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LETTER TO THE EDITOR

Combined Cabergoline and Metformin in Patients with Polycystic Ovarian Disease with Hyperprolactinemia: Methodological Concerns

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Dear Editor,

I read with interest the article titled "Efficacy of combined cabergoline and metformin compared to metformin alone on cycle regularity in patients with polycystic ovarian disease with hyperprolactinemia: A randomized clinical trial" by Dr. Elsersy published in your esteemed journal [1]. However, I am concerned about the author's seeming disregard for proper methodological design and accurate representation of data throughout this article.

The author included patients with hyperprolactinemia; however, one of the study groups received metformin plus placebo tablets. Metformin could reduce the prolactin level only if administered in high doses (2.5–3 g) [2]. The author used a dose of 1 g daily which is considered too low dose for therapy. Therefore, it is not surprising to find no difference between prolactin levels before and after treatment in this group. Higher doses may be necessary to achieve the prolactin lowering effect of metformin. Another point that hyperprolactinemia should be considered an exclusion criterion for diagnosis of polycystic ovarian syndrome (PCOS).

I am disappointed that the author did not provide any report on sample size calculation. It should be emphasized that in a randomized controlled trial (RCT), sample size calculation should be done based on the primary outcome measure. What outcome did the author consider in the study groups and what is the reference did she use to provide baseline outcome data. Additionally, the study protocol was not registered on the clinical trials registry Web sites.

I can understand that no patient was lost during the 3-month follow-up period, although it seems non-logical in RCTs, but I wonder that none of the study participants became pregnant during the course of treatment. The author mentioned that there was significant decrease in body weight, androgen levels, prolactin levels and improvement in cycle regularity. How the author can explain that no woman became pregnant after this great improvement.

The authors should clarify exactly the primary and secondary outcomes of the study. Additionally, there were some methodological concerns as no mention of the trade names of the used drugs, the identity and manufacturing of the placebo tablets, the cycle day at which the laboratory investigations were done especially if the patient was amenorrheic, the parity status of the patients. The author should add patients with only irregular cycles in the inclusion criteria.

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Missing from Elsersy's results is to report the adverse effects of the drugs. I can't believe that all patients were compliant in taking both medications for this long time although their well-known adverse effects [3]. The author must present the definition of adverse effects.

Elsersy states "the results of other researchers who concluded that the administration of cabergoline can normalize androgen levels and improve the menstrual irregularity in women with PCOS" but does not provide any evidence for this claim [1]. Instead, she provided an irrelevant citation: Corbet et al. [4] who report the methods of prevention of ovarian hyperstimulation syndrome. The author states in the discussion that "the patients who sought for pregnancy were excluded due to the limited data available as regards the safety profile and teratogenicity of cabergoline [1]." Although she provided no citations for this information, cabergoline is classified as FDA pregnancy risk category B.

Finally, I think that the short duration of the study is a major limiting factor to find out any benefit with regard to regulation of the menstrual cycle and body mass index. Moreover, follow-up of ovulation and seeking pregnancy are usually the main reasons for seeking treatment in the reproductive age group unlike the teenage group with PCOS which was not included in the study.

Compliance with Ethical Standards

Conflict of interest The author declares there is no conflict of interest, and there are no financial disclosures to be made.

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