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REVIEW

The role of AMH in the pathophysiology of polycystic ovarian syndrome

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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.

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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

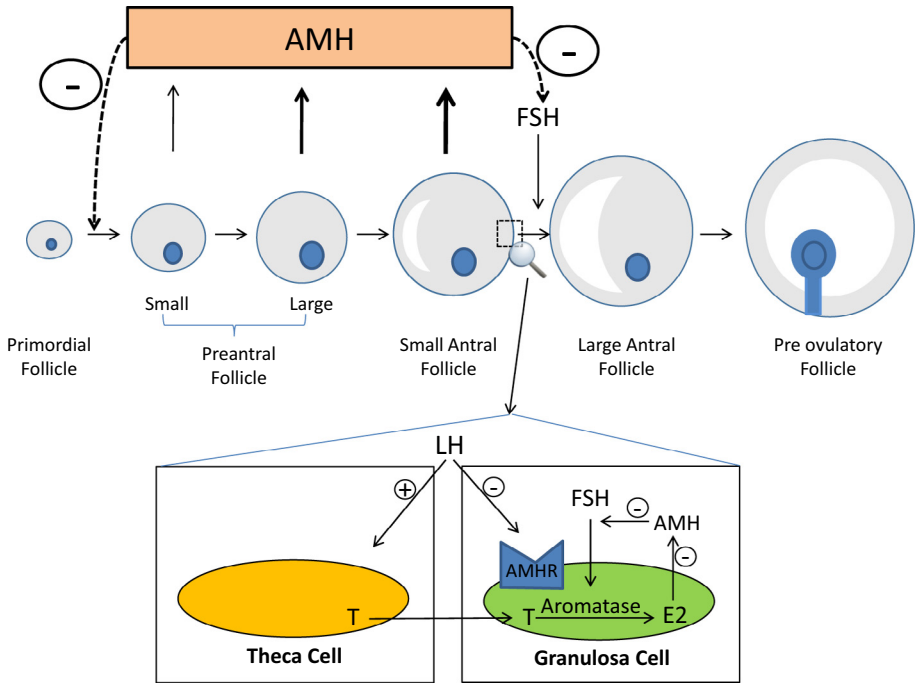

Figure 1 AMH production and action according to follicular stage. AMH is secreted primarily from pre-antral and small antral follicles. The inhibitory actions of AMH are shown on the FSH-independent initial recruitment of primary follicles from the primordial follicle pool and on the FSH-dependent follicular maturation and selection of the dominant follicle by decreasing follicular sensitivity to FSH. The inset shows the interplay between AMH, FSH and LH actions at the molecular level. AMH inhibits FSH-induced aromatase expression in granulosa cells, reducing the conversion of testosterone to oestradiol, which inhibits AMH in turn. In addition to stimulating theca cell to produce testosterone, LH acts directly on granulosa cells down-regulating the expression of AMHRII. AMHRII = anti-Müllerian hormone receptor II; E2 = oestradiol; T = testosterone.

study, AMH was shown to reduce aromatase mRNA expression in cAMP-stimulated cells and LH receptor mRNA expression in porcine granulosa cells stimulated with FSH (Diclemente et al., 1994). Similarly, AMH treatment has been demonstrated to result in decreased aromatase mRNA expression and activity as well as oestradiol production in human granulosa cells (Grossman et al., 2008; Pellatt et al., 2007a). Consistent with this, AMH has been shown to reduce the growth of early growing follicles by 40 ± 50% following 4 – 5 days in culture (Weenen et al., 2004). AMH-induced decrease in granulosa cells sensitivity to FSH was also confirmed *in vivo* as AMH-deficient mice were more sensitive to FSH than the wild-type ones (Durlinger et al., 2001).

AMH signals through two types of serine–threonine kinase transmembrane receptors known as type I receptor (AMHRI) and type II receptor (AMHRII) which are present on gonads and Müllerian ducts (La Marca and Volpe, 2006). Interaction of AMH with its receptors stimulates a signalling pathway which involves Smad proteins (Massague and Chen, 2000). Granulosa cells of pre-antral and small antral follicles have a high expression of AMH and AMH receptor mRNA (Hirobe et al., 1992). Interestingly, the presence of AMHRII mRNA has been identified in theca cells along with granulosa luteal cells (GLC), suggesting the possibility of an AMH-based signalling pathway between these cells during folliculogenesis (Hanna et al., 2006). Collectively, the role of AMH in folliculogenesis appears to be the inhibition of premature recruitment and maturation of follicles. Once the follicles reach the large antral stage, the expression of AMH is downregulated and these follicles become more sensitive to FSH leading to increased oestrogen production, follicular selection and subsequent ovulation in the normal ovary.

Role of AMH in PCOS pathogenesis

It is well known that PCOS ovaries comprise a higher number of pre-antral and small antral follicles (Franks et al., 2000, 2006; Hughesdon, 1982), indicating arrest of follicular development at the stage when AMH production is greatest. Indeed, several studies have demonstrated that serum AMH concentration is elevated in PCOS women compared with women with normal ovaries (Fallat et al., 1997; Laven et al., 2004; Mulders et al., 2004; Pellatt et al., 2007a). In addition, the concentration of AMH in follicular fluid from women with anovulatory PCOS was found to be 5-fold greater compared with ovulatory women (Das et al., 2008). Moreover, Pellatt *et al*. showed that AMH production per granulosa cell is increased on average 75-fold in granulosa cells of anovulatory PCOS compared with granulosa cells of normal ovaries (Pellatt et al., 2007a). Catteau-Jonard *et al*. corroborated these findings showing that granulosa cells of polycystic ovaries have increased AMH mRNA expression (Catteau-Jonard et al., 2008). Taken together, these data suggest that it is not only the increased number of follicles, with resultant increased granulosa cell mass, but also greater production by individual granulosa cells that is underlying AMH overproduction in PCOS. Several studies have demonstrated that AMH is

correlated with severity of PCOS manifestations, including oligo/amenorrhoea, hyperandrogenism and polycystic ovarian morphology (Eldar-Geva et al., 2005; Homburg et al., 2013; Lin et al., 2011; Pigny et al., 2003; Piouka et al., 2009; Tal et al., 2014) lending support to the notion that AMH is not only a biomarker of disease but actually contributes to PCOS pathogenesis.

