCs are used. No COCs users appeared increases in Lumbar Spine BMD and radius. Only BMD of Lumbar spine increased in 30μg EE COCs users but no increase noted in 15μg EE COCs users. Brajic *et al.* (2) in a wide observational study in adolescents in Canada concluded that BMD changes did not related to estrogen dose and age at starting COCs but users had less hip region peak BMD than non users. RCT confirmation noted that needed to happen.

Especially, COCs are used in post-adolescence and in college life (about 18-24 years old). Almstedt *et al.* (3) in their study on college-aged girls that used COCs over 12 months, noted decreased BMD acquisition, declines in lumbar spine and high bone turnover. Additionally, Carmine Nappi *et al.* (4) in a clinical trial compared the effect on BMD of COCs than contained 3mg dospirenone and 75 μg gestodene as progestogen. The estrogen was 30 μg ethinyl/estadiol. No difference noted between them but *versus* no COC users they had an equal positive influence on bone turnover. Carmine Nappi *et al.* (5) in a different clinical trial compared the impact of low dose (20μg EE and 75 μg gestodene) and ultra low dose (15 μg EE and 60 μg gestodene) on BMD and bone turnover. There they suggested that both COCs types had similar positive effect on bone turnover but no impact on BMD. However, Dong-Yun Lee *et al.* (6) concluded in absence of effect on BMD in post-adolescent young women, when a study was conducted on women aged 20-30 on women operated for endometrioma and followed postoperative OCs therapy. Also, correlation was not found between BMDs in different duration or age of starting this therapy. The only correlation was found on dose of OCs. The difference concerned the doses 20μg and 30 μg.

Premenopausal and Perimenopausal women

Premenopause is when the woman has no symptoms of perimenopause or menopause. It takes place at the reproductive years of a woman's life and at this time can exist some small hormonal changes but they are not noticeable. A lot of healthcare professional don't use this term. Perimenopause is a transitional time in a woman's life, a transition to menopause and the end of reproductive years. It often starts at 40 to 44 years old and is characterized by changes in menstrual cycle, in physical and in emotional stage. It can last 2 to 10 years.

S.L. Liu *et al.* (7) in their review support that there is good evidence that oral contraceptives have a positive effect on BMD in perimenopausal women and "hypothalamic" oligo/amenorrheic premenopausal women. The same outcome has the review by Gambacciani *et al.* (8) in perimenopause and in these premenopausal estrogen deficiency situations and when anovulatory cycles exist. But when ovarian impairment has not started and the ovarian function is normal, COCs have no benefit on BMD.

This point of view on premenopausal women with healthy ovarian function supports Vannessa D Sherk *et al.* (9). They conclude that in this stage of woman's life, COCs don't affect BMD. Weight and BFLBM (Bone Free Lean Body Mass) are important factors. Additionally, Sørdal T *et al.* (20) in their RCT approve that COCs used for 2 years have no effect on BMD in premenopausal women and also add that there is no difference when using the monophasic COC containing 2.5mg nomegestrol acetate/1.5mg 17β-estradiol or 150μg levonorgestrel/ 30μg ethinylestradiol. Di Carlo *et al.* (21) concludes to the same outcome after 6 months use of COC containing dienogest/ oestradiol valerate. On the other hand, it is noteworthy to refer here to a multicenter study by J.C. Prior *et al.* (2) that in a sample of 524 premenopausal women in Canada, the COCs users had significantly lower BMD values for trochanter and spine than non-users.

As mentioned before during perimenopause COCs have a bone sparing effect. In a clinical trial by Gambacciani *et al.* (23) compared the impact of different low dose COCs on BMD. Only the progestin component was different among the compared COCs. The estrogen was 20 μg EE and the progesting was 0.15mg desogestrel or 0.1 mg levonogestrel or 0.75 mg gestodene. No difference was noticed between them and all increased BMD *versus* non-users ($p<0.05$).

