Published in final edited form as:
Fertil Steril. 2013 July ; 100(1): 2–11. doi:10.1016/j.fertnstert.2013.05.023.

Ontogeny of Polycystic Ovary Syndrome and Insulin Resistance In Utero and Early Childhood

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Abstract

PCOS is a prevalent hyperandrogenic infertility and cardiometabolic disorder that increases a woman's lifetime risk of type 2 DM. It is heritable and intensely familial. Progress towards a cure has been delayed by absence of an etiology. Evidence is mounting, however, for *in utero* T excess, together with gestational hyperglycemia, contributing to either early differentiation of PCOS or phenotypic amplification of its genotypes. Abnormal endocrine, ovarian and hyperinsulinemia traits are detectable as early as 2-months of age in daughters of women with PCOS, with adiposity enhancement of hyperinsulinemia during childhood potentially contributing to hyperandrogenism and LH excess by adolescence. These findings encourage increasing clinical focus on early childhood markers for adiposity and hyperinsulinemia accompanying ovarian and adrenal endocrine abnormalities that precede a diagnosable PCOS phenotype. They raise the possibility for lifestyle or therapeutic intervention prior to and during pregnancy or during childhood and adolescence alleviating the manifestations of a familial genetic predisposition to PCOS.

Keywords

fetal androgen excess; gestational hyperglycemia; developmental programming; childhood obesity; insulin resistance

Polycystic ovary syndrome (PCOS) phenotypes

Women with PCOS are diagnosed from at least two out of the following: [1] testosterone (T) excess, [2] intermittent or absent menstrual cycles (~90% accompaniment by LH excess), and [3] polycystic ovaries (>90% accompaniment by anti-mullerian hormone (AMH) excess) (1). This "Rotterdam consensus" diagnosis (2) was recently affirmed as the "gold standard" for PCOS at an evidence-based conference at NIH (3) (http://prevention.nih.gov/workshops/2012/pcos/docs/PCOS_Final_Statement.pdf). It permits four distinct PCOS phenotypes: (a) all three criteria; (b) testosterone excess and intermittent/absent menstrual

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Financial disclosures: D.H.A. is a consultant for Viamet Pharmaceuticals, Inc., Morrisville, NC. F.B. has nothing to disclose.

cycles; (c) testosterone excess and polycystic ovaries; and (d) intermittent/absent menstrual cycles and polycystic ovaries. The first two phenotypes effectively comprise the NIH criteria for PCOS (4).

While a common origin for all PCOS phenotypes is debated (5–9), etiological clarity is confounded by phenotypic variability. For example, weight loss (9–11), insulin sensitizer treatment (12) or increasing age (13) can each ameliorate more severe PCOS phenotypes with all three criteria or testosterone excess and intermittent/absent menstrual cycles, into milder PCOS phenotypes with only testosterone excess and polycystic ovaries or intermittent/absent menstrual cycles and polycystic ovaries. PCOS symptomology is particularly alleviated by bariatric surgery-enabled weight loss (14). In contrast, obesity exaggerates phenotypic presentation in PCOS (14–16). Epigenetic and environmental factors can thus diminish or exacerbate PCOS phenotype independently of genetic predisposition. In this context, it is relevant to note that reproductive and hyperandrogenic dysfunction predominate in young women with PCOS, while PCOS women in their later years have more pronounced cardio-metabolic disorders (2, 13). Progress towards a cure for PCOS, and its increased lifetime risk of type 2 diabetes mellitus (type 2 DM) and cardiovascular disease (17, 18), is thus impeded by an obscured pathogenic origin. This mini-review will explore *in utero* origins for PCOS and accompanying insulin resistance (19–21), the ontogeny of adolescent PCOS, the role of insulin resistance in its pathogenesis, and early childhood factors related to the effect of obesity that may influence the impact of any hereditary component (Figure 1).