The role of AMH in ovulatory dysfunctions in PCOS

Previous studies have directed our attention towards the role of AMH in inhibiting folliculogenesis by interference with the concentration and the actions of FSH in the ovaries (Josso et al., 2001; Pellatt et al., 2010; Singer et al., 2009). Interestingly, several investigators have reported that AMH concentrations are correlated with the degree of ovulatory dysfunction. Laven *et al*. showed that normogonadotrophic anovulatory women with or without PCOS have higher AMH concentrations than their normo-ovulatory counterparts, and that serum AMH is correlated with menstrual cycle duration (Laven et al., 2004). Moreover, Pellatt *et al*. have suggested that PCOS can be divided into anovulatory and ovulatory based on the serum AMH concentrations as women with anovulatory PCOS were found to have 18 times higher AMH concentrations than the women with ovulatory PCOS with no overlapping areas (Pellatt et al., 2010). Pigny *et al*. investigated the correlation of serum AMH concentrations with FSH in PCOS and found a positive correlation between AMH concentration and small antral follicle number ($P < 0.0001$) but a negative correlation with serum FSH concentration ($P < 0.04$), suggesting the role of increased AMH in the follicular arrest in PCOS by inhibiting FSH early in folliculogenesis (Pigny et al., 2003). They also reported that AMH concentration is tightly correlated with the 2 – 5 mm but not the 6 – 9 mm follicular number (Pigny et al., 2003), implying that greater AMH concentrations would reflect a greater number of AMH-producing 2 – 5 mm follicles. Interestingly, in a different study by the same group, the authors reported a strong negative relationship between the 2 – 5 mm and the 6 – 9 mm follicular numbers, suggesting the presence of a physiological negative influence from the 2 – 5 mm follicle pool on the terminal follicle growth at the time of selection (Dewailly et al., 2007). Importantly, the authors noted that the 2 – 5 mm follicular number was positively correlated with the severity of the menstrual disorder in PCOS, being highest in women with amenorrhoea (Dewailly et al., 2007). Subsequently, Park *et al*. reported that adolescent girls with oligomenorrhoea have elevated AMH concentrations compared with normo-ovulatory controls (Park et al., 2010a). Moreover, Tal *et al*. recently reported that serum AMH concentration had a strong predictive ability for amenorrhoea in their study population of women with elevated AMH, having 91.7% specificity and 79.4% sensitivity in predicting amenorrhoea when the threshold AMH concentration was 11.4 ng/ml (Tal et al., 2014). Taken together, these observations suggest that anovulatory PCOS women have an increased number of AMH-producing small antral follicles (2 – 5 mm), presumably creating an extreme AMH-dominated micro-environment, which impairs the action of FSH on the selectable follicles leading to anovulation. However, these observations provide only indirect evidence for AMH role in PCOS-related anovulation. Further studies are warranted to directly assess the effects of inhibiting AMH action on folliculogenesis and PCOS manifestations using in-vitro and experimental animal models.

While it is likely that elevated AMH contributes to the pathogenesis of anovulation in PCOS, the cause/s of its increased production remain unknown. However, factors which are closely related to PCOS pathophysiology such as increased LH, androgen levels and insulin resistance may be implicated (**Figure 2**). Several studies have shown that serum AMH is correlated with LH and androgen levels (Eldar-Geva et al., 2005; Homburg et al., 2013; Lin et al., 2011; Pigny et al., 2003; Piouka et al., 2009; Tal et al., 2014). LH increases AMH production 4-fold in granulosa cells of PCOS ovaries but not of normal ovaries (Pellatt et al., 2007a). In addition, LH has been shown to increase AMH expression in granulosa cells of oligo/anovulatory women but not of ovulatory PCOS and control women, and had no effect on AMHRII expression in granulosa cells of oligo/anovulatory PCOS women while decreasing its expression in granulosa cells of ovulatory PCOS and control women (Pierre et al., 2013), suggesting a role for LH in AMH overexpression and AMH-induced follicular arrest. Moreover, androgens play a role in stimulating early (FSH independent) stages of follicular growth (Vendola et al., 1998; Weil et al., 1999) and may thus contribute to increased AMH production. However, Carlsen *et al*. reported that 6-month androgen suppression with dexamethasone did not change AMH concentrations, suggesting that other mechanisms are likely responsible for the induction and maintenance of AMH production in PCOS women (Carlsen et al., 2009).

Another candidate which may contribute to elevated AMH in PCOS is insulin. Compensatory hyperinsulinaemia secondary to insulin resistance is found in PCOS and Homeostatic Model Assessment (HOMA-IR) has been shown to be correlated with the AMH concentrations in this population (La Marca et al., 2004a, 2004b). Nardo *et al*. found a positive correlation between AMH and fasting insulin levels in women with and without PCOS (Nardo et al., 2009). This could be explained by an abnormal effect of insulin on AMH secretion from granulosa cells as suggested by Park *et al*. in women without PCOS (Park et al., 2010b), or may be due to increased androgen production in the presence of hyperinsulinaemia in PCOS (Park et al., 2010b). Further research is required in this area to characterize the nature of the association between insulin and AMH concentrations and to delineate the mechanism for insulin-dependent elevation of AMH in PCOS.