Postmenopausal women

Although contraceptive methods are not used in postmenopausal women, exists interesting information in the bibliography about the effect of contraceptives on postmenopausal women. It seems that in postmenopausal women oral contraceptives have a positive impact on BMD. Shuying Wei *et al.* (24) performed a cross-sectional study on 491 women aged 50-80. The results were that women that have ever used OCs had higher total body BMD (6%, $p<0.001$). An important association was found on duration of use on total body and spine BMD. Additionally, N. Taechakraichana *et al.* (25) in a randomized trial of OCs and HRT on BMD in postmenopausal women found that both of them increased lumbar spine and hip BMD. Especially OCs decreased more bone turnover. The OC was used as a cyclic regimen and contained 30 μg ethinyl estradiol and 150 μg desogestrel for 21 day/cycle and 5mg medrogestone for 10days/cycle for 12 months. Similar were the results when D Kritz-Silverstein *et al.* (26) examined the long-term impact of prior 6 or more year use of OCs on BMD. Postmenopausal women who have ever used OCs had higher BMDs of lumbar spine and femoral neck, but no ultradistal wrist or radius, than never users.

Progestin-only pills

Progestin-only pills may have no impact on BMD when the user experiences normal ovarian activity and menstruation. However, in hypoestrogenic situations the use of POPs may suppress the ovarian activity and increase the risk of low BMD. Clinical trials need to be conducted to investigate this further (7). Trémollières *et al.* (8) in their review also notes that the bone impact of OCs appears to be related with the degree of suppression of oestrogen levels. No effect of POPs on bone health is observed but there is reported that some POPs with strong antigonadotrophic activity have not been evaluated, especially in hypoestrogenic circumstances. It is important to be mentioned that the impact of high- and low- dose oral progestogens on BMD has not be studied and further research on this field need to be conducted (29).

Estrogen Deficiency

It is interesting to refer to the impact of OCs in some situations, where a woman suffers estrogen deficiency. Estrogen deficiency leads often to reduction of BMD. In these situations hormonal therapy or OCs are commonly used. This deficiency can be met in anorexia nervosa, hypothalamic amenorrhea, premature ovarian insufficiency or failure and many more cases.

Merki-Feld *et al.* (30) in their review conclude that COCs have no negative impact on adolescents with anorexia nervosa. No statistically significant effect on lumbar spine or hip BMD is observed in the RCT of Strokosch *et al.* (31),where they examined the effect of low dose COCs (180-250 μg norgestimate/35 μg EE).

Additionally, in women with functional hypothalamic amenorrhoea the systematic review and meta-analysis of Aalberg *et al.* (32) showed that estrogen therapy with OCs doesn't improve the patient's BMD. Also, in patients with premature ovarian insufficiency the treatment with OCs or hormonal therapy[HT] noted inconsistent results. No decrease was noted but further research is needed to be done on this topic (33).Finally, one RCT of Cartwright *et al.* (34) concluded that in premature ovarian failure, hormone replacement with OCs or hormone replacement therapy [HRT] is better than no treatment and HRT has better outcome than OCs but there was limitations and further research need to be done.

Depot medroxyprogesterone acetate injection (DMPA)

DMPA is a widely used contraception method and has contributed effectively to the reduction of unintended pregnancies. However, there is a great concern about its impact on BMD. Kaunitz *et al.* (35) in

their review observe that long-term use of DMPA may decrease the spinal BMD but this impact seems to be reversed after discontinuation. The review of Banks *et al.* (36) agrees that DMPA users have a lower average BMD than no users and adds that DMPA when taken for a longer duration leads to a greater reduction of BMD than short-term use.

It is important to refer to the use of DMPA on adolescents. A comparative study by Cromer *et al.* (37) examined the impact of DMPA, Levonorgestrel implants and COCs during adolescence on BMD. After 1 year of use DMPA led to 1.5% reduction of BMD and after 2 years 3%. 1 year of implant use increased BMD by 2.5% and COCs 1.5%. 2 year of Implant use increased BMD by 9.3%. (1 year use p <00.2, 2 year use p <0.001). Taking into account that in this stage of life 50% of bone mass is accrued, it seems that DMPA should not be used in adolescents. Rome *et al.* (38) agree with this conclusion on DMPA but supports that OCs (20mg EE/100mg levonorgestrel) also decrease BMD in adolescence.

