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Translational Insight Into Polycystic Ovary Syndrome (PCOS) From Female Monkeys with PCOS-like Traits

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Abstract

Genetics-based studies of women with polycystic ovary syndrome (PCOS) implicate >20 PCOS risk genes that collectively account for <10% of PCOS. Clinicians now consider that either rare alleles or non-genetic, potentially epigenetic, developmental origins may contribute key pathogenic components to >90% of PCOS cases. Animal models convincingly demonstrate excess fetal testosterone exposure in females as a reliable, epigenetic, developmental origin for PCOS-like traits. In particular, nonhuman primates (NHPs) provide the most faithful emulation of PCOS-like pathophysiology, likely because of close similarities to humans in genomic, developmental, reproductive and metabolic characteristics, as well as aging. Recent appreciation of potential molecular mechanisms contributing to enhanced LH action in both PCOS women (GWAS-based) and PCOS-like monkeys (DNA methylation-based) suggest commonality in pathogenic origins. This review examines the translational relevance of NHP studies to PCOS, identifying characteristics of newborn females at risk for PCOS-like traits and potential prepubertal treatment interventions to ameliorate PCOS onset.

Keywords

Androgen excess; developmental origins; fetal programming; Barker hypothesis; gestational hyperglycemia; lipotoxicity; animal models

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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BACKGROUND

Polycystic ovary syndrome (PCOS), while prevalent (~15%), highly familial, and with an onset in adolescence, has no known cause [1]. Women with PCOS exhibit at least two of the following three diagnostic criteria: clinical or biochemical hyperandrogenism, intermittent or absent menstrual cycles and/or polycystic ovaries. Establishing the diagnosis of PCOS in adolescence, however, is contentious because of considerable overlap between true PCOS and normal, transient adolescent androgen excess, intermittent menstrual cycles and metabolic fluctuations [2, 3]. Accompanying PCOS sequelae include luteinizing hormone (LH) hypersecretion, antimullerian hormone (AMH) overproduction, insulin resistance and obesity, together with increased risks for metabolic syndrome, type 2 diabetes, gestational diabetes and endometrial cancer [1]. PCOS pathophysiology thus extends well beyond ovarian dysfunction to include hypothalamic dysregulation and, perhaps more concerning, increased risks for metabolic disease and cancer associated with long-term morbidity and mortality [4, 5].

Contemporary understanding of PCOS considers its etiology as polygenic, with developmental origins likely preceding puberty [1, 6, 7]. At least 21 replicated candidate genes have been identified, regulating gonadotropin secretion and action, extracellular matrix development and a variety of common cellular functions [6, 8]. Each, however, accounts for only a small percentage of the estimated 70% heritability of PCOS, implying a considerable epigenetic contribution to the phenotypic expression of PCOS [9, 10]. The most comprehensive epigenetic phenotypes that mimic PCOS arise from animal models that employ experimentally-induced fetal testosterone(T) excess to permanently induce ('program') PCOS-like reproductive and metabolic traits in female rodents [11–13], sheep [14, 15] and nonhuman primates(NHPs) [16, 17]. The absence of a naturally occurring PCOS animal model, however, has hindered progress towards understanding pathogenic mechanisms that may bestow both genetic and epigenetic contributions to the etiology of PCOS.

Macaque monkeys, including rhesus (*Macaca mulatta*) and cynomolgus (*M. fascicularis*), share over 90% of their genome with humans, and provide close parallels throughout fetal, infant and juvenile development in regards to reproduction, metabolism and aging [17]. Experimental induction of T excess in fetal female rhesus macaques during early-to-mid gestation provides the most faithful emulation of PCOS in women (Table 1) [17–19]. Apart from humans, moreover, female macaques are unique in exhibiting naturally-occurring, PCOS-like phenotypes [20, 21], as well as demonstrating concomitant external genital biomarkers indicative of fetal T excess [21–23]. Gestational T excess, whether experimentally-induced or naturally-occurring, may thus provide an early developmental origin for life-long epigenetic changes to the female macaque genome that closely mimic both genetic and epigenetic components of PCOS women.

This review will consider the developmental origins of PCOS-like traits in T-exposed female fetal macaques by first exploring a newborn female phenotype preceding adult PCOS-like pathophysiology, and then discussing how such findings may forge translational approaches to basic science and clinical medicine in the field of PCOS. We will focus on T exposure

during early-to-mid gestation, and not late gestation or starting before puberty, since the former best emulates PCOS in the NHP model [17]. We will include preliminary studies of naturally-occurring high T adult female monkeys as an additional NHP model that combines genetic/epigenetic components in the developmental origin for PCOS and its accompanying sequelae in PCOS women.

HYPERANDROGENIC GESTATIONAL CONTRIBUTIONS TO PCOS-LIKE TRAITS

Neuroendocrine-Related

From rodents [11–13] and sheep [14, 15] to NHPs [16–18], animal studies overwhelmingly demonstrate how fetal T excess, and likely accompanying gestational hyperglycemia and hyperinsulinemia [24–26], provide developmental origins for PCOS-like phenotypes. Experimental induction of T exposure in NHPs is achieved by daily injection of macaque dams with 10–15 mg T propionate (TP) during early-to-mid gestation. Such maternal treatment overwhelms substantial placental capacity to aromatize and inactivate T, and raises circulating T levels in fetal females to those normally found in comparably aged fetal males [27]. This discrete androgen excess distinguishes the fetal NHP model from those in non-primates, such as sheep [26], because fetal estradiol in NHPs remains at normal female levels and does not increase [27], due in part to estrogen conjugation.

Following cessation of TP injections at mid-gestation, circulating fetal levels of pituitary LH and follicle stimulating hormone (FSH) dramatically increase, likely due to escape from T-imposed negative feedback and consequent increased release of hypothalamic gonadotropin-releasing hormone (GnRH), illustrating a possible male-like outcome of T programming on negative feedback at the fetal female hypothalamus-pituitary level [27]. T-exposed fetal females thus resemble fetal males in precocious development of negative feedback regulation of GnRH/LH [28], likely mediated through de-sensitized estradiol and/or progesterone mediated mechanisms [13, 18, 29, 30]. Such PCOS-like, de-sensitized negative feedback regulation of GnRH/LH is also pronounced in T-exposed female rodents [31] and sheep [32], but unlike those non-primate species, positive feedback regulation of the ovulation-inducing LH surge remains functional in T-exposed and high T adult female monkeys, as it does in PCOS and high T women (Table 1). Adult T-exposed female NHPs, in contrast to fetal counterparts, do not exhibit elevated circulating FSH levels probably due to matured ovarian negative feedback, and emulating PCOS women in whom FSH levels are either normal or low [33].

In a recent revival of the importance of this neuroendocrine-related PCOS pathophysiology, genetic studies in women implicate dysregulated LH release [10, 34, 35, 36] or action [6, 9, 37–40] in the PCOS pathogenic mechanism. In the T-exposed NHP model, altered gene expression involving LH signaling is also implicated from gene network analysis of DNA methylation changes in T-exposed infant and adult monkeys [41]. In the T-exposed female sheep model, deficient LH signaling also has been recently implicated in abnormal ovarian follicle development [42]. Taken together, these findings suggest that dysfunctional LH signaling may promote ovarian hyperandrogenism [40], which impairs steroid negative

feedback to further exaggerate LH hypersecretion [43], implicating excessive LH release as a primary characteristic of women who ultimately manifest PCOS. This feed-forward amplification hypothesis is illustrated in Fig. 2. Figure 3 additionally illustrates the overlap between recently hypothesized molecular dysfunction of LH signaling in PCOS [40] and related LH signaling abnormalities identified through DNA methylation analyses of T-exposed female monkeys [41].

Ovarian-Related

No endogenous fetal hyperandrogenism becomes apparent in T-exposed fetal female monkeys following exogenous induction of T excess [27]. Postnatal evidence of their exogenous T exposure presents in the form of lengthened anogenital distance (a biomarker of fetal T exposure) that is positively correlated with their duration of exogenous T treatment [23]. Interestingly in this regard, naturally occurring high T females may also experience fetal hyperandrogenism. They exhibit positive correlations between circulating androgen levels and anogenital distance, as well as between clitoral volume and postnatal age. These associations strongly suggest that naturally occurring high T females experience endogenous T excess from at least mid-gestation [21–23]. Recently, lengthened newborn anogenital distance [44], and mid-gestation amniotic fluid T excess [45], have been shown in daughters of women with PCOS, strongly implicating mid-gestational T excess during human female fetal development with the likely acquisition of PCOS in later life. Certainly, the fetal human mid-gestational ovary has developed androgen biosynthetic capacity and androgen receptors [46, 47], in analogous ovarian developmental progression to the monkey [48].

