REVIEW

Developmental programming of insulin resistance: are androgens the culprits?

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Abstract

Insulin resistance is a common feature of many metabolic disorders. The dramatic rise in the incidence of insulin resistance over the past decade has enhanced focus on its developmental origins. Since various developmental insults ranging from maternal disease, stress, over/undernutrition, and exposure to environmental chemicals can all program the development of insulin resistance, common mechanisms may be involved. This review discusses the possibility that increases in maternal androgens associated with these various insults are key mediators in programming insulin resistance. Additionally, the intermediaries through which androgens misprogram tissue insulin sensitivity, such as changes in inflammatory, oxidative, and lipotoxic states, epigenetic, gut microbiome and insulin, as well as data gaps to be filled are also discussed.

Key Words

- fetal
- steroids
- androgen antagonist
- insulin sensitizer

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Introduction

Insulin resistance is a characteristic feature of many metabolic disorders, including the metabolic syndrome, type 2 diabetes mellitus (T2DM), obesity, non-alcoholic fatty liver disease (NAFLD), polycystic ovary syndrome (PCOS), gestational diabetes mellitus, and others. Traditionally, genetics and lifestyle are considered the main contributors to the development of these disorders of insulin resistance (Nilsson & Ling 2017, Zheng *et al.* 2018). However, the dramatic rise in incidence of this pathology during the last decades cannot be adequately explained by genetic predisposition and lifestyle changes alone. Accumulating evidence suggests factors acting during early fetal development are additional contributors (Franks *et al.* 2013, Vaiserman & Lushchak 2019). As fetal growth and differentiation are largely dependent on the maternal and intrauterine hormonal milieu during early development, hormones and factors that change the hormonal milieu during the fetal ontogeny may have an important role in the development of insulin resistance.

Hormonal influences during fetal differentiation are so critical that even mild and transient changes in maternal and intrauterine hormone levels within accepted physiological limits can affect the trajectory of normal fetal growth (Miranda & Sousa 2018). Of these hormones, steroid hormones play a significant and widespread role in the long-term organization of fetal organ systems (Fowden & Forhead 2004, Seckl & Holmes 2007).

Steroidal influences on tissue organization stem from the plasticity of the fetus, a feature entrenched in the physiological process of fetal development and differentiation, which is most clearly evident in the process of sexual differentiation. Prior to sexual differentiation primitive gonads and reproductive structures are bipotential, and based on the genetic sex and under the influence of sex hormones, they develop into either male or female gonads and reproductive organs (Jost *et al.* 1973, Jost 1983). The presence of the Y chromosome in the male, for example, leads to production of

testis-determining factor (TDF/sex-determining region Y (SRY)), a transcription factor that directs the development of bipotential gonads into testes. The developing testes produce hormones, including Mullerian-inhibiting substance/anti-Mullerian hormone (MIS/AMH) and testosterone. This hormonal milieu induces regression of the Mullerian ducts, which are otherwise destined to form female reproductive structures, and promotes the development of Wolffian ducts into male reproductive structures. The steroid hormone testosterone further promotes maturation of these structures and organization of the reproductive neuroendocrine axis and reproductive behavior. Gonadal sexual differentiation begins early in gestation in humans (Rabinovici & Jaffe 1990), and during this critical window, inappropriate exposure of the female fetus (XX chromosomal complement) to excess testosterone leads to virilization of reproductive organs and masculinization of reproductive behaviors (Berenbaum 2002). These observations are embedded in classical physiology and demonstrate the plasticity of the developing fetus and the importance of the maternal and fetal steroid hormone milieu in shaping fetal developmental trajectories (McEwen 1992).

This plasticity allows the fetus to respond to the prevailing maternal environment, which induces cellular and molecular changes to allow phenotypic adaptations. This process is termed 'developmental plasticity', and in theory aids in improving the offspring's chances for survival in the external environment (Laubach *et al.* 2018, Lema 2020). However, the organizational changes that allow short-term survival often prove to be maladaptive in the long term by augmenting risk for non-communicable diseases such as T2DM (Hales & Barker 1992), metabolic syndrome (Rinaudo & Wang 2012), and obesity (Breier *et al.* 2001). This concept has been formalized as the Developmental Origins of Health and Disease (DOHaD) hypothesis and is of relevance to many maternal and environmental insults (Barker 2004, 2007, Gluckman & Hanson 2004, Wadhwa *et al.* 2009, Padmanabhan *et al.* 2010a, Barouki *et al.* 2012). Hormones, particularly steroid hormones, play a critical role in mediating the influence of these internal and external environmental signals and direct either adaptive or maladaptive responses in the developing fetus (Dufty *et al.* 2002).

Adaptive organizational changes often remain dormant, requiring an activational step to unmask the programmed phenotypic and behavioral changes. An example of such activational processes is evident in reproductive behavior. While the neurocircuitry required for reproductive behaviors is organized during early

development, these pathways remain relatively quiescent prior to puberty, requiring subsequent stimulation by sex steroids to induce appropriate adult reproductive behavior (Romeo 2003). Similarly, the maladaptive organizations induced during early life in metabolic systems may remain dormant until activated by prevailing postnatal environmental cues, with hormones including steroids serving as mediators of this activational process (Puttabyatappa *et al.* 2016).

The reprogramming associated with fetal exposure to steroids at abnormal concentrations or at inappropriate times are often detrimental, culminating in a diverse array of adult pathologies. Inappropriate exposure to steroids can occur through disease, maternal stress, adverse maternal nutritional states, and environmental stressors, including exposure to chemicals with the potential to disrupt steroid hormone signaling (Padmanabhan *et al.* 2016). Since adverse conditions and exposures not only impact the maternal hormonal milieu but also the fetal hormonal environment, the placenta serves as a critical intermediary in this developmental process by acting as a conduit between the maternal and fetal compartments while also serving as a steroidogenic organ (Strauss *et al.* 1996, Wooding & Burton 2008); thus, the placenta plays a critical role in regulating fetal exposures to maternal and environmental factors. Data from the Helsinki Birth Cohort have shown that abnormal placenta are linked with development of adult onset cardiometabolic diseases in the offspring (Thornburg *et al.* 2010). Therefore, conditions that compromise placental function either through direct maternal-fetal transfer or through altered placental steroidogenesis (e.g. preeclampsia, gestational diabetes, and endocrine-disrupting chemicals (EDCs)) (Nugent & Bale 2015) contribute to inappropriate fetal exposure to steroids with potential consequences on fetal development and the long-term health of the offspring.

Androgen programming of insulin resistance

Insulin secreted from pancreatic beta-cells maintains postprandial nutrient homeostasis through stimulation of anabolic processes: increasing glucose influx into muscle and adipose tissue, protein and glycogen synthesis in muscle and liver, lipid synthesis and storage in liver and adipose tissue, and through inhibition of fatty acid oxidation, lipolysis, glycogenolysis, and gluconeogenesis (Guo 2014). A failure to respond to insulin and achieve these physiological effects defines insulin resistance and results in compensatory increases in beta-cell insulin

secretion. Lack of responsiveness to insulin occurs at systemic, tissue, and cellular levels as a result of increases in inflammation, oxidative stress, hypoadiponectinemia, and dyslipidemia; all of which negatively affect insulin action and tissue function (Hocking *et al.* 2013, Burgos-Moron *et al.* 2019, Iwabu *et al.* 2019). At the cellular level, reduced insulin response may result from insulin receptor desensitization or reduced expression, suppression of members of the insulin receptor signaling pathway and associated regulatory network, and mitochondrial and endoplasmic reticulum dysfunction (Flamment *et al.* 2012, Guo 2014, Gonzalez-Franquesa & Patti 2017).