Levonorgestrel-releasing intrauterine system (LNG-IUS)

LNG-IUS is also a widely used, efficient and with high continuation rates contraception method. According to Danielsson *et al.* (39) this method is safe and efficient for all age groups and has no adverse effects on BMD. Mansour's review (40) concludes with the same outcome. Also, when LNG-IUS is compared with the non hormonal copper Tcu380A IUD, it is shown that they have the same outcome and no adverse effect on BMD in 2 years (41) or 7-10 year use (42). When LNG-IUS is compared with DMPA for a period of 3 years Wong *et al.* (43) noticed bone gain in LNG-IUS users and bone loss in DMPA users.

In conclusion, not all contraceptives have the same impact on BMD. Their influence varies between their different types, different doses of components, and different patient's stage of life or hormonal status .Low-dose (COCs) may be detrimental to the Bone Mineral Density (BMD) of adolescents but they are more protective than ultra low-dose COCs. During premenopause and perimenopause, only when the ovarian function starts to be affected, does it seems that COCs have a positive influence on BMD. In postmenopausal women, COCS have bone sparing effect. Progestin only-pills may not affect BMD, but further research in this field needs to be conducted. Depot medroxyprogesterone acetate injection (DMPA) has a negative impact on BMD, especially in adolescents, which is duration related but evidence shows that BMD recovers after discontinuation. Levonorgestrel-releasing intrauterine system (LNG-IUS) has no impact on BMD.

However, there is a need for more concerted methods of study on this topic. Several limitations have been noticed during the research of the bibliography. Wide variations between studies, wide age ranges, different lengths of follow-up and especially for adolescents there is no long term follow up to investigate possible long term effects. Also, BMD is measured in different sites of the body between studies, such as lumbar spine or femoral neck or hip or form arm or ankle. Some studies use dual-x-ray absorptiometry and others single energy x-ray absorptiometry. Many studies have not adjusted other key factors that influence BMD such as diet, exercise, age and BMI as surprisingly few women with severe osteoporosis undergo workup for secondary cause (44). Also, a lot of studies define as COC, medicines with different dosages and types of estrogen and progesterone.

So we conclude that there is a need for better design, methods and analytic models. Also, there is noticed a gap in the literature about the impact of different POPs on BMD. Especially those with strong antigonadotrophic activity.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Cooper DB, Patel P, Mahdy H. Oral Contraceptive Pills, in: StatPearls. StatPearls Publishing, Treasure Island (FL). 2022.
2. Dey P. Bone Mineralisation, Contemporary Topics about Phosphorus in Biology and Materials. IntechOpen. 2020.
3. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis : report of a WHO study group [meeting held in Rome from 22 to 25 June 1992]
4. Hadji P, Colli E, Regidor PA. Bone health in estrogen-free contraception. Osteoporos Int. Osteoporos Int. 2019;30(12):2391-2400.
5. Khosla S, Oursler MJ, Monroe DG. Estrogen and the Skeleton. Trends Endocrinol Metab. 2012;23(11):576-581.
6. Paterni I, Granchi C, Katzenellenbogen JA, Minutolo F. Estrogen receptors alpha (ERα) and beta (ERβ): subtype-selective ligands and clinical potential. Steroids. 2014;90:13-29.
7. Khalid AB, Krum SA. Estrogen receptors alpha and beta in bone. Bone. 2016;87:130-135.
8. Ziglar S, Hunter TS. The effect of hormonal oral contraception on acquisition of peak bone mineral density of adolescents and young women. J Pharm Pract. 2012;25(3):331-340.
9. Warholm L, Petersen KR, Ravn P. Combined oral contraceptives' influence on weight, body composition, height, and bone mineral density in girls younger than 18 years: a systematic review. Eur J Contracept Reprod Health Care. 2012;17(4):245-253.
10. Cromer BA. Bone mineral density in adolescent and young adult women on injectable or oral contraception. Curr Opin Obstet Gynecol. 2003;15(5):353-357.
11. Cibula D, Skrenkova J, Hill M, Stepan JJ. Low-dose estrogen combined oral contraceptives may negatively influence physiological