As another biomarker of fetal T exposure, adult second-to-fourth (2D: 4D) finger length ratio correlates with anogenital distance and duration of exogenous T in female NHPs [23]. Consistent with a fetal T origin, women with PCOS also exhibit lengthened 2D: 4D finger length ratios [49, 50], although another study found a more masculinized finger length ratio in PCOS women [51]. To illustrate PCOS-like dysfunction programmed by gestational exposure to excess T in female monkeys, Fig. 2 employs a fetal origins of disease approach [52, 53], with an emphasis on LH and T excess as causal factors that develop into a feed-forward, amplification loop. As illustrated in Fig. 2, early onset elevation of circulating insulin levels (as discussed below) may contribute additional metabolic dysfunction to such a feed-forward process.

Following birth, infant T-exposed female monkeys are hyper-androgenic [27]. Their endogenous hyperandrogenism may originate from ovarian production, potentially driven by high circulating LH levels acting on LH receptors in the ovary [54]. The early onset of this hyperandrogenic function in young female, T-exposed monkeys emulates increased 5 alpha-reductase activity found in 1–3 year old daughters of women with PCOS [7], suggesting comparably developmental onsets of PCOS-like androgenic activity in female monkeys and humans. The ovaries of infant T-exposed monkeys, however, are not polycystic and contain age-appropriate numbers of follicles, but exhibit diminished follicle commitment to growth (unpublished results) suggestive of disrupted follicle development. By adolescence, prior fetal T exposure delays menarche and promotes luteal phase insufficiency in initial

menstrual cycles compared to controls [55], suggesting a perturbed hypothalamic-pituitary-ovarian axis at the onset of reproductive maturity in PCOS-like animals.

In contrast to female infant monkeys that experienced T excess during early-to-mid gestation, 40% of similarly T-exposed females when adult exhibit large, polycystic ovaries [18] with accompanying ovarian [56] and adrenal [57] hyperandrogenism combined with intermittent or absent menstrual cycles [18]. Increased body mass index (BMI) exaggerates absence of menstrual cycles [58]. The adult T-exposed monkeys thus show all the diagnostic hallmarks of women with PCOS, including the diversity of phenotypes defined by NIH [59], “Rotterdam” [60] or Androgen Excess-PCOS Society criteria [61]. When monkey equivalents of the PCOS diagnostic criteria are applied to individual T-exposed adult female macaques [62], 42% exhibit classic PCOS (combining the two PCOS phenotypes: hyperandrogenism + intermittent/absent cycles + polycystic ovaries; and hyperandrogenism + intermittent/absent cycles) and 25% show the milder two forms (hyperandrogenism + polycystic ovaries; and intermittent/absent cycles + polycystic ovaries). Surprisingly, phenotyping these monkeys as PCOS-like accounts for only 67% of T-exposed adult females. Neither mild variations in duration of T exposure [23, 62], and elevation of circulating fetal T levels [27], nor reliable responses of androgen sensitive fetal tissues [23], explain the absence of PCOS-like phenotypes in 33% of T-exposed females or differences in PCOS-like phenotypic expression. Different maternal responses to T-exposure (see Metabolic-related section, below) and/or differences in fetal female genome may be key modifiers of endogenous or exogenous fetal T exposure. Such phenotypic diversity from a discrete, homogenous gestational elevation of T may reflect multiple “hits” contributing to the development of adult disease: namely, genetic variation upon which epigenetic reprogramming from gestational T or glucose excess (see below) promotes susceptibility to PCOS-like phenotypic expression in the presence of increased postnatal weight gain. Animal and human studies are increasingly implicating such complex developmental origins.

Metabolic-Related

In addition to gestational T exposure, fetal T-exposed female monkeys experience transient, mid-gestational hyperglycemia from their dams’ diminished ability to regulate glucose [24], a trait emulated by T-treated pregnant ewes that deliver T-exposed female lambs [25]. As might be expected from such gestational hyperglycemia, fetal female size increases, along with a ~5% enlarged ultrasonography-assessed head diameter, elevated late gestation circulating insulin levels (exceeding the control range in 33–55% of cases), and abnormal fetal lipids levels [24]. Gestational T exposure per se, however, may also induce fetal hyperinsulinemia, since direct injections of T into fetal female sheep induce hyperinsulinemic responses to glucose [63], and beta cells of such T-exposed fetal females express androgen receptors [63]. These findings raise the possibility of combined contributions from fetal T excess and gestational hyperglycemia on subsequent development of female offspring hyperinsulinemia, as illustrated in Fig. 2.

Consistent with these findings in T-exposed female monkeys, pre- and peripubertal daughters of women with PCOS exhibit hyperinsulinemic responses to glucose when compared to peers born to women without PCOS [64–66]. Pancreatic decompensation [67,

68] and insulin resistance become obvious in PCOS daughters later in puberty [68, 69], but may have been undetected at a younger age due to the absence of dynamic testing.

As expected in hyperglycemic pregnancies, 55% of newborn T-exposed infants are transiently hypoglycemic, exhibit relative hyperinsulinemia [24], and demonstrate a greater proportion of beta-to-alpha cells in their pancreatic islets, the latter positively correlated with infant insulin levels [70]. Taken together, these results suggest onset of abnormal pancreatic islet beta cell function and morphology in infancy that precedes PCOS-like insulin-related defects in adulthood [71]. Not surprisingly, relative hyperinsulinemia in hyperandrogenic T-exposed infants that are insulin sensitive accelerates the increase in body weight over time [24].

At menarche, T-exposed females are older and heavier than contemporary controls [55]. In adulthood, T-exposed adult female monkeys exhibit preferential accumulation of visceral fat without differences in BMI [72, 73], DNA methylation changes in visceral fat gene promoter sites [41], and a defect in subcutaneous abdominal adipogenesis [74]. Taken together, these results suggest a diminished ability to safely store lipid in subcutaneous adipose depots, resulting in dyslipidemia from lipotoxicity with insulin resistance, pancreatic beta cell and islet morphology defects, as well as type 2 diabetes mellitus [66–68, 70]. Such adult female metabolic dysfunction may result from a combination of gestational hyperglycemia and T excess promoting postnatal insulin-driven fat storage, in parallel with T-constrained subcutaneous adipogenesis, leading to lipotoxicity and metabolic dysfunction. Fig. 2 illustrates this metabolically-related programming in our experimentally induced, T-exposed monkeys, with an emphasis on hyperinsulinemia and T excess as causal factors. The development of hyperinsulinemia from insulin resistance with reduced hypothalamic steroid negative feedback leading to LH hypersecretion would constrain through androgen excess the capacity of normal adipose to safely store fat, leading to lipotoxicity, metabolic dysfunction and reproductive PCOS-like traits, as has also been proposed for girls who will likely manifest PCOS [66, 68]. The combination of reproductive and metabolic developmental origins may thus comprise a more complete fetal origin for PCOS, since gestational diabetes, common among pregnant women with PCOS [77, 78], increases the incidence of obesity-related insulin resistance in offspring [79, 80], but not the full PCOS phenotype. Interestingly, recent exploration of molecular pathogenesis underlying LH signaling dysfunction in PCOS also implicates dysfunctional insulin signaling, as illustrated in Fig. 3 modified from [40], suggesting that molecular bases for PCOS-like phenotypes among women, and possibly monkeys, may have common elements. Weight gain linked to dyslipidemia is certainly part of a hyperandrogenic adolescent progression into PCOS in women [82].

Pre-Pubertal Exposure to Exogenous High T

One NHP model, employing a pre-pubertal onset of exogenous high T treatment, induces transient LH hypersecretion and increased body weight, but without accompanying ovarian hyperandrogenism, menstrual cycle dysfunction and altered glucose regulation [83]. Subsequent addition of a high fat diet, increases body weight in T-exposed and control females, but increases ovarian follicle recruitment in T-exposed females alone [19]. Such

polyfollicular ovarian presentation, however, occurs without ovarian hypersecretion of AMH [83], in contrast to elevated AMH levels found in PCOS women and their daughters [84, 85]. At present, it is unclear whether initiating such exposure to high T preceding puberty produces mild aspects of PCOS-like traits or merely induces anabolic hormone-like disruption of female physiology.

Translation Relevance of NHP High T Female Models to PCOS

One major translational issue exists, however, between NHP models and curative therapies in humans. At present, we cannot safely obtain blood samples from human fetuses during mid-gestation in order to confirm high circulating T levels in girls who will develop PCOS as adults [71]. So our ability to link fetal T exposure with development of PCOS in women remains unattainable, and constrains development of a preventive health-care strategy. Therefore, since current clinical practice has yet to develop safe and routine methods for evaluation of the human fetal hormonal milieu, investigation of developmental origins of PCOS in humans has relied on indirect assessments or postnatal outcomes considered as biomarkers of fetal T excess. In this regard, anogenital distance and lengthened 2D: 4D finger length ratio, biomarkers of mid-gestation fetal T exposure characteristic of T-exposed female monkeys [23], are associated with PCOS [44, 49–50]. Naturally occurring high T female monkeys also exhibit an association between circulating T levels and anogenital distance [22]. These reports increasingly provide circumstantial evidence for mid-gestation androgen excess in PCOS pregnancies.

In addition, since pregnant PCOS women have elevated circulating T levels [86, 87], subtle reductions in placental aromatase [88] may expose female offspring to elevated T during gestation. Interestingly, elevated mid-gestation serum T levels in PCOS mothers predict in their adolescent daughters elevated levels of AMH, a transforming growth factor- β (TGF- β) superfamily protein normally produced by granulosa cells of preantral and small antral ovarian follicles [89]. As elevated AMH levels are characteristic of adolescents and women with PCOS [84, 90] and newborn daughters of PCOS women [85], such high AMH levels may represent a cross-generational outcome of hyperandrogenism on the development of PCOS in daughters. Mid-gestational human female fetuses may generate their own T excess (Fig. 1) as their ovaries become capable of producing [46] and responding [47] to androgens, as evidenced by elevated mid-gestational amniotic fluid levels of T in fetal daughters of women with PCOS [45].

Perinatal studies vary in their support of gestational T exposure as a fetal programming origin for PCOS, possibly because onset of labor variably reduces T levels in umbilical cord blood [91]. In studies of umbilical cord venous blood levels in newborn daughters born to women with PCOS, one study shows elevated T levels [92], whereas two studies show reduced androstenedione levels [88, 93] and one shows normal T levels [87]. In a fourth study involving adolescent girls diagnosed with PCOS, and including an inherently high prevalence (~28%) of diagnosis at this young age, umbilical cord blood shows no elevation in T levels [94]. With the fetal ovary as a key site for gestational T excess during mid-gestational target tissue differentiation [44, 45], studies of infants at birth are likely to be too late to detect any remaining hormonal differences [95]. Quantification of androgens in the

scalp hair of newborn, however, holds promise for discerning prevailing fetal androgen levels during the third trimester [96] and a more relevant measure of fetal T levels.

Overall, the current evidence from NHP and non-primate models, together with human studies, implicates the gestational environment in the ontogeny of PCOS. Such a hypothesis supports a long-standing developmental origins basis for PCOS [58, 97, 98] that may provide key opportunities to implement early intervention.

Therapeutic Translation from Animal Models to Treatment of PCOS Women

To date, no NHP studies have attempted prenatal or pre-pubertal therapies to prevent or ameliorate PCOS-like outcomes. Therapeutic treatment of adult T-exposed females, however, has been conducted using six months of daily insulin sensitizer (PPAR-gamma agonist, pioglitazone). Such treatment of T-exposed females with insulin sensitizer restores ovulatory menstrual cycles, diminishes ovarian androgenic responses, improves insulin-mediated glucose regulation without weight gain, but does not correct LH hypersecretion [99]. Impaired insulin signaling thus underlies both impaired glucose regulation and ovarian dysfunction, as found in PCOS women [100] and T-exposed ewes [101]. Notably, hypothalamic dysregulation of LH release may not involve a component of impaired insulin signaling in T-exposed monkeys, and pioglitazone is inconsistent in its ameliorating effects on LH hypersecretion in PCOS women [102, 103]. This potential separation of dysfunctional components of PCOS pathogenesis is reflected in the hypothetical mechanism illustrated in Fig. 2.

Prenatal therapies, however, have been attempted in sheep, employing anti-androgen (androgen receptor antagonist, flutamide) and insulin sensitizer (PPARgamma agonist, rosiglitazone) administration to ewe dams receiving T injections during early-to-mid gestation. In T-exposed female lambs, prenatal anti-androgen normalizes anogenital distance, prevents early onset of puberty, normalizes LH surge responses to estrous synchronization in the first breeding season, but does not ameliorate metabolic abnormalities [15, 25]. In comparison, insulin sensitizer prenatal treatment prevents insulin resistance and normalizes onset of puberty. As both prenatal treatments normalize puberty onset, perturbed androgenic and metabolic aspects of the fetal environment may regulate hypothalamic-mediated onset of reproductive maturity.

Proposing to treat pregnant PCOS women with anti-androgen or insulin sensitizers, however, are not attractive options. Anti-androgens compromise male fetal development and development of normal female behavior [104]. Insulin sensitizers, such as pioglitazone and rosiglitazone, are potential teratogens [105]. The insulin sensitizer, metformin, while a class B drug categorized as safe for pregnant women, has raised concerns regarding increased infant weight gain and elevated basal glucose levels in pre-adolescent daughters of PCOS women [106, 107], although high AMH and estradiol levels are normalized in infant daughters of PCOS women who received metformin throughout pregnancy [85]. Evaluating efficacy of prenatal treatments in ameliorating PCOS-like outcomes in NHP models could provide timely translatable findings (in ~5–8 years) without risk to future human generations.

A safer approach involves pre-pubertal intervention to ameliorate PCOS onset. In T-exposed sheep, anti-androgen or metformin treatments commencing before puberty ameliorate aspects of reproductive dysfunction, including precocious puberty [53]. Not surprisingly, insulin sensitizer treatment alone or combined with anti-androgen, has proved efficacious in ameliorating reproductive and metabolic dysfunction in adolescent girls suspected of having PCOS or demonstrating hyperandrogenic anovulation [108, 109]. Early clinical intervention in adolescents suspected of having PCOS, however, needs to be delayed until at least 2 years after menarche due to the transient changes in ovarian function that accompany the onset of puberty [1, 110]. Early intervention, however, may be the key to efficacious prevention of PCOS pathogenesis illustrated in Fig. 2. In this respect, beneficial outcomes following therapeutic reversal of adiposity and insulin resistance in adolescent girls with hyperinsulinemic hyperandrogenism (attributes that commonly precede PCOS) are encouraging. One year of combined anti-androgen and insulin sensitizer treatment enabled at least 9–12 months (study ongoing) of normal, ovulatory menstrual cycles following cessation of treatment. In contrast, onset of anovulation followed cessation of an identical duration of oral contraceptive therapy in a comparable hyperinsulinemic and hyperandrogenic peer group [111].

CONCLUSION

NHP, sheep and many rodent models, identify T excess during fetal life as a reliable developmental origin for PCOS-like traits. Recent genetic and morphological studies of PCOS women and their daughters have also implicated developmental origins, fetal T excess and potentially epigenetic changes in the etiology of PCOS. Future studies employing individual genotyping of NHPs with naturally occurring high T and PCOS-like traits may shed novel insight on molecular mechanisms contributing to the pathogenesis of PCOS.

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Biography



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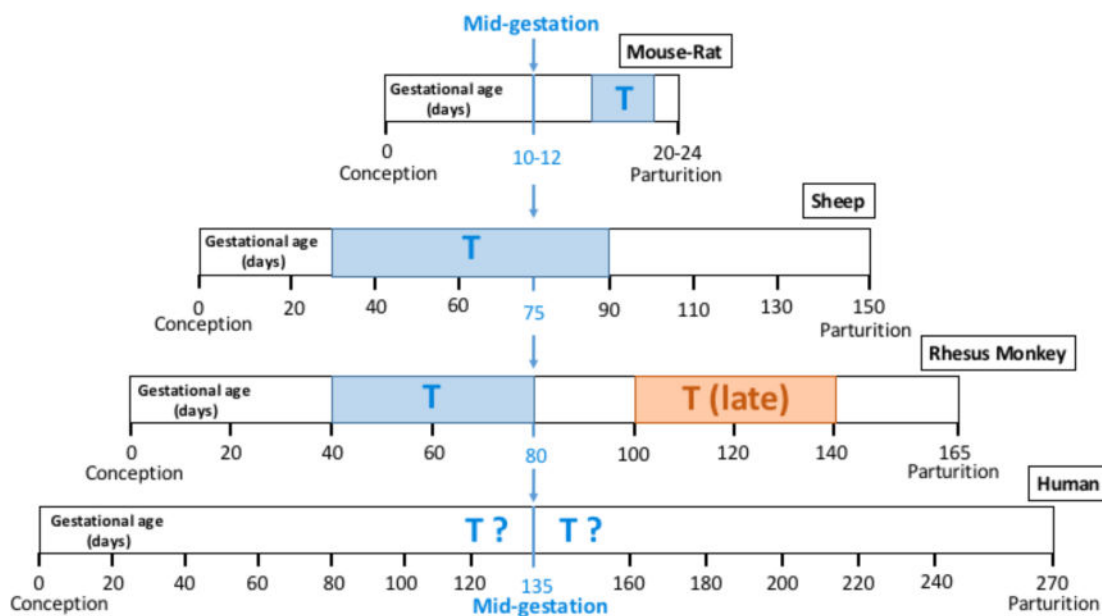


Fig. (1).

