Published in final edited form as:

Expert Rev Endocrinol Metab. 2019 March ; 14(2): 131–143. doi:10.1080/17446651.2019.1576522.

Hyperandrogenic Origins of Polycystic Ovary Syndrome – Implications for Pathophysiology and Therapy

David H Abbott[1,3], **Daniel A Dumesic**[4], **Jon E Levine**[1,2]

[1]Department of Obstetrics and Gynecology, University of Wisconsin, Madison, WI, USA.

[2]Department of Neuroscience, University of Wisconsin, Madison, WI, USA.

[3]Department of Wisconsin National Primate Research Center, University of Wisconsin, Madison, WI, USA.

[4]Department of Obstetrics and Gynecology, David Geffen School of Medicine, University of California, Los Angeles, CA, USA.

Abstract

Introduction: Polycystic ovary syndrome (PCOS) diagnosis comprises combinations of female hyperandrogenism, menstrual irregularity and polycystic ovaries. While it is a familial and highly prevalent endocrine disorder, progress towards a cure is hindered by absence of a definitive pathogenic mechanism and lack of an animal model of naturally occurring PCOS.

Areas covered: These include an overview of PCOS and its potential etiology, and an examination of insights gained into its pathogenic origins. Animal models derived from experimentally-induced hyperandrogenism during gestation, or from naturally-occurring PCOS-like traits, most reliably demonstrate reproductive, neuroendocrine and metabolic pathogenesis.

Expert Commentary: Genetic studies, while identifying at least 17 PCOS risk genes, account for <10% of women with PCOS. A number of PCOS risk genes involve regulation of gonadotropin secretion or action, suggesting a reproductive neuroendocrine basis for PCOS pathogenesis. Consistent with this notion, a number of animal models employing fetal androgen excess demonstrate epigenetic induction of PCOS-like traits, including reproductive neuroendocrine and metabolic dysfunction. Monkey models are most comprehensive, while mouse models provide molecular insight, including identifying the androgen receptor, particularly in neurons, as mediating androgen-induced PCOS-like programming. Naturally-occurring female hyperandrogenism is also demonstrated in monkeys. Animal models are poised to delineate molecular gateways to PCOS pathogenesis.

Keywords

hyperandrogenism; developmental origin of adult disease; animal models; androgen excess; impaired negative feedback; infertility; anovulation; obesity; insulin resistance

Corresponding author: David H Abbott, PhD, Department of Obstetrics and Gynecology and Wisconsin National Primate Research Center, 1223 Capitol Court, Madison, WI 53715, USA. abbott@primate.wisc.edu.

1. Introduction

Polycystic ovary syndrome (PCOS) is generally a hyperandrogenic women's disorder that confers significant morbidity, including proven associations with type 2 diabetes (T2D), vascular dysfunction, obesity, infertility and cancer [1]. Despite exceptionally high prevalence, its heavy burden on health care resources, and substantial clinical and basic science research [2], PCOS remains underappreciated and underfunded [3–5].

New evidence-based, International Guidelines for the Assessment and Management of PCOS [6] reinforce the 2003 Rotterdam criteria [7] and promise increased clinical consensus, patient awareness and more rapid, accurate diagnosis. The International Guidelines require at least two of the following components, excluding other endocrine disorders: clinical and/or biochemical hyperandrogenism, intermittent or absent ovulatory menstrual cycles, and/or a polycystic ovary. These criteria diagnose four well recognized PCOS phenotypes (Table 1), three of which exhibit hyperandrogenism, mostly of ovarian theca cell origin [11,12]. A recent evidence-based International Consortium Update has additionally refined the controversial diagnosis and treatment of PCOS in adolescents [13]. Adolescent diagnosis requires clinical and/or biochemical hyperandrogenism along with intermittent or absent ovulatory menstrual cycles. With adolescents, however, no consistent evidence has yet defined when persistent intermittent or absent menstrual cycles become clinically relevant and separate from those of non-PCOS adolescents [14], so an arbitrary time interval of >2 years beyond menarche is used [13].

In vivo latent or extant (functional) ovarian hyperandrogenism in PCOS women is demonstrable by endocrine stimulation of ovarian theca cell LH receptors resulting in hyperandrogenic steroid hormone responses [12]. *In vitro* maintenance of ovarian theca cells in culture reveals persisting, constitutive hyperandrogenism in theca cells obtained from women with PCOS [11]. In addition, androgen excess within the adrenal cortex [15], abdominal subcutaneous adipose depots [16], and other extra-ovarian sources [17], supplement ovarian hyperandrogenism. More recently, non-conventional androgens, including 11-ketotestosterone and 11-keto dihydrotestosterone (11-oxygenated C19 steroids), have been recognized as the most prevalent bioactive androgens in both the circulation and adipose depots of women with PCOS [18]. Since 11-oxygenated C19 steroids likely bind circulating sex hormone binding globulin (SHBG) less avidly than T [19], and women with PCOS commonly exhibit diminished circulating levels of SHBG [20], circulating androgens in PCOS may constitute a more substantially bioavailable source of hyperandrogenism than is currently appreciated.

Not surprisingly, a number of PCOS risk genes regulating gonadotropin and ovarian function are proposed as enabling ovarian hyperandrogenism, having been identified from family-based and extensive genome-wide association studies (GWAS), as well as rare gene variant association testing (whole exome sequencing) [21–23]. While encouraging the promise of future PCOS risk assessments from an individual's genotype leading to tailored clinical management, such putative PCOS risk genes account for <10% of PCOS phenotypes [22,24]. At least 17 replicated PCOS risk genes have emerged from several genetic studies involving human populations around the world [25–29]. The risk genes regulate a variety of

reproductive and metabolic function, including gonadotropin secretion (*FSHB*), gonadotropin action and ovarian function *(LHCGR, FSHR, DENND1A, RAB5/SUOX, HMGA2, C9orf3, YAP1, TOX3, RAD50, FBN3 and AMH*) and metabolic function (*THADA, GATA/NEIL2, ERBB4, SUMOP11, INSR and KRR1*) [21,22,25,31].

To move forward, there is clear and demonstrable need to identify:

- **a.** more PCOS risk genes, as each confers only a small degree of PCOS-trait risk,
- **b.** rare gene variants, as each may confer unduly large degrees of PCOS risk,
- **c.** epigenetic mechanisms altering a wide range of gene expression that confer risk for PCOS, and
- **d.** altered maternal-fetal environments contributing developmental programming to overall phenotype.

Current thinking embraces a combination of polygenic, epigenetic and developmental contributions to PCOS pathogenesis that are ameliorated by lifestyle or exaggerated by obesity [1,12,30,31].

2. Genetic pathogenic origins for PCOS

PCOS is highly familial and heritable, with hyperandrogenism emerging as the most heritable trait [32]. In twin studies, concordance for presence or absence of PCOS reaches 71% for maternal, and 38% for paternal, twins [33,34]. Up to 46% of reproductive-aged sisters of women with PCOS exhibit one of the three hyperandrogenic PCOS phenotypes [32,35]. In addition, as might be expected from pronounced metabolic dysfunction accompanying most PCOS phenotypes, mothers and fathers of women with PCOS have increased prevalence of T2D, metabolic syndrome and dyslipidemia [34,36]. PCOS risk genes, nevertheless, do not associate with T2D or obesity [22]. Genetic studies of T2D risk genes utilize substantially larger numbers (up to ~10^6) of study subjects [37], orders of magnitude greater than GWAS studies of women with PCOS. Risk genes for T2D account for 23% of its heritability in women [37], well below its ~50% heritability estimated from twin and family studies [38], and reminiscent of the “heritability gap” encountered in PCOS studies. Interestingly in this regard, maternal-fetal environmental modification of the fetal female epigenome may contribute additional transgenerational transmission of T2D. Gestationally diabetic *in utero* environments [39], as well as intrauterine poor nutrition and fetal growth restriction [40], are implicated in contributing additional developmental, and likely epigenetic [41], programming in women with T2D.

Both PCOS and T2D thus appear to comprise complex polygenic pathogenic origins with additional contributions from metabolically perturbed intrauterine environments. Therapeutic approaches emerging from such novel understanding are likely to be diverse, and require precision-based clinical management centered upon combinations of individual genotype, epigenotype and intrauterine environments.

3. Epigenetic pathogenic origins for PCOS

Three major mechanisms regulate the epigenome by changing the structure of chromatin without altering DNA base-pair sequences. They include gene promoter site DNA methylation, posttranslational histone modifications and RNA-mediated gene regulation. Testosterone, along with its biopotent androgenic and estrogenic metabolites, as well as glucose, are all effective epigenetic modifiers of PCOS phenotypic expression that commonly includes both hyperandrogenism and glucose intolerance [1,42]. In primates, including humans, bioactive androgens drive the majority of phenotypic sexual differentiation in multiple organ systems, including the brain [43]. Increased or decreased DNA methylation can diminish or enhance, respectively, mRNA transcription of inherited gene variants [44]. In addition, in only XX individuals, substantially increased DNA methylation of genes such as *IGF2* and *INS* confer paternal transmission of respective gene variants and provide examples of sex-specific gene imprinting contributing epigenetic transmission of traits that could manifest components of PCOS pathophysiology [45].

Different patterns and degrees of DNA methylation at any single gene locus, however, are specific to each organ system or cell type within an individual. Consequently, unlike GWAS, there is less certainty as to how genome-wide methylation studies (GWMS) generalize beyond an organ or cell type. DNA is differentially methylated in a variety of organ systems in women with PCOS [13,46] and may arise during gestation, since DNA extracted from mixed umbilical cord blood obtained from term offspring born to women with PCOS demonstrates differential gene methylation patterns compared to DNA extracted from term offspring born to non-PCOS women [47]. Gene-targeted DNA methylation studies of *LHCGR* have reported its hypomethylation in blood cells and subcutaneous adipose of women with PCOS, concurrent with increased *LHCGR* gene expression in these same cells or tissues [48–50]. If comparable hypomethylation of *LHCGR* occurs in PCOS ovarian theca cells, it would likely cause or amplify both increased protein expression of *LHCGR* [51] and hyperandrogenic responses to LH pulses [52]. GWMS and bioinformatic pathway analyses have identified clusters of differentially methylated genes in PCOS women that regulate a variety of cell functions, including carbohydrate and lipid metabolism, neurotransmitter signaling, immune response pathways (including inflammation), ovarian steroidogenic and metabolic functions, cancer-related pathways and extra-cellular matrix interactions [47,49,53,54]. Notably, there are commonalities between identified PCOS risk genes and differentially methylated genes in PCOS women, including *LHCGR, RAB5/SUOX, AMH/AMHR2* and *INSR*, suggesting convergence of molecular pathogenic mechanisms around the same critical genes.

