Children born to women with PCOS - short and long-term impact on health and development
Narrative review

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Short narrative abstract

Maternal PCOS status may negatively influence offspring infant and childhood growth, cardiometabolic health, reproductive health and neurodevelopment. Current findings across studies are divergent, often because of small numbers of subjects, as well as heterogeneous selection criteria, ethnicity and definition of control groups. Co-existing maternal obesity, pregnancy complications and comorbidity make it difficult to identify the contribution of maternal PCOS. Large, prospective, international multiethnic studies with standardized investigation protocols and questionnaires on PCOS-offspring health and development are needed.

Capsule

Maternal PCOS may impair offspring growth, cardiometabolic and reproductive health, as well as neurodevelopment. There is urgent need for large-scale international studies on children born to women with PCOS.

Running title: Health of children born to PCOS women

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Introduction

Polycystic ovary syndrome (PCOS) affects ~10-15 % of women depending on diagnostic criteria used (1, 2). Clinical presentations vary with ethnicity, but there is a high prevalence of overweight and obesity in women with PCOS (3, 4). Obesity does not seem to cause PCOS, but rather worsens symptoms and clinical presentation (5-7). Not surprisingly, PCOS prevalence increases with increasing body mass index (BMI) in subjects recruited from clinical settings (8, 9), and adiposity enhancement of PCOS is less distinct in subjects recruited from unselected populations (10, 11). A woman's awareness of exhibiting PCOS signs and symptoms is generally poor and varies greatly. Only 30% of affected women were aware of PCOS symptomology in an Australian birth cohort of unselected women, while in Denmark, 10% of pregnant women knew they had PCOS (2, 12). In the Swedish national diagnosis registry, less than 1% of women were diagnosed with PCOS (13). The majority of clinical PCOS studies were performed on subjects with a previously known PCOS diagnosis, already seeking medical assistance for their symptomology. Thus, much of our knowledge regarding PCOS is based on selected clinical referrals and seriously affected individuals. Women with diagnosed PCOS have higher prevalence of comorbidities compared to controls (14, 15). Infertility and subfertility have dominated clinical research involving PCOS subjects during the last 3-4 decades, providing substantial evidence for increased prevalence of pregnancy complications and less favorable pregnancy outcomes compared to women without PCOS, including preterm delivery, as well as development of gestational diabetes (GDM) and hypertensive disorders (16-18). Studies diverge, however, in their findings of early miscarriage risk in women with PCOS: some report increased risk, while others do not (16, 19).

There is an increasing focus on both somatic and neurodevelopmental health of infant and prepubertal children born to women with PCOS (PCOS-off). PCOS status, and associated obesity, metabolic dysfunction, maternal comorbidity and pregnancy complications, are likely to provide suboptimal intrauterine environments (20-23). In combination with a significant genetic component, and consistent with the Barker hypothesis (24), a detrimental impact is expected on PCOS-off health (25-27). In these regards, we therefore aim to briefly review growth, development and long-term health consequences for offspring born to women with PCOS.

Intra-uterine exposure to a hyperandrogenic environment

Both pregnant and non-pregnant women with PCOS have increased circulating androgen levels compared to healthy women (28). Intrauterine hyperandrogenism is suggested as a potential transcriptional inducer of impaired long-term health in offspring born to women with PCOS (29-31). Potential sources of fetal androgen excess are high circulating maternal levels, placental injury, fetal hyperinsulinemia and fetal hyperandrogenism. All of these have been reported in PCOS. A reduced synthesis of sex hormone binding globulin (SHBG), as in obesity and insulin resistant states, diminished expression of placental aromatase enabling maternal testosterone excess to access the intrauterine environment, impaired placental maturation, as well as maternal hyperglycemia-induced fetal insulin excess, are all PCOS-related mechanisms with the potential to increase fetal female androgen levels (30, 32-36). Nonhuman primate models for PCOS make it abundantly clear that without some form of compromised placental function, higher primate and human placentae can prevent androgens to access to the intrauterine environment until maternal testosterone levels approximate those found in adult males (37) A hyperandrogenic environment provided by mothers with PCOS may impair fetal growth, as suggested by animal models. In rodents excess maternal dihydrotestosterone (DHT) induced diminished placental weight, fetal growth restriction and offspring metabolic dysfunction (34). In sheep, maternal testosterone (T) exposure resulted in fetal and offspring growth restriction and offspring catchup growth. In other sheep models, however, maternal T exposure does not alter fetal growth or glucose regulation (38). Maternal T exposure does not alter somatometrics or body weight in female fetuses and infants in nonhuman primate models (39). In humans, similarly diverse fetal and offspring outcomes associate with hyperandrogenic gestations, including a negative correlation between maternal T levels and fetal growth in a random sample of Caucasian women (40), and the presence (41) or absence (16) of fetal and offspring growth impairments in girls born to women with PCOS.

