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REVIEW

The role of AMH in the pathophysiology of polycystic ovarian syndrome

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Reshef Tal is currently completing his Reproductive Endocrinology and Infertility fellowship at the Yale University School of Medicine. He received his medical degree and PhD in Molecular Biology from the Sackler School of Medicine at Tel-Aviv University (Israel). He completed a post-doctoral research fellowship at the Samuel Lunenfeld Institute in University of Toronto. He subsequently completed his residency in Obstetrics and Gynecology at Maimonides Medical Center (NY). His research is focused upon AMH as a predictor of ovarian reserve and assisted reproductive technology outcomes, and understanding the role of angiogenesis and stem cells in reproductive biology and pathology.

Abstract Polycystic ovarian syndrome (PCOS) affects 5 – 10% of reproductive age women, but its pathogenesis is still poorly understood. The aim of this review is to collate evidence and summarize our current knowledge of the role of anti-Müllerian hormone (AMH) in PCOS pathogenesis. AMH is increased and correlated with the various reproductive and metabolic/endocrine alterations in PCOS. AMH plays an inhibitory role in follicular development and recruitment, contributing to follicular arrest. AMH inhibitory action on FSH-induced aromatase production likely contributes to hyperandrogenism in PCOS, which further enhances insulin resistance in these women. Elevated serum AMH concentrations are predictive of poor response to various treatments of PCOS including weight loss, ovulation induction and laparoscopic ovarian drilling, while improvement in various clinical parameters following treatment is associated with serum AMH decline, further supporting an important role for AMH in the pathophysiology of this syndrome. This review emphasizes the need for understanding the exact mechanism of action of AMH in the pathophysiology of PCOS. This may lead to the development of new treatment modalities targeting AMH to treat PCOS, as well as help clinicians in prognostication and better tailoring existing treatments for this disease.

KEYWORDS: AMH, hyperandrogenism, insulin resistance, ovulatory dysfunction, pathophysiology, PCOS

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in reproductive age affecting 5 – 10% of women, and is the leading cause of ovulatory dysfunction (Diamanti-Kandarakis et al., 1999; Franks, 1995; Knochenhauer et al., 1998). According to the Rotterdam 2003 consensus, two out of three criteria are required for the diagnosis of this syndrome: oligo- or anovulation, clinical or biochemical hyperandrogenism and/or polycystic ovaries on ultrasound (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). It can also be associated with insulin resistance, obesity and altered gonadotrophin release. PCOS was first described by Stein and Leventhal in 1935 in a series of seven patients with polycystic ovaries, amenorrhoea, infertility and hirsutism (Stein and Leventhal, 1935). It is now well established that ovarian hyperthecosis and increased androgen production are central to the endocrine disturbance in PCOS. In addition, numerous genetic and environmental factors have been postulated to interact and play a role in the underlying pathophysiology of this syndrome (Vink et al., 2006). PCOS is clearly familial in a large majority of cases and molecular genetic pathways have been implicated in the metabolic and biochemical alterations associated with PCOS (Escobar-Morreale et al., 2005; Urbanek, 2007). In addition to genetic predisposition, environmental exposure is thought to play a major role in PCOS development. This notion is supported by experiments in rhesus monkeys injected with androgens during pregnancy showing that their female offspring had polycystic ovarian morphology and various PCOS-like manifestations (Abbott et al., 2002). However, despite many decades of extensive research, the exact aetiology and pathogenesis of this complex disorder remain largely unknown.

Anti-Müllerian hormone (AMH) is an important regulator of folliculogenesis in the ovaries (Visser et al., 2006). It is secreted by granulosa cells of the ovarian follicles and its serum levels are elevated 2- to 3- fold in women with PCOS in comparison with normo-ovulatory women, consistent with the increased number of small antral follicles in PCOS (Laven et al., 2004; Pigny et al., 2003). However, it is unclear whether AMH is simply a marker which is increased in PCOS, or actually an important contributing factor to its pathophysiology. This article will review the role of AMH in ovarian physiology and the accumulating evidence implicating AMH in the pathogenesis of PCOS. Improved understanding of the association between AMH and PCOS may pave the way for development of new therapies for PCOS.