In addition to DNA methylation contributions, initial studies of overexpression of Template Activating Factor-1beta (SET) in PCOS ovaries [55] implicate posttranslational histone modification in PCOS pathophysiology. SET enables formation of the inhibitor of histone acetyltransferase (INHAT) complex that inhibits histone acetylation, potentially contributing to SET-mediated upregulation of ovarian follicle HSD3B2 and CYP17A1 gene expression [56], key genes regulating androgen biosynthesis. Anti-SET drugs, developed as anti-cancer therapies, hold promise as epigenetically-based, anti-androgen treatments for women with PCOS.

Furthermore, PCOS-associated differences in circulating concentrations of microRNAs implicate an additional epigenetic component of small, non-coding RNAs mediating translational repression of gene expression in female hyperandrogenism and metabolic dysfunction. MicroRNA-based pathway analysis algorithms implicate androgen-mediated programming and altered fatty acid metabolism in PCOS pathogenic phenotype separate from obesity-associated changes in microRNA expression [57].

4. Maternal-fetal environments contribute pathogenic origins for PCOS

During human pregnancies, about 40% of girls exhibit fetal male-like circulating concentrations of unbound, bioavailable T during early-to-mid gestation [58]. This is relevant to PCOS since amnionic fluid from daughters of women with PCOS contains male-similar T levels in mid-gestation, exceeding levels in mid-gestation daughters of women without PCOS [59]. As mid-gestation amnionic fluid T originates from the fetus [60], elevated T levels suggest hyperandrogenism in fetal daughters of women with PCOS during a crucial, developmental window [61–63] when comparable circulating T excursions into the fetal male range generate PCOS-like traits in gestational T-exposed female rhesus monkeys [64] and sheep [65]. In short-gestation rodents, late gestation and the immediate post-partum period provide a comparable developmentally vulnerable period for females [66]. Adult manifestation of PCOS-like traits emanating from a hyperandrogenic fetal environment reveal the life-long impact on females of *in utero* androgen excess. Approximately 50% of daughters born to PCOS women develop signs and symptoms of PCOS by adolescence [67], indicating the substantial risk for PCOS phenotype accompanying female *in utero* androgen excess in humans [66].

Pregnant women with PCOS retain hyperandrogenism throughout pregnancy [68], together with elevated AMH levels [63] and reduced placental aromatase expression [70]. Despite population differences [71], ~40% of PCOS women experience gestational diabetes [72] and other pregnancy complications [73], with maternal diabetes predisposing offspring to metabolic dysfunction in later life through fetal hyperinsulinemia [74]. A recent mouse model suggests that increasing AMH levels in pregnancy (as seen in PCOS women) can promote both LH-mediated maternal T excess and reduced placental aromatization of maternal androgens [69], thereby contributing maternal T to fetal hyperandrogenism in their female offspring. Establishing a comparable pathogenic PCOS mechanism in humans, however, still remains to be demonstrated.

Post-natal consequences of *in utero* androgen excess are found as early as the newborn for women with PCOS. Infant daughters not only exhibit transient facial sebum [75], a biomarker of prior T exposure [76], but also demonstrate an elongated anogenital distance [77], a reliable biomarker for early-to-mid gestation androgen excess [78]. Newborn daughters of women with PCOS also exhibit elevated AMH levels indicative of increased numbers of ovarian antral follicles, a PCOS trait. In adulthood, women with PCOS retain an elongated anogenital distance [79–81], typical of gestational T-exposed, adult PCOS-like female monkeys [78] and sheep [65]. An altered 2D:4D finger length ratio is also associated with both fetal androgen excess and PCOS, in women [82], their prepubertal daughters [59] and adult, early-to-mid gestation, T-exposed PCOS-like monkeys [78], since similar T- and

E_2-regulated genes control differentiation of gonads, hands and feet. In addition, prepubertal daughters of women with PCOS excrete increased concentrations of dihydrotestosterone (DHT) metabolites in their urine compared to prepubertal girls of women without PCOS [83], indicating increased 5-alpha reductase activity, and perhaps amplified target tissue androgen action, well before the onset of PCOS signs and symptoms at puberty.

Mixed umbilical cord blood androgen levels from human female fetuses at term, however, have yielded inconsistent results in support of late gestation fetal hyperandrogenism in daughters of PCOS women. Increased T or androstenedione levels are reported in two studies [84,85], equivalent levels in one [86], and diminished levels in a further two [70,87]. Labor onset and duration, together with increasing term gestational age, however, diminish umbilical cord androgen levels and likely often confound understanding of late gestation female androgenic states from this measure [88]. Moreover, no sex differences remain between circulating T levels in male and female human fetuses by late gestation [58], suggesting endocrine studies of term births are unlikely to reveal developmental hyperandrogenism previously experienced by newborn.

5. Hyperandrogenic maternal-fetal environments contribute pathogenic PCOS-like origins in animal models

5.1. Nonhuman female primates

As illustrated in Table 2, maternal T exposure in monkeys during early-to-mid gestation is more effective at inducing reproductive and metabolic PCOS-like signs and symptoms in female offspring than T exposure during late gestation, reinforcing the concept of a particularly vulnerable, mid-gestational, developmental window for fetal T reprogramming of PCOS-like traits in females of long gestation species. Maternal T levels approximating those found in adult male rhesus monkeys are required, however, to exceed aromatization, inactivation and binding globulin abilities of pregnant nonhuman primate females and deliver fetal male levels of T to fetal females [64]. Pregnant non-primate mammals do not have the same degree of androgen-abrogating capabilities [64].

Mid-gestation excessive maternal weight gain and transient hyperglycemia, accompanied by fetal hyperglycemia, are all T-induced metabolic sequelae contributing potential additional reprogramming to exposed female fetuses [135]. As late gestation T exposure-induced PCOS-like traits demonstrate, however, a degree of fetal female monkey vulnerability to T reprogramming (and its gestational metabolic sequelae) remains beyond mid-gestation (Table 2). An increased incidence of gestational diabetes, as well as increased or diminished birthweight [13], accompany PCOS gestations and therefore closely emulate the metabolic compromise of hyperandrogenic gestation in monkeys [135]. Importantly, metabolically compromised gestation, alone, including obese monkeys and women [136], and women with T2D, is insufficient to cause PCOS. T compromised gestation, however, reprograms female neurocircuitry controlling energy balance and increases vulnerability to fetal metabolic compromise [135].

Phenotypic manifestation of early-to-mid gestation T reprogramming of female monkeys begins with mid-gestation increase in fetal head size, followed in late gestation by hypolipidemia and fetal LH hypersecretion [64,135]. LH hypersecretion persists into early infancy, accompanied by modest hyperandrogenism [64], reflecting precocious development of insensitive negative feedback regulation of gonadotropin-releasing hormone (GnRH)/LH in the absence of mature ovarian hormone levels providing homeostatic constraint. While birthweight is normal, accompanying metabolic dysfunction includes newborn hypoglycemia, accelerated infant weight gain and relative hyperinsulinemia related to defective pancreatic beta cell compensation for insulin sensitivity and excessive beta-to-alpha cell ratio in infant pancreatic islets [135,137]. Increased fetal growth, neonatal hypoglycemia and subsequent accelerated postnatal growth are typical of human gestations complicated by excessive maternal weight gain and hyperglycemia [137], and such gestations greatly increase the risk of developing T2D in adulthood [138].

During adolescence, menarche is delayed by ~6 months in both early-to-mid and late gestation T- and dihydrotestosterone (DHT)-exposed female monkeys [96], but such pubertal delay is absent when lower amounts of T are administered to monkey dams [97]. Subsequent onset of menstrual cycles in early-to-mid gestation T-exposed monkeys is accompanied by a prolonged succession of luteal insufficiency [96], demonstrating adolescent origins of ovulatory cycle dysfunction, an attribute of hyperandrogenic adolescent girls presenting with PCOS [13]. Equivalency of action between T and DHT suggests androgen receptor-mediated fetal programming of at least one PCOS-like trait in nonhuman primates.

Early-to-mid gestation T-exposed adult female monkeys are comprehensive phenotypic, and likely epigenetic [91], mimics of women with PCOS. Ovarian and adrenal hyperandrogenism co-occur with intermittent and absent menstrual cycles, as well as large, polyfollicular ovaries [90,91]. Elevated LH levels are omnipresent, driven by increased hypothalamic GnRH pulse frequency and increased pituitary gonadotrope response to GnRH, both likely resulting from diminished sensitivity to E_2- and progesterone-mediated negative feedback regulation [139], all neuroendocrine traits found in women with PCOS [140,141]. Oocyte developmental competence is compromised in PCOS-like monkeys [93], and may reflect contributions from increased adiposity that accompanies diminished oocyte quality in women with PCOS [142]. Circulating AMH levels in T-exposed monkeys, however, do not exceed those of controls, and exhibit an exaggerated, age-related decline [143]. While absence of AMH excess is atypical for women with PCOS, PCOS women over 30 years of age demonstrate a steeper decline in circulating AMH levels than their non-PCOS counterparts [144]. Early-to-mid gestation T reprogramming of ovarian follicle granulosa cells may therefore be less pronounced than ovarian theca, stroma or oocytes, and an extra-ovarian source of fetal hyperandrogenism, alone, may be insufficient to reprogram granulosa cell AMH hypersecretion or increase follicle number and proliferation. Additional ovarian pathogenesis, perhaps involving AMH or extra-cellular matrix dysfunction [22,23], appears necessary to fully replicate a PCOS ovary.

Accompanying metabolic dysfunction is just as pronounced in adult T-exposed monkeys as in PCOS women, despite the monkeys' non-obesogenic diet. Increased monkey visceral fat accumulation [99], or "metabolic obesity" [145], likely arises from PCOS-like

hyperandrogenic adipogenic constraint, limiting SC adipocyte maturation and safe lipid storage [146]. Such pro-lipotoxic traits may contribute to hyperlipidemia-associated insulin resistance, impaired pancreatic beta cell compensation and compromised islet size [137] enabling increased progression to T2D [91]. Consistent with gestational origins of PCOS-like metabolic dysfunction, increased postnatal weight gain is associated with increased risk of PCOS in women [13], as well as T2D [138]. Interestingly, DNA methylation array analysis of visceral adipose identifies transforming growth factor beta (TGF-beta) signaling as the most significantly altered pathway in adult, T-exposed female monkeys [147], implicating an influential signaling pathway regulating adipocyte catabolism (brown or beige adipose, BAT) and adipocyte accumulation of lipid (white adipose, WAT) that may enable positive energy balance [148,149] favoring weight gain.

