DHEA as a miracle drug in the treatment of poor responders; hype or hope?

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**ABSTRACT:** Dehydroepiandrosterone (DHEA) is being presented as a miracle-drug for the treatment of women responding poorly to gonadotrophin stimulation, while the debate on its actual effectiveness is still ongoing. We would like to present how insufficient the current evidence is to warrant a conclusion that DHEA supplementation is an effective treatment for women with diminished ovarian reserve. We believe that large-scale, well-designed confirmatory studies are necessary to prove the efficacy of DHEA before it can be recommended for routine use.

**Key words:** ovarian reserve / counselling / assisted reproduction / dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) supplementation has been hailed in the IVF world as a potential breakthrough for improving ovarian reserve in women responding poorly to gonadotrophin stimulation and in women of advanced age. DHEA supplementation for at least 3 months has been shown to be associated with spontaneous and treatment-induced pregnancies in women with very high FSH or very low anti-mullerian hormone (AMH) levels (Mamas and Mamas, 2009a; Gleicher and Barad, 2010). Benefits of DHEA supplementation have been reported since the beginning of this decade (Casson et al., 2000; Barad and Gleicher, 2005, 2006; Barad et al., 2007; Gleicher et al., 2009, 2010a,b; Sonmezer et al., 2009; Mamas and Mamas, 2009a,b, Wiser et al., 2010). However, the studies cited earlier have been criticized by the scientific community for their improper study design and low quality of evidence. It is time to reconsider whether clinicians should be offering DHEA to their patients based on reliable scientific evidence or whether to regard it as an empirical drug with possible but no proved benefit. We would like to present why the current evidence is insufficient to warrant widespread use of DHEA as an effective treatment for women with diminished ovarian reserve (DOR).

DHEA is an endogenous adrenal steroid that has been promoted to reverse the effects of aging and is used also by athletes as a performance booster substitute for anabolic steroids (Arlt, 2004). It is considered as a food supplement in many countries and sold over the counter without prescription. However, in some European countries, it is only available as a prescription drug. Even in these countries, it is commonly used ‘off label’, which means outside the scope of its approved indications. As with other dietary supplements, the purity and potency of commercially available formulations of DHEA are not known. Analysis of commercially available DHEA products found that DHEA content ranged from 0 to 150% of the labelled amount (Parasrampuria et al., 1998; Thompson et al., 2000). The commercial products are not derived from human sources, but they are manufactured from yams. Various side effects, including acne, hair loss, hirsutism and deepening of voice, have been reported with the use of physiological doses of DHEA in women. Facial hair growth and voice changes may be irreversible (Sadock and Sadock, 2008). Beyond its virilizing effects, short-term use of DHEA may result in reduced high-density lipoprotein cholesterol as well as impaired insulin sensitivity and glucose tolerance (Morales et al., 1998). Other side effects such as hepatic dysfunction, hypertension, acute manic symptoms, seizures in women prone to convulsions and palpitations have also been reported (Sahelian and Borken, 1998; Kline and Jaggers, 1999; Markowitz et al., 1999; Karp et al., 2009). DHEA inhibits cytochrome p450 3A4 in vitro, and could increase serum concentrations of many drugs metabolized by this isozyme (Nakamura et al., 2002).

The evidence on DHEA use in women to enhance the ovarian reserve is based on retrospective analyses (Gleicher et al., 2010b), prospective self-controlled studies (Casson et al., 2000; Barad and Gleicher, 2006; Sonmezer et al., 2009, Gleicher et al., 2010a), case reports/series (Barad and Gleicher, 2005; Mamas and Mamas, 2009b), case–control studies (Barad et al., 2007; Gleicher et al., 2009) and a single randomized controlled trial (Wiser et al., 2010). Casson et al. was the first to suggest a beneficial effect of DHEA supplementation in patients with DOR. In a self-controlled trial, they...
reported five women with a history of poor response, defined as less than two mature follicles or a peak estradiol (E_2) level of 500 pg/ml despite high levels of stimulation. These patients showed increased peak E_2 levels (939.8 ± 418.9 versus 266.3 ± 69.4 pg/ml, P = 0.02) and yielded more oocytes (2.2 versus 1) following DHEA treatment (Casson et al., 2000). This report was criticized due to its methodological errors such as bias caused by the change in the stimulation protocol, as well as the type and dose of gonadotrophins administered (van Weering et al., 2001).