Genetic origins for PCOS

Heritability of PCOS, particularly hyperandrogenism (22), is readily apparent in twin (23) and genetic (24–26) studies, demonstrating considerable familial clustering of the syndrome (27). Currently, however, only a few PCOS susceptibility genes have been repeatedly identified in studies of women with Chinese or European ancestry: allelic variants of fibrillin-3 (*FBN3*) or DENN/MADD domain containing 1A (*DENND1A*) (28–31), and variants of luteinizing hormone receptor (*LHR*) (31–33).

FBN3 encodes for an extra-cellular matrix protein that regulates TGF-beta signaling. Its PCOS-associated allelic variant, A8, manifests a metabolically distinct phenotype, including insulin resistance (34). *FBN3* expression, however, is confined to early-to-mid gestation in many organs and tissues, including the ovary (35, 36). Such a gestational stage includes a period of fetal developmental at which T-exposure induces altered DNA methylation of TGF-beta regulating genes and subsequent PCOS-like traits (37). Since the degree and type of fibrillin expression contributes to differences in elasticity of cell extracellular matrix interactions and storage of TGF-beta, fibrillins may provide gestationally relevant (35), tissue specific bases for cell-mediated engagement of extracellular matrix-stored TGF-beta in proliferation, differentiation, and apoptosis (38, 39). *DENND1A* regulates Rab GTPases (40) and is involved in intra-cellular vesicle trafficking, including calcium regulated exocytosis in pituitary cells that may include exocytosis of gonadotropins (41). In the ovary, variants of *LHR* may diminish or enhance pituitary LH stimulation of ovarian theca and stroma cell testosterone production, ovarian follicle development, LH surge-induced ovulation and corpus luteum function (42), while in adipocytes, *LHR* variants may alter LH stimulation of adipogenesis (43). Variants in these multi-organ system genes could contribute genetic determination of PCOS phenotypes for reproductive and metabolic pathophysiology. Neither these, nor other less robust gene candidates, however, are associated with the majority of PCOS subjects in any population study (44) potentially reflecting suspected multi-genic origins of PCOS with or without accompanying developmental environment contributions (27).

Adolescent PCOS: Insulin Resistance

Insulin resistance and/or hyperinsulinemia are major components of PCOS in obese, but also in lean, adult women affected by this condition (45). A similar profile is present in adolescent girls with PCOS with ~50% lower insulin sensitivity compared with obese controls of similar age, body composition and abdominal adiposity (46). This increased insulin resistance is associated with increased risk for type 2DM and cardiovascular disease in these young adolescents. In a clinic setting, adolescent girls with PCOS have a high prevalence of impaired glucose tolerance with 30% diagnosed with prediabetes and ~4% with type 2DM (47). In the National Health and Nutrition Examination Survey (NHANES III), girls with PCOS were 4.5 times more likely to fulfill the criteria for the metabolic syndrome than age matched girls after adjusting for BMI and indices of insulin resistance (48). The role of insulin resistance in the pathogenesis of adolescent PCOS is supported by the improvement of the hyperandrogenic profile with the use of insulin sensitizers such as metformin (49) or lifestyle changes with an aggressive weight loss program (50).

No diagnostic clarity exists for pre-pubertal or adolescent girls with PCOS, however, as ovarian function is either in immature quiescence or too closely resembles PCOS in normal adolescence (51–53). Carmina and colleagues (54) propose delaying a PCOS diagnosis in adolescents until they are at least two years post-menarche and have at least two years of intermittent or absent menstrual cycles. Thus discerning care has to be given to reports involving PCOS adolescents. The origins of childhood insulin resistance and adolescent predisposition to PCOS have been linked to *in utero* adverse events (55, 56), a presentation with premature adrenarche in early childhood (57–60) together with major roles of family history and obesity (61) (Figure 1).

In utero exposure: effects of the hyperandrogenic PCOS environment

Animal studies, from rodents (62, 63) and sheep (64) to monkeys (8, 19), repeatedly demonstrate how fetal T excess, and possibly accompanying gestational hyperglycemia and hyperinsulinemia (65), determine a variety of PCOS-like phenotypes in adulthood, including the diversity encompassed by the “Rotterdam consensus” criteria (66). Current technology, however, prevents safe quantification of human fetal hormonal exposure during early-to-mid gestation (67), so investigations of fetal origins of PCOS in women rely on indirect assessments or postnatal outcomes of fetal T excess.

PCOS mothers contribute elevated maternal circulating levels of T to the gestational environment (68), and subtle perturbations in placental function (69), in addition to gestational hyperglycemia (70), which may compromise protection of their fetal daughters. Interestingly, elevated mid-gestation maternal T levels predict high AMH levels in adolescent daughters (71). Since elevated AMH is a characteristic of adolescents and women with PCOS (72) and newborn daughters of PCOS women (70, 73), such associations suggest a cross-generational relationship between the degree of maternal hyperandrogenism and development of PCOS in daughters. Mid-gestational daughters can contribute androgen excess when the fetal ovary can produce (74) and respond (75) to androgens. Elevated, mid-gestational amniotic fluid levels of T in fetal daughters of women with PCOS (76) are consistent with a fetal source for T excess in female offspring with an increased risk of PCOS.

Perinatal studies are mixed 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 (77). In newborn daughters born to women with PCOS, one study shows elevated T levels in umbilical venous blood (78), whereas another two studies show reduced umbilical cord blood androstenedione levels (69, 79). In a third study involving adolescent girls

diagnosed with PCOS including, as discussed below, an inherently high prevalence (~28%) of diagnosis at this young age, umbilical cord blood shows no elevation in T levels (80). With the ovary as a key fetal site for gestational T excess at a critical mid-gestational age for target organ differentiation (20), studies at the time of birth are likely too late to detect any remaining hormonal differences (67, 74). Perhaps consistent with this latter conclusion, two studies of non-pregnant PCOS women (81, 82) demonstrate positive correlations between adult T levels or hirsutism scores and the finger length ratio between the 2nd and 4th fingers, an anthropometric trait established *in utero* (83–85). PCOS-like monkeys show analogous positive correlations between the same finger length ratio and duration of T exposure during early-to-mid, but not late, gestation (41), implying that finger length associations in PCOS may indicate fetal T exposure during early-to-mid gestation.

Elusive *In Utero* Origins of PCOS in Humans

Notwithstanding a recent study showing mid-gestational elevations in amniotic fluid T levels in daughters of PCOS women (76), the basic problem with confirming developmental origins of PCOS in humans is an absence of evidence for fetal T excess (Table 1). Even though girls born to women with PCOS are at increased risk of PCOS in adulthood, studies have yet to link excess fetal T levels in mid-gestational girls with the onset of PCOS in adulthood (86, 87). The absence of evidence arises, in part, because of the technical and ethical challenges posed by blood sampling from mid-gestation human fetuses (67, 87). However, this “absence of evidence is not evidence of absence” (Carl Sagan, 1934–1996), but is at times considered as such (88). Furthermore, while the expression of aromatase in the PCOS placenta is indeed diminished (69), and potentially failing to prevent fetal T excess in PCOS pregnancies (68), the degree of diminished aromatase required to result in T excess in female fetuses is extremely rare (89). In recent studies of hypertensive preeclamptic pregnancies, on the other hand, findings suggest comprehensive reduction in placental ability to synthesize estrogens (90, 91), indicating a more common gestational impairment of T aromatization than is currently considered. It is therefore not too surprising that no association is found between high maternal, mid-gestational T levels and subsequent development of PCOS in daughters (80). It is fetal exposure to T that is key (92).

Other investigators have examined putative postnatal biomarkers of fetal T exposure in females. The latter, however, have not been validated against fetal T levels and can be inappropriately used to discount fetal T excess in PCOS women, including the sexually dimorphic ratio of 2nd to 4th finger length that can be diminutive in men (66, 85), but is inconsistently so in PCOS women (81, 82, 93). In monkeys, the same fetal T exposure that induces PCOS-like traits does not diminish this finger length ratio (66). Furthermore, women who gestated with a male co-twin show inconsistent expression of masculinized traits (94), thus an absence of PCOS prevalence among women with male co-twins (95) is not strong evidence for lack of fetal T exposure prior to PCOS onset. Variable phenotypes in women with PCOS also do not pose difficulties for a common fetal T origin (86), since variability in PCOS-like phenotypes ensues from fetal T exposure in animal models (37, 66).

There remains, however, an absence of evidence for mid-gestational T excess in human female fetuses, perhaps accompanied by gestational hyperglycemia, fetal hyperinsulinemia and their sequelae, that precedes PCOS phenotype development during adolescence. Until this information gap is closed, perhaps by determining T content in newborn baby hair and gaining a retrospective assessment of prior gestational T exposure, an *in utero* origin for PCOS will remain in dispute despite compelling animal evidence (8, 64) (Table 1).

Intrauterine Programming: Insulin Resistance

Epidemiologic and clinical studies conducted largely in adult populations suggest a link between *in utero* events, particularly fetal growth restriction, and subsequent risk of type 2DM and cardiovascular disease in humans (96, 97). This “Intrauterine Programming” or fetal origins hypothesis indicates that *in utero* factors lead to permanent changes in organ function and predisposes individuals exposed to fetal growth restriction to a variety of metabolic diseases. The increased risk for these metabolic diseases has been linked to increased insulin resistance in young individuals exposed to adverse *in utero* environment and born small for gestational age (SGA) (98, 99). A study of infants at 1 year of age demonstrates that SGA infants with catch-up growth are less insulin sensitive (with higher fasting insulin and higher triglycerides) than appropriate for gestational age (AGA) infants, despite their continuing lower weight and BMI (100). The picture is compounded by the influence of “catch-up” growth (101), with the highest levels of insulin resistance reported in children of low birth weight, but with subsequent high BMI and fat mass in childhood (102, 103). For example, in 9-year-old prepubertal children, hyperinsulinemic clamp studies show reduced insulin sensitivity in SGA children, compared with AGA, especially in SGA children with catch-up growth and a high BMI (104). These studies support an overall relationship between fetal growth restriction and increased adiposity and insulin resistance starting early in the childhood period.

In addition to *in utero* environmental factors, genetic polymorphisms modulate insulin resistance parameters in SGA individuals that may partly explain the variable degree of insulin resistance in subjects exposed to an adverse *in utero* environment (105). At the other extreme, over nutrition of the fetus appears to have long-term effects on obesity, insulin resistance, and predisposition to disorders of glycemic regulation. Offspring of mothers with diabetes during pregnancy have a higher frequency of childhood obesity and earlier onset of impaired glucose tolerance (106, 107) and type 2 DM (108). Rates of impaired glucose regulation are around 20% in adolescent offspring of mothers who have diabetes during pregnancy (107). The increased risk, however, is not restricted to mothers with diabetes during their gestation. In the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, a continuous relationship was observed between maternal hyperglycemia in the non-diabetic range and infant birth weight and cord blood C-peptide levels (109, 110). Given the effect of insulin on modulating ovarian (111) and adrenal steroidogenesis (112), a role of intrauterine adverse events which lead to insulin resistance and/or hyperinsulinemia may predispose adolescents to PCOS (Figure 1).

Intrauterine Programming: Under- and Over-Nutrition and PCOS

In addition to the relationship between fetal undernutrition and insulin resistance/ hyperinsulinemia, such *in utero* environments can affect ovarian development and function, as well as adrenal function (55, 113) (Figure 1). Such potential fetal programming of PCOS, however, may be restricted to some populations such as those of Spanish or Iranian descent (55, 114, 115). Postmenarcheal Catalan girls with a history of low birth weight, catch-up growth, hyperinsulinemia and precocious pubarche have an exaggerated (50%) prevalence of PCOS that manifests as oligomenorrhea, hirsutism and hyperandrogenemia (55).

