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Maternal polycystic ovarian syndrome and offspring growth: The Upstate KIDS Study

Griffith A. Bell, PhD[1], **Rajeshwari Sundaram, PhD**[1], **Sunni L. Mumford, PhD**[1], **Hyojun Park, PhD**[1], **Miranda Broadney, MD**[1], **James Mills, MD, MS**[1], **Erin M. Bell, PhD**[2], **Edwina H Yeung, PhD**[1]

[1]Epidemiology Branch, Division of Intramural Population Health Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

[2]Department of Environmental Health Services, University at Albany, State University of New York, Albany, NY

Abstract

Background: Polycystic ovarian syndrome (PCOS) is the most common cause of female infertility, and is associated with higher levels of circulating androgens. Exposure to higher levels of androgens in utero may be a risk factor for obesity among children of women with PCOS.

Methods: We examined whether maternal PCOS was associated with differences in offspring growth and obesity in the Upstate KIDS study, a prospective cohort study of infants born in New York State (excluding New York City) oversampled for fertility treatments and multiple births. Measurements of offspring length/height and weight were recorded at doctor's visits through three years of age. PCOS diagnosis was self-reported by mothers at baseline. We used linear mixed models with robust standard errors to estimate differences in growth by maternal PCOS exposure. We used logistic regression to examine whether infants experienced rapid weight gain at 4, 9, and 12 months. Growth measures were reported by 4,098 mothers for 4,949 children (1745 twins). Of these, 435 mothers (10.6%) had a diagnosis of PCOS.

Results: Compared to children born to mothers without PCOS, children of mothers with PCOS did not have significant differences in weights (4.81g; 95% CI: −95.1, 104.7), lengths/heights (0.18cm; 95% CI: −0.16, 0.52), and BMIs (−0.14kg/m^2; 95% CI: −0.30, 0.01) through 3 years of age. We also observed no association between maternal PCOS and offspring rapid weight gain.

Conclusions: Overall, we found little evidence to suggest that maternal PCOS influences early childhood growth in this large, prospective cohort study.

Keywords

PCOS; growth; diabetes; cohort

Correspondence to: Edwina Yeung, 6710B Rockledge Dr, MSC 7004, Bethesda, MD 20817, USA, 301-435-6921, yeungedw@mail.nih.gov.

BACKGROUND

Polycystic ovarian syndrome (PCOS) is the most common cause of female infertility.[1] Approximately 6-15% of women in the United States have PCOS.[2] PCOS is a complex syndrome with several characteristic features, including obesity, insulin resistance, hyperandrogenemia and ovarian cysts. Mothers with PCOS are at increased risk of gestational diabetes, hypertension, endothelial dysfunction, and preeclampsia, which can alter the fetal endocrine environment, leading to adverse outcomes in offspring,[2] such as low birth weight, metabolic derangements, congenital abnormalities, and perinatal mortality.[3]

While relationships between maternal PCOS and birth outcomes have been well-studied, few studies have examined whether maternal PCOS has effects on early childhood growth, and results of these studies are mixed.[2–4] One small study of boys born to mothers with PCOS reported higher body weight in infancy and childhood compared to boys born to mothers without PCOS.[5] A study of girls born to mothers with PCOS which paid particular attention to PCOS phenotyping using NIH criteria in cases and controls found no difference in body size in adolescence compared to offspring born to mothers without PCOS.[6] Most studies relied on only one measurement of growth, and were smaller in size ($n<300$).[7, 8] Other studies have found that offspring were more likely to be born small for gestational age (SGA), and children born SGA are often at higher risk of smaller stature in childhood and adolescence.[7, 9, 10] Animal studies have suggested PCOS exposure is associated with heavier offspring potentially due to insulin resistance and related *in utero* hyperglycemia exposure.[2, 11] No large cohort studies have examined whether young children born to mothers with PCOS show differences in growth compared to young children born to mothers without PCOS.

