Reviewer’s report

Title: Low-dose combined oral contraceptives use is associated to lower bone mineral content variation in adolescents over a one-year period

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Reviewer: Jan Stepan

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In this randomized study of 12 months of one dose of ethinyl estradiol, the authors address the important issue of the effect of oral contraceptives on bone mass gain in healthy female volunteers between 12 and 20 years old, who were post menarche and had regular menstrual cycles. Data on this topic are few and it is still debated whether there is an impact on bone density accrual or not. The main finding was an impairment of bone growth on low dose contraceptive. The article is clearly written, is concise, clear and well organized.

There are three main limitations:
1. The relatively small number of girls studied.
2. Statistical evaluation of results of this study is needed.
3. The short period of treatment (12 months) seems not sufficient to observe any relevant change in bone density even in growing subjects, and does not allow for impact of longer-term effects of a change in the bone physiology. Especially, rate of bone gain is very different in very young subjects (12 years old) and 20 year old women.

The authors presented reasonable explanations regarding these two points, but a deeper discussion is needed (especially for the third point).

Minor comments
2. Methods. A sentence on EE and desogestrel administration is missing in the Methods.
3. Please, state the short-term in-vivo precision errors for lumbar spine and total body BMC; state the long-term precision error using the Hologic phantom. Did daily scanning of a phantom show absence of machine drift during the study?
4. Was the sampling and storage done for the measurement of biochemical markers?
5. I don’t think the assay for estradiol detects the ethinyl estradiol concentrations. This should be stated in the methods section because it is easy to get confused with serum measurements of 17-beta estradiol vs ethinyl estradiol.
6. Results. Change in BMD compared with baseline should be provided instead of Variation.

7. Was BMC change significant after adjustment for age and body size?

8. Was change in BMD significant when normalized using Z-scores?

9. Discussion. The authors should note that the ethinyl estradiol is much more potent at activating the estrogen receptors than estradiol, so that with COC's the overall activation of estrogen receptors is not measured by serum levels of 17-beta estradiol. Furthermore, the COC's have major effects on SHBG so the bioavailable estrogen should be considered.

10. The discussion correctly notes that estrogens are important in growth hormone metabolism, but it does not discuss the difference between endogenous effects and exogenous effects (J Clin Endocrinol Metab. 2004 Dec;89(12):6185-92).

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests' below.