Mechanisms of intergenerational transmission of polycystic ovary syndrome

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Abstract

Developmental origins of adult disease (DoHAD) refers to critical gestational ages during human fetal development and beyond when the endocrine metabolic status of the mother can permanently program the physiology and/or morphology of the fetus, modifying its susceptibility to disease after birth. The aim of this review is to address how DoHAD plays an important role in the phenotypic expression of polycystic ovary syndrome (PCOS), the most common endocrinopathy of women characterized by hyperandrogenism, oligo-anovulation and polycystic ovarian morphology. Clinical studies of PCOS women are integrated with findings from relevant animal models to show how intergenerational transmission of these central components of PCOS are programmed through an altered maternal endocrine–metabolic environment that adversely affects the female fetus and long-term offspring health. Prenatal testosterone treatment in monkeys and sheep have been particularly crucial in our understanding of developmental programming of PCOS because organ system differentiation in these species, as in humans, occurs during fetal life. These animal models, along with altricial rodents, produce permanent PCOS-like phenotypes variably characterized by LH hypersecretion from reduced steroid-negative feedback, hyperandrogenism, ovulatory dysfunction, increased adiposity, impaired glucose-insulin homeostasis and other metabolic abnormalities. The review concludes that DoHAD underlies the phenotypic expression of PCOS through an altered maternal endocrine–metabolic environment that can induce epigenetic modifications of fetal genetic susceptibility to PCOS after birth. It calls for improved maternal endocrine–metabolic health of PCOS women to lower their risks of pregnancy-related complications and to potentially reduce intergenerational susceptibility to PCOS and its metabolic derangements in offspring.

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Introduction

Alterations in maternal physiology can permanently program adult disease in offspring (Dumesic et al. 2014). Known as the developmental origins of adult disease (DoHAD), this concept originates from the Barker hypothesis, which posits how adverse influences on fetal development cause permanent changes in offspring physiology and metabolism after birth, increasing the risk for disease in adulthood (Neel 1962, Barker 2002). Accordingly, fetal stress from maternal undernutrition favors survival of offspring with the greatest capacity for energy storage to survive prolonged nutrient deprivation after birth, with low birth weight followed by infant catch-up growth predisposing individuals to chronic adult disease in today’s nutrient plentiful environment (Desai et al. 2013). Teleologically, fetal undernutrition favors genes important for energy conservation (i.e., thrifty genotype), which would be beneficial in times of food scarcity, but would lead to obesity and diabetes when food becomes abundant later in life (Neel 1962). Original findings (Barker & Osmond 1986) that regions of England with the highest infant mortality rates in the early 20th century subsequently had the highest mortality rates from coronary heart disease decades later were supported by later studies showing an association between low birth weight and adult development of cardiovascular disease (CVD), hypertension, insulin resistance and type 2 diabetes mellitus (Barker 2002).

Maternal overnutrition, on the other hand, also can predispose offspring to adult disease. A ‘U-shaped curve’ in infant birthweight relative to obesity, hypertension and insulin resistance shows that birthweight deviation from an optimal in utero environment, regardless of direction, increases the risk of developing metabolic syndrome in later life (Desai et al. 2013). Collectively, therefore, impaired fetal nutrient availability from placental insufficiency accompanies low infant birth
weight, while conversely successful fetal adaptation to maternal nutrient overabundance (i.e. obesity) favors large-for-gestational age infants (Dumesic et al. 2014).

These different endocrine–metabolic environments in pregnancy have important developmental implications for women with polycystic ovary syndrome (PCOS), a heterogeneous syndrome characterized by luteinizing hormone (LH) hypersecretion, hyperandrogenism, menstrual irregularity and polyfollicular ovarian morphology (Chang & Dumesic 2018). The aim of this review is to examine how an altered maternal–fetal environment can program adult disease through epigenetic modifications of fetal genetic susceptibility to PCOS after birth, as evidenced by clinical studies of PCOS women integrated with animal models using discrete experimentally induced prenatal testosterone excess to program a permanent PCOS-like phenotype (Dumesic et al. 2007, 2014).