The Spanish investigators also report a relationship between low birth weight, premature adrenarche and subsequent early puberty (116, 117). Also, in a relatively small longitudinal study (from 2–8 years of age), SGA girls from Spain (birth weight < −2 SD) who had spontaneous catch-up growth compared with girls born AGA, are more likely to have increased body mass index (BMI) at age 8, increased fat mass and abdominal adiposity. This is associated with higher leptin levels, higher dehydroepiandrosterone sulphate (DHEAS)

and lower sex hormone binding globulin (SHBG) and adiponectin in the SGA girls (118). Other investigators, however, report no relationship between low birth weight and serum DHEAS levels in short children 3–9 years of age (119). Studies from France do not show a relationship between low birth weight and premature adrenarche (120). Also, in studies of older French women, those with low birth weight were more hyperinsulinemic than controls, but did not show evidence of hyperandrogenism (121). On the other hand, in a large United Kingdom birth cohort evaluated at age 8 years, adrenal androgen levels were inversely related to birth weight SD score in each sex. After adjusting for childhood weight, children who showed rapid postnatal weight gain between 0 and 3 years of age had higher DHEAS and androstenedione levels at 8 years (122). In a retrospective Australian study of 89 children (79 girls) with precocious pubarche, 65% were overweight at diagnosis, 35% had a history of SGA and 24% had a history of prematurity. In this latter study, both prematurity and SGA were associated with precocious pubarche, as was obesity, irrespective of size at birth (123).

Consistent with an early origin of PCOS, studies by Ibanez and colleagues suggest that commencing metformin therapy before menarche in girls with premature pubarche and low birth weight, may prevent or delay the development of hirsutism, androgen excess, oligomenorrhea, and the diagnosis of PCOS more effectively than shorter-duration metformin therapy commencing after menarche (124). In the absence of other longitudinal studies clearly establishing a link between SGA, premature adrenarche and PCOS, however, these findings need to be interpreted with caution. Studies of SGA girls in northern Spain, evaluated at 14 to 18 years of age, report an ~20% smaller uterine size and an ~40% reduction in their ovarian volume compared with AGA controls (125). SGA girls also have elevated LH and fasting insulin, as well as an excess of abdominal fat compared with AGA peers. These SGA associations, however, are not confirmed by other researchers (126). In other studies of ovarian reserve, AMH levels in short 3–10 year old (average age of 6.24 years), prepubertal SGA girls are similar to those in AGA girls of similar age and gestational age, possibly indicating that the follicle pool is not affected in relationship to SGA status (127). This is unlike the findings of Sir-Petermann and colleagues who show higher AMH levels in SGA infants with catchup growth by 2–3 month of age (128). The discrepancy may be related to different ages and effect of early catch-up growth. It is unclear from these studies if there is altered follicular reserve or function in SGA girls, but a recent longitudinal study suggests that AMH levels vary little within individual healthy girls from childhood through adolescence, so that single AMH measurements may be representative of prepubertal ovarian populations of pre-antral and antral follicles (129).

In contradistinction to the effects of fetal growth restriction, over-nutrition *in utero* has also been related to higher risk of PCOS. Higher birth weight in girls born to overweight mothers is a risk factor for developing PCOS by 40–42 years of age (130). In a retrospective birth cohort study of singleton females, there is a 5% increase in the risk of developing adult hyperandrogenism when birth weight is high (56). On the other hand, thinness at birth, reflected in a low ponderal index (low birth weight for length), is associated with higher risk for developing all three PCOS diagnostic criteria in adulthood (56). As Davies and colleagues point out, higher birth weight may translate into higher risk for adiposity, and thus functional hyperandrogenism, as adipose tissue is androgenic (131, 132). In contrast, the risk of PCOS in relation to a low ponderal index may indicate a relationship between adverse *in utero* events and subsequent insulin resistance (133). Overall, these studies indicate that at least some metabolic components of the PCOS phenotype are programmed *in utero*, in particular the tendency for higher fat mass, visceral adiposity and insulin resistance (Figure 1).