Developmental exposure to various insults can lead to programming of insulin resistance as evident from clinical, epidemiological, and experimental studies (Table 1). While steroid hormones can directly influence insulin action as evident from sex-specific differences in glucose homeostasis and adipose distribution (Mauvais-Jarvis 2015, Varlamov *et al.* 2015), the evidence that developmental insults can lead to changes in maternal steroids especially androgens (Table 2) and induce insulin resistance (Table 1) point to androgens as potential culprits in the developmental programming of insulin resistance. Examples of conditions that result in excessive maternal androgen exposure include virilizing congenital adrenal hyperplasia (CAH) and the PCOS. In CAH, mutations in the 21-hydroxylase enzyme, which is required for biosynthesis of mineralocorticoids and glucocorticoids, results in androgen excess with consequential fetal exposure (Parsa & New 2017); importantly, these offspring exhibit postnatal signs of reduced insulin sensitivity (Tamhane *et al.* 2018). Evidence indicates that during pregnancy women with PCOS have higher androgen levels with associated disruptions in placental steroidogenesis (Sir-Petermann *et al.* 2002, Maliqueo *et al.* 2013), which likely combine to result in excess fetal androgen exposure. Daughters of these women show signs of metabolic derangements, including hyperinsulinemia during adolescence (Sir-Petermann *et al.* 2009). Maternal stress not only increases maternal glucocorticoids levels (Dunkel Schetter 2011), but it also induces a hyperandrogenic maternal hormonal milieu (Barrett & Swan 2015). A 30-year follow-up study reported hyperinsulinemia among offspring born to mothers administered glucocorticoids during pregnancy (Dalziel *et al.* 2005). Maternal under- and over-nutrition have both been linked with the programming of obesity, T2DM, and insulin resistance (Duque-Guimaraes & Ozanne 2013, Vaiserman 2017). In addition to direct effects of the altered nutritional state, these conditions also alter the maternal androgenic milieu (Mossa *et al.* 2019,

Pasquali & Oriolo 2019). For example, maternal obesity is associated with increased androgen levels (Whyte *et al.* 2007, Arnon *et al.* 2016, Maliqueo *et al.* 2017, Pasquali & Oriolo 2019), suggesting a potential role for androgens in the programming of offspring phenotypes in such nutritional models.

Environmental EDCs, especially those that have the capacity to influence androgen biosynthesis or bioavailability as well as those that modulate androgen receptor signaling, are also potential contributors to androgenic programming of metabolic disorders such as insulin resistance (Diamanti-Kandarakis *et al.* 2009, Gore *et al.* 2015). Rapid industrialization has led to widespread fetal and offspring exposure to EDCs through maternal-fetal transfer both across the placenta and via lactation, resulting in exposure during critical susceptibility windows (Masuda *et al.* 1978, Ando *et al.* 1985, Bowman & Choudhury 2016). Many naturally occurring compounds (e.g. phytoestrogens, including genistein and coumestrol) as well as anthropogenic chemicals (e.g. industrial solvents and lubricants (e.g. polychlorinated biphenyls (PCBs), polybrominated biphenyls, and dioxins), plasticizers (e.g. bisphenol A (BPA)), pesticides (e.g. dichlorodiphenyltrichloroethane (DDT)), fungicides (e.g. vinclozolin), and pharmaceutical agents (e.g. diethylstilbestrol)) (Kabir *et al.* 2015) are EDCs that can serve as steroid mimics and activate steroid receptor signaling. Meta-analyses conducted by the National Toxicology Program and analyses of the National Health and Nutrition Examination Survey 2003–2004 data have shown strong associations between the incidence of T2DM and persistent organic pollutants (DDT and PCBs) and BPA (Lang *et al.* 2008, Taylor *et al.* 2013). Especially concerning is the fact that many of these EDCs are detectable in pregnant women and cord blood (Woodruff *et al.* 2011, Lee *et al.* 2017, Goodrich *et al.* 2019), thus suggesting the potential for these chemicals to disrupt fetal and offspring developmental trajectories. Maternal exposure to BPA and phthalates have been shown to alter maternal androgen milieu (Takeuchi *et al.* 2004, Sathyanarayana *et al.* 2017) raising the possibility that the programming effects of these EDCs may be mediated via alterations in the maternal androgenic milieu. Apart from their agonistic/antagonistic actions (De Falco *et al.* 2015), EDCs can indirectly affect the prevailing steroid milieu by modulating rate-limiting enzymes involved in steroid hormone biosynthesis and/or metabolism (Sanderson 2006, Tabb & Blumberg 2006). Evidence that EDCs affect steroid biosynthesis comes from data demonstrating reduced placental aromatase

Table 1 Developmental insults with consequential insulin resistance in the offspring.

Maternal insult	Model			
	Humans	Macaques	Ruminants	Rat
Disease state	Virilizing CAH (Tamhane <i>et al.</i> 2018) PCOS (Sir-Petermann <i>et al.</i> 2009) Gestational Diabetes (Kubo <i>et al.</i> 2014)	See Table 3 for gestational hyperandrogenic experimental models		
Undernutrition	Dutch Hunger Winter (Painter <i>et al.</i> 2005) Chinese Famine (Li <i>et al.</i> 2010) Leningrad Siege study (Stanner <i>et al.</i> 1997) Pune Maternal Nutrition study (Yajnik <i>et al.</i> 2008) Obesity during pregnancy (Boney <i>et al.</i> 2005, Zhang <i>et al.</i> 2011)		Nutrition restricted sheep (Gardner <i>et al.</i> 2005, Ford <i>et al.</i> 2007, Todd <i>et al.</i> 2009, George <i>et al.</i> 2012)	Maternal hyperglycemia (Aerts <i>et al.</i> 1990, Gauguier <i>et al.</i> 1990) Maternal caloric restriction (Palou <i>et al.</i> 2012); protein restriction (Fernandez-Twinn <i>et al.</i> 2005); micronutrient (Zinc) deficiency (Jou <i>et al.</i> 2010)
Overnutrition		Overfed baboons; preweaning (Lewis <i>et al.</i> 1986) High fat diet fed rhesus macaques (McCurdy <i>et al.</i> 2009)	Overfed sheep (Burt <i>et al.</i> 2007, Long <i>et al.</i> 2010)	Maternal high fat diet (Buckley <i>et al.</i> 2005, Cerf <i>et al.</i> 2005, Taylor <i>et al.</i> 2005) Western diet/high fat-high sugar diet (Nivoit <i>et al.</i> 2009); early postnatal overnutrition and catch-up growth (Berends <i>et al.</i> 2013) Gestational glucocorticoid administration (Nyirenda <i>et al.</i> 1998, O'Regan <i>et al.</i> 2004)
Stress	Dutch and Chinese Famines and Seize of Leningrad (see above); 1998 ice storm (Dancause <i>et al.</i> 2013); Severe hyperemesis gravidarum (Ayyavoo <i>et al.</i> 2013)		Heat stress (Camacho <i>et al.</i> 2017); Gestational glucocorticoid administration (Gatford <i>et al.</i> 2000, Long <i>et al.</i> 2012, 2013)	
EDC - Bisphenol A (BPA)	NHANES survey (Lang <i>et al.</i> 2008)		Sheep gestational BPA treatment (Veiga- Lopez <i>et al.</i> 2016)	Gestational BPA treatment (Ma <i>et al.</i> 2013, Li <i>et al.</i> 2014b)
EDC - Phthalates	Korean Ewha Birth and Growth Cohort Study (Han <i>et al.</i> 2019); Young Taiwanese (YOTA) Cohort Study (Chen <i>et al.</i> 2017) NHANES survey (James-Todd <i>et al.</i> 2012)			Gestational BPA treatment (Alonso-Magdalena <i>et al.</i> 2006, 2010, Angle <i>et al.</i> 2013) Gestational and lactational Di(2-ethylhexyl) phthalate treatment (Hunt <i>et al.</i> 2017)

CAH, congenital adrenal hyperplasia; EDC, endocrine-disrupting chemical; NHANES, National Health and Nutrition Examination Survey; PCOS, polycystic ovary syndrome; TNDM29, transient neonatal diabetes mellitus locus 29.

Table 2 Induction of hyperandrogenemic maternal hormone milieu by developmental insults.

Maternal insult	Maternal androgen milieu
Disease state	
• PCOS	Sir-Petermann <i>et al.</i> 2002
• Virilizing CAH	Parsa and New 2017
• Gestational diabetes	Morisset <i>et al.</i> 2013
• Preeclampsia	Acromite <i>et al.</i> 1999
Undernutrition	Mossa <i>et al.</i> 2019
Overnutrition	Whyte <i>et al.</i> 2007 , Arnon <i>et al.</i> 2016 , Maliqueo <i>et al.</i> 2017 , Pasquali and Oriolo 2019
Stress	Barrett and Swan 2015
EDC - Bisphenol A	Takeuchi <i>et al.</i> 2004 , Rutkowska and Rachon 2014
EDC - Phthalates	Sathyanarayana <i>et al.</i> 2017

CAH, congenital adrenal hyperplasia; EDC, endocrine-disrupting chemical; PCOS, polycystic ovary syndrome.

