

# Should androgen supplementation be used for poor ovarian response in IVF?

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**ABSTRACT:** Poor ovarian response is reported in 9–24% of IVF cycles. Several interventions have been proposed to improve the outcome, although evidence to support these has been scant. There has been interest in the use of adjuvant androgens in this context and a recent worldwide survey showed that nearly a quarter of IVF clinicians used dehydroepiandrosterone (DHEA) in poor responders. We examine the rationale for the use of adjuvant androgens and suggest that the current clinical uncertainty should be addressed by a randomized controlled trial of DHEA in poor responders.

**Key words:** poor ovarian response / androgens / IVF treatment

## Introduction

Delayed childbearing in women has been a significant demographic trend in the western world (Te Velde, 1998; Botting and Dunnell, 2000). A consequence of this is the marked increase in the numbers of older women who seek fertility treatment but often fail to respond satisfactorily to ovarian stimulation. In the UK, IVF cycles involving women aged 40 years or over accounted for 9.2% of cycles in 1991, 10.7% in 2000 and 15.5% in 2006 (HFEA, 2011). The overall incidence of poor ovarian response has been reported to vary between 9 and 24% (Keay et al., 1997). A recent international survey involving 196 IVF centres in 45 countries reported an increase in the burden of poor ovarian response over the last decade (IVF Worldwide Survey, 2010). Although the focus should be on interventions to encourage women not to delay childbearing, a number of social and economic barriers need to be addressed before this can become a reality.

Several interventions to improve IVF outcomes for women with previous or anticipated poor ovarian response have been proposed. These include various regimens for pituitary suppression, ovarian stimulation and the use of adjuvant therapies (Pandian et al., 2010). However, there is insufficient evidence to support the use of specific interventions to improve IVF treatment outcomes in poor responders (Surrey and Schoolcraft, 2000; Tarlatzis et al., 2003; Sunkara et al., 2007; Loutradis et al., 2008; Kyrou et al., 2009; Pandian et al., 2010). The management of women who respond poorly to ovarian stimulation remains a challenge to clinicians and patients who often turn to new options in the absence of robust evidence.

In recent years, a number of studies have suggested that dehydroepiandrosterone (DHEA) may be effective in poor responders (Casson et al., 2000; Barad and Gleicher, 2006; Barad et al., 2007; Wisner et al., 2010). Over a quarter (25.8%) of IVF clinicians surveyed in 45 countries stated that they add DHEA as an adjuvant to IVF treatment protocols in women with poor ovarian response (IVF Worldwide Survey, 2010). DHEA is a crucial precursor steroid to human sex steroid synthesis and is converted to androgens or estrogens based on the expression of steroidogenic enzymes present in peripheral target tissues, including the ovarian follicle (Haning et al., 1993). DHEA, of predominantly adrenal but also ovarian origin, is the major source of androgen synthesis in women, following its conversion via androstenedione to testosterone (Arlt et al., 1998) and exogenous DHEA can serve as an androgen replacement tool in women (Arlt et al., 1999).

In this article, we explore the mechanism of action of androgens in folliculogenesis, examine the evidence supporting its use and consider its use in women with either proven or expected poor ovarian response.

## Mechanism of action: is there a biological plausibility for androgens in folliculogenesis?

In mice, estrogens promote ovarian follicular growth and granulosa cell proliferation (Payne and Runser, 1959; Smith and Bradbury, 1961), but in primates estrogens are either inactive or exert an inhibitory effect on ovarian folliculogenesis (Dierschke et al., 1994; Koering et al.,

1994; Zelinski-Wooten and Stouffer, 1996). According to the two cell/two gonadotrophin theory, androgens play an essential role in ensuring adequate follicular steroidogenesis in humans (Ryan et al., 1968). Produced primarily by the theca cells, they are believed to act as a substrate for the aromatase activity of the granulosa cells, which converts the androgens to estrogens. Androgens exert a direct autocrine and/or paracrine effect to regulate follicular function, and immunohistochemistry studies have identified androgen receptor expression in human follicles (Horie et al., 1992; Suzuki et al., 1994).

Androgen receptors are abundant in the granulosa cells of healthy pre-antral and antral follicles of rhesus monkeys and their expression is up-regulated by androgen administration (Vendola et al., 1998; Weil et al., 1998). Androgens also augment FSH receptor expression in the granulosa cells and have been thought to promote follicular growth and estrogen biosynthesis by amplifying the effects of FSH in rhesus monkeys (Weil et al., 1999). In a study on murine models of conditional granulosa cell and oocyte-specific deletion of the androgen receptor, a positive correlation between androgen receptor and FSH receptor expression was found, supporting the notion that androgens may prevent pre-antral follicle growth and prevent atresia (Sen and Hammes, 2010). Similarly, it has recently been shown that, in human granulosa cells from small antral follicles, androgen receptor mRNA and androgen levels in follicular fluid correlate with FSH receptor mRNA expression (Nielsen et al., 2011).

Taken together, there thus appears to be a growing body of evidence which suggests that androgens may have a specific action in pre-antral and small antral follicles, prior to serving as a substrate for estradiol ( $E_2$ ) synthesis in larger follicles. Given this evidence and along with data from initial studies on exogenous DHEA replacement in women (Morales et al., 1994; Diamond et al., 1996; Casson et al., 1998), Casson et al. first postulated the hypothesis that oral administration of DHEA before gonadotrophin stimulation would enhance the response in women with poor ovarian response.