Effect of Childhood Obesity

Obesity has been associated with early adrenarche and subsequent PCOS. Higher BMI Z-score has been associated with pubarche and early puberty in the National Health and Nutrition Examination survey (NHANES) (134). Childhood obesity, in particular visceral adiposity is a major determinant of insulin resistance in youth (135, 136). In the presence of normal beta cell function, insulin resistance is compensated by increased insulin secretion and hyperinsulinemia. The effect of obesity on insulin sensitivity is compounded by the physiologic insulin resistance of puberty (137). This hyperinsulinemia may drive premature adrenarche and the latter may be a precursor for subsequent PCOS in genetically predisposed girls, in particular in those in whom the phenotype is amplified by catch-up growth (Figure 1).

Daughters of women with PCOS evaluated during early childhood (age 4–8) and early puberty (age 9–13) have exaggerated adrenarche compared with girls of non-PCOS women of similar pubertal stage and BMI (57). This is in accordance with the role of hyperinsulinemia in ovarian (138) and adrenal hyperandrogenism (139). In high-risk obese girls with premature adrenarche of ethnic minority descent, androgen levels are inversely related to insulin sensitivity measured by intravenous glucose tolerance test (140). Moreover, girls with premature adrenarche and low insulin sensitivity compared with the group with relatively normal insulin sensitivity manifest higher ACTH stimulated androgen levels, higher free T and lower sex hormone binding globulin (140).

In other studies, peripubertal obesity in girls is associated with hyperandrogenemia (higher T, unbound (free) T, DHEAS and lower SHBG) and elevated insulin levels during each stage of pubertal development (141). Unbound T is five times as great in obese early-pubertal girls compared with normal weight peers of the same pubertal stage. Insulin levels correlated inversely with unbound T after adjusting for age, pubertal stage, insulin, LH, and DHEAS (141). The etiology of the hyperandrogenemia in obese girls is unclear. Knudsen and colleagues report wide variability in T levels across BMI Z-scores in obese girls (142) suggesting that obesity, alone, is not sufficient to produce hyperandrogenemia. In their study (142), the predictors of unbound T, after adjusting for BMI z-score, age and pubertal stage, were morning LH levels and fasting insulin. This is consistent with a role of obesity-related insulin resistance in driving hyperandrogenemia in these girls through an effect of insulin on adrenal and ovarian steroidogenesis (143), manifesting as early adrenarche (144) and subsequent PCOS (145). Such hyperandrogenemia appears to modulate gonadotropin levels. Obese peripubertal girls were found to have increased LH frequency, but low LH amplitude, and Tanner 3–5 girls have decreased overnight LH pulse amplitude compared with normal weight girls (146). These changes may reflect initial effect of obesity on LH pulses (147). Subsequently, hyperandrogenaemia reduces the inhibition of gonadotropin-releasing hormone pulse frequency by progesterone, causing rapid LH pulse secretion and further increasing ovarian androgen production (147–149). A similarly altered developmental trajectory in early-to-mid gestation T exposed PCOS-like monkeys (8) and comparable phenotype in peri-pubertally T-exposed female monkeys (150) are consistent with insulin-mediated weight gain amplifying postnatal expression of PCOS.

Effect of Family History: Endocrine and metabolic dysfunction starting in adolescence

PCOS prevalence rises to 20%–40% in families of women with PCOS (17, 151). Daughters and sisters of women with PCOS have higher levels of adrenal and ovarian androgens from adolescence into adulthood (57, 152–156). In addition, daughters, sisters, brothers, mothers, and fathers of women with PCOS exhibit insulin resistance, hyperinsulinemia, and/or

impaired glucose tolerance (153–158). In adolescence, daughters of women with PCOS compared with controls of similar BMI z-score, waist to hip ratio and birth weight, exhibit a higher prevalence of hirsutism and greater ovarian volumes at different stages of pubertal development (155). Metabolic evaluation reveals increased 2-hour insulin levels during the oral glucose tolerance test with similar levels of glucose, an indication of insulin resistance, compared to their Tanner and BMI matched controls (155). Three additional studies confirm this pre-adolescent or adolescent onset of hyperinsulinemic responses in daughters or sisters of women with PCOS that accompany insulin resistance (153, 159, 160).

