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Maternal polycystic ovarian syndrome and early offspring development

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STUDY QUESTION: Is maternal polycystic ovarian syndrome (PCOS) associated with developmental delays in offspring?

SUMMARY ANSWER: Offspring of mothers with PCOS were at higher risk of failure on the Ages and Stages Questionnaire (ASQ).

WHAT IS KNOWN ALREADY: There is growing evidence that offspring of mothers with PCOS may be at higher risk for developmental disorders due to potential exposure to hyperandrogenism and insulin resistance. Few studies exist regarding maternal PCOS and early childhood development in the USA.

STUDY DESIGN, SIZE, DURATION: The Upstate KIDS Study is a population-based prospective cohort study of infants born between 2008 and 2010 in New York State (excluding New York City), originally designed to study—and finding no impact of—infertility treatment exposure on child development. Children were followed up to 36 months of age. In all, 4453 mothers completed one or more developmental screening instruments for 5388 children (35.5% twins) up to 36 months of age.

PARTICIPANTS/MATERIALS, SETTING, METHODS: In our study, 458 mothers (10.3%) reported a healthcare provider's diagnosis of PCOS, as well as the related treatment received, on the baseline study questionnaire. Parents completed the ASQ on their child's development at 4, 8, 12, 18, 24, 30 and 36 months of age to assess fine motor, gross motor, communication, personal–social functioning and problem-solving cognitive domains. We used generalized linear mixed models to estimate odds ratios (OR) between PCOS diagnosis and failures in the ASQ adjusted for maternal age, race, BMI, education, marital status, smoking, alcohol consumption, diabetes, insurance and plurality.

MAIN RESULTS AND THE ROLE OF CHANCE: Diagnosis of PCOS was associated with increased risk of the offspring failing the fine motor domain (adjusted odds ratio (aOR) = 1.77; 95% CI: 1.09, 2.89), largely driven by higher risk in female singletons (aOR = 2.23; 1.16, 4.29). Twins of mothers with PCOS had higher risk of failing the communication (aOR = 1.94; 1.19, 3.18) and personal–social functioning (aOR = 1.76; 1.12, 2.77) domains compared to twins born to mothers without PCOS. Compared to offspring of women without PCOS, offspring of women who reported receiving no treatment for their PCOS had a stronger association with failing the ASQ (aOR = 1.68; 0.95, 2.75) than the association among offspring of women who reported PCOS treatment (aOR = 1.16; 0.79, 1.73).

LIMITATIONS, REASONS FOR CAUTION: Further study is needed to confirm the role of maternal PCOS in early offspring development with provider-validated diagnosis of PCOS.

WIDER IMPLICATIONS OF THE FINDINGS: If confirmed, these findings suggest that offspring of women with PCOS may be at increased risk for developmental delay.

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Introduction

Polycystic ovarian syndrome (PCOS) is the most common cause of infertility among women, with a prevalence ranging from 5 to 15% depending on diagnostic criteria (Kosidou *et al.*, 2016). PCOS is characterized by hyperandrogenism (elevated levels of circulating androgen hormone in women), presence of polycystic ovaries and menstrual irregularities (Fauser *et al.*, 2012; Palomba *et al.*, 2012; Conway *et al.*, 2014; Doherty *et al.*, 2015; Dumesic *et al.*, 2015; Joham *et al.*, 2016; Sirmans and Pate, 2013). The etiology of PCOS is not well understood. PCOS is thought to be a strongly heritable disorder, with studies in twins indicating genetic factors may account for up to 70% of cases (Legro *et al.*, 1998; Vink *et al.*, 2006; Dumesic *et al.*, 2015). Women with PCOS may be at higher risk for metabolic syndrome, type 2 diabetes mellitus and cardiovascular disease (Dokras *et al.*, 2012; Fauser *et al.*, 2012; Dumesic *et al.*, 2015; Sirmans and Pate, 2013). Although PCOS is commonly diagnosed during adolescence, it is also frequently diagnosed following weight gain or fertility complications (Dumesic *et al.*, 2015). Clinical presentation of PCOS is heterogeneous, although it commonly includes menstrual dysfunction, obesity and hirsutism as well as other manifestations of hyperandrogenism (Dumesic *et al.*, 2015). Growing evidence from human and animal studies suggests that exposure to prenatal androgens *in utero* is associated with increased risk of developmental abnormalities (Manson, 2008; Auyeung *et al.*, 2009, 2010; Hines, 2011; Hu *et al.*, 2015; Kosidou *et al.*, 2015, 2016). Indeed, maternal diagnosis of PCOS and/or elevated fetal testosterone has been linked to pervasive developmental disabilities, autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) (Boomsma *et al.*, 2006; Auyeung *et al.*, 2009, 2010; Palomba *et al.*, 2010; Doherty *et al.*, 2015; Kosidou *et al.*, 2015, 2016; Palomba and La Sala, 2016; Puttabyatappa *et al.*, 2016). While a few studies have examined the relationship between maternal PCOS and offspring development, none have done so in a large, prospective birth cohort study in the USA, or explored this relationship among large populations of twins, who are particularly at risk for perinatal and developmental complications (Buck Louis *et al.*, 2014). Using a population-based US sampling framework, our study objective was to explore the relationship between maternal PCOS and development in offspring through 3 years of age (Buck Louis *et al.*, 2014).