Exposure to excess androgens in fetal life is hypothesized to result in epigenetic alterations leading to the developmental programming of PCOS-like features (42-44). There is both direct (45, 46) and indirect (47, 48) evidence that children born to PCOS mothers are exposed to excess androgens. Direct measurements of fetal androgens have been reported in term umbilical cord blood. Some studies found increased levels of T (46) and androstenedione (49, 50) in PCOS offspring, while others did not (51, 52). Term umbilical vein DHT and androstenedione levels in 36 PCOS-offspring correlated positively with maternal levels (53). Umbilical cord androgens at birth, however, do not necessarily reflect fetal androgen exposure at mid-pregnancy, when high androgen levels strongly influence offspring

developmental programming (54). Increased mid-pregnancy amniotic fluid levels of T were detected in women with PCOS, and their female offspring (PCOS-d) had greater 2:4 digit ratios – a biomarker of intrauterine andr(55)ogen excess (45). Increased ano-genital distance and sebum production in newborn girls – other reliable biomarkers of androgen exposure in utero – are reported in PCOS-d. These postnatal biomarkers indicate increased risk of developing PCOS or other androgen-related disorders (47, 48).

At birth

Intrauterine growth plays an important role for long-term development and health (24). Birth anthropometrics might provide indications of the intrauterine environment, as well as the present and future health of the offspring (56, 57). Intrauterine fetal growth restriction has been associated with type 2 diabetes (T2D) and cardiovascular diseases (24, 57, 58), while large fetal size is associated with increased risk of cancer, obesity and glucose intolerance (59). Both lower, similar and increased gestational growth is reported for PCOS-off compared to control offspring (control-off).

A meta-analysis by Qin of 17 studies, found increased risk for lower birth weight in PCOS-off (17). In contrast, a more recent meta-analysis (16) found no association of either small for gestational age (SGA) or large for gestational age (LGA**)** newborns with PCOS pregnancies. Adjustments for maternal BMI, gestational weight gain and gestational age, however, were not performed. In sub-group analyses on overweight and obese mothers, nevertheless, significantly more SGA babies were born to PCOS compared to non-PCOS women (16). In contrast, a large Australian age-matched, case-control register study reporting lower birth weight and higher rate of SGA in PCOS-off compared to control-off (60) lost statistical significance when adjustments were made for gestational age and pregnancy risk factors. Two studies with matched/similar maternal pre-gestational BMI, showed lower birth weight and /or more SGA in PCOS-off (61, 62) while one study reported on similar birth weight (51)

In a national registry study in Sweden, women with PCOS gave birth to more LGA babies than those without a PCOS diagnosis. Only 0.3 % in this population, however, were identified as PCOS (13), suggesting insufficient diagnosis of PCOS in this study population. One Danish cohort study registered birth anthropometrics in more detail (12). They found no difference in birthweight, ponderal index and abdominal circumference between PCOS-off and control-off (adjusted for maternal age, BMI, parity, smoking and gestational age and gender) (12).