bone mineral density acquisition during adolescence. Eur J Endocrinol. 2012;166(6):1003-1011.
12. Brajic TS, Berger C, Schlammerl K, Macdonald H, Kalyan S, Hanley DA, Adachi JD, Kovacs CS, Prior JC; CaMos Research Group Combined hormonal contraceptives use and bone mineral density changes in adolescent and young women in a prospective population-based Canada-wide observational study. J Musculoskelet Neuronal Interact. 2018;18(2):227-236.
13. Almstedt HC, Cook MM, Bramble LF, Dabir DV, LaBrie JW. Oral contraceptive use, bone mineral density, and bone turnover markers over 12 months in college-aged females. J Bone Miner Metab. 2020;38(4):544-554.
14. Nappi C, Di Spiezio Sardo A, Greco E, Tommaselli GA, Giordano E, Guida M. Effects of an oral contraceptive containing drospirenone on bone turnover and bone mineral density. Obstet Gynecol. 2005;105(1):53-60.
15. Nappi C, Di Spiezio Sardo A, Acunzo G, Bifulco G, Tommaselli GA, Guida M, Di Carlo C. Effects of a low-dose and ultra-low-dose combined oral contraceptive use on bone turnover and bone mineral density in young fertile women: a prospective controlled randomized study. Contraception. 2003;67(5):355-359.
16. Lee DY, Oh YK, Yoon BK, Choi D. Effects of long-term postoperative oral contraceptive use for the prevention of endometrioma recurrence on bone mineral density in young women. Gynecol Endocrinol. 2014;30(10):751-754.
17. Liu SL, Lebrun CM. Effect of oral contraceptives and hormone replacement therapy on bone mineral density in premenopausal and perimenopausal women: a systematic review. Br J Sports Med. Ιανουάριος 2006;40(1):11-24.
18. Gambacciani M, Monteleone P, Ciaponi M, Sacco A, Genazzani AR. Effects of oral contraceptives on bone mineral density. Treat Endocrinol. 2004;3(3):191-196.
19. Sherk VD, Howard CD, Bemben MG, Bemben DA. Influence of Body Composition, Oral Contraceptive Use, and Physical Activity on Bone Mineral Density in Premenopausal Women. Int J Exerc Sci. 2009;2(1):28-37.
20. Sørdal T, Grob P, Verhoeven C. Effects on bone mineral density of a monophasic combined oral contraceptive containing nomegestrol acetate/17β-estradiol in comparison to levonorgestrel/ethinylestradiol. Acta Obstet Gynecol Scand. 2012; 91(11):1279-1285.
21. Di Carlo C, Gargano V, Sparice S, Tommaselli GA, Bifulco G, Schettino D, Nappi C. Short-term effects of an oral contraceptive containing oestradiol valerate and dienogest on bone metabolism and bone mineral density: an observational, preliminary study. Eur J Contracept Reprod Health Care. 2013;18(5):388-393.
22. Prior JC, Kirkland SA, Joseph L, Kreiger N, Murray TM, Hanley DA, Adachi JD, Vigna YM, Berger C, Blondeau L, Jackson SA, Tenenhouse A. Oral contraceptive use and bone mineral density in premenopausal women: cross-sectional, population-based data from the Canadian Multicentre Osteoporosis Study. CMAJ. 2001;165(8): 1023-1029.
23. Gambacciani M, Cappagli B, Lazzarini V, Ciaponi M, Fruzzetti F, Genazzani AR. Longitudinal evaluation of perimenopausal bone loss: effects of different low dose oral contraceptive preparations on bone mineral density. Maturitas. 20 2006; 54(2):176-180.
24. Wei S, Venn A, Ding C, Foley S, Laslett L, Jones G. The association between oral contraceptive use, bone mineral density and fractures in women aged 50-80 years. Contraception. 2011;84(4):357-362.
25. Taechakraichana N, Limpaphayom K, Ninlagarn T, Panyakhamlerd K, Chaikittisilpa S, Dusitsin N. A randomized trial of oral contraceptive and hormone replacement therapy on bone mineral density and coronary heart disease risk factors in postmenopausal women. Obstet Gynecol. 2000;95(1):87-94.
26. Kritz-Silverstein D, Barrett-Connor E. Bone mineral density in postmenopausal women as determined by prior oral contraceptive use. Am J Public Health. 1993;83(1):100-102.
