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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 & PCOS Society Annual Meeting in Munich, Germany (AEPCOS 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.

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Conflict of interest
The authors have no conflicts of interest.

Keywords

Developmental programming; clomiphene citrate; aromatase inhibitors; metformin; lifestyle intervention; advanced glycated end products; inflammation; statins; congenital adrenal hyperplasia; hirsutism

Introduction

PCOS is found in ~15% 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≥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 *THADA* (thyroid associated protein) [10, 11, 12] and *DENND1A* (DENN/MADD domain containing 1A) [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 peri-pubertal 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].

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 multi-disciplinary 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 [33–36]. Exposing fetal males to similar gestational treatment [37, 38] induces abnormalities in male reproductive and metabolic function. Reproductive consequences in T-exposed rams include reduced number and motility of spermatozoa [39], accompanied by higher numbers of Sertoli cells and fewer germ cells per seminferous tubule [40]. Endocrine abnormalities accompanying male germ

cell abnormalities include increases in 1) FSH responsiveness to GnRH analogue treatment, 2) amplitude of spontaneously occurring LH pulses, and 3) testicular receptor expression for FSH and transforming growth factor-β1 (TGF-β1), together with a negative correlation between anti-mullerian hormone (AMH) and TGF-β3 expression [39, 40]. 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 [41–45]. 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 [46]. 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 [46]. 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 [47, 48], prepubertal insulin defects may provide important developmental precursors in the expression of adult PCOS [34], as suggested by both PA monkey and sheep models [35, 46]. Evidence of fetal T-exposure preceding PCOS in women, however, is still inconclusive with studies of umbilical cord blood showing increased [49] or decreased [50] androgen levels among newborn daughters of women with PCOS. Interestingly, an epigenomic study of PA monkeys implicates altered TGF-β signaling in the most significantly differentially methylated pathways in both infants and adults [51], 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 [52, 53]. Since the degree and type of fibrillin expression contributes to differences in elasticity of cell-extracellular matrix interactions and storage of TGF-β, fibrillins may provide gestationally relevant [54], tissue-specific foundations for cell-mediated engagement of extracellular matrix-stored TGF-β in proliferation, differentiation and apoptosis [55, 56] 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 [57–59]. 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 [60].

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” [61]. 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 healthcare 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 [62], 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 [63], elevated levels of pro-inflammatory markers, including monocyte chemo-attractant protein-1, are discernible independent of obesity [64–66]. 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 [67]. Hyperandrogenism, whether extant in women with PCOS or induced by testosterone therapy in normal women, enhances an inflammatory response in mononuclear (pre-macrophage) lymphocytes when they are exposed to a hyperglycemic environment equivalent to glucose intolerance or poorly controlled diabetes [68]. Such inflammatory-prone macrophages can infiltrate both ovaries and adipose depots, enhancing androgen biosynthesis and cytokine release, respectively [67].

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 [69]. In women with PCOS, circulating AGEs concentrations are increased, independently of obesity, and are positively correlated with T and AMH concentrations [70, 71]. Immunohistochemical localization of (AGEs) and their receptor (RAGE) are increased in polycystic compared to normal ovaries [72]. In the ovarian microenvironment of PCOS, AGEs may contribute to insulin resistance, dysregulation of folliculogenesis, ovarian steroidogenesis and altered collagen synthesis [71, 72]. In the latter regard, as AGEs stimulate extracellular matrix production and abnormal collagen cross-linking in the ovary [73], they may contribute to altered TGF-β signaling in the PCOS

ovary. Reduced dietary intake of AGEs improves metabolic and reproductive aspects of PCOS [70], and may thus ameliorate progression of PCOS symptomology.

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 [74–76]. 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-1β, IL-6, and TNF-α [77–80].

The Diabetes Prevention Program study demonstrates, that in the general population, both metformin and intensive lifestyle modification reduce incident T2DM, and when successful, lifestyle modification is more efficacious than metformin [81]. 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, 82]. Measurement of AMH appears to be a predictor of response to lifestyle intervention [83]. Metformin treatment, alone or in combination with lifestyle modification, has been helpful to ameliorate metabolic syndrome risk factors among women with PCOS [84, 85]. 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 [85]. In the future, genetic polymorphisms may categorize women as potential responders and non-responders to metformin treatment [85, 86]. The magnitude of weight loss, rather than the specific agent or modality for lifestyle intervention, appears to be more important for metabolic improvement [87, 88].

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 [89] 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 [90]. 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 [91].

One alternative to CC involves using the AIs, letrozole and anastrozole, which decrease estrogen concentrations without affecting estrogen receptor action [92]. 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 [92, 93] in terms of ovulation rate and pregnancy [94]. Inexplicably, letrozole remains off-label for induction of ovulation in most countries, despite clear evidence that it produces fewer congenital abnormalities than CC [95].

