Impact of Polycystic Ovary Syndrome, Metabolic Syndrome, Obesity, and Follicular Growth Arrest in Women Health

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7.1 Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women in reproductive age. Depending on the diagnostic criteria used, the prevalence varies between 8% and 13% [1–4]. This syndrome was initially defined as a reproductive disease characterized by the presence of hyperandrogenism (HA), ovulatory dysfunction, and polycystic ovaries. However, growing data have shown the strong association with metabolic dysfunction. Although PCOS has been recognized clinically for more than 80 years, there has been an evolving set of diagnostic criteria and definition of PCOS phenotypes. In 1990, the National Institutes of Health (NIH) criteria defined PCOS diagnosis based on the presence of clinical or biochemical HA and chronic oligo-anovulation (OA) [1]. Subsequently, Rotterdam Consensus Criteria (2003) established a new diagnostic definition, including HA, OA, and polycystic ovarian morphology (PCOM) diagnosed by transvaginal ultrasound. This consensus introduced two new phenotypes: hyperandrogenic ovulatory (HA + PCOM) or non-hyperandrogenic anovulatory phenotypes (OA + PCOM), not previously considered [2]. The Androgens Excess and PCOS Society (2006) proposed an amendment to Rotterdam Consensus criteria: clinical or biochemical androgen excess was compulsory, including oligo-anovulation and polycystic ovarian morphology as secondary criteria [3]. Finally, new modifications were introduced by International PCOS Network (2018) about PCOM definition [4]. These different criteria have amplified the PCOS phenotype spectrum in a 30-year period of time.

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Ovulatory dysfunction, defined by the presence of oligo-anovulation and PCOM, is observed in up to 75% of the PCOS women [5]. These features are the clinical expression of disrupted folliculogenesis, characterized by follicular arrest [6, 7], follicle stockpiling [8, 9], and alteration in the follicle dominance mechanism [10, 11], which occurs within the ovary environment.

Follicular growth arrest is one of the main features of folliculogenesis disruption. It leads to the classical PCOM characterized follicle stockpiling of less than 10 mm in diameter in the ovarian cortex. This phenomenon underlies an impaired selection of one dominant follicle, despite the presence of an excess number of selectable follicles [8, 10, 12]. The current understandings of the mechanisms underlying follicular growth arrest in PCOS are limited. Recent data suggest that defective follicle selection occurs due to extra-ovarian mechanisms such as FSH/LH pituitary secretion and defective action over theca and granulosa cells [13–15], and intraovarian mechanism such as increase androgen thecal cell secretion, and higher anti-müllerian hormone (AMH) expression by granulosa cells [11, 14, 16, 17], and defective angiogenesis which may impair follicular development [6, 18–20].

In the present chapter, we will review the possible extra-ovarian and intraovarian mechanisms involved in follicle growth arrest PCOS and its relation with metabolic syndrome.

7.2 PCOS and Metabolic Syndrome Linkage

Metabolic syndrome (MS) is present in 24–43% of women with PCOS [21]. Multiple studies show that women with classic PCOS phenotypes (HA + OA + PCOM or HA + OA) have higher insulin levels, insulin resistance, obesity, and dyslipidemia prevalence [21–23]. The prevalence of MS in these phenotypes are higher than in non-classic PCOS phenotypes (HA + PCOM or OA + PCOM) (odds ratio [OR] 2.1 in classic PCOS vs. 1.62 in non-classic phenotypes) [24, 25]. Additionally, an increased risk of MS is observed in obese (OR 1.75) and lean PCOS women (OR 1.45), when compared with body mass index (BMI)-matched control groups [24, 25]. On the other hand, the presence of HA, higher BMI, and ovulatory dysfunction are independent predictors of MS in PCOS patients [4, 5, 23].

Finally, reduction in BMI and adiposity are correlated with a recovery of cyclic menses with a parallel improvement of the MS [4, 26–28], suggesting that there is a relation between metabolic dysfunction and folliculogenesis disruption in PCOS.

7.2.1 Insulin Resistance and Hyperinsulinism in PCOS

Insulin resistance (IR) is a common feature in PCOS and metabolic syndrome. Insulin resistance is found in approximately 44–85% PCOS women, and it is higher in obese PCOS subjects (80–95%) [29–32]. Recent studies have shown that PCOS has heterogeneous pathophysiology characterized by an intimate interrelation of

hyperandrogenism, IR, and compensatory hyperinsulinemia and its effects on different target tissues [27, 33, 34].