Polycystic ovarian syndrome

Women with PCOS by NIH criteria (i.e., hyperandrogenism with oligo-anovulation, excluding other endocrinopathies) have insulin resistance from abnormal insulin signaling and metabolic dysfunction in insulin-responsive tissues, with increased total abdominal and visceral fat independent of obesity (Dumesic et al. 2016, Chang & Dumesic 2018). One-third to one-half of these PCOS women in the United States have metabolic syndrome, which is 2–3 times greater in prevalence than that of age-matched women without PCOS and worsened by obesity (Moran et al. 2010). The prevalence of metabolic syndrome is also lower in PCOS women from countries where obesity is less frequent (Carmina et al. 2006, Moran et al. 2010). Moreover, 40% of PCOS women develop glucose intolerance or type 2 diabetes by the fourth decade of life (Legro et al. 1999), increasing their risk for pregnancy complications, including diabetes, pregnancy-induced hypertension, pre-eclampsia, preterm birth, impaired endovascular trophoblast invasion and abnormal placentation, with potential fetal programming effects on the offspring (Dumesic et al. 2014).

Genetic contributions to PCOS

Twin studies estimate the heritability of PCOS as 71%, and 38% for monozygotic vs dizygotic twins, respectively (Chang & Dumesic 2018) and are supported by a recent longitudinal study of daughters born to women with PCOS and followed from infancy to post-menarche, suggesting a 62% transmission of PCOS phenotype (Crisosto et al. 2019). Similarly, reproductive-aged sisters of women with PCOS have an increased prevalence of a hyperandrogenic PCOS phenotype (Chang & Dumesic 2018), as do parents of PCOS women with a higher risk of metabolic dysfunction (Sir-Petermann et al. 2002a).

Nevertheless, genetic susceptibility to PCOS by gene-wide association studies accounts for <10% of its heritability to date, with at least 17 replicated PCOS risk genes from different human populations involving reproduction (FSHB, LHCGR, FSHR, DENND1A, RAB5/SUOX, HMGA2, C9orf3, YAP1, TOX3, RAD50, FBXN3 and AMH) and metabolism (THADA, GATA/NEIL2, ERBB4, SUMOP11, INSR and KRR1) (Abbott et al. 2019). Consequently, PCOS appears to have complex polygenic, pathogenic origins that are susceptible to endocrine–metabolic influences during pregnancy to account for its remaining heritability and variable phenotypic expression (Abbott et al. 2019). Shared genetic traits across all PCOS phenotypes, whether clinically diagnosed by NIH, Rotterdam criteria or self-reported, implicate common underlying pathophysiological mechanisms involving neuroendocrine, metabolic and reproductive contributions (Day et al. 2018).

The maternal environment in PCOS

Understanding how the maternal environment of PCOS women affects their offspring must consider obesity as a covariable since two-thirds of women in the United States are overweight or obese, as are one-half of Australian and one-third of Danish women (ASRM 2015). Maternal obesity is strongly associated with several pregnancy and perinatal complications, including gestational diabetes and hypertension, preeclampsia, preterm delivery, stillbirth, early neonatal death and small, as well as large-for-gestational age infants (ASRM 2015). Obese women also are more likely than average-weight women to have infants with heart defects, ventral wall defects, neural tube defects and multiple anomalies (ASRM 2015). From a DoHAD perspective, maternal obesity increases the risk of premature mortality from a cardiovascular event in their adult offspring, adjusting for maternal age, social class, gestational age, infant sex and birth weight, implying intergenerational programming of metabolic disease (Reynolds et al. 2013).

An important question is whether PCOS women are at increased risk for metabolic dysfunction in pregnancy compared to other pregnant women. Preconception hyperandrogenemia and glucose intolerance in PCOS women predict several suboptimal maternal and neonatal outcomes, including preeclampsia (Christ et al. 2019). During pregnancy, PCOS women continue to have greater serum androgen levels, higher fasting and 2-h post-prandial insulin values (Sir-Petermann et al. 2002b, Kent et al. 2018) and elevated anti-Mullerian hormone (AMH) levels (Kent et al. 2018, Tata et al. 2018) compared to normal women. Subsequently, the prevalence of gestational diabetes, glucose intolerance and type 2 diabetes in PCOS women is 3- to 5-fold higher than that of other women, independent of age or body mass index (BMI), and is worsened by obesity (Teede et al. 2018). Contributing to these events, normal
and overweight PCOS women gain more weight by mid-gestation than pregnant women without PCOS (Kent et al. 2018), with about 40% of PCOS women developing gestational diabetes and other pregnancy complications (Abbott et al. 2019). During pregnancy, moreover, PCOS versus normal women exhibit exaggerated dyslipidemia and elevated circulating inflammatory markers that predict greater risks of gestational diabetes, hypertensive disorders and adverse obstetrical/neonatal outcomes, respectively (Palomba et al. 2014a,b).

