# Intrauterine Environment and Polycystic Ovary Syndrome

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## Abstract

The maternal–fetal environment plays an important role in developmental programming of adult disease. Metabolic and hormonal dysfunction during human fetal development accompanies gestational diabetes as a common occurrence in mothers with polycystic ovary syndrome (PCOS), while human fetal androgen excess from congenital adrenal hyperplasia or virilizing tumors precedes PCOS-like symptoms after birth. To date, clinical studies of infant blood levels at term have yet to confirm that human fetal androgen excess promotes PCOS development after birth. Earlier in development, however, circulating androgen levels in the second trimester female human fetus can normally rise into the male range. Furthermore, midgestational amniotic testosterone levels are elevated in female fetuses of PCOS compared with normal mothers and might influence fetal development because experimentally induced fetal androgen excess in animals produces a PCOS-like phenotype with reproductive and metabolic dysfunction. Such alterations in the maternal–fetal environment likely program adult PCOS by epigenetic modifications of genetic susceptibility of the fetus to PCOS after birth. Understanding this phenomenon requires advanced fetal surveillance technologies and postnatal assessment of midgestational androgen exposure for new clinical strategies to improve reproduction in PCOS women, optimize long-term health of their offspring, and minimize susceptibility to acquiring PCOS in future generations.

**Keywords**
- polycystic ovary syndrome
- hyperandrogenism
- hyperinsulinemia
- adiposity
- developmental programming
- fetal development

Polycystic ovary syndrome (PCOS) is a heterogeneous syndrome in women characterized by luteinizing hormone (LH) hypersecretion, ovarian hyperandrogenism, oligo-anovulation, and hyperinsulinemia from insulin resistance. The 1990 National Institutes of Health (NIH)–National Institute of Child Health and Human Development Conference of PCOS in 1990 recommended that the diagnostic criteria should be hyperandrogenism and/or hyperandrogenemia with oligo-anovulation, excluding other endocrinopathies, including congenital adrenal hyperplasia (CAH), Cushing syndrome, thyroid dysfunction, hyperprolactinemia, androgen-producing tumors, and drug-induced androgen excess.[1] With a 6.6% estimated prevalence of NIH-defined PCOS in the United States, the annual economic burden of treating PCOS-related diabetes, menstrual dysfunction, and anovulatory infertility was $4.4 billion in 2005, not considering inflation or pregnancy-related complications, including gestational diabetes, preeclampsia, and miscarriage.[2]

In 2003, the Rotterdam consensus expanded the diagnostic criteria of PCOS to include at least two of the following

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**Table 1** Reduced second to fourth digit (finger) ratio as a marker of androgen excess in utero in women with PCOS[16–19]

| Author | Participant | PCOS definition | Findings |
|---|---|---|---|
| Cattrall et al 2005 | 70 PCOS<br>70 NL women | NIH | Reduced 2D:4D ratio in right hand of PCOS vs. normal women |
| Lujan et al 2010 | 98 PCOS<br>51 NL women | Rotterdam | No difference 2D:4D ratio; 2D:4D ratio positively correlates with hirsutism, free androgen index, and ovarian volume |
| Lujan et al 2010 | 96 PCOS<br>48 NL women<br>50 men | Rotterdam | No difference 2D:4D ratio by computer analysis; 2D:4D ratio positively correlates with hirsutism, testosterone, and free androgen index |
| Palomba et al 2012 | 30 PCOS<br>545 NL women | Rotterdam (all androgen excess) | Increased 2D:4D ratio in 4–11 years old daughters of PCOS vs. normal mothers |

Abbreviation: NIS, National Institutes of Health; NL, normal; PCOS, polycystic ovary syndrome.

three features: (1) clinical or biochemical hyperandrogenism, (2) oligo-anovulation, and (3) polycystic ovaries (PCOs), excluding the previously described endocrinopathies.[3] These newer Rotterdam criteria for PCOS combine all patients defined by 1990 NIH criteria (i.e., classic PCOS) with additional women with either (1) clinical/biochemical hyperandrogenism and PCO (i.e., ovulatory PCOS) or (2) PCO with ovulatory dysfunction (but without signs of androgen excess). As a result, the 6 to 10% worldwide prevalence of PCOS by 1990 NIH criteria has increased to about twice that level using broader Rotterdam criteria due to the inclusion of multiple PCOS phenotypes.[4–6] As the most common PCOS phenotype, classic PCOS has the greatest reproductive and metabolic dysfunction,[7,8] while ovulatory PCOS patients have a lower body mass index (BMI) and lesser degrees of hyperinsulinemia and hyperandrogenism than classic PCOS patients. Women with combined PCO and oligo-anovulation (without androgen excess), who do not fulfill the diagnosis of PCOS by the Androgen Excess Society, appear least affected.[7–9]