## Adjuvant androgens in ovarian stimulation protocols for poor responders: outcome data

Casson et al. (2000) were the first to report an improved ovarian response to gonadotrophin stimulation following oral administration of DHEA in a case series involving five women with previous poor ovarian response. A few years later, Barad and Gleicher (2005) described a case of a 43-year-old woman in whom gonadotrophin stimulation following DHEA supplementation resulted in higher peak  $E_2$  concentrations, and higher numbers of oocytes and embryos. Soon after this case report, the same group conducted an observational study on 25 women (Barad and Gleicher, 2006) and reported a significant increase in the numbers of oocytes retrieved and embryos transferred following DHEA treatment. The average duration of administration of DHEA was 17.6 weeks at a daily dose of 75 mg orally. In 2007, Barad et al. (2007) published the results of another observational study of DHEA involving 190 women with diminished ovarian reserve; 89 women in the study group had 75 mg daily of oral micronized DHEA for up to 4 months before the IVF treatment,

whereas 101 women in the control group had IVF treatment without DHEA. The clinical pregnancy rate in the DHEA group was significantly higher compared with the control group (28.1 versus 10.9%;  $P < 0.01$ ).

Recently, the first randomized controlled trial (RCT) of oral DHEA supplementation in poor responders showed a significantly improved cumulative live birth rate in the DHEA group compared with the control group (23.1 versus 4%;  $P = 0.05$ ) (Viser et al., 2010). However, this study was small with only 33 women enrolled. The 33 women underwent 51 IVF cycles and the cumulative live birth rate was reported, raising questions regarding the study design. Other randomized trials comparing other forms of androgens (testosterone gel or patches) in poor responders undergoing controlled ovarian stimulation for IVF treatment have also been published (Massin et al., 2006; Fabregues et al., 2009; Kim et al., 2011). A recent meta-analysis of RCTs of adjuvant androgens (DHEA and testosterone) in women with poor ovarian response showed a significantly higher ongoing pregnancy/live birth rate in the androgen supplementation group compared with the control group following IVF treatment (relative risk = 2.08; 95% confidence interval 1.10, 3.93;  $P = 0.02$ ) (Sunkara and Coomarasamy, 2011). It was, however, acknowledged that the included studies were small and there was clinical and methodological heterogeneity across the four included RCTs. For example, the individual studies varied in their inclusion criteria, type of androgen and duration of supplementation and only one study (Massin et al., 2006) was blinded and used placebo in the control group.

## How should the data be interpreted?

Could we consider androgens to be promising for poor responders given the biological rationale and the evidence from observational studies and clinical trials? Should oral DHEA be the preferred androgen as it is more likely to result in more physiological serum concentrations compared with testosterone gel or patches? Is DHEA the new anti-ovarian ageing supplement? Available data suggest potential benefit but are not sufficiently conclusive to warrant an immediate change in practice. Moreover, there are no data on the potential side effects of DHEA which requires administration for at least 3–4 months prior to gonadotrophin stimulation. In women with already compromised ovarian reserve, could this delay be detrimental to their chances of success? The data on the use of adjuvant androgens in poor responders can be challenged on the basis of clinical heterogeneity and poor trial quality. As yet there are no RCTs, on the use of adjuvant androgens in poor responders, that have been adequately powered to detect clinically meaningful differences in robust outcomes such as live birth rate, nor are there any data on cost effectiveness, side effects and safety. There does not seem to be any agreement on either the dose or the duration of androgen pretreatment even with the more widely used DHEA. It is also worth noting that none of the studies that have employed DHEA administration for enhancement of ovarian reserve has characterized the androgen status of the participating women prior to treatment, precluding any attempts at identifying a subgroup of women who would benefit most from the intervention.

## Conclusion

Meanwhile, as women continue to delay childbearing, the problem of ovarian ageing among those seeking fertility will continue to grow. This in turn will lead to an increase in the incidence of poor ovarian response and the risk of suboptimal IVF outcomes. Clinicians have resorted to a plethora of interventions to address this and DHEA supplementation has been advocated in recent years. However, robust data from RCTs showing an improvement in live birth rate following DHEA supplementation in women with poor ovarian response are lacking. Nearly, a quarter of IVF clinicians appear to be using DHEA supplements despite the insufficient evidence to recommend this practice. Opinion is clearly divided on this issue, and the prevailing uncertainty perhaps suggests that it is time to evaluate the clinical and cost effectiveness of DHEA in the context of a large well-designed multicentre randomized controlled trial. Androgen excess is likely to result in follicular arrest at the antral stage, as regularly observed in the context of polycystic ovary syndrome. It is thus important, during androgen supplementation, to avoid grossly supraphysiological levels of androgens in the circulation and within the ovary. Current regimens vary between 12 and 16 weeks and the protocol of any proposed trial should take this into account when finalizing the dose and duration of androgen use. If there is sufficient uncertainty around this issue, there may even be some merit in evaluating the effect of alternative durations of androgen therapy compared with no treatment. The preference of using DHEA as the intervention over other androgen preparations could be justified because DHEA results in more physiological levels compared with testosterone supplementation which results in supraphysiological androgen levels (Shifren *et al.*, 2000).

## Authors' roles

S.K.S. wrote the manuscript. A.C. and W.A. appraised it critically for important intellectual content. S.B. conceived the idea and contributed to writing the manuscript.

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## Conflict of interest

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