METHODS

We used data from the Upstate KIDS study, a population-based, prospective cohort study of children born 2008-10 in New York State (excluding New York City)[12]. Briefly, the study aimed to examine the effects of infertility treatment on child health outcomes[12]. Eligible children were identified using the New York State livebirth registry. All singletons whose birth certificates indicated they were conceived using fertility treatments and all multiple births, regardless of conception method, were recruited. Singleton children not conceived using infertility treatments were frequency matched to singletons who were conceived using treatments by region of residence using a 3:1 ratio. Data from mothers and their children were included if the mothers reported PCOS status and the children had at least one growth measurement. In total, 5,034 mothers enrolled with their 6,171 children. Children with at least one growth measurement were included for analysis.

Exposure measurement

Mothers completed a baseline questionnaire at 4 months post-pregnancy which included questions about demographic, gynecologic and reproductive health, diet and lifestyle factors regarding the pregnancy, and child(ren) enrolled in the study. Mothers were asked whether a

doctor or health care provider had ever diagnosed them with PCOS. Women with PCOS but without provider diagnosis could not be ascertained, however.

Outcome measurement

Mothers were given child health journals in their study invitation packets, and were encouraged to use them to record weight and length/height as measured at visits with healthcare providers through three years of age. Questionnaires were sent to mothers every 4-6 months that included questionnaires to capture growth data recorded in the journals. Questionnaires featured a grid that allowed mothers to record multiple growth entries at different points in time as the child aged. Entries in which a child's length decreased by more than 1 cm from the previous measurement were excluded. Height and weight were standardized using z-scores based on World Health Organization Child Growth Standards. We also examined whether infants had rapid weight gain at the 4, 9, and 12-month time periods. Rapid weight gain was assessed by examining the observed differences in weight between the 4, 9, and 12-month periods and comparing them to predicted differences at those periods. Briefly, predicted standard deviation scores (SDS) were generated using an individual child's change in weight over time, and those scores were compared to children in the rest of the sample. If a child's SDS was above 0.5 in the 4 or 9-month period, or above 0.67 for the 12-month period, they were classified as having rapid weight gain.[13]

Statistical analyses

We generated descriptive statistics of demographic and biological characteristics for participants with and without PCOS. We used generalized linear mixed models to explore the differences between self-report of maternal PCOS and growth parameters in offspring up to 36 months of age. All models used an infant-level random intercept to account for repeated measures of growth over time, and a maternal-level intercept to account for multiple births. We also examined whether offspring experienced rapid weight gain or growth in the 4, 9, or 12-month periods using logistic regression. Sampling weights were applied to all models to account for oversampling of twins and infants conceived by fertility treatment.

The following covariates from birth certificates and maternal self-report were used: maternal age at delivery, race/ethnicity, highest achieved educational level, marital status, health insurance status, plurality, maternal smoking during pregnancy (yes/no), alcohol consumption during pregnancy (yes/no), history of infertility treatment, pre-pregnancy diabetes, and pre-pregnancy BMI. Missing covariate data (but not outcome data) was imputed using Markov chain Monte Carlo multiple imputation. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Of 5,034 mothers enrolled in the study, 4,438 reported at least one measurement of growth for the enrolled child and of those, 4,098 also reported PCOS status. Mothers with PCOS were more likely to be better educated, overweight or obese, used infertility treatment, have pre-pregnancy diabetes, and have private insurance compared to mothers without PCOS

(Table 1). Mothers with PCOS were also less likely to smoke or drink alcohol while pregnant compared to mothers without PCOS.

Offspring of mothers with PCOS were not significantly different in size compared to offspring of mothers without PCOS. In fully adjusted analyses (Table 2), these children had nonsignificant differences in weight (4.81g, 95% Confidence Interval(CI): −95.09, 104.71), length (0.18cm, 95% CI: −0.16, 0.52), and BMI (−0.14kg/m^2, 95% CI: −0.30, 0.01). Use of weight, length, and BMI measures standardized using z-scores also showed no difference. When examining singletons and twins separately or by infant gender, we also observed no differences in weight, length, or BMI. We also observed no difference by gender (not shown). In our analysis of rapid weight gain, we found no evidence of differences by maternal PCOS status after adjustment for confounders (Supplemental Material), among all children or when examining singletons and twins separately. In an analysis stratified by fertility treatment, we observed only slight differences that did not change our results (Supplemental Material). In all, we found no significant evidence that children born to mothers with PCOS had higher odds of rapid weight gain compared to children born to mothers without PCOS in this time window.