27. Heller RL, Cameron S, Johnstone A, Cochrane R, Glasier A. Bone mineral density in progestogen-only implant and pill users with amenorrhoea: a pilot study. BMJ Sex Reprod Health. 2022;48(1):69-70.
28. Trémollières F. [Effect of hormonal contraception on bone mineral density]. Gynecol Obstet Fertil. 2005;33(7-8):520-525.
29. Sarfati J, de Vernejoul MC. Impact of combined and progestogen-only contraceptives on bone mineral density. Joint Bone Spine. 2009;76(2):134-138.
30. Merki-Feld GS, Bitzer J. Contraception in adolescents with anorexia nervosa. Is there evidence for a negative impact of combined hormonal contraceptives on bone mineral density and the course of the disease? Eur J Contracept Reprod Health Care. 2020; 25(3):213-220.
31. Strokosch GR, Friedman AJ, Wu SC, Kamin M. Effects of an oral contraceptive (norgestimate/ethinyl estradiol) on bone mineral density in adolescent females with anorexia nervosa: a double-blind, placebo-controlled study. J Adolesc Health. 2006;39(6):819-827.
32. Aalberg K, Stavem K, Norheim F, Russell MB, Chaibi A. Effect of oral and transdermal oestrogen therapy on bone mineral density in functional hypothalamic amenorrhoea: a systematic review and meta-analysis. BMJ Open Sport Exerc Med. 2021;7(3):e001112.
33. Fine A, Busza A, Allen LM, Kelly C, Wolfman W, Jacobson M, Lega IC. Comparing estrogen-based hormonal contraceptives and hormone therapy on bone mineral density in women with premature ovarian insufficiency: a systematic review. Menopause. 2022;29(3):351-359.
34. Cartwright B, Robinson J, Seed PT, Fogelman I, Rymer J. Hormone Replacement Therapy Versus the Combined Oral Contraceptive Pill in Premature Ovarian Failure: A Randomized Controlled Trial of the Effects on Bone Mineral Density. J Clin Endocrinol Metab. 2016;101(9):3497-3505.
35. Kaunitz AM. Long-acting hormonal contraception: assessing impact on bone density, weight, and mood. Int J Fertil Womens Med. 1999;44(2):110-117.
36. Banks E, Berrington A, Casabonne D. Overview of the relationship between use of progestogen-only contraceptivesband bone mineral density. BJOG. 2001;108(12):1214-1221.
37. Cromer BA, Blair JM, Mahan JD, Zibners L, Naumovski Z. A prospective comparison of bone density in adolescent girls receiving depot medroxyprogesterone acetate (Depo-Provera), levonorgestrel (Norplant), or oral contraceptives. J Pediatr. 1996;129(5):671-676.
38. Rome E, Ziegler J, Secic M, Bonny A, Stager M, Lazebnik R, Cromer BA. Bone biochemical markers in adolescent girls using either depot medroxyprogesterone acetate or an oral contraceptive. J Pediatr Adolesc Gynecol. 2004;17(6):373-377.
39. Gemzell-Danielsson K, Inki P, Heikinheimo O. Recent developments in the clinical use of the levonorgestrel-releasing intrauterine system. Acta Obstet Gynecol Scand. 2011;90(11):1177-1188.
40. Mansour D. The benefits and risks of using a levonorgestrel releasing intrauterine system for contraception. Contraception. 2012;85(3):224-234.
41. Yang KY, Kim YS, Ji YI, Jung MH. Changes in bone mineral density of users of the levonorgestrel-releasing intrauterine system. J Nippon Med Sch. 2012;79(3):190-194.
42. Bahamondes MV, Monteiro I, Castro S, Espejo-Arce X, Bahamondes L. Prospective study of the forearm bone mineral density of long-term users of the levonorgestrel-releasing intrauterine system. Hum Reprod. 2010;25(5):1158-1164.
43. Wong AY, Tang LC, Chin RK. Levonorgestrel-releasing intrauterine system (Mirena) and Depot medroxyprogesterone acetate (Depoprovera) as long-term maintenance therapy for patients with moderate and severe endometriosis: a randomised controlled trial. Aust NZJ Obstet Gynaecol. 2010;50(3):273-279.
44. Nguyen K, Chen X, Hughes T, Hofflich H, Woods GN, McCowen KC. Surprisingly Few Women with Severe Osteoporosis by Bone Densitometry Undergo Workup for Secondary Causes - A Retrospective Evaluation. Acta Endocrinologica-Bucharest 2021; 17(4):537-542.