

## **Androgen supplementation, a model for therapeutic interventions into early stages of follicle maturation in humans**

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A woman's ovarian reserve (OR) is made up of resting follicles (primordial follicles) and growing follicles (the so-called growing follicle pool). Once a follicle is recruited out of the resting pool into the growing follicle pool, a journey of maturation takes place over approximately 2-4 months. As follicles advance through progressive maturation stages from primary over secondary to small pre-antral follicles, etc, some follicles arrest, undergo apoptosis and are absorbed. Only a small fraction of originally recruited follicles, therefore, reaches the last 2 weeks of follicle maturation, - the so-called gonadotropin-sensitive stage of folliculogenesis.

Since modern fertility care was initiated with the original gonadotropin experiments by Gemzel and Lunenfeld in the late 50s, the field has practically exclusively concentrated on the gonadotropin-dependent stage of follicle maturation. When the ovaries of infertility patients are stimulated, follicles already in the last 2 weeks of follicle maturation are stimulated. This means that these follicles have already undergone weeks to months of maturation and, with them the oocytes they contain. It also means that the quality of the follicle and its oocyte by that stage has, likely, already to a great degree been determined by ovarian environmental events. In other words, the follicle's/oocyte's fate is already predetermined. As oocyte quality also almost completely determines embryo quality, the latter is also largely determined by that point.

The last 60 years of modern infertility care, thus, practically exclusively attempted to improve an already largely predetermined end product. Not surprisingly, ovarian stimulation, therefore, has made little progress.

We here argue that attempts to improve ovarian stimulation beyond currently existing boundaries, have to acknowledge interventions into earlier stages of follicle maturation, especially small growing follicle stages. Androgen supplementation in women with low OR offers a good example: Convincing experimental small and large animal models demonstrated the importance of adequate androgen (i.e. testosterone) levels during small growing follicle stages. At those stages, androgens, synergistically with FSH, promote follicular growth by enhancing granulosa cell sensitivity to FSH. Though prospectively randomized studies are lacking, lower level evidence strongly supports androgen supplementation in relatively hypoandrogenic women with low OR.

Similarly, it is reasonable to assume that human growth hormone (HGH) supplementation might benefit follicle maturation at early growing follicle stages since IGF1 has been demonstrated to benefit follicle growth especially at these early stages. Interventions at early follicle growing stages, however, have to consider that affected small growing follicles require another 6-8 weeks to reach gonadotropin-dependency, meaning that neither androgen nor HGH supplementation makes sense unless started at least 6-8 weeks before IVF cycle start.

**Translational relevance:** This presentation offers the paradigm chance of expanding current infertility treatments from only the last 2 weeks into earlier stages of follicle maturation. Androgen and HGH supplementation of small growing follicles in women with low OR represent only 2 potential examples. As we learn how the ovarian environment changes with advancing female age, additional potential supplementations at such early growing follicle stages will become obvious.