

# Emerging concepts about prenatal genesis, aberrant metabolism and treatment paradigms in polycystic ovary syndrome

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**Abstract** The interactive nature of the 8th Annual Meeting of the Androgen Excess and PCOS Society Annual Meeting in Munich, Germany (AEPPOS 2010) and subsequent exchanges between speakers led to emerging concepts in PCOS regarding its genesis, metabolic dysfunction, and clinical treatment of inflammation, metabolic dysfunction, anovulation and hirsutism. Transition of care in congenital adrenal hyperplasia from

pediatric to adult providers emerged as a potential model for care transition involving PCOS adolescents.

**Keywords** Developmental programming · Inflammation · Advanced glycosylated end products · Congenital adrenal hyperplasia · Hirsutism · Statins · Clomiphene citrate · Aromatase inhibitors · Metformin · Lifestyle intervention

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## Introduction

Depending on the diagnostic criteria, PCOS is found in ~6–10 % (NIH) or ~15 % (Rotterdam) of women in their reproductive years [1] and is characterized by androgen excess, ovulatory dysfunction, and polycystic ovaries [2]. While PCOS contributes to ~75 % of anovulation-related infertility [3], it also accounts for 12–28 % of overweight and obese (BMI  $\geq$  25) women, 15–36 % of women with type 2 diabetes mellitus (type 2 DM) [4–7], and doubling of the lifetime risk for cardiovascular disease [8]. Women with “classic” PCOS, diagnosed by NIH criteria alone, have greater risk of cardiovascular disease and type 2 DM than those diagnosed by non-NIH criteria [8, 9]. Genetic susceptibility loci for PCOS, identified by recent genome-wide association studies, particularly implicate genes involved in cytoplasmic function in multiple organ systems, including thyroid adenoma associated protein (THADA) [10–12] and DENN/MADD domain containing 1A (DENND1A) [10, 11]. Polymorphisms of genes involved in glucose homeostasis, including adipocyte fatty acid binding protein (FABP4) [13] and adiponectin [14], are also associated with PCOS, but PCOS-linked variants differ from those associated with type 2 DM [15].

Typical of a complex disease, however, progress in PCOS treatment has been limited due to incomplete knowledge of its pathogenesis, despite its high heritability [16, 17]. What is clear, nevertheless, is that pre- or peripubertal metabolic dysfunction is one of the first phenotypic traits observed in adolescent girls likely to develop PCOS [18, 19]. This is alarming as obesity now affects ~15 % of American children [20, 21]. Obesity commonly associates with peri-pubertal hyperandrogenemia in girls [22–26], a trait combination increasingly considered antecedent to PCOS [27, 28].

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AEPCOS 2010 provided an update regarding multiple aspects of PCOS, including its potential genesis, inflammation as an initiator of and/or contributor to PCOS, and emerging treatment paradigms related to inflammation, metabolic dysfunction, anovulation, and hirsutism. While the major focus of the meeting related to PCOS, three other relevant areas were also highlighted: (1) transition of care in congenital adrenal hyperplasia (CAH) from pediatric to reproductive/internal medicine endocrinology [29, 30] that may provide a model for clinical transition of PCOS adolescents, (2) androgen influences on the pilo-sebaceous unit and treatment options [31], and (3) the recently formed Australian National Polycystic Ovary Syndrome Alliance (<http://www.adelaide.edu.au/robinson-institute/mediareleases/pcos/>), an organization comprising PCOS patients and their close relatives, together with researchers and health care professionals, that is developing evidence-based guidelines and multidisciplinary care models that promise comprehensive care solutions targeted on prevention of PCOS complications [32].

