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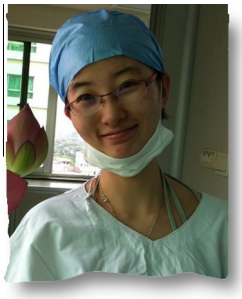
ARTICLE

Predictive value of androgens and multivariate model for poor ovarian response

Jing Guo, Qingxue Zhang, Yu Li, Jia Huang, Wenjun Wang, Lili Huang, Xiaomiao Zhao *,[1], Dongzi Yang *,[1]

Department of Obstetrics and Gynecology, Sun Yat—Sen Memorial Hospital of Sun Yat—Sen University, Guangzhou, Guangdong, China

* Corresponding authors. *E-mail addresses:* zhaoxmiao@163.com (X Zhao), yangdz@mail.sysu.edu.cn (D Yang). [1] Dongzi Yang and Xiaomiao Zhao contributed equally as the co-corresponding authors.



Dr Guo is a PhD student of reproductive endocrinology and infertility at the Memorial Hospital of Sun Yat-sen University of China, with a special focus on assisted reproduction technology. She is specialized in female reproductive endocrinology. Dr Guo's current research includes strategies for predicting poor ovarian response, investigating the basic mechanisms involved in the effects of vitamin D on oocyte development and maturation and describing the abnormal metabolism with polycystic ovarian syndrome.

Abstract No single or multivariate model is effective for predicting poor ovarian response (POR) with satisfactory sensitivity and specificity. This study investigated whether dehydroepiandrosterone sulphate (DHEAS) or basal testosterone concentrations could be effective predictors of POR defined by the Bologna criteria. This retrospective study included 79 poor responders and 128 normal responders. Serum FSH, LH, oestradiol, DHEAS and testosterone concentrations on day 3 of the menstrual cycle before the treatment cycle were measured. All patients received standard ovarian stimulation with FSH under pituitary suppression with gonadotrophin-releasing hormone agonist. DHEAS concentration was not significantly different between poor and normal responders or between pregnant and nonpregnant women. Basal testosterone, unlike DHEAS concentration, was predictive, but with limited ability as a single predictor, for POR. The multivariate model composed of age, AFC, FSH, FSH/LH and testosterone was reliably predictive for POR (ROC_{AUC} = 0.976, cut-off point >0.51, sensitivity 88.6%, specificity 98.3%) and clinical pregnancy (ROC_{AUC} = 0.716, cut-off point ≤−0.22, sensitivity 75%, specificity 62.5%) and was better than antral follicle count for predicting both POR and clinical pregnancy. This multivariate model might be useful for identifying patients at risk of poor response in order to optimize the stimulation regimens.

KEYWORDS: dehydroepiandrosterone sulphate, IVF, multivariate model, poor ovarian response, pregnancy outcome, testosterone

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Introduction

Delayed childbearing in women has been a significant demographic trend, with the consequence of a marked increase in the numbers of older women who often fail to respond satisfactorily to ovarian stimulation (Sunkara et al., 2012). A proportion of women (2–30%) undergoing ovarian stimulation experience poor response (Hendriks et al., 2005), which results in treatment cancellation and reduced live birth rate. A recent international survey involving 196 IVF centres in 45 countries reported an increase in the burden of poor ovarian response (POR) over the last decade (IVF Worldwide Survey, 2010). Identification of women at increased risk for POR prior to IVF could be useful, as this could either prevent unnecessary continuation of treatment (Klinkert et al., 2004) or help to make individual interventions in order to maximize ovarian response (Klinkert et al., 2005).

Several reviews have showed the predictive value of single and combined tests performed in basal conditions. Of all the tests, antral follicle count (AFC) and anti-Müllerian homone (AMH) has the best sensitivity and specificity for predicting POR (Broekmans et al., 2006; La Marca et al., 2010; Verhagen et al., 2008). However, even the best ovarian reserve marker at the best cut-off value is associated with a false positive rate of 10–20% (Broekmans et al., 2006; Ferraretti et al., 2011), which may have negative consequences on the couple's life since false positive results might incorrectly prohibit these women from undergoing IVF (La Marca et al., 2010). Besides, the accuracy of predicting the occurrence of pregnancy is very limited for all tests (Broekmans et al., 2006; Broer et al., 2009). In addition, more than 35–41 definitions for POR were used in these studies, implying a troublesome issue in clinical application. The Bologna criteria developed by European Society for Human Reproduction and Embryology consensus in 2011 for the first time reached an agreement on universal definition of POR (Ferraretti et al., 2011). A single and simple test demonstrating a better performance for predicting POR than the currently available tests would be preferable.