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 [96], obesity [97], duration of treatment, influence of cytokines on insulin secretion, and direct action at the level of the ovary [98]. 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 [99, 100]. Treatment with metformin, however, may be helpful for clomiphene-resistant, non-obese women [32, 101]. Nevertheless, questions regarding its mechanism(s) of action, treatment protocol, and efficacy in ovulation induction remain to be addressed [102]. 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 [103]. 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 [104]. Common “cutaneous hyperandrogenism” skin disorders such as acne, androgenetic alopecia and seborrhea involve overexpression of androgen biosynthetic enzymes and hyper-responsiveness of androgen receptors [105], as most patients exhibit normal circulating androgen levels [103, 106].

Hirsutism is not only a cosmetic problem, but can also diminish self-esteem while engaging anxiety and depression [107]. A multidisciplinary and individualized therapeutic approach is thus required [108]. Life-style changes and cosmetic measures are first-line therapeutic modalities. Pharmacological treatment includes topical eflornithine, oral contraceptive pills, antiandrogens, and insulin sensitizers [109]. 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 testosterone concentrations [110]. 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 less than 50% of patients, thus hirsute women frequently require additional cosmetic measures [111].

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 [112]. 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 [113].

Conclusions

Studies into the pathogenesis of PCOS identify androgenic, glycemic and inflammatory contributions that implicate disordered TGF-β 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 eight 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.

References

1. Fauser BC, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, Carmina E, Chang J, Yildiz BO, Laven JS, Boivin J, Petraglia F, Wijeyeratne CN, Norman RJ, Dunaif A, Franks S, Wild RA, Dumesic D, Barnhart K. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril. 2012; 97:28–38.e25. [PubMed: 22153789]
2. Abbott DH, Tarantal AF, Dumesic DA. Fetal, infant, adolescent and adult phenotypes of polycystic ovary syndrome in prenatally androgenized female rhesus monkeys. Am. J. Primatol. 2009; 71:776–784. [PubMed: 19367587]
3. Franks S. Polycystic ovary syndrome. H. Engl. J. Med. 1995; 333:853–861.
4. Yildiz BO, Knochenhauer ES, Azziz R. Impact of obesity on the risk for polycystic ovary syndrome. J. Clin. Endocrinol. Metab. 2008; 93:162–168. [PubMed: 17925334]
5. Azziz R, Marin C, Hoq L, Badamgarav E, Song P. Health care-related economic burden of the polycystic ovary syndrome during the reproductive life span. J. Clin. Endocrinol. Metab. 2005; 90:4650–4658. [PubMed: 15944216]
6. Talbott EO, Zborowski JV, Rager JR, Kip KE, Xu X, Orchard TJ. Polycystic ovarian syndrome (PCOS): a significant contributor to the overall burden of type 2 diabetes in women. J. Womens Health (Larchmt). 2007; 16:191–197. [PubMed: 17388735]
7. Alvarez-Blasco F, Botella-Carretero JI, San Millan JL, Escobar-Morreale HF. Prevalence and characteristics of the polycystic ovary syndrome in overweight and obese women. Arch. Intern. Med. 2006; 166:2081–2086. [PubMed: 17060537]
8. Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, Futterweit W, Lobo R, Norman RJ, Talbott E, Dumesic DA. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. J. Clin. Endocrinol. Metab. 2010; 95:2038–2049. [PubMed: 20375205]
9. Dilbaz B, Ozkaya E, Cinar M, Cakir E, Dilbaz S. Cardiovascular disease risk characteristics of the main polycystic ovary syndrome phenotypes. Endocrine. 2011; 39:272–277. [PubMed: 21547513]

