Intergenerational Influences between Maternal Polycystic Ovary Syndrome and Offspring: An Updated Overview

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Polycystic ovary syndrome (PCOS) is the most common heterogeneous endocrine disorder. Affecting 5%-10%[1] of reproductive-aged women, PCOS is characterized by hyperandrogenemia, anovulation, and insulin resistance (IR), with long-term effects throughout the different stages of a woman's life. During gestation, women with PCOS have greater androgen concentrations.[2] Intrauterine exposure to high androgen concentrations may cause fetal reprogramming or placental changes through epigenetic regulation or other mechanisms, thus causing changes in multiple systems in the offspring and ultimately affecting growth and development. The hormonal and metabolic alterations have been found in brothers of women with PCOS,[3,4] which may reflect the effects of PCOS susceptibility genes or programming effects of the intrauterine environment. Furthermore, a greater risk of pregnancy complications,[5-7] the use of metformin during pregnancy,[8] and maternal metabolic abnormalities (including obesity or IR[9,10]) may be implicated in the effects on offspring.

Previous studies have concluded that maternal PCOS could have an effect on the health of offspring, but the potential mechanism has not yet been fully elucidated; this mechanism is highly likely to be the result of interactions between environmental and genetic factors. Studying the effects of maternal PCOS on offspring development is an important complement to its etiology. The aim of the present review is to systematically illustrate the possible contributing factors involved in the effects of maternal PCOS on the health of offspring and their potential health consequences.

PCOS and Intrauterine Androgen Exposure

High fetal androgen exposure may be the result of a combined effect of high maternal androgen concentrations,[2,11] placental injury,[12] and fetal androgen production.[13] The anogenital distance (the distance between the cranial edge of the anus and the base of the clitoris) is longer in daughters of women with PCOS,[14] reflecting androgen exposure in utero. Congenital adrenal hyperplasia, a known example of intrauterine androgen excess of fetal origin, can lead to the development of the PCOS phenotype.[15] Based on the Barker hypothesis,[16] an abnormal uterine milieu may induce fetal reprogramming of critical processes, permanently programing the physiology, function, or morphology of the fetus, which can manifest in long-term health consequences. In addition to prenatal androgen excess, other perinatal insults, such as maternal stress, gestational undernutrition, and smoking, may be implicated in the programmed outcomes and may be involved in the common mechanisms.[17] Androgens may have joint effects with other factors, such as insulin.[17]

Testosterone treatment during gestation is thought to advance placental differentiation, although it fails to maintain placental function at later stages, resulting in intrauterine growth restriction[18] and reduced placental weights.[19] A previous study has confirmed the role of hypoxia and inflammation in the mechanism of androgen-induced placental changes.[20] Elevated androgen levels during pregnancy could affect placental blood flow due to uterine vascular function impairment[21] or impairment of placental angiogenesis.[22] Bishop et al found that placental blood volume was decreased in female rhesus macaques after treatment of testosterone or Western-style diets at gestational day 30.[23] In rats, increased maternal testosterone levels impact placental amino acid delivery through the downregulation of specific amino acid transporter activity.[24]

Intrauterine androgen exposure also is involved in epigenetic regulation of the processes involved in steroid production and metabolism. Using a mouse model of prenatal androgen exposure, Risal et al confirmed transgenerational alterations of gene expression and reproductive and metabolic dysfunction in female offspring.[25] Cleys et al found that prenatal androgenization reduced global DNA methylation of placentomes at gestational day 90 and increased placental expression of androgen receptors.[26] A similar result was found in androgenized zebrafish offspring, which exhibit global hypomethylation.[27]

AMH	anti-mullerian hormone
GABA	Gamma-aminobutyric acid
GnRH	Gonadotropin-releasing hormone
GWAS	Genome-wide association studies
IR	insulin resistance
PCOS	Polycystic ovary syndrome

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Prenatally androgenized animal models, including rats, mice, sheep, and rhesus monkeys, have long been used to simulate the PCOS phenotype for the purpose of exploring the underlying effects of androgen hyperexposure on offspring and the relevant pathomechanisms. The benefits and limitations of these models have been extensively reviewed.[28] Due to the differences in endocrine systems among species, the developmental stage should be considered when evaluating the phenotypic changes of experimental animals. For example, Abbott et al described the progression to the adult phenotype in fetal, infant, and adolescent female rhesus monkeys after prenatal androgenization.[29] A growing body of literature suggests a susceptibility window during fetal development.[17] In experiments in animals, exposure to androgen excess at different gestational weeks induces different phenotypes,[30,31] and it has been shown that the actions of androgens during critical window can regulate the development of specific organs.[32]

Effects on the Reproductive System of Offspring

Daughters born to women with PCOS show features of PCOS during peripubertal period.[33] During the onset of puberty, dehydroepiandrosterone sulfate concentrations are increased,[34] and during puberty, increased testosterone levels and lower sex hormone-binding globulin have been described.[35] These manifestations may reflect an early stage in the development of PCOS for these at-risk girls. Prenatally androgenized rats exhibit elevated serum androstenedione and testosterone concentrations in young adulthood.[36] Similar findings have been observed in experiments of prenatally androgenized adult female rhesus monkeys, which demonstrate hyperandrogenism, luteinizing hormone hypersecretion, and polyfollicular ovaries.[29,31] Elevated levels of androgens in PCOS progeny, however, may be caused by multiple factors, including hyperinsulinemic stimulation,[15] placental changes,[19] and feedback promotion from elevated luteinizing hormone.[37]

Prenatal exposure to androgen excess has been shown to impact the neuroendocrine system and thereby affect periovulatory hormonal dynamics and ovulation. Gonadotropin-releasing hormone (GnRH) neurons receive a main input from gamma-aminobutyric acid (GABA)ergic neurons.[38] GABA plays a major role in the regulation of GnRH neuron activity and secretion.[39] Increased GABAergic inputs to GnRH cells are manifested in prenatally androgenized mice,[40] which may lead to increased GnRH secretion.[39] This may interact with other neuroendocrine effects. For example, kisspeptin is a key regulator that acts upstream of GnRH.[41] Prenatal testosterone reduces kisspeptin/neurokinin B/dynorphin (KNDy)-KNDy inputs, in contrast to its induction of GABA inputs to GnRH neurons. It is likely we have only a partial understanding of the overall dysregulation of GnRH during gestational exposure to testosterone excess.[42] Sheep with prenatal testosterone treatment manifest disruptions in responsiveness to progesterone negative feedback[43] and to both estrogen positive and negative feedback.[44,45] A previous review reported that prenatal androgenization resulted in accelerated GnRH pulse generators or resistance to the negative feedback effect of gonadal steroids, which might damage estrogen's ability to induce progesterone receptor expression.[46]

Some studies have shown that daughters of women with PCOS exhibited increased ovarian volume and greater anti-Müllerian hormone levels, which may be early signs of PCOS development.[33,47,48] A comparative analysis of ovarian biopsies between women with PCOS and controls showed that there were fundamental differences between polycystic and normal ovaries as early as the early follicular development process[49] or perhaps early programming in utero. The elevated anti-Müllerian hormone concentrations in 2- to 3-month-old daughters of women with PCOS may reflect the presence of an increased ovarian follicular pool in intrauterine life.[50] In addition, prenatally androgenized adult female rat offspring also manifest increased preantral and antral follicles and fewer preovulatory follicles, corpora lutea, as well as cystic follicles,[51] and a multifollicular ovarian phenotype was found in studies with prenatal testosterone-treated animals.[31,52]

Ovarian function also has been proven to be altered by perinatal androgen excess. Abbott et al hypothesized that altered negative feedback regulation of luteinizing hormone and the compensatory hyperinsulinemia from IR might destroy ovulatory function and eventually cause anovulation.[53] Another study, however, argued that derangement of early follicle development could account for the ovulation disorder.[54] In addition, testosterone-treated male lambs show an apparent decrease in the number of germ cells,[55] together with a decrease in the weight of their testicles[55]; in adulthood, these sheep are also found to have a lower ejaculate volume[55] and reduced sperm count and motility.[56]

Sheep treated with excess testosterone in utero from 30 to 90 days of gestation (term is 145 days) were virilized at birth, with an obvious phallic structure and elevated anogenital ratio, which were not observed in sheep with excess testosterone treatment from 60 to 90 days.[30] Similar manifestations have been found in female rat and mouse models and female monkeys,[47,57,58] reinforcing that prenatal androgen exposure during critical periods of development can lead to testosterone-induced developmental programming of female phenotype.