Emerging data suggest that the phenotypic expression of adult PCOS may be influenced by the endocrine–metabolic status of the maternal–fetal environment.[5] This hypothesis agrees with the increased prevalence of PCOS in women with classical CAH from 21 hydroxylase deficiency or congenital adrenal virilizing tumors,[10–13] and with the ability of discrete experimentally induced prenatal testosterone excess to program a permanent PCOS-like phenotype in several species.[14]

This article addresses the developmental origins of PCOS, whereby maternal maladaptations to pregnancy at a critical gestational age permanently alter fetal susceptibility to PCOS phenotypic expression after birth. This theory of developmental origins of PCOS is based on the premise that alterations in the maternal–fetal environment permanently program adult disease by epigenetic modifications of genetic susceptibility of the fetus to disease after birth.

## Endocrine Antecedent to Polycystic Ovary Syndrome

Women with congenital adrenal virilizing tumors or classical CAH from 21 hydroxylase deficiency have an increased risk of developing a PCOS-like syndrome in adulthood.[10–13] Such gestational susceptibility to androgens implicates exposure of the female fetus to androgen excess as a modifier of PCOS phenotypic expression after birth. To date, however, a relationship between hyperandrogenism in utero and PCOS phenotypic expression in adulthood has been elusive. Women born to the opposite sex twins, for example, do not display an increased prevalence of PCOS-like features, although presumably they share a prenatal environment with a male co-twin that increases their exposure to testosterone.[15] Using relative finger length as an anatomical marker of in utero androgen exposure, some,[16,17] but not all,[18,19] women with PCOS have altered length of the second finger relative to the fourth finger as a male characteristic that correlates with hyperandrogenism and ovarian volume (►**Table 1**).[18–20] Adult female rhesus monkeys with PCOS-like features induced by early-to-midgestation testosterone excess also exhibit alteration of the same finger length ratio, implying an association between PCOS and finger length mediated by prenatal androgen excess.[21] Elevated umbilical cord testosterone levels also occur in some,[22,23] but not all,[24,25] newborns of mothers with PCOS, but such study findings are inconsistent, perhaps from differences in placental steroidogenesis[24,25] or to cord blood collection at term,[22,24,26] a time point past the critical period of human ovarian differentiation.[27–29]

Perhaps more importantly, amniotic fluid testosterone levels in the second trimester of human development are normally higher in the male than in the female fetus, allowing a wider range of testosterone levels to differentially affect fetal development compared with term umbilical vein blood testosterone concentrations that are similar between sexes.[30] Second trimester amniotic fluid testosterone levels also are elevated in female fetuses of PCOS compared with normal mothers (►**Table 2**),[17] suggesting that androgen overproduction can occur during human female fetal development under certain pregnancy conditions.[31] Given these findings, therefore, androgen action during the second trimester of human development may influence the developmental programming of the female fetus, assuming a critical time interval in a susceptible fetus when developmental programming occurs.

**Table 2** Second trimester amniotic fluid testosterone levels (nmol/L) from pregnant women with and without hyperandrogenic polycystic ovary syndrome[17]

| | *N* | Mean | SD |
|---|---|---|---|
| Control mothers | | | |
| Male fetus | 21 | 0.80[a] | 0.16 |
| Female fetus | 24 | 0.36 | 0.10 |
| PCOS mothers | | | |
| Male fetus | 17 | 0.87[a] | 0.21 |
| Female fetus | 13 | 0.53[b] | 0.12 |

Abbreviations: PCOS, polycystic ovary syndrome; SD, standard deviation.
[a]$p < 0.001$ fetal sex difference.
[b]$p < 0.02$ female fetus, control versus PCOS mother.

