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New PCOS-like phenotype in older infertile women of likely autoimmune adrenal etiology with high AMH but low androgens☆

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ABSTRACT

How anti-Müllerian hormone (AMH) and testosterone (T) interrelate in infertile women is currently largely unknown. We, therefore, in a retrospective cohort study investigated how infertile women with high-AMH (AMH ≥75th quantile; n = 144) and with normal-AMH (25th–75th quantile; n = 313), stratified for low-T (total testosterone ≤19.0 ng/dL), normal-T (19.0–29.0 ng/dL) and high-T (>29.0 ng/dL) phenotypically behaved. Patient age, follicle stimulating hormone (FSH), dehyroepiandrosterone (DHEA), DHEA sulphate (DHEAS), cortisol (C), adrenocorticotrophic hormone (ACTH), IVF outcomes, as well as inflammatory and immune panels were then compared between groups, with AMH and T as variables. We identified a previously unknown infertile PCOS-like phenotype, characterized by high-AMH but, atypically, low-T, with predisposition toward autoimmunity. It presents with incompatible high-AMH and low-T (<19.0 ng/dL), is restricted to lean PCOS-like patients, presenting delayed for tertiary fertility services. Since also characterized by low DHEAS, low-T is likely of adrenal origina, and consequence of autoimmune adrenal insufficiency since also accompanied by low-C and evidence of autoimmunity. DHEA supplementation in such patients equalizes low- to normal-T and normalizes IVF cycle outcomes. Once recognized, this high-AMH/low-T phenotype is surprisingly common in tertiary fertility centers but, currently, goes unrecognized. Its likely adrenal autoimmune etiology offers interesting new directions for investigations of adrenals control over ovarian function via adrenal androgen production.

1. Introduction

Produced by granulosa cells (GCs), anti-Müllerian hormone (AMH) represents functional ovarian reserve (FOR), also called the small growing follicle pool, which ultimately determines quantity and quality of oocytes/embryos obtained during in vitro fertilization (IVF) [1]. Follicle stimulating hormone (FSH) also describes aspects of FOR; AMH and FSH, however do not always (inversely) fully correlate because, to a degree, they describe different components of FOR [2]. In IVF above age 38, hormone ratios per retrieved oocytes with FSH were, for example, significantly associated with pregnancy chances but not ratios with AMH [3]. Also, among all possible FSH/AMH combinations, the seemingly contradictory combination of high-FSH/high-AMH, surprisingly,

Abbreviations: ACTH, adrenocorticotrophic hormone; AI, adrenal insufficiency; AMH, anti-Müllerian hormone; AR, androgen receptor; C, cortisol; CP, clinical pregnancies; CRP, C-reactive protein; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosteroen sulphate; FSH, follicle stimulating hormone; FOR, functional ovarian reserve; GCs, granulosa cells; hMG, human menopausal gonadotropin; Ig, immunoglobulin; IL-6, interleukin 6; IVF, in vitro fertilization; LB, live births; PCOS, polycystic ovary syndrome; SHBG, sex hormone binding globulin; T, testosterone; TPO, thyroid peroxidase.

☆ This study offers evidence for a new PCOS-like phenotype in infertile women, characterized by high-AMH but low-testosterone, likely due to autoimmune adrenal insufficiency. Fertility is restored by androgen supplementation.

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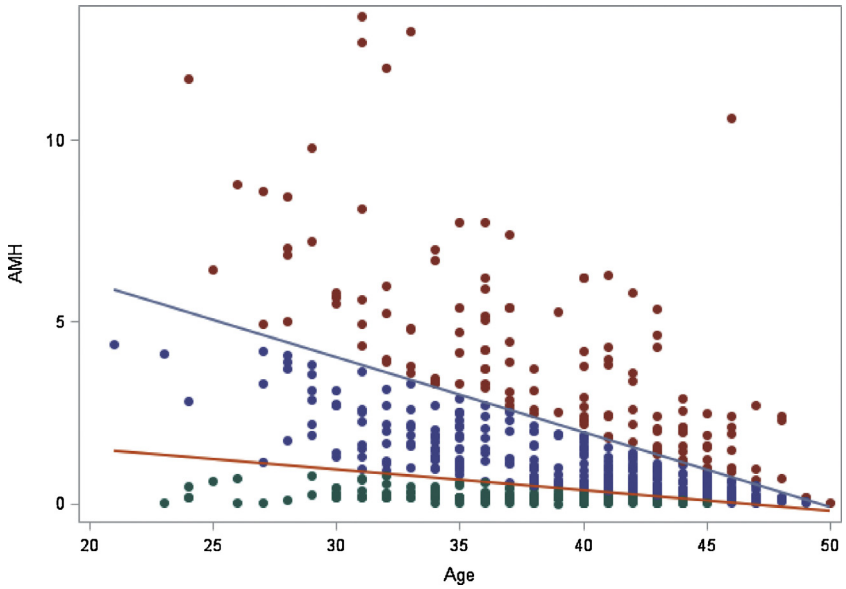