10. Chen ZJ, Zhao H, He L, Shi Y, Qin Y, Shi Y, Li Z, You L, Zhao J, Liu J, Liang X, Zhao X, Zhao J, Sun Y, Zhang B, Jiang H, Zhao D, Bian Y, Gao X, Geng L, Li Y, Zhu D, Sun X, Xu JE, Hao C, Ren CE, Zhang Y, Chen S, Zhang W, Yang A, Yan J, Li Y, Ma J, Zhao Y. Genome-wide association study identifies susceptibility loci for polycystic ovary syndrome on chromosome 2p16.3, 2p21 and 9q33.3. Nat Genet. 2011; 43:55–59. [PubMed: 21151128]
11. Goodarzi MO, Jones MR, Li X, Chua AK, Garcia OA, Chen YD, Krauss RM, Rotter JI, Ankener W, Legro RS, Azziz R, Strauss JF 3rd, Dunaif A, Urbanek M. Replication of association of DENND1A and THADA variants with polycystic ovary syndrome in European cohorts. J Med Genet. 2012; 49:90–95. [PubMed: 22180642]
12. Zhao H, Xu X, Xing X, Wang J, He L, Shi Y, Shi Y, Zhao Y, Chen ZJ. Family-based analysis of susceptibility loci for polycystic ovary syndrome on chromosome 2p16.3, 2p21 and 9q33.3. Hum Reprod. 2012; 27:294–298. [PubMed: 22081247]
13. Hu W, Qiao J. Expression and regulation of adipocyte fatty acid binding protein in granulosa cells and its relation with clinical characteristics of polycystic ovary syndrome. Endocrine. 2011; 40:196–202. [PubMed: 21720879]
14. Jia H, Yu L, Guo X, Gao W, Jiang Z. Associations of adiponectin gene polymorphisms with polycystic ovary syndrome: a meta-analysis. Endocrine. 2012 Jan 22. [Epub ahead of print].
15. Saxena R, Welt CK. Polycystic ovary syndrome is not associated with genetic variants that mark risk of type 2 diabetes. Acta Diabetol. 2012 Mar 3. [Epub ahead of print].
16. Legro RS, Driscoll D, Strauss JF 3rd, Fox J, Dunaif A. Evidence for a genetic basis for hyperandrogenemia in polycystic ovary syndrome. Proc. Natl. Acad. Sci. U.S.A. 1998; 95:14956–14960. [PubMed: 9843997]
17. Vink JM, Sadrzadeh S, Lambalk CB, Boomsma DI. Heritability of polycystic ovary syndrome in a Dutch twin-family study. J. Clin. Endocrinol. Metab. 2006; 91:2100–2104. [PubMed: 16219714]
18. Coviello AD, Legro RS, Dunaif A. Adolescent girls with polycystic ovary syndrome have an increased risk of the metabolic syndrome associated with increasing androgen levels independent of obesity and insulin resistance. J. Clin. Endocrinol. Metab. 2006; 91:492–497. [PubMed: 16249280]
19. Marshall JC. Obesity in adolescent girls: is excess androgen the real bad actor? J. Clin. Endocrinol. Metab. 2006; 91:393–395. [PubMed: 16461952]
20. Dietz WH. Health consequences of obesity in youth: childhood predictors of adult disease. Pediatrics. 1998; 101:518–525. [PubMed: 12224658]
21. Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. JAMA. 2004; 291:2847–2850. [PubMed: 15199035]
22. McCartney CR, Prendergast KA, Chhabra S, Eagleson CA, Yoo R, Chang RJ, Foster CM, Marshall JC. The association of obesity and hyperandrogenemia during the pubertal transition in girls: obesity as a potential factor in the genesis of postpubertal hyperandrogenism. J. Clin. Endocrinol. Metab. 2006; 91:1714–1722. [PubMed: 16492701]
23. McCartney CR. Maturation of sleep-wake gonadotrophin-releasing hormone secretion across puberty in girls: potential mechanisms and relevance to the pathogenesis of polycystic ovary syndrome. J. Neuroendocrinol. 2010; 22:701–709. [PubMed: 20492363]
24. Blank SK, McCartney CR, Helm KD, Marshall JC. Neuroendocrine effects of androgens in adult polycystic ovary syndrome and female puberty. Semin. Reprod. Med. 2007; 25:352–359. [PubMed: 17710731]
25. Blank SK, McCartney CR, Marshall JC. The origins and sequelae of abnormal neuroendocrine function in polycystic ovary syndrome. Hum. Reprod. Update. 2006; 12:351–361. [PubMed: 16670102]
26. McCartney CR, Blank SK, Prendergast KA, Chhabra S, Eagleson CA, Helm KD, Yoo R, Chang RJ, Foster CM, Caprio S, Marshall JC. Obesity and sex steroid changes across puberty: evidence for marked hyperandrogenemia in pre- and early pubertal obese girls. J. Clin. Endocrinol. Metab. 2007; 92:430–436. [PubMed: 17118995]
27. Rosenfield RL. Clinical review: Identifying children at risk for polycystic ovary syndrome. J. Clin. Endocrinol. Metab. 2007; 92:787–796. [PubMed: 17179197]