Materials and methods

The published literature was searched for relevant publications using PubMed, Medline and Google Scholar databases until November 2015 with combinations of the search terms "polycystic ovarian syndrome", "PCOS", "antimullerian hormone", "AMH", "pathogenesis, 'ovulatory dysfunction'", "hyperandrogenism", "insulin resistance", "ovulation induction", "IVF", "metformin", "laparoscopic ovarian drilling" and "treatment outcome". Only original articles in English were included.

AMH and ovarian physiology

AMH aka Müllerian inhibiting substance (MIS) is a homodimeric glycoprotein hormone that belongs to the transforming growth factor-β superfamily (Cate et al., 1986). It is structurally related with the 35 other members of this superfamily, which includes growth differentiation factors, inhibins and bone morphogenetic proteins (BMP), some of which are also involved in the process of folliculogenesis in the ovaries (Knight and Glister, 2006). While most of these ligands show a broad expression pattern and a wide range of functions, the expression of AMH is restricted to the gonads and AMH is thought to exert its effects only on reproductive organs (Massague and Chen, 2000).

The gene which encodes for AMH is localized on the small arm of chromosome 19 (Cohen-Haguenauer et al., 1987). AMH is produced as a pro-hormone, which after secretion undergoes cleavage to generate a transforming growth factor-beta-like noncovalently-linked biologically active C-terminal fragment (Pepinsky et al., 1988; Wilson et al., 1993). AMH in the female is produced exclusively by ovarian granulosa cells (Ueno et al., 1989), its concnetration declines with age and become undetectable after menopause (Vigier et al., 1984). The concentration of this hormone slightly fluctuates during different phases of the menstrual cycle but not significantly enough to affect its measurement (Cook et al., 2000; Streuli et al., 2009).

AMH is also found in Sertoli cells and plays an integral role in the embryonic development of the reproductive tract and sex differentiation by inhibiting the development of Müllerian ducts (Rajpert-De Meyts et al., 1999; Rey et al., 2003). During embryogenesis, if AMH production is absent or its receptors are defective, Müllerian ducts persist to form the Fallopian tubes, uterus and upper one third of the vagina (Behringer et al., 1994).

During human folliculogenesis, AMH protein expression begins at the primary follicle stage, highest expression is detected in FSH-dependent pre-antral and small antral follicles of ≤4 mm in diameter, and AMH expression gradually declines in subsequent stages and is absent in follicles larger than 8 mm (Stubbs et al., 2005; Weenen et al., 2004). Studies measuring AMH messenger RNA (mRNA) expression in granulosa cells of isolated human follicles and AMH protein concentration in follicular fluid confirmed this pattern of expression (Andersen et al., 2010; Jeppesen et al., 2013; Modi et al., 2006). Baarends *et al*. studied *in vivo* the expression of AMH and anti-Müllerian hormone receptor type II (AMHRII) mRNA in adult rat ovaries and suggested the role of FSH and oestrogens in down-regulation of expression of AMH and AMHRII mRNA during differentiation of small antral follicles into large antral follicles (Baarends et al., 1995). Cessation of AMH production from larger antral follicles ≥10 mm, is thought to be essential for dominant follicle selection (Pellatt et al., 2007a; Visser et al., 2006) (**Figure 1**).

It is well established that AMH acts as an important inhibitory factor for follicular growth. AMH-null mice exhibit accelerated folliculogenesis with increased numbers of growing follicles resulting in early depletion of ovarian follicles (Durlinger et al., 1999, 2001). In-vitro, AMH treatment of rat granulosa cells leads to a reduction in FSH and cAMP-stimulated aromatase activity (Diclemente et al., 1994). In the same