The pathogenesis of IR in PCOS is complex and incompletely dilucidated. Insulin resistance is traditionally defined as a decreased ability of insulin to mediate these metabolic actions (glucose uptake, glucose production, and lipolysis) while preserving its mitogenic and steroidogenic actions. The primary mechanism of IR (Fig. 7.1) is insulin receptor post-bind signaling defect in the peripheral organs [31, 35]. An increase in the phosphorylation rate on serine rather than tyrosine residue in the insulin receptor and IRS-1 has been frequently described [35]. The latter leads to a diminished translocation of glucose transporter 4 (GLUT-4) to the cytoplasmic membrane, which finally leads to compensatory hypersecretion of insulin to overcome this defect [34, 35].

Several studies have shown that adipose tissue of PCOS women has decreased insulin sensitivity. A lower level of GLUT-4 protein has been found in subcutaneous adipocytes of PCOS women compared to weight-match controls [36]. Similar findings are observed in obesity and type 2 diabetes mellitus (T2D) that can be improved by weight loss [35, 37, 38]. However, weight loss does not always improve insulin sensitivity in PCOS patients. The persistence of this metabolic defect in adipocytes is observed in the absence of obesity, T2D, or after weight loss; in lean PCOS phenotypes, suggests an intrinsic IR defect [35, 39, 40]. Moreover, recent studies have shown that insulin action on glucose metabolism in granulosa-lutein cell cultures is sharply diminished, similarly to what is observed in the muscle cell and adipocytes. These data suggest an impairment of insulin's metabolic pathway in reproductive and non-reproductive tissues in PCOS [41].

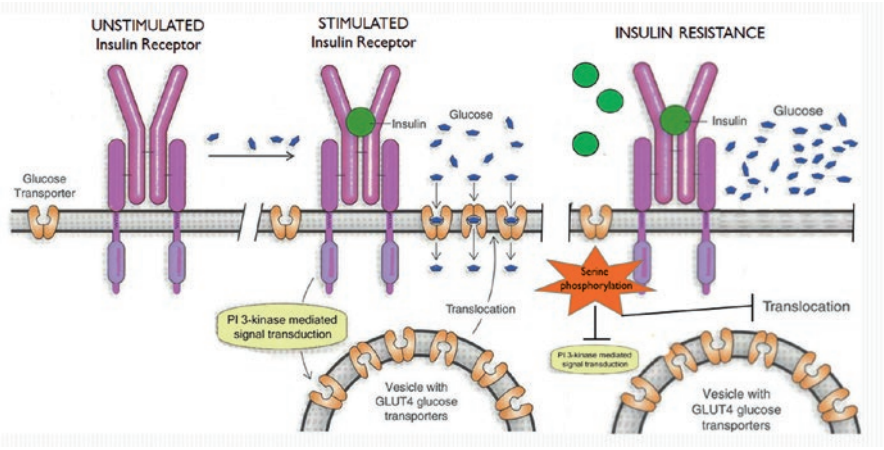

Fig. 7.1 Mechanism of insulin resistance in polycystic ovary syndrome. An excess of phosphorylation of serine rather than tyrosine residue in the insulin receptor and IRS-1 is found, leading to a diminished translocation of glucose transporter 4 (GLUT-4) to the cytoplasmic membrane. The latter leads to reduced glucose uptake by the cell, insulin resistance, and compensatory hypersecretion of insulin to overcome this defect. (adapted from [34])

As described above, the steroidogenic and mitotic functions of insulin signaling are preserved. Multiple studies have demonstrated that insulin and insulin-like growth factor-1 (IGF-1) receptors are expressed in theca and granulosa cells. Higher levels of circulating insulin bind to its receptor and IGF-1 receptor in theca cell, amplifying LH action. Compensatory hyperinsulinemia leads to an increase in CYP17 activity, rendering a higher androgen secretion [27, 31]. On the other hand, different studies have shown than insulin also induces theca cell hyperplasia [34, 35, 42]. Additionally, hyperinsulinemia has a negative effect over the liver, reducing the hepatic synthesis of SHBG, leading to increased free testosterone levels [34]. Thus, IR and compensatory hyperinsulinemia are responsible for or can aggravate hyperandrogenemia in PCOS.