Metabolic Effects

Sir-Petermann et al found metabolic alterations in daughters of women with PCOS when compared with controls.[35] Previous studies demonstrated that prenatal androgen excess disturbed insulin-glucose hemodynamics in adult female rhesus monkeys and induced IR in prenatally androgenized adult rats.[59,60] Padmanabhan et al found that the programming of reduced insulin sensitivity in prenatal testosterone-treated ewes was thought to be caused by the androgenic action of testosterone.[61] Furthermore,

intrauterine androgen excess may alter islet morphology and islet development.[62] Beta cells were significantly increased in prenatally androgenized female ovine fetuses, and basal insulin secretion and glucose-stimulated insulin were elevated during puberty.[63]

A dehydroepiandrosterone-induced PCOS mouse model manifests increased body fat and triglyceride contents in both the serum and liver at age 12-13 weeks.[64] Prenatal androgen exposure may result in hepatic damage by decreasing the expressional levels of 2 mRNAs involved in the synthesis of malonyl-CoA, the first limiting factor in lipogenesis, which serves a protective role in the development of hepatic steatosis.[65] Gestational androgen excess also leads to an increase in the relative proportion of small adipocytes.[66,67] These changes may aggravate IR, leading to a vicious cycle.

Intrauterine androgen excess may not only increase the body mass index of offspring,[68] but it also may affect the distribution of fat. Adult female rhesus monkeys prenatally treated with androgens show an increase in total abdominal and intra-abdominal fat depots.[67] This pattern of deposition may be caused by a decrease in lipolysis induced by catecholamine and β-adrenergic receptor binding,[67] further enhanced by hyperinsulinemia, eventually leading to preferential accumulation of abdominal adiposity.[67] Because the distribution of body fat is sexually dimorphic, prenatal androgen excess also may induce a masculinized pattern of visceral fat accumulation.[67]

Cardiovascular Effects

A recent meta-analysis reported the subtle signs of compromised cardiometabolic health in children of women with PCOS, especially for the female offspring.[69] King et al found that prenatally androgenized female sheep had mild hypertension in adulthood, possibly related to activation of the sympathetic nervous system, lipid abnormalities, and other increased cardiovascular risk factors.[70] Previous research further identified a novel androgen-mediated mechanism through transcriptional regulation of protein kinase C-δ, which led to enhanced vasoconstriction and hypertension in adult female rats offspring.[71] Prenatal exposure to excess androgens could have a negative impact on cardiovascular function by increasing systolic blood pressure and diastolic blood pressure and lowering heart rate in adult prenatally androgenized rats. This also has been associated with intestinal microbial dysbiosis.[72] The presence of hyperandrogenism in women with PCOS may adversely program the cardiovascular system in their offspring. Excess testosterone exposure altered left ventricular tissue differentiation, induced myocardial disarray (multifocal), and increased cardiomyocyte diameter in 2-year-old female sheep.[73] Vyas et al found that excess prenatal testosterone contributed to adverse left ventricular remodeling, which increased the gene expression of molecular markers associated with insulin signaling and cardiac hypertrophy and stress.[73] This study suggested that excess prenatal testosterone exposure might underlie the activation of the cardiac insulin signaling pathway, inducing activation of mTORC1 (mammalian target of rapamycin complex 1), and ultimately leading to cardiac hypertrophy.[73]

Neuropsychiatric Effects

One matched case-control study conducted in Sweden of 23 748 children with autism spectrum disorder and 208 796 controls found that maternal PCOS increased the odds of autism by 59% among the offspring after adjusting for confounding factors.[74] Fetal testosterone levels in amniotic fluid are positively correlated with autistic traits.[75,76] Brain structural differentiation is altered in patients with autism compared with control groups; the total number and numerical density of Purkinje cells in the cerebellum are reduced, and neuronal density also is reduced in some brain regions, such as the lateral nucleus, the nucleus accumbens, and the putamen.[77] Mice treated prenatally with testosterone show increased dendritic spines and filopodia, synaptic instability, and abnormal morphology of dendritic spines and filopodia during the developmental stage of synapse formation, which may be the synaptic basis of neurodevelopmental deficits that lead to autistic-like behavior.[78]

The potential distinction between male and female individuals in autism phenotype remains to be elucidated. As the "extreme male brain" theory has proposed, prenatal testosterone exposure could account for male vulnerability to autism spectrum disorders and sex differences in behavior.[79] Lombardo et al confirmed that fetal testosterone was associated with the volume of some sexually dimorphic brain areas and identified the important effect of fetal testosterone on promoting sex differences in neuroanatomy.[80] Lombardo et al later identified that fetal testosterone reduced functional connectivity between social brain default mode subsystems in adolescent male but had no impact in female individuals.[81] The sex difference in autism also may be due to the action of sex hormones, as androgens increase the vulnerability of male patients, whereas estrogen and oxytocin exert protective effects in female patients.[82]

A significant association between maternal androgen excess and anxiety-like behavior in female offspring has been confirmed.[83] Intrauterine androgen exposure increases the expression of Adra1b and Crhr2 in the amygdala and disrupts Crh function in the hypothalamus, leading to activation of the central noradrenergic system and the hypothalamic–pituitary axis.[83] Experiments with testosterone microinjections into the amygdala inducing anxiety-like behavior showed that androgen receptor activation was an important intermediate link.[84]

Children born to women with PCOS are also at greater risk of a diagnosis of attention-deficit/hyperactivity disorder,[85] and maternal PCOS is reported to increase the odds of attention deficit disorder in offspring by 42%.[86] Because this is more common in boys than girls,[87] the finding that daughters of women with PCOS have a greater rates of attention deficit disorder suggests that prenatal androgen excess may influence the development of male-predominant

neuropsychiatric disorders in female offspring.[88] Furthermore, according to the research by Mereness et al, intrauterine androgen excess generated circadian misalignment and had direct and tissue-specific effects on clock gene expression.[89] More research is required, however, to determine how androgen excess affects circadian clocks.