## Prenatal genesis of PCOS: is there a role for prenatal androgens?

Female mammalian fetuses exposed to fetal male levels of testosterone (T) express PCOS-like reproductive and metabolic traits in adulthood [2, 33–35]. Exposing fetal males to similar gestational treatment [36, 37] induces abnormalities in male reproductive and metabolic function. Reproductive consequences in T-exposed rams include reduced number and motility of spermatozoa [38], accompanied by higher numbers of Sertoli cells and fewer germ cells per seminiferous tubule [39]. Endocrine abnormalities accompanying male germ cell abnormalities include increases in (1) FSH responsiveness to GnRH analog treatment, (2) amplitude of spontaneously occurring LH pulses, and (3) testicular receptor expression for FSH and transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1), together with a negative correlation between anti-müllerian hormone (AMH) and TGF- $\beta$ 3 expression [38, 39]. Taken together, these findings suggest that prenatal exposure to exogenous T in males may act as an endocrine disruptor, leading to an altered adult testicular environment that includes disruption of the blood–testis barrier and diminished spermatogenesis. In humans, close male relatives of women with PCOS have comparable metabolic dysfunction to their PCOS female kin, including dyslipidemia and insulin resistance that are accompanied by elevated DHEAS concentrations [40–44]. Results from T-exposed rams suggest that male relatives of women with PCOS warrant investigation of their fertility.

In T-exposed female monkeys, daily subcutaneous injections of T propionate into their dams contribute to transient hyperglycemia derived from mild-to-moderate

maternal glucose intolerance [45]. T-exposed females exhibit subtle increases in both fetal and neonatal body size and a degree of transient newborn hypoglycemia. T-exposed female infants have a relative hyperinsulinemic response to glucose [45]. Such insulin hypersecretion in insulin sensitive, T-exposed female infants may explain their modest weight gain, due to insulin's anabolic actions, that may lead to increased weight accumulation prior to puberty. As preadolescent and adolescent daughters of women with PCOS show subtle hyperinsulinemia from insulin resistance before manifesting an obvious PCOS phenotype [46, 47], prepubertal insulin defects may provide important developmental precursors in the expression of adult PCOS [2], as suggested by both PA monkey and sheep models [34, 45]. Evidence of fetal T-exposure preceding PCOS in women, however, is still inconclusive with studies of umbilical cord blood showing increased [48] or decreased [49] androgen levels among newborn daughters of women with PCOS. Interestingly, an epigenomics study of PA monkeys implicates altered TGF- $\beta$  signaling in the most significantly differentially methylated pathways in both infants and adults [50], suggesting that PA monkeys may epigenetically mimic PCOS in women. In support of this notion, a dinucleotide repeat (D19S884) that maps to intron 55 within the fibrillin 3 (*FBN3*) gene has been the most consistent genetic region associated with familial PCOS [51, 52]. Since the degree and type of fibrillin expression contributes to differences in elasticity of cell-extracellular matrix interactions and storage of TGF- $\beta$ , fibrillins may provide gestationally relevant [53], tissue-specific foundations for cell-mediated engagement of extracellular matrix-stored TGF- $\beta$  in proliferation, differentiation, and apoptosis [54, 55] that may engender PCOS.

### **Pediatric to adult transition of endocrine clinical care in CAH: lessons for management of adolescent girls with PCOS**

In order to enable patients with CAH to become productive, responsible citizens, transition from pediatric to adult health care needs to be a purposeful, planned transfer between providers [56–58]. An assessment of patient readiness should consider medical, psychosocial, educational, cognitive, emotional, and vocational needs. Expectations and differences in health care delivery systems between pediatric and adult care will be experienced, including a shift in treatment goals from a focus on linear growth and “on-time” puberty to concerns related to fertility, sexuality, bone health, and risks for cardiovascular disease.

Adolescents may feel uncomfortable in both pediatric and adult waiting rooms. Pediatricians, staff, and parents may have difficulty “letting go” and transferring their

long-term relationship to adult healthcare providers. Over-involvement of parents can lead to adolescents feeling excluded and thwarted from participating in their own health care; ultimately this undermines the adolescent's emerging autonomy and self-responsibility [59]. Parents need to make the transition from being the “CEO” of their child's health care to becoming the consultant, and eventually, a bystander while the child ascends from a consumer to the “CEO” [60]. There are thus relationship reconfigurations from doctor–parent–patient to doctor–patient.

Patient behaviors such as texting and playing games on cell phones, increased risk-taking behavior, poor adherence to recommendations, and disinterest in participating in discussions frustrate health care providers and parents. Adult health care providers assume that their adolescent and young adult patients are active partners who are knowledgeable about their disorder, are autonomous, and are capable of negotiating the health care system. Some adolescents, however, especially those with chronic disorders, may be unprepared and unready to participate as an active partner in their own health care. Suboptimal transitions can lead to mediocre connections with adult health-care providers that can culminate in “drop-out” from healthcare.

Knowledge about self-management does not always predict good adherence. For some CAH adolescents and young adults, non-adherence to recommendations may represent a conscious decision to minimize the intrusiveness of the disease. Problem solving or brainstorming discussions to find creative solutions regarding adherence to the recommended management regimens and transition to adult healthcare may be invaluable, and may enable care transition in hyperandrogenic adolescent girls at risk for PCOS [61], in addition to those who manifest CAH.

### **Inflammation in PCOS: is it the initiator or just a contributor to metabolic dysfunction?**

While obesity provides a considerable proinflammatory contribution to PCOS [62], elevated levels of proinflammatory markers, including monocyte chemo-attractant protein-1, are discernible independent of obesity [63–65]. Other features include increased lipid peroxidation, increased markers of endothelial dysfunction, and decreased haptoglobin concentrations. Evidence is accumulating that inflammation may contribute to the genesis of PCOS [66]. Hyperandrogenism, whether extant in women with PCOS or induced by androgen therapy in normal women, enhances an inflammatory response in mononuclear (pre-macrophage) leukocytes when they are exposed to a hyperglycemic environment equivalent to

glucose intolerance or poorly controlled diabetes [67]. Such inflammatory-prone macrophages can infiltrate both ovaries and adipose depots, enhancing androgen biosynthesis and cytokine release, respectively [66].

Not surprisingly, therefore, inflammation and metabolic dysfunction are frequent co-morbidities among women with PCOS. Advanced glycated end products (AGEs) are a class of nutrients implicated in the pathogenesis of cardio-metabolic disturbances, insulin resistance, and possibly, direct ovarian dysfunction. AGEs are products of non-enzymatic glycation and oxidation of proteins from endogenous or exogenous (dietary) sources that are known to accumulate in diverse clinical conditions or developmental stages, including type 2 DM, renal failure, and aging [68]. In women with PCOS, circulating AGEs concentrations are increased, independently of obesity, and are positively correlated with T and AMH concentrations [69, 70]. Immunohistochemical localization of (AGEs) and their receptor (RAGE) are increased in polycystic compared to normal ovaries [71]. In the ovarian microenvironment of PCOS, AGEs may contribute to insulin resistance, dysregulation of folliculogenesis, ovarian steroidogenesis and altered collagen synthesis [70, 71]. In the latter regard, as AGEs stimulate extracellular matrix production and abnormal collagen cross-linking in the ovary [72], they may contribute to altered TGF- $\beta$  signaling in the PCOS ovary. Reduced dietary intake of AGEs improves metabolic and reproductive aspects of PCOS [69], and may thus ameliorate progression of PCOS symptomatology.

### **Emerging treatment paradigms in PCOS: approaches to ameliorate metabolic aberration, anovulatory infertility and hirsutism**

#### **Metabolic aberration**

Statins, competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, interfere with cholesterol synthesis, ultimately improving lipid profiles and decreasing inflammation. Primarily due to statin-induced inhibition of isoprenylation, *in vitro* studies have demonstrated that statins inhibit proliferation of, and diminish androgen production in, ovarian theca-interstitial cells [73–75]. Statins may thus offer many advantages for women with PCOS. Specifically, statins reduce hyperandrogenism, improve lipid profiles, and decrease levels of several markers of inflammation and endothelial dysfunction including C-reactive protein, soluble vascular cell adhesion molecule-1 (sVCAM), IL-1 $\beta$ , IL-6, and TNF- $\alpha$  [76–79].

The Diabetes Prevention Program study demonstrates, that in the general population, both metformin and intensive lifestyle modification reduce incident type 2 DM, and

when successful, lifestyle modification is more efficacious than metformin [80]. Lifestyle intervention, involving dietary action, exercise and psychological help, remains an important first-line therapy for management of the metabolic syndrome in women with PCOS [32, 81]. Measurement of AMH appears to be a predictor of response to lifestyle intervention [82]. Metformin treatment, alone or in combination with lifestyle modification, has been helpful to ameliorate metabolic syndrome risk factors among women with PCOS [83, 84]. Specifically, obese women with PCOS, and those with features of the metabolic syndrome at presentation, appear to particularly benefit from metformin treatment in terms of higher HDL cholesterol, lower diastolic blood pressure, and lower BMI [84]. In the future, genetic polymorphisms may categorize women as potential responders and non-responders to metformin treatment [84, 85]. The magnitude of weight loss, rather than the specific agent or modality for lifestyle intervention, appears to be more important for metabolic improvement [86, 87].

#### **Anovulatory infertility**

With regard to enabling ovulation induction, metformin in addition to clomiphene citrate (CC) and aromatase inhibitors (AIs), provides distinct clinical opportunities and challenges. The advantages of CC as the first-line option for ovulation induction [88] include extensive, long-term experience with its use, low cost, and efficacy. Yet, its mixed agonist/antagonist profile, together with an increased potential for multiple births and their sequelae, encourage consideration of other options [89]. Laparoscopic ovarian drilling (LOD) is considered a second-line treatment option for PCOS women who are CC resistant, and appears equally effective as gonadotropins, but with fewer multiple pregnancies [32]. LOD in PCOS women with less pronounced hyperandrogenism and insulin resistance improves subsequent ovulatory responses to CC in about one-third of cases [90].

One alternative to CC involves using the AIs, letrozole and anastrozole, which decrease estrogen concentrations without affecting estrogen receptor action [91]. The efficient estrogen-lowering properties of AIs temporarily release the hypothalamus from the negative feedback effect of estrogen inducing an increased discharge of FSH. Although the end result of an increased discharge of FSH is common to both AIs and CC, AIs have no direct effect on estrogen receptors conferring several potential advantages for ovulation induction including: (1) no deleterious effect on cervical mucus or endometrium; (2) the negative feedback mechanism remains intact enabling regulation of the FSH discharge when estrogen is produced, thus reducing the prevalence of multiple follicle development, and consequently, of multiple pregnancies when compared to CC;

and (3) shorter half-life. Available data indicate that letrozole is as effective or more effective than CC, with fewer multiple pregnancies [91, 92] in terms of ovulation rate and pregnancy [93]. Inexplicably, letrozole remains off-label for induction of ovulation in most countries, despite clear evidence that it produces fewer congenital abnormalities than CC [94].

Metformin has multiple direct and indirect actions that benefit women with PCOS. Its effects on ovulation are likely to depend on several factors, such as the degree of insulin resistance and prevailing hyperinsulinemia [95], obesity [96], duration of treatment, influence of cytokines on insulin secretion, and direct action at the level of the ovary [97]. Although metformin should not be considered as a pro-ovulatory drug, short-term use may restore ovulation in ~20 % of anovulatory women with PCOS. In PCOS patients with anovulatory infertility who have not been previously treated, the administration of metformin plus CC is no more effective than CC alone [98, 99]. Treatment with metformin, however, may be helpful for clomiphene-resistant, non-obese women [32, 100]. Nevertheless, questions regarding its mechanism(s) of action, treatment protocol, and efficacy in ovulation induction remain to be addressed [101]. Randomized controlled trials are necessary to establish optimal ovulation induction treatment.