In pubertal stages Tanner IV and V, the daughters of PCOS women have higher basal and leuprolide stimulated LH and 17-hydroxyprogesterone (17-OHP) levels, lower SHBG and higher and free androgen index (155). Elevated 17-OHP levels were replicated in separate study of adolescents (159). These studies indicate that metabolic abnormalities commonly associated with PCOS in women occur at least by the early pubertal stages and become more manifest with the progression of puberty in genetically predisposed females. Of note, the testosterone levels in stages IV and V correlate positively with 2-h insulin levels in adolescent daughters of women with PCOS (155). In addition, AMH levels, a marker of follicular development, are higher in daughters of women with PCOS at all Tanner stages and those with the highest AMH values have lower FSH concentrations and higher stimulated levels of insulin during Tanner stages I, II, and III (72). The PCOS adolescent daughter group with higher AMH levels may reflect a group at higher risk of metabolic abnormalities in adulthood. Overall, these studies are consistent with a genetic predisposition to PCOS manifesting in early childhood, with possible amplification of phenotype depending on the degree of accompanying metabolic dysfunction (Figure 1).

Conclusion

PCOS is a highly prevalent reproductive and cardiometabolic disorder that greatly increases a woman's lifetime risk of infertility, type 2 DM and cardiovascular disease. It is heritable and intensely familial. Progress towards a cure has been hindered by absence of pathogenic mechanism. Circumstantial evidence is mounting, however, for *in utero* T excess, together with gestational hyperglycemia, contributing to either early differentiation of PCOS or amplification of its phenotypes. Abnormal endocrine, ovarian and hyperinsulinemic traits are detectable as early as 2-months of age in daughters of women with PCOS, with adiposity enhancement of hyperinsulinemia during childhood potentially contributing to hyperandrogenemia and LH excess expression by adrenarche and adolescence (Figure 1), abnormal developmental trajectories emulated by PCOS-like monkeys (8). These findings encourage increasing clinical focus on establishing childhood markers for increased adiposity and hyperinsulinemia accompanying ovarian and adrenal endocrine abnormalities that precedes PCOS in adolescence and young adulthood. They raise the possibility for lifestyle or therapeutic intervention prior to and during pregnancy (70), and/or during childhood and adolescence (124), preventing familial genetic predisposition to PCOS from manifesting a diagnostic phenotype in adulthood. The circumstantial nature of the evidence, however, that links fetal T exposure to postnatal development of PCOS in humans (Table 1), requires additional population studies to clarify androgenic beginnings.

Acknowledgments

Financial support: D.H.A. is supported, in part, by National Institutes of Health P50 HD044405 (to Andrea Dunaif, MD) and P51 RR000167 (Wisconsin National Primate Research Center). F.B. is supported, in part, by National Institutes of Health R03 HD059798 and USDA ARS 6250-5100-054.