28. Geller DH, Pacaud D, Gordon CM, Misra M. of the Drug and Therapeutics Committee of the Pediatric Endocrine Society. State of the Art Review: Emerging Therapies: The Use of Insulin Sensitizers in the Treatment of Adolescents with Polycystic Ovary Syndrome (PCOS). Int. J. Pediatr. Endocrinol. 2011 Aug 26.2011:9. [PubMed: 21899727]
29. Witchel SF, Azziz R. Congenital adrenal hyperplasia. J Pediatr Adolesc Gynecol. 2011; 24:116–126. [PubMed: 21601808]
30. Auchus RJ, Witchel SF, Leight KR, Aisenberg J, Azziz R, et al. Guidelines for the Development of Comprehensive Care Centers for Congenital Adrenal Hyperplasia: Guidance from the CARES Foundation Initiative. Int J Pediatr Endocrinol. 2011; 2010(2010):275213. Epub 2011 Jan 10. [PubMed: 21274448]
31. Chen WC, Zouboulis CC. Hormones and the pilosebaceous unit. Dermatoendocrinol. 2009; 1:81–86. [PubMed: 20224689]
32. Teede HJ, Misso ML, Deeks AA, Moran LJ, Stuckey BG, Wong JL, Norman RJ, Costello MF. Guideline Development Groups. Assessment and management of polycystic ovary syndrome: summary of an evidence-based guideline. Med J Aust. 2011; 195:S65–S112. [PubMed: 21929505]
33. Dumesic DA, Abbott DH, Padmanabhan V. Polycystic ovary syndrome and its developmental origins. Rev. Endocr. Metab. Disord. 2007; 8:127–141. [PubMed: 17659447]
34. Abbott DH, Tarantal AF, Dumesic DA. Fetal, infant, adolescent and adult phenotypes of polycystic ovary syndrome in prenatally androgenized female rhesus monkeys. Am. J. Primatol. 2009; 71:776–784. [PubMed: 19367587]
35. Padmanabhan V, Veiga-Lopez A, Abbott DH, Recabarren SE, Herkimer C. Developmental programming: impact of prenatal testosterone excess and postnatal weight gain on insulin sensitivity index and transfer of traits to offspring of overweight females. Endocrinology. 2010; 151:595–605. [PubMed: 19966179]
36. Roland AV, Nunemaker CS, Keller SR, Moenter SM. Prenatal androgen exposure programs metabolic dysfunction in female mice. J. Endocrinol. 2010; 207:213–23. [PubMed: 20713501]
37. Veiga-Lopez A, Steckler TL, Abbott DH, Welch KB, MohanKumar PS, Phillips DJ, Refsal K, Padmanabhan V. Developmental programming: impact of excess prenatal testosterone on intrauterine fetal endocrine milieu and growth in sheep. Biol. Reprod. 2011; 84:87–89. [PubMed: 20739662]
38. Bruns CM, Baum ST, Colman RJ, Eisner JR, Kemnitz JW, Weindruch R, Abbott DH. Insulin resistance and impaired insulin secretion in prenatally androgenized male rhesus monkeys. J. Clin. Endocrinol. Metab. 2004; 89:6218–6223. [PubMed: 15579780]
39. Recabarren SE, Rojas-García PP, Recabarren MP, Alfaro VH, Smith R, Padmanabhan V, Sir-Petermann T. Prenatal testosterone excess reduces sperm count and motility. Endocrinology. 2008; 149:6444–6448. [PubMed: 18669598]
40. Rojas-García PP, Recabarren MP, Sarabia L, Schön J, Gabler C, Einspanier R, Maliqueo M, Sir-Petermann T, Rey R, Recabarren SE. Prenatal testosterone excess alters Sertoli and germ cell number and testicular FSH receptor expression in rams. Am. J. Physiol. Endocrinol. Metab. 2010; 299:E998–E1005. [PubMed: 20858754]
41. Coviello AD, Sam S, Legro RS, Dunaif A. High prevalence of metabolic syndrome in first-degree male relatives of women with polycystic ovary syndrome is related to high rates of obesity. J. Clin. Endocrinol. Metab. 2009; 94:4361–4366. [PubMed: 19837913]
42. Sam S, Coviello AD, Sung YA, Legro RS, Dunaif A. Metabolic phenotype in the brothers of women with polycystic ovary syndrome. Diabetes Care. 2008; 31:1237–1241. [PubMed: 18332151]
43. Sam S, Sung YA, Legro RS, Dunaif A. Evidence for pancreatic beta-cell dysfunction in brothers of women with polycystic ovary syndrome. Metabolism. 2008; 57:84–89. [PubMed: 18078863]
44. Legro RS, Kunselman AR, Demers L, Wang SC, Bentley-Lewis R, Dunaif A. Elevated dehydroepiandrosterone sulfate levels as the reproductive phenotype in the brothers of women with polycystic ovary syndrome. J. Clin. Endocrinol. Metab. 2002; 87:2134–2138. [PubMed: 11994353]