Materials and Methods

Study setting and participants

The Upstate KIDS study is a population-based, prospective cohort of children born in New York State (excluding New York City) between July 2008 and May 2010, and was designed to study the effects of infertility treatment on child growth and development (Buck Louis *et al.*, 2014). The New York State livebirth registry was used to identify eligible children. All infants whose birth certificates indicated they were conceived using fertility treatments were invited to participate in the study, as were all births of multiples regardless of conception method. Singletons conceived without use of fertility treatments were frequency matched to area of residence of those who were conceived using fertility treatments at a 3:1 ratio. A total of 5034 mothers enrolled, and 4886 mothers completed the baseline questionnaire (4 months postpartum), which included questions about PCOS. In all, 3478 Singletons and 1910 twins with at least one developmental score captured by the Ages and Stages Questionnaire (ASQ) were included for analysis. Detailed descriptions of the recruitment procedures and the validity of the sampling framework are available elsewhere (Buck Louis *et al.*, 2014).

Ethical approval

Study protocols were approved by the New York State Department of Health and the University at Albany (State University of New York) institutional review boards. Prior to collection of data, written informed consent was obtained from all parents.

Exposure assessment

Mothers completed a baseline questionnaire at 4 months postpartum to provide personal demographics, gynecologic and reproductive health, diet and lifestyle data related to the study pregnancy. Mothers were asked whether a doctor or healthcare provider had ever diagnosed them with PCOS, and whether they received any treatment (untreated, treated with medication, treated with surgery). Those who reported any 'Yes' answer were categorized as having PCOS. In secondary analysis, to better understand if treatment had an impact on results, we combined the treated with medication and treated with surgery into a single 'treated PCOS' group due to the small numbers ($n = 24$) reporting surgery.

Outcome assessment

Child development: the ASQ and parental report

The ASQ is a well-validated screening tool designed for early assessment of developmental delays (Gollenberg *et al.*, 2010; Limbos and Joyce, 2011; Guevara *et al.*, 2013). Mothers completed questions about their child's development at 4–6, 8, 12, 18, 24, 30 and 36 months of age. The second edition of the ASQ was used for children at 4–12 months of age, while the third edition was used for children 18–36 months of age. ASQs were required to be completed within the specified age windows in order to be considered valid (Bricker *et al.*, 1999; Squires, 2009). Five developmental domains were assessed in the ASQ: fine motor, gross motor, communication, personal–social functioning and problem-solving. Each question was scored using a point system, with each 'yes' being 10 points, 'sometimes' being 5 points, and 'not yet' being 0 points. Points were summed for each domain, with a range of 0–300 points. Scores were adjusted for gestational age through 24 months (Squires, 2009). Children were considered to have 'failed' the screening for a specific domain if their scores were two standard deviations below the age-specific US national average for that domain (Limbos and Joyce, 2011). Failure on any domain triggered a follow-up with the parents, and a repeat ASQ was administered on the failed domains by specially trained staff. If the child failed the follow-up screening for that domain, or no follow-up screen was conducted, the child was considered to have failed that ASQ domain (Squires *et al.*, 1997; Gollenberg *et al.*, 2010). Children who did not fail on the follow-up screen were considered to have passed. Children with a failure in any ASQ domain were

referred for evaluation by the New York State Early Intervention Program (EIP) and possible referral to free developmental services.