It is also possible that genetic factors may underlie AMH overexpression in PCOS. Kevenaar *et al*. investigated the role of ALK2, its receptor and their encoding gene ACVR1 gene, which are involved in AMH/BMP signalling, in the aberrant follicle development in PCOS. They found an association between a genetic variant of ACVR1 with AMH concentrations and folliculogenesis in PCOS suggesting the role of ALK2 signaling in ovulatory disturbances in PCOS (Kevenaar et al., 2009). Stubbs *et al*. investigated the role of AMH in the transition of primordial follicles to primary follicles in women with normal and polycystic ovaries and found AMH immunostaining in fewer primordial follicles in polycystic ovaries of anovulatory women in comparison with normo-ovulatory women with polycystic ovaries (Stubbs et al., 2005). However, the intensity of AMH staining in pre-antral and antral follicles was not

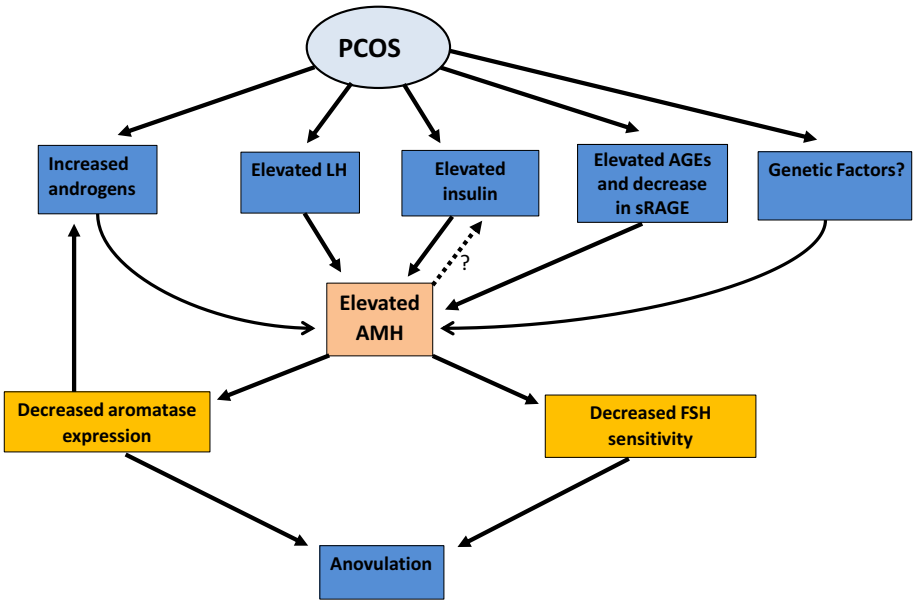

Figure 2 The various factors leading to elevated anti-Müllerian hormone (AMH) and the downstream effects of AMH overproduction. Overproduction of AMH in polycystic ovarian syndrome (PCOS) could be due to several factors which are abnormally elevated (LH, androgens, insulin, advanced-glycation end products [AGE]) or decreased (soluble receptor for AGE [sRAGE]) in PCOS. In addition, genetic factors such as variants of ACVR1 gene likely contribute to AMH overexpression. The abnormal increase in AMH diminishes aromatase expression and follicular sensitivity to FSH leading to anovulation and hyperandrogenism. The exact relationship between AMH and insulin resistance has not been fully elucidated.

different between these groups. Based on these observations, it may be postulated that AMH exhibits less inhibition on primordial follicles in anovulatory PCOS women, leading to increased early folliculogenesis and accumulation of pre-antral and small antral follicles, resulting in AMH overproduction.

AMH and hyperandrogenism in PCOS

Androgens are produced in theca interna cells and converted to oestrogens in granulosa cells by the action of aromatase (Erickson et al., 1979). LH stimulates steroidonegenesis by producing androgens from theca interna cells. Elevated serum AMH concentration in PCOS has been shown to be positively associated with androgen levels such as serum testosterone and androstenedione (Carlsen et al., 2009; Cassar et al., 2014; Pigny et al., 2003; Piltonen et al., 2005), supporting the notion that AMH may contribute to the development of hyperandrogenism in women with PCOS. While the specific mechanism/s of action of AMH leading to hyperandrogensim in PCOS has not yet been fully elucidated, such effect may be mediated by the reduction in aromatase activity in granulosa cells of polycystic ovaries (Laven et al., 2002; Pellatt et al., 2007b). di Clemente *et al.* found reduced aromatase activity and mRNA expression in response to AMH in rat fetal ovaries (di Clemente et al., 1992). Grossman *et al.* investigated the role of AMH in the expression of cytochrome P450 aromatase (CYP19) mRNA and protein in human GLC and demonstrated significant reduction in FSH-induced oestradiol production via AMH-induced inhibition of CYP19 gene expression and cytochrome P450 aromatase activity in GLC. The authors proposed this interaction as a possible explanation for the association of high AMH concentrations and low FF oestradiol concentrations in PCOS (Grossman et al., 2008). Similar decrease in FSH-induced aromatase mRNA expression and oestrogen production in response to AMH has also been recently reported by Chang et al. (2013). In addition to direct inhibitory effects of AMH on granulosa cell aromatase expression/activity leading to increased androgen levels, it can be conceptualized that AMH may have a paracrine effect on theca interna cells given the presence of AMHRII in these cells, leading to theca cell dysregulation in PCOS (Ingraham et al., 2000). It can be speculated that AMH-dependent inhibition of FSH-induced aromatase activity may also lead to the abnormal follicular development in PCOS (Jonard and Dewailly, 2004). Furthermore, a study by Kevenaar *et al.* provides a possible genetic explanation for a mechanistic link between AMH and androgen levels. The investigators found an association between AMH gene Ile (49) Ser polymorphism and androgen levels in women with PCOS, which may be due to AMH influence on FSH-induced aromatase activity (Kevenaar et al., 2008). Of note, the existing evidence highlights the role of AMH in hyperandrogenism associated with PCOS, but there are several other factors that also contribute to the metabolic and hormonal dynamics in PCOS.

AMH and metabolic manifestations

The rate of metabolic syndrome in PCOS is two to three times greater than healthy women of the same age group (Apridonidze et al., 2005). The most common metabolic

abnormalities associated with PCOS are insulin resistance (IR) and obesity, affecting anovulatory women more than ovulatory women with PCOS, which also play an important role in regulation of androgen levels (Conway and Jacobs, 1993). Although IR is amplified by increasing obesity, women with PCOS are more insulin resistant than can be accounted for by their obesity alone (Dunaif et al., 1989, 1992). It has been suggested that IR can affect AMH concentrations and also be associated with hyperandrogensim related with PCOS (Baillargeon and Nestler, 2006). However, evidence regarding the association between elevated AMH and IR as well as other metabolic manifestations of PCOS is conflicting.