From a mechanistic perspective, maternal hyperandrogenemia from PCOS is unlikely to directly program PCOS in offspring if placental aromatization is normal (Hickey et al. 2009), although reduced aromatase activity in term placenta from PCOS women has been reported (Maliqueo et al. 2013). Nevertheless, mid-gestation maternal testosterone levels positively associate with high AMH levels in adolescent female offspring, suggesting that elevations in mid-gestation maternal testosterone perturb subsequent ovarian function in daughters (Hart et al. 2010). More probable, however, maternal metabolic dysfunction in PCOS mothers compromises placental function of a female fetus with a genetic susceptibility to PCOS, promoting fetal hyperinsulinemia as a cause for hyperandrogenism and altered folliculogenesis in utero (Dumesic et al. 2007, 2014, Palomba et al. 2012, 2015, Abbott et al. 2019).

### The fetal environment

Increased susceptibility to type 2 diabetes and obesity in offspring of type 1 diabetic mothers is metabolically determined in utero. Adolescent offspring of mothers with type 1 diabetes have increased body weight, dyslipidemia and insulin resistance predicted by their previous exposure to hyperinsulinemia in utero (Weiss et al. 2000). As adults, offspring of mothers with gestational or type 1 diabetes who were previously exposed to fetal hyperglycemia exhibit epigenetic changes in subcutaneous (SC) adipose, including decreased leptin promoter methylation, increased leptin gene and protein expression, decreased mitochondrial function and impaired fat storage (Hansen et al. 2017).

Therefore, maternal metabolic abnormalities likely affect the human fetal ovary during the second trimester of development when the primordial follicular pool gets established. Mid-trimester human fetal ovaries have several steroidogenic enzymes, genes encoding steroid-signaling pathways and receptors to steroids, insulin and insulin-like growth factors (Cole et al. 2006, Chang & Dumesic 2018). They also can metabolize pregnenolone sulfate to DHEA and androstenedione, and secrete DHEA, progesterone and estrone, with lesser amounts of androstenedione, estradiol and testosterone in vitro (Chang & Dumesic 2018). Lacking functional LH-like receptors (Wilson & Jawad 1979), however, mid-trimester human fetal ovaries are likely less responsive than testes to the transient mid-gestational rise in fetal gonadotropins, which causes a transient sexual dimorphism in amniotic androgen levels that disappears by birth (Beck-Peccoz et al. 1991, Palomba et al. 2012, Chang & Dumesic 2018).

Instead, human fetal ovaries probably produce androgens in response to hyperinsulinemia in vivo, contributing to a transient mid-gestational rise of serum androgen levels into the normal male range in 40% of female fetuses that diminish below male levels in term umbilical cord blood (Beck-Peccoz et al. 1991). As evidence for mid-gestational fetal hyperandrogenism accompanying an altered endocrine–metabolic maternal environment, amniotic fluid testosterone levels are elevated in female fetuses of PCOS (Palomba et al. 2012) and diabetic (Barbieri et al. 1986) mothers alike, while hyperplasia of theca and pancreatic beta cells accompany ovarian theca-lutein cysts in hirsute female stillbirth offspring of diabetic women (Driscoll et al. 1960, Hultquist & Olding 1981). Umbilical cord testosterone levels at birth also are elevated in some (Barry et al. 2010), but not all (Anderson et al. 2010), female infants of PCOS mothers. Consequently, elongated anogenital distance, a reliable postnatal biomarker of mid-gestational fetal hyperandrogenism (Barrett et al. 2018), can be found in both female infants of PCOS mothers and in women with PCOS (Sanchez-Ferrer et al. 2017, Wu et al. 2017).