(CYP19) expression in trophoblast cultures treated with BPA ([Chu *et al.* 2018](#)), reduced 3β -hydroxysteroid dehydrogenase and CYP19 in the JEG 3 placental cell line treated with phthalate metabolites ([Xu *et al.* 2016](#)), and increased 7α -hydroxylase/17,20-lyase (CYP17) expression in ovarian cells exposed to BPA ([Zhou *et al.* 2008](#)). In addition, EDC-mediated disruption in hepatic steroid hormone metabolism could influence steroid bioavailability. EDCs have been shown to bind nuclear receptors such as the aryl hydrocarbon receptor (AhR) and pregnane X receptor (PXR) and regulate the expression of hepatic enzymes that metabolize steroid hormones ([Mikamo *et al.* 2003](#), [Sanderson 2006](#), [Tabb & Blumberg 2006](#)). For example, AhR binding of PCB or dioxin upregulates expression of *CYP1A1*, *CYP1A2*, and *CYP1B1* ([Kohn *et al.* 1993](#), [Wakui *et al.* 2006](#), [Tarnow *et al.* 2019](#)), while alkylphenols and DDT acting through PXR inhibit hepatic clearance of estradiol in rats ([El-Hefnawy *et al.* 2017](#)). Overall these data indicate the capacity for EDCs to act indirectly as well as directly to influence the maternal and fetal steroidal milieu and contribute to the programming of insulin resistance, a premise requiring further study.

Experimental animal models provide robust direct evidence in support of steroidal programming of insulin resistance ([Table 3](#)). For instance, gestational androgen treatment culminates in insulin resistance during adulthood in female offspring of rodents, sheep, and non-human primates ([Roland *et al.* 2010](#), [Abbott *et al.* 2016](#), [Cardoso & Padmanabhan 2019](#)). In sheep, days 30–90 of gestation encompass the period of organization of metabolic systems ([Padmanabhan & Veiga-Lopez 2014](#)). The main metabolic defects observed in adult sheep treated prenatally with testosterone from days 30 to 90 of gestation include peripheral insulin resistance with compensatory hyperinsulinemia and associated dyslipidemia, oxidative stress, and hepatic steatosis

([Padmanabhan *et al.* 2010b](#), [Veiga-Lopez *et al.* 2013](#), [Puttabyatappa & Padmanabhan 2017](#)). Similarly, animal models of gestational glucocorticoid administration have documented adverse fetal programming of the hypothalamic-pituitary-adrenal (HPA) axis and long-term effects during adulthood on cardiometabolic function ([Moisiadis & Matthews 2014](#), [Constantinof *et al.* 2016](#)). Gestational exposure to EDCs in various animal models also provide direct evidence for the role of steroidal disruption in programming insulin resistance. Such evidence is available for a wide range of EDCs, including BPA and phthalate metabolites ([Strakovsky *et al.* 2015](#), [Provisiero *et al.* 2016](#), [Veiga-Lopez *et al.* 2016](#)). The developmental impact of protein restriction (a model of undernutrition) and high fat/western diet feeding (a model of overnutrition) have been studied in both rodents and nonhuman primates ([Friedman 2015](#), [Neri & Edlow 2015](#), [Ong & Ozanne 2015](#), [Nicholas *et al.* 2016](#)). Although all these conditions are associated with offspring insulin resistance with coincident increases in maternal androgens ([Table 2](#)), androgen ablation studies are required to ascertain whether androgens are indeed the programmers of insulin resistance in these scenarios.

Androgen programming of peripheral insulin resistance

Peripheral insulin resistance is characterized by clinical findings of hyperglycemia, hyperinsulinemia, and impaired glucose tolerance. Evidence supportive of androgen programming of peripheral insulin resistance in the offspring comes from studies in mice, sheep, and rhesus macaques treated with testosterone during gestation ([Roland *et al.* 2010](#), [Abbott *et al.* 2016](#), [Cardoso & Padmanabhan 2019](#)). Comparative studies of sheep treated prenatally with testosterone and dihydrotestosterone (DHT, a non-aromatizable and more

Table 3 Developmental programming of insulin resistance by gestational androgen.

Animal model		Insulin resistance	Remarks
Species	Treatment		
Rhesus Macaques	Testosterone GD 40–80 (term 160)	Yes	<i>Fetal</i> : transient hyperglycemia and hyperinsulinemia (Abbott et al. 2010) <i>Infants</i> : increased basal insulin and beta cell number (Nicol et al. 2014) <i>Adulthood</i> : impaired disposition index, a measure of beta cell function and the ability to dispose glucose load (Eisner et al. 2000) Impaired glucose tolerance in adulthood (Eisner et al. 2000)
Rhesus Macaques	Testosterone GD 100–115 (term 164)	Yes	
Sheep (Suffolk)	Testosterone GD 30–90 (term 147)	Yes	<i>Juvenile period</i> : decreased insulin sensitivity (Recabarren et al. 2005 , Cardoso et al. 2016) <i>Prepubertal period</i> : decreased (Padmanabhan et al. 2010a) or normal (Recabarren et al. 2005 , Cardoso et al. 2016) insulin sensitivity based on proximity to puberty <i>Postpubertal/early adulthood</i> : normal (Recabarren et al. 2005 , Cardoso et al. 2016) or increased (Veiga-Lopez et al. 2013) insulin sensitivity <i>Adulthood</i> : Reduced insulin sensitivity (Padmanabhan et al. 2010b) Reduced insulin sensitivity at prepubertal age (Padmanabhan et al. 2010a)
Sheep (Suffolk)	DHT GD 30–90 (term 147)	Yes	
Sheep (Suffolk)	Testosterone GD 60–90 (term 147)	Yes	Reduced insulin sensitivity in adulthood (Padmanabhan et al. 2010b)
Sheep (Scottish Greyface x Texel)	Testosterone GD 62–102 (term 147)	Yes	Adult age: normal glucose homeostasis but elevated basal insulin levels (Hogg et al. 2011)
Rat (Wistar)	Testosterone GD 20 (term 21)	Yes	Single injection of testosterone during gestation impaired insulin sensitivity with normal HOMA index and glucose tolerance (Noroozzadeh et al. 2015)
Rat (Wistar)	Testosterone GD 15–19 (term 21)	Yes	Female offspring were insulin resistant compared male offspring, and this phenotype was prevented by flutamide or tamoxifen co-administration (Hu et al. 2015)
Rat (Sprague Dawley)	DHT GD 16–19 (term 21)	Yes	Insulin resistance observed at pubertal age (Yan et al. 2013)
Rat (Wistar)	Testosterone (5.0 mg daily) GD 16–19 (term 21)	No	Administration of 5 mg testosterone daily did not affect insulin sensitivity, but animals developed lipid disturbances and hepatic steatosis (Sun et al. 2012)
Rat (Sprague Dawley)	DHT Day 35–125 postnatal	Yes	Hyperglycemia and hyperinsulinemia with increased body weight and perirenal fat at the end of the treatment period ^a (Yanes et al. 2011)
Rat (Wistar)	DHT Day 21–111 postnatal	Yes	Decreased insulin sensitivity at the end of 90-day DHT treatment ^a (Mannerås et al. 2007)
Rat (Wistar)	Letrazole Day 21–111 postnatal	No	No effect on insulin sensitivity at the end of 90-day DHT treatment (Mannerås et al. 2007)
Rat (Wistar)	Estradiol Valerate Single injection Day 56 postnatal	No	No change in insulin sensitivity or androgen levels (Stener-Victorin et al. 2005)
Rat (Sprague Dawley)	DHEA Day 21–41 postnatal	Yes	Higher fasting glucose and insulin ^a (Wang et al. 2004)
Rat (Sprague Dawley)	Testosterone Day 28–48 postnatal	Yes	Hyperinsulinemia with reduced rate of glucose uptake ^a (Holmäng et al. 1990)
Mouse (C57BL/N6)	Letrazole Day 28–88 postnatal	Yes	Impaired glucose tolerance at unspecified age ^a (Kauffman et al. 2015)
Mouse (C57BL/6J)	DHT GD 16–18 (term 20)	No	No effect on fasting glucose levels or insulin levels at 3 and 16 weeks of age (Caldwell et al. 2014)
Mouse (C57BL/6J)	DHT Day 21–111 postnatal	No	No effect on fasting glucose levels or insulin levels at 16 weeks of age ^a (Caldwell et al. 2014)
Mouse (C57BL/6J)	DHEA Day 21–111 postnatal	No	No effect on fasting glucose levels or insulin levels at 16 weeks of age ^a (Caldwell et al. 2014)
Mouse (C57BL/6J)	Letrozole Day 21–111 postnatal	No	No effect on fasting glucose levels or insulin levels at 16 weeks of age ^a (Caldwell et al. 2014)
Mouse (C57BL/6J)	DHT Day 19–109 postnatal	Yes	Glucose intolerant at the end of a 90-day DHT treatment ^a (van Houten et al. 2012)
Mouse (CBB6/F1)	DHT GD 16–18 (term 20)	Yes	Prepuberty through adulthood: impaired glucose intolerance (Roland et al. 2010)

^aObservations made either during treatment or end of treatment period – whether these effects are programmed or due to activational effects is not known.