### Hirsutism

Androgens affect several functions of human skin, such as sebaceous gland growth and differentiation, hair growth, epidermal barrier homeostasis, and wound healing [102]. Not surprisingly, therefore, PCOS is one of the most common diagnoses associated with hirsutism (excessive hair growth in androgen-dependent areas). Hirsutism, quantified by a modified Ferriman–Gallway scoring system, is attributed to increases in circulating androgen concentrations, sensitivity of the pilo-sebaceous unit to androgens, or a combination of these. A thorough medical history and physical examination is necessary, however, to discriminate hirsutism from generalized excessive hair growth (hypertrichosis). The skin and the pilo-sebaceous unit express steroid hormone receptors and are capable of synthesizing several hormones, including androgens [31]. Over the past decade, steroid hormones, phospholipid hormones, and retinoids have all been shown to play pivotal roles in the development of pilo-sebaceous units, the lipogenesis of sebaceous glands, and hair cycling [103]. Common “cutaneous hyperandrogenism” skin disorders such as acne, androgenetic alopecia and seborrhea involve overexpression of androgen biosynthetic enzymes and hyper-responsiveness of androgen receptors [104], as the most patients exhibit normal circulating androgen levels [102, 105].

Hirsutism is not only a cosmetic problem, but can also diminish self-esteem while engaging anxiety and depression [106]. A multidisciplinary and individualized therapeutic approach is thus required [107]. Lifestyle changes and cosmetic measures are first-line therapeutic modalities. Pharmacological treatment includes topical eflornithine, oral contraceptive pills, anti-androgens, and insulin sensitizers [108]. Topical eflornithine may be used in women suffering from facial hirsutism as a single agent or as an adjuvant to medical treatment. Oral contraceptive pills are recommended for women with mild hirsutism or may be added to an antiandrogen drug as an adjuvant agent to reduce the hirsutism score and to prevent pregnancy. Oral contraceptives decrease ovarian androgen production, increase sex hormone binding globulin concentration, and decrease free T-concentrations [109]. The specific progestin used in an oral contraceptive influences the extent of the anti-androgenic action. Despite recent concerns about clustering of cardiovascular risk factors among women with PCOS, no unequivocal data showing adverse cardiometabolic outcomes with the use of oral contraceptives have been reported. Adjunctive anti-androgens include spironolactone, cyproterone acetate, finasteride and flutamide. Metformin is not particularly useful in treating hirsutism. Overall, systemic therapies reduce hair growth in <50 % of patients, thus hirsute women frequently require additional cosmetic measures [110].

Androgenic alopecia is another manifestation of androgen excess in which the pattern of hair loss differs between women and men. Women tend to show generalized thinning whereas men lose hair in distinct regions. Treatment includes reduction of DHT synthesis, androgen receptor blockade and attenuation of steroidogenesis [111]. Both hirsutism and androgenic alopecia would benefit from the development of specific inhibitors to 17,20 lyase, a key step in androgen biosynthesis beyond cortisol production, that would provide relief for androgen overproduction without diminishing endogenous glucocorticoid release [112].

### Conclusions

Studies into the pathogenesis of PCOS identify androgenic, glycemic, and inflammatory contributions that implicate disordered TGF- $\beta$  signaling and suggest mechanistic commonality in affected male kin. Novel approaches add and diversify the therapeutic options available to treat infertility in women with PCOS. PCOS signs and symptoms, including metabolic dysfunction and hirsutism, are ameliorated by lifestyle and/or therapeutic intervention. Enabling engaged and interactive transition from adolescent to adult healthcare in CAH patients provides insight



for care transition in PCOS. AEPCOS, within a brief period of 8 years, has encouraged an integrated understanding of androgen excess and PCOS through international conferences supporting educational discussion of major advances in the field, including those summarized herein.

**Conflict of interest** The authors have no conflicts of interest.

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