this study micronized DHEA is administered orally 2 months prior to ovarian stimulation in patients with unexplained infertility and with a previous poor response to ovarian stimulation. The authors make the assumption that DHEA administration raises follicular insulin-like growth factor-1 (IGF-1) concentrations, which by a paracrine effect could enhance the gonadotrophin effect. IGF-1 may modulate ovarian follicular development but it is not mandatory. Women with Laron-type dwarfism lacking IGF factors are capable of conceiving spontaneously (Menashe et al., 1991). However, their second assumption, namely that exogenous administered DHEA will affect ovarian response in its role as a steroid prohormone, is very unlikely because the endogenous androgen precursors are already present in surplus amounts compared to oestradiol. The rate-limiting step in steroid hormone synthesis thus appears to be the conversion of cholesterol into pregnenolone and not precursor availability (Strauss and Penning, 1999).

Another point of criticism is that the study is based on several methodological misconceptions. First, the control cycle consists of a vigorous gonadotrophin stimulation, while the study stimulation cycle consisted of two ampoules rFSH 75 IU twice a day. It is not explained in detail what a ‘vigorous’ stimulation is. The dosage in the control cycle and the study cycle should have been identical. Secondly, for statistical purposes, a major confounder is introduced by using two different FSH preparations: urinary FSH in the control cycles and recombinant FSH in the experimental cycles. There may be a different ovarian response to stimulation with rFSH, as is the case in normal responders (Schats et al., 2000). Taken together, the authors cannot conclude that DHEA administration is responsible for the observed augmentation of ovarian response because it is just as likely to be the result of using a different FSH preparation and dosage in the experimental cycles.

Thirdly, the statistical analysis is confounded by the fact that one out of five patients is enrolled twice in this study. This particular patient accounts for the two extreme peak oestradiol values and therefore contributes unproportionally to the data presented.

Finally the reason why the authors measure and report the subjects’ baseline serum dehydroepiandrosterone-sulphate (DHEA-S) and testosterone concentrations before and after treatment with DHEA is not given. Baseline serum oestradiol and serum IGF-1 concentrations would have been more logical.

In conclusion, an interesting theory is not tested in a proper methodological way and the results therefore have little scientific value.

References


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Dear Sir,

We appreciate the comments made by van Weering et al. (2001) regarding our manuscript (Casson et al., 2000). We agree that our case series represents very preliminary data, which certainly requires more formal confirmation prior to dissemination into clinical practice. However, several of the points made in their Letter to the Editor deserve some clarification.

While it is true that the paracrine ovarian IGF-1 axis is not necessary for successful folliculogenesis and conception, there is much data demonstrating the gonadotrophin-augmenting relevance of this effect (Yeh and Adashi, 1999). The correspondents’ contention that the IGF-1 effect is not necessary does not negate the possibility that DHEA augmentation may improve ovarian response in certain patients.

They also felt that speculation regarding the role of DHEA as a prohormone for follicular steroid production was not correct, despite Hanings’ data to the contrary (Hanings et al., 1993). It is also true, as van Weering and co-workers state, that follicles destined for atresia are androgenic, however mature or dominant follicles are oestrogen dominant. Finally, if as van Weering and co-workers state, the rate limiting step in ovarian steroidogenesis is side chain cleavage, what better way to circumvent this effect than administer DHEA, a 19-carbon steroid?

We fully appreciate the shortcomings of this study, particularly the use of rFSH in the study cycles. We have read with interest the study by Schats et al. (Schats et al., 2000) showing improved response with rFSH over highly purified urinary FSH in normal responders undergoing IVF with ovarian down regulation. Of course the very modest improvement they saw may not hold in our poor responder population, who were not down-regulated. Additionally, the one patient in our series with the most vigorous response to DHEA used highly purified urinary FSH in both the control and DHEA-augmented cycles.

Van Weering et al. made two other comments about our case series. They noted quite correctly that the patient with the most vigorous response to adjunctive DHEA administration had two cycles in the series. That this may skew the results is uncontested. However, assessment of the data using only her first cycle, or with her cycle averages, yielded the same pattern of statistical significance as our reported data. They also noted that baseline oestradiol concentrations were not
reported. They were however, measured and did not differ between the groups. We did not measure concentrations and agree the results might have been interesting.

We understand fully the limitations of our case series, and the very preliminary nature of our conclusions. However, on the basis of our observations, we believe the possible beneficial effect of DHEA on ovarian stimulation in poor responder populations is certainly worthy of further investigation.

References

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