DHT, dihydrotestosterone; GD, gestational days.

active metabolite of testosterone) provide direct evidence that insulin resistance is programmed specifically through the androgenic actions of testosterone (Padmanabhan *et al.* 2010b). The involvement of androgens in the programming of insulin resistance is also supported by evidence of hyperinsulinemia during adolescence in daughters born to women with PCOS (Sir-Petermann *et al.* 2009) who have higher androgen levels during pregnancy (Sir-Petermann *et al.* 2002). The insulin resistance evident in offspring from pregnancies of women with CAH (Reisch *et al.* 2011), maternal disease states such as PCOS and gestational diabetes (Sir-Petermann *et al.* 2009, Bianco & Josefson 2019), nutritional deficit/excess (Godfrey *et al.* 2017, Ong & Guest 2018), stress (Moisiadis & Matthews 2014, Facchi *et al.* 2019), and environmental EDC exposures (Gore *et al.* 2015, Veiga-Lopez *et al.* 2016, Sargis & Simmons 2019) along with the evidence that these conditions induce increased maternal androgen levels (Table 2) (Takeuchi *et al.* 2004, Whyte *et al.* 2007, Rutkowska & Rachon 2014, Barrett & Swan 2015, Arnon *et al.* 2016, Maliqueo *et al.* 2017, Parsa & New 2017, Sathyanarayana *et al.* 2017), point to androgens as a likely culprit in the programming of peripheral insulin resistance, a premise that needs to be formally tested using interventional strategies such as androgen antagonism.

Androgen programming of tissue-specific insulin resistance

Disruptions in both insulin-responsive tissues (liver, muscle, and adipose tissue) as well as in insulin-producing tissues (pancreas) collaborate in the development of systemic and tissue-level insulin resistance. Tissue effects of insulin involve ligand binding to the insulin receptor (IR) that triggers downstream signaling events, including phosphorylation of protein kinase B (AKT), mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), and the mammalian target of rapamycin (mTOR) (Saltiel & Kahn 2001, Guo 2014). Collectively, these signaling events promote glucose uptake as well as lipid and protein anabolic metabolism. Therefore, impairment at any level of the insulin signaling pathway may result in insulin resistance with consequential hyperglycemia (Rask-Madsen & Kahn 2012). Evidence to date points to the role that developmental steroid exposures, especially androgens, play in programming tissue-specific insulin sensitivity. The following sections address the androgen programming of insulin sensitivity at metabolic targets, namely, liver, muscle, adipose tissue, pancreas, brain, and cardiac tissues.

Liver

Liver is a critical regulator of metabolic physiology, with insulin playing a central role in glucose, protein, and lipid metabolism. In the liver, insulin reduces blood glucose levels by inhibiting gluconeogenesis and glycogenolysis while promoting glycogen synthesis. Gluconeogenesis is inhibited by insulin-stimulated AKT-mediated phosphorylation of the transcription factor forkhead box protein O1 (FOXO1), which downregulates expression of gluconeogenic enzymes, including phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) (Guo 2014). Glycogen synthesis is stimulated through AKT-dependent phosphorylation and inhibition of glycogen synthase kinase-3 beta (GSK3B), which promotes the dephosphorylation and activation of glycogen synthase. AKT-dependent inhibition of tuberous sclerosis protein-2 (TSC2) consequently activates mTORC1 and ribosomal protein S6 kinase (S6K), which promote protein synthesis (Inoki *et al.* 2002) and stimulate transcription of sterol regulatory element-binding protein 1 (SREBP1), resulting in increased expression of lipogenic genes (Ruiz *et al.* 2014).

Studies addressing the programming of offspring hepatic insulin sensitivity by maternal disease state are not available in humans; however, data from animal models of developmental insults show defects at multiple levels of the insulin signaling pathway. For instance, both male and female offspring born to obese sheep manifest decreased protein abundance of IR, phosphorylated AKT, and phosphorylated FOXO1 (Nicholas *et al.* 2013). Similarly, male offspring of obese mice manifest decreased levels of insulin receptor substrate (IRS) 1, phosphorylated IRS1, and phosphorylated AKT as well as increased levels of GSK3B (Martin-Gronert *et al.* 2010). Hyperinsulinemia and hyperglycemia observed in male offspring born to pregnant rats treated with dexamethasone, a model of fetal exposure to excess glucocorticoids, is also accompanied by increased expression and activity of the gluconeogenic enzyme PEPCK, suggesting defects in hepatic insulin signaling (Drake *et al.* 2005). Gestational treatment with BPA in mice also reduced expression of *Irs2*, *Akt2*, *G6pc*, and *Srebp1* in the liver of both male and female offspring (Van der Meer 2015). All of the above discussed maternal insults (obesity, stress, and EDC exposure) provide evidence in support of the hypothesis that gestational insults that program the development of hepatic insulin resistance and systemic hyperinsulinemia are also associated with increases in maternal androgens (Table 2) (Takeuchi *et al.* 2004, Whyte *et al.* 2007, Rutkowska & Rachon 2014, Barrett & Swan 2015,

Arnon *et al.* 2016, Maliqueo *et al.* 2017). The commonality of androgen excess in these pathophysiological states suggests that androgens are a likely contributor to the programming of these metabolic defects. Importantly, the exact developmental changes observed after these programming events may vary depending on both the timing of the insult and the life period during which analyses are performed. For example, while gestational testosterone treatment induces higher mTOR protein level and greater phosphorylation of S6K and GSK3B in the livers of female fetal day 90 sheep suggesting an insulin sensitive state (Lu *et al.* 2016), *IR2*, *IRS2*, *AKT*, and *mTOR* mRNA are downregulated in adult life (Nada *et al.* 2010) indicative of an insulin resistant hepatic phenotype. The reduced hepatic insulin sensitivity during adult life is supported by evidence of reduced phosphorylation of AKT under insulin-stimulated conditions in prenatally testosterone-treated female sheep (Lu *et al.* 2016). Co-treatment with an androgen antagonist prevented the fetal, but not the adult, changes in insulin signaling, indicating that the consequences of androgen programming during adult life may be subject to activational inputs and thus masked or unmasked by the prevailing adult hormone milieu. For example, increases in modulators of insulin sensitivity such as lipid accumulation in the liver leading to hepatic steatosis, inflammation, and oxidative stress during adult life of all animal models discussed above (McCurdy *et al.* 2009, Ashino *et al.* 2012, Lynch *et al.* 2017, Puttabyatappa *et al.* 2017, 2019b, Shimpi *et al.* 2017) may aid in maintaining the insulin resistant state programmed by gestational insults. Although hepatic lipid accumulation is also observed in offspring of gestationally DHT-treated mice, the mechanisms by which this develops and the disruptions in the insulin signaling cascade remains to be determined (Caldwell *et al.* 2014).