45. Recabarren SE, Smith R, Rios R, Maliqueo M, Echiburú B, Codner E, Cassorla F, Rojas P, Sir-Petermann T. Metabolic profile in sons of women with polycystic ovary syndrome. J. Clin. Endocrinol. Metab. 2008; 93:1820–1826. [PubMed: 18230657]
46. Abbott DH, Bruns CR, Barnett DK, Dunaif A, Goodfriend TL, Dumesic DA, Tarantal AF. Experimentally induced gestational androgen excess disrupts glucoregulation in rhesus monkey dams and their female offspring. Am. J. Physiol. Endocrinol. Metab. 2010; 299:E741–E751. [PubMed: 20682841]
47. Kent SC, Gnatuk CL, Kunselman AR, Demers LM, Lee PA, Legro RS. Hyperandrogenism and hyperinsulinism in children of women with polycystic ovary syndrome: a controlled study. J. Clin. Endocrinol. Metab. 2008; 93:1662–1669. [PubMed: 18270257]
48. Sir-Petermann T, Codner E, Pérez V, Echiburú B, Maliqueo M, Ladrón de Guevara A, Preisler J, Crisosto N, Sánchez F, Cassorla F, Bhasin S. Metabolic and reproductive features before and during puberty in daughters of women with polycystic ovary syndrome. J. Clin. Endocrinol. Metab. 2009; 94:1923–1930. [PubMed: 19223518]
49. Barry JA, Kay AR, Navaratnarajah R, Iqbal S, Bamfo JE, David AL, Hines M, Hardiman PJ. Umbilical vein testosterone in female infants born to mothers with polycystic ovary syndrome is elevated to male levels. J. Obstet. Gynaecol. 2010; 30:444–446. [PubMed: 20604643]
50. Anderson H, Fogel N, Grebe SK, Singh RJ, Taylor RL, Dunaif A. Infants of women with polycystic ovary syndrome have lower cord blood androstenedione and estradiol levels. J. Clin. Endocrinol. Metab. 2010; 95:2180–2186. [PubMed: 20228162]
51. Xu N, Kwon S, Abbott DH, Geller DH, Dumesic DA, Azziz R, Guo X, Goodarzi MO. Epigenetic Mechanism Underlying the Development of Polycystic Ovary Syndrome (PCOS)-Like Phenotypes in Prenatally Androgenized Rhesus Monkeys. PLoS One. 2011; 6(11):e27286. [PubMed: 22076147]
52. Stewart DR, Dombroski BA, Urbanek M, Ankener W, Ewens KG, Wood JR, Legro RS, Strauss JF 3rd, Dunaif A, Spielman RS. Fine mapping of genetic susceptibility to polycystic ovary syndrome on chromosome 19p13.2 and tests for regulatory activity. J. Clin. Endocrinol. Metab. 2006; 91:4112–4117. [PubMed: 16868051]
53. Ewens KG, Stewart DR, Ankener W, Urbanek M, McAllister JM, Chen C, Baig KM, Parker SC, Margulies EH, Legro RS, Dunaif A, Strauss JF 3rd, Spielman RS. Family-based analysis of candidate genes for polycystic ovary syndrome. J. Clin. Endocrinol. Metab. 2010; 95:2306–2315. [PubMed: 20200332]
54. Hatzirodos N, Bayne RA, Irving-Rodgers HF, Hummitzsch K, Sabatier L, Lee S, Bonner W, Gibson MA, Rainey WE, Carr BR, Mason HD, Reinhardt DP, Anderson RA, Rodgers RJ. Linkage of regulators of TGF-{beta} activity in the fetal ovary to polycystic ovary syndrome. FASEB. J. 2011; 25:2256–2265. [PubMed: 21411746]
55. Massam-Wu T, Chiu M, Choudhury R, Chaudhry SS, Baldwin AK, McGovern A, Baldock C, Shuttleworth CA, Klelty CM. Assembly of fibrillin microfibrils governs extracellular deposition of latent TGF beta. J. Cell Sci. 2010; 123(Pt 17):3006–3018. [PubMed: 20699357]
56. Sengle G, Ono RN, Sasaki T, Sakai LY. Prodomains of transforming growth factor beta (TGFbeta) superfamily members specify different functions: extracellular matrix interactions and growth factor bioavailability. J. Biol. Chem. 2011; 286:5087–5099. [PubMed: 21135108]
57. Kruse B, Riepe FG, Krone N, Bosinski HAG, Kloehn S, Partsch CJ, Sippell WG, Mönig H. Congenital adrenal hyperplasia – how to improve the transition from adolescence to adult life. Exp Clin Endocrinol Diabetes. 2004; 112:343–355. [PubMed: 15239019]
58. Conway GS. Congenital adrenal hyperplasia: adolescence and transition. Horm Res. 2007; 68(suppl 5):155–157. [PubMed: 18174736]
59. Grosse SD, Schechter MS, Kulkarni R, Lloyd-Puryear MA, Strickland B, Trevathan E. Models of comprehensive multidisciplinary care for individuals in the United States with genetic disorders. Pediatrics. 2009; 123:407–412. [PubMed: 19117908]
60. Rosen D. Between two worlds: bridging the cultures of child health and adult medicine. J Adolesc Health. 1995; 17:10–16. [PubMed: 7578156]