Fig. 1. Declining AMH levels with age for normal- and high-AMH patients. The figure demonstrates declining AMH levels for normal- (blue dots) and high-AMH patients (red dots), with red and blue lines defining 25th and 75th quantiles.

produced best IVF outcomes, including 4.34 times odds of high oocyte yield and 1.93 times odds of clinical pregnancy [4]. We, ever since, have searched for an explanation for these findings.

High AMH reflects good FOR and, therefore, usually large oocyte yields [1]. Good FOR and large oocyte yields are also fairly typical in the polycystic ovary syndrome (PCOS), often also characterized by high androgen levels [5]. How AMH and T in infertile women, however, relate has so far not been investigated.

The importance of intraovarian testosterone (T) concentrations for normal follicle development, has been properly appreciated only over the last decade [6]. For lack of prospectively randomized studies still controversial, androgen supplementation is, nevertheless, increasingly utilized to normalize low-T in infertile women with poor FOR [6].

We, consequently, hypothesized that intraovarian androgen-activity in ovaries may be a contributing factor to high-FSH/high-AMH patients being most successfully in IVF cycles [4], and initiated here reported investigation of infertile women with high- and normal-AMH levels, stratified for low-, normal- and high-T. Unexpectedly, the study revealed a previously unknown infertility phenotype, characterized by high age-specific AMH but, in contrast to classical PCOS phenotypes, with low-T.

This manuscript describes how this new phenotype is clinically diagnosed and confirmed. We also present evidence for adrenal origin of its hypoandrogenism and its likely autoimmune etiology, and demonstrate that androgen supplementation prior to IVF cycle start normalizes otherwise reduced pregnancy chances. Here described findings, finally, also explain why high-FSH/high-AMH patients produce best IVF outcomes [4], thereby opening interesting new research avenues for further exploration of androgen-driven functional interconnectivity between adrenals and ovaries.

2. Methods

2.1. Patients

This study involved 457 consecutive infertility patients, identified in our center's anonymized electronic research data bank as fulfilling the following selection criteria: Patients of all ages were eligible in first IVF cycles at our center if baseline AMH and T had been obtained at time of initial presentation, they demonstrated normal or high AMH, with normal AMH defined as age-specific 25th to 75th quantile (normal-AMH group; n = 313), and high AMH defined as age-specific AMH ≥75th quantile (high-AMH group; n = 144). Fig. 1 presents age-specific AMH values of here studied patients.

Tables 1 and 2 demonstrate the study groups' abnormal (high) FSH values and, therefore, that our center serves a highly adversely selected patient population of relatively advanced age. Because these patients are prognostically unfavourable, they undergo a more comprehensive medical evaluation than younger women before acceptance into fertility treatments. Patients with significant medical problems, including metabolic disease, are usually excluded from treatments, unless their medical condition has been normalized, and medical clearance has been obtained from the treating medical specialist for fertility treatments. Almost all patients in this study, therefore, represented high-FSH patients. Patients with high-AMH in Table 1, therefore, almost uniformly qualified as high-FSH/high-AMH phenotypes, as previously described [4].

In both study groups normal- and high-AMH patients were further stratified into patients with low-T (≤19.0 ng/dL), normal-T 19.0–29.0 ng/dL) and high-T (>29.0 ng/dL). T values represent total rather than free T since we previously reported that, after androgen supplementation, total T marginally better reflects improvements of FOR (as assessed by AMH) [7].

2.2. IVF cycles

Our center follows a strict cycle stimulation protocol in older women and women with abnormal FSH and/or AMH levels. Prior to IVF cycle start, all such patients are pre-supplemented with micronized dehydroepiandrosterone (DHEA, Fertinatal®, 25 mg TID, Fertility Nutraceuticals LLC, New York, N.Y) for at least 6–8 weeks until total testosterone (T) levels are at least around 30 ng/dL [8]. Concomitantly, patients are also supplemented with CoQ10, 333 mg TID, (Ovoenergen,® Fertility Nutraceuticals, LLC, New York, N.Y.) [9]. Both supplementations are maintained until positive pregnancy test.