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Letter from original author re. Does telomerase activity have an effect on infertility in patients with endometriosis? Methodological Issues

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Dear Editor,

We greatly appreciate the thoughtful comments from Dr. Almasi-Hashiani et al. on the article entitled "Does telomerase activity have an effect on infertility in patients with endometriosis?" (1). We are delighted that you are interested in the study.

We agree with the sample size limitation of the study, which can alter the statistical power of the concluded results. As we mentioned in the article, endometrial sampling was one of the steps taken in designing the study, and the invasiveness of this procedure was the main limitation in reaching the targeted sample size. Virginity and enrolled patients' desire for future fertility were the main reasons for refusing the procedure. As a result, only 65.3% of all eligible patients consented for participation. Those who did participate were divided into three groups of equal size; within each group, we ensured that approximately equal numbers of participants were in secretory and proliferative phases of the menstrual cycle. We agree entirely with the authors' point that increase in the sample size will enhance the power and significance of the results.

The non-random selection of treatment cohorts also was mentioned by Dr. Almasi-Hashiani. As mentioned in our article, this study is a non-randomized trial and the treatment cohort, i.e. surgical intervention, was applied according to the underlying condition. To avoid ethical issues, patients who underwent a hysterectomy and bilateral salpingo-oophorectomy surgery for benign gynecological conditions were enrolled in the control group. This grouping led to the age difference between endometriosis and healthy control groups. On the other hand, infertile and fertile patients in endometriosis group were in different decades due to the nature of this underlying condition. Based on the sample size for each study group, only one parameter, age, was chosen and adjusted as the most prominent confounder. Significance was established after adjustment. Only one confounder was adjusted in order to account for sample size and to avoid over-adjustment bias (2).

We thank Dr. Almasi-Hashiani for pointing out that “multiple testing problems” or “look elsewhere effect” is likely to occur in this study. From the statistical point of view, this design may seem like it employs multiple testing to achieve a significant p-value. However, we aimed to assess all conditions, which are important from the clinical aspect. As mentioned in the article, telomerase activity is strongly associated with menstrual cycle phases. The highest activity was shown in proliferative phase, whereas it was undetectable in the secretory phase (3). Based on these facts, we aimed to assess the activity in different cycle phases. Such assessment, therefore, necessitated more than one comparison. However, from the clinical perspective, patient groups with and without endometriosis could not be assumed to be the same for fertile and infertile patients. Therefore, analyses of different clinical groups were performed separately. A significant result was found only in the secretory phase of infertile endometriosis group, which supports our initial hypothesis. We would also reemphasize that further studies with larger sample sizes would be required for more powerful results.

Sincerely,

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2. Schisterman EF, Cole SR, Platt RW. Overadjustment bias and unnecessary adjustment in epidemiologic studies. Epidemiology (Cambridge, Mass). 2009;20(4):488.
3. Kim CM, Oh YJ, Cho SH, Chung DJ, Hwang JY, Park KH, et al. Increased telomerase activity and human telomerase reverse transcriptase mRNA expression in the endometrium of patients with endometriosis. Human reproduction (Oxford, England). 2007;22(3):843-9.