61. Kieckhefer GM, Trahms CM. Supporting development of children with chronic conditions: from compliance toward shared management. Pediatric Nursing. 2000; 26:354–363. [PubMed: 12026469]
62. Carmina E, Oberfield SE, Lobo RA. The diagnosis of polycystic ovary syndrome in adolescents. Am J Obstet Gynecol. 2010; 203:201.e1-5. [PubMed: 20435290]
63. Lindholm A, Blomquist C, Bixo M, Dahlbom I, Hansson T, Sundström Poromaa I, Burén J. No difference in markers of adipose tissue inflammation between overweight women with polycystic ovary syndrome and weight-matched controls. Hum Reprod. 2011; 26:1478–1485. [PubMed: 21478181]
64. Glintborg D, Andersen M, Richelsen B, Bruun JM. Plasma monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1alpha are increased in patients with polycystic ovary syndrome (PCOS) and associated with adiposity, but unaffected by pioglitazone treatment. Clin. Endocrinol. (Oxf). 2009; 715:652–658. [PubMed: 19170716]
65. Escobar-Morreale HF, Luque-Ramírez M, González F. Circulating inflammatory markers in polycystic ovary symdrome: a systematic review and metaanalysis. Fertil. Steril. 2011; 95:1048–1058.e1-2. [PubMed: 21168133]
66. Toulis KA, Goulis DG, Mintziori G, Kintiraki E, Eukarpidis E, Mouratoglou SA, Pavlaki A, Stergianos S, Poulasouchidou M, Tzellos TG, Makedos A, Chourdakis M, Tarlatzis BC. Meta-analysis of cardiovascular disease risk markers in women with polycystic ovary syndrome. Hum. Reprod. Update. 2011; 17:741–760. [PubMed: 21628302]
67. González F. Inflammation in Polycystic Ovary Syndrome: Underpinning of insulin resistance and ovarian dysfunction. Steroids. 2011 Dec 8. [Epub ahead of print].
68. Gonzalez F, Nair KS, Daniels JK, Basal E, Schimke JM. Hyperandrogenism Sensitizes Mononuclear Cells to Promote Glucose-Induced Inflammation in Lean Reproductive-Age Women. Am J Physiol Endocrinol Metab. 2012; 302:E297–306. [PubMed: 22045316]
69. Ramasamy R, Vannucci SJ, Yan SS, Herold K, Yan SF, Schmidt AM. Advanced glycation end products and RAGE: a common threat in aging, diabetes, neurodegeneretion, and inflammation. Glycobiology. 2005; 15:16R–28R.
70. Diamanti-Kandarakis E, Katsikis I, Piperi C, Kandaraki E, Piouka A, Papavassillou AG, Panidis D. Increased serum Advanced Glycation End products is a distinct finding in lean women with PCOS. Clin. Endocrinol. (Oxf). 2008; 69:634–641. [PubMed: 18363886]
71. Diamanti-Kandarakis E, Piouka A, Livadas S, Piperi C, Katsikis I, Papavassillou AG, Panidis D. Anti-mullerian hormone is associated with advanced glycosylated end products in lean women with polycystic ovary syndrome. Eur. J. Endocrinol. 2009; 160:847–853. [PubMed: 19208775]
72. Diamanti-Kandarakis E, Piperi C, Patsouris E, Korkolopoulou P, Panidis D, Pawelczyk L, Papavassiliou AG, Duleba AJ. Immunohistochemical localization of advanced glycation end-products (AGEs) and their receptor (RAGE) in polycystic and normal ovaries. Histochem. Cell. Biol. 2007; 127:581–589.
73. Papachroni KK, Piperi C, Levidou G, Korkolopoulou P, Pawelczyk L, Diamanti-Kandarakis E, Papavassiliou AG. Lysyl oxidase interacts with AGE signalling to modulate collagen synthesis in polycystic ovarian tissue. J. Cell. Mol. Med. 2010; 14:2460–2469. [PubMed: 19583806]
74. Rzepczynska IJ, Piotrowski PC, Wong DH, Cress AB, Villanueva J, Duleba AJ. Role of Isoprenylation in Simvastatin-Induced Inhibition of Ovarian Theca-Interstitial Growth in the Rat. Biol. Reprod. 2009; 81:850–855. [PubMed: 19571257]
75. Izquierdo D, Foyouzi N, Kwintkiewicz J, Duleba AJ. Mevastatin inhibits ovarian theca-interstitial cell proliferation and steroidogenesis. Fertil. Steril. 2004; 82(Suppl 3):1193–1197. [PubMed: 15474095]
76. Sokalska A, Piotrowski PC, Rzepczynska IJ, Cress A, Duleba AJ. Statins Inhibit Growth of Human Theca-Interstitial Cells in PCOS and Non-PCOS Tissues Independently of Cholesterol Availability. J. Clin. Endocrinol. Metab. 2010; 95:5390–5394. [PubMed: 20826585]
77. Banaszewska B, Pawelczyk L, Spaczynski RZ, Duleba AJ. Effects of Simvastatin and Metformin on Polycystic Ovary Syndrome after Six Months of Treatment. J. Clin. Endocrinol. Metab. 2011; 96:3493–3501. [PubMed: 21865358]