Effects on Growth and Development

A recent large prospective cohort study found that greater maternal salivary testosterone/estradiol ratios were associated with a greater risk of small for gestational age offspring.[90] High levels of androgens during pregnancy are associated with growth restriction in utero[91] by influencing the nutrient transport and blood supply to the placenta,[92] among other effects. Growth restriction in utero is associated with adverse perinatal outcomes and long-term complications. Smith et al described a negative correlation between maternal androgen levels in early pregnancy and weight, body length, and several girth measurements using marmoset models.[93] Although a large population-based cohort study reported that large for gestational age offspring were more common in women with PCOS, this may be related to the presence of pregnancy complications.[94]

Effects on Intestinal Flora

The role of intestinal flora in the regulation of the brain–gut axis has received increasing attention. Adult prenatally androgenized rats exhibit intestinal microbial dysbiosis and an altered abundance of bacteria involved in the production of short-chain fatty acid metabolites, which may be related to increased risk for hypertension and cardiovascular disease.[72] In addition, a positive correlation is found between the severity of autism and the severity of gastrointestinal dysfunction.[95]

Genetic Predisposition

In familial clustering and twin studies,[96] genetic factors are involved in the etiology of PCOS. Genome-wide association studies (GWAS) have confirmed a range of candidate genes and loci for PCOS.[97,98] Chen et al identified 11 risk loci associated with PCOS by analyzing genome-wide association data in Han Chinese women.[98] The majority of the candidate genes at the associated loci are involved in insulin signaling, reproductive hormone function, and type 2 diabetes.[98] Transmission disequilibrium testing, used to evaluate family-based associations, was performed to explore the potential contribution of candidate genes and further confirmed the role of susceptibility loci in PCOS.[99,100] GWAS also have been conducted in other ethnic population cohorts, including in Korean and European cohorts.[101] Previous genetic studies have confirmed at least 18 reproducible PCOS risk genes involving reproduction (FSHB, LHCGR, FSHR, DENND1A, RAB5/SUOX, HMGA2, C9orf3, YAP1, TOX3, RAD50, FBN3, and AMH) and metabolic functions (THADA, GATA/NEIL2, ERBB4, SUMOP11, INSR, and KRR1).[102,103] Shared loci have been identified between women with different phenotypes or from different ethnic groups.[104] Replicated loci were found in European cohorts involving women with the National Institutes of Health phenotype of PCOS. This study was complementary to a Chinese cohort involving Rotterdam phenotypes, further indicating the etiologic roles of gonadotropins in the pathogenesis of PCOS.[104] A recent genome-wide meta-analysis also found similar genetic architecture for common susceptibility variants among different diagnostic criteria.[105] It was reported recently that distinct subtypes have different genetic architectures,[106] which may indicate the limited ability of the National Institutes of Health and the Rotterdam diagnostic criteria in identifying biologically distinct subtypes of PCOS.[106] Phenome-wide association studies, which can explore the association between different phenotypes and specific genetic variants,[101] may be conducted in future.

GWAS have largely advanced our understanding of the genetic mechanisms of PCOS, but to date, the loci identified by GWAS account for less than 10% of PCOS heritability.[107] Epigenetic programming induced by the altered maternal endocrine–metabolic environment seems to be an important contributor.[108] Another hypothesis is that rare genetic variants with larger phenotypic effects play a key role in the pathogenesis.[109] Through whole-genome sequencing and targeted resequencing, Gorsic et al identified 17 variants in the anti-mullerian hormone (AMH) gene with decreased signaling potential, which could reduce AMH's inhibition of CYP17 activity in androgen biosynthesis, thus resulting in hyperandrogenemia.[110] The researchers later confirmed that variants in AMH and its type II receptor contributed to the etiology of PCOS.[111] Recently, rare variants in DENND1A have been found to be significantly associated with the altered reproductive and metabolic functions in PCOS by using family-based whole genome sequencing.[112] A homozygous GNRHR mutation was reported in a familial case with three women diagnosed with PCOS via whole-exome sequencing.[113]

Pregnancy Complications

Women with PCOS are at significantly greater risk of developing gestational diabetes mellitus, pregnancy-induced hypertension, and preeclampsia.[5] Pregnancy complications could have an impact on neonatal outcomes and the long-term health of offspring, independent of PCOS-related features. The association between maternal gestational diabetes and the risk of metabolic disease in the offspring has been well established.[6] Glucose is transported through the placenta, causing fetal hyperglycemia and hyperinsulinemia, which may be the main cause of fetal macrosomia in infants of mothers with gestational diabetes.[114] Furthermore, exposure to maternal hyperglycemia may induce epigenetic changes.[6,115] Gestational diabetes also predisposes offspring to an increased risk of cardiovascular disease.[116-118] Maternal preeclampsia also is associated with increased systolic and

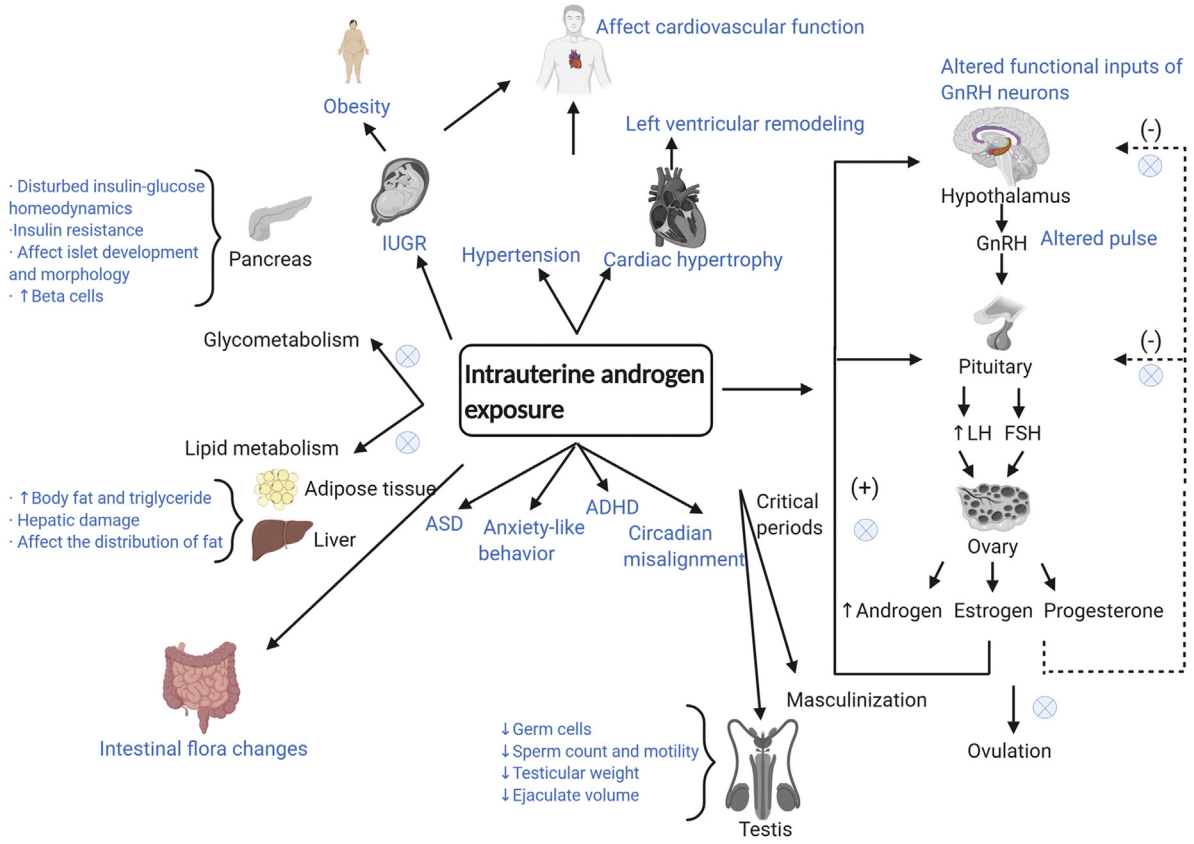

Figure. Schematic showing the effects of intrauterine androgen hyperexposure on the reproductive, metabolic, cardiovascular, and neuropsychiatric system; physical development; and intestinal flora in offspring. Figure created with BioRender.com. *ADHD*, attention-deficit/hyperactivity disorder; *ASD*, autism spectrum disorder; *FSH*, follicle-stimulating hormone; *IUGR*, intrauterine growth restriction; *LH*, luteinizing hormone.