Muscle

Muscle is largely responsible for postprandial glucose disposal, with insulin promoting glucose uptake through AKT stimulation of GLUT4 protein translocation to the cell membrane (Dimitriadis *et al.* 2011). While disease states such as PCOS are associated with aberrant skeletal muscle gene expression and signaling pathways (Nilsson *et al.* 2018, Hansen *et al.* 2019, Shen *et al.* 2019, Stepto *et al.* 2019), generational studies addressing developmental insults in androgen programming of muscle-specific insulin signaling disruptions is lacking in humans. However, in animal models of maternal obesity, which show increased maternal androgen levels (Whyte *et al.* 2007, Arnon *et al.* 2016, Maliqueo *et al.* 2017,

Pasquali & Oriolo 2019) and offspring insulin resistance, muscle-specific disruptions in insulin signaling and GLUT4 levels are evident. One study of male offspring born to obese pregnant rats found reduced levels of skeletal muscle *Glut4* expression (Simar *et al.* 2012), while another study in rat offspring (of unspecified sex) had reduced expression of *Ir* and *Glut4* in muscle (Bayol *et al.* 2005). In sheep models of maternal obesity, insulin resistance in the offspring is associated with reduced expression of insulin signaling intermediates when both male and female offspring were assessed together (Yan *et al.* 2010). Similarly, female mice born to obese dams exhibited reduced IRS1 and PI3K protein levels as well as decreased AKT phosphorylation at serine residue 473 (i.e. site of activation by insulin) in the skeletal muscle (Shelley *et al.* 2009). The associated increased levels of maternal androgens during pregnancy that occur in both mice and humans with obesity (Whyte *et al.* 2007, Arnon *et al.* 2016, Maliqueo *et al.* 2017, Pasquali & Oriolo 2019) suggest that androgens may be involved in the programming of offspring muscle insulin resistance in the context of maternal obesity. Studies of gestationally testosterone-treated sheep support this premise with the observation of decreased phosphorylated-GSK3B and GLUT4 protein levels in female fetuses at fetal day 90 and impaired insulin stimulation of AKT phosphorylation in adult female offspring (Lu *et al.* 2016). Although GLUT4 levels have not been examined during adulthood, the reduced AKT phosphorylation is likely to result in reduced GLUT4 membrane translocation in adult sheep as well, likely resulting in increased glucose levels.

Adipose

As in muscle, adipose tissue glucose uptake is primarily driven by insulin; however, because adipose tissue accounts for only 5–10% of whole body glucose uptake, it has only a minor role in postprandial glucose regulation (Dimitriadis *et al.* 2011). Despite this fact, adipose tissue influences the insulin sensitivity of other tissues through release of free fatty acids and adipokines (Rosen & Spiegelman 2006, Tchernof & Despres 2013); as such, increased adiposity and adipose dysfunction are major risk factors for the development of insulin resistance (Kahn & Flier 2000). Because of this role of adipose tissue, the majority of studies examining adipose programming by developmental insults such as maternal obesity is focused on the assessment of adipose tissue phenotype.

The hyperandrogenic state of PCOS likely contributes to the insulin resistance in the absence or presence of obesity (Dumesic *et al.* 2007). Importantly, the daughters

born to mothers with PCOS also manifest insulin resistance (Sir-Petermann *et al.* 2009), suggesting that the maternal hyperandrogenic state of PCOS may contribute to the developmental programming of insulin resistance across generations. At the level of adipose tissue, several studies in women with PCOS, mostly conducted on subcutaneous adipose tissue (SAT), have found adipose tissue to be insulin resistant (Cree-Green *et al.* 2015, 2017, Dumesic *et al.* 2019); other studies have found adipose to be more insulin sensitive (Corbould & Dunaif 2007, Ciaraldi *et al.* 2009). In studies demonstrating adipose insulin resistance, disruptions are evident at multiple levels of insulin signaling, including: (1) a rightward shift in the insulin dose–response curve for insulin-stimulated glucose uptake in isolated adipocytes (Ciaraldi *et al.* 1992); (2) reduced phosphorylation of IRS1 and IRS2 (Qiu *et al.* 2005, Wang *et al.* 2005); (3) hyperactivation of GSK3B that is resistant to insulin-stimulated downregulation (Chang *et al.* 2008); and (4) decreased expression of *GLUT4* (Rosenbaum *et al.* 1993). These findings are supportive of androgens gestationally programming adipose insulin resistance. Considering that the majority of women with PCOS are also obese, the increased adiposity per se may further amplify the programmed insulin sensitivity defects induced by androgen excess. This premise is supported by several observations, including: (1) treatment of female rhesus macaques with testosterone from menarche (a developmental programming window) coupled with a Western diet leads to greater insulin resistance than that observed in either the testosterone-treated or Western diet-fed conditions alone (True *et al.* 2017); and (2) gestational testosterone treatment coupled with postnatal obesity in female sheep leads to earlier impairments in insulin sensitivity compared to offspring only exposed to testosterone (Padmanabhan *et al.* 2010b). Interestingly, gestational testosterone treatment promoted preferential accumulation of metabolically deleterious visceral adipose tissue (VAT) in female rhesus macaques (Eisner *et al.* 2003), indicating that the steroidal programming of metabolism includes disruption of adipocyte insulin signaling and adipose mass and distribution. Male offspring from dams gestationally stressed by diet-induced obesity in mice (Fernandez-Twinn *et al.* 2014) and caloric-restricted rats (Berends *et al.* 2013) manifest insulin resistance and impaired adipose insulin signaling characterized by reduced levels of *Ir2*, *Irs1*, phosphatidylinositol-3-kinases (Pi3k), and *Akt*. Associated increases in maternal androgen levels in these models (Table 2) (Maliqueo *et al.* 2017, Mossa *et al.* 2019) suggest that programming of insulin resistance in adipose tissue may be androgen dependent.

In stark contrast, a lack of change in the phosphorylation states of AKT, mTOR, ERK, GSK3B, and S6K during fetal life as well as increased mRNA expression of *IR2*, *mTOR*, *AKT*, *PI3K*, and peroxisome proliferator-activated receptor gamma (PPAR γ) in the VAT with increased insulin-stimulated phosphorylated-AKT in the VAT and SAT in adult female offspring of gestationally testosterone-treated sheep (Nada *et al.* 2010, Lu *et al.* 2016) reflect an insulin-sensitive state in adipose tissue. Whether these differences in adipose insulin sensitivity programmed by gestational insults is due to differences in the adipose depot examined, species- or sex-specific differences, developmental time point studied, or differences in adipocyte differentiation (adipocyte hypertrophy in PCOS and offspring of obese mice (Manneras-Holm *et al.* 2011, Caldwell *et al.* 2014, Ibanez *et al.* 2018) vs adipocyte hypotrophy in gestational testosterone-treated sheep (Cardoso *et al.* 2016)) requires further examination.

Pancreas

As insulin resistance is often accompanied by compensatory increases in insulin secretion, impairment in pancreatic beta-cells can contribute to compromised insulin sensitivity, potentially through inappropriate insulin secretion (Shanik *et al.* 2008). In pregnant women hyperandrogenemia during pregnancy (Gozukara *et al.* 2015) is associated with the development of gestational diabetes leading to the development of insulin resistance in the offspring (Bianco & Josefson 2019), disruptions in beta-cell function and development of compensatory hyperinsulinemia (Singh *et al.* 2006, Kelstrup *et al.* 2013). Similarly, in rat models of maternal high fat feeding, male offspring have disrupted beta-cell gene expression characteristic of impaired function (Agarwal *et al.* 2019) and impaired insulin signaling (e.g. reduced *IRS1* and *AKT* with increased *FOXO1* expression) (Brighenti *et al.* 2016). As high-fat diet-fed dams exhibit hyperandrogenemia during gestation (Whyte *et al.* 2007, Arnon *et al.* 2016, Maliqueo *et al.* 2017), androgens may program beta-cell disruptions in the offspring. The identification of pancreatic beta-cell defects with associated elevations in basal insulin secretion in female fetuses born to gestationally testosterone-treated sheep support such a notion (Rae *et al.* 2013). Another study of testosterone administration at gestational days 62 and 82 showed that female fetuses had increased beta-cell numbers at both fetal and adolescent ages with elevated basal insulin secretion (Ramaswamy *et al.* 2016), suggesting androgen programming of beta-cell dysfunction that leads to hyperinsulinemia. The observation that this phenotype

was evident only in animals that received testosterone and not diethylstilbestrol or dexamethasone during gestation imply specific involvement of androgens in the steroidal programming of beta-cell dysfunction (Ramaswamy *et al.* 2016).