A Norwegian RCT study reported similar birth weight z-score in PCOS-off as in a national reference population adjusted for gestational age and gender. Shorter newborn length z-score, however, was found in the same study indicating fatter newborns born to women with PCOS (63). Interestingly, another study reported higher leptin concentrations in term cord blood of PCOS-off, commonly indicative of increased adiposity (50). Higher stillbirths and perinatal mortality (16, 60, 64), more congenital anomalies and lower Apgar scores (60, 65), more admission to neonatal intensive care unit (17, 60, 64) and more hospitalization (65) are found in PCOS-off. Table 1 summarizes study outcomes.

Reflections

Most studies report on slightly lower or comparable birth weight or SGA rates in PCOS-off. Data are scarce on body composition of newborns, which would be more informative in the view of long-term health. There is considerable variation in pre-pregnancy maternal BMI, but statistical adjustments for gestational weight gain and gestational age are not always made. Selection of subjects and ethnic diversity may also explain some of the contradictory results. Scandinavian (12, 63) and Dutch (51) studies tend to show normal birth weights in PCOS-off, while Chilean (62) and Iranian (61) studies report lower birth weights.

Offspring birthweight increases with increasing maternal pre-pregnant BMI (66). Higher birth weight and increased numbers of LGA babies would be expected from PCOS mothers as they are more overweight, gain more weight in pregnancy and have 3.5-fold increase of GDM (17). A "hidden" growth restriction and altered body composition may be present in newborns of some PCOS women, despite seemingly normal birth weight. Birth weight, however, is a poor surrogate marker for suboptimal intrauterine environment or fetal growth restriction, as it does not reveal fat/lean body mass ratio or body composition. Randomized controlled studies are lacking on optimal maternal nutrition and weight gain through pregnancy for women with PCOS. Future studies should monitor intrauterine growth and fetal circulation, and measure body composition, to shed light on the potential mechanisms and effects of interventions on fetal anthropometry and wellbeing. Systematic registration of clinical signs of intrauterine androgen impact on female fetuses, such as ano-genital distance and increased sebum production, would help to disentangle the role of intrauterine androgens from other potential factors influencing growth and development in humans. In these regards, nonhuman primate models for PCOS, including females with naturally occurring PCOS-like traits (67), as well as females with fetal (34) or peripubertal (68) T induction of PCOS-like traits, could provide viable models for mechanistic studies exploring genetic and epigenetic contributions.

Childhood – pre-puberty

Growth

In childhood, BMI predicts the presence of cardio-metabolic risk factors and is associated with morbidity later in life (69-72). High BMI tends to persist into adolescence and adulthood, and the risk of persistent high BMI increases with age (73). While waist-circumference and waist-to-height ratio are measures of central adiposity, and are highly correlated to BMI, they predict cardio-metabolic risk factors independently of BMI, and appear to provide additional BMI-related cardio-metabolic risk (74-76) .

Few studies report on PCOS-off anthropometric measurements after birth. No meta-analyses have been performed. A Danish, prospective cohort study showed higher BMI in PCOS-off at 3 years of age and faster catch-up growth in PCOS-off (12). The study included a broad spectrum of PCOS phenotypes. Both maternal PCOS status and obesity increased the risk of childhood obesity. A recent, population-based, prospective cohort study from the US, found no difference in growth at 3 years of age; PCOS-off had similar length, weight and BMI z-scores as control-off in fully adjusted models (77). No evidence for catch-up growth or increased obesity was found. In a Norwegian study, PCOS-off tended to increase more in weight and length during the first 6 months of life compared to a gender-adjusted national reference population. BMI z-score, however, did not differ from the reference population at any age up to 4 years (78). At 8-years of age, while the same cohort still maintained population-typical BMI, height and weight, they exhibited higher waist-to-height ratio and waist circumference, indicating centralized fat accumulation in PCOS-off (79).

Cardiometabolic risk and endocrine status

A very recent Dutch study observed subtle, but distinct, cardiovascular and metabolic abnormalities in pre-pubertal PCOS-off, comprising early arterial stiffness, left ventricular dilatation, as well as higher carotid intima thickness, triglycerides and LDL (80).

Indices of altered glucose metabolism, exemplified by higher basal glucose and/or insulin levels, have also been observed in PCOS-off in childhood (81-83). Early metabolic derangements measured as lower adiponectin in pre-pubertal PCOS-off are reported from a population of Spanish descent in Chile (83).