diastolic blood pressure in offspring.[119] It is well-known that preeclampsia increases the risk of adverse fetal outcomes, including fetal growth restriction.[120] Endothelial dysfunction induced by preeclampsia may play an essential role in the pathophysiology of preeclampsia and future cardiovascular risk in offspring. Epigenetic changes, the genetic basis, and the release of several signaling molecules may be involved in this latent mechanism.[121] Testosterone levels are elevated in women with preeclampsia, and the vascular and placental effects may be mediated through the actions of testosterone.[92] Furthermore, preeclampsia increases the risk of autism in children.[7] Placental insufficiency induces oxidative stress and impacts nutrient supply, which may lead to neurodevelopmental compromise.[7]

Medication Use

Metformin is considered a first-line drug to treat type 2 diabetes and gestational diabetes, by increasing tissue insulin sensitivity, reducing insulin concentrations, and inhibiting hepatic glucose production. Although metformin can be transferred through the placenta, it is considered safe throughout pregnancy.[122] However, Hjorth-Hansen et al described larger head sizes in the offspring of overweight women with PCOS, which was notable in utero.[123] Data from another study suggested that prenatal metformin exposure could affect the metabolic phenotype of the offspring in mice, including impaired glucose tolerance and increased fasting glucose.[124] Tartarin et al showed that metformin exposure had a potentially damaging impact on the development of fetal testes in mice and humans, including the decreased Sertoli cells and the nurse cells of germ cells.[125] Forcato et al reported that exposure to metformin during gestation and lactation might be associated with theca and/or granulosa cell programming and thus led to the reproductive alterations in female offspring of rats.[126] The same research team had shown previously that metformin exposure induced changes in reproductive parameters in adult male offspring in rats.[127]

Maternal Metabolic Abnormalities

Previous studies have reported that maternal nutrition, hormones, and the metabolic environment affect the metabolism of the offspring.[128] The disturbed metabolic environment in utero induced by maternal IR or hyperinsulinemia has been

proven to impact an offspring's long-term health. Maternal IR is associated with birth weight and the incidence of large for gestational age infants, independent of maternal obesity and glucose levels.[129] Similar to this finding, Isganaitis et al also found that maternal IR could independently cause metabolic disorders in male IR-exposed pups, even in absence of hyperglycemia or obesity.[130] Maternal IR also is correlated with IR and hepatic immune system dysfunctions in offspring.[131,132] Schmitz et al discovered that maternal obesity and perinatal hyperinsulinemia led to hippocampal IR in adult male offspring of mice, which might play a vital role in hippocampal plasticity and the neurocognitive outcomes of offspring.[133] Maternal IR may impair synaptic plasticity and memory multi-generationally through epigenetic changes.[10]

Other Factors

Other potentially relevant factors related to PCOS may be involved in affecting the health of offspring. Previous research showed that advanced glycation end-products may relate to the pathogenesis of PCOS, which can induce the generation of oxidative stress and proinflammatory cytokines through activating key intracellular signaling pathways.[134] And prenatal exposure to endocrine-disrupting chemicals may induce fetal programming alterations.[135,136] Recently, excess prenatal anti-Müllerian hormone exposure has been shown to trigger hyperandrogenism, leading to masculinization of the sexually dimorphic brain areas regulating reproduction in the female fetus and a PCOS-like neuroendocrine phenotype.[137]

Conclusions and Future Directions

The impact of maternal PCOS on the offspring is complex and multifactorial. As shown in the **Figure**, The effect of prenatal androgen hyperexposure on the development of offspring is multidimensional, traversing all stages of fetal development. We speculate that epigenetic alterations and placental changes may be the central roles of androgen. IR may interact with intrauterine androgen excess to affect the intrauterine environment and fetal programming. Hyperinsulinemia has been found to be positively associated with androgen levels during pregnancy.[138] In addition, IR and high insulin levels may affect placental function through effects on amino acid transport, angiogenesis, and other mechanisms, which overlap with the actions of androgens.[139] A previous study showed that co-treatment with 5α-dihydrotestosterone and insulin in pregnant rats led to fetal loss.[140] Little research has been conducted on how androgens interact with IR. Modern genetic approaches have made considerable progress in elucidating the pathogenesis of PCOS. GWAS conducted in Chinese, Korean, and European populations have identified several susceptibility loci associated with PCOS, providing insight into the genetic contribution and biological pathway in PCOS. Next-generation sequencing is expected to identify rare genetic variants contributing to PCOS. Due to the heterogeneity and complexity of PCOS, we should analyze its impact on offspring from a more comprehensive and systematic perspective. Although the etiology of PCOS is not yet completely understood, intergenerational research has advanced our knowledge. ■

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Data statement

Data sharing statement available at www.jpeds.com.

References

1. Li R, Zhang Q, Yang D, Li S, Lu S, Wu X, et al. Prevalence of polycystic ovary syndrome in women in China: a large community-based study. Hum Reprod 2013;28:2562-9.
2. Sir-Petermann T, Maliqueo M, Angel B, Lara HE, Perez-Bravo F, Recabarren SE. Maternal serum androgens in pregnant women with polycystic ovarian syndrome: possible implications in prenatal androgenization. Hum Reprod 2002;17:2573-9.
3. Sam S, Coviello AD, Sung YA, Legro RS, Dunaif A. Metabolic phenotype in the brothers of women with polycystic ovary syndrome. Diabetes Care 2008;31:1237-41.
4. Torchen LC, Kumar A, Kalra B, Savjani G, Sisk R, Legro RS, et al. Increased antimüllerian hormone levels and other reproductive endocrine changes in adult male relatives of women with polycystic ovary syndrome. Fertil Steril 2016;106:50-5.
5. Palomba S, de Wilde MA, Falbo A, Koster MP, La Sala GB, Fauser BC. Pregnancy complications in women with polycystic ovary syndrome. Hum Reprod Update 2015;21:575-92.
6. Damm P, Houshmand-Oeregaard A, Kelstrup L, Lauenborg J, Mathiesen ER, Clausen TD. Gestational diabetes mellitus and long-term consequences for mother and offspring: a view from Denmark. Diabetologia 2016;59:1396-9.
7. Walker CK, Krakowiak P, Baker A, Hansen RL, Ozonoff S, Hertz-Picciotto I. Preeclampsia, placental insufficiency, and autism spectrum disorder or developmental delay. JAMA Pediatr 2015;169:154-62.
8. Rowan JA, Rush EC, Plank LD, Lu J, Obolonkin V, Coat S, et al. Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition and metabolic outcomes at 7-9 years of age. BMJ Open Diabetes Res Care 2018;6:e000456.
9. Drake AJ, Reynolds RM. Impact of maternal obesity on offspring obesity and cardiometabolic disease risk. Reproduction 2010;140:387-98.
10. Fusco S, Spinelli M, Cocco S, Ripoli C, Mastrodonato A, Natale F, et al. Maternal insulin resistance multigenerationally impairs synaptic plasticity and memory via gametic mechanisms. Nat Commun 2019;10:4799.
11. Maliqueo M, Lara HE, Sanchez F, Echiburu B, Crisosto N, Sir-Petermann T. Placental steroidogenesis in pregnant women with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol 2013;166:151-5.
12. Palomba S, Russo T, Falbo A, Di Cello A, Tolino A, Tucci L, et al. Macroscopic and microscopic findings of the placenta in women with polycystic ovary syndrome. Human Reprod 2013;28:2838-47.
13. Torchen LC, Idkowiak J, Fogel NR, O'Neil DM, Shackleton CH, Arlt W, et al. Evidence for increased 5α-reductase activity during early