### Animal models for PCOS

#### Reproduction

To understand causal mechanisms underlying these human maternal–fetal relationships, animal models have employed prenatal exposure to androgen excess in rodents, monkeys and sheep to induce metabolic and reproductive abnormalities resembling PCOS (Dumesic et al. 2007, Padmanabhan & Veiga-Lopez 2013, Abbott et al. 2019). Prenatally testosterone-treated monkeys and sheep have been essential animal models used to program a permanent PCOS-like phenotype of LH hypersecretion, ovarian/adrenal hyperandrogenism (monkeys) or functional hyperandrogenism (androgen receptor upregulation, sheep), ovulatory dysfunction and impaired glucose-insulin homeostasis (Dumesic et al. 2007) (Table 1). This is because tissue differentiation in these species is completed during fetal life (i.e., precocial species), as in humans (Fig. 1A, B and C), unlike mice in which only partial differentiation is completed before birth (i.e., altricial species) (Padmanabhan et al. 2007).

#### Neuroendocrine dysfunction

Neuroendocrine PCOS-like traits in adult prenatally testosterone-treated female rhesus monkeys (Abbott et al. 2008) and sheep (Padmanabhan & Veiga-Lopez 2013)
are characterized by LH hypersecretion from reduced hypothalamic sensitivity to steroid negative feedback and enhanced GnRH pulsatility (Robinson et al. 1999, 2002, Sarma et al. 2005, Padmanabhan et al. 2006, Abbott et al. 2018). Adult rats exposed to prenatal testosterone also exhibit LH hypersecretion and hyperandrogenism (Tehrani et al. 2014). Furthermore, prenatal androgen antagonism with the antiandrogen, flutamide, restores normal LH surge characteristics in prenatally testosterone-treated sheep (Padmanabhan et al. 2015) and estrous cyclicity in mice (Sullivan & Moenter 2004).

Reduced hypothalamic sensitivity to progesterone negative feedback on LH secretion also is a hallmark of PCOS women (Chhabra et al. 2005) and is similarly restored with flutamide (Eagleson et al. 2000, Chhabra et al. 2005). Comparable neuroendocrine abnormalities are found in adolescent hyperandrogenic girls, likely representing a precursor to adult PCOS (Lundgren et al. 2018). Moreover, PCOS women show a sexually dimorphic pattern of exaggerated early LH responsiveness to GnRH analog that more closely resembles that of men or women with congenital adrenal virilizing disorders (e.g., classical CAH and adrenal virilizing carcinoma) than normal women (Rosenfield et al. 1990, Barnes et al. 1994). These common characteristics between prenatally testosterone-treated animal models of PCOS and PCOS women implicate androgen excess during human fetal development with permanently reduced steroid negative feedback on LH and enhanced GnRH pulsatility that persists into adult life.

### Ovarian dysfunction

Developmental programming of ovarian function resembling that of PCOS has been more controversial. Prenatal testosterone treatment in both monkeys and sheep induces female subfertility, which includes impaired quality of primate oocytes (Dumesic et al. 2002, Steckler et al. 2007b). Enlarged, polyfollicular ovaries also occur in both animal models (Abbott et al. 1997, Padmanabhan et al. 2006, 2012) as well as in prenatally testosterone-treated adult rats (Tehrani et al. 2014) and are accompanied by hyperandrogenism in prenatally testosterone-treated rhesus monkeys (Abbott et al. 2002) and rats (Tehrani et al. 2014) and by ovarian androgen receptor upregulation in prenatally testosterone-treated sheep (Ortega et al. 2009). Polyfollicular ovaries, however, do not occur in prenatally dihydrotestosterone-treated sheep (Steckler et al. 2007a), suggesting endocrine–metabolic actions on the fetal ovaries other than androgen. Moreover, an exaggerated age-related decline in serum AMH levels from normal values in testosterone-exposed monkeys is atypical of PCOS (Dumesic et al. 2009).

In contrast to these animal models, AMH overproduction is a characteristic of PCOS women. Elevated serum AMH levels in PCOS women represent the opposing effects of stimulatory reproductive (hyperandrogenism and increased antral follicle number) versus inhibitory metabolic (body fat) factors (Guedikian et al. 2018), although some PCOS women may have a steeper age-related decline in circulating AMH levels than normal women (Ahmad et al. 2018).