Subsequent to this report, Barad and Gleicher published a series of articles on this subject. In their first report, they presented an unusual case of a 42.7 years old woman who had started to take DHEA by herself and undergone nine IVF treatment cycles in 11 months to produce 66 embryos (Barad and Gleicher, 2005). Her peak E_2 level in the first trial was 1211 pmol/ml and it increased up to >18000 pmol/ml in her eighth trial. Subsequently, Barad and Gleicher published a self-controlled study on 25 patients with DOR that was defined as a history a prior IVF cycle with less than four oocytes and uniformly poor quality embryos (Barad and Gleicher, 2006). Following DHEA supplementation, an increased oocyte yield (4.4 ± 0.5 versus 3.4 ± 0.5, P < 0.05), a higher fertilization rate (67 versus 39%, P < 0.001) and a higher embryo grade (3.4 ± 0.09 versus 2.9 ± 0.1, P < 0.02) were achieved. This was followed by a case-control study comparing 89 patients with DOR who had used DHEA with 101 matched controls (Barad et al., 2007). The definition of DOR was different in this trial and it was defined as the presence of an elevated age-specific FSH concentration (>7 mIU/ml under the age 33, >7.9 mIU/ml for ages 33–37, >8.4 mIU/ml for ages 38–40 and >8.5 mIU/ml after the age 41). The treatment group showed an increased pregnancy rate (28.4 versus 11.9%, P < 0.05) following DHEA use for a mean duration of 73 days (Barad et al., 2007). The same authors also compared miscarriage rates in patients who had used DHEA with those rates reported in the National US IVF database and suggested that the DHEA-supplemented group had significantly lower miscarriage rates (Gleicher et al., 2009).

More recently Gleicher et al. in a prospective self-controlled study, showed that DHEA supplementation increased AMH levels in patients with DOR in parallel with the duration of use, and the increase was more prominent in younger women (Gleicher et al., 2010a). Furthermore, women who had an increase in AMH levels following DHEA supplementation were more likely to become pregnant.

Gleicher’s group published another retrospective case-control study comparing 22 women who had been using DHEA with 44 age-matched women serving as controls and showed a lower rate of embryonic aneuploidy in the DHEA group (38.2 versus 61%) as detected by preimplantation genetic screening (Gleicher et al., 2010b). It was interesting though, patients who had been diagnosed as DOR and started DHEA according to their age-specific baseline FSH or abnormally low age-specific AMH levels produced a mean number of 9.6 oocytes and their age-matched control group produced a mean number of 11.7 oocytes. The authors did not provide any information about aneuploidy rates, rates of undiagnosed embryos and FISH error, number of blastomeres biopsied, and whether abnormal FISH results were confirmed by further whole-embryo analysis. Although authors suggested that the second or third month of DHEA supplementation offers the best chance to lower aneuploidy, the short treatment group demonstrated the greatest reduction in aneuploidy.

Gleicher and Barad lead the research and publications on DHEA supplementation in DOR. In the defence of criticism regarding the lower level of evidence provided in their reports, they complained about the sole reliance on RCTs, while discarding the rest of the evidence that may provide a good source of information even though they do not belong to a certain format (Gleicher and Barad, 2010). The authors also report how difficult it is to conduct a randomized trial, when patients are resistant to randomization under the stress of the fast running ovarian clock and note that they already had to abandon two registered RCTs for that reason (Gleicher and Barad, 2010). They suggest that RCTs should not be over-valued and medical treatment strategies and decisions could be built on the best available evidence as well rather than on underpowered or poor quality RCTs. They have also declared their conflict of interest for the patents they claim for therapeutic benefits of DHEA in women with DOR (Gleicher and Barad, 2010).

There are two other groups that shared their experience with DHEA effects on DOR. A case series was reported from Greece presenting five patients with post-menopausal FSH levels who conceived following 45–189 days of DHEA supplementation (Mamas and Mamas, 2009a). Another self-controlled study from Turkey compared the IVF performance of 19 women with DOR before and after DHEA (Sonmez et al., 2009). The definition of DOR was also different than the other reports and defined as a history of cycle cancellation due to low E_2 levels (<130 pg/ml) on the sixth day of cycle or on the hCG day (<450 pg/ml) or less than four retrieved oocytes. Interestingly, the mean peak E_2 level before DHEA use was reported to be 875 pg/ml, which was higher than the levels accepted in the inclusion criteria. After 90–180 days of DHEA supplementation, these patients had an increased number of follicles (3 ± 0.7 versus 1.9 ± 1.3, P < 0.05) and metaphase II oocytes (4 ± 1.8 versus 2.1 ± 1.8, P < 0.05), an increased number of Day 3 high quality embryos: 1.9 ± 0.8 versus 0.7 ± 0.6, P < 0.05) as well as higher pregnancy rates (47.4 versus 10.5%, P < 0.01).

Abstracts that have not reached publication do not provide any better information or higher level of evidence on the subject. Gleicher’s group presented a historical case-control study that compared 88 women on DHEA supplementation with 1010 women as the control group and reported an increased pregnancy rate and decreased time to conception (Brill et al., 2006). Motta et al. in a prospective self-controlled pilot study of eight women failed to observe any difference in the number of oocytes and embryo quality following 3 months of DHEA supplementation (Motta et al., 2006). Borman et al. found no difference in the mean DHEA levels in poor and relatively good responder patients (Borman et al., 2010). Finally, Hyman et al. in a prospective self-controlled study reported an increase in the antral follicle count and number of oocytes as well as better embryo quality following 3 months of DHEA use (Hyman et al., 2010). These authors also reported that there was no change in AMH levels after DHEA supplementation, challenging the findings of Gleicher and Barad (2010a).

Unpublished studies registered in the Clinical Trials website are not very promising either. There are four studies that are currently recruiting participants and the estimated completion dates are announced as the first half of 2013 (NCT00948857, NCT00650754,
NCT01129947, NCT01129830). One study is not yet open for participant recruitment although it should have been completed by December 2008 (NCT00549081). These data show us that our expectations for a high level of scientific evidence will not be realized until late 2013.

It is interesting to see that no contradictory reports have been published so far. Three explanations can be proposed for the absence of contradictory reports. There may be no contradictory findings related to DHEA supplementation and all groups who have been using it have experienced similar results and preferred not to publish similar types of reports. Alternatively, there may be contradictory findings, but researchers may be waiting to have a sample size of sufficient power to report their findings. The other explanation could be the possibility of a publication bias. It is a well-known fact that caregivers who seek more therapeutic options that they can offer to patients have a greater interest in viewing positive results (Evers, 2000). A cohort study of trials supporting new drug applications showed that the likelihood of publication was correlated with statistically significant results (odds ratio 2.96, 95% confidence interval 1.24–7.06) (Lee et al., 2008).

Despite their limitations, well-designed, optimal quality RCTs are still considered to be the most reliable source of evidence. Wiser’s study showed us that it is hard but still possible to perform RCT on patients with a poor ovarian response (Wiser et al., 2010). A group of 33 women younger than 42 years of age who either yielded fewer than five oocytes, had poor quality embryos or had cycle cancellation due to poor ovarian response were randomized to receive 75 mg DHEA or nothing for an average duration of 13.5 weeks prior to undergoing repeat treatment using the same ovarian stimulation protocol (Wiser et al., 2010). There was no significant difference between the DHEA and control groups in terms of primary outcome measures (peak E2 levels, mean number of retrieved oocytes and embryo quality). Among 17 patients in the DHEA group, there were seven pregnancies (26.9%) and six live births (23.1%) following 26 treatment cycles. However, among 16 patients in the control group, there were only three pregnancies (12%) and a single live birth (4%). The difference between live birth rates was reported as statistically significant ($P = 0.05$).

As the only RCT published up to date, this study also has many limitations. The study lacks a priori sample size calculation and this was explained by the unreliability of power analysis in the absence of data regarding the potential effect of DHEA on live birth rates (Wiser et al., 2010). The authors sustained the study until the sample size reached a point where a statistically significant difference could be drawn between the study and control groups. They claimed that the sample size had enough power to compare live birth rates between the groups even though live birth rates were a secondary outcome measure. In exploratory analyses, particularly when conducted in search of favourable evidence, the effect sizes of outcomes having particularly favourable estimates are probably overestimated because of random high bias that can, in later experience with the treatment, lead to regression to the mean (Fleming, 2010). Furthermore, the study was neither blinded nor placebo-controlled. The patients and staff were aware that a potentially promising supplement was being tested. One cannot rule out the possibility that patients allocated to the control group may have used the medication that was available over the counter. Further concerns have been voiced regarding the analysis of data and the validity of the conclusion of Wiser’s study (Kolibianakis et al., 2011). In their very recently published letter to the Editor, Kolibianakis et al. suggested that a study design that allows the patients to perform more than a single IVF cycle necessitates the use of life table analysis or Kaplan–Meier survival analysis to assess the probability of pregnancy or live birth as opposed to the Fisher’s exact test used by the authors. Even when analysed using inappropriate statistical methods, the data provided in the RCT could not support the conclusion that DHEA supplementation was associated with an improvement in live birth rates (Kolibianakis et al., 2011).

The possible mechanism that has been suggested is a direct effect of DHEA on the aging ovary by increasing the pool of follicles up to the pre-antral stage or reducing apoptosis of the originally recruited follicles or affecting non-dysfunctional events happening during meiosis (Gleicher et al., 2010a,b). Gleicher presents DHEA as the first medication to improve the ovarian environment to obtain better oocyte and embryo quality as well as higher pregnancy and lower miscarriage rates (Gleicher et al., 2010a). At the moment, there is no evidence of this effect at the molecular, cellular or tissue level in animal or human tissue models.

Is DHEA the Holy Grail? We are hopeful but not convinced. Although findings reported in the literature merit further consideration, until well-designed large-scale studies prove beyond considerable doubt that DHEA improves ovarian reserve, its use should at best be regarded as experimental. The literature is overwhelmed with medications and therapies that have failed to fulfill their promise in scientifically rigorous studies of yielding evidence that they are indeed beneficial. Until then, clinicians should resist the temptation of offering remedies that have not proved to be effective. Lack of harm should not be considered an indication for suggesting the use of medications that are even available over the counter. The woman with DOR who suffered several unsuccessful attempts at ovarian stimulation is prone to exploitation from pharmaceutical companies and healthcare providers alike. We believe that large-scale, well-designed confirmatory studies are necessary to prove the efficacy of DHEA before it could be recommended for routine use. Indications, optimal dose and duration of treatment should also be determined. These concerns should be shared by physicians, the pharmaceutical industry and regulatory agencies.

Authors’ roles
K.Y. played a role in major contribution to conception and design, the acquisition, analysis and interpretation of data, drafting the article and final approval of the version to be published. B.U. made a substantial contribution to conception and design, drafting and revising the article critically, and final approval of the version to be published.

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