Heart

Cardiac tissue uses free fatty acids as its primary source of energy; however, it also utilizes glucose during fetal life and periods of stress (Abel 2004). As in skeletal muscle, insulin influences glucose uptake and storage in the myocardium. Maternal weight gain and obesity are associated with the development of cardiovascular defects (Gaillard 2015). In sheep models of maternal obesity, offspring manifest hyperinsulinemia with increased activation of AKT, ERK, and mTOR in cardiac tissues with cardiac hypertrophy (Fernandez-Twinn *et al.* 2012). As gestational obesity is associated with increases in maternal androgens (Table 2) (Whyte *et al.* 2007, Arnon *et al.* 2016, Maliqueo *et al.* 2017), these cardiac changes may be programmed by androgens. In support of this, gestationally testosterone-treated sheep also exhibit elevated expression of *mTORC1* and increased phosphorylation of PI3K, AKT, and mTOR with associated cardiac hypertrophy (Vyas *et al.* 2016).

Brain

The function of insulin in the brain is not confined to regulation of glucose availability from the periphery. Insulin influences neuronal function, and disruptions in brain insulin action is thought to be a basis for neurodegenerative and mood disorders as well as the metabolic syndrome (Kleinridders *et al.* 2014). In addition, there is crosstalk between insulin and appetite regulators, including orexigens such as neuropeptide Y (NPY) and anorexigens such as proopiomelanocortin (POMC) (Breton 2013, Vogt & Bruning 2013), which influence systemic tissue-level insulin sensitivity. Gestational insults that program peripheral insulin resistance (e.g. diet-induced maternal obesity) also induce insulin resistance in the male rat hippocampus with reduced levels of *Ir2*, *Pi3k*, and *Akt* levels (Gomes *et al.* 2018). Similar changes have also been observed in female offspring of gestationally testosterone-treated sheep with reduced *IR2* levels in the hypothalamic arcuate nucleus, an effect that was reversed with gestational androgen antagonist treatment (Cernea *et al.* 2016). These data coupled with the fact that maternal androgens are elevated in animal models of diet-induced obesity (Whyte *et al.* 2007, Arnon *et al.* 2016,

Maliqueo *et al.* 2017) indicate that insulin resistance in these neurons may be programmed by androgens. Surprisingly, male offspring of gestationally estradiol-treated mice had decreased hypothalamic *IR* mRNA and protein expression associated with the development of insulin resistance (Wang *et al.* 2018), indicating the potential for estrogenic mediation of insulin resistance as well. However, the finding that androgen receptor antagonists reversed the decrease in *IR* expression in the hypothalamic arcuate nucleus in prenatal testosterone-treated sheep effectively rules out estrogen as the mediator in this model and point to androgens as the culprits.

Mediators of androgen programming of insulin resistance

Steroid hormones elicit their actions through direct actions and via intermediaries to reorganize pathways involved in insulin production and function. Direct actions may involve signaling through their nuclear or membrane receptors with consequential alterations in gene transcription and signal transduction that regulate metabolic functions (Faulds *et al.* 2012). Indirect actions may be facilitated via alterations in the inflammatory, oxidative, or lipotoxic state as well as through the involvement of epigenetic modifications. More recently, the role of the gut microbiome in the developmental programming and pathogenesis of insulin resistance has also been suggested.

Inflammation

Inflammation is a complex process that involves the production of cytokines and other inflammatory mediators as well as the activation and invasion of immune cells; these effects are associated with the metabolic dysfunction associated with obesity and T2DM (Esser *et al.* 2014). While physiological inflammatory modulation of processes regulated by adrenocortical steroids are involved in the processes of lung maturation and parturition (Keelan 2018) as well as in the sex steroid programming of behavioral sexual dimorphism (McCarthy *et al.* 2017), maternal disease states (e.g. gestational diabetes (Pantham *et al.* 2015), preeclampsia (Gomez-Lopez *et al.* 2019, Tenorio *et al.* 2019), maternal stress, obesity, and exposure to EDCs) that lead to the development of offspring insulin resistance (Godfrey *et al.* 2017, Facchi *et al.* 2019, Sargis & Simmons 2019) are also associated with pathophysiological maternal

inflammation (Schmatz *et al.* 2010, Ingvorsen *et al.* 2015, Ozias *et al.* 2015, Alfaradhi *et al.* 2016, Dewi *et al.* 2017, Dudele *et al.* 2017, Bansal *et al.* 2018, Gu *et al.* 2018, Zota *et al.* 2018, Desplats *et al.* 2019, Kelley *et al.* 2019a, Song *et al.* 2020) and an altered androgen milieu (Table 2) (Acromite *et al.* 1999, Takeuchi *et al.* 2004, Whyte *et al.* 2007, Morisset *et al.* 2013, Rutkowska & Rachon 2014, Vejrazkova *et al.* 2014, Barrett & Swan 2015, Arnon *et al.* 2016, Maliqueo *et al.* 2017, Sathyanarayana *et al.* 2017) in both humans and animals. These findings implicate androgens and inflammatory processes in the programming of insulin resistance. Strong associations exist between inflammatory biomarkers and cortisol in mothers with major depressive disorder (Osborne *et al.* 2018) as well as placental inflammation following maternal exposure to BPA in the sheep (Song *et al.* 2020). As these states are associated with an increased androgenic maternal milieu (Takeuchi *et al.* 2004, Rutkowska & Rachon 2014, Barrett & Swan 2015), it is possible that inflammatory state in these situations also involve androgens. The finding that gestational treatment with testosterone leads to placental inflammation in sheep (Kelley *et al.* 2019b), and the female offspring of these animals develop insulin resistance (Padmanabhan *et al.* 2010b) lend support to the possibility that gestational androgen-mediated programming of offspring insulin resistance may involve inflammatory pathways. Further studies are needed to establish the absolute contribution of inflammatory processes to programmed metabolic dysfunction and to determine if inflammation is the key mediator of the androgenic programming of insulin resistance.

Oxidative stress

Physiological levels of reactive oxygen species (ROS) aid in placentation and fetal development by virtue of their role in cell signaling and gene transcription. However, breakdown of antioxidant defense mechanisms and accumulation of ROS lead to oxidative stress (Lushchak 2014), with consequential damage to cellular components, including proteins, lipids, DNA, and cellular organelles (Valko *et al.* 2007). Developmental stress arising from maternal disease states (Zhu *et al.* 2015, Tenorio *et al.* 2019), maternal obesity (Valko *et al.* 2007), and stress (Lorigooini *et al.* 2019, Venkatesh *et al.* 2019), as well as from environmental chemical exposures (Ferguson *et al.* 2014, Neier *et al.* 2015, Veiga-Lopez *et al.* 2015, Watkins *et al.* 2015, Puttabyatappa *et al.* 2019a) are associated with maternal oxidative stress (Luo *et al.* 2006, Valko *et al.* 2007), a known contributor to the developmental

origins of insulin resistance (Thompson & Al-Hasan 2012, Rodriguez-Rodriguez *et al.* 2018). Because these conditions are also associated with changes in the maternal androgen milieu (Table 2) (Acromite *et al.* 1999, Sir-Petermann *et al.* 2002, Takeuchi *et al.* 2004, Whyte *et al.* 2007, Morisset *et al.* 2013, Rutkowska & Rachon 2014, Barrett & Swan 2015, Arnon *et al.* 2016, Maliqueo *et al.* 2017, Sathyanarayana *et al.* 2017), the fetal programming of insulin resistance likely involve crosstalk between androgen signaling and oxidative stress pathways. Evidence for involvement of oxidative stress in the androgen programming of insulin resistance also comes from strong associations between steroid hormone-disrupting EDCs (e.g. phenols, parabens, and phthalate metabolites) and maternal and fetal oxidative stress in epidemiologic studies (Ferguson *et al.* 2014, Veiga-Lopez *et al.* 2015, Watkins *et al.* 2015, Puttabyatappa *et al.* 2019a) along with the induction of offspring insulin resistance after gestational exposure to these same EDCs in animal models (Angle *et al.* 2013, Rajesh & Balasubramanian 2014, Veiga-Lopez *et al.* 2016). Apart from their steroid potential, EDCs such as BPA and phthalates are also associated with increases in maternal androgen levels (Takeuchi *et al.* 2004, Rutkowska & Rachon 2014, Sathyanarayana *et al.* 2017) implicating androgens as potential mediators in inducing a pro-oxidant state. Other studies have shown that high-fat diet induces obesity (Hariri & Thibault 2010), placental oxidative stress (Lin *et al.* 2011b), and insulin resistance in offspring (Matsuzawa-Nagata *et al.* 2008) and antioxidant supplementation during pregnancy ameliorates hyperinsulinemia in offspring (Sen & Simmons 2010). These findings suggest a direct involvement of maternal oxidative stress in the programming of offspring insulin resistance. Since maternal obesity is associated with increases in maternal androgen levels (Whyte *et al.* 2007, Arnon *et al.* 2016, Maliqueo *et al.* 2017), androgens may be involved in increasing the oxidative stress. This premise is supported by the observation that gestational exposure to testosterone in sheep leads to increases in placental oxidative stress (Kelley *et al.* 2019b) and induction of insulin resistance in the female offspring (Padmanabhan *et al.* 2010b). However, key questions remain regarding the relative contribution of androgen excess and oxidative stress and their interactions in the programming of offspring insulin resistance.