Covariates

We selected confounders *a priori* based on content knowledge and the literature for potential associations between maternal PCOS and childhood development. We examined the following covariates: maternal age, race/ethnicity (non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, Hispanic/Latino, mixed race or ethnicity/other), marital status (married/living as married, single) highest level of education completed at the time of birth (<high school, high school or General Educational Development (GED) equivalent, some college, college, advanced degree), parity, maternal smoking history during pregnancy (yes/no), any alcohol consumption during pregnancy (yes/no), history of diabetes (yes/no), history of mood disorder including depression (yes/no), and pre-pregnancy BMI (underweight <18.5 kg/m^2, normal 18.5–25 kg/m^2, overweight 25–30 kg/m^2, obese >30 kg/m^2). Some pregnancy complications such as low birthweight and pre-eclampsia are likely caused by PCOS and thought to be mediators on the pathway between PCOS and developmental delays, and thus were not adjusted for in the analysis.

Statistical analyses

We used generalized linear mixed models with robust standard errors to estimate odds ratios (OR) and two-sided 95% CIs for the association between maternal PCOS and failures in any domain of the ASQ 4 months through 36 months of age. Singletons and twins were included in the overall analysis and then analyzed separately. We examined the associations between maternal PCOS and failure on ASQ domains individually as well as failure on any domain. To account for repeated measures of infants and for twin births, we used models with random intercepts and autoregressive covariance structure for infants and mothers. We used these models to examine the associations between PCOS and each of the five domains of the ASQ specifically. We derived sampling weights based on vital records data of births during the study enrollment period for region of birth, plurality and infertility treatment. These were used in all analyses to account for oversampling by infertility treatment and plurality in the study design, making the results more generalizable to the underlying population from which the sample was drawn (Buck Louis *et al.*, 2014). To account for missing data in covariates, Monte Carlo Markov chain multiple imputation with 25 imputations was used. We explored whether associations between PCOS and ASQ failure differed by infant gender through stratified analyses, as a previous study observed sex-specific associations (Palomba *et al.*, 2012). Women with PCOS are more likely to use fertility treatments, so we also explored whether infertility treatment modified the association between maternal PCOS and risk of ASQ failure in offspring (Palomba *et al.*, 2015). Because treatment for PCOS can reduce circulating androgens and insulin resistance, we also performed a stratified analysis to examine whether treatment for PCOS influenced the results (Kurzthaler *et al.*, 2014). Since PCOS is associated with mood disorders, which might influence reporting of infant outcomes, we performed an analysis adjusting for maternal mood disorder (Sirmans and Pate, 2013). All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Mothers with PCOS were more likely to be obese, be nulliparous, have undergone fertility treatment, have gestational diabetes, be more highly educated, have private insurance, and be married or living as married, than mothers without PCOS (Table I). Mothers with PCOS were much more likely to have undergone fertility treatment than mothers without PCOS. They were also less likely to smoke or use alcohol while pregnant. Children of mothers with PCOS were of similar gestational age and birthweight compared to children born to mothers without PCOS.

Exposure to maternal PCOS was associated with failing any domain of the ASQ in unadjusted analyses (OR = 1.62, 95% CI: 1.17, 2.25), but attenuated after adjustment for covariates (adjusted OR (aOR) = 1.36, 95% CI: 0.97, 1.89). PCOS was associated with higher odds of ASQ failure in the fine motor domain in both unadjusted (OR = 2.30, 95% CI: 1.61, 3.29) and adjusted analyses (aOR = 1.69, 95% CI: 1.16, 2.44) (Table II). Among twins, exposure to maternal PCOS was associated with higher odds of ASQ failure in the communication (aOR = 1.94, 95% CI: 1.19, 3.18) and personal–social functioning (adjusted OR = 1.76, 95% CI: 1.12, 2.77) domains. Females were generally at higher risk for ASQ failures than males in adjusted analyses (Table III). In sensitