Steroid hormone pretreatments in assisted reproductive technology

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Adequate availability and FSH sensitivity of ovarian antral follicles and coordination of their growth during controlled ovarian hyperstimulation (COH) rank among factors that may determine outcome, particularly in patients presenting ovarian function defects and so-called "poor responders." Growing evidence indicates that both factors are positively influenced by steroid hormone pretreatments. First, data from studies conducted in both animals and in women exposed to virilizing androgen doses indicate that androgen pretreatments may increase follicle responsiveness to FSH and/or the number of growing follicles in the ovary, thereby constituting an interesting perspective in the management of "poor responders." Second, overcoming pre-COH heterogeneities in antral follicle sizes, which are more pronounced in "poor responders," to achieve adequate coordination of multiple follicular growth during COH also is contributive. For this, suppression or attenuation of the premature FSH increase during the preceding late luteal phase using sex steroid pretreatments (oral contraceptives, synthetic progestogens, or estradiol), or additional strategies such as premenstrual GnRH antagonist administration has been shown to be effective. The present paper will critically review proposed mechanisms and clinical results of sex steroid hormone pretreatments in these two different indications as an effort to optimizing COH outcome. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)

Key Words: Follicular synchronization, androgens, oral contraceptives, estradiol, GnRH antagonist, small antral follicles, controlled ovarian hyperstimulation

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Controlled ovarian hyperstimulation (COH) is a critical process that may affect assisted reproductive technology outcomes. Paralleling the important developments made during the past years on the prediction of ovarian follicle status, particularly with the widespread use of ovarian function biomarkers, and on new biopotent and safe drugs that are able to adequately drive follicle growth and differentiation, clinical strategies for the adequate preparation of ovarian follicles to COH have also been proposed. Often based on different properties of sex steroids, these pretreatments essentially target the improvement of availability and FSH sensitivity of antral follicles as well as the coordination of their growth during COH and may be decisive, particularly in patients presenting ovarian function defects and in so-called "poor responders." Unfortunately, because a clear and logical definition of this latter category of patients is still lacking, despite some frustrating and ambiguous efforts that have been made during the past years (European Society for Human Reproduction and Embryology consensus on the definition of "poor response" to ovarian stimulation for in vitro fertilization: the Bologna criteria), we had to take into consideration each author's criteria. The present paper will address this issue by critically analyzing the proposed mechanisms and clinical results of some pretreatments such as androgens, oral contraceptives (OCs) and estradiol, with a special look at difficult cases.

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ANDROGEN PRETREATMENTS

Rationale of Androgen Pretreatments

Androgen receptors (ARs) are present in ovarian follicles, particularly during the basal growth phase (1). Although their specific role remains to be clarified, work conducted in rhesus monkeys has shown that strong testosterone doses stimulate basal follicle growth regardless of the menstrual cycle phase or gonadotropin effect, with a remarkable increase in the number of growing follicles and granulosa and thecal cell proliferation, as well as a reduction in granulosa cell apoptosis (2, 3). In addition, mRNA of FSH receptors and ARs are colocalized in growing follicles, and a correlation exists between the expression levels of both of these genes in monkeys receiving androgen treatment (3). These data, which have been later corroborated in women (4), suggest that androgens exert a facilitating role on follicle responsiveness to FSH.

They also offer a plausible explanation to the characteristic FSH hypersensitivity (4), antral follicle excess (5, 6), and exacerbated granulosa cell proliferation and steroidogenesis (7) in patients with polycystic ovary syndrome (PCOS). Furthermore, a PCOS-like phenotype could have been reproduced in normal women who were chronically exposed to considerable amounts of androgens due to other pathologies, such as congenital adrenal hyperplasia or some virilizing tumors (8–10).

Clinical Results of Androgen Pretreatments

Based on these basic science and clinical observations, some authors have been encouraged to study the potential effects of androgen pretreatments in women having previously responded poorly to COH. Yet the most challenging aspect in this field remains to identify the right way of pharmacologically increasing androgen concentration at the follicular level to reproduce the dramatic stimulation in folliculogenesis without unacceptable side effects. Therefore, some clinical approaches have been proposed. The most straightforward of them is the systemic administration of androgens by either a prohormone, DHEA (11–13), or testosterone (14–17). Whereas other approaches also can be used to increase intraovarian availability of androgens, such as stimulation of thecal production by administering LH activity (LH or hCG) (18–20) or aromatase inhibition (21–24), they are beyond the scope of this paper which is focused on steroid pretreatments.

The first clinical strategy for increasing intraovarian androgen concentration in women with ovarian defects was based on the daily administration of DHEA (11). Those authors elected to use 80 mg/d DHEA starting 2 months before COH in five intrauterine insemination candidates, who were <41 years of age and had previously responded poorly to COH (11). In that uncontrolled study including a limited number of subjects, the authors observed a significant improvement of the output of COH. It is noteworthy, however, that they failed to explain the reasons for having chosen the 80 mg/d dose. Following that paper, additional authors have become interested in evaluating the DHEA pretreatment effect on ovarian response markers as well as on the COH outcome (11–13, 25–40). All of them elected to use DHEA doses and treatment duration that were roughly inspired by those initially adopted by Casson et al. (11). Therefore, expanding the initial results, some investigators observed an increase in serum antimüllerian hormone (AMH) levels, a reliable biomarker of antral follicle quantity (27, 37, 39) and/or antral follicle count (28, 29, 37, 39) after 12–16 weeks of 75 mg/d DHEA oral administration. If such an increase in AMH levels (27, 37, 39) is related to a direct stimulatory effect of androgen treatment or is rather a mere result of the resulting increase in follicle number remains to be elucidated (13, 25, 26, 29, 30, 32). Yet the DHEA-driven changes in serum AMH levels and antral follicle count could not be corroborated in other publications (34). Similarly, for some investigators (12, 28, 29, 35, 37, 39, 40) but not all (36, 38), similar DHEA regimens were associated with an increase in oocyte yield, fertilized oocytes, and transferred embryos in COH cycles, which may also suggest an improvement in oocyte quality (13, 31–33).

Together, these conflicting views regarding DHEA pretreatments in "poor responders," which were all derived, regarding doses and duration of administration, from the original regimen proposed by Casson et al. (11), should prompt larger randomized controlled trials to clarify the role, if any, of DHEA pretreatment in COH outcome. Moreover, if administration schemes different from that described by Casson et al. (11) regarding doses and duration of administration could produce more striking results than those published hitherto also needs to be clarified.

Another possible approach to increase follicular androgen concentrations and possibly boost folliculogenesis and follicle sensitivity to FSH is transdermal testosterone administration. Balasch et al. (14) analyzed the ovarian response to COH in 25 "poor responders" receiving a 5-day testosterone pretreatment, in a nonrandomized trial. They observed a marked improvement in the ovarian response to COH (fivefold increase in the number of oocytes) in ~80% of cases, together with a pregnancy rate of 30%. Incidentally, antral follicle count before FSH administration was increased after androgen treatment compared with the two preceding COH cycles (14). To further test their pilot results, the same group conducted a randomized controlled trial involving 31 testosterone-pretreated women and 31 control women (16). It showed that "poor responders" receiving testosterone as previously reported (14) had reduced COH cancellation rates compared with control subjects (32% vs. 71%, respectively) (16). In support of these observations, later trials from another group (41, 42) using slightly different testosterone regimens (12.5 mg/d for 2–4 weeks before COH or 12.5 mg/d for 3 weeks, respectively) also observed an improvement in COH outcome. Finally, a meta-analysis published in 2014, in which "poor responder" patients received transdermal testosterone gel 12.5 mg/d for 21 days, confirmed earlier findings (43). Unfortunately, other investigators could not corroborate these encouraging results. Massin et al. (15), in a placebo-controlled study, failed to show any improvement of ovarian response to COH in 24 "poor responders" who received testosterone gel (15 mg/d) for 15 days before FSH treatment. The lack of effectiveness of transdermal testosterone pretreatment observed by Massin et al. (15) was later confirmed by two other studies, one using testosterone patches (2.5 mg/d) for 12 days (17) and the other using a daily dose of 10 mg testosterone gel applied for 21 days (44) before COH. As with the use of DHEA, the conflicting results on the effectiveness of transdermal testosterone pretreatment in improving ovarian response to COH may be, at least in part, attributed to intraovarian bioavailability issues, because these steroids could not be, by design, administered at virilizing doses.

ORAL CONTRACEPTIVE AND ESTRADIOL PRETREATMENTS

Rationale of Oral Contraceptive and Estradiol Pretreatments

During the early 1990s, short GnRH agonist (45, 46) and GnRH antagonist (47, 48) regimens were both associated with reduced treatment duration, gonadotropin