7.2.2 Role of Adipose Tissue in Insulin Resistance in PCOS

In the last years, it has been found that adipose tissue plays a vital role in the development, improvement, or deterioration of IR and consequent follicle arrest in PCOS.

Adipose tissue is an endocrine organ that not only regulates glucose, lipid metabolism, and energy expenditure but also has an essential role in inflammation, immunity, and reproductive function. Obesity is defined as an abnormal accumulation of lipids in the adipose tissue. Obesity or abnormal fat body distribution is observed in PCOS women. Obesity and abdominal fat accumulation associate with a higher risk of ovulatory dysfunction, IR, and MS development in PCOS women [43, 44].

Obesity is observed in 44–88% of PCOS women [45]. Increased accumulation of abdominal adipose tissue has been found in PCOS patients. Body composition measurements by DXA scan have demonstrated that obese and lean PCOS women have higher total body fat and visceral adipose tissue storage when compared to BMI-matched controls [46, 47]. Recently, Ezeh et al. found an increased whole body fat-to-lean mass in obese and lean PCOS women. This excess of total fat mass was positively associated with higher free testosterone, fasting insulin levels, and HOMA-IR index [48].

It has been established that increased visceral adiposity is associated with increased catecholamine-induced lipolysis. The higher free fatty acid plasmatic levels delivered to the liver induce a reduction of insulin clearance and increasing IR, causing follicle growth impaired by the mechanism associated with IR described above [49, 50].

However, adipose can exert a direct effect over the ovarian function. Adipose tissue dysfunction (ATD) is frequently observed in obese PCOS women [45, 51]. ATD is characterized by abnormal adipokine secretion and low-grade chronic inflammation [45, 52].

Deregulation of adipokines secretion had been described in ATD associated with PCOS. Leptin and adiponectin are the most frequently studied since they play an essential role in ovarian function. Increased leptin levels are observed in obesity and PCOS [52]. In vitro studies have shown that higher leptin levels can inhibit follicle

growth [27, 45, 51]. On the other hand, adiponectin levels are reduced in obesity and obese PCOS women [53, 54]. Lower adiponectin levels are associated with an increase in insulin resistance. Different studies have shown that lower adiponectin levels are related to increased LH secretion in the pituitary and lower estradiol secretion from granulosa cells [30, 54].

Low-grade chronic inflammation is characterized mainly by higher TNF-alfa and IL-6 levels [45]. TNF-alfa induces IR by inhibiting adiponectin secretion, increasing free fatty acid levels, and reducing GLUT-4 expression in peripheral tissues [55]. TNF-alfa exerts direct effects over the ovary. In vitro studies have shown that TNF-alfa stimulates proliferation and steroidogenesis in theca cells [43, 51]. It also facilitates insulin and IGF-1 action over theca cells. Recent studies have shown that TNF-alfa levels are strongly related to IR and HA in PCOS but not to BMI [44].

Higher levels of IL-6 and TNF-alfa levels are associated with the infiltration of monocyte-derived macrophages of the ovarian tissue. The local ovarian inflammatory reaction stimulates CYP17 activity, increasing ovarian androgen secretion [27, 45, 54].

7.2.3 Role of Androgen in Insulin Resistance

Hyperandrogenism is observed in at least 84.7% of PCOS patients, depending on the diagnostic criteria used [4, 5, 34]. Hyperandrogenic PCOS phenotypes (HA + OA + PCOM; HA + OA; HA + PCOM) have higher prevalence con IR, T2D, and dyslipidemia compared to non-hyperandrogenic PCOS phenotype (OA + PCOM) [23, 56]. Various studies have proposed that extremely low or high levels of androgens are associated with an increased risk of cardiovascular disease [57]. Daan et al. have shown that higher levels of androgens are associated with higher triglycerides and insulin, the prevalence of T2D and hypertension in different hyperandrogenic states in women, including PCOS [58].

