Original Articles

Reproductive Biology Section

No evidence to support the concept that low serum dehydroepiandrosterone (DHEA) sulfate (s) levels are associated with less oocyte production or lower pregnancy rates

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Summary

Purpose: To determine if in a population of women with diminished oocyte reserve as evidenced by day 3 serum follicle stimulating hormone (FSH) levels > 12 mIU/ml women with lower dehydroepiandrosterone sulfate (DHEA-s) levels produce fewer oocytes or have lower pregnancy rates following in vitro fertilization-embryo transfer (IVF-ET) compared to women with higher levels. *Methods:* The women were divided into poor responders (producing ≤ 4 oocytes) following oocyte retrieval or good responders (≥ 5 oocytes). Mean DHEA-s levels were compared in poor vs good responders and in the subgroups of those who conceived vs those who did not conceive. *Results:* The data clearly showed no association with low DHEA-s levels and response to controlled ovarian hyperstimulation or pregnancy rates. *Conclusions:* In women with elevated serum FSH low DHEA levels do not suggest that supplementation with DHEA would improve response or pregnancy rate. These data do not preclude the possibility that there is a small subset of women with normal oocyte reserve who also fail to respond to controlled ovarian hyperstimulation for some unknown reason and the problem could be remediable by DHEA supplementation.

Key words: Dehydroepiandrosterone sulfate levels; Diminished oocyte reserve; In vitro fertilization-embryo transfer.

Introduction

There are studies that demonstrate marked augmentation of serum insulin-like growth factor I (IGF-I) with oral administration of physiological dehydroepiandrosterone (DHEA) [1-4]. In a small uncontrolled case series of five women Casson *et al.* claimed that the mean serum estradiol (E2) increased in poor responders to gonadotropins from 266 pg/ml to 939.8 pg/ml after two months of DHEA pretreatment [4]. Casson *et al.* suggested that improvement in response to gonadotropins by pre-treatment with DHEA is particularly suited for women with low DHEA sulfate levels [4]. It should be noted that the five poor responder cases reported by Casson *et al.* all had normal serum follicle stimulating hormone (FSH) levels [4].

Subsequently a case was reported by Barad and Gleicher which showed that a 43-year-old woman who had responded poorly with only two oocytes retrieved increased to 18 oocytes with nine months of DHEA supplementation [5]. This was followed by a larger case-controlled series (n = 25) by the same authors who claimed that 16 weeks of DHEA supplementation (25 mg 3 x daily) led to a significantly increased number of fertilized oocytes and an increase number of day 3 embryos [6]. In contrast to the cases reported by Casson *et al.* where the day 3 serum FSH was normal, the study by Barad and Gleicher only used women with elevated day 3 serum FSH [4-6].

A more recent study by Sonmezer *et al.* also suggested improved ovarian response and pregnancy rates and embryo quality in poor responders following DHEA supplementation [7].

A previous study by Haning *et al.* found that plasma DHEA-s serves as a prehormone for 48% of follicular fluid testosterone during treatment with menotropins [8]. Thus Casson *et al.* suggested that one possible explanation for their observation of improved responses to gonadotropins in poor responders by pretreatment with DHEA may be by increasing the follicular androgen pool and thus increasing advancement of pre-antral to antral follicles which could then respond to gonadotropins [4].

The present retrospective study aimed to further explore the impact of low serum DHEA-s levels in women with diminished oocyte reserve as evidenced by increased day 3 serum FSH by comparing DHEA levels in those with a lower yield of oocytes vs those with a better response. The study would also determine if lower levels of serum DHEA-s may be associated with lower pregnancy rates following embryo transfer.

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Materials and Methods

This was a retrospective study. This study used a population of women < 40 years old with diminished oocyte reserves undergoing in vitro fertilization-embryo transfer (IVF-ET). Diminished oocyte reserve was defined by a day 3 serum follicle stimulating hormone (FSH) level ≥ 12 mIU/ml. DHEA sulfate levels were drawn prior to initiation of follicle stimulating drugs.

Subjects were grouped according to whether the woman was a relatively poor responder (≤ 4 oocytes retrieved) or a relatively good responder (≥ 5 oocytes). Only the first IVF cycle was evaluated to determine oocyte response.

Subjects were also grouped according to those achieving a pregnancy vs those who did not, both in their first cycle and then within three cycles of embryo transfers. Mean DHEA-s levels were compared in each of these cohorts.

Analysis of variance (ANOVA) was used to compare the mean levels of DHEA. Pregnancy rates were compared using Fisher's exact test.

Results

Evaluating 39 first IVF-ET cycles, the mean serum DHEA-s (μg/dl) for poor responders who did not conceive was 148.0 ± 82.8 vs 143.9 ± 47.7 for those that did conceive (p = NS, ANOVA). The mean serum DHEA-s (μg/dl) for relatively good responders who did not conceive (14 cycles) was 138.5 ± 26.4 vs 103.5 ± 41.9 for those that did conceive (p = NS, ANOVA). In fact, opposite to what might have been expected the mean DHEA-s (μg/dl) level for poor responders (145.7 ± 83.3) was significantly higher than the mean level of good responders (122.3 ± 40.4) ($p < .05$, ANOVA).

Without controlling for ovarian response and given only one cycle to conceive, 24 IVF-ET cycles had positive pregnancy tests and 37 IVF-ET cycles had negative tests. The mean DHEA-s (μg/dl) levels were 119.1 ± 50.3 for those who conceived vs 151.8 ± 85.6 for those not conceiving ($p < .05$, ANOVA). Opposite to expectation the mean level of DHEA-s was significantly higher in those women failing to conceive.

Given three cycles to conceive, 52 had positive pregnancy tests and 86 had negative tests. The mean DHEA-s levels were 140.7 ± 57.3 for those who conceived vs 154.1 ± 91.4 for those not conceiving (p = NS, ANOVA).

Because the range of DHEA-s levels was so large we also looked at the difference in pregnancy rates for the ten lowest values and the ten highest values. The mean DHEA-s was 70.4 ± 23.2 for the 10 lowest values vs 243.2 ± 64.4 for the ten highest values ($p \leq 0.05$, ANOVA). The clinical (gestational sac at 8 weeks) and live delivered PRs for the low DHEA-s group were 40.0 and 30.0% vs 20 and 20% for the high DHEA-s group (p = NS, Fisher's exact test).

Discussion

In 1984 a concept was presented that women with apparent overt ovarian failure might still have oocytes remaining that could result in normal pregnancies. However, the antral follicles still present are resistant to endogenous and exogenous gonadotropins because the chronic elevation of serum FSH down-regulates the FSH receptors in the follicles [9]. This concept was supported by the demonstration that lowering the elevated serum FSH in women in apparent menopause by either estrogen (especially ethinyl estradiol) or leuprolide acetate induced a rate of ovulation in 100 women that was much higher than could be explained by chance alone [10]. A reasonable rate of live deliveries showed that these oocytes have good potential to achieve normal pregnancies in contrast to the belief of other authors [10-15].

Mamas and Mamas have also claimed to have "reversed menopause" using DHEA supplementation and reported pregnancies [16, 17]. Though we have also published reversal of menopause and pregnancy with lowering of FSH using GnRH agonist or antagonist, to date we have not had a successful reversal of menopause with DHEA supplementation [18, 19]. It is not that we do not believe the reports from Mamas and Mamas but it is that we suspect that the reason for its failure in our hands is that we only try it in desperation in women who have failed to ovulate by using most commonly ethinyl estradiol (the advantage of ethinyl estradiol over other estrogens is that it does not contribute to the serum estradiol measurement) or GnRH agonists or antagonists [18-20].

Thus based on not finding any difference in response when serum DHEA-s levels are low vs normal or with lower DHEA levels in poor responders who fail to achieve pregnancies vs succeed in achieving pregnancies we suspect that the mechanism of improvement in the studies using DHEA supplementation is related to the suppression of FSH and restoration of FSH receptors in the follicle both from conversion of DHEA to estradiol and also resting the ovaries from previous treatment with high levels of exogenous gonadotropins. It has been shown that in women in apparent menopause and in poor responders good follicular response can be achieved by merely stopping the follicle maturing drugs [21, 22].

Based on these other aforementioned studies using DHEA supplementation which showed a positive benefit in response and pregnancy rates, DHEA supplementation can be added to the pharmacologic options in resistant ovary syndrome and premature ovarian failure [23]. The recorded pregnancy rates for this present study support the concept that quality of oocytes from women with diminished oocyte reserve are much more comparable to their age peers with normal oocyte reserve than women of advanced reproductive age [24].

Though it appears that low DHEA-s levels are not etiologic in the low response and poor pregnancy rates seen following traditional higher dosage gonadotropin stimulation, it should be recalled that the original study by Cassen *et al.* evaluated poor responders with normal serum FSH-levels but low DHEA-s [4]. Perhaps this is a unique group where low DHEA levels may play an etiologic role in the poor oocyte response. If indeed the mechanism of improvement in ovarian response after pretreatment with DHEA is related to its conversion to estra-

diol with FSH suppression the use of ethinyl estradiol may be more reliable in FSH suppression and devoid of androgen side effects.

References

[1] Morales A.J., Nolan J.J., Nelson J.C., Yen S.S.: "Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age". *Clin. Endocrinol. Metab.*, 1994, *78*, 1360.

[2] Diamond P., Cusan L., Gomez J.L., Belanger A., Labrie F.: "Metabolic effects of 12-month percutaneous dehydroepiandrosterone replacement therapy in postmenopausal women". *J. Endocrinol.*, 1996, *150*, 543.

[3] Casson P.R., Carson S.A., Buster J.E., Lindsay M.S., Pisarska, M.D.: "Replacement dehydroepiandrosterone in elderly: rationale and prospects for the future". *Endocrinologist*, 1998, *8*, 187.

[4] Casson P.R., Santoro N., Elkind-Hirsch K., Carson S.A., Hornsby P.J., Abraham G. *et al.*: "Postmenopausal dehydroepiandrosterone administration increases free insulin-like growth factor-I and decreases high-density lipoprotein: a six month trial". *Fertil. Steril.*, 1998, *70*, 107.

[5] Barad D., Gleicher N.: "Increased oocyte production after treatment with dehydroepiandrosterone". *Fertil. Steril.*, 2005, *84*, 756.

[6] Barad D., Gleicher N.: "Effect of dehydroepiandrosterone on oocyte and embryo yeilds, embryo grade and cell number in IVF". *Hum. Reprod.*, 2006, *21*, 2845.

[7] Sonmezer M., Ozmen B., Cil A.P., Ozkavukcu S., Tasci T., Olmus H., Atabekoglu C.S.: "Dehydroepiandrosterone supplementation improves ovarian response and cycle outcome in poor responders". *Reprod. BioMed, Online.*,2009, *19*, 508.

[8] Haning R.V. Jr., Hackett R.J., Flood C.A., Loughlin J.S., Zhao Q.Y., Longcope C.: "Plasma dehydroepiandrosterone sulfate serves as a prehormone for 48% of follicular fluid testosterone during treatment with menotropins". *J. Clin. Endocrinol. Metab.*, 1993, *76*, 1301.

[9] Check J.H., Chase J.: "Ovulation induction in hypergonadotropic amenorrhea with estrogen and human menopausal gonadotropin therapy". *Fertil. Steril.*, 1984, *42*, 919.

[10] Check J.H., Nowroozi K., Chase J.S., Nazari A., Shapse D., Vaze M.: "Ovulation induction and pregnancies in 100 consecutive women with hypergonadotropic amenorrhea". *Fertil. Steril.*, 1990, *53*, 811.

[11] Nasseri A., Mukherjee T., Grifo J.A., Noyes N., Krey L., Copperman A.B.: "Elevated day 3 serum follicle stimulating hormone and/or estradiol may predict fetal aneuploidy". *Fertil. Steril.*, 1999, *71*, 715.

[12] Muasher S.J., Oehninger S., Simonetti S., Matta J., Ellis L.M., Liu H.-C. *et al.*: "The value of basal and/or stimulated serum gonadotropin levels in prediction of stimulation response and in vitro fertilization outcome". *Fertil. Steril.*, 1988, *50*, 298.

[13] Fenichel P., Grimaldi M., Olivero J.F., Donzeau M., Gillet J.Y., Harter M.: "Predictive value of hormonal profiles before stimulation for in vitro fertilization". *Fertil. Steril.*, 1989, *51*, 845.

[14] Kolibianakis E., Zikopoulos K., Camus M., Tounaye H., Van Steirteghem A., Devroey P.: "Modified natural cycle for IVF does not offer a realistic chance of parenthood in poor responders with high day 3 FSH levels as a last resort prior to oocyte donation". *Hum. Reprod.*, 2004, *19*, 2545.

[15] Roberts J.E., Spandorfer S., Fasoulitotis S.J., Kashyap S., Rosenwaks Z.: "Taking a basal follicle-stimulating hormone history is essential before initiating in vitro fertilization". *Fertil. Steril.*, 2005, *83*, 37.

[16] Mamas L., Mamas E.: "Premature ovarian failure and dehydroepiandrosterone". *Fertil. Steril.*, 2009, *91*, 644.

[17] Mamas L., Mamas E.: "Dehydroepiandrosterone supplementation in assisted reproduction: rationale and results". *Curr. Opin. Obstet. Gynecol.*, 2009, *21*, 306.

[18] Check JH, Wu CH, Check M: The effect of leuprolide acetate in aiding induction of ovulation in hypergonadotropic hypogonadism: A case report. Fertil Steril 1988;49:542-543.

[19] Check J.H., Katsoff B.: "Ovulation induction and pregnancy in a woman with premature menopause following gonadotropin suppression with the gonadotropin releasing hormone antagonist, cetrorelix - a case report". *Clin. Exp. Obstet. Gynecol.*, 2008, *35*, 10.

[20] Check J.H.: "Multiple uses of ethinyl estradiol for treating infertility". *Clin. Exp. Obstet. Gynecol.*, 2010, *37*, 249.

[21] Check J.H.: "The concept and treatment methodology for inducing ovulation in women in apparent premature menopause". *Clin. Exp. Obstet. Gynecol.*, 2009, *36*, 70.

[22] Check J.H.: "Multiple follicles in an unstimulated cycle despite elevated gonadotropins in a perimenopausal female". *Gynecol. Obstet. Invest.*, 1992, *33*, 190.

[23] Check J.H.: "Pharmacological options in resistant ovary syndrome and premature ovarian failure". *Clin. Exp. Obstet. Gynecol.*, 2006, *33*, 71.

[24] Check J.H., Cohen R.: "Evidence that oocyte quality in younger women with diminished oocyte reserve is superior to those of women of advanced reproductive age". *Med. Hypotheses*, 2010, *74*, 264.

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