Does a compromised placenta contribute to transgenerational transmission of metabolic dysfunction in polycystic ovary syndrome?

Polycystic ovary syndrome (PCOS) comprises at least two of the following: hyperandrogenism, intermittent or absent menstrual cycles, and polycystic ovaries. It affects 15%–20% of women in their reproductive years, compromising their fertility, fecundity, and cardiometabolic health (1). Assisted reproduction is a common prerequisite for a high conception rate in women with PCOS; but regardless of method of conception, pregnant women are at increased risk for pregnancy-induced hypertension, preeclampsia, gestational diabetes, spontaneous preterm labor, need for cesarean delivery, and thus severe maternal morbidity. In all, 60%–70% of daughters inherit PCOS from their mothers, likely due to a combination of genetic, epigenetic, and developmental contributions enabling fetal hyperandrogenism, a developmental commonality that may precede all PCOS phenotypes (1). Not surprisingly, PCOS places a multi-billion-dollar burden on health care resources in the United States alone, yet progress toward a cure is impeded by a complex developmental etiology.

The placenta of offspring born to PCOS mothers, however, has long been suspected of aiding and abetting in the developmental origins of PCOS, with its morphological and functional integrity undermined by maternal hyperandrogenism, obesity, gestational diabetes, and chronic low-grade inflammation, leading to diminished uteroplacental perfusion, placental insufficiency, and inadequate aromatization of androgens (1, 2). Direct evidence for maternal hyperandrogenic induction of placental dysfunction comes from animal models of PCOS generated by maternal gestational testosterone (T) excess (1). Gestational T-exposed female rhesus monkey offspring exhibit the most comprehensive PCOS-like adult phenotypes, including many of the metabolic impairments that accompany PCOS in women, such as type 2 diabetes (1). Male monkey conspecifics, similarly exposed to maternal hyperandrogenism, exhibit comparable insulin resistance and pancreatic β-cell decompensation to T-exposed females, and emulate glucoregulatory impairments demonstrated by male relatives of women with PCOS (1). During hyperandrogenic monkey pregnancies, the villous hemochorial placenta exhibits diminished placental blood volume (3), and likely reduced placental blood flow, contributing to a relatively hypoxic fetal environment (3, 4). The addition of diet-induced maternal obesity (DIO) to hyperandrogenic monkey pregnancies increases maternal gestational weight gain and body fat (3, 4), as well as maternal hyperglycemia and insulin resistance (3), together with diminished expression of placental glucose transporters and decreased placental angiogenesis (4). By late gestation, female monkey fetuses are hypolipidemic (1) as well as smaller and fatter (3), whereas fetal males are longer and heavier (3). Of newborn gestational T-exposed female monkeys, 50% are hypoglycemic; birthweights are normal for both sexes (1, 4); and infant females exhibit exaggerated weight gain, along with epigenetic changes in white adipocytes that precede and accompany adult dysfunctional adipogenesis and hyperlipidemia (1).

In Sun and colleagues' most recent clinical observation study (5), our understanding of compromised placental function and morphology during hyperandrogenic PCOS gestation is taken one step further. This report not only confirms PCOS placental morphological and steroidogenic pathology, but also demonstrates hormonal and metabolic programming of exposed infants (5). Clinically referred, pregnant Chinese women with a single fetus, and without pregnancy-induced hypertension, gestational diabetes, or other endocrine abnormalities during pregnancy, were selected from pre-pregnancy Rotterdam PCOS criteria, excluding other endocrine disorders, and delivered by cesarean section (C-section) at term (5). The PCOS women were age-matched to pregnant women without PCOS, but were on average overweight prior to pregnancy, unlike controls. The rationale for C-section, however, was not given, and histories relating to the use of assisted reproductive technology, parity, previous pregnancy complications, smoking, and medication were also absent. Typical of pregnant hyperandrogenic women with PCOS, and in contrast to control women, gestational weight gain exceeded recommended guidelines and was ~40% greater in women with PCOS (5). By term, women with PCOS had elevated circulating levels of cholesterol and apolipotropin B, but control-comparable glucoregulatory parameters and levels of circulating cytokines, except for diminished levels of anti-inflammatory interleukin-10 (5). Taken together, these term blood parameters suggest a hyperlipidemic, pro-inflammatory maternal environment.

Because the majority of births delivered male infants in women with and without PCOS, and the study subject numbers are relatively small, the offspring sex bias precluded statistical analyses of daughters alone. Placental weights, birth weights, and birth lengths were comparable, and the latter were typical for gestational age (5). Fetal umbilical cord blood parameters indicated hyperlipidemia in offspring born to women with PCOS, with respect to increased levels of total cholesterol and high-density lipoprotein (HDL), as well as adrenal hyperandrogenism (5). When analyses were limited to male offspring, circulating sex hormone binding globulin (SHBG) was diminished and dehydroepiandrosterone sulfate (DHEAS) was increased in those infants born to PCOS women compared to those born to controls.

As anticipated from previous reports (1, 2), term placentas from hyperandrogenic PCOS pregnancies presented with infarction and intravillous fibrin deposition, calcification, and increased intervillous space, the latter suggestive of adaptation to a hypoxic environment (5). It was not clear, however, from which placental locations the sampled portions were taken. As there is considerable intraplacental variability in integrity and functionality at term, this is a concern. The placentas sampled from women with PCOS, compared to

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controls, however, exhibited increased protein expression for estrogen receptor−β, but comparable expression for estrogen receptor−α, androgen receptor, aromatase, 17β-hydroxysteroid dehydrogenase 2, and Toll-like receptor 4 (5). Increased placental estrogen receptor−β has been associated with increased placental production of vasoconstrictive prostanoids and with calcification-linked vascular injury, and thus may indicate abnormal vascular structure and function compromising PCOS placental function. In addition, proteomic identification of reduced placental fibronectin production in placentas from PCOS women (5) suggests diminished intercellular adhesion and villous remodeling within the PCOS placenta, as well as suboptimal engagement with uterine endometrium. When coincident with increased placental estrogen receptor−β expression, diminished placental fibronectin expression could contribute to the more frequent occurrence of pregnancy-induced hypertension, preeclampsia, and diminished placental oxygen and nutrient exchange in pregnant women with PCOS (1, 2). Such potential placental molecular underpinnings could provide novel insight into differential metabolic fetal programming of male and female offspring inducing adult metabolic phenotypes associated with familial PCOS (1). Without additional understanding of placental dysfunction during gestation in women with PCOS, however, it is difficult to envisage how such structural and metabolically related placental perturbations enable fetal hyperandrogenism. The strength of this study, nevertheless, is the uniformity of absent major pregnancy complications and deliveries managed by C-section, potentially providing insight into minimally compromised PCOS placentas.

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