childhood in daughters of women with polycystic ovary syndrome. J Clin Endocrinol Metab 2016;101:2069-75.
14. Barrett ES, Hoeger KM, Sathyanarayana S, Abbott DH, Redmon JB, Nguyen RHN, et al. Anogenital distance in newborn daughters of women with polycystic ovary syndrome indicates fetal testosterone exposure. J Dev Orig Health Dis 2018;9:307-14.
15. Dumesic DA, Goodarzi MO, Chazenbalk GD, Abbott DH. Intrauterine environment and polycystic ovary syndrome. Semin Reprod Med 2014;32:159-65.
16. de Boo HA, Harding JE. The developmental origins of adult disease (Barker) hypothesis. Aust N Z J Obstet Gynaecol 2006;46:4-14.
17. Padmanabhan V, Cardoso RC, Puttabyatappa M. Developmental programming, a pathway to disease. Endocrinology 2016;157:1328-40.
18. Beckett EM, Astapova O, Steckler TL, Veiga-Lopez A, Padmanabhan V. Developmental programing: impact of testosterone on placental differentiation. Reproduction 2014;148:199-209.
19. Sun M, Maliqueo M, Benrick A, Johansson J, Shao R, Hou L, et al. Maternal androgen excess reduces placental and fetal weights, increases placental steroidogenesis, and leads to long-term health effects in their female offspring. Am J Physiol Endocrinol Metab 2012;303:E1373-85.
20. Kelley AS, Puttabyatappa M, Ciarelli JN, Zeng L, Smith YR, Lieberman R, et al. Prenatal testosterone excess disrupts placental function in a sheep model of polycystic ovary syndrome. Endocrinology 2019;160:2663-72.
21. Chinnathambi V, Blesson CS, Vincent KL, Saade GR, Hankins GD, Yallampalli C, et al. Elevated testosterone levels during rat pregnancy cause hypersensitivity to angiotensin II and attenuation of endothelium-dependent vasodilation in uterine arteries. Hypertension 2014;64:405-14.
22. Metzler VM, de Brot S, Robinson RS, Jeyapalan JN, Rakha E, Walton T, et al. Androgen dependent mechanisms of pro-angiogenic networks in placental and tumor development. Placenta 2017;56:79-85.
23. Bishop CV, Stouffer RL, Takahashi DL, Mishler EC, Wilcox MC, Slayden OD, et al. Chronic hyperandrogenemia and western-style diet beginning at puberty reduces fertility and increases metabolic dysfunction during pregnancy in young adult, female macaques. Human Reprod 2018;33:694-705.
24. Sathishkumar K, Elkins R, Chinnathambi V, Gao H, Hankins GD, Yallampalli C. Prenatal testosterone-induced fetal growth restriction is associated with down-regulation of rat placental amino acid transport. Reprod Biol Endocrinol 2011;9:110.
25. Risal S, Pei Y, Lu H, Manti M, Fornes R, Pui HP, et al. Prenatal androgen exposure and transgenerational susceptibility to polycystic ovary syndrome. Nat Med 2019;25:1894-904.
26. Cleys ER, Halleran JL, Enriquez VA, da Silveira JC, West RC, Winger QA, et al. Androgen receptor and histone lysine demethylases in ovine placenta. PLoS One 2015;10:e0117472.
27. Xu N, Chua AK, Jiang H, Liu NA, Goodarzi MO. Early embryonic androgen exposure induces transgenerational epigenetic and metabolic changes. Mol Endocrinol 2014;28:1329-36.
28. Puttabyatappa M, Cardoso RC, Padmanabhan V. Effect of maternal PCOS and PCOS-like phenotype on the offspring's health. Mol Cell Endocrinol 2016;435:29-39.
29. Abbott DH, Tarantal AF, Dumesic DA. Fetal, infant, adolescent and adult phenotypes of polycystic ovary syndrome in prenatally androgenized female rhesus monkeys. Am J Primatol 2009;71:776-84.
30. Wood RI, Foster DL. Sexual differentiation of reproductive neuroendocrine function in sheep. Rev Reprod 1998;3:130-40.
31. Abbott DH, Barnett DK, Bruns CM, Dumesic DA. Androgen excess fetal programming of female reproduction: a developmental aetiology for polycystic ovary syndrome? Human Reprod Update 2005;11:357-74.
32. Welsh M, Saunders PT, Sharpe RM. The critical time window for androgen-dependent development of the Wolffian duct in the rat. Endocrinology 2007;148:3185-95.
33. Sir-Petermann T, Codner E, Perez V, Echiburu B, Maliqueo M, Ladron de Guevara A, et al. Metabolic and reproductive features before and during puberty in daughters of women with polycystic ovary syndrome. J Clin Endocrinol Metab 2009;94:1923-30.
34. Maliqueo M, Sir-Petermann T, Perez V, Echiburu B, de Guevara AL, Galvez C, et al. Adrenal function during childhood and puberty in daughters of women with polycystic ovary syndrome. J Clin Endocrinol Metab 2009;94:3282-8.
35. Sir-Petermann T, Maliqueo M, Codner E, Echiburu B, Crisosto N, Perez V, et al. Early metabolic derangements in daughters of women with polycystic ovary syndrome. J Clin Endocrinol Metab 2007;92:4637-42.
36. Shah AB, Nivar I, Speelman DL. Elevated androstenedione in young adult but not early adolescent prenatally androgenized female rats. PLoS One 2018;13:e0196862.
37. Abbott DH, Barnett DK, Levine JE, Padmanabhan V, Dumesic DA, Jacoris S, et al. Endocrine antecedents of polycystic ovary syndrome in fetal and infant prenatally androgenized female rhesus monkeys. Biol Reprod 2008;79:154-63.
38. Sullivan SD, Moenter SM. Prenatal androgens alter GABAergic drive to gonadotropin-releasing hormone neurons: implications for a common fertility disorder. Proc Natl Acad Sci USA 2004;101:7129-34.
39. Watanabe M, Fukuda A, Nabekura J. The role of GABA in the regulation of GnRH neurons. Front Neurosci 2014;8:387.
40. Moore AM, Prescott M, Marshall CJ, Yip SH, Campbell RE. Enhancement of a robust arcuate GABAergic input to gonadotropin-releasing hormone neurons in a model of polycystic ovarian syndrome. Proc Natl Acad Sci USA 2015;112:596-601.
41. Pinilla L, Aguilar E, Dieguez C, Millar RP, Tena-Sempere M. Kisspeptins and reproduction: physiological roles and regulatory mechanisms. Physiol Rev 2012;92:1235-316.
42. Cernea M, Padmanabhan V, Goodman RL, Coolen LM, Lehman MN. Prenatal testosterone treatment leads to changes in the morphology of KNDy neurons, their inputs, and projections to GnRH Cells in female sheep. Endocrinology 2015;156:3277-91.
43. Veiga-Lopez A, Ye W, Phillips DJ, Herkimer C, Knight PG, Padmanabhan V. Developmental programming: deficits in reproductive hormone dynamics and ovulatory outcomes in prenatal, testosterone-treated sheep. Biol Reprod 2008;78:636-47.
44. Sharma TP, Herkimer C, West C, Ye W, Birch R, Robinson JE, et al. Fetal programming: prenatal androgen disrupts positive feedback actions of estradiol but does not affect timing of puberty in female sheep. Biol Reprod 2002;66:924-33.
45. Sarma HN, Manikkam M, Herkimer C, Dell'Orco J, Welch KB, Foster DL, et al. Fetal programming: excess prenatal testosterone reduces postnatal luteinizing hormone, but not follicle-stimulating hormone responsiveness, to estradiol negative feedback in the female. Endocrinology 2005;146:4281-91.
46. Foecking EM, McDevitt MA, Acosta-Martinez M, Horton TH, Levine JE. Neuroendocrine consequences of androgen excess in female rodents. Horm Behav 2008;53:673-92.
47. Hakim C, Padmanabhan V, Vyas AK. Gestational hyperandrogenism in developmental programming. Endocrinology 2017;158:199-212.
48. Crisosto N, Codner E, Maliqueo M, Echiburú B, Sánchez F, Cassorla F, et al. Anti-Müllerian hormone levels in peripubertal daughters of women with polycystic ovary syndrome. J Clin Endocrinol Metab 2007;92:2739-43.
49. Webber LJ, Stubbs S, Stark J, Trew GH, Margara R, Hardy K, et al. Formation and early development of follicles in the polycystic ovary. Lancet 2003;362:1017-21.
50. Sir-Petermann T, Codner E, Maliqueo M, Echiburú B, Hitschfeld C, Crisosto N, et al. Increased anti-Müllerian hormone serum concentrations in prepubertal daughters of women with polycystic ovary syndrome. J Clin Endocrinol Metab 2006;91:3105-9.
51. Tehrani FR, Noroozzadeh M, Zahediasl S, Piryaei A, Azizi F. Introducing a rat model of prenatal androgen-induced polycystic ovary syndrome in adulthood. Exp Physiol 2014;99:792-801.
52. Padmanabhan V, Veiga-Lopez A. Animal models of the polycystic ovary syndrome phenotype. Steroids 2013;78:734-40.