Exacerbated adrenarche was seen in 30% of Chilean PCOS-off compared to control-off (82).

Larger ovarian volumes and increased numbers of small-sized antral follicles were reported in pre-pubertal PCOS-d (84), with correspondingly increased AMH levels highly suggestive of

PCOS-like ovarian morphology in pre-pubertal PCOS-d (85). Table 2 summarizes the studies on maternal PCOS effects during childhood.

Reflections

Childhood catch-up growth, increased BMI and abdominal fat accumulation are all potential markers of cardio-metabolic risk factors, and all are found in PCOS-off. Already early in life, more direct markers of atherosclerosis and dyslipidemia, which are associated with later increased risk of CVD, deteriorate with increasing age. On the other hand, one study describes no difference in anthropometrics exhibited by PCOS-off compared to controls (86). Considered together, subtle changes in BMI, fat distribution and markers of atherosclerosis and hyperlipidemia in early childhood may reliably predict increased risk for subsequent metabolic and cardio-vascular ill health in PCOS-off. Inconsistency in PCOS-off childhood presentation may reflect differences in study design, selection of subjects and ethnicity. Importantly, it is still unclear whether the metabolic risk factors in PCOS are also transformed to higher cardiovascular morbidity and mortality.

Peri-pubertal girls

A US case-control study found no difference in BMI, body composition, ovarian volume or sex steroids and salivary insulin levels in peri-pubertal PCOS-d vs. control-d (87). Except for a more android fat distribution and more hirsutism in late puberty, transition through puberty was comparable between PCOS-d and control-d in non-Hispanic, Caucasian girls (87). Two studies found comparable waist-to-hip ratios between PCOS-d and control-d (82, 88).

Insulin has the potential to enhance ovarian follicular development by increasing the numbers of granulosa cells per follicle, by stimulating granulosa cells to produce more AMH (89, 90), or by enhancing steroidogenesis (91). Accordingly, higher ovarian volumes, and higher levels of AMH, T and 2-h insulin, are all present in peri-pubertal PCOS-d, indicating larger cohorts of growing follicles (polyfollicular ovaries) (89). Ovarian volume and AMH levels remain high during progressive Tanner stages of pubertal development in PCOS-off suggesting polyfollicular development and ovarian dysfunction from early childhood (92), not surprisingly producing positive associations between levels of AMH and both ovarian dysfunction and metabolic derangement (92). Decreased insulin sensitivity and increased T levels were measured in the same group of PCOS-d, pointing to a higher risk of developing PCOS later in life (92). In late puberty, PCOS-d were more obese, hirsute and had more frequent menstrual irregularities, higher T and free androgen index FAI (87). (85). (85). Table 2 summarizes the studies on maternal PCOS-effects during peri-puberty.

Reflections

The existing studies on PCOS-d are heterogeneous in selection of participants, design and measured variables. It is difficult to determine whether inconsistencies in potential pre-PCOS presentations are due to selection bias, ethic variations or both. PCOS phenotype and BMI of the mother may potentially influence pre-pubertal ovarian function of their daughters, leading to larger ovaries, more growing follicles and higher circulating AMH levels. PCOS-d from a Chilean cohort seem to have a more perturbed pubertal development compared to PCOS-d from a US-study. In both cohorts, however, PCOS-d displayed more central fat distribution and more signs of hyperandrogenism than control-d. Whether specific subgroups of maternal PCOS phenotype or ethnic differences result in more strident pre-PCOS presentation in PCOS-d needs to be determined.

Boys

Metabolic and reproductive features are reported for a Chilean cohort of sons born to women with PCOS (PCOS-s) compared to age-matched control sons (control-s) (93, 94). From early childhood to adulthood, PCOS-s exhibit higher BMI and waist circumference, as well as increased total cholesterol and LDL levels. The PCOS-s associated differences in waist circumference, total cholesterol and LDL levels disappeared, however, when adjusted for BMI. Insulin resistance became evident in PCOS-s with increasing age and did not disappear after adjustment for BMI in adulthood (94). It is debatable whether statistically adjusting for BMI is biologically appropriate, as increased BMI may be an effect of being born to a woman with PCOS. In a Norwegian study, PCOS-s had similar weight and BMI z-scores, but higher waist-to-height ratio z-scores, compared to a national age and gender adjusted reference population, indicating more abdominal fat accumulation in PCOS-s (79).

