Evaluating Serum HE4: Some Serious Considerations

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Dear Dr Papageorghiou,

We have perused with great interest the scholarly article "Serum HE4 predicts progestin treatment response in endometrial cancer and atypical hyperplasia: A prognostic study" by Chloe Barr et al. [1]. We applaud the authors' diligent efforts in investigating a biomarker that could independently predict the response to conservative therapy. However, we wish to draw attention to certain noteworthy aspects upon a comprehensive evaluation.

Firstly, it is noteworthy that all the women who participated in the study underwent a preliminary endometrial biopsy before the initiation of progestin. However, there is no mention of whether women with relative contraindications such as cervical stenosis, coagulopathy or obstructive cervical lesions were sampled if they were included in the study. It is essential to consider these factors as they can significantly affect the accuracy and reliability of the biopsy results. Furthermore, it is necessary to note that insufficient tissue sampling is a common complication of endometrial biopsy, with an average of 31% of tissues obtained requiring improvement [2]. Considering that this is typically more prevalent in postmenopausal women, and 61% of the participants were 50 years or older, it is crucial to standardize the volume of tissue obtained to ensure fair and precise results. As outlined in the study, the primary form of progestin therapy was levonorgestrel-releasing intrauterine system (LNG-IUS). Still, for women whose devices had been misplaced more than once, an alternative treatment of oral medroxyprogesterone acetate 500mg was administered twice daily. This raises a concern regarding whether these women were closely monitored for compliance with the prescribed treatment regimen. This is particularly important as non-compliance, particularly with extended oral therapies, is a common issue that, if present, could skew the study's findings. The prognostic potential of pretreatment serum HE4 in predicting therapeutic response has been extensively researched; however, studies have also reported elevated serum HE4 levels in various other cancers, including ovarian, pancreatic, breast, lung, and stomach [3]. Therefore, it is crucial to exclude such patients thoroughly, as their inclusion could lead to inaccurate results by falsely accounting for the non-responder count.

Moreover, serum HE4 levels are also known to be influenced by renal function and status, necessitating adjustment [4]. It is, therefore, essential to consider and standardize these factors when analyzing the serum HE4 levels to obtain reliable and valid results. Lastly, it should be noted that a CLEIA technique was employed for analysis, which has been reported to significantly overestimate serum HE4 as compared to EIA [5]. This may raise concerns regarding the validity of the reported findings, and hence, caution must be exercised when interpreting the results.

The study focused on endometrial biopsy in women receiving progestin therapy, but potential complications such as insufficient tissue sampling and the inclusion of women with contraindications were not addressed. The study primarily used LNG-IUS but also administered oral medroxyprogesterone acetate, and compliance monitoring was not discussed. Serum HE4 levels were examined, but patients with other cancers or renal issues were not excluded, and the CLEIA technique used for analysis may have overestimated results. Therefore, caution is necessary when interpreting the findings of this study.

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