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**Title: BASELINE HYPERANDROGENEMIA AND OOCYTE MATURATION IN WOMEN UNDERGOING IN VITRO FERTILIZATION**

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**Study Question (25):** Do women with baseline hyperandrogenemia have differential ovarian response, oocyte maturation, and/or embryo quality as compared to normoandrogenemic women?

**Summary Answer (25):** Despite greater ovarian responsiveness, hyperandrogenemic patients had similar oocyte yield, blastulation, and aneuploidy compared to normoandrogenemic women. Hyperandrogenemia was associated with reduced oocyte maturity.

**What is Known Already (100):** While serum androgen levels have been proposed to have an important impact on early follicular development and granulosa cell proliferation, the relationship with ovarian stimulation outcome and oocyte/embryo maturation and quality remains unclear. In women with diminished ovarian reserve, treatment with exogenous androgens has been used in efforts to increase oocyte quantity and quality. Conversely, hyperandrogenemia has been proposed as a cause for reduced oocyte maturity and quality in patients with polycystic ovarian syndrome (PCOS). To clarify the relationship between endogenous androgens and oocyte/embryo maturity and quality, we examined the relationship between baseline hyperandrogenemia and the outcome of ovarian stimulation for IVF.

**Study design, size, duration (75):** This is a retrospective cohort study, including 97 hyperandrogenemic patients (69.4% PCOS; 4.7% congenital adrenal hyperplasia (CAH)) and 635 normoandrogenemic patients (72.9% PCOS; 5.0% CAH) who underwent 162 and 996 IVF cycles, respectively. Patients underwent testing of serum androgen levels as part of routine fertility work up prior to undergoing IVF. Approximately half of the cycles in both the subject and control group involved the utilization of preimplantation genetic screening (51.9% vs 51.4%, respectively).

**Participants/materials, settings, methods (75):** Patients presented to a private IVF clinic, from 2010 to 2017, and underwent serum free testosterone and DHEAS testing and were categorized as hyperandrogenemic or normoandrogenemic. PCOS was diagnosed according to Rotterdam criteria. Baseline demographics, ovarian reserve, response to stimulation, oocyte yield, IVF laboratory outcomes, and embryo quality were compared using student's t-test and chi-square test. Multivariate linear and

logistic regression analyses (controlling for age and ovarian reserve) assessed whether baseline hyperandrogenemia associated with ovarian response, embryo development, and embryo ploidy.

**Main results and the role of chance (200):** Hyperandrogenemic patients with elevated serum free testosterone ( $95.8 \pm 155.4$  vs.  $24.4 \pm 17.7$ ,  $p < 0.0001$ ) and DHEAS ( $523.4 \pm 1066.9$  vs.  $171.3 \pm 82.9$ ,  $p < 0.0001$ ) were similar in age ( $34.3 \pm 4.8$  vs.  $34.8 \pm 5.0$ ,  $p = 0.3$ ), compared with controls. Study patients had significantly greater anti-mullerian hormone (AMH) ( $8.5 \pm 13.1$  vs.  $5.0 \pm 5.7$ ,  $p = 0.008$ ) and basal antral follicle count (BAFC) ( $17.6 \pm 11.3$  vs.  $15.4 \pm 9.8$ ,  $p = 0.04$ ). Groups significantly differed by stimulation protocol, with a higher proportion of GnRH antagonist protocol use in hyperandrogenemic patients (75.3% vs. 67.1%,  $p = 0.04$ ) and GnRH agonist downregulation in controls (18.1% vs. 9.9%,  $p = 0.003$ ). The cumulative dose of gonadotropins used was similar ( $3249.3 \pm 1854.1$  vs.  $3057.9 \pm 1417.2$ ,  $p = 0.2$ ) among groups. Controlling for age and ovarian reserve, study patients received more days of ovarian stimulation as compared to controls ( $\beta = 0.5$ ,  $p = 0.0007$ ). Hyperandrogenemia was not associated with the odds of cycle cancellation due to lack of response (OR 1.35 (95% CI 0.68-2.69),  $p = 0.4$ ), the number of eggs retrieved ( $\beta = -0.8$ ,  $p = 0.3$ ), the degree of blastulation ( $\beta = 0.0004$ ,  $p = 0.9$ ), blastocysts amenable to trophectoderm biopsy ( $\beta = 0.03$ ,  $p = 0.4$ ), and the degree of embryonic aneuploidy ( $\beta = -0.009$ ,  $p = 0.8$ ). Patients with baseline hyperandrogenemia had reduced oocyte maturity ( $\beta = -0.04$ ,  $p = 0.04$ ).

**Limitations, reasons for caution (50):** This analysis is retrospective, and therefore vulnerable to confounding bias. While the multivariate model aimed to account for possible confounders, our findings should be supported by future studies that prospectively analyze the effect of hyperandrogenemia on ovarian stimulation in all patients, accounting for their ovulatory status and underlying diagnosis.

**Wider implications of the findings (50):** Baseline hyperandrogenemia was not correlated with egg/embryo yield or quality. However, there was an association with reduced oocyte maturity. Further studies should assess whether hyperandrogenemic patients with poor oocyte maturity in prior cycles could benefit from androgen suppression treatment prior to stimulation, and/or increased stimulation duration.

**Study funding/competing interests:** Not applicable

**Trial registration number:** This study was approved by the Western Institutional Review Board (Study Number: 1167398).