One study has reported increased AMH levels in childhood, suggesting increased Sertoli cell number or activity among PCOS-s. Pubertal down-regulation of AMH occurred normally without affecting Leydig cell differentiation. In adulthood, PCOS-s had smaller testicle volumes, but similar semen production (93).

Reflections

PCOS-s were overweight, exhibiting central adiposity and increased markers for CVD risk. Pubertal development in PCOS-s seems unaffected. The fertility status of PCOS-s, however, is unknown.

Adults

There are few long-term, follow-up clinical studies on PCOS-off reaching adult age (93). A large Australian data linkage study on 3,626 PCOS-off and 35,340 age matched control-off found increased risk of endocrine and metabolic disorders, psychological development disorder, respiratory tract diseases including asthma, musculoskeletal and connective tissue diseases in fully adjusted models (60).

Neurodevelopmental outcomes

Autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD) have recently gained much attention related to PCOS. Both conditions are sexually dimorphic, male-skewed, neurodevelopmental disorders. Male-female ratios of 3:1 -16:1 are reported for ASD, and 3:1 ratio for ADHD (95).

Studies on T in amniotic fluid suggest a link between prenatal androgen exposure and autistic traits (96, 97). Several (96-99), but not all (100), studies support the hypothesis that early exposure to T may modify brain development and mediate increased risk for ASD. Elevated amniotic fluid T and androstenedione levels were found in children who later developed autistic traits (100) As women with PCOS have increased circulating levels of T in pregnancy and may provide a hyperandrogenic environment for their fetuses (47, 48) , the focus on the neurodevelopmental health of their offspring has increased. In a nonhuman primate model for PCOS, fetal T exposure altered socio-sexual behavior in pre-pubertal and adult, PCOS-like female offspring (101) and diminished social interactions in adult, T-exposed male offspring (102).

In a small, case-control study of selected hyperandrogenic mothers with PCOS, PCOS-d had higher scores for Autism-Spectrum Quotient (AQ-C), lower Empathy Quotient (EQ-C) scores and higher Systemizing Quotient (SQ-C) scores compared to daughters of healthy mothers (45) . Amniotic T levels correlated significantly to AQ-C, EQ-C and SQ-C. None of the PCOS-d, however, were given an ASD diagnosis (45).

Maternal PCOS diagnosis increased the risk of ASD, by 60% in adjusted models, in both PCOS-s and PCOS-d, aged 4-17 years, in a large, population based, nationwide, matched, case-control study from Sweden. The risk was twofold increased if the mothers with PCOS were obese (103). The weakness of this study is that only 0.7% of the population was identified having PCOS, probably representing the "worst cases". These findings were supported by a large, matched, case-control study conducted in the UK (104). The first-born

offspring of mothers with PCOS had 35% increased odds of ASD, after adjustments for maternal metabolic and psychiatric comorbidities.

ADHD is the most common psychiatric disorder in childhood, affecting 4-14% (105, 106), three times more common in boys than in girls (107). A 50% increased prevalence of ADHD is identified among adult women with PCOS in a large nationwide Swedish registry study (108). Relationships between prenatal hormones and ADHD are not established. A large population-based data registry study from Sweden showed that PCOS-off had a 40% increased risk of ADHD after adjustment for confounders. The risk increased with worsening maternal cardio-metabolic features. If PCOS mothers were obese and had metabolic syndrome, the risk of ADHD in offspring increased to nearly 3-fold (109). (85). Table 3 summarizes the studies on maternal PCOS-effects on neurodevelopment.