The potential stimulating role of androgens on folliculogenesis has been suggested by a number of basic research studies and illustrated by some pathophysiological conditions and clinical models (Fanchin et al., 2011). To assess the possible action of androgens on human ovary, some investigators focused on the potential effect of androgen pretreatment before ovarian stimulation. Whether androgen supplementation is an effective treatment for POR remains highly controversial (Urman and Yakin, 2012; Yakin and Urman, 2011); however, some studies have reported encouraging outcomes, including improved ovarian response and live birth rate, with systemic administration of either dehydroepiandrosterone (DHEA) or testosterone (Gleicher et al., 2010; Kim et al., 2011). However, it is worth noting that none of the studies has characterized the androgen status of the participating women prior to treatment (Sunkara et al., 2012).

According to the 'androgen hypothesis' for treating ovarian function defects (Fanchin et al., 2011), the current study investigated whether DHEAS or testosterone concentrations could be effective predictors for POR. As a second target, the accuracy of a multivariate model for predicting POR following the Bologna criteria was estimated.

Materials and methods

Study population

All patient information was obtained from the database of the Centre for Reproductive Medicine and fertility. Study patients were recruited consecutively in this retrospective study. Study patients fulfilling the inclusion criteria from March 2011 to March 2013 were defined as either poor or normal responders.

According to the Bologna criteria (Ferraretti et al., 2011), POR in this study was defined if one of the following four features was present: (i) AFC $\leq$5 follicles and age $\geq$40 years; (ii) age $\geq$40 years and a previous POR ($\leq$3 oocytes collected with a conventional stimulation protocol in which at least 150 IU FSH was consumed per day); (iii) AFC $\leq$5 follicles and a previous POR; and (iv) two episodes of POR after maximal stimulation (cycle was cancelled for following the development of less than three growing follicles).

Normal responders who were considered as the control population satisfied all the following conditions simultaneously: (i) their first IVF–embryo transfer (fresh) cycle; (ii) $\geq$5 oocytes with a conventional stimulation protocol; and (iii) age $\leq$35 years, AFC $\geq$7 follicles and basal FSH $<$13 IU/l.

Exclusion criteria were patients who received androgen supplementation at any time before enrolment. Patients with endocrine disorders or anatomical abnormalities were excluded, including polycystic ovarian syndrome (PCOS), abnormal thyroid function and hyperprolactinaemia, as well as uterine malformation, submucous myoma and multiple myomata. PCOS was diagnosed according to the Rotterdam criteria (Rotterdam ESHRE/ASRM–Sponsored PCOS Consensus Workshop Group, 2004). Hyperandrogenaemia was defined as serum DHEAS $>$4.92 μmol/l or testosterone $>$2.39 nmol/l (Zhao et al., 2011). Thyroid function was screened by serum thyroid-stimulating hormone (0.55–4.78 mU/l), triiodothyronine (0.92–2.79 nmol/l), thyroxine (58.1–140.6 nmol/l), free triiodothyronine (3.5–6.5 pmol/l) and free thyroxine (11.5–22.7 pmol/l) combined with the clinical symptoms and signs. Anatomical abnormalities were discovered by abdominal ultrasound scanning and transvaginal sonography scanning.

On day 3 of a spontaneous menstrual cycle within 3 months before fresh IVF cycle, a blood sample was taken in the morning to evaluate basal hormone (FSH, LH, oestradiol, testosterone, DHEAS) concentrations. On the same day, transvaginal sonography was performed to obtain AFC and ovarian volume. As recommended (Broekmans et al., 2010), the follicles visualized and counted were 2–10 mm in size, and the numbers of follicles in both ovaries were added to obtain the total AFC. The volume of each ovary was calculated by measuring the ovarian diameters in three perpendicular directions and the final result was calculated automatically. The volumes of both ovaries were added to obtain a mean value which was defined as mean ovarian volume.