Recent studies have shown a pleiotropic action of androgens over different organs that may lead to metabolic dysfunction in PCOS. Androgens play an essential role in body fat distribution, inducing android fat distribution. Obese and lean PCOS women have higher total body fat and visceral adipose tissue storage than BMI-matched controls [46, 47]. Moreover, under chronic flutamide treatment, PCOS women exhibit a decrease in abdominal fat depots [54]. In vitro studies have shown that androgens increase the size of adipocytes in subcutaneous adipose tissue [54, 59]. Hypertrophic adipocyte is more susceptible to local inflammation, macrophage infiltration that may impair insulin sensitivity, leading to ATD [49]. HA reduces the lipolytic rate of the adipose tissue, leading to an excessive depot of lipids in the cell. Excessive lipid accumulation causes lipotoxicity. This phenomenon is characterized by an impaired function of the endoplasmic reticulum and mitochondria, which finally increases insulin resistance on the cell [49]. Androgens also modulate adipokine secretion by the adipose tissue. Several studies have shown testosterone reduces adiponectin secretion, which is a crucial factor of insulin resistance development as stated earlier [49, 55].

HA also has adverse effects on skeletal muscle. Higher androgens levels are associated with reduced insulin-stimulated glucose uptake. Other studies have found that HA is associated with a diminished capillary density in the skeletal muscle, thereby hampering insulin access and insulin action in muscle cells [45, 54].

The high ovarian androgen production observed in PCOS is mainly due to increased androgen synthesis by ovarian theca cells. In vitro studies have shown that PCOS theca cells are more sensitive to insulin and LH-stimulated androgen secretion than those from healthy women [41]. The increased sensitivity is due to a higher expression of steroidogenic proteins and enzymes, such as StAR, 3-BHSD, cytochrome P450c17, that leads to HA [34, 39]. Additionally, an intrinsic cytochrome P450c17 hyperactivity even in the absence of LH or insulin stimuli [31].

7.3 Metabolic Syndrome, Hyperandrogenism, and Follicular Growth Arrest in PCOS

As described in previous sections of this chapter, PCOS has a complex pathophysiology that strongly links IR and HA.

The accumulated data suggest the presence of a common mechanism that leads to the development of the metabolic syndrome and follicular growth arrest in PCOS. Multiple studies have demonstrated that insulin and androgens receptors are also present in the hypothalamus and pituitary. Animal model studies have shown that insulin can increase LH pulse frequency and secretion. Euglycemic-hyperinsulinemic clamp studies have shown that hyperinsulinemia increases GnRH pulse frequency, LH pulse amplitude, and secretion in PCOS women [35]. A higher LH pulse frequency and amplitude of LH are also observed in lean PCOS, suggesting an inherent impaired pituitary function [35].

Ovarian HA causes a higher androgen influx to the adipocytes. HA increases aromatase activity leading to higher estradiol secretion from the adipose tissue [55]. Higher androgens and estradiol levels exert a negative feedback over FSH secretion, reducing FSH secretion [34]. These events lead to an increase in the LH:FSH ratio [10, 15, 27, 34]. Lower FSH levels are associated with lower aromatase activity in the granulosa. It has also been observed that under HA reduces granulosa cell proliferation and causing the resistance to FSH action [10]. According to the latter, granulosa cell dysfunction appears to contribute to theca cell overproduction of androgens.

These data suggest that IR and HA can lead to a higher LH/FSH ratio and a lower FSH sensitivity of granulosa cells, causing antral follicle growth impairment and follicular growth arrest in PCOS [15]. This way, a vicious circle in PCOS has been described, where hyperandrogenism favors abdominal fat accumulation and insulin resistance (Fig. 7.2). That reciprocally facilitates the hypersecretion of androgens in PCOS patients [27, 44, 60].

According to the mechanism described above, obesity has a binary effect over follicle arrest: (1) it could induce or worsen IR inducing increasing LH:FSH ratio and androgen secretion, and (2) a direct effect over the ovary leading to intraovarian hyperandrogenism and local inflammation.

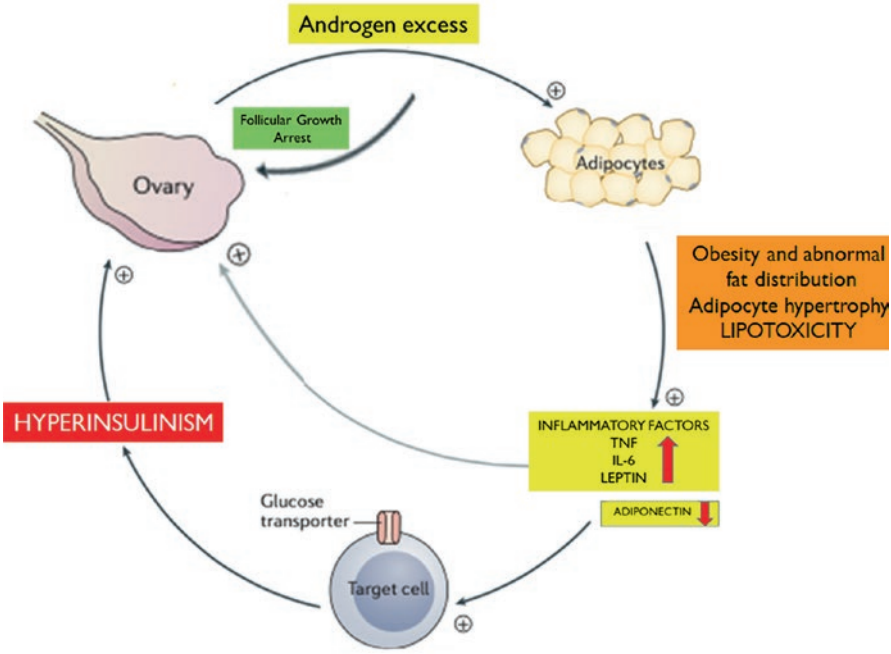

Fig. 7.2 Role of adipose tissue in insulin resistance and hyperandrogenemia. A vicious circle between abdominal fat accumulation and hyperandrogenism is observed in PCOS. Hyperandrogenism favors abdominal fat accumulation and insulin resistance. Adipose tissue excess facilitates the hypersecretion of androgens in PCOS patients by adipose tissue dysfunction. Deregulation of adipokine secretion, low-grade chronic inflammation, and lipotoxicity are observed. This phenomenon leads to hyperandrogenemia and follicle growth arrest, affecting the LH/FSH ratio and a direct effect on the ovary. (Adapted from [27])

These findings are strengthened by the fact that weight loss of abdominal fat reduction in PCOS women recovers regular menses, ovulation, and clinical pregnancy. These data suggest that weight loss could restore folliculogenesis in some PCOS phenotypes. Thus it has become one of the main recommendations for the management of PCOS to improve fertility and reduce long-term complications.

7.4 Intraovarian Mechanism of Follicular Growth Arrest in PCOS

Folliculogenesis is divided into two phases: a gonadotropin-independent period and a gonadotropin-dependent period. The gonadotropin-independent period comprehends the growth from primordial to the small antral follicle and is regulated mainly by local growth factors. On the other hand, the gonadotropin-dependent period comprehends the growth from small antral follicles to the Graafian follicle. FSH

and LH mainly regulate the selection, dominance process. The impaired LH and FSH secretion observed in PCOS, and its mechanism described above can explain the absence of selection and follicle dominance that are part of the follicular growth arrest. Nevertheless, it does not explain the stockpiling and persistence of the small antral follicle in the ovarian cortex.

In the last years, a significant amount of data has been generated in the knowledge of intraovarian control of gonadotropin-independent follicle growth and some of the mechanisms underlying the accumulation and persistence of small antral follicles.

7.5 Anti-Müllerian Hormone (AMH) and Follicular Growth Arrest

AMH is a glycoprotein hormone belonging to the TGF-β superfamily. It is secreted by granulosa cells of preantral and small antral follicles [14, 16]. This hormone controls two critical stages: it inhibits the growth from the primordial-to-primary follicle stage. It inhibits the selection of small antral follicles that enter the gonadotropin-dependent period [61].