Development

A large prospective, population based, cohort study in the US explored the relationship between maternal PCOS diagnosis and fine motor, gross motor, communication, personal-social, problem solving abilities with the Ages and Stages Questionnaire (ASQ)(86) . Maternal PCOS diagnosis was associated with higher risk of delayed development at the age of 3 years, affecting all domains in early childhood (86). PCOS-d were more affected than PCOS-s. Interestingly, PCOS mothers in this study had higher education, and lower alcohol consumption and smoking in pregnancy, but were more obese. Hyperinsulinemia, insulin resistance and obesity are overlapping features with PCOS, and are associated with developmental delays (110). PCOS, however, seems to be an independent factor in ASQ-failure after adjustment for BMI and GDM (86).

Reflections

Both clinical and registry studies indicate increased risk of delayed and adverse development of ASD and ADHD among PCOS offspring. It is important to underline that overall risk for autism among offspring of women with PCOS is rare, thus, such risk should not be overestimated. Obesity, insulin resistance and hyperinsulinemia may further increase the prevalence and aggravate the presentation of neurodevelopmental disturbances, by either increased hyperandrogenism or other mechanisms. Encouragement of lifestyle changes, weight reduction before pregnancy and adherence to weight gain guidelines may potentially improve neurodevelopment in children of obese women with PCOS. Focused attention to identify and support PCOS-off with developmental delay, ASD and ADHD is important.

Treatment effects

Diet and lifestyle interventions, metformin and inositol are possible treatments for PCOS during pregnancy. The potential effects of these treatments on offspring health have only been investigated for metformin. A non-randomized, US study revealed no deviation in growth until 18 months of age for metformin exposed children compared to gender specific normative data (111). A pooled individual patient data (IPD) analysis of in all 790 PCOS pregnancies from three RCTs, the pilot, the PregMet and the PregMet2-studies, were performed (112). The three RCTs compared metformin (1.7g or 2 g daily) to placebo from first trimester to delivery. The IPD showed that metformin treatment resulted in fewer late miscarriages and preterm births, less maternal weight gain, similar birth weight, birth length, and frequencies of SGA and LGA newborns, together with larger head circumference (112). Follow-up data from 25 children from the first RCT, the pilot study, revealed no difference in growth or body composition between metformin and placebo exposed children at 8-years of age (113). In a questionnaire-based follow-up at 1-year of age of 197 children from the second RCT (the PregMet study), children exposed to metformin were heavier than children in the placebo group (114). In a follow-up study of 182 children from the pilot and the PregMet-studies, metformin exposed children had higher BMI from 6 months to 4 years of age (78). At 8-years of age, metformin exposed PCOS-off from the PregMet study had higher BMI z-score, waist circumference z-score and waist-to-height ratio, and prevalence of obesity compared to placebo exposed children (79). Metformin *in utero* thus further increases the risk of inferior cardio-metabolic health in PCOS-off beyond that induced by PCOS, alone.

Conclusions

Maternal PCOS status negatively affects offspring health. At times, however, it is difficult to determine the impact of maternal PCOS status, alone, from synergistic or counteracting factors on offspring health, including obesity, pre-pregnancy metabolic status, pre-existing co-morbidity, weight gain in pregnancy, pregnancy complications and postnatal nutrition and lifestyle.

PCOS-off have an increased risk for both absolute and relative intrauterine growth restriction with subsequent abdominal fat accumulation, with or without excess weight gain. There are indications, in some populations of PCOS-d, for perturbed peri-pubertal development. Early risk markers of cardiovascular diseases are also reported. PCOS-s are more obese and exhibit a centralized fat distribution, as well as insulin resistance in adult age, indicating increased impaired glucose metabolism. Research data are more congruent on the neurodevelopment of

PCOS-off. Both clinical and register studies indicate increased risk of ASD, ADHD and delayed neurodevelopment in PCOS-off. Concurrent maternal obesity and inferior metabolic health additionally increased this risk. There is a need for large prospective clinical studies with a multi-ethnic and multidisciplinary approach to survey the impact of maternal PCOS status on their offspring. Well-designed, appropriately sized RCTs should clarify the effect of diet and lifestyle interventions to optimize pre-pregnancy interventions, pregnancy care and follow-up of the offspring.

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