## Ontogeny of the Human Fetal Ovary

If true, a pivotal issue is the ability of the second trimester human fetal ovary to produce androgen during early folliculogenesis. Human ovarian folliculogenesis begins in early fetal development, when germ cells migrate to the gonadal ridge and multiply by mitosis until approximately 20 weeks of gestation, reaching a maximum number of approximately 7 million (►**Fig. 1**).[32] Oogonial mitosis becomes superimposed with meiosis between 14 and 26 weeks of gestation, as ovigerous cords, packed with oogonia and oocytes, develop into abundant primordial and primary follicles, along with occasional secondary follicles.[27] Simultaneously, a loose network of primary interstitial cells, containing 17a hydroxylase-17, 20-lyase (P450c17), the major steroidogenic enzyme responsible for androgen production, develops within the stroma as it differentiates in response to local paracrine factors, including extracellular matrix proteins, or fibrillins.[27,33] Prominent between 15 and 19 weeks of gestation, these primary interstitial cells[27] are replaced between 27 and 32 weeks of gestation by other P450c17 immunoreactive cells, which collect around growing primary follicles to form the theca interna layer of emerging secondary and small Graafian follicles, joined shortly thereafter by additional P450c17 immunoreactive cells in the hilum. By midgestation, the human fetal ovary has the capacity to produce and detect sex steroids, including androgen and estrogen,[27,29,34–38] with estrogen believed to regulate folliculogenesis and oocyte development in utero.[39–41] Together, endocrine (i.e., gonadotropins) and paracrine facilitators of follicular growth (i.e., androgens, growth factors such as activin and insulin-like growth factors [IGF]) interact with survival and atresia factors to establish the maximal germ cell endowment of the fetal ovary, which then diminishes to approximately 1 to 2 million at birth and 300,000 by menarche.[28,32]

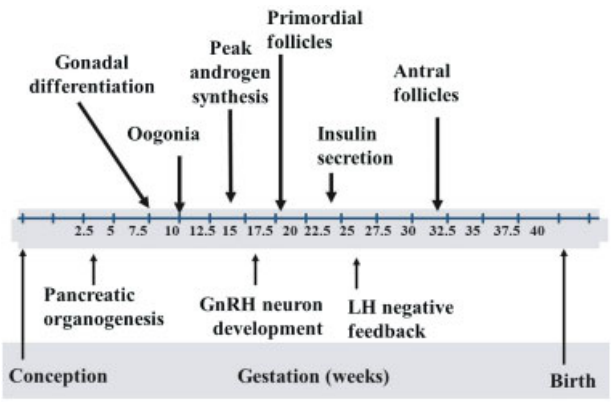


**Figure 1** Ontogeny of human fetal development.

During the second trimester of human fetal development, a transient rise of pituitary gonadotropins increases androgen production by the testes compared with the ovary, temporarily elevating circulating androgen levels in the male compared with the female fetus.[28,42] This sexual dimorphism in androgen production by the human fetus disappears by birth.[28,42] At midgestation, human fetal ovaries also have several steroidogenic enzymes; genes encoding multiple steroid signaling pathways; and receptors to steroids, insulin, IGF-I, and IGF-II.[27,29,34,35] They do not, however, have functional LH-like receptors.[37] Nevertheless, cultured human fetal ovaries at this gestational age can metabolize pregnenolone sulfate to dehydroepiandrosterone (DHEA) and androstenedione[36] and also can secrete in decreasing amounts DHEA, progesterone, and estrone, with lesser amounts of androstenedione, estradiol, and testosterone.[37]

Therefore, although lacking functional LH-like receptors, midgestational human fetal ovaries may produce androgens in vivo, particularly in response to insulin, which may contribute to wide variation in fetal androgen production, as evidenced by 40% of midgestational female fetuses having elevated serum androgen levels into the normal male range.[41,42] This hypothesis agrees with previous reports in diabetic women of elevated amniotic fluid testosterone levels,[43] along with findings of hirsutism, ovarian thecalutein cysts, and thecal cell hyperplasia in their female stillbirth offspring.[44,45]