### Placental aromatization

Whether maternal testosterone can serve as a source of fetal hyperandrogenism or a programming mechanism for a PCOS-like phenotype in female offspring remains unclear. Gestational AMH excess in mice, however, can induce LH-mediated maternal testosterone excess with reduced placental aromatization of maternal androgens, potentially programming a PCOS-like phenotype in female offspring (Tata et al. 2018).
Reduced aromatase activity in term placenta from PCOS women also has been reported (Maliqueo et al. 2013), potentially increasing exposure of female fetuses to androgen excess. PCOS-related enhancement of fetal hyperandrogenism through placental dysfunction agrees with metabolically compromised PCOS placenta exhibiting features related to hypoxia, a condition known to downregulate placental aromatase (Koster et al. 2015, Kumar et al. 2018). Maternal androgens of PCOS mothers, however, may not substantially contribute to programming PCOS in their offspring due to sufficient placental aromatization (Hickey et al. 2009).

More likely, an altered maternal endocrine–metabolic environment accompanying both PCOS and placental compromise (Koster et al. 2015, Palomba et al. 2015) probably promotes fetal ovarian hyperandrogenism via hyperinsulinemia acting as a secretagogue in utero, with complex androgen-insulin interactions reprogramming sensitive target tissues in susceptible female offspring (Dumesci et al. 2007, 2014, Abbott et al. 2019).

**Metabolism**

Prenatally testosterone-treated monkeys and sheep as precocial species provide mechanistic links between endocrine–metabolic dysfunction in pregnancy and its long-term reproductive and metabolic consequences in offspring. In prenatally testosterone-treated monkeys and sheep, maternal glucose intolerance causes transient hyperinsulinemia in their female fetuses. Specifically, prenatal testosterone treatment in rhesus monkeys impairs maternal glucose tolerance and

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**Figure 1** Timing of developmental programming of critical target tissues in (A) rhesus monkeys, (B) sheep and (C) humans as precocial species (Abbott et al. 2005, Padmanabhan & Veiga-Lopez 2013).
stimulates fetal insulin release, which then potentiates insulin action within the fetus (Abbott et al. 2010). Prenatal testosterone treatment in sheep reduces progesterone levels and induces hyperinsulinemia (Abi Salloum et al. 2015). But when prenatally testosterone-treated sheep are co-treated simultaneously with either flutamide or rosiglitazone, maternal progesterone levels are improved, while juvenile insulin resistance and early adult hyperleptinemia are prevented (Cardoso et al. 2016).

In addition, mid-gestation fetal sheep ovaries express LH receptors with expression levels responsive to the prevailing androgen environment (Hogg et al. 2011). These endocrine–metabolic interactions during pregnancy are also influenced by placental function, which further modifies the in utero environment to program offspring in different ways.

**Metabolic dysfunction**

Mid-gestational prenatal testosterone treatment in rhesus monkeys and sheep programs adipose dysfunction and insulin resistance in adult offspring (Dumesic et al. 2007, Padmanabhan et al. 2010). Prenatally testosterone-treated female rhesus monkeys develop a PCOS-like phenotype characterized by progressive metabolic dysfunction with age, insulin resistance and preferential abdominal adiposity accompanied by hyperlipidemia (Eisner et al. 2000, 2003, Bruns et al. 2007, Zhou et al. 2007). Early-to-mid-gestation testosterone-treated female rhesus monkeys exhibit increased visceral fat (Eisner et al. 2003), adipose insulin resistance and impaired insulin secretion (Zhou et al. 2007, Abbott et al. 2019), while late gestation testosterone-treated females have increased total body (non-visceral) fat (Bruns et al. 2007), impaired insulin sensitivity and intact pancreatic insulin secretion, contributing to 27.3 and 11.1% rates of type 2 diabetes in the former and latter females, respectively. A TGF-β signaling pathway involving altered DNA methylation patterns of visceral fat in early-to-mid-gestation testosterone-treated female rhesus monkeys implies an epigenetic basis for reprogramming of adipose (Xu et al. 2011).

Adult prenatally testosterone-treated sheep also develop impaired insulin sensitivity (Recabarren et al. 2005, Padmanabhan et al. 2010, Cardoso et al. 2016), along with hypertension and hypercholesterolemia after puberty (King et al. 2007) as important metabolic abnormalities, although their long-term risks of developing increased adiposity and diabetes with age remain unclear since studies were performed through only 2 years of life (i.e. prime reproductive life). Interestingly, adult rats exposed to prenatal testosterone also exhibit insulin resistance in the absence of overt glucose intolerance (Noroozzadeh et al. 2015).