78. Duleba AJ, Banaszewska B, Spaczynski RZ, Pawelczyk L. Simvastatin improves biochemical parameters in women with polycystic ovary syndrome: results of a prospective, randomized trial. Fertil. Steril. 2006; 85:996–1001. [PubMed: 16580386]

79. Kaya C, Cengiz SD, Berker B, Demirtas S, Cesur M, Erdogan G. Comparative effects of atorvastatin and simvastatin on the plasma total homocysteine levels in women with polycystic ovary syndrome: a prospective randomized study. Fertil. Steril. 2009; 92:635–642. [PubMed: 18692805]

80. Sathyapalan T, Kilpatrick ES, Coady AM, Atkin SL. The effect of atorvastatin in patients with polycystic ovary syndrome: a randomized double-blind placebo-controlled study. J. Clin. Endocrinol. Metab. 2009; 94:103–108. [PubMed: 18940877]

81. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. H. Engl. J. Med. 2002; 346:393–403.

82. Moran LJ, Pasquali R, Teede HJ, Hoeger KM, Norman RJ. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. Fertil. Steril. 2009; 92:1966–1982. [PubMed: 19062007]

83. Moran LJ, Noakes M, Clifton PM, Norman RJ. The use of anti-mullerian hormone in predicting menstrual response after weight loss in overweight women with polycystic ovary syndrome. J. Clin. Endocrinol. Metab. 2007; 92:3796–3802. [PubMed: 17652213]

84. Cheang KI, Huszar JM, Best AM, Sharma S, Essah PA, Nestler JE. Long-term effect of metformin on metabolic parameters in the polycystic ovary syndrome. Diab. Vasc. Dis. Res. 2009; 6:110–119. [PubMed: 20368201]

85. Jablonski KA, McAteer JB, de Bakker PI, Franks PW, Pollin TI, Hanson RL, Saxena R, Fowler S, Shuldiner AR, Knowler WC, Altshuler D, Florez JC. Diabetes Prevention Program Research Group. Common variants in 40 genes assessed for diabetes incidence and response to metformin and lifestyle intervention in the diabetes prevention program. Diabetes. 2010; 59:2672–2681. [PubMed: 20682687]

86. Gambineri A, Tomassoni F, Gasparini DI, Di Rocco A, Mantovani V, Pagotto U, Altieri P, Sanna S, Fulghesu AM, Pasquali R. Organic cation transporter 1 polymorphisms predict the metabolic response to metformin in women with the polycystic ovary syndrome. J. Clin. Endocrinol. Metab. 2010; 95:E204–E208. [PubMed: 20660041]

87. Sathyapalan T, Cho LW, Kilpatrick ES, Coady AM, Atkin SL. A comparison between rimonabant and metformin in reducing biochemical hyperandrogenaemia and insulin resistance in patients with polycystic ovary syndrome (PCOS): a randomized open-label parallel study. Clin. Endocrinol. (Oxf). 2008; 69:931–935. [PubMed: 18410553]

88. Eid GM, Cottam DR, Velcu LM, Mattar SG, Korytkowski MT, Gosman G, Hindi P, Schauer PR. Effective treatment of polycystic ovarian syndrome with Roux-en-Y gastric bypass. Surg. Obes. Relat. Dis. 2005; 1:77–80. [PubMed: 16925218]

89. Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. Fertil. Steril. 2008; 89:505–522. [PubMed: 18243179]

90. Abu Hashim H, El-Shafei M, Badawy A, Wafa A, Zaglol H. Does laparoscopic ovarian diathermy change clomiphene-resistant PCOS into clomiphene-sensitive? 2011; 284:503–507.

91. Johnson NP, Stewart AW, Falkiner J, Farquhar CM, Milsom S, Singh VP, Okonkwo QL, Buckingham KL. REACT-NZ (REproduction And Collaborative Trials in New Zealand), a multi-centre fertility trials group. PCOSMIC: a multi-centre randomized trial in women with PolyCystic Ovary Syndrome evaluating Metformin for Infertility with Clomiphene. Hum. Reprod. 2010; 25:1675–1683. [PubMed: 20435692]

92. Polyzos NP, Tzioras S, Badawy AM, Valachis A, Dritsas C, Mauri D. Aromatase inhibitors for female infertility: a systematic review of the literature. Reprod. Biomed. Online. 2009; 19:456–471. [PubMed: 19909585]

93. Vause TD, Cheung AP, Sierra S, Claman P, Graham J, Guillemin JA, Lapensée L, Steward S, Wong BC. Society of Obstetricians and Gynaecologists of Canada. Ovulation induction in polycystic ovary syndrome: No. 242, May 2010. Int. J. Gynaecol. Obstet. 2010; 111:95–100. [PubMed: 20848729]