Interestingly, administration of a peroxisome proliferator-activated receptor gamma (PPARG or NR1C3) agonist, pioglitazone, a nuclear transcription factor crucial for adipocyte maturation, to early-to-mid gestation T-exposed monkeys in adulthood improves glucoregulation, lipid levels, ovulatory menstrual cyclicity and diminishes their hyperandrogenic environment, reminiscent of its actions in women with PCOS [94].

5.2. Non-primate female mammals

Non-primate models of *in utero* androgen excess emulate many of the reproductive and metabolic traits found in PCOS women and T-exposed monkeys (Table 2). With their relative ease of manipulation, these models have generated a plethora of incisive pharmacological and molecular manipulations that provide key insight into pathogenic mechanisms engaged by fetal androgen excess (recently reviewed by [150–152]). Differential gestational timing or duration of androgen exposure in female sheep (Table 2), illustrate the skew in gestational vulnerability to PCOS-like reprogramming of both reproductive and metabolic traits reported in female monkeys, and suggest that longer durations of T exposure commencing before mid-gestation induce a more pronounced PCOS-like phenotype. By late gestation, following cessation of maternal early-to-late T administration, increased ovarian theca cell expression of CYP17A1 and increased release of androstenedione are already present [115]. Postnatally, however, circulating androgen levels in such T-exposed sheep are not elevated, but ovarian androgen receptor expression is increased suggesting “functional hyperandrogenism” within an androgen target organ [153]. Early-to-late DHT exposure, while recapitulating T reprogramming of reproductive traits and insulin resistance, does not disrupt maturation of regular ovarian cycles or ovarian morphology (Table 2), suggesting limits to androgen receptor-mediated PCOS-like reprogramming in sheep. Maternal co-administration of the androgen receptor antagonist, flutamide, along with T during early-to-late gestation prevents early puberty, and likely LH hypersecretion, as well as onset of ovulatory dysfunction, PCOS-like ovarian morphology and ovarian steroidogenic abnormalities [154].

Gestational flutamide co-treatment (Table 2), however, fails to prevent metabolic phenotype, including insulin resistance, adipogenic constraint, hyperlipidemia and fatty liver [111], again demonstrating limits to androgen receptor-mediated, PCOS-like reprogramming. In this regard, flutamide treatment of adult female mice previously exposed to fetal DHT

reverses their acyclicity [124], and in some PCOS women, improves fertility, menstrual cyclicity and LH levels [155], as well as normalizing progesterone negative feedback regulation of episodic GnRH/LH release [141].

Gestational co-administration of rosigltazone, a PPAR gamma agonist, along with T during early-to-late gestation (Table 2), prevents insulin resistance and early puberty onset, and likely LH hypersecretion, in T-exposed female lambs, but does not prevent adipogenic dysfunction, hyperlipidemia and fatty liver [111]. In this regard, it is interesting that treatment of late gestation DHT-exposed female offspring as adults with the insulin sensitizer, metformin, restores normal cyclicity, as well as normalizing androgen and LH levels. Taken together, these findings suggest that while reprogramming of a variety of PCOS-like reproductive traits involves androgen receptor and/or insulin-mediated actions, adipogenic and lipogenic traits may involve additional reprogramming, perhaps engaging estrogenic T metabolites and metabolically-related regulators of the epigenome, such as excess glucose.

Mouse models have predominantly used the non-aromatizable androgen, DHT, to induce late gestation fetal androgen excess and PCOS-like reprogramming (e.g., [156–159]). Late gestation DHT administered to female GnRH-green fluorescent protein (GFP)-transgenic mouse dams produces PCOS-like female offspring exhibiting hyperandrogenism, intermittent/absent cycles, aberrant ovarian follicle morphology, LH hypersecretion derived from accelerated episodic GnRH release, fatty liver and enlarged adipocytes, without accompanying increased adiposity and insulin resistance [123,124,158,159]. Elegant use of genetic manipulation to globally delete androgen receptor (ARKO) protects fetal female mice from fetal DHT-induced, PCOS-like reprogramming, including absence of intermittent/absent cycles, aberrant follicle morphology and enlarged adipocytes [155]. Neural androgen receptor expression may be particularly crucial for DHT-mediated, PCOS-like reprogramming since selective deletion of neuronal androgen receptor expression, NeuroARKO, provides the best protection against peri-pubertal onset, DHT induction of PCOS-like traits [157]. NeuroARKO mice, however, have not yet been challenged with gestational DHT exposure to ascertain if absence of neuronal androgen receptor abrogates fetal androgen PCOS-like reprogramming.

GnRH-GFP transgenic mice have also allowed neuro-immunohistochemical assessment of hypothalamic changes that may underlie PCOS-like reprogramming of GnRH release and its negative feedback regulation. Late gestation DHT increases anatomical and functional gamma-aminobutyric acid (GABA) neuronal connectivity to GnRH neurons, generating increased firing rate of GnRH neurons, as well as LH hypersecretion, related to diminished progesterone negative feedback regulation [123,124,155,159]. Such enhanced GABA excitatory connectivity, originating at least in part from the hypothalamic arcuate nucleus, is established before puberty, when circulating androgen levels are low [158,159]. Since GABA, but not GnRH, neurons express detectable levels of progesterone, estrogen and androgen receptors, aberrant GABA excitatory connectivity may mediate diminished progesterone (and E_2) negative feedback regulation demonstrated by fetal androgen excess female mice, and potentially rats, sheep and monkeys. Unexpectedly, long-term administration of flutamide to adult, prenatally DHT-treated female mice normalizes

neuronal connectivity between GABA and GnRH neurons, as well ovarian cyclicity and follicle morphology [158,159], suggestive of normalized circulating LH levels and negative feedback regulation of GnRH/LH. Such therapeutic reversal of developmentally programmed abnormal morphology and function implicates a crucial role for extant, extra-ovarian androgen excess in maintaining neuronal reprogramming and its PCOS-like sequelae. The implication, emphasized by sheep and transgenic mouse studies, is that diminished androgen production and action in specific adult organ systems may effectively normalize “inherited” PCOS traits. A fundamental component of PCOS pathogenesis may therefore comprise mechanisms maintaining ovarian and extra-ovarian hyperandrogenism postnatally that become essential for maintenance of adult PCOS-like traits exemplified in Table 2.

6. Expert Commentary

Accumulating evidence from studies of PCOS animal models, together with concurring, mostly circumstantial, evidence from human studies, establishes a hyperandrogenic developmental origin for PCOS and PCOS-like phenotypes as a credible pathogenic origin for PCOS in women. Gestational androgen excess, whether administered via the dam or directly to the fetus (as T or DHT), epigenetically reprograms female developmental trajectory to mimic PCOS phenotypes to varying extents depending on timing of T exposure and mammalian species used (Table 2). Androgen receptors, particularly those expressed by neurons, enact much, but not all, hyperandrogenic programming [156,157]. Even a laboratory population of naturally occurring hyperandrogenic female monkeys, exhibiting both PCOS-like traits and external genital characteristics suggestive of prior gestational T exposure, implicate a component of developmental pathogenic hyperandrogenism [8]. Gestational T excess generating adult PCOS-like phenotype has thus progressed from a “paradigm shift” in clinical understanding of concepts concerning PCOS pathogenesis [160], to delineation of molecular gateways engaging PCOS-like pathophysiology and transgenerational transmission of phenotype [66,152].

Translating understanding of PCOS pathogenesis gained from animal models into clinical practice, however, poses considerable challenge. For example, anti-androgen therapy such as flutamide co-administered to pregnant ewes along with excess T prevents fetal programming of reproductive traits in female offspring [111]. On the other hand, when administered without accompanying T excess to monkey dams, flutamide-exposed female offspring exhibit masculinized vocalizations as infants [161], and in adulthood demonstrate subtle cognitive dysfunction [162] and diminished interest in engaging with infants [163]. Without a reliable prediction of gestational age at onset, nor knowledge of the degree or duration of T-excess in human pregnancies carrying fetal fetuses at risk for PCOS after birth, the risk of detrimental postnatal outcomes, such as those reported for gestational flutamide-exposed female monkeys [163], outweigh potential benefits from ameliorating PCOS reproductive traits.

Gestational application of insulin sensitizers, based on initial promising results suggesting abrogation of PCOS-related metabolic dysfunction in female offspring (glitazones: sheep [114], humans [164]; metformin: humans [164,165]), have since provided a cautionary

lesson in the unintended consequences of premature gestational intervention. In a recent long-term randomized clinical trial of daily metformin or placebo to pregnant PCOS women from at least 12 weeks of gestation, newborn girls exposed to metformin during gestation had increased head size [166], followed by subsequent increased adiposity and insulin resistance by ~4 years of age compared to age similar control peers who were also born to women with PCOS [167]. In other words, whatever PCOS-associated metabolic traits were transmitted from mother to daughter, gestational exposure to metformin enhanced transgenerational transmission of metabolic dysfunction [168], the exact opposite of the anticipated outcome. Potential causes include robust placental growth hormone responses that counteract metformin's anti-gluconeogenic action in pregnant mothers to impair improved glucose-insulin homeostasis [168,169], and metformin inhibition of fetal mitochondrial respiration, causing activation of the AMPK tumor-suppressive pathway to promote catabolic-energy saving reactions and block anabolic ones [170], potentially combining maternal gestational calorie excess with fetal nutrient deficiency.

A more effective translation of animal model findings into paradigm changes in clinical practice may be to reliably identify young girls at risk for PCOS and initiate lifestyle intervention strategies before puberty. Since reliable, and safely accomplished, fetal indicators are beyond current technical and medical capability, neonatal or infant biomarkers such as increased measures of sebum content in forehead wipes [75], anogenital distance [77] or circulating AMH levels [171], may become sufficiently refined to provide specific and sensitive tests. Early interventions effectively ameliorating onset and degree of expression of PCOS traits hold some promise in diminishing subsequent severity of PCOS symptomology. For example, 6-month's treatment of adolescent hyperandrogenic girls with combined, low-dose anti-androgen and combined insulin sensitizer (spironolactone, pioglitazone and metformin), delayed (for ~1.5–2 years) subsequent return of hyperandrogenism and anovulatory cycles compared to hyperandrogenic adolescents receiving oral contraceptives alone [13].