AMH plays an inhibitory role in follicular development, preventing the premature recruitment and maturation of follicles [62]. AMH secretion is maximal at the preantral and small antral stages in human follicles, and decreases in the large follicle PCOS ovaries have a higher number of pre-antral and antral follicles, indicating that follicular growth arrest occurs when AMH production is high [63]. Multiple studies have documented higher AMH levels in PCOS women than healthy women [64–67]. Moreover, other studies have suggested that AMH levels reflect the severity of PCOS [68]. MH levels are higher in anovulatory PCOS women compared with ovulatory PCOS women [69]. Hypersecretion of AMH by granulosa cells could impair follicular growth. AMH could increase FSH threshold small antral follicles, reducing granulosa cell sensitivity to FSH in the luteal-follicular phase transition causing follicle growth arrest [70]. AMH also blocks androgen conversion into estrogens by inhibiting aromatase activity, causing hyperandrogenism [71, 72]. Other authors found that follicular AMH levels are negatively correlated with FSH concentrations, indicating that AMH levels predict follicle responsiveness to FSH in ovulation induction cycles [17, 73].

Several studies suggested that androgens increase the secretion of AMH, which regulates the growth of primordial follicles. Androgen-induced AMH expression provides negative feedback inhibiting follicle growth because of HA [10, 61]. Finally, AMH influences transcription of genes in granulosa cells through Smad proteins and regulates gene expression to maintain primordial follicles in their arrested state [16].

The cause of AMH increased production is unknown. However, other factors related to PCOS pathophysiology such as LH, and androgen levels may be implicated. LH increases AMH expression in granulosa cells of anovulatory PCOS women, but not in ovulatory PCOS women or normal women, suggesting a role for

LH in AMH overexpression inducing follicular arrest [74, 75] However, AMH appears primarily related to androgen status, suggesting a direct and predominant role of androgens in the pathophysiology of reproductive dysfunction including follicular growth arrest [10].

Several studies have shown that women with classic PCOS also have higher AMH, androgens levels [4, 5]. These phenotypes are frequently associated with ovulatory dysfunction, expressed as PCOM or OA [1–4]. HA and higher AMH levels inhibit follicle growth that is clinically observed by the presence of PCOM, ovulatory dysfunction, and a higher FSH threshold [10, 71]. Several studies have shown that weight loss, reduction of abdominal fat, or improvement of IR leads to a decrease in androgens levels, FSH follicle threshold, restoring follicle growth, and ovulation. Interestingly, this metabolic and reproductive improvement is not associated with a decrease of AMH levels [26, 34]. The latter suggests the presence of additional mechanisms responsible for follicular growth arrest.

7.6 Dysregulation of Ovarian Angiogenesis and Estrogen Metabolites in the Follicular Growth Arrest

Regulation of the ovary angiogenesis is critical for follicular growth and ovulation and the subsequent development and regression of the corpus luteum [19, 76]. Follicular atresia is associated with inadequate development of the thecal vasculature [77]. On the other hand, abnormalities of ovarian angiogenesis in PCOS increase the risk of ovarian hyperstimulation syndrome during ovulation induction [78, 79].

The importance of vascular endothelial growth factor (VEGF) in ovarian function is well known [80, 81]. Previous studies have shown that the HIF-1α/VEGF signaling pathway plays a crucial role in both angiogenesis and tumor growth [82, 83]. HIF-1α is known to regulate cellular adaptation to hypoxic conditions. Stabilized HIF-1α translocates to the nucleus and binds to the hypoxia-response elements of several target genes (such as VEGF) that are involved in the modulation of angiogenesis [82–84]. Additionally, FSH induces angiogenesis by stimulating HIF-1α expression and VEGF secretion [85, 86]. Previously, Levin et al. found a strong correlation between VEGF levels in follicular fluid (FF), follicle growth, and the number of mature oocytes retrieved in IVF cycles [87]. The latter suggests that an impaired follicle vascularization has adverse effects on oocyte maturation. VEGF expression is low during preantral follicle growth and increases in granulosa cells and theca cells through dominant follicle development [77].

Järvela et al. studied follicular vascularization in the follicle of PCOS and non-PCOS women undergoing controlled ovarian hyperstimulation for IVF treatment, using three-dimensional power Doppler ultrasound. These authors found a reduced follicular vascularization in ovaries of PCOS women compared to normal women after GnRH treatment but not after gonadotropin stimulation [88].

The latter suggests that an impaired follicle vascularization has adverse effects on oocyte maturation. It seems plausible that abnormal angiogenesis can be involved in the follicular growth arrest and infertility in PCOS.