**Adipogenic dysfunction**

Subcutaneous (SC) adipose normally increases lipid storage capacity through adipocyte enlargement and new adipocyte formation to buffer fatty acid influx when caloric intake exceeds energy utilization (Romacho et al. 2014). Prenatally, testosterone-treated adult rhesus monkeys have an impaired ability to increase SC lipid storage relative to BMI (Bruns et al. 2007), suggesting abnormal adipogenesis, whereby multipotent adipose stem cells (ASCs) first undergo commitment to preadipocytes and then differentiate into newly formed adipocytes (Chazenbalk et al. 2013). Using adipogenic gene markers, SC abdominal adipose of aging early testosterone-treated females shows impaired preadipocyte differentiation into adipocytes (i.e. decreased C/EBPα) accompanying hyperandrogenemia and enhanced earlier ASC commitment to preadipocytes (i.e. increased ZFP423) possibly compensating for subsequent impaired preadipocyte differentiation (Keller et al. 2014). In agreement, prenatal Zfp423 knockout in mice fed a high-fat diet exaggerates diet-induced obesity, ectopic fat deposition and insulin resistance (Shao et al. 2017). In support of developmental programming as a contributor to such events, studies of prenatally testosterone-treated juvenile female sheep show increased ASC commitment to preadipocytes and decreased preadipocyte differentiation of visceral adipocytes, with the later prevented by dual prenatal flutamide/rosiglitazone co-treatment (Puttabyatappa et al. 2018).

In normal human SC abdominal adipose, androgen inhibits early-stage human SC abdominal adipogenesis, induces insulin resistance and impairs catecholamine-stimulated lipolysis through reduced protein expression of β2-adrenergic receptor and hormone-sensitive lipase (HSL) independent of BMI or age (Dicker et al. 2004, Arner 2005, Corbould 2007, Chazenbalk et al. 2013) (Fig. 2). Similarly, in nonobese insulin-resistant PCOS women, SC abdominal adipose exhibits lipolytic catecholamine resistance from diminished protein levels of β2-adrenergic receptor, HSL and protein kinase A regulatory-Ιβ component (PKA-RegIβ) (Ek et al. 1997, Faulds et al. 2003). Such androgen-related events in vivo would likely constrain SC fat storage and cause lipotoxicity from ectopic lipid accumulation in non-adipose tissues (Chazenbalk et al. 2013), agreeing with findings in normal-weight PCOS women of altered SC abdominal ASC gene expression of adipogenic/angiogenic functions involving testosterone through TGF-β signaling (Dumesic et al. 2019).

In the absence of systemic testosterone, however, cultured SC abdominal ASCs from normal-weight PCOS women show exaggerated ASC commitment to preadipocytes followed by enhanced adipocyte lipid content during mature adipocyte formation that
negatively and positively correlate with circulating fasting glucose and androgen levels, respectively (Fisch et al. 2018). Such exaggerated ASC commitment to preadipocytes in cultured SC abdominal ASCs from these PCOS women, possibly accompanying intra-adipocyte hyperandrogenism (O’Reilly et al. 2017), likely represents a regulatory mechanism to maintain glucose-insulin homeostasis during accelerated fat accretion (Fisch et al. 2018), as evident in nonobese PCOS women by an altered gene expression favoring SC abdominal lipid metabolism (Chazenbalk et al. 2012).

In contrast, human visceral fat normally shows increased lipolytic activity and resistance to testosterone inhibition of catecholamine-induced lipolysis compared to SC abdominal fat, despite both fat depots expressing androgen receptors (Dicker et al. 2004). In addition, visceral adipose of nonobese PCOS women shows exaggerated catecholamine-induced lipolysis accompanying normal antilipolytic insulin action (Ek et al. 2002, Arner 2005). This suggests that upregulation of visceral fat lipolysis from a functional increase in the PKA-HSL complex could promote insulin resistance secondary to elevated portal free fatty acids (Ek et al. 2002, Arner 2005). In normal-weight PCOS women, therefore, such a phenomenon could promote lipolysis for fatty acid oxidation through insulin resistance to curtail fat accretion over time, as previously shown in nondiabetic Pima Indians with a proclivity toward excess weight gain (Swinburn et al. 1991).