Direct correlation between serum AMH and insulin resistance, as measured by (HOMA-IR), was first reported by La Marca *et al.* (2004b) in a study which included 14 women with PCOS. Consistent with this observation, a cross-sectional study by Fonseca *et al.* showed significantly higher AMH concentrations in PCOS patients with IR in comparison to PCOS patients without IR (Fonseca et al., 2014). Moreover, Nardo *et al.* assessed the relationships between AMH and IR in a study of 49 patients with PCOS and 183 without PCOS undergoing IVF treatment and found a positive correlation between AMH concentrations and HOMA-IR as well as insulin levels, and a negative correlation between AMH and HOMA-B in both groups, suggesting that the relationship between AMH and IR is independent of PCOS status (Nardo et al., 2009). Skalba *et al.* also reported a positive correlation between AMH and HOMA-IR in a study which included 87 women with PCOS and 50 non-PCOS controls (Skalba et al., 2011).

In contrast, other studies did not find an association between AMH and IR. Eldar-Geva *et al.* failed to find any association between AMH and insulin sensitivity in 19 women with PCOS and hyperandrogenism (group A), 10 women with PCOS without hyperandrogenism (group B), and 23 normal ovulatory women (group C) as controls who underwent ovarian stimulation with long down-regulation protocol (Eldar-Geva et al., 2005). Other small studies also failed to find an association between AMH and IR (Caglar et al., 2013; Cassar et al., 2014). While it is possible that study size may have played a role in these negative findings, several larger studies reported similar negative findings. In a study which included 59 PCOS and 45 non-PCOS women, Pigny *et al.* found no significant correlation between AMH concentrations and fasting insulin (Pigny et al., 2003). Moreover, several studies of Asian women with PCOS reported no significant association between AMH and IR (Chen et al., 2008; Chun, 2015; Tian et al., 2014). Notably, the PCOS women in these studies were relatively leaner than in the others. **Table 1** summarizes the available evidence on the association between AMH and IR. The conflicting data on the association between AMH and IR may be partly explained by heterogeneity in study populations. In addition, AMH has been shown to be negatively correlated with body mass index (BMI) in some studies but not others (Fleming et al., 2015) and since insulin resistance is closely associated with obesity, the complex relationship between AMH and BMI may be an important confounder in studies evaluating the association between AMH and IR. Therefore, larger studies which carefully control for BMI and other confounders are needed to further explore the nature of the interaction between AMH and IR.

The role of increased oxidative stress as well as products of oxidation such as advanced glycation end (AGE) products and their receptors (RAGE) has been increasingly recognized in the ovulatory and metabolic disturbances associated with PCOS (Diamanti-Kandarakis et al., 2005, 2008), and recently a link to AMH has been suggested. Advanced glycation end products are the products of nonenzymatic modification of proteins, lipids and nucleic acids by glucose. Their generation is accelerated by conditions such as diabetes and IR (Unoki and Yamagishi, 2008), and AGE have been shown to be elevated in serum as well as ovaries of PCOS women (Diamanti-Kandarakis et al., 2007, 2008). Furthermore, AGE have been shown to interfere with insulin signalling in granulosa cells (Diamanti-Kandarakis et al., 2015). In contrast to RAGE, the soluble receptor for RAGE (sRAGE) is an extracellular form of RAGE which circulates in the blood binding AGE and reducing their free circulating levels, thus preventing the adverse intracellular events of AGE-RAGE interaction (Kalea et al., 2009). Diamanti-Kandarakis *et al.* demonstrated a positive correlation between elevated AMH concentrations and AGE in women with PCOS. They further showed that elevation in both AMH and AGE was more pronounced in women with anovulatory PCOS, suggesting an interrelated role for these molecules in ovulatory dysfunction in PCOS (Diamanti-Kandarakis et al., 2009). Moreover, Irani *et al.* reported that vitamin D supplementation, which is known to improve various manifestations of PCOS (Irani et al., 2015), led to a decrease in serum AMH accompanied by an increase in serum concentrations of sRAGE in women with PCOS (Irani et al., 2014b). Recently, Merhi *et al.* showed that treatment of cultured cumulus cells with AGE resulted in increased mRNA expression of the AMHRII but not AMH, and also led to increased AMH-induced SMAD 1/5/8 phosphorylation, effects that were suppressed by concomitant treatment with vitamin D (Merhi et al., 2015). Taken together, these data suggest that AGE potentiate the action of AMH in the ovary and that the combined action of AGE and AMH, which are upregulated in PCOS, may contribute to ovulatory dysfunction as well as various metabolic complications in PCOS such as insulin resistance. However, it is still unknown whether AMH may directly affect insulin action locally in the ovary or systemically, and further studies are warranted to evaluate the possible influence of AMH on the action of AGE in the ovary.

AMH and infertility

Does AMH have a role in PCOS-related subfertility? The answer is not straightforward but there are several studies which may provide important clues to this question. Studies have shown that AMH concentrations can be used as a predictor of menstrual response after weight loss in overweight and obese women with PCOS. Moran *et al.* studied the effect of weight loss treatment on the regulation of menstrual cycles in PCOS and found lower baseline AMH concentrations in responders ($P < 0.02$) in comparison to non-responders suggesting the use of pretreatment AMH as an important clinical predictor of the response to weight loss in PCOS (Moran et al., 2007). Thomson *et al.* also reported improvement in menstrual cyclicity and ovulatory function following weight loss in overweight and obese women with PCOS who had lower pretreatment AMH concentrations; however, weight loss did not result in a decrease in AMH concentrations (Thomson et al., 2009). Weight loss improved the menstrual and reproductive functions in these women with PCOS who already had lower baseline AMH

Table 1 Studies evaluating the association between serum AMH and insulin resistance in PCOS women.