## Abnormalities of the PCOS Maternal–Fetal Environment

To date, however, the link between androgen excess in utero and the maternal environment remains unclear. Maternal serum androgen levels in midgestation are greater in PCOS than in normal women,[46] but are unlikely to directly program PCOS in offspring if placental aromatization is normal,[26] even though reduced aromatase activity in term placenta from women with PCOS likely contributes to elevated maternal androgen production.[25] Rather, an increased risk of developing maternal glucose intolerance in women with PCOS may induce intrauterine hyperglycemia, which may stimulate fetal insulin release as a secretagogue for ovarian androgen production and/or folliculogenesis in the female fetus.[47–50] In support of this, prenatal testosterone administration to female rhesus monkeys impairs maternal–fetal glucose–insulin homeostasis and stimulates fetal insulin release,[51] consistent with several animal models establishing links

between gestational hyperglycemia, fetal androgen excess, and various adult PCOS-like phenotypes.[52]

Such maternal–fetal environment dysfunction may underlie several endocrine antecedents of PCOS previously reported in girls born to mothers with PCOS. For example, infant girls born to mothers with PCOS exhibit antimullerian hormone overproduction as a marker of growing follicles, which persists in prepubertal life (along with exaggerated ovarian responsiveness to leuprolide administration) and improves when mothers with PCOS receive metformin in pregnancy, beginning at or before conception.[53,54] In addition, serum leptin levels in newborns of PCOS women positively correlate with birth weight and maternal BMI at midgestation.[55] During puberty, enlarged ovaries and hyperinsulinemia in female children of PCOS women coexist with LH hypersecretion and androgen excess.[56–58]

In addition to glucose intolerance, PCOS women in pregnancy are also at increased risk of developing diabetes, pregnancy-induced hypertension, preeclampsia, preterm birth, impaired endovascular trophoblast invasion, and abnormal placentation,[17,47–50,59] all of which may alter developmental programming of the infant. Successful fetal adaptation to maternal nutrient overabundance favors the development of large-for-gestational age infants, contributing to the positive association between maternal BMI at term and infant birth weight.[24,60,61] On the contrary, impaired fetal nutrient availability from placental insufficiency likely accompanies low infant birth weight associated with maternal diabetes,[61] PCOS pregnancies in Chilean and Iranian women,[23,62] and precocious puberty accompanying PCOS in northern Spanish women.[63] Therefore, different pathophysiological mechanisms, based on the endocrine–metabolic status of the maternal–fetal environment, likely influence the birth weight of infants born to PCOS women.

Such pathophysiological mechanisms may also exert subtle developmental programming effects on the fetus after birth despite normal infant birth weight.[24,50,64–67] For example, exposure of female rhesus monkeys to prenatal testosterone excess impairs fetal glucose–insulin homeostasis without affecting infant birth weight and alters the trajectory of neonatal growth after birth.[51] As adults, female rhesus monkeys exposed to prenatal testosterone show disrupted development of subcutaneous abdominal adipocytes,[68] mimicking androgen inhibition of human adipose stem cell commitment to preadipocyte formation[69] and possible effects on a more primitive population of human adipose stem cells with pluripotent stem characteristics.[70]

## Genetic and Epigenetic Mechanisms

The inherited nature of PCOS has been well established by family and twin studies. The prevalence of PCOS in female first-degree relatives of affected women is 20 to 40%, substantially higher than the general population prevalence.[71,72] Twin studies comparing the correlation of PCOS diagnosis between monozygotic and dizygotic twins have estimated the heritability of PCOS as 70%, suggesting that most susceptibility arises from genetic factors.[73] Heritability is commonly assumed to reflect the effects of inherited genomic variation; however, it may also reflect the effects from shared disease-predisposing environments. The latter is particularly relevant when considering that adverse intrauterine environments may contribute to disease risk, for example, daughters of a woman with PCOS would be exposed to the same intrauterine environment. Thus, fetal androgen excess and consequent reprogramming may contribute to some portion of the 70% heritability.

Despite little progress in candidate gene studies of small sample sizes, genome-wide association studies (GWAS) in large Chinese cohorts with robust replication recently have identified variants in 11 genomic regions (loci) as risk factors for PCOS.[74,75] Assuming the gene nearest to each variant is responsible for the risk-altering effect, the GWAS discoveries include *DENND1A*, *LHCGR*, *THADA*, *FSHR*, *C9orf3*, *YAP1*, *RAB5B/SUOX*, *HMGA2*, *TOX3*, *INSR*, and *SUMO1P1*. Only *LHCGR*, *FSHR*, and *INSR*, which encode receptors for LH/hCG, FSH, and insulin, respectively, have clear functional relevance to the pathophysiology of PCOS. How the remaining genes might influence PCOS remains unknown.