Lipotoxicity

Excess accumulation of triglycerides in non-adipose tissues results in both acute and chronic cellular dysfunction,

a process termed lipotoxicity (Weinberg 2006). These effects may be due either to direct lipotoxic effects or indirect induction of inflammation and oxidative stress as a result of lipid peroxide production. Observations in women with gestational diabetes and obesity as well as in animal models mimicking these conditions show increased maternal, placental, and fetal lipid accumulation (Diamant *et al.* 1982, McCurdy *et al.* 2009, Li *et al.* 2011, Dong *et al.* 2013, Visiedo *et al.* 2013, Pruis *et al.* 2014, Saben *et al.* 2014, Jeve *et al.* 2015). Since these conditions also result in offspring insulin resistance (Matsuzawa-Nagata *et al.* 2008, Bianco & Josefson 2019), lipotoxicity may be a contributing factor in the developmental programming of insulin action. Since these maternal conditions are also associated with increased maternal androgens (Table 2) (Whyte *et al.* 2007, Morisset *et al.* 2013, Arnon *et al.* 2016, Maliqueo *et al.* 2017), androgens may also play a role in the development of lipotoxicity. The observation in sheep models that gestational testosterone treatment increases placental lipid accumulation (Kelley *et al.* 2019b) supports such a possibility. Similar increases in placental lipotoxicity are also observed in sheep models of gestational BPA treatment (Song *et al.* 2020). As BPA exposure during pregnancy can increase maternal androgens (Takeuchi *et al.* 2004, Rutkowska & Rachon 2014) and are known to induce insulin resistance (Veiga-Lopez *et al.* 2016), maternal androgens might contribute to development of later-life insulin resistance through lipotoxicity.

Epigenetics

Another mechanism by which steroids program metabolic pathways in offspring involves epigenetic alterations. Epigenetic changes include changes in DNA methylation, histone modifications, and expression of noncoding RNAs, all of which can lead to alterations in gene expression. Considering steroids are known to modulate developmentally programmed epigenetic changes (Forger 2018), androgen-induced epigenetic modifications of genes involved in insulin action in insulin target tissues or insulin production from pancreatic beta-cells are likely contributors to the developmental origins of insulin resistance (Sharma *et al.* 2017, Ebrahimi *et al.* 2019, Kerr *et al.* 2019).

Epigenetic modulation via DNA methylation involves addition of a methyl group to cytosines by DNA methyltransferases (DNMTs), resulting in changes in gene transcription (Ciccarone *et al.* 2018). DNA methylation is involved in the developmental programming of insulin resistance (Davegardh *et al.* 2018, Zhou *et al.* 2018),

including in conditions associated with maternal disease states (Elliott *et al.* 2019, Kamrani *et al.* 2019), obesity (Fernandez-Twinn *et al.* 2019), stress (Cao-Lei *et al.* 2016), and following exposure to EDCs (Stel & Legler 2015, Rahmani *et al.* 2018). Additional support comes from observations of (1) DNA methylation of hepatic genes involved in insulin and glucocorticoid receptor signaling in mice with fetal exposure to glucocorticoids under conditions of maternal food restriction (Ogawa *et al.* 2014); (2) the strong association that exists between gestational BPA levels and genome-wide DNA methylation and transcriptome changes in human fetal liver (Faulk *et al.* 2015); and (3) hypermethylation of DNA in the pancreas and liver of offspring from gestationally BPA-treated mice and rats, respectively (Rajesh & Balasubramanian 2014, Bansal *et al.* 2017). Because all of these conditions are also associated with increases in maternal androgen levels (Table 2) (Sir-Petermann *et al.* 2002, Takeuchi *et al.* 2004, Whyte *et al.* 2007, Morisset *et al.* 2013, Rutkowska & Rachon 2014, Barrett & Swan 2015, Arnon *et al.* 2016, Maliqueo *et al.* 2017), the possibility exists that DNA methylation changes underlying the programming of insulin resistance in these scenarios may be a consequence of increased maternal androgens. Confirmation of the involvement of androgen-mediated DNA methylation in the programming of insulin resistance requires ablation studies with androgen antagonists and prevention of DNA methylation changes via maternal folic acid supplementation (Ly *et al.* 2016).

Epigenetic regulation through histone modifications includes acetylation, methylation, ubiquitination, phosphorylation, and sumoylation, all of which affect transcriptional activity through modification of the structure and conformation of chromatin and/or by the differential recruitment of transcriptional co-repressors or co-activators (Bannister & Kouzarides 2011). Histone alterations are brought about by enzymes that include 'writers' such as histone acetyltransferases (HATs) and histone methyltransferases (HMTs) that modify histones as well as 'erasers' such as histone deacetylases (HDACs) and lysine demethylases (KDMs) that remove these modifications (Hyun *et al.* 2017). The impact of developmental insults on the programming of insulin resistance through histone modifications is understudied (Vaiserman & Lushchak 2019). Evidence of a possible role of steroid-mediated histone modifications in fetal programming comes from the reprogramming of stress responses by fetal glucocorticoid exposures that induce transcriptional changes of genes involved in hypothalamic-pituitary-adrenal axis function through

histone modifications (Dirven *et al.* 2017). Altered expression of the pancreatic beta-cell differentiation gene *PDX1* in gestationally protein-restricted and BPA-treated rats (Park *et al.* 2008, Chang *et al.* 2016) as well as altered hepatic gene expression in gestationally high-fat diet-fed macaques and BPA-treated mice (Aagaard-Tillery *et al.* 2008, Strakovsky *et al.* 2015) are both associated with histone modifications. Of interest, these gestational manipulations lead to increases in maternal androgen levels (Takeuchi *et al.* 2004, Whyte *et al.* 2007, Rutkowska & Rachon 2014, Barrett & Swan 2015, Arnon *et al.* 2016, Maliqueo *et al.* 2017) and offspring insulin resistance (Rinaudo & Wang 2012). Gestational testosterone treatment in sheep also increased expression of *PDX1* in female fetuses (Rae *et al.* 2013), lending support to the possibility that androgen programming of insulin homeostasis may occur via histone modifications, a premise that needs formal testing.

The epigenetic regulation of insulin resistance may also be mediated via changes in noncoding RNAs (Desai *et al.* 2015, De Rosa *et al.* 2018), which include microRNAs (miRNAs), short (~18–25 nucleotide), long (exceeding 200 nucleotides), and circular RNAs, of which miRNAs are the best studied. The evidence that steroidal programming involves miRNAs comes from sexual differentiation of neonatal mice brain (Morgan & Bale 2017). The role of miRNAs in androgen programming of insulin resistance is supported by observations that miRNA expression is increased after maternal insults that promote an androgenic maternal hormone milieu (Table 2) and program insulin resistance, such as maternal disease states (Poirier *et al.* 2017, Hemmatzadeh *et al.* 2020), diet-induced obesity (Benatti *et al.* 2014, Mendez-Mancilla *et al.* 2018, Puppala *et al.* 2018), growth restriction (Zheng *et al.* 2017, Hromadnikova *et al.* 2019), stress (Cao-Lei *et al.* 2016, Wu *et al.* 2016), and BPA exposure (Lin *et al.* 2017, Martinez-Ibarra *et al.* 2019) in both humans and animal models. The observation that gestational testosterone treatment increases expression of miRNAs that target insulin signaling, albeit in fetal ovaries (Luense *et al.* 2011), along with findings that their offspring develop insulin resistance during adulthood (Padmanabhan *et al.* 2010b), raise the possibility that reprogramming of insulin resistance by androgens may also involve changes in expression of miRNA associated with insulin signaling genes in metabolic tissues.