53. Abbott DH, Dumesic DA, Franks S. Developmental origin of polycystic ovary syndrome —a hypothesis. J Endocrinol 2002;174:1-5.
54. Carmina E. Reproductive system outcome among patients with polycystic ovarian syndrome. Endocrinol Metab Clin North Am 2015;44:787-97.
55. Recabarren SE, Recabarren M, Sandoval D, Carrasco A, Padmanabhan V, Rey R, et al. Puberty arises with testicular alterations and defective AMH expression in rams prenatally exposed to testosterone. Domest Anim Endocrinol 2017;61:100-7.
56. Recabarren SE, Rojas-Garcia PP, Recabarren MP, Alfaro VH, Smith R, Padmanabhan V, et al. Prenatal testosterone excess reduces sperm count and motility. Endocrinology 2008;149:6444-8.
57. Ramezani Tehrani F, Noroozzadeh M, Zahediasl S, Piryaei A, Hashemi S, Azizi F. The time of prenatal androgen exposure affects development of polycystic ovary syndrome-like phenotype in adulthood in female rats. Int J Endocrinol Metab 2014;12:e16502.
58. Abbott AD, Colman RJ, Tiefenthaler R, Dumesic DA, Abbott DH. Early-to-mid gestation fetal testosterone increases right hand 2D:4D finger length ratio in polycystic ovary syndrome-like monkeys. PLoS One 2012;7:e42372.
59. Eisner JR, Dumesic DA, Kemnitz JW, Abbott DH. Timing of prenatal androgen excess determines differential impairment in insulin secretion and action in adult female rhesus monkeys. Clin Endocrinol Metab 2000;85:1206-10.
60. Noroozzadeh M, Ramezani Tehrani F, Sedaghat K, Godini A, Azizi F. The impact of prenatal exposure to a single dose of testosterone on insulin resistance, glucose tolerance and lipid profile of female rat's offspring in adulthood. J Endocrinol Invest 2015;38:489-95.
61. Padmanabhan V, Veiga-Lopez A, Abbott DH, Recabarren SE, Herkimer C. Developmental programming: impact of prenatal testosterone excess and postnatal weight gain on insulin sensitivity index and transfer of traits to offspring of overweight females. Endocrinology 2010;151:595-605.
62. Nicol LE, O'Brien TD, Dumesic DA, Grogan T, Tarantal AF, Abbott DH. Abnormal infant islet morphology precedes insulin resistance in PCOS-like monkeys. PLoS One 2014;9:e106527.
63. Ramaswamy S, Grace C, Mattei AA, Siemienowicz K, Brownlee W, MacCallum J, et al. Developmental programming of polycystic ovary syndrome (PCOS): prenatal androgens establish pancreatic islet alpha/beta cell ratio and subsequent insulin secretion. Sci Rep 2016;6:27408.
64. Huang Y, Gao JM, Zhang CM, Zhao HC, Zhao Y, Li R, et al. Assessment of growth and metabolism characteristics in offspring of dehydroepiandrosterone-induced polycystic ovary syndrome adults. Reproduction 2016;152:705-14.
65. Abruzzese GA, Heber MF, Ferreira SR, Velez LM, Reynoso R, Pignataro OP, et al. Prenatal hyperandrogenism induces alterations that affect liver lipid metabolism. J Endocrinol 2016;230:67-79.
66. Cardoso RC, Veiga-Lopez A, Moeller J, Beckett E, Pease A, Keller E, et al. Developmental programming: impact of gestational steroid and metabolic milieus on adiposity and insulin sensitivity in prenatal testosterone-treated female sheep. Endocrinology 2016;157:522-35.
67. Eisner JR, Dumesic DA, Kemnitz JW, Colman RJ, Abbott DH. Increased adiposity in female rhesus monkeys exposed to androgen excess during early gestation. Obe Res 2003;11:279-86.
68. Wu L, Yao R, Zhang Y, Wang Y, Li T, Chen M, et al. The association between digit ratio (2D:4D) and overweight or obesity among Chinese children and adolescents: a cross-sectional study. Early Hum Dev 2019;136:14-20.
69. Gunning MN, Sir Petermann T, Crisosto N, van Rijn BB, de Wilde MA, Christ JP, et al. Cardiometabolic health in offspring of women with PCOS compared to healthy controls: a systematic review and individual participant data meta-analysis. Human Reprod Update 2020;26:103-17.
70. King AJ, Olivier NB, Mohankumar PS, Lee JS, Padmanabhan V, Fink GD. Hypertension caused by prenatal testosterone excess in female sheep. Am J Physiol Endocrinol Metab 2007;292:E1837-41.
71. Blesson CS, Chinnathambi V, Hankins GD, Yallampalli C, Sathishkumar K. Prenatal testosterone exposure induces hypertension in adult females via androgen receptor-dependent protein kinase Cdelta-mediated mechanism. Hypertension 2015;65:683-90.
72. Sherman SB, Sarsour N, Salehi M, Schroering A, Mell B, Joe B, et al. Prenatal androgen exposure causes hypertension and gut microbiota dysbiosis. Gut Microbes 2018;9:400-21.
73. Vyas AK, Hoang V, Padmanabhan V, Gilbreath E, Mietelka KA. Prenatal programming: adverse cardiac programming by gestational testosterone excess. Sci Rep 2016;6:28335.
74. Kosidou K, Dalman C, Widman L, Arver S, Lee BK, Magnusson C, et al. Maternal polycystic ovary syndrome and the risk of autism spectrum disorders in the offspring: a population-based nationwide study in Sweden. Mol Psychiatry 2016;21:1441-8.
75. Auyeung B, Ahluwalia J, Thomson L, Taylor K, Hackett G, O'Donnell KJ, et al. Prenatal versus postnatal sex steroid hormone effects on autistic traits in children at 18 to 24 months of age. Mol Autism 2012;3:17.
76. Auyeung B, Baron-Cohen S, Ashwin E, Knickmeyer R, Taylor K, Hackett G. Fetal testosterone and autistic traits. Br J Psychol 2009;100:1-22.
77. Wegiel J, Flory M, Kuchna I, Nowicki K, Ma SY, Imaki H, et al. Stereological study of the neuronal number and volume of 38 brain subdivisions of subjects diagnosed with autism reveals significant alterations restricted to the striatum, amygdala and cerebellum. Acta Neuropathol Commun 2014;2:141.
78. Hatanaka Y, Wada K, Kabuta T. Abnormal instability, excess density, and aberrant morphology of dendritic spines in prenatally testosterone-exposed mice. Neurochemistry Int 2015;85-86:53-8.
79. Knickmeyer RC, Baron-Cohen S. Fetal testosterone and sex differences in typical social development and in autism. J Child Neurol 2006;21:825-45.
80. Lombardo MV, Ashwin E, Auyeung B, Chakrabarti B, Taylor K, Hackett G, et al. Fetal testosterone influences sexually dimorphic gray matter in the human brain. J Neurosc 2012;32:674-80.
81. Lombardo MV, Auyeung B, Pramparo T, Quartier A, Courraud J, Holt RJ, et al. Sex-specific impact of prenatal androgens on social brain default mode subsystems. Mol Pychiatry 2020;25:2175-88.
82. Pfaff DW, Rapin I, Goldman S. Male predominance in autism: neuroendocrine influences on arousal and social anxiety. Autism Res 2011;4:163-76.
83. Manti M, Fornes R, Qi X, Folmerz E, Linden Hirschberg A, de Castro Barbosa T, et al. Maternal androgen excess and obesity induce sexually dimorphic anxiety-like behavior in the offspring. FASEB J 2018;32:4158-71.
84. Hu M, Richard JE, Maliqueo M, Kokosar M, Fornes R, Benrick A, et al. Maternal testosterone exposure increases anxiety-like behavior and impacts the limbic system in the offspring. Proc Natl Acad Sci USA 2015;112:14348-53.
85. Berni TR, Morgan CL, Berni ER, Rees DA. Polycystic ovary syndrome is associated with adverse mental health and neurodevelopmental outcomes. J Clin Endocrinol Metab 2018;103:2116-25.
86. Kosidou K, Dalman C, Widman L, Arver S, Lee BK, Magnusson C, et al. Maternal polycystic ovary syndrome and risk for attention-deficit/hyperactivity disorder in the offspring. Biol Psychiatry 2017;82:651-9.
87. Barnett R. Attention deficit hyperactivity disorder. Lancet 2016;387:737.
88. Cesta CE, Öberg AS, Ibrahimson A, Yusuf I, Larsson H, Almqvist C, et al. Maternal polycystic ovary syndrome and risk of neuropsychiatric disorders in offspring: prenatal androgen exposure or genetic confounding? Psychol Med 2020;50:616-24.
89. Mereness AL, Murphy ZC, Sellix MT. Developmental programming by androgen affects the circadian timing system in female mice. Biol Reprod 2015;92:88.
90. Svensson K, Just AC, Fleisch AF, Sanders AP, Tamayo-Ortiz M, Baccarelli AA, et al. Prenatal salivary sex hormone levels and birthweight-for-gestational age. J Perinatol 2019;39:941-8.

