Does DHEA supplementation in IVF patients result in supraphysiological DHEA-S serum concentrations?

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Dear Editor,

We read with interest the paper by Franasiak et al. entitled “Dehydroepiandrosterone (DHEA) supplementation results in supraphysiologic DHEA-S serum concentrations and progesterone assay interference that may impact clinical management in IVF” [1]. This paper provided evidence that DHEA supplementation could lead to increased circulating DHEA-S concentrations and clinically significant false elevations in progesterone results. This interference is particularly relevant at the progesterone concentration where the embryo transplant is decided [2]. However, we have concerns regarding discrepancies on the DHEA-S concentrations reported by these authors through the manuscript.

The units reported in Fig. 2 of the authors’ article is $\mu\text{g/dL}$ while the remainder of the text and figure/table legends use $\mu\text{g/mL}$ [1]. The authors also claim in their conference abstract [3] that the concentration of the Siemens ADVIA Centaur DHEA-S controls range from 0 to $>1500 \mu\text{g/mL}$. However, the package insert indicates that these materials have concentrations of 0 to $1500 \mu\text{g/dL}$ ($0\text{--}15.0 \mu\text{g/mL}$). In addition, a review of commercially available DHEA-S assays reveals that the analytical and reportable range for DHEA-S is $0\text{--}1500 \mu\text{g/dL}$ ($0\text{--}15 \mu\text{g/mL}$) (Table 1). We also replicated part of the experiment performed by the authors [1] using our Siemens ADVIA Centaur assay. We measured an aliquot of our high and low DHEA-S calibrator on the progesterone assay to

determine degree of cross reactivity. Our $0 \mu\text{g/dL}$ DHEA-S calibrator yielded a progesterone of 0.4 ng/mL while our highest DHEA-S calibrator ($1500 \mu\text{g/dL}$ or $15.0 \mu\text{g/mL}$) yielded a progesterone of 1.0 ng/mL . These inconsistencies between the results of our investigations and those of Franasiak et al. can be explained by the use of incorrect units in the authors’ publication and conference abstract.

There are also physiological arguments against the very high DHEA-S concentrations referenced by Franasiak et al. Our harmonized reference interval for DHEA-S in Northern Alberta, Canada, is $<405 \mu\text{g/dL}$ ($<4.1 \mu\text{g/mL}$) for females aged 11–50 years. Serum DHEA-S concentration in females without oral DHEA supplementation were reported in the range of $13,100\text{--}14,200 \mu\text{g/dL}$ ($131\text{--}142 \mu\text{g/mL}$), which is $33 \times$ higher than our reference interval. They further reported that patients with oral DHEA-S supplementation showed a doubling of serum DHEA-S concentration in the range of $28,400\text{--}29,300 \mu\text{g/dL}$ ($284\text{--}293 \mu\text{g/mL}$). This supraphysiological DHEA-S concentration is difficult to achieve unless mega-doses of DHEA oral supplements are consumed in concert with impaired metabolism and excretion.

In conclusion, we believe that the DHEA-S concentrations reported by Franasiak et al. [1] should be in $\mu\text{g/dL}$ instead of $\mu\text{g/mL}$. When the corrected units are used, serum DHEA-S concentrations in IVF patients not on DHEA supplements will be $131\text{--}142 \mu\text{g/dL}$ ($1.3\text{--}1.4 \mu\text{g/mL}$), while those receiving DHEA will be $284\text{--}392 \mu\text{g/dL}$ ($2.8\text{--}3.9 \mu\text{g/mL}$). These results are consistent with our current reference intervals as well as the physiological circulating DHEAS concentrations reported in the literature [4–6]. Fortunately, many manufacturers have verified that their progesterone assays are not significantly affected by DHEA-S at these physiological concentrations, with the exception that Siemens assays reported up to a 370% increase in progesterone when DHEA-S was $500 \mu\text{g/dL}$ ($5.0 \mu\text{g/mL}$). Nevertheless, Franasiak et al. should be

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Table 1 Summary of DHEA-S reportable ranges from the package inserts of five different assay manufacturers

Instrument	Reportable range for DHEA-S (µg/dL)
Abbott ARCHITECT	0–1500
Beckman Coulter	0–1000
Roche Cobas	0.1–1000
Siemens ADVIA Centaur	3–1500
Siemens Immulite	15–1000

commended for their idea of studying the effects of DHEA supplementation on progesterone concentrations in patients undergoing IVF. Although DHEA-S remains within the reference interval for patients treated with DHEA and the interference on progesterone assays occur at a much lower concentration than initially reported [7], this interference is particularly relevant at the progesterone concentration where the transplant of the embryo is decided.

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