Diagrammatic representation of gestational ages at fetal T exposure resulting in PCOS-like traits (blue boxes with T) in female mice and rats [11–13], sheep [14, 15] and rhesus monkeys [16–18]. All gestational periods are aligned at mid-gestation. Effective T exposure drifts progressively earlier in gestation when comparing rodents to sheep to monkeys, reflecting relatively earlier onset of organ differentiation with respect to both mid-gestation and parturition in sheep and monkeys. In monkeys, however, late gestation T exposure (brown box with “T (late)”) produces a sufficient degree of PCOS-like phenotype to suggest that, at least in primates, the gestational developmental window for T programming of PCOS-like traits may span either side of mid-gestation [17, 18]. The hypothesized mid-gestational ages during which girls may be vulnerable to fetal T exposure contributing to PCOS development (blue “T?”) avoid the potential for obvious genital virilization in early gestation (ambiguous genitalia are rare in newborn daughters of women with PCOS), are consistent with occurrence of high T levels in PCOS daughters during mid-gestation [45] and with the ability of the human fetal ovary to synthesize and respond to T [46, 47], and take into account the continuing vulnerability for T exposure inducing PCOS-like attributes beyond mid-gestation [17].

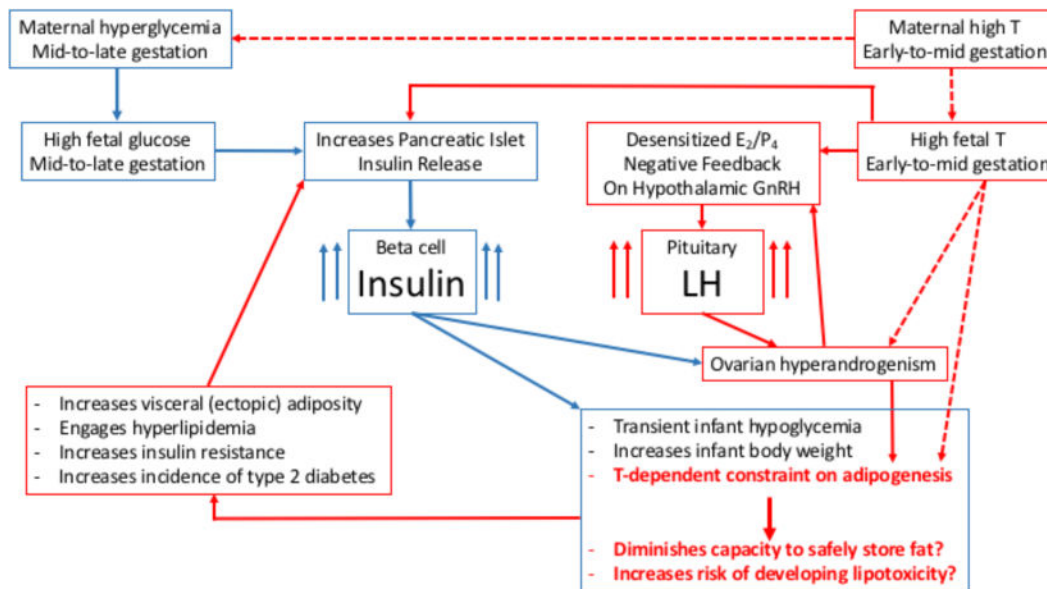


Fig. (2). Diagrammatic representation of hypothesized contributions from fetal testosterone (T) excess and gestational hyperglycemia to subsequent LH and insulin hypersecretion and postnatal PCOS-like metabolic and reproductive pathophysiology in NHP models for PCOS. Dashed arrows indicate hypothesized fetal programming that has not yet been demonstrated in sheep or monkeys.