DICSUSSION

We found little evidence that being born to mothers with PCOS was associated with differences in weight, length/height or BMI in the first 36 months of life. We also did not observe an association when examining associations within singletons and twins separately. We found little evidence of an association between maternal PCOS and rapid weight gain.

This is the first report examining maternal PCOS and early childhood growth from a large, prospective cohort study. Our study confirms results of studies reporting no associations between maternal PCOS and offspring growth in adolescents and those whose mothers were prescribed medication for PCOS.[6, 7, 14] Treatment with medication may have reduced the PCOS-related hyperandrogenic and insulin resistance-associated exposures in utero. Information on specific medications mothers with PCOS may have used before or during pregnancy was unavailable in our study, but use of treatment for PCOS may contribute to our finding of no association. A study of dizygotic twins found no differences in growth between opposite-sex and same-sex twins in utero, suggesting that exposure to androgens in utero had little impact on height and BMI in adulthood.[15] Exposure to higher levels of circulating androgens in utero have been associated with greater body weight gain in infantile development in some animal studies, however[2]. A study reporting differences in BMI among boys by PCOS exposure was small in size (n=136) and did not adjust for confounding, which may have biased the results[5].

Methodological strengths and limitations of this study should be considered. This was a large, population-based prospective cohort study with repeated measurements of child growth and detailed measurement of confounders. PCOS status was measured by self-report prior to measurement of growth outcomes, so growth measures could not have influenced PCOS reporting. Questionnaires were not able to distinguish between different PCOS phenotypes however, which may be relevant to child growth impact. As there can be a long

delay between symptom presentation and diagnosis in PCOS, women who did not undergo fertility treatment may have a larger proportion of undiagnosed PCOS, which may bias estimates towards the null. It is possible that mothers with lower SES may be underdiagnosed for PCOS. If misclassification occurred by SES, this may falsely lower estimates of growth among children of mothers without PCOS. Hence, we cannot rule out missing potentially small effects. Weight and length/height may be measured inaccurately, however we are unaware of data suggesting reporting of size would systematically vary by PCOS status in such a way that would bias our findings.

In conclusion, we found that children born to mothers with PCOS grew similarly compared to children born to mothers without PCOS. PCOS can be heritable and affect adult weight and metabolic function, however we did not find evidence that growth was programmed *in utero* and measurable in children born to mothers with PCOS[2].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is already known on this subject?

Polycystic ovarian syndrome (PCOS) is the most common cause of infertility, and is associated with higher levels of androgens in women. Studies of hyperandrogenic mothers have shown increased risk of adverse birth outcomes in offspring, however few studies have examined whether exposure to maternal PCOS in utero is associated with differences in early childhood growth.

What does this study add?

In this population-based, longitudinal birth cohort study of mothers and their offspring in New York State, we saw little evidence of differences early childhood growth by maternal PCOS status. This is reassuring for mothers with PCOS and their families.

Table I.

Descriptive characteristics of mothers and their children by maternal polycystic ovarian syndrome (PCOS) status, Upstate KIDS Study