Authors	Population characterstics	Age (years)	BMI (kg/m^2)	Study size	Study design	Factors measured	Main findings
Pigny et al., 2003	Women with and without PCOS (Rotterdam criteria)	PCOS: mean age 27.4 Control: mean age, 28.3	PCOS: mean BMI 26.7 Control: mean BMI 23.1	104 women; 59 symptomatic PCOS, 45 non-PCOS controls	Cross-sectional	Serum AMH concentrations and fasting insulin between days 2 and 7 after the last menstrual period	No significant correlation between AMH concentrations and fasting insulin (r = –0.024, P = NS)
La Marca et al., 2004b	Women with PCOS (defined by presence of oligo/amenorrhoea with hyperandrogenism) and control women	Mean age 23	Mean BMI 24.6	14 women with PCOS and 15 non-PCOS women	Cross-sectional	Serum AMH concentrations and HOMA-IR	Positive correlation between HOMA score and serum AMH l concentrations (r = 0.621, P < 0.05)
Eldar-Geva et al., 2005	Women with PCOS (Rotterdam consensus) and hyperandrogenism (group A), women with PCOS without hyperandrogenism (group B), normal ovulatory women as controls (group C) undergoing ovarian stimulation with GnRHa long protocol	20–39	GroupA: 27.7 ± 6.1 Group B: 27.2 ± 7.5 Group C: 25.1 ± 4.5	19 women in group A, 10 women in group B, and 23 women in group C	Prospective	Baseline serum AMH and fasting insulin levels	Women with PCO have higher serum AMH concentrations during ovarian stimulation than controls; No correlation between AMH and fasting insulin levels (r = –0.10, P = NS)
Chen et al., 2008	Women with PCOS (as per Rotterdam criteria)	26 (21–35)	23.05 (17.61 – 37.11)	99 women with PCOS	Cross-sectional	AMH concentrations and HOMA-IR	Negative association between AMH and HOMA-IR (γ = –0.220; P = 0.030)
Nardo et al., 2009	PCOS (as per Rotterdam criteria) and non-PCOS patients undergoing IVF	22–41	>19 but <30	49 patients with PCOS and 183 without PCOS	Prospective	Serum AMH, insulin, HOMA-IR, HOMA-B	Positive correlation between AMH concentrations and HOMA-IR (r = 0.40, P = 0.004), negative correlation between AMH and HOMA-B in both groups (r = –0.60, P = 0.046)
Skalba et al., 2011	Women with and without PCOS (as per Rotterdam criteria)	18–35	Normal weight: 18.5 to 24.9 Overweight: > 25	87 women with PCOS and 50 women without PCOS as healthy controls	Prospective	AMH concentration and HOMA-IR	Positive correlation between AMH and HOMA-IR (r = 0.31, P < 0.001)
Caglar et al., 2013	Women with and without PCOS (as per Rotterdam Criteria)	Mean age: 26	Mean BMI: 22	34 women with PCOS and 21 non-PCOS controls	Prospective	Serum AMH, HOMA-IR, QUICKI	No significant correlation between AMH and QUICKI or HOMA-IR (r = 0.068, P = NS and r = –0.010, P = NS, respectively)
Fonseca et al., 2014	Group A: women with PCOS (as per Rotterdam criteria) and IR; Group B: women with PCOS without IR; Group C: controls without PCOS	20 – 44	Mean BMI: Group A: 28.9 Group B: 23.8, Group C: 22.6	Group A: 26 women Group B: 30 women Group C: 30	Cross-sectional	Serum AMH, insulin levels, HOMA-IR	Higher AMH concentrations in PCOS patients with IR (5.90 ng/ml) in comparison to PCOS patients without IR (4.45 ng/ml) and controls (2.84 ng/m) (P = 0.001)
Cassar et al., 2014	Lean and overweight women with and without PCOS (as per Rotterdam criteria)	Lean control = 27 ± 6, Lean PCOS = 27 ± 4, Overweight control = 35 ± 4, Overweight PCOS = 29 ± 5	Lean control = 21·9 ± 4·6 Lean PCOS = 23·0 ± 4·7 Overweight control = 34·3 ± 5·1 Overweight PCOS = 34·2 ± 4·6	22 lean and 21 overweight women with PCOS; 19 lean and 16 overweight non-PCOS controls	Cross-sectional	Serum AMH and HOMA-IR	Increased AMH concentrations in lean and overweight women with PCOS and positive association with hyperandrogenism but not IR (P < 0.001)
Tian et al., 2014	Women with PCOS (NIH criteria) and control group	27.90 ± 4.14 to 29.62 ± 4.33	<25	160 PCOS women and 40 women in control group	Prospective	Serum AMH, HOMA-IR, QUICKI	Negative correlation between AMH concentrations and HOMA-IR (r = –0.038, P = NS) and a positive correlation with QUICKI (r = 0.063, P = NS)
Chun, 2015	Women with PCOS (as per Rotterdam criteria)	18 – 33	Group 1: 21.78 ± 4.13, Group 2: 22.62 ± 7.18	95 Korean women with PCOS. Group 1 (AMH <10 n = 53) Group 2 (AMH >10, n = 42)	Retrospective	Serum AMH, HOMA-IR, QUICKI	No correlation between AMH concentrations and HOMA-IR (r = 0.121, P = NS) and QUICKI (r = 0.003, P = NS)

AMH = anti-Müllerian hormone; BMI = body mass index; COH = controlled ovarian hyperstimulation; HOMA = Homeostatic Model Assessment; HOMA-B = homeostatic model assessment of steady state beta cell function; HOMA-IR = homeostatic model assessment of tissue insulin sensitivity; IR = insulin resistance; MIS = Müllerian-inhibiting substance; PCOS = polycystic ovary syndrome; QUICKI index = Quantitative Insulin Sensitivity Check Index.

concentrations and which was not further affected by weight loss. Moreover, response to ovulation induction also appears to be related to pre-treatment AMH concentrations. In a study which included 68 obese PCOS women, El-Halawaty et al. (2007) found a significant difference in serum AMH concentration between PCOS women who responded to ovulation induction with clomiphene citrate versus those who were non-responders. A threshold value of AMH <1.2 ng/ml was found to predict response to clomiphene citrate in obese women with PCOS (sensitivity 71%, specificity 65.7%). Similarly, in a study of 60 anovulatory women with PCOS who underwent ovulation induction with clomiphene citrate, serum AMH concentration at baseline was found to be predictive of ovulation and pregnancy. Ovulation and pregnancy rates were significantly higher (97%, $P < 0.001$, and 46%, $P = 0.034$) in patients with low AMH (<3.4 ng/ml) versus women with AMH 3.4 ng/ml or greater (48% and 19%) (Mahran et al., 2013). It may be postulated that in those women with anovulatory PCOS who have very high granulosa cell production of AMH, as reflected by profoundly elevated serum AMH concentrations, the inhibitory actions of AMH on folliculogenesis cannot be overcome by weight loss treatment or gentle ovulation induction regimens.