Microbiome

The identification of bacteria and/or their DNA in amniotic fluid, fetal membranes, umbilical cord blood,

placenta, and meconium indicate that gut colonization begins during *in utero* life (Li *et al.* 2014a). Gut microbiota are required for host metabolism and fetal development, while reduced microbial diversity and dysbiosis is associated with gastrointestinal and systemic disorders, including obesity and insulin resistance (Wang *et al.* 2016). This is confirmed by studies in germ-free animals that consume more calories, become overweight, and exhibit insulin resistance and dyslipidemia (Laugette *et al.* 2011). This association of dysbiosis with the development of insulin resistance (Wang *et al.* 2016, Codagnone *et al.* 2019) coupled with the observation that infants born to mothers with obesity or stress have altered gut microbiota (Collado *et al.* 2010, Zijlmans *et al.* 2015, Codagnone *et al.* 2019) and increased maternal androgens (Table 2) with consequential programming of offspring insulin resistance collectively suggest the potential for steroidal programming of insulin resistance through alterations in the microbiome. Although the influence of steroids on the gut microbiota have been explored (Huang *et al.* 2015, Tetel *et al.* 2018), the role of the microbiome in androgen programming is not established. There is evidence that gestational exposure to stress in mice (Gur *et al.* 2017), treatment of pregnant rats with the native steroid testosterone (Gur *et al.* 2017), or exposure of pregnant mice to EDCs such as BPA or synthetic estrogens (Javurek *et al.* 2016) all lead to altered gut microbiota. Since these gestational insults are associated with increased maternal androgens (Table 2) and can program insulin resistance, it is possible that androgen-induced gut microbial changes may be involved in androgen reprogramming of insulin responsiveness and development of insulin resistance. The finding that transplantation of gut microbiota from woman with PCOS into mice resulted in insulin resistance (Qi *et al.* 2019) indicates that further studies using fecal microbiota transplantation can be used to assess the relative contribution of gut microbiota in androgen programming of insulin resistance.

Insulin

An intriguing hypothesis set forth by published data and evident in clinical practice is the capacity of insulin to drive the development of insulin resistance (Gavin *et al.* 1974, Rizza *et al.* 1985, Shanik *et al.* 2008, Erion & Corkey 2017). In the context of developmental programming, it is interesting to note that gestational hyperinsulinemia observed in gestational diabetes mellitus and obesity are associated with the development of insulin resistance-associated conditions in the offspring later in life

(Bellamy *et al.* 2009, Ruchat *et al.* 2013, Nicholas *et al.* 2016). Importantly, a major hormonal change associated with increased maternal androgens is hyperinsulinemia as androgen-mediated increases in insulin levels during pregnancy is evident in hyperandrogenic pregnant women with PCOS (Radon *et al.* 1999, Sir-Petermann *et al.* 2007) and pregnant sheep treated with testosterone (Abi Salloum *et al.* 2015). As such, programming of offspring insulin resistance by gestational testosterone excess may be mediated via increased levels of insulin itself. Indeed, since multiple conditions are also associated with increase in maternal androgens (Table 2) (Whyte *et al.* 2007, Morisset *et al.* 2013, Arnon *et al.* 2016, Maliqueo *et al.* 2017), the possibility androgen-mediated increases in maternal insulin levels contribute to programming of insulin resistance cannot be excluded. Moreover, it is interesting to speculate how such a scenario could establish a potential positive feedback loop in which persistent or even transient androgen excess increases insulin levels that then increase insulin resistance prompting further

insulin release and potentiation of the effect. Intriguingly, insulin's potential role as a mediator of androgen-induced insulin resistance is supported by evidence that the metabolic disruptions observed in prenatally testosterone-treated sheep can be ameliorated by co-treatment with an insulin sensitizer (Puttabyatappa *et al.* 2017). Importantly, while suggesting a potential route by which androgens induce insulin resistance, such a mechanism would also provide support for potential interventions, including insulin sensitizers as well as exercise.

Conclusions and future directions

The 'thrifty phenotype hypothesis' proposed by Hales and Barker first explained how malnutrition during pregnancy leads to poor fetal growth and the programming of maladaptive metabolic responses in the developing fetus (Barker 2005). One of the key metabolic reprogramming events is the establishment of insulin responsiveness,

Figure 1

Schematic showing the potential link between developmental insults and increase in maternal androgen levels that program the onset of insulin resistance in the offspring. The increase in maternal androgens probably utilizes various mediators including changes in inflammatory state, oxidative stress, lipotoxicity, epigenetic, gut microbiome and insulin to bring about metabolic reprogramming leading to development of insulin resistance. Images used were sourced from open-source resources: www.pixabay.com, www.openclipart.org, and www.cleanpng.com.

which leads to the development of insulin resistance. Since then this hypothesis has evolved into the DOHaD hypothesis, which captures the impact of wide ranging insults occurring during critical *in utero* and postnatal developmental windows on the reprogramming of metabolic functions. Critically, the mechanisms by which these developmental insults program later-life insulin resistance are still unresolved. As discussed above, a commonality among the various insults promoting insulin resistance (e.g. maternal disease states, stress, over/undernutrition, lifestyle, and exposure to EDCs) is alterations in the maternal steroid hormone milieu with specific increases in androgen levels (Fig. 1 and Table 2) (Takeuchi *et al.* 2004, Whyte *et al.* 2007, Rutkowska & Rachon 2014, Barrett & Swan 2015, Arnon *et al.* 2016, Maliqueo *et al.* 2017). Since steroids, and especially androgens, play a major role in establishing the program of sexual differentiation at both the gonadal and brain levels, exposure to excess androgens during critical periods of organization of metabolic functions may also influence the programming of metabolic tissues, potentially resulting in maladaptive changes that manifest as adult onset metabolic dysfunction, including insulin resistance. Human observations of insulin resistance among offspring born to mothers with high testosterone levels during pregnancy (e.g. women with PCOS) (Sir-Petermann *et al.* 2009) as well as in animal models of gestational treatment with androgens (Table 3) (Roland *et al.* 2010, Abbott *et al.* 2016, Cardoso & Padmanabhan 2019) support this conjecture. Despite this evidence, however, further studies are needed to confirm the relative contribution of androgens in programming insulin resistance due to other maternal insults through the use of specific androgen receptor antagonists or other molecular approaches.

Another key observation arising from this discussion is that many of the studies conducted thus far have been confined to one sex of the offspring. Studies using rodent models have also grouped both sexes together to interpret findings. As it is now established that developmental insults have sex-specific effects (Dearden *et al.* 2018), future studies in both humans and animal models are required to be performed in both sexes. As sexual dimorphism is also apparent in placental function (Kalisch-Smith *et al.* 2017), studying the sex-based differences in this key mediator of maternal-fetal transport are also required. Another challenge to consider is the sensitivity of specific developmental periods to respective *in utero* or postnatal insults since the same exposure at different times during prenatal life can lead to a wide spectrum of effects (Selevan *et al.*

2000). Additionally, as studies in animal models allow longitudinal and direct assessment of relevant target tissues to empower investigation of potential inter- and trans-generational transfer of traits, the comparability of the most sensitive window(s) for exposures in animal models are essential to provide comparison data across species, which in turn will identify those critical windows of vulnerability to be targeted for policy development and risk management. Considering pregnancies associated with hyperandrogenic state such as PCOS, preeclampsia, obesity, and stress are common in clinical practice, the establishment of androgens as mediators driving adverse metabolic programming in offspring will aid in the development of targeted clinical interventions to overcome the long-term effects of developmental insults that drive insulin resistance by restoring and supporting a normal maternal steroid milieu. Developing such interventions may hold immense potential for addressing the early-life origins of metabolic dysfunction that are epidemic across the globe.

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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