	Total		Polycystic ovarian syndrome			
			No		Yes	
Maternal characteristics						
Total mothers: n (%)	4,098	100	3,663	89.4	435	10.6
Maternal age at delivery, years: Mean (SD)	30.8	5.9	30.71	6.0	31.2	4.6
Maternal race (White): n (%)	3,405	83.9	3,032	82.8	373	858
Maternal education: n (%)						
High school or less	622	15.2	586	16.0	36	8.3
High school - Some college	1,250	30.5	1,106	30.2	144	33.1
Beyond some college	2,226	54.3	1,971	53.8	255	58.6
Marital status (Married): n (%)	3,678	89.8	3,262	89.1	416	95.6
Prepregnancy BMI: n (%)						
Underweight (<18.5)	98	2.40	93	2.5	5	1.20
Normal weight (18.5 – 25)	1,883	46.0	1,759	48.0	124	28.5
Overweight (25 – 30)	1,037	25.3	944	25.8	93	21.4
Obese (>30)	1,080	26.4	867	23.7	213	49.0
Smoking during pregnancy: n (%)	527	12.9	490	13.4	37	8.5
Drinking during pregnancy: n (%)	525	12.8	481	13.1	44	10.1
Infertility treatment: n (%)	1,289	31.5	976	26.6	313	72.0
Prepregnancy diabetes: n (%)	47	1.1	31	0.90	16	3.7
Private insurance: n (%)	3,193	77.9	2,801	76.5	392	90.1
Offspring characteristics						
Total infants: n (%)	4,949	100	4,406	n/a	543	n/a
Infant sex: n (%)						
Male	2,527	51.1	2,247	51.0	280	51.6
Female	2,422	48.9	2,159	49.0	263	48.4
Gestational age, weeks: Mean (SD)	37.7	2.6	37.8	2.6	37.3	2.8
Fertility treatment: n (%)	1,660	33.5	1,252	28.4	408	75.1
Plurality: n (%)						
Singleton	3,204	64.7	2,880	65.4	324	59.7
Twin[1]	1,745	35.3	1,526	34.6	219	40.3

[1] N=43 twins where only 1 of a pair included (N=3 with PCOS).

Table II.

Difference in growth measures from birth through 3 years of age comparing offspring of mothers with PCOS to offspring of mothers without PCOS in the Upstate KIDS Study

	Unadjusted				Fully adjusted			
		Lower	Upper			Lower	Upper	
	Beta	95% CI	95% CI	p-value	Beta	95% CI	95% CI	p-value
All children (n=4,098)								
Weight (g)	119.79	−48.07	287.64	0.16	4.81	−95.09	104.71	0.92
Weight for age (z-score)	−0.09	−0.19	0.02	0.10	−0.06	−0.15	0.04	0.24
Length (cm)	0.94	0.26	1.63	0.01	0.18	−0.16	0.52	0.30
Length for age (z-score)	−0.02	−0.16	0.12	0.78	0.04	−0.08	0.16	0.48
BMI (kg/m^2)	−0.16	−0.32	0.00	0.05	−0.14	−0.30	0.01	0.07
BMI (z-score)	−0.12	−0.23	−0.02	0.02	−0.09	−0.19	0.01	0.08
Singletons (n=3,204)								
Weight (g)	186.11	−71.79	444.02	0.16	2.96	−128.03	133.94	0.96
Weight for age (z-score)	−0.01	−0.13	0.11	0.86	−0.08	−0.20	0.05	0.22
Length (cm)	1.20	0.26	2.14	0.01	0.26	−0.18	0.71	0.25
Length for age (z-score)	0.13	−0.03	0.29	0.11	0.07	−0.09	0.23	0.41
BMI (kg/m^2)	−0.07	−0.27	0.14	0.53	−0.18	−0.38	0.02	0.07
BMI (z-score)	−0.08	−0.20	0.05	0.25	−0.13	−0.26	0.00	0.06
Twins (n=894)								
Weight (g)	224.14	−35.74	484.02	0.09	−3.07	−119.72	113.57	0.96
Weight for age (z-score)	0.05	−0.09	0.18	0.48	−0.05	−0.18	0.07	0.41
Length (cm)	0.84	−0.24	1.93	0.13	−0.05	−0.43	0.34	0.81
Length for age (z-score)	0.06	−0.13	0.25	0.55	−0.02	−0.19	0.15	0.80
BMI (kg/m^2)	−0.03	−0.29	0.23	0.83	−0.08	−0.31	0.15	0.49
BMI (z-score)	0.00	−0.17	0.16	0.97	−0.04	−0.19	0.11	0.58

Fully adjusted model adjusted for maternal age, maternal body mass index, age at exam, race/ethnicity, marital status, private insurance, education, smoking during pregnancy, drinking during pregnancy, any diabetes, and plurality