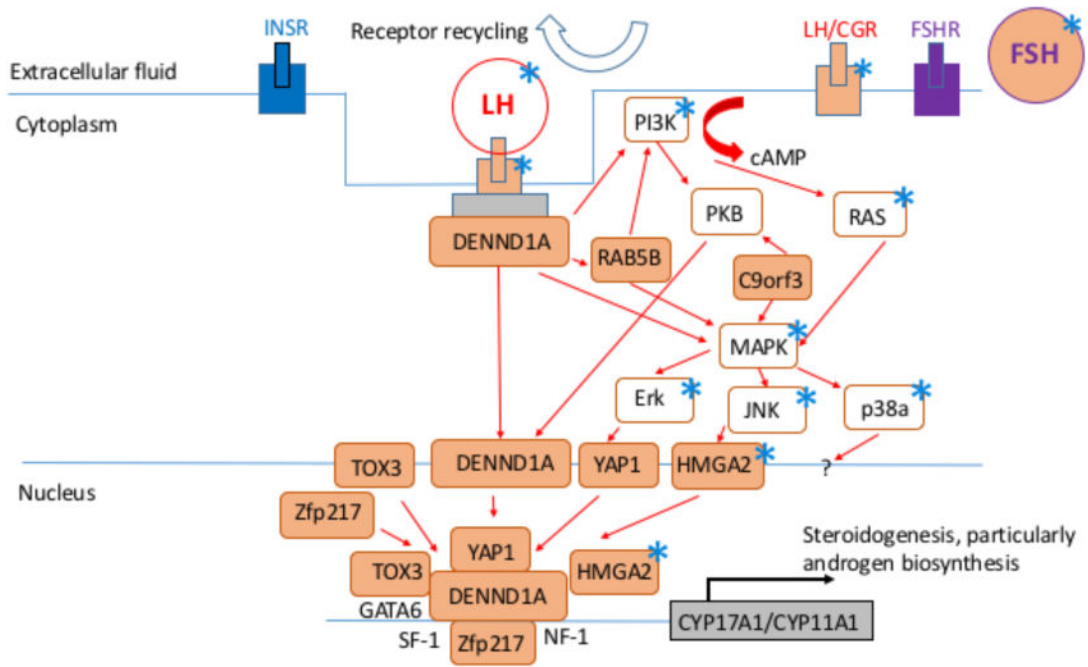


Fig. (3). Diagrammatic representation of hypothesized molecular mechanism of LH signaling dysfunction in PCOS women modified from [40]. Each asterisk indicates a molecule also identified in the most significant signaling pathway or gene network from DNA methylation analyses of visceral adipose from infant and adult T-exposed female monkeys [41].

Table 1

Fetal, infant and adult phenotypic characteristics of PCOS-like monkeys, PCOS and High T Women.

Trait	PA Monkeys ^d			Prepubertal T ^b		High T monkeys ^c		PCOS ^d		High T ^e	
	Fetus	Infant	Adult	Adult	Adult	Adult	Women	Women	Women	Women	
Ovarian											
High T	+	+	+	-	+ ^e	+	+ ^e	+ ^e	+	+	
High AMH	NA	-	-	-	+	+	+	+	+	+	
Polycystic ovaries	?	-	+	+	?	?	+	+	-	-	
Intermittent/absent menstrual cycles	NA	NA	+ ^f	-	- ^e	- ^e	+ ^e	+ ^e	+	+	
Hypothalamic-Pituitary											
High LH	+	+	+	+	+	+	+	+	+	+	
Increased frequency LH release	?	?	+	+	+	+	+	+	?	?	
Decreased E2/P4 negative feedback	?	?	+	-	?	?	+	+	?	?	
Positive feedback (LH surge)	NA	NA	+	+	+	+	+	+	+	+	
Metabolic											
Increased body weight or BMI	+/- ^g	+	-	+	-	-	+	+	-	-	
Increased visceral fat	NA	?	+	-	?	?	+/- ^h	+	?	?	
Increased type 2 diabetes	NA	-	+	-	-	-	+	+	-	-	
Pancreatic defect	?	+	+	-	?	?	+	+	?	?	
Lipid abnormalities	+	-	+	-	?	?	+	+	?	?	
Maternal gestational hyperglycemia	+	+	?	NA	?	?	+	+	?	?	

^aRef# [17]

^bRef # [19]

^cRef # [21,22]

^dRef # [1]

^eRef # [112]

^fAmeliorated by insulin sensitizer treatment [99]

^g + because of ~5% increase in fetal head width at mid-gestation; - because of normal birth weight [24]

^hNot all studies find increased visceral fat in PCOS women [113,114]

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