On the other hand, the secretion of estradiol throughout the ovarian cycle depends upon follicle recruitment and selection of a single dominant follicle followed by the LH/FSH surge, which ends the program of FSH-dependent steroidogenesis [89]. Estrogens can be metabolized in the ovary by alternative pathways to form estrogen metabolites with endogenous action (EMs). It has been established that other signaling pathways rather than the classical estradiol receptor pathway mediate EMs action [90, 91].

We have extensively studied the role of VEGF and EMs in ovarian angiogenesis, particularly in human corpus luteum function. We found that EMs such as 2-methoxyestradiol (2-ME2) and 2-methoxyestrone (2-ME1) have an anti-angiogenic effect. On the other hand, 16-ketoestradiol (16-kE2) and 4-hydroxyestrone (4-OHE1) have a pro-angiogenic effect, during the development and regression of corpus luteum [84, 92, 93]. Interestingly, these metabolites also participate in follicular development.

Data recently published by our group have demonstrated, for the first time, the importance of pro-angiogenic estrogen metabolites in healthy follicular development and follicular growth arrest in PCOS. In unstimulated ovarian cycles, we have found lower pro-angiogenic EMs and VEGF levels in the follicular fluid (FF) of small antral follicles of PCOS women compared to fertile women with regular menstrual cycles [[20], in press] (Table 7.1). On the other hand, in the IVF-stimulated cycles, the exogenous gonadotropin administration increases pro-angiogenic EMs and VEGF FF levels in PCOS and control women. Similar pro-angiogenic EMs and VEGF levels in FF were found in PCOS compared to control women in IVF treatment for male infertility at the time of oocyte pick up [[20], in press]. These data suggest that the administration of exogenous gonadotrophins during ovulation induction increases intrafollicular angiogenic factors and angiogenesis in PCOS, restoring follicular growth. The latest results are in agreement with previous publications that showed the presence of a pro-angiogenic intrafollicular environment in PCOS women undergoing IVF treatment [94]. These data strongly suggest the

Table 7.1 Intrafollicular levels of AMH, VEGF and estrogens metabolites (EMs) in follicle of women with spontaneous cycles and PCOS women with follicular arrest

	Ovulary (n = 10) (antral follicle)	PCOS (n = 10) (antral follicle)	Ovulatory (n = 10) (dominant follicle)
AMH (ng/mL)	213.2 ± 28.0	546 ± 16.7[a]	2.9 ± 0.09[b]
VEGF (pg/mL)	503.2 ± 101.40	33.1 ± 5.9[a]	6529.6 ± 514.3[b]
∑EMs pro-angio/ ∑EMs anti-angio ratio	1.59	0.35[a]	1.15

Note: ∑ EMs = sum of estrogens metabolites
EMs pro-angio (2-OHE2, 16KE2, 4-OHE1). EMs anti-angio (2-ME2, 2-ME1)
[a]Comparing the difference between antral follicles of ovulatory and PCOS women ($P < 0.05$). Values are mean ± SEM
[b]Comparing the difference between antral and dominant follicles of ovulatory women ($P < 0.05$). Values are mean ± SEM