94. Tredway D, Schertz JC, Bock D, Hemsey G, Diamond MP. Anastrozole vs. clomiphene citrate in infertile women with ovulatory dysfunction: a phase II, randomized, dose-finding study. Fertil. Steril. 2011; 95:1720-4.e1-8. [PubMed: 21300344]

95. Tulandi T, Martin J, Al-Fadhli R, Kabli N, Forman R, Hitkari J, Librach C, Greenblatt E, Casper RF. Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate. Fertil. Steril. 2006; 85:1761–1765. [PubMed: 16650422]

96. Palomba S, Falbo A, Zullo F, Orio F jr. Evidence-based and potential benefits of metformin in the polycystic ovary syndrome: a comprehensive review. Endocr. Rev. 2009; 30:1–50. [PubMed: 19056992]

97. Pasquali R, Gambineri A, Pagotto U. The impact of obesity on reproduction in women with polycystic ovary syndrome. Br. J. Obstet. Gynecol. 2006; 113:1148–1159.

98. Diamanti-Kandarakis E, Christakou CD, Kandaraki E, Economou FN. Metformin: an old medication of new fashion: evolving new molecular mechanisms and clinical implications in polycystic ovary syndrome. Eur. J. Endocrinol. 2010; 162:193–212. [PubMed: 19841045]

99. Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, Steinkampf MP, Coutifaris C, McGovern PG, Cataldo NA, Gosman GG, Nestler JE, Giudice LC, Leppert PC, Myers ER. Cooperative Multicenter Reproductive Medicine Network. Clomiphene, Metformin, or Both for Infertility in the Polycystic Ovary Syndrome. N. Engl J. Med. 2007; 356:551–566. [PubMed: 17287476]

100. Palomba S, Pasquali R, Orio F Jr, Nestler JE. Clomiphene citrate, metformin or both as first-step approach in treating anovulatory infertility in patients with polycystic ovary syndrome (PCOS): a systematic review of head-to-head randomized controlled studies and meta-analysis. Clin. Endocrinol. (Oxf). 2009; 70:311–321. [PubMed: 18691273]

101. Creanga AA, Bradley HM, McCormick C, Witkop CT. Use of metformin in polycystic ovary syndrome: a meta-analysis, Obstet. Gynecol. 2008; 111:959–968.

102. Franks S. When should an insulin sensitizing agent used in the treatment of polycystic ovary syndrome? . Clin. Endocrinol. (Oxf). 2011; 74:148–151. [PubMed: 21121941]

103. Makrantonaki E, Zouboulis CC. Androgens and ageing of the skin. Curr Opin Endocrinol Diabetes Obes. 2009; 16:240–245. [PubMed: 19390323]

104. Zouboulis CC. The human skin as a hormone target and an endocrine gland. Hormones (Athens). 2004; 3:9–26. [PubMed: 16982574]

105. Zouboulis CC. The skin as an endocrine organ. Dermatoendocrinol. 2009; 1:250–252. [PubMed: 20808511]

106. Zouboulis CC, Chen WC, Thornton MJ, Qin K, Rosenfield R. Sexual hormones in human skin. Horm Metab Res. 2007; 39:85–95. [PubMed: 17326004]

107. Drosdzol A, Skrzypulec V, Plinta R. Quality of life, mental health and self-esteem in hirsute adolescent females. J Psychosom Obstet Gynaecol. 2010; 31:168–175. [PubMed: 20626242]

108. Escobar-Morreale HF, Carmina E, Dewailly D, Gambineri A, Kelestimur F, Moghetti P, Pugeat M, Qiao J, Wijeyaratne CN, Witchel SF, Norman RJ. Epidemiology, diagnosis and management of hirsutism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society. Hum Reprod Update. 2011 Nov 6. [Epub ahead of print].

109. Dokras A. Mood and anxiety disorders in women with PCOS. Steroids. 2011 Dec 9. [Epub ahead of print].

110. Paparodis R, Dunaif A. The Hirsute woman: challenges in evaluation and management. Endocr Pract. 2011; 17:807–818. [PubMed: 21856600]

111. Lumachi F, Basso SM. Medical treatment of hirsutism in women. Curr Med Chem. 2010; 17:2530–2538. [PubMed: 20491644]

112. Sinclair R, Patel M, Dawson TL Jr, Yazdabadi A, Yip L, Perez A, Rufaut NW. Hair loss in women: medical and cosmetic approaches to increase scalp hair fullness. Br J Dermatol. 2011; 165(Suppl 3):12–18. [PubMed: 22171680]

113. Yamaoka M, Hara T, Hitaka T, Kaku T, Takeuchi T, Takahashi J, Asahi S, Miki H, Tasaka A, Kusaka M. Orteronel (TAK-700), a novel non-steroidal 17,20-lyase inhibitor: Effects on steroid synthesis in human and monkey adrenal cells and serum steroid levels in cynomolgus monkeys. J Steroid Biochem Mol Biol. 2012 Jan 12. [Epub ahead of print].