Such preventive approaches would be predicted as highly beneficial from two current, mutually inclusive concepts of PCOS pathogenesis: adipogenic constraint [172] and gestational hyperandrogenism [66]. Both concepts predict early onset of lipotoxicity and a feedforward loop between compensatory hyperinsulinemia and hyperandrogenemia. Diminishing progression towards accumulation of such pathophysiology holds promise to profoundly transform clinical management of PCOS from belated reaction to proactive restraint.

7. Five Year View

New International Guidelines [6] indicate significant momentum towards evidence-based, clinical diagnostic clarity and consensus worldwide enabling greater consistency in diagnosis and timely management of women with PCOS. Most clinical focus will remain on ameliorating adult symptomology. Clinical studies ameliorating androgen-driven adipogenic constraint [173], potentially preceded by increased prepubertal adiposity [13], may provide insight into novel therapeutic targets diminishing consequent metabolic and reproductive dysfunction [14]. Until reliable pre-PCOS symptomology biomarkers are identified from

infancy through late adolescence, it will be difficult to justify proactive intervention until PCOS is diagnosed at least 2 years following menarche [13,14]. In this regard, longitudinal pediatric studies hold potential to reveal prepubertal ages at which girls at risk for PCOS may exhibit signs and symptoms preceding a PCOS diagnosis [174]. Advances in gestational interventions are unlikely, however, given recent clinical trial outcomes utilizing metformin and subsequent prepubertal onset of overweight and metabolic dysfunction beyond those of peers at similar risk of developing PCOS [167,168].

Within basic and translational science, recent advances in molecular and genetic understanding of PCOS-like pathophysiology in animal models promise new initiatives targeting neuroendocrine, adipogenic and androgenic function. Continuing refinement of organ and cell-type specific genetic editing in mice will delineate molecular gateways to specific components of PCOS pathogenesis, building on current organ-specific, androgen receptor knockout mouse models [152,157]. New developments in mouse neuro-optogenetics and neuro-chemogenetics will provide additional opportunities to manipulate molecular action engaged in hypothalamic regulation of reproductive and metabolic function [175] in PCOS-like models.

In female nonhuman primates, viral vector technology enabling gene-specific silencing in the hypothalamus is promising new insight into understanding molecular mechanisms regulating accumulation of body fat and accompanying pathophysiology [176]. Since viral vectors also enable specific gene editing of nonhuman primate embryos [177], analogous technology may permit embryonic transfection with individual PCOS risks genes and evaluation of subsequent PCOS-like trait expression in nonhuman primates, such as marmoset monkeys. In a parallel approach in naturally occurring hyperandrogenic female monkeys [8], identifying functional gene variants at genetic loci known for risk of PCOS in women with concurrent PCOS-like phenotypic traits would confirm variant-specific pathophysiology and encourage limited proactive clinical gene therapy.

References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

1. Dumesic DA, Oberfield SE, Stener-Victorin E, et al. Scientific Statement on the Diagnostic Criteria, Epidemiology, Pathophysiology, and Molecular Genetics of Polycystic Ovary Syndrome. Endocr Rev. 2015;36(5):487–525. [PubMed: 26426951] ** Comprehensive and contemporary review of PCOS, its clinical diagnosis, management and potential origins.
2. Azziz R, Marin C, Hoq L, et al. Health care-related economic burden of the polycystic ovary syndrome during the reproductive life span. J Clin Endocrinol Metab. 2005;90(8):4650–4658. [PubMed: 15944216]
3. Azziz R. Polycystic Ovary Syndrome. Obstet Gynecol. 2018;132(2):321–336. [PubMed: 29995717]
4. Brakta S, Lizneva D, Mykhalchenko K, et al. Perspectives on Polycystic Ovary Syndrome: Is Polycystic Ovary Syndrome Research Underfunded? J Clin Endocrinol Metab. 2017;102(12):4421–4427. [PubMed: 29092064]
5. Dokras A, Saini S, Gibson-Helm M, et al. Gaps in knowledge among physicians regarding diagnostic criteria and management of polycystic ovary syndrome. Fertil Steril. 2017;107(6):1380–1386.e1. [PubMed: 28483503]

6. Teede HJ, Misso ML, Costello MF, et al., International PCOS Network. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertil Steril. 2018;110(3):364–379. [PubMed: 30033227] ** Comprehensive review of new international guidelines for diagnosis and management of PCOS.
7. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004;81(1):19–25.
8. Abbott DH, Rayome BH, Dumesic DA, et al. Clustering of PCOS-like traits in naturally hyperandrogenic female rhesus monkeys. Hum Reprod. 2017;32;923 [PubMed: 28333238]
9. Norman RJ, Dewailly D, Legro RS, et al. Polycystic ovary syndrome. Lancet. 2007;370(9588):685–697. [PubMed: 17720020]
10. Wild RA, Carmina E, Diamanti-Kandarakis E, et al. 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(5):2038–2049. [PubMed: 20375205]
11. Nelson VL, Qin KN, Rosenfield RL, et al. The biochemical basis for increased testosterone production in theca cells propagated from patients with polycystic ovary syndrome. J Clin Endocrinol Metab. 2001;86(12):5925–5933. [PubMed: 11739466]
12. Rosenfield RL, Ehrmann DA. The Pathogenesis of Polycystic Ovary Syndrome (PCOS): The Hypothesis of PCOS as Functional Ovarian Hyperandrogenism Revisited. Endocr Rev. 2016;37(5):467–520. [PubMed: 27459230]
13. Ibáñez L, Oberfield SE, Witchel S, et al. An International Consortium Update: Pathophysiology, Diagnosis, and Treatment of Polycystic Ovarian Syndrome in Adolescence. Horm Res Paediatr. 2017;88(6):371–395. [PubMed: 29156452] ** Comprehensive contemporary review of diagnosis, management and development of PCOS in adolescence.
14. Witchel SF, Oberfield S, Rosenfield RL, et al. The Diagnosis of Polycystic Ovary Syndrome during Adolescence. Horm Res Paediatr. 2015;83:376–389.
15. Azziz R, Black V, Hines GA, et al. Adrenal androgen excess in the polycystic ovary syndrome: sensitivity and responsivity of the hypothalamic-pituitary-adrenal axis. J Clin Endocrinol Metab. 1998;83(7):2317–2323. [PubMed: 9661602]
16. O'Reilly MW, Kempegowda P, Walsh M, et al. AKR1C3-Mediated Adipose Androgen Generation Drives Lipotoxicity in Women With Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 2017;102(9):3327–3339. [PubMed: 28645211] * Extra-ovarian adipose source of hyperandrogenism amplifies lipotoxicity in PCOS women.
17. Kraynak M, Flowers MT, Shapiro RA, et al. Extraovarian gonadotropin negative feedback revealed by aromatase inhibition in female marmoset monkeys. Am J Physiol Endocrinol Metab. 2017;313(5):E507–E514. [PubMed: 28679622]
18. O'Reilly MW, Kempegowda P, Jenkinson C, et al. 11-Oxygenated C19 Steroids Are the Predominant Androgens in Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 2017;102(3): 840–848. [PubMed: 27901631]
19. Bobe J, Guiguen Y, Fostier A. Diversity and biological significance of sex hormone-binding globulin in fish, an evolutionary perspective. Mol Cell Endocrinol. 2010;316(1):66–78. [PubMed: 19772892]
20. Handelsman DJ, Teede HJ, Desai R, et al. Performance of mass spectrometry steroid profiling for diagnosis of polycystic ovary syndrome. Hum Reprod. 2017;32(2):418–422. [PubMed: 27999117]
21. McAllister JM, Legro RS, Modi BP, et al. Functional genomics of PCOS: from GWAS to molecular mechanisms. Trends Endocrinol Metab. 2015;26(3):118–124. [PubMed: 25600292] * Review functionally links PCOS risk genes with hyperandrogenism in women.
22. Dunaif A. Perspectives in Polycystic Ovary Syndrome: From Hair to Eternity. J Clin Endocrinol Metab. 2016;101(3):759–768. [PubMed: 26908109] * Commentary provides frank, contextual understanding of current issues in PCOS pathogenesis.
23. Gorsic LK, Kosova G, Werstein B, et al. Pathogenic Anti-Müllerian Hormone Variants in Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 2017;102(8):2862–2872. [PubMed: 28505284]

24. Escobar-Morreale HF. Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. Nat Rev Endocrinol. 2018;14(5):270–284. [PubMed: 29569621] * Very recent comprehensive review of PCOS diagnosis, management and pathogenesis.
25. Crespo RP, Bachega TASS, Mendonça BB, et al. An update of genetic basis of PCOS pathogenesis. Arch Endocrinol Metab. 2018;62(3):352–361. [PubMed: 29972435]
26. Chen ZJ, Zhao H, He L, et al. Genome-wide association study identifies susceptibility loci for polycystic ovary syndrome on chromosome 2p16.3, 2p21 and 9q33.3. Nat Genet. 2011;43(1):55–59. [PubMed: 21151128]
27. Liu H, Zhao H, Chen ZJ. Genome-Wide Association Studies for Polycystic Ovary Syndrome. Semin Reprod Med. 2016;34(4):224–229. [PubMed: 27513023]
28. Jones MR, Chua AK, Mengesha EA, et al. Metabolic and cardiovascular genes in polycystic ovary syndrome: a candidate-wide association study (CWAS). Steroids. 2012;77(4):317–322. [PubMed: 22178785]
29. Hayes MG, Urbanek M, Ehrmann DA, et al. Genome-wide association of polycystic ovary syndrome implicates alterations in gonadotropin secretion in European ancestry populations. Nat Commun. 2015;6:7502. [PubMed: 26284813] * GWAS study implicates PCOS risk gene regulating reproductive neuroendocrinology as a fundamental heritable component of PCOS pathogenesis.
30. Pau CT, Mosbruger T, Saxena R, et al. Phenotype and Tissue Expression as a Function of Genetic Risk in Polycystic Ovary Syndrome. PLoS One. 2017;12(1):e0168870. [PubMed: 28068351]
31. Teede HJ, Joham AE, Paul E, et al. Longitudinal weight gain in women identified with polycystic ovary syndrome: results of an observational study in young women. Obesity (Silver Spring). 2013;21(8):1526–1532. [PubMed: 23818329]
32. Legro RS, Driscoll D, Strauss JF 3rd, et al. Evidence for a genetic basis for hyperandrogenemia in polycystic ovary syndrome. Proc Natl Acad Sci U S A. 1998;95(25):14956–14960. [PubMed: 9843997]
33. Vink JM, Sadrzadeh S, Lambalk CB, et al. Heritability of polycystic ovary syndrome in a Dutch twin-family study. J Clin Endocrinol Metab. 2006;91(6):2100–2104. [PubMed: 16219714]
34. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev. 2012;33(6):981–1030. [PubMed: 23065822]
35. Strauss JF 3rd. Some new thoughts on the pathophysiology and genetics of polycystic ovary syndrome. Ann N Y Acad Sci. 2003;997:42–48. [PubMed: 14644808]
36. Sir-Petermann T, Angel B, Maliqueo M, et al. Prevalence of Type II diabetes mellitus and insulin resistance in parents of women with polycystic ovary syndrome. Diabetologia. 2002;45(7):959–964. [PubMed: 12136394]
37. Mahajan A, Taliun D, Thurner M, et al. Fine-mapping T2D loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. Nat Genet. 2018 10 8. doi: 10.1038/s41588-018-0241-6. [Epub ahead of print]
38. Meigs JB, Cupples LA, Wilson PW. Parental transmission of T2D: the Framingham Offspring Study. Diabetes. 2000;49(12):2201–2207. [PubMed: 11118026]
39. Dabelea D, Hanson RL, Lindsay RS, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. Diabetes. 2000;49(12):2208–2211. [PubMed: 11118027]
40. Barker DJ, Fall CH. Fetal and infant origins of cardiovascular disease. Arch Dis Child. 1993;68(6):797–799. [PubMed: 8333778]
41. Sommese L, Benincasa G, Lanza M, et al. Novel epigenetic-sensitive clinical challenges both in type 1 and type 2 diabetes. J Diabetes Complications. 2018;32(11):1076–1084. [PubMed: 30190170]
42. Ortiz-Flores AE, Luque-Ramírez M, Escobar-Morreale HF. Pharmacotherapeutic management of comorbid polycystic ovary syndrome and diabetes. Expert Opin Pharmacother. 2018 10 5:1–12.
43. Nugent BM, Bale TL. The omniscient placenta: Metabolic and epigenetic regulation of fetal programming. Front Neuroendocrinol. 2015;39:28–37. [PubMed: 26368654]

44. Corso-Díaz X, Jaeger C, Chaitankar V, et al. Epigenetic control of gene regulation during development and disease: A view from the retina. Prog Retin Eye Res. 2018;65:1–27. [PubMed: 29544768]
45. Moore GE, Abu-Amero SN, Bell G, et al. Evidence that insulin is imprinted in the human yolk sac. Diabetes. 2001;50(1):199–203. [PubMed: 11147788]
46. Li S, Zhu D, Duan H, et al. The epigenomics of polycystic ovarian syndrome: from pathogenesis to clinical manifestations. Gynecol Endocrinol. 2016;32(12):942–946. [PubMed: 27425146]
47. Lambertini L, Saul SR, Copperman AB, et al. Intrauterine Reprogramming of the Polycystic Ovary Syndrome: Evidence from a Pilot Study of Cord Blood Global Methylation Analysis. Front Endocrinol (Lausanne). 2017;8:352. [PubMed: 29326659]
48. Wang P, Zhao H, Li T, et al. Hypomethylation of the LH/choriogonadotropin receptor promoter region is a potential mechanism underlying susceptibility to polycystic ovary syndrome. Endocrinology. 2014;155(4);1445–1452. [PubMed: 24527662]
49. Jones MR, Brower MA, Xu N, et al. Systems Genetics Reveals the Functional Context of PCOS Loci and Identifies Genetic and Molecular Mechanisms of Disease Heterogeneity. PLoS Genet. 2015;11(8);e1005455. [PubMed: 26305227] * GWAS study demonstrates population differences in PCOS risk genes and their potential contribution to phenotypic diversity.
50. Song J, Luo S, Li SW. miRNA-592 is downregulated and may target LHCGR in polycystic ovary syndrome patients. Reprod Biol. 2015;15(4);229–237. [PubMed: 26679164]
51. Comim FV, Teerds K, Hardy K, et al. Increased protein expression of LHCG receptor and 17α-hydroxylase/17–20-lyase in human polycystic ovaries. Hum Reprod. 2013;28(11):3086–3092. [PubMed: 24014605]
52. Hirshfeld-Cytron J, Barnes RB, Ehrmann DA, et al. Characterization of functionally typical and atypical types of polycystic ovary syndrome. J Clin Endocrinol Metab. 2009;94(5):1587–1594. [PubMed: 19240152]
53. Wang XX, Wei JZ, Jiao J, et al. Genome-wide DNA methylation and gene expression patterns provide insight into polycystic ovary syndrome development. Oncotarget. 2014;5(16);6603–6610. [PubMed: 25051372]
54. Yu YY, Sun CX, Liu YK, et al. Genome-wide screen of ovary-specific DNA methylation in polycystic ovary syndrome. Fertil Steril. 2015;104(1);145–153.e6. [PubMed: 25956362]
55. Jiang SW, Xu S, Chen H, Liu X, Tang Z, Cui Y, Liu J. Pathologic significance of SET/I2PP2A-mediated PP2A and non-PP2A pathways in polycystic ovary syndrome (PCOS). Clin Chim Acta. 2017;464:155 [PubMed: 27836688]
56. Xu B, Gao L, Cui Y, Gao L, Dai X, Li M, Zhang Y, Ma X, Diao F, Liu J. SET protein up-regulated testosterone production in the cultured preantral follicles. Reprod Biol Endocrinol. 2013;11:9. [PubMed: 23421880]
57. Murri M, Insenser M, Fernández-Durán E, San-Millán JL, Luque-Ramírez M, Escobar-Morreale HF. Non-targeted profiling of circulating microRNAs in women with polycystic ovary syndrome (PCOS): effects of obesity and sex hormones. Metabolism. 2018;86:49 [PubMed: 29410349]
58. Beck-Peccoz P, Padmanabhan V, Baggiani AM, et al. Maturation of hypothalamic-pituitary-gonadal function in normal human fetuses: circulating levels of gonadotropins, their common alpha-subunit and free testosterone, and discrepancy between immunological and biological activities of circulating follicle-stimulating hormone. J Clin Endocrinol Metab. 1991;73(3);525–532. [PubMed: 1908479]
59. Palomba S, Marotta R, Di Cello A, et al. Pervasive developmental disorders in children of hyperandrogenic women with polycystic ovary syndrome: a longitudinal case-control study. Clin Endocrinol (Oxf). 2012;77(6);898–904. [PubMed: 22612600]
60. Schindler AE. Hormones in human amniotic fluid. Monogr Endocrinol. 1982;21;1–158. [PubMed: 6810103]
61. Goy RW, Bercovitch FB, McBrair MC. Behavioral masculinization is independent of genital masculinization in prenatally androgenized female rhesus macaques. Horm Behav. 1988;22(4): 552–571. [PubMed: 3235069]

62. Roselli CE, Estill CT, Stadelman HL, et al. Separate critical periods exist for testosterone-induced differentiation of the brain and genitals in sheep. Endocrinology. 2011;152(6):2409–2415. [PubMed: 21447635]
63. Dean A, Sharpe RM. Clinical review: Anogenital distance or digit length ratio as measures of fetal androgen exposure: relationship to male reproductive development and its disorders. J Clin Endocrinol Metab. 2013;98(6):2230–2238. [PubMed: 23569219]
64. Abbott DH, Barnett DK, Levine JE, et al. Endocrine antecedents of polycystic ovary syndrome in fetal and infant prenatally androgenized female rhesus monkeys. Biol Reprod. 2008;79 (1);154–163. [PubMed: 18385445]
65. Veiga-Lopez A, Steckler TL, Abbott DH, et al. Developmental programming: impact of excess prenatal testosterone on intrauterine fetal endocrine milieu and growth in sheep. Biol Reprod. 2011;84(1);87–96. [PubMed: 20739662]
66. Abbott DH, Levine JE, Dumesic DA. Translational Insight Into Polycystic Ovary Syndrome (PCOS) From Female Monkeys with PCOS-like Traits. Curr Pharm Des. 2016;22(36);5625–5633. [PubMed: 27426126] * Recent review of developmental androgen programming of PCOS-like phenotypes in nonhuman primates models.
67. Cesta CE, Månsson M, Palm C, et al. Polycystic ovary syndrome and psychiatric disorders: Co-morbidity and heritability in a nationwide Swedish cohort. Psychoneuroendocrinology. 2016;73;196–203. [PubMed: 27513883]
68. Sir-Petermann T, Maliqueo M, Angel B, et al. Maternal serum androgens in pregnant women with polycystic ovarian syndrome: possible implications in prenatal androgenization. Hum Reprod. 2002;17(10);2573–2579. [PubMed: 12351531]
69. Tata B, Mimouni NEH, Barbotin AL, et al. Elevated prenatal anti-Müllerian hormone reprograms the fetus and induces polycystic ovary syndrome in adulthood. Nat Med. 2018;24(6):834–846. [PubMed: 29760445] * Gestational AMH excess induces maternal and fetal androgen programming of PCOS-like phenotypes in mice.
70. Maliqueo M, Lara HE, Sánchez F, et al. Placental steroidogenesis in pregnant women with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol. 2013;166(2);151–155. [PubMed: 23122578]
71. Fux-Otta C, Maliqueo M, Echiburú B, et al. Pregnancy outcomes in women with polycystic ovary syndrome in two Latin American populations. J Obstet Gynaecol. 2018 38(6):750–755. [PubMed: 29537320]
72. Palm CVB, Glintborg D, Kyhl HB, et al. Polycystic ovary syndrome and hyperglycaemia in pregnancy. A narrative review and results from a prospective Danish cohort study. Diabetes Res Clin Pract. 2018 4 22 pii: S0168–8227(18)30554–0. Doi: 10.1016/j.diabres.2018.04.030.
73. Bahri Khomami M, Boyle JA, Tay CT, et al. Polycystic ovary syndrome and adverse pregnancy outcomes: Current state of knowledge, challenges and potential implications for practice. Clin Endocrinol (Oxf). 2018 2 20. doi: 10.1111/cen.13579.
74. Weiss PAM, Scholz HS, Haas J, et al. Long-term follow-up of diabetes of mothers with type I diabetes. Evidence for hereditary and nonhereditary transmission of diabetes and precursors. Diabetes Care 2000;23;905. [PubMed: 10895839]
75. Homburg R, Gudi A, Shah A, et al. A novel method to demonstrate that pregnant women with polycystic ovary syndrome hyper-expose their fetus to androgens as a possible stepping stone for the developmental theory of PCOS. A pilot study. Reprod Biol Endocrinol. 2017;15:61. [PubMed: 28789693]
76. Giacomoni PU, Mammone T, Teri M. Gender-linked differences in human skin. J Dermatol Sci. 2009;55:144–149. [PubMed: 19574028]
77. Barrett ES, Hoeger KM, Sathyanarayana S, et al. Anogenital distance in newborn daughters of women with polycystic ovary syndrome indicates fetal testosterone exposure. J Dev Orig Health Dis. 2018 Jan 9:1–8. doi: 10.1017/S2040174417001118.* First report of non-invasive newborn anatomical biomarker for girls at risk for PCOS.
78. Abbott AD, Colman RJ, Tiefenthaler R, et al. Early-to-mid gestation fetal testosterone increases right hand 2D:4D finger length ratio in polycystic ovary syndrome-like monkeys. PLoS One. 2012;7(8):e42372 [PubMed: 22927929]

79. Sánchez-Ferrer ML, Mendiola J, Hernández-Peñalver AI, et al. Presence of polycystic ovary syndrome is associated with longer anogenital distance in adult Mediterranean women. Hum Reprod. 2017;32;2315 [PubMed: 29025054]
80. Wu Y, Zhong G, Chen S, et al. Polycystic ovary syndrome is associated with anogenital distance, a marker of prenatal androgen exposure. Hum Reprod. 2017;32;937 [PubMed: 28333243]
81. Hernández-Peñalver AI, Sánchez-Ferrer ML, Mendiola J, et al. Assessment of anogenital distance as a diagnostic tool in polycystic ovary syndrome. Reprod Biomed Online. 2018 10 6 pii: S1472–6483(18)30461–9. doi: 10.1016/j.rbmo.2018.08.020. [Epub ahead of print]
82. Lujan ME, Bloski TG, Chizen DR, et al. Digit ratios do not serve as anatomical evidence of prenatal androgen exposure in clinical phenotypes of polycystic ovary syndrome. Hum Reprod. 2010;25;204 [PubMed: 19855107]
83. Torchen LC, Idkowiak J, Fogel NR, et al. Evidence for Increased 5α-Reductase Activity During Early Childhood in Daughters of Women With Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 2016;101;2069 [PubMed: 26990942]
84. Barry JA, Kay AR, Navaratnarajah R, et al. Umbilical vein testosterone in female infants born to mothers with polycystic ovary syndrome is elevated to male levels. J Obstet Gynaecol. 2010;30;444 [PubMed: 20604643]
85. Daan NM, Koster MP, Steegers-Theunissen RP, et al. Endocrine and cardiometabolic cord blood characteristics of offspring born to mothers with and without polycystic ovary syndrome. Fertil Steril. 2017;107;261 [PubMed: 28228318]
86. Caanen MR, Kuijper EA, Hompes PG, et al. Mass spectrometry methods measured androgen and estrogen concentrations during pregnancy and in newborns of mothers with polycystic ovary syndrome. Eur J Endocrinol. 2016;174;25 [PubMed: 26586837]
87. Anderson H, Fogel N, Grebe SK, et al. Infants of women with polycystic ovary syndrome have lower cord blood androstenedione and estradiol levels. J Clin Endocrinol Metab. 2010;95;2180 [PubMed: 20228162]
88. Hollier LP, Keelan JA, Hickey M, et al. Measurement of androgen and estrogen concentrations in cord blood: accuracy, biological interpretation, and applications to understanding human behavioral development. Front Endocrinol (Lausanne). 2014;5;64 [PubMed: 24829559]
89. Abbott DH, Dumesic DA, Eisner JR, et al. Insights into the development of polycystic ovary syndrome (PCOS) from studies of prenatally androgenized female rhesus monkeys. Trends Endocrinol Metab. 1998;9(2):62. [PubMed: 18406243]
90. Abbott DH, Dumesic DA, Eisner JR, et al. The prenatally androgenized female rhesus monkey as a model for polycystic ovarian syndrome In: Azziz R, Nestler JE and Dewailly D (eds). Androgen Excess Disorders in Women. Philadelphia, Lippencott-Raven Press, 1997, pp. 369–382.
91. Abbott DH, Nicol LE, Levine JE, et al. Nonhuman primate models of polycystic ovary syndrome. Mol Cell Endocrinol. 2013;373(1–2):21. [PubMed: 23370180]
92. Eisner JR, Dumesic DA, Kemnitz JW, et al. Timing of prenatal androgen excess determines differential impairment in insulin secretion and action in adult female rhesus monkeys. J Clin Endocrinol Metab. 2000;85(3):1206. [PubMed: 10720063]
93. Dumesic DA, Schramm RD, Peterson E, et al. Impaired developmental competence of oocytes in adult prenatally androgenized female rhesus monkeys undergoing gonadotropin stimulation for in vitro fertilization. J Clin Endocrinol Metab. 2002;87;1111 [PubMed: 11889174]
94. Zhou R, Bruns CM, Bird IM, et al. Pioglitazone improves insulin action and normalizes menstrual cycles in a majority of prenatally androgenized female rhesus monkeys. Reprod Toxicol. 2007;23:438. [PubMed: 17306503]
95. 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(9): 776. [PubMed: 19367587]
96. Goy RW, Robinson JA. Prenatal exposure of rhesus monkeys to patent androgens: morphological, behavioral and physiological consequences In: Hunt VR, Smith MK, Worth D (eds) Banbury report II: environmental factors in human growth and development. Cold Spring Harbor Laboratory, Cold Spring Harbor, pp 355–378.

97. Zehr JL, Van Meter PE, Wallen K. Factors regulating the timing of puberty onset in female rhesus monkeys (Macaca mulatta): role of prenatal androgens, social rank, and adolescent body weight. Biol Reprod. 2005;72;1087. [PubMed: 15625235]

98. Herman RA, Jones B, Mann DR, et al. Timing of prenatal androgen exposure: anatomical and endocrine effects on juvenile male and female rhesus monkeys. Horm Behav. 2000;38(1):52. [PubMed: 10924287]

99. Abbott DH, Barnett DK, Bruns CM, et al. Androgen excess fetal programming of female reproduction: a developmental aetiology for polycystic ovary syndrome? Hum Reprod Update. 2005;11(4):357. [PubMed: 15941725]

100. Pepe GJ, Maniu A, Aberdeen G, et al. Insulin resistance elicited in postpubertal primate offspring deprived of estrogen in utero. Endocrine. 2016 12;54(3):788–797. [PubMed: 27770396]

101. Pepe GJ, Lynch TJ, Albrecht ED. Regulation of baboon fetal ovarian development by placental estrogen: onset of puberty is delayed in offspring deprived ofestrogen in utero. Biol Reprod. 2013;89(6):132. [PubMed: 24132960]

102. Kim SO, Aberdeen G, Lynch TJ, et al. Adipose and Liver Function in Primate Offspring with Insulin Resistance Induced by Estrogen Deprivation in Utero. Endocrinol Diabetes Metab J. 2017;1(3).

103. Pepe GJ, Maniu A, Aberdeen G, et al. Estrogen Regulation of Fetal Adrenal Cortical Zone-Specific Development in the Nonhuman Primate Impacts Adrenal Production of Androgen and Cortisol and Response to ACTH in Females in Adulthood. Endocrinology. 2016;157(5):1905. [PubMed: 26990066]

104. Clarke IJ, Scaramuzzi RJ, Short RV. Ovulation in prenatally androgenized ewes. J Endocrinol. 1977;73(2):385. [PubMed: 864374]

105. Veiga-Lopez A, Moeller J, Patel D, et al. Developmental programming: impact of prenatal testosterone excess on insulin sensitivity, adiposity, and free fatty acid profile in postpubertal female sheep. Endocrinology. 2013;154(5):1731. [PubMed: 23525243]

106. Robinson JE, Forsdike RA, Taylor JA. In utero exposure of female lambs to testosterone reduces the sensitivity of the gonadotropin-releasing hormone neuronal network to inhibition by progesterone. Endocrinology. 1999;140(12):5797. [PubMed: 10579346]

107. Recabarren SE, Padmanabhan V, Codner E, et al. Postnatal developmental consequences of altered insulin sensitivity in female sheep treated prenatally with testosterone. Am J Physiol Endocrinol Metab. 2005;289(5):E801. [PubMed: 16215166]

108. Smith P, Steckler TL, Veiga-Lopez A, et al. Developmental programming: differential effects of prenatal testosterone and dihydrotestosterone on follicular recruitment, depletion of follicular reserve, and ovarian morphology in sheep. Biol Reprod. 2009;80(4):726. [PubMed: 19092114]

109. Padmanabhan V, Veiga-Lopez A. Sheep models of polycystic ovary syndrome phenotype. Mol Cell Endocrinol. 2013;373(1–2):8. [PubMed: 23084976]

110. Abi Salloum B, Herkimer C, Lee JS, et al. Developmental programming: prenatal and postnatal contribution of androgens and insulin in the reprogramming of estradiol positive feedback disruptions in prenatal testosterone-treated sheep. Endocrinology. 2012;153(6):2813 [PubMed: 22454153]

111. Padmanabhan V, Veiga-Lopez A, Herkimer C, et al. Developmental Programming: Prenatal and Postnatal Androgen Antagonist and Insulin Sensitizer Interventions Prevent Advancement of Puberty and Improve LH Surge Dynamics in Prenatal Testosterone-Treated Sheep. Endocrinology. 2015;156(7):2678. [PubMed: 25919188]

112. Veiga-Lopez A, Lee JS, Padmanabhan V. Developmental programming: insulin sensitizer treatment improves reproductive function in prenatal testosterone-treated female sheep. Endocrinology. 2010;151(8):4007. [PubMed: 20555028]

113. Abi Salloum B, Veiga-Lopez A, Abbott DH, et al. Developmental programming: exposure to testosterone excess disrupts steroidal and metabolic environment in pregnant sheep. Endocrinology. 2015 6;156(6):2323 [PubMed: 25763641]