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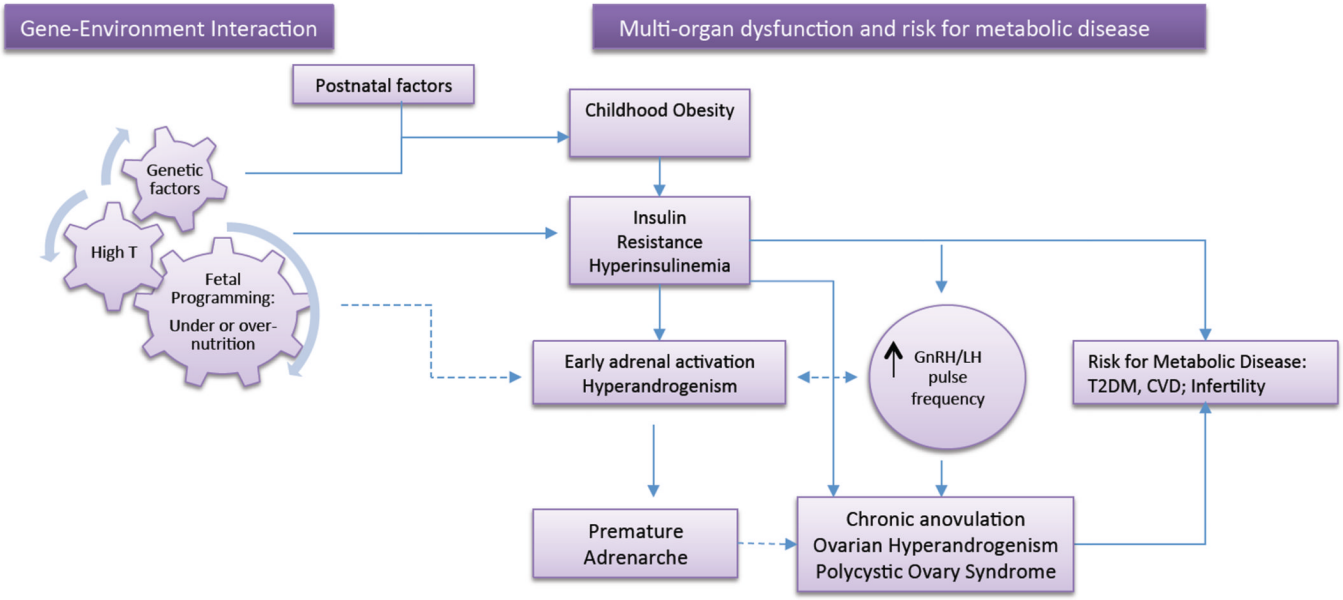

Figure 1.

Proposed ontogeny of PCOS with manifestations starting in childhood: Interaction of genetic and environmental factors shape the intrauterine environment leading to epigenetic changes and alteration of organ function at several levels. Childhood obesity and its associated insulin resistance further enhance the manifestations of genetic/epigenetic traits predisposing to hyperandrogenism, including effects on steroidogenesis and hypothalamic/pituitary function. The dashed lines represent relationships that have not been clearly established.

Table 1

Human data most relevant to *in utero* origins of PCOS.

a. Human findings consistent with developmental origins for PCOS

- T concentration is high in mid-gestational amniotic fluid obtained from daughters of pregnant women with PCOS (76)
- T concentration is high in umbilical cord blood from girls of pregnant PCOS women at term (78)
- High circulating AMH in infant daughters of women with PCOS (70)
- Increased incidence of PCOS in women with classical adrenal hyperplasia or fetal T-secreting tumor, and thus fetal T excess (60)
- Thinness at birth associates with the presence of all three PCOS diagnostic criteria in adulthood, while high birth weight associates with hyperandrogenism in adult women (56)
- 2nd to 4th finger length ratio (this trait is determined *in utero*) positively correlates with adult T levels in PCOS women (81, 82), as predicted from PCOS-like monkeys (66)
- Male-like, diminutive 2nd to 4th finger length ratio (trait is determined *in utero*) found in women with PCOS (93)

b. Human findings inconsistent with developmental origins for PCOS

- Low androstenedione and no elevated T in umbilical cord blood from girls of pregnant PCOS women at term (70, 79)
- High umbilical cord T levels in girls of normal women at term do not associate with adolescent appearance of PCOS (80)
- Women with male co-twins, and so potentially exposed to excess fetal T, do not have increased incidence of PCOS (95)
- Male-like, diminutive 2nd to 4th finger length ratio (trait is determined *in utero*) not found in women with PCOS (81, 82)