91. Carlsen SM, Jacobsen G, Romundstad P. Maternal testosterone levels during pregnancy are associated with offspring size at birth. Eur J Endocrinol 2006;155:365-70.
92. Kumar S, Gordon GH, Abbott DH, Mishra JS. Androgens in maternal vascular and placental function: implications for preeclampsia pathogenesis. Reproduction 2018;156:R155-67.
93. Smith AS, Birnie AK, French JA. Maternal androgen levels during pregnancy are associated with early-life growth in Geoffroy's marmosets, Callithrix geoffroyi. Gen Comp Endocrinol 2010;166:307-13.
94. Roos N, Kieler H, Sahlin L, Ekman-Ordeberg G, Falconer H, Stephansson O. Risk of adverse pregnancy outcomes in women with polycystic ovary syndrome: population based cohort study. BMJ 2011;343:d6309.
95. Tomova A, Husarova V, Lakatosova S, Bakos J, Vlkova B, Babinska K, et al. Gastrointestinal microbiota in children with autism in Slovakia. Physiol Behav 2015;138:179-87.
96. Vink JM, Sadrzadeh S, Lambalk CB, Boomsma DI. Heritability of polycystic ovary syndrome in a Dutch twin-family study. J Clin Endocrinol Metab 2006;91:2100-4.
97. Chen ZJ, Zhao H, He L, Shi Y, Qin Y, Shi Y, et al. Genome-wide association study identifies susceptibility loci for polycystic ovary syndrome on chromosome 2p16.3, 2p21 and 9q33.3. Nat Genet 2011;43:55-9.
98. Shi Y, Zhao H, Shi Y, Cao Y, Yang D, Li Z, et al. Genome-wide association study identifies eight new risk loci for polycystic ovary syndrome. Nat Genet 2012;44:1020-5.
99. Zhao H, Xu X, Xing X, Wang J, He L, Shi Y, et al. Family-based analysis of susceptibility loci for polycystic ovary syndrome on chromosome 2p16.3, 2p21 and 9q33.3. Hum Reprod 2012;27:294-8.
100. Zhao S, Tian Y, Gao X, Zhang X, Liu H, You L, et al. Family-based analysis of eight susceptibility loci in polycystic ovary syndrome. Sci Rep 2015;5:12619.
101. Hiam D, Moreno-Asso A, Teede HJ, Laven JSE, Stepto NK, Moran LJ, et al. The genetics of polycystic ovary syndrome: an overview of candidate gene systematic reviews and genome-wide association studies. J Clin Med 2019;8:1606.
102. Abbott DH, Dumesic DA, Levine JE. Hyperandrogenic origins of polycystic ovary syndrome - implications for pathophysiology and therapy. Expert Rev Endocrinol Metab 2019;14:131-43.
103. McAllister JM, Legro RS, Modi BP, Strauss JF III. Functional genomics of PCOS: from GWAS to molecular mechanisms. Trends Endocrinol Metab 2015;26:118-24.
104. Hayes MG, Urbanek M, Ehrmann DA, Armstrong LL, Lee JY, Sisk R, et al. Genome-wide association of polycystic ovary syndrome implicates alterations in gonadotropin secretion in European ancestry populations. Nat Commun 2015;6:7502.
105. Day F, Karaderi T, Jones MR, Meun C, He C, Drong A, et al. Large-scale genome-wide meta-analysis of polycystic ovary syndrome suggests shared genetic architecture for different diagnosis criteria. PLoS Genet 2018;14:e1007813.
106. Dapas M, Lin FTJ, Nadkarni GN, Sisk R, Legro RS, Urbanek M, et al. Distinct subtypes of polycystic ovary syndrome with novel genetic associations: an unsupervised, phenotypic clustering analysis. PLoS Med 2020;17:e1003132.
107. Crespo RP, Bachega T, Mendonca BB, Gomes LG. An update of genetic basis of PCOS pathogenesis. Arch Endocrinol Metab 2018;62:352-61.
108. Dumesic DA, Hoyos LR, Chazenbalk GD, Naik R, Padmanabhan V, Abbott DH. Mechanisms of intergenerational transmission of polycystic ovary syndrome. Reproduction 2020;159:R1-13.
109. Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, et al. Finding the missing heritability of complex diseases. Nature 2009;461:747-53.
110. Gorsic LK, Kosova G, Werstein B, Sisk R, Legro RS, Hayes MG, et al. Pathogenic anti-Müllerian hormone variants in polycystic ovary syndrome. J Clin Endocrinol Metab 2017;102:2862-72.
111. Gorsic LK, Dapas M, Legro RS, Hayes MG, Urbanek M. Functional genetic variation in the anti-müllerian hormone pathway in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2019;104:2855-74.
112. Dapas M, Sisk R, Legro RS, Urbanek M, Dunaif A, Hayes MG. Family-based quantitative trait meta-analysis implicates rare noncoding variants in DENND1A in polycystic ovary syndrome. J Clin Endocrinol Metab 2019;104:3835-50.
113. Caburet S, Fruchter RB, Legois B, Fellous M, Shalev S, Veitia RA. A homozygous mutation of GNRHR in a familial case diagnosed with polycystic ovary syndrome. Eur J Endocrinol 2017;176:K9-14.
114. Kc K, Shakya S, Zhang H. Gestational diabetes mellitus and macrosomia: a literature review. Ann Nutr Metab 2015;66(suppl 2):14-20.
115. Hjort L, Martino D, Grunnet LG, Naeem H, Maksimovic J, Olsson AH, et al. Gestational diabetes and maternal obesity are associated with epigenome-wide methylation changes in children. JCI insight 2018;3.
116. Krishnaveni GV, Veena SR, Jones A, Srinivasan K, Osmond C, Karat SC, et al. Exposure to maternal gestational diabetes is associated with higher cardiovascular responses to stress in adolescent indians. J Clin Endocrinol Metab 2015;100:986-93.
117. Pathirana MM, Lassi ZS, Roberts CT, Andraweera PH. Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus in utero: systematic review and meta-analysis. J Dev Orig Health Dis 2020;11:1-18.
118. Kampmann FB, Thuesen ACB, Hjort L, Bjerregaard AA, Chavarro JE, Frystyk J, et al. Increased leptin, decreased adiponectin and FGF21 concentrations in adolescent offspring of women with gestational diabetes. Eur J Endocrinol 2019;181:691-700.
119. Ferreira I, Peeters LL, Stehouwer CD. Preeclampsia and increased blood pressure in the offspring: meta-analysis and critical review of the evidence. J Hypertens 2009;27:1955-9.
120. Odegård RA, Vatten LJ, Nilsen ST, Salvesen KA, Austgulen R. Preeclampsia and fetal growth. Obstet Gynecol 2000;96:950-5.
121. Giachini FR, Galaviz-Hernandez C, Damiano AE, Viana M, Cadavid A, Asturizaga P, et al. Vascular dysfunction in mother and offspring during preeclampsia: contributions from Latin-American countries. Curr Hypertens Rep 2017;19:83.
122. Sivalingam VN, Myers J, Nicholas S, Balen AH, Crosbie EJ. Metformin in reproductive health, pregnancy and gynaecological cancer: established and emerging indications. Hum Reprod Update 2014;20:853-68.
123. Hjorth-Hansen A, Salvesen O, Engen Hanem LG, Eggebo T, Salvesen KA, Vanky E, et al. Fetal growth and birth anthropometrics in metformin-exposed offspring born to mothers with PCOS. J Clin Endocrinol Metab 2018;103:740-7.
124. Salomaki H, Vahatalo LH, Laurila K, Jappinen NT, Penttinen AM, Ailanen L, et al. Prenatal metformin exposure in mice programs the metabolic phenotype of the offspring during a high fat diet at adulthood. PLoS One 2013;8:e56594.
125. Tartarin P, Moison D, Guibert E, Dupont J, Habert R, Rouiller-Fabre V, et al. Metformin exposure affects human and mouse fetal testicular cells. Hum Reprod 2012;27:3304-14.
126. Forcato S, Montagnini BG, de Goes MLM, da Silva Novi DRB, Inhasz Kiss AC, Ceravolo GS, et al. Reproductive evaluations in female rat offspring exposed to metformin during intrauterine and intrauterine/lactational periods. Reprod Toxicol 2019;87:1-7.
127. Forcato S, Novi D, Costa NO, Borges LI, Goes MLM, Ceravolo GS, et al. In utero and lactational exposure to metformin induces reproductive alterations in male rat offspring. Reprod Toxicol 2017;74:48-58.
128. Xita N, Tsatsoulis A. Fetal origins of the metabolic syndrome. Ann N Y Acad Sci 2010;1205:148-55.
129. Yamashita H, Yasuhi I, Fukuda M, Kugishima Y, Yamauchi Y, Kuzume A, et al. The association between maternal insulin resistance in mid-pregnancy and neonatal birthweight in uncomplicated pregnancies. Endocr J 2014;61:1019-24.
130. Isganaitis E, Woo M, Ma H, Chen M, Kong W, Lytras A, et al. Developmental programming by maternal insulin resistance: hyperinsulinemia, glucose intolerance, and dysregulated lipid metabolism in male offspring of insulin-resistant mice. Diabetes 2014;63:688-700.
131. Coles N, Patel BP, Birken C, Hanley AJ, Retnakaran R, Hamilton JK. Determinants of insulin resistance in children exposed to gestational diabetes in utero. Pediatr Diabetes 2021. https://doi.org/10.1111/pedi.13104