114. Cardoso RC, Burns A, Moeller J, et al. Developmental Programming: Insulin Sensitizer Prevents the GnRH-Stimulated LH Hypersecretion in a Sheep Model of PCOS. Endocrinology. 2016;157:4641. [PubMed: 27792406]

115. Hogg K, Young JM, Oliver EM, et al. Enhanced thecal androgen production is prenatally programmed in an ovine model of polycystic ovary syndrome. Endocrinology. 2012;153;450 [PubMed: 22087026]
116. Rae M, Grace C, Hogg K, Wilson LM, McHaffie SL, Ramaswamy S, MacCallum J, Connolly F, McNeilly AS, Duncan C. The pancreas is altered by in utero androgen exposure: implications for clinical conditions such as polycystic ovary syndrome (PCOS). PLoS One. 2013;8(2):e56263. [PubMed: 23457541]
117. Hogg K, Wood C, McNeilly AS, Duncan WC. The in utero programming effect of increased maternal androgens and a direct fetal intervention on liver and metabolic function in adult sheep. PLoS One. 2011;6(9):e24877. [PubMed: 21935484]
118. Ramaswamy S, Grace C, Mattei AA, Siemienowicz K, Brownlee W, MacCallum J, McNeilly AS, Duncan WC, Rae MT. Developmental programming of polycystic ovary syndrome (PCOS): prenatal androgens establish pancreatic islet α/β cell ratio and subsequent insulin secretion. Sci Rep. 2016;6:27408. [PubMed: 27265420]
119. Wu XY, Li ZL, Wu CY, et al. Endocrine traits of polycystic ovary syndrome in prenatally androgenized female Sprague-Dawley rats. Endocr J. 2010;57(3):201. [PubMed: 20057162]
120. Slob AK, den Hamer R, Woutersen PJ, et al. Prenatal testosterone propionate and postnatal ovarian activity in the rat. Acta Endocrinol (Copenh). 1983;103(3):420. [PubMed: 6880571]
121. Demissie M, Lazic M, Foecking EM, et al. Transient prenatal androgen exposure produces metabolic syndrome in adult female rats. Am J Physiol Endocrinol Metab. 2008;295(2):E262. [PubMed: 18544644]
122. Foecking EM, McDevitt MA, Acosta-Martínez M, Horton TH, Levine JE. Neuroendocrine consequences of androgen excess in female rodents. Horm Behav. 2008;53(5):673 [PubMed: 18374922]
123. Sullivan SD, Moenter SM. Prenatal androgens alter GABAergic drive to gonadotropin-releasing hormone neurons: implications for a common fertility disorder. Proc Natl Acad Sci U S A. 2004;101;7129 [PubMed: 15096602]
124. Roland AV, Nunemaker CS, Keller SR, Moenter SM. Prenatal androgen exposure programs metabolic dysfunction in female mice. J Endocrinol. 2010;207(2):213 [PubMed: 20713501]
125. Fagman JB, Wilhelmson AS, Motta BM, Pirazzi C, Alexanderson C, De Gendt K, Verhoeven G, Holmäng A, Anesten F, Jansson JO, Levin M, Borén J, Ohlsson C, Krettek A, Romeo S, Tivesten Å. The androgen receptor confers protection against diet-induced atherosclerosis, obesity, and dyslipidemia in female mice. FASEB J. 2015;29(4):1540 [PubMed: 25550469]
126. Walters KA, Edwards MC, Tesic D, Caldwell ASL, Jimenez M, Smith JT, Handelsman DJ. The Role of Central Androgen Receptor Actions in Regulating the Hypothalamic-Pituitary-Ovarian Axis. Neuroendocrinology. 2018;106(4):389 [PubMed: 29635226]
127. Fisher CR, Graves KH, Parlow AF, et al. Characterization of mice deficient in aromatase (ArKO) because of targeted disruption of the cyp19 gene. Proc Natl Acad Sci U S A. 1998;95(12):6965 [PubMed: 9618522]
128. Misso ML, Murata Y, Boon WC, Jones ME, Britt KL, Simpson ER. Cellular and molecular characterization of the adipose phenotype of the aromatase-deficient mouse. Endocrinology. 2003;144(4):1474 [PubMed: 12639931]
129. Van Sinderen M, Steinberg G, Jorgensen SB, et al. Sexual dimorphism in the glucose homeostasis phenotype of the Aromatase Knockout (ArKO) mice. J Steroid Biochem Mol Biol. 2017;170:39 [PubMed: 27353462]
130. Schomberg DW, Couse JF, Mukherjee A, Lubahn DB, Sar M, Mayo KE, Korach KS. Targeted disruption of the estrogen receptor-alpha gene in female mice: characterization of ovarian responses and phenotype in the adult. Endocrinology. 1999;140(6):2733. [PubMed: 10342864]
131. Park CJ, Zhao Z, Glidewell-Kenney C, Lazic M, Chambon P, Krust A, Weiss J, Clegg DJ, Dunaif A, Jameson JL, Levine JE. Genetic rescue of nonclassical ERα signaling normalizes energy balance in obese Erα-null mutant mice. J Clin Invest. 2011;121(2):604 [PubMed: 21245576]
132. Risma KA, Clay CM, Nett TM, Wagner T, Yun J, Nilson JH. Targeted overexpression of luteinizing hormone in transgenic mice leads to infertility, polycystic ovaries, and ovarian tumors. Proc Natl Acad Sci U S A. 1995;92(5):1322 [PubMed: 7877975]

133. Nilson JH, Abbud RA, Keri RA, Quirk CC. Chronic hypersecretion of luteinizing hormone in transgenic mice disrupts both ovarian and pituitary function, with some effects modified by the genetic background. Recent Prog Horm Res. 2000;55:69 [PubMed: 11036934]

134. Kero JT, Savontaus E, Mikola M, Pesonen U, Koulu M, Keri RA, Nilson JH, Poutanen M, Huhtaniemi IT. Obesity in transgenic female mice with constitutively elevated luteinizing hormone secretion. Am J Physiol Endocrinol Metab. 2003;285(4):E812 [PubMed: 12773309]

135. 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(5):E741 [PubMed: 20682841]

136. Sullivan EL, Rivera HM, True CA, et al. Maternal and postnatal high-fat diet consumption programs energy balance and hypothalamic melanocortin signaling in nonhuman primate offspring. Am J Physiol Regul Integr Comp Physiol. 2017;313;R169 [PubMed: 28404581]

137. Nicol LE, O'Brien TD, Dumesic DA, et al. Abnormal infant islet morphology precedes insulin resistance in PCOS-like monkeys. PLoS One. 2014;9;e106527 [PubMed: 25207967]

138. Martin B, Sacks DA. The global burden of hyperglycemia in pregnancy – Trends from studies in the last decade. Diabetes Res Clin Pract. 2018 4 19 pii: S0168–8227(18)30490-X. doi: 10.1016/j.diabres.2018.04.003.

139. Abbott DH, Vepraskas SH, Horton TH, et al. Accelerated Episodic Luteinizing Hormone Release Accompanies Blunted Progesterone Regulation in PCOS-like Female Rhesus Monkeys (Macaca Mulatta) Exposed to Testosterone during Early-to-Mid Gestation. Neuroendocrinology. 2018;107(2):133–146. [PubMed: 29949806] * Gestational androgen excess programs for GnRH/LH hypersecretion linked to insensitivity to progesterone negative feedback in PCOS-like monkeys.

140. Daniels TL, Berga SL. Resistance of gonadotropin releasing hormone drive to sex steroid-induced suppression in hyperandrogenic anovulation. J Clin Endocrinol Metab. 1997;82;4179. [PubMed: 9398736]

141. Eagleson CA, Gingrich MB, Pastor CL, et al. Polycystic ovarian syndrome: evidence that flutamide restores sensitivity of the gonadotropin-releasing hormone pulse generator to inhibition by estradiol and progesterone. J Clin Endocrinol Metab. 2000;85;4047 [PubMed: 11095431]

142. Broughton DE, Moley KH. Obesity and female infertility: potential mediators of obesity's impact. Fertil Steril. 2017;107;840 [PubMed: 28292619]

143. Dumesic DA, Patankar MS, Barnett DK, et al. Early prenatal androgenization results in diminished ovarian reserve in adult female rhesus monkeys. Hum Reprod. 2009;24;3188 [PubMed: 19740899]

144. Ahmad AK, Kao CN, Quinn M, et al. Differential rate in decline in ovarian reserve markers in women with polycystic ovary syndrome compared with control subjects: results of a longitudinal study. Fertil Steril. 2018;109;526 [PubMed: 29428308]

145. Lee S, Arslanian S. Body Composition and Cardiorespiratory Fitness Between Metabolically Healthy Versus Metabolically Unhealthy Obese Black and White Adolescents. J Adolesc Health. 2018 10 31 pii: S1054-139X(18)30408-7. doi: 10.1016/j.jadohealth.2018.08.024. [Epub ahead of print]

146. Keller E, Chazenbalk GD, Aguilera P, et al. Impaired preadipocyte differentiation into adipocytes in subcutaneous abdominal adipose of PCOS-like female rhesus monkeys. Endocrinology. 2014;155;2696 [PubMed: 24735327]

147. Xu N, Kwon S, Abbott DH, et al. Epigenetic mechanism underlying the development of polycystic ovary syndrome(PCOS)-like phenotypes in prenatally androgenized rhesus monkeys. PLoS One. 2011;6;e27286 [PubMed: 22076147]

148. Pervin S, Singh V, Tucker A, et al. Modulation of transforming growth factor-β/follistatin signaling and white adipose browning: therapeutic implications for obesity related disorders. Horm Mol Biol Clin Investig. 2017;31(2).

149. Sam S. Differential effect of subcutaneous abdominal and visceral adipose tissue on cardiometabolic risk. Horm Mol Biol Clin Investig. 2018;33(1).

150. Padmanabhan V, Cardoso RC, Puttabyatappa M. Developmental Programming, a Pathway to Disease. Endocrinology. 2016;157;1328 [PubMed: 26859334]

151. Moore AM, Campbell RE. Polycystic ovary syndrome: Understanding the role of the brain. Front Neuroendocrinol. 2017;46:1 [PubMed: 28551304]

152. Walters KA, Gilchrist RB, Ledger WL, et al. New Perspectives on the Pathogenesis of PCOS: Neuroendocrine Origins. Trends Endocrinol Metab. 2018 9 5 pii: S1043–2760(18)30149–8. doi: 10.1016/j.tem.2018.08.005. [Epub ahead of print]** Review outlines gene editing progress in mouse models and proposes neural molecular gateways for PCOS pathogenesis.