**Altered SC abdominal adipocyte size**

The size distribution of adipocytes within an adipose depot represents a balance between adipocyte enlargement and new adipocyte formation to buffer fatty acid influx (Romacho et al. 2014). An increased proportion of small SC abdominal adipocytes occurs in prenatally testosterone-treated adult rhesus monkeys and sheep (Veiga-Lopez et al. 2013, Keller et al. 2014). This altered adipocyte morphology in early adult, prenatally testosterone-treated sheep occurs when visceral adiposity and insulin sensitivity are still normal and precedes metabolic dysfunction in later life, perhaps as a compensatory adaptation to the perturbed intrauterine environment (Cardoso et al. 2016). Interestingly, reduced adipocyte size in prenatally testosterone-treated sheep is not reversed with flutamide co-treatment, implying endocrine–metabolic mechanisms apart from androgen, including possible estrogen action in this species (Cardoso et al. 2016, Puttabyatappa et al. 2018).

An increased proportion of small SC abdominal adipocytes also occurs in normal-weight PCOS women (Dumesic et al. 2016) and precedes the development of enlarged mature adipocytes in overweight PCOS women (Manneras-Holm et al. 2011), explaining why some, but not all, such individuals maintain normal glucose-insulin homeostasis (Chang & Dumesic 2018). In this regard, enhanced small adipocyte formation accompanying ZFP423 upregulation and epigenetic changes in the ZFP423 promoter region protect against insulin resistance in humans (Longo et al. 2018). That regional fat depots develop in the human fetus between 14 and 28 weeks of gestation supports the hypothesis that abdominal fat can be developmentally programmed during early-to-mid-gestation (Poissonnet et al. 1988) (Fig. 1).

**Maternal–fetal interactions**

Padmanabhan et al. 2006). In prenatally testosterone-treated fetal sheep, these events accompany advanced placental differentiation (Beckett et al. 2014) that is insufficient to maintain placental function during late gestation, leading to intrauterine growth retardation, mainly in female offspring (Beckett et al. 2014), followed by postnatal weight gain (or catch-up growth) (Manikkam et al. 2004) and insulin resistance in adulthood (Cardoso et al. 2016). Moreover, precocious puberty occurs in prenatally testosterone-treated sheep independent of body weight and is prevented by prenatal co-treatment with flutamide or rosiglitazone, confirming pubertal timing as a programmed androgen-insulin-mediated event (Padmanabhan et al. 2015). Therefore, prenatally testosterone-treated sheep and rats may be suitable models for placental insufficiency, particularly since these sheep also have hypertension and myocardial changes associated with left ventricular hypertrophy (King et al. 2007, Vyas et al. 2016), while the rodents have increased mortality (Wolf et al. 2004).

In contrast, prenatally testosterone-treated rats have a normal birth weight, with exaggerated weight gain by 30 days of age (Tehrani et al. 2014). Similarly, early prenatally testosterone-treated female monkeys have a normal birth weight, with an increase in body weight beginning in early infancy (Herman et al. 2000, Abbott et al. 2007, 2008, 2010) followed by delayed puberty as seen in males and an adult PCOS-like phenotype. Mechanisms beyond testosterone-induced developmental programming likely exist since exposure of monkeys to prenatally testosterone excess impairs glucose–insulin homeostasis without affecting body weight in both adult sexes (Abbott et al. 2007).

From a human perspective, macrosomic infants of obese glucose-intolerant mothers represent successful fetal adaptation to maternal nutrient overabundance (Mane et al. 2017). On the other hand, low infant birthweight in women with impaired placental aromatization and diminished uteroplacental perfusion represents impaired fetal nutrient availability from placental insufficiency (Tanguy et al. 1981, Thomssin et al. 1982). Both large and small for gestational age infants have been reported in pregnant women with PCOS (Palomba et al. 2014a,b), with birth weight and maternal mid-gestational BMI positively correlated with newborn adiposity as determined by cord blood leptin levels (Maliqueo et al. 2009).

