

Response to “Perspectives on ‘Assessment of hormone measurement methods in girls with premature adrenarche, polycystic ovary syndrome, and non-classical congenital adrenal hyperplasia’”

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We would like to express our gratitude to the authors of the commentary for their careful evaluation of our article¹, and we would like to respond to the letter entitled “Perspectives on the Assessment of hormone measurement methods in girls with premature adrenarche, polycystic ovary syndrome, and non-classical congenital adrenal hyperplasia”.² In this response, we endeavor to address each point raised in the letter.

Passing-Bablok regression and Bland-Altman analyses are statistical tools in method comparison studies.³ The primary objective of our study was to evaluate the diagnostic performance of hormones measured by two different methods in clinically established diagnostic groups, rather than to assess interchangeability between the methods. The Wilcoxon signed-rank test was used to compare paired hormone measurements due to its capacity for analyzing dependent non-parametric data.⁴ This evaluation facilitated the statistical analysis of measurement differences between assays, thereby providing background information for interpreting the results of the receiver operating characteristic (ROC) analysis.

We would like to express our appreciation to the authors for highlighting the discrepancy between the area under the curve (AUC) value of androstenedione for polycystic ovary syndrome (PCOS) reported in the abstract (AUC: 0.949) and the value presented in the results section (AUC: 0.792). This difference arose from an earlier version of ROC analysis, which was subsequently updated after adjustments for age and Tanner stage. The correct AUC value is 0.792, as reported in the results and depicted in Figure 2. The value in the abstract represents a typographical oversight. Therefore, we are publishing a corrigendum to correct this mistake.⁵

Pre-analytical variables are known to influence steroid hormone measurements, and the retrospective design of the study limited our ability to standardize all aspects of sample collection. However, in PCOS cases, blood sampling was consistently performed on the third day of menstruation, as outlined in the methods section. Additionally, in our center, steroid hormone analyses are routinely carried out in the early morning after an overnight fasting period of 8-10 hours. A regression analysis was specifically designed to mitigate

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variability stemming from different pubertal stages. It is clear that future prospective studies should incorporate enhanced control for these factors.

We thank the authors for highlighting the well-recognized issue of immunoassay cross-reactivity in the measurement of DHEAS. Indeed, the findings of our study demonstrated that electrochemiluminescence immunoassay (ECLIA) yielded higher dehydroepiandrosterone sulfate (DHEAS) values compared with those obtained by liquid chromatography – tandem mass spectrometry (LC-MS/MS) across all diagnostic groups. It was observed that the DHEAS levels measured by the ECLIA method exhibited a higher AUC, while maintaining a low level of specificity. As previously mentioned in the discussion, DHEAS is not a biologically active androgen, its association with clinical premature adrenarche (PA) is weak, and its diagnostic value is limited despite higher sensitivity. Consequently, this study does not provide evidence that immunoassay-based DHEAS is superior to other methods. Instead, these findings suggest that DHEAS is an unreliable marker for PA and should be interpreted with caution. Furthermore, we concur that LC-MS/MS-derived 11-ketotestosterone has the potential to serve as a promising biomarker, and we have cited this evidence accordingly in the manuscript.¹

We extend our gratitude to the authors for their meticulous review. It is our hope that the aforementioned clarification will adequately address each point raised.

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Conflict of interest

The authors declare that there is no conflict of interest.

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