153. Ortega HH, Salvetti NR, Padmanabhan V. Developmental programming: prenatal androgen excess disrupts ovarian steroid receptor balance. Reproduction. 2009;137;865 [PubMed: 19261835]

154. Veiga-Lopez A, Moeller J, Abbott DH, et al. Developmental programming: rescuing disruptions in preovulatory follicle growth and steroidogenesis from prenatal testosterone disruption. J Ovarian Res. 2016;9;39. [PubMed: 27357284]

155. De Leo V, Lanzetta D, D'Antona D, et al. Hormonal effects of flutamide in young women with polycystic ovary syndrome. J Clin Endocrinol Metab. 1998;83;99 [PubMed: 9435423]

156. Caldwell AS, Eid S, Kay CR, et al. Haplosufficient genomic androgen receptor signaling is adequate to protect female mice from induction of polycystic ovary syndrome features by prenatal hyperandrogenization. Endocrinology. 2015;156(4):1441. [PubMed: 25643156]

157. Caldwell ASL, Edwards MC, Desai R, et al. Neuroendocrine androgen action is a key extraovarian mediator in the development of polycystic ovary syndrome. Proc Natl Acad Sci U S A. 2017;114;E3334 [PubMed: 28320971] * Androgen action in the brain key to PCOS-like pathogenesis in mice.

158. Silva MS, Prescott M, Campbell RE. Ontogeny and reversal of brain circuit abnormalities in a preclinical model of PCOS. JCI Insight. 2018;3(7).* Extant androgen in female mice key to maintaining fetal androgen programming of hypothalamic morphology supporting LH, as well as T, hypersecretion.

159. Moore AM, Prescott M, Marshall CJ, et al. Enhancement of a robust arcuate GABAergic input to gonadotropin-releasing hormone neurons in a model of polycystic ovarian syndrome. Proc Natl Acad Sci U S A 2015;112:596. [PubMed: 25550522]

160. Dunaif A, Chang RJ, Franks S, et al. Polycystic Ovary Syndrome: Current Controversies, from the Ovary to the Pancreas. 2008 Humana Press, Totowa, NJ.

161. Tomaszycki ML, Gouzoules H, Wallen K. Sex differences in juvenile rhesus macaque (Macaca mulatta) agonistic screams: life history differences and effects of prenatal androgens. Dev Psychobiol. 2005;47(4):318–327. [PubMed: 16284962]

162. Herman RA, Wallen K. Cognitive performance in rhesus monkeys varies by sex and prenatal androgen exposure. Horm Behav. 2007;51(4):496–507. [PubMed: 17335823]

163. Wallen K. Hormonal influences on sexually differentiated behavior in nonhuman primates. Front Neuroendocrinol. 2005;26(1):7–26. [PubMed: 15862182]

164. Holt RI, Lambert KD. The use of oral hypoglycaemic agents in pregnancy. Diabet Med. 2014;31(3):282–91. [PubMed: 24528229]

165. Glueck CJ, Pranikoff J, Aregawi D, et al. Prevention of gestational diabetes by metformin plus diet in patients with polycystic ovary syndrome. Fertil Steril. 2008;89(3):625–634. [PubMed: 17678910]

166. Hjorth-Hansen A, Salvesen Ø, Engen Hanem LG, et al. Fetal Growth and Birth Anthropometrics in Metformin-Exposed Offspring Born to Mothers With PCOS. J Clin Endocrinol Metab. 2018;103(2):740–747. [PubMed: 29165598]

167. Hanem LGE, Stridsklev S, Júlíusson PB, et al. Metformin Use in PCOS Pregnancies Increases the Risk of Offspring Overweight at 4 Years of Age: Follow-Up of Two RCTs. J Clin Endocrinol Metab. 2018;103(4):1612–1621. [PubMed: 29490031] * Clinical trial provides cautionary tale concerning therapeutic gestational intervention to ameliorate PCOS onset in girls at risk for PCOS.

168. Barbour LA, Scifres C, Valent AM, et al. A cautionary response to SMFM statement: pharmacological treatment of gestational diabetes. Am J Obstet Gynecol. 2018;219(4):367.e1–367.e7. [PubMed: 29959933]

169. Løvvik TS, Carlsen SM, Steffensen B, et al. Metformin Treatment of Pregnant Women with Polycystic Ovary Syndrome - A Randomized, Nordic Multi-Center Trial. OR33–4. Endocr Rev 2018;38(2, Suppl.):OR33–4.

170. Biondani G, Peyron JF. Metformin, an Anti-diabetic Drug to Target Leukemia. Front Endocrinol (Lausanne). 2018;9:446. [PubMed: 30147674]

171. Sir-Petermann T, Codner E, Maliqueo M, et al. Increased anti-Müllerian hormone serum concentrations in prepubertal daughters of women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2006;91(8):3105–3109. [PubMed: 16720659]

172. de Zegher F, Lopez-Bermejo A, Ibáñez L. Adipose tissue expandability and the early origins of PCOS. Trends Endocrinol Metab. 2009;20(9):418–423. [PubMed: 19796964]

173. Dumesic DA, Akopians AL, Madrigal VK, et al. Hyperandrogenism Accompanies Increased Intra-Abdominal Fat Storage in Normal Weight Polycystic Ovary Syndrome Women. J Clin Endocrinol Metab. 2016;101(11):4178–4188. [PubMed: 27571186] * Study demonstrates testosterone-mediated adipogenic constraint in abdominal subcutaneous adipose depot in normal weight women with PCOS and its potential to contribute to lipotoxcity.

174. Harnois-Leblanc S, Trottier A, Leblanc S, et al. Evolution of metabolic alterations 5 Years after early puberty in a cohort of girls predisposed to polycystic ovary syndrome. Reprod Biol Endocrinol. 2017;15(1):56. [PubMed: 28738839]

175. Han SY, Clarkson J, Piet R, et al. Optical Approaches for Interrogating Neural Circuits Controlling Hormone Secretion. Endocrinology. 2018;159(11):3822–3833. [PubMed: 30304401]

176. Levine JE, Kraynak M, Willging MM, et al. Hypothalamic ERa Gene Silencing Induces Obesity in Female Rhesus Monkeys. Endocr. Rev 2018;39(2) Suppl:SUN-072.

177. Seita Y, Tsukiyama T, Iwatani C, et al. Generation of transgenic cynomolgus monkeys that express green fluorescent protein throughout the whole body. Sci Rep. 2016;6:24868. [PubMed: 27109065]

Table 1.

Classification of Phenotypes in women with PCOS Diagnosed by Rotterdam Criteria and Their Differential Contribution to Clinical Referral versus Unselected Human Populations

	PCOS Phenotype[1] (% of PCOS individuals)			
Female Population	**Type A**	**Type B**	**Type C**	**Type D**
PCOS women[2] (from clinical referrals)	49	13	14	17
PCOS women[3] (from unselected human populations)	25	19	35	20

[1]Type A: hyperandrogenism or hirsutism (HA) + intermittent/absent cycles (OD) + (polycystic ovary morphology) (PCOM); Type B: HA + OD; Type C: HA + PCOM; Type D: OD + PCOM, as described in [8].

[2]Derived from [1,9,10]

[3]Derived from [8]

Table 2.

PCOS-like reproductive and metabolic traits exhibited by fetal androgen excess animal models in adulthood, and by naturally occurring, hyperandrogenic adult female monkeys.

Species	Gestation stage	Route, treatment	Hyper-androgenism	Intermittent, absent cycles	Polycystic ovaries	Diminished fertility	Increased LH	Increased adiposity	Insulin resistance	Pancreatic defect	Key Citations
Monkey	Early-to-mid	M, TP	+	+	+	+	+	+	+	+	[89–95]
	Early-to-mid	M, DHTP	?	+	?	?	?	?	?	?	[96]
	Early-to-mid	M, T (low dose)	−	−	?	−	+	?	?	?	[97,98]
	Late	M, TP	+	+	?	−	−	+	−	−	[99]
	Late	M, letrozole[a]	−	+	−	?	−	−	+	−	[100–103]
	Naturally occurring	None	+	−	+	+	+	?	+[d]	?	[8]
Sheep	Early-to-late	M, T	+/−	+	+	+	+	+	+	?	[104–107]
	Early-to-late	M, DHT	−	+	−	?	+	?	?	?	[108,109]
	Early-to-late	M, T, flutamide[b]	−	−	−	?	−	+	+	?	[110–111]
	Early-to-mid	M, T, rosiglitazone[c]	−	+	?	?	−	+	−	?	[111,112]
	Mid-to-late	M, T	−	−	−	+	+	−	+	?	[113–115]
	Mid-to-late	F, T	−	?	?	?	?	−	+	?	[116–118]
Rat	Late	M, T	+	+	−	+	+	+	−	?	[119,120]
	Late	M, DHT	+	+	Cystic	+	+	+	?	?	[121,122]
Mouse	Late	M, DHT	+	+	−	+	+	−	−	+	[123,124]
	Late	M, AMH	+	+	Cystic	+	+	−	−	−	[69]
	All	ARKO	−	+	−	+	−	−	?	?	[125,126]
	All	NeuroARKO	−	−	+	−	−	−	?	?	[127]
	All	AromKO	+	+	Cystic	+	+	+	−	?	[128,129]
	All	ERaKO	+	+	Cystic	+	+	+	+	?	[130,131]
	All	LHR excess	+	+	Hemorrhagic	+	+	+	+	?	[132–134]

Key to terms used:

[a] letrozole, aromatase enzymatic inhibitor resulting in gestational maternal hyperandrogenism;

[b] flutamide, androgen receptor antagonist (anti-androgen);

[c] rosiglitazone, PPAR gamma agonist (pro-adipogenic);

[d] unpublished results; M, administered to dam; F, administered to fetus; P, propionate; DHT, dihydrotestosterone; letrozole, aromatase inhibitor; ARKO, androgen receptor knockout; NeuroARKO, neuron-specific ARKO; AromKO, aromatase knockout; ERaKO, estrogen receptor alpha knockout; LHR, LH receptor; Cystic, large follicle cysts and Hemorrhagic, blood clot-filled follicles, but neither pathology emulates PCOS-like, excessively numerous, non-dominant antral follicles.