Nevertheless, variants in some of these established PCOS susceptibility genes might influence fetal reprogramming of PCOS by altering (1) fetal or maternal androgen production, (2) fetal responsiveness to androgen exposure, (3) placental steroid production or clearance, or (4) placenta-related (e.g., placental insufficiency, abnormal placentation) as well as pregnancy-related (e.g., preeclampsia, pregnancy-induced hypertension, gestational diabetes) complications. For example, perhaps fetal ovaries with inherited PCOS-predisposing variants in *LHCGR*, unlike normal fetal ovaries,[37] express functional receptors, promoting excessive LH-stimulated androgen production at midgestation. Alternatively, *INSR* variation may increase fetal ovarian responsiveness to insulin, thereby promoting ovarian androgen production in the fetus in response to its own hyperinsulinemia from maternal hyperglycemia. That several PCOS genes (*THADA*, *HMGA2*, and *SUOX*) have also been implicated in diabetes[76–78] raises the possibility that fetal reprogramming is related to disturbed maternal–fetal glucose homeostasis. Equally important, several of these loci (*LHCGR/FSHR* region, *INSR*, and *TOX3*) are associated with anthropometric measures (BMI, waist circumference, and height),[79,80] which could affect fetal reprogramming through fetal growth, while *C9orf3* codes for aminopeptidase O, a testicular and placental protease generating angiotensin IV from angiotensin III,[81] which might promote placental dysfunction, pregnancy-induced hypertension, and fetal androgen excess.

Although the molecular mechanism of reprogramming by intrauterine events is unknown, epigenetic changes induced by an altered in utero environment is a likely mechanism.[82] Epigenetic refers to modifications of genomic DNA that can be passed to subsequent generations (such as DNA methylation and histone modification), allowing the environment to have permanent changes on gene expression. Rodents[83,84] and rhesus monkeys[85] experimentally exposed to androgen excess in utero have been found to exhibit alterations in DNA methylation at specific genes. Of interest, one of these genes is *LHCGR*,[83] one of

the susceptibility genes discovered by GWAS in humans,[75] which demethylated would likely be overexpressed and capable of promoting fetal androgen excess and enhancing LH stimulation of adipogenesis.[86] Such altered LH signaling in visceral fat of LH hypersecreting infant and adult monkeys, exposed to androgen excess in utero, has been linked with differential DNA methylation of specific gene promoter sites in this fat depot,[85] which may be constrained by testosterone in its capacity to safely store fat.[68,69]

## Future Directions

Future studies need to examine how alterations in the maternal–fetal environment program adult PCOS by epigenetic modifications of fetal genetic susceptibility to PCOS after birth. If metabolic disorders of pregnancy, such as PCOS, obesity, and diabetes mellitus, induce androgen overproduction by the midgestational human fetal ovary, then advanced fetal surveillance technologies and postnatal assessment of intrauterine androgen exposure will be required to understand whether adult PCOS can be reprogramed in susceptible female offspring. Equally important, abnormal placentation may simultaneously affect fetal adaptation to maternal nutrient availability, with altered placental DNA methylation[87] or other epigenetic and metabolic abnormalities influencing fetal growth, infant birth weight, and long-term physiology of the offspring.[43,88,89] As the number of robust susceptibility loci for PCOS emerges from ongoing GWAS data, additional studies will be needed to interrogate the possible role of these genes in fetal reprogramming of PCOS.

Finally, experimental constraints on using human fetal tissue for biomedical research limit our knowledge of the relationships between the human fetus and its maternal environment. Therefore, new knowledge of how developmental programming affects human health requires animal models to explore the probable fetal origins of adult disease. Such animal studies need to examine how developmentally relevant endocrine/paracrine factors and genes interact to govern human fetal development, including the role of ovarian steroidogenesis in the developmental programming of target tissues. With such information, new clinical strategies promise to improve the endocrine–metabolic status of women with PCOS in pregnancy, optimize long-term health of their offspring, and minimize susceptibility to acquiring PCOS and its metabolic derangements in future generations.

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