Evidence for the negative role that elevated AMH plays in the fertility of PCOS women also comes from studies on IVF in this population. While AMH concentrations were higher in the follicular fluid aspirates at the time of oocyte retrieval from the anovulatory women undergoing IVF in comparison to the ovulatory women, these follicular levels were lower in the women who attained pregnancy (Desforges-Bullet et al., 2010).

The evidence that high AMH concentrations are associated with poor assisted reproductive outcome in PCOS women may appear to contradict existing evidence that high AMH is correlated with good IVF response. However, while it is well established that AMH is correlated with ovarian response and is a good predictor of oocyte yield following assisted reproductive technology, it is still controversial whether it may also be associated with qualitative outcomes of assisted reproductive technology (La Marca et al., 2007; Muttukrishna et al., 2005). A recent meta-analysis by Iliodromiti *et al*. concluded that AMH was a weak predictor of live birth outcome in patients following IVF (Iliodromiti et al., 2014). Moreover, most of these studies have been conducted on women with unspecified ovarian reserve or non-PCOS women. Accumulating data on the association between AMH and assisted reproductive outcome in PCOS have been very conflicting.

Aleyasin *et al*. investigated the relationship between AMH concentrations and assisted reproductive technology outcome in 60 PCOS patients and found a statistically significant positive correlation between the AMH concentrations and the number of oocytes retrieved, presence of mature oocytes and embryo transfer. However, in their study AMH was not found to be associated with clinical pregnancy outcome (AUC = 0.543, for cut-off of AMH >4.8 ng/ml) (Aleyasin et al., 2011). In contrast, Kaya *et al*. showed in their study of 60 women with PCOS that day 3 serum AMH concentration ≥3.2 ng/ml was a predictor of IR and clinical pregnancy rate (CPR) with 72.1% and 75.6% sensitivity and 72.7% and 77.3% specificity, respectively (Kaya et al., 2010). Xi *et al*. also investigated the predictive value of AMH on day 3 of IVF cycle in 164 PCOS women and divided the clinical outcomes according to <25th, 25 to 75th, or >75th AMH percentiles. Among these three groups, they found comparable fertilization rate and quantity of good quality embryos, but lower embryo implantation rates were observed in the high AMH group in comparison to the low and average AMH groups ($P < 0.01$) (Xi et al., 2012). In addition, the authors found a non-significant trend towards lower clinical pregnancy rates in the high AMH group compared with the other two groups (Xi et al., 2012). In a different study, Sahmay *et al*. found no significant correlation between AMH concentrations and CPR in 150 women with PCOS who underwent IVF as CPR were 27.8%, 35.0% and 37.8% in <25%, 25%–75% and >75% percentiles of AMH concentrations (Sahmay et al., 2013). In a recent meta-analysis, we showed that in spite of some weak association of AMH with implantation and clinical pregnancy rate outcomes, AMH displayed a trend toward weaker predictability of clinical pregnancy in women with PCOS (pooled diagnostic OR 1.18, AUC 0.60) compared with women with unspecified or diminished ovarian reserve (pooled diagnostic OR 2.097, AUC 0.634) (Tal et al., 2015). This particularly weak association of AMH with pregnancy outcome in PCOS could be explained by considering the association of AMH with the pathogenesis of the syndrome (Lin et al., 2011). AMH is correlated with PCOS severity and has a good predictive accuracy for PCOS, making it a good candidate for being added as a criterion for the diagnosis of this syndrome (Iliodromiti et al., 2013). Elevated AMH concentration in PCOS is largely due to increased AMH production by individual follicles rather than increased follicle number (Pellatt et al., 2007a), which may confound its association with ovarian reserve and/or quality, thus explaining the poor predictability of AMH for pregnancy outcome in this population of women.

A better understanding of the interplay between AMH and assisted reproduction outcomes in women with PCOS may help clinicians find a distinct role for AMH measurement in this population.

AMH in response to treatment in PCOS

Several lines of evidence demonstrate a close association between changes in serum AMH concentrations and improvement in PCOS manifestations in response to treatment, providing further support to the notion that AMH is causally related to PCOS pathophysiology.

Significant reduction in AMH concentrations was noted after 6-month metformin therapy in PCOS (Piltonen et al., 2005). In another study, the decrease in AMH concentration was a delayed response and recognized after eight months of metformin treatment (but not four months), and was proposed to be due to increased follicle recruitment in a better endocrine environment of less insulin (Fleming et al., 2005). In contrast, a short duration of metformin treatment (one week) in patients with PCOS did not affect AMH concentrations despite a significant reduction in the number of antral follicles (Bayrak et al., 2007). The association between serum concentration of AMH and treatment response was also established in the setting of ovulation induction with clomiphene citrate in obese PCOS patients. El-Halawaty *et al*. evaluated AMH concentration in obese women with PCOS after ovulation induction with clomiphene citrate and found a significant decrease in AMH concentrations in responders compared with non-responders suggesting that AMH plays a role

Table 2 Effect of treatment of PCOS on serum AMH concentrations.

Authors	Population characterstics	Age (years)	BMI (kg/m^2)	Size	Study design	Intervention	Factors measured	Main findings
Piltonen et al., 2005	Women with PCOS (Rotterdam criteria)	20–41	18–41	26 women with PCOS	Prospective	Metformin 1500 mg daily for 6 months ($n = 14$) vs. 1000 mg daily for 3 months followed by 2000 mg daily for 3 months ($n = 12$)	Effect of metformin on serum AMH concentrations, follicle number and ovarian volume	Decrease in AMH concentrations in women with PCOS after metformin treatment with no difference between the two dosing protocols (Pre-treatment mean AMH concentration 87.5 vs. 81.4 pmol/l after 6 months of metformin treatment, $P < 0.01$)
Fleming et al., 2005	Obese women with PCOS (Rotterdam criteria)	Mean 30.2	Mean 37.1	82 obese women with PCOS	Prospective randomized trial	Metformin treatment for 4 months and 8 months (500 mg three times daily or 850 mg three times daily)	Change in serum AMH over 4 and 8 months	Decrease in AMH was noted only after 8 months of metformin treatment (7.9 vs. 6.1 ng/ml, $P = 0.0005$) and was similar between the 500 mg and 850 mg dose groups; significant reduction in weight and increase in ovulation rate ($P = 0.0001$)
Bayrak et al., 2007	Women with PCOS (diagnosed by oligoanovulation and hyperandrogenism) with and without IR	23–36	23.4–36	5 women IR + PCOS, 5 women with PCOS without IR, 4 control women	Prospective	Metformin 850 mg daily for 1 week	Concentrations of serum AMH and inhibin B, AFC; Serum concentrations of T, FSH, and LH, fasting glucose/insulin ratio.	No change in AMH concentrations after one week of metformin therapy
El-Halawaty et al., 2007	Obese women with PCOS (Rotterdam criteria) and obese normo-ovulatory women as control group (BMI > 30)	PCOS: 28.21 ± 4.8 Control: 27.65 ± 5.70	PCOS: 36.7 ± 5.75 Control: 36.4 ± 5.67	68 obese women with PCOS and 17 normo-ovulatory controls	Prospective	Clomiphene citrate (150 mg daily) for 5 days beginning cycle day 3	Serum AMH as a predictor of clomiphene citrate induced OI	Marked reduction in AMH concentrations in obese women with PCOS who responded to clomiphene citrate treatment ($P = 0.0081$); cut-off value of 1.2 ng/ml predicted response to OI with 71% sensitivity, and 65.7% specificity)
Irani et al., 2015	Vitamin D-deficient women with or without PCOS (Rotterdam criteria with serum AMH > 4 ng/ml replacing sonographic criteria)	PCOS: 27.0 ± 0.9 Control: 28.7 ± 1.3	PCOS: 27 ± 1.3 Control: 28.5 ± 1.5	67 women with ($n = 22$) or without ($n = 45$) PCOS	Prospective randomized controlled trial	Supplementation of 1,25-Dihydroxy- vitamin D3 (50,000 IU once weekly for 8 weeks)	Serum levels of sRAGE and AMH were measured at baseline and 8 weeks after vitamin D supplementation	Vitamin D3 replacement decreases serum AMH concentrations in women with PCOS ($P = 0.003$), associated with increase in serum sRAGE ($P = 0.03$); No change in AMH in non-PCOS women
Seyam et al., 2014	Group 1- anovulatory women with PCOS (Rotterdam criteria) undergoing LOD; Group-2 received incremental doses (50–150 mg) of CC; Group-3 healthy women	25–40	20–30	Group-1 ($n = 40$), group-2 ($n = 30$), group-3 ($n = 20$)	Prospective controlled	Laparoscopic ovarian drilling (LOD) or incremental doses of CC	Evaluation of serum AMH concentrations before and after treatment; AFC and summed ovarian volume (SOV) by TVS	AMH concentrations decreased in PCOS group following LOD from 5.99 ± 2.3 pretreatment to 3.4 ± 1.7, 3.2 ± 1.7 and 3.1 ± 1.5 ng/ml in one week, 3- months and 6- months post treatment ($P = 0.0001$). After 6 months of LOD, 75% women had regular cycles with ovulation rate of 60% vs. 63.33% regular cycles and 63.33% ovulation rate in CC group
Amer et al., 2009	Anovulatory women with PCOS (Rotterdam criteria)	LOD: 28.4 (0.9) CC: 28.1 (2.0)	LOD: 26.9 (0.6) CC: 24.7 (1.7)	PCOS women undergoing LOD ($n = 29$) or receiving CC ($n = 18$)	Prospective	Laparoscopic ovarian drilling (LOD) or CC treatment	Measurement of serum AMH concentration before and one week after treatment	Significant reduction in AMH concentrations from 6.1 (pre-treatment) to 4.6, 4.3 and 4.6 ng/ml after LOD at 1 week, 3 months and 6 months, respectively ($P = 0.003$); AMH concentration was predictive of ovulation after LOD with 78% sensitivity and 76% specificity
Weerakiet et al., 2007	PCOS (Rotterdam criteria) women with or without LOD, and healthy controls	LOD group: 33.9 ± 4.15, PCOS group: 32.9 ± 3.91, Control group: 33.8 ± 4.52	LOD group: 24.15 ± 5.28, PCOS group: 24.86 ± 6.70, Control group: 23.58 ± 4.45	PCOS women who had LOD ($n = 21$); PCOS women without LOD ($n = 21$); non- PCOS women ($n = 21$)	Cross-sectional	Laparoscopic ovarian drilling (LOD)	Day-3 serum anti-Müllerian hormone (AMH) concentrations	A non-significant trend towards lower AMH concentrations in the LOD (4.60 ± 3.16 ng/ml) vs. the PCOS (5.99 ± 3.36 ng/ml) group; lower FSH in PCOS group in comparison with LOD and control group ($P < 0.01$); A non-significant trend towards lower androgens in LOD group ($P = NS$)
Elmashad, 2011	Anovulatory CC resistant women with PCOS (Rotterdam criteria) and healthy control group	18–35	26.7 ± 2.4	Anovulatory CC resistent women with PCOS ($n = 23$); Control group ($n = 20$)	Prospective controlled	Laparoscopic ovarian drilling (LOD)	Plasma AMH concentration and ovarian stromal 3D power Doppler blood flow	Significant reduction in plasma levels of AMH and the ovarian stromal power Doppler flow indices following LOD, with a positive correlation between the two parameters ($r = 0.55$, $P = 0.006$; $r = 0.60$, $P = 0.002$; and $r = 0.016$, $P = 0.013$ for VI, FI, and VFI, respectively); Ovulation rate 73.9%, spontaneous pregnancy rate 26.1%
Hendriks et al., 2014	PCOS women (as per all three of the Rotterdam criteria and luteinizing hormone (LH) > 6.5)	18–45	Laser group: 31.0 ± 8.6 DLS group: 26.0 ± 9.4	Women with PCOS undergoing laser evaporation ($n = 12$) vs. diagnostic laparoscopy ($n = 9$)	Prospective controlled	Laparoscopic ovarian laser evaporation or diagnostic laparoscopy	Serum AMH and endocrine changes before and up to 5 days following laparoscopic laser evaporation or DLS	In the first hours after surgery, both groups showed decrease in AMH. However, testosterone, androstenedione and AMH remained at lower than baseline levels only in laser in comparison with DLS group ($P < 0.05$); In laser group 41.7% patients had ovulation within 28 days of the procedure, while in DLS group OI was started without wait for spontaneous ovulation

AFC = antral follicle count; AMH = anti-Müllerian hormone; BMI = body mass index; CC = clomiphene citrate; DLS = diagnostic laparoscopy; EE = ethinylestradiol; FG = Ferriman-Gallwey score; FI = flow index; FSH = follicle-stimulating hormone; LOD = laparoscopic ovarian drilling; mFG = modified Ferriman-Gallwey score; MIS = Müllerian-inhibiting substance; OC's = Oral contraceptives; OI = Ovulation induction; PCOS = polycystic ovary syndrome; SOV = summed ovarian volume; T = Testosterone; TVS = transvaginal ultrasound examination; VI = vascularization index; VFI = vascularization flow index.

in responsiveness to clomiphene citrate treatment (El-Halawaty et al., 2007). Alternatively, the decrease in AMH may simply be related to follicular development to a stage associated with less AMH production, similar to that which occurs following treatment with gonadotrophins (La Marca et al., 2004a).

Supplementation of 1,25-Dihydroxy-vitamin D3 (vit. D3) in PCOS women who are vit. D3-deficient has been shown to improve elevated androgen levels, insulin resistance and menstrual cyclicity (Pal et al., 2012; Selimoglu et al., 2010). Abnormally elevated AMH concentrations in PCOS women were decreased following vit. D3 administration suggesting that AMH may be mechanistically linked to vit D3-induced beneficial effects in PCOS (Irani and Merhi, 2014a; Irani et al., 2014b). This change in AMH following vit. D3 supplementation may be attributed to the presence of a vitamin D response element on AMH gene promoter which has been shown to be triggered by the active form of vitamin D in prostate cancer cells (Krishnan et al., 2007; Malloy et al., 2009).

Accumulating evidence suggests that reduction in AMH concentrations is associated with treatment response following laparoscopic ovarian drilling (LOD) in PCOS. Several studies on PCOS women reported that serum AMH concentrations were decreased following LOD (Amer et al., 2009; Elmashad, 2011; Seyam et al., 2014; Weerakiet et al., 2007). Hendriks *et al*. reported similar findings following laparoscopic laser evaporation, noting a sustained decrease in serum AMH only in PCOS women who underwent ovarian laser evaporation but not control PCOS patients who underwent diagnostic laparoscopy (Hendriks et al., 2014). In addition, AMH concentrations were significantly decreased and were correlated with reduced ovarian power Doppler blood flow indices in PCOS women following LOD (Elmashad, 2011). Moreover, in the study by Amer *et al*. pre-operative serum AMH concentration was shown to be predictive of treatment response to LOD as reflected by significantly greater ovulation rate in women with lower pre-treatment AMH concentration. In their study, AMH cut-off level of 7.7 ng/ml was predictive of ovulation following LOD with 78% sensitivity and 76% specificity (Amer et al., 2009). Although the mechanism of LOD is still unclear, it is thought to be mediated by the destruction of ovarian theca cell mass associated with rapid decrease in androgen levels leading to the beneficial clinical effects observed in PCOS women following LOD (Flyckt and Goldberg, 2011). However, it is unknown whether the decrease seen in AMH following LOD is simply reflective of the destruction of AMH-producing granulosa cells, or is actually mechanistically related to the clinical improvement. The predictive ability of pre-operative AMH concentration for treatment success would argue for the latter. It is possible that decreased local ovarian production of AMH following LOD may lead to increased follicular responsiveness to FSH and release from the follicular arrest. Further experimental studies are needed to investigate this possibility. **Table 2** summarizes the studies reporting serum AMH concentrations before and after various PCOS treatments.

Future perspectives: AMH inhibition as possible treatment for PCOS?

As previously discussed, AMH up-regulation appears to be central to the pathophysiology of PCOS. Therefore, future interventions aimed at inhibiting AMH action such as AMH-specific antibodies or antagonists may prove to be clinically useful in improving various aspects of this syndrome. The possible use of an antibody that blocks AMH or AMHRII action in the ovary may lead to similar consequences as the knockout of the AMH gene or its receptor in mice (Durlinger et al., 1999, 2001). An increase in the number of primordial follicles recruited, increased antral follicle sensitivity to FSH and consequently improvement in ovulatory dysfunction should be expected. Moreover, due to AMH inhibitory action on aromatase expression, AMH inhibition may be expected to result in greater conversion of androgens to oestrogens and improvement in hyperandrogenism. For over three decades, different antibodies against bovine or human AMH or AMHRII have been developed (Legeai et al., 1986, 1988; Salhi et al., 2004; Vigier et al., 1982). The monoclonal antibody mAb 12G4, the first mAb to be raised against human AMHRII, has recently shown promise for ovarian cancer immunotherapy by targeting human ovarian cancer cells *in vitro* and *in vivo* in a nude mouse xenograft model (Kersual et al., 2014). The development of a humanized version of the anti-AMHRII antibody 12G4, named 3C23K, is ongoing and could prove useful for ovarian and other gynaecologic AMHRII-positive cancers. Experimental studies are warranted to evaluate the potential of such AMH antibodies or antagonists in the treatment of PCOS.

Conclusions

This review summarizes the existing evidence regarding the contribution of AMH to the pathophysiology of PCOS and its various manifestations. In conclusion, AMH plays an inhibitory role in follicular development and recruitment, contributing to anovulation. It also likely promotes hyperandrogenism and insulin resistance in PCOS. Elevated serum AMH concentrations are predictive of poor response to various treatments of PCOS including weight loss, ovulation induction and laparoscopic ovarian drilling, while clinical improvement in various parameters following treatment is associated with serum AMH decline, further supporting an important role for AMH in the pathophysiology of this syndrome. Further basic and experimental studies will be paramount in improving our understanding of AMH related pathophysiology of PCOS, which may lead to development of new therapies for this disorder.

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