Poor intrauterine growth and low birth weight accompany precocious puberty and PCOS in northern Spanish women (Ibanez et al. 1996, 1998) and in PCOS pregnancies in Chilean and Iranian women (Sir-Petermann et al. 2005, Mehrabian & Kelishadi 2012), but not in larger groups of Finnish (Lahtinen et al. 2003) and Dutch individuals (Sadrzadeh et al. 2003, Koster et al. 2015). Low or normal birth weight in some infants of pregnant women with PCOS can accompany placental abnormalities, including chronic villitis/intervillositis, impaired decidual trophoblast invasion and reduced placental size, that limit nutrient delivery to the fetus and may (Palomba et al. 2014c) or may not (Koster et al. 2015) reduce the ratio of fetal to placental weight.

Since infants of PCOS mothers also can have normal birth weights (Lahtinen et al. 2003, Dumesic et al. 2014), developmental programming of adiposity can occur in the human fetus (Poissonnet et al. 1988) without altering infant birth weight, yet still increase the risk of excessive postnatal weight gain and onset of PCOS in susceptible offspring. Mechanisms independent of testosterone-induced developmental programming are supported by findings that male relatives of PCOS women exhibit metabolic dysfunction similar to that of their female relatives (Dumesic et al. 2007, Yilmaz et al. 2018). Additional transgenerational transmission of PCOS through the male line is also supported by a strong association of genetic variants previously linked to male-pattern balding with PCOS phenotypes (Day et al. 2018).

Endocrine antecedents of PCOS

Endocrine antecedents of PCOS occur in female infants born to PCOS mothers and further emphasize that interactions between genes of the fetus and the endocrine–metabolic environment of pregnancy may program offspring after birth. Infant girls born to PCOS versus non-PCOS mothers exhibit increased sebum production by the pilosebaceous unit as a marker of prenatal androgen excess (Homburg et al. 2017). They also exhibit AMH overproduction as a marker of growing follicles, which persists in prepubertal life and improves, along with exaggerated ovarian responsiveness to GnRH analog administration, when PCOS mothers receive metformin in pregnancy, beginning at or before conception (Sir-Petermann et al. 2006, Crisosto et al. 2012). Consistent with these findings, female children of PCOS women have enlarged ovaries and hyperinsulinemia that precede onset of LH hypersecretion and androgen excess during puberty in some (Crisosto et al. 2007, Kent et al. 2008, Sir-Petermann et al. 2009), but not all (Legro et al. 2017) studies.

From a metabolic perspective, adiposity of infants from PCOS women positively correlates with birth weight and maternal mid-gestational BMI (Maliqueo et al. 2009), the latter of which increases disproportionately in normal and overweight PCOS women compared to other pregnant women (Kent et al. 2018). Infant males born to PCOS mothers exhibit higher body weight and develop insulin resistance in adulthood as a risk factor for acquiring type 2 diabetes (Recabarren et al. 2008). Although metformin use in pregnancy appears to improve some ovarian characteristics in female offspring of PCOS mothers (Sir-Petermann et al. 2006, Crisosto et al. 2012), increased childhood adiposity, insulin resistance and increased newborn head size following gestational treatment of
PCOS women with metformin demonstrates the need to minimize gestational interventions in humans (Hanem et al. 2019). In addition, interactions between genes of the susceptible fetus and maternal PCOS endocrine–metabolic environment are likely further altered by postnatal environmental inputs, since widespread epigenomic remodeling occurs throughout human aging, being inherited across generations through non-genetic mechanisms (Benayoun et al. 2015, Simpkin et al. 2016).

Conclusion

The collective data suggest that epigenetic changes in fetal life may impact the developmental origins of PCOS, assuming a critical time interval of fetal susceptibility beginning in early-to-mid-gestation when developmental programming occurs (Dumesic et al. 2007, Abbott et al. 2019). By inducing permanent PCOS-like phenotypes characterized by LH hypersecretion from reduced steroid negative feedback, hyperandrogenism, ovulatory dysfunction and impaired glucose–insulin homeostasis, animal models of prenatal testosterone treatment support clinical studies of PCOS women in providing insights into when developmental programming occurs during human development, how placental function alters the maternal–fetal relationship to affect fetal growth, and perhaps why birth weights of PCOS women differ throughout the world. Improved maternal endocrine–metabolic health of PCOS women to lower their risk of pregnancy-related complications could potentially reduce intergenerational susceptibility to PCOS and its metabolic derangements in offspring.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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