132. Thorn SR, Baquero KC, Newsom SA, El Kasmi KC, Bergman BC, Shulman GI, et al. Early life exposure to maternal insulin resistance has persistent effects on hepatic NAFLD in juvenile nonhuman primates. Diabetes 2014;63:2702-13.
133. Schmitz L, Kuglin R, Bae-Gartz I, Janoschek R, Appel S, Mesaros A, et al. Hippocampal insulin resistance links maternal obesity with impaired neuronal plasticity in adult offspring. Psychoneuroendocrinology 2018;89:46-52.
134. Merhi Z, Kandaraki EA, Diamanti-Kandarakis E. Implications and future perspectives of AGEs in PCOS pathophysiology. Trends Endocrinol Metab 2019;30:150-62.
135. Palioura E, Diamanti-Kandarakis E. Polycystic ovary syndrome (PCOS) and endocrine disrupting chemicals (EDCs). Rev Endocr Metab Disord 2015;16:365-71.
136. Rutkowska AZ, Diamanti-Kandarakis E. Polycystic ovary syndrome and environmental toxins. Fertil Steril 2016;106:948-58.
137. Tata B, Mimouni NEH, Barbotin AL, Malone SA, Loyens A, Pigny P, et al. Elevated prenatal anti-Mullerian hormone reprograms the fetus and induces polycystic ovary syndrome in adulthood. Nat Med 2018;24:834-46.
138. Dokras A, Spaczynski RZ, Behrman HR, Duleba AJ. Testosterone levels in pregnant women correlate with the insulin response during the glucose tolerance test. Fertil Steril 2003;79:492-7.
139. Kampmann U, Knorr S, Fuglsang J, Ovesen P. Determinants of maternal insulin resistance during pregnancy: an updated overview. J Diabetes Res 2019;2019:5320156.
140. Zhang Y, Zhao W, Xu H, Hu M, Guo X, Jia W, et al. Hyperandrogenism and insulin resistance-induced fetal loss: evidence for placental mitochondrial abnormalities and elevated reactive oxygen species production in pregnant rats that mimic the clinical features of polycystic ovary syndrome. J Physiol 2019;597:3927-50.