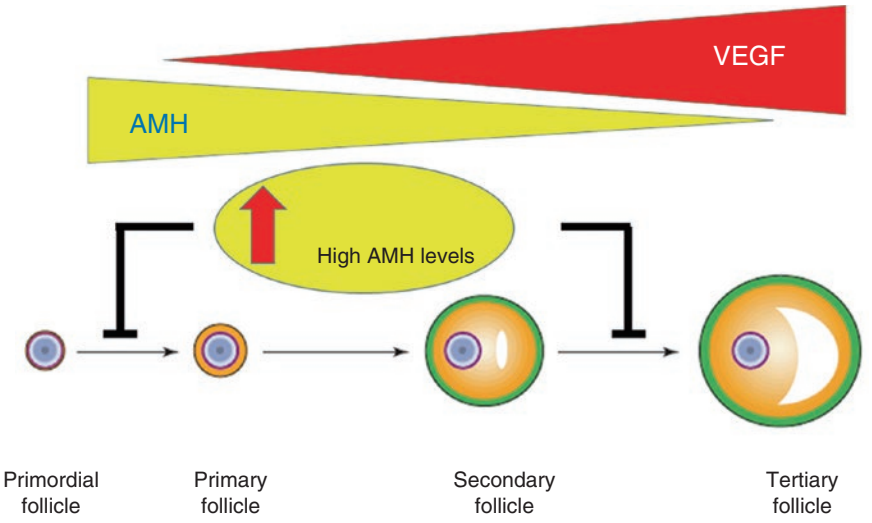

Fig. 7.3 Anti-müllerian hormone and follicle growth. AMH is secreted by granulosa cells of pre-antral and small antral follicles. It controls two critical stages in follicle growth. Higher AMH expression in PCOS follicle may impair follicular growth. The possible mechanisms involved are the inhibition of aromatase activity and estradiol secretion, an increase of the FSH threshold of small antral follicles leading to an FSH resistance, and diminished vascularization due to a decrease of proangiogenic EMs and VEGF intrafollicular levels

importance of angiogenesis in follicular growth, suggesting that an altered balance of pro- and anti-angiogenic factors could induce follicular arrest observed in PCOS.

As we mentioned earlier, AMH plays a crucial role in PCOS pathogenesis (Fig. 7.3). Previous publications have shown that AMH inhibits TGF beta signaling pathways, leading to decreased cell differentiation and angiogenesis [95]. In a recent study, we found high AMH levels and low VEGF and pro-angiogenic EMs levels in FF of arrested follicles of PCOS women in unstimulated cycles ([20], in press). In summary, high AMH levels present in PCOS reduce sensitivity to FSH and are detrimental to follicular angiogenesis, resulting in follicular growth arrest.

7.7 Conclusions

PCOS is one of the most frequent endocrine diseases in women. It was initially described as a reproductive disease. However, growing data have shown a strong association with metabolic dysfunction.

Ovulatory dysfunction and metabolic syndrome are more frequently found in severe PCOS phenotypes. Insulin resistance and hyperandrogenemia are critical factors in PCOS pathophysiology and are strongly interrelated. A vicious circle where hyperandrogenism favors abdominal fat accumulation and insulin resistance has been described in PCOS. Furthermore, IR reciprocally facilitates the hypersecretion of androgens in PCOS patients.

In the last years, several mechanisms responsible for follicular growth arrest have been described. Extraovarian mechanism of follicle arrest demonstrates a crucial role of inheriting or acquired insulin resistance, because abdominal fat accumulation can induce or worsen hyperandrogenism in PCOS. Hyperandrogenism and HI can cause an impairment of FSH and LH secretion, leading to follicle arrest. The improvement of the MS by weight loss or medical treatment can restore follicle growth ovulation in some PCOS phenotypes, but not in all of them.

Different intraovarian mechanisms of follicular growth arrest have been recently suggested:

- Hyperinsulinemia is associated with theca cell hyperplasia and higher secretion of androgens.
- Intraovarian hyperandrogenism is associated with diminished atresia of theca cells.
- Higher AMH expression in PCOS follicle granulosa cells impairs follicular development and estradiol secretion by inhibiting aromatase activity.
- Higher AMH levels increase the FSH threshold of small antral follicles, leading to an FSH resistance.
- Higher AMH levels in FF are associated with lower proangiogenic EMs and VEGF intrafollicular level.

These data suggest that PCOS has an altered intrafollicular environment characterized by impaired theca-granulosa communication and higher AMH levels that decrease follicle FSH sensitivity and reduce angiogenesis, leading to follicular growth arrest. This inherent ovarian condition can be deteriorated by an extraovarian factor such as insulin resistance secondary to abnormal fat distribution or obesity.

The latter exemplifies the complex endocrine and paracrine mechanism related to metabolic follicle syndrome and its relation to follicle growth arrest in PCOS.

The precise mechanism that causes hyperandrogenism and hyperinsulinism and follicle growth arrest in a specific PCOS phenotype is not fully understood. Until now, PCOS treatment is based on reducing IR by weight loss, insulin sensitizers, and ovarian gonadotropin stimulation to improve hyperandrogenemia, metabolic syndrome, and restore follicle growth.

Future studies necessary to design a tailored treatment to tackle the predominant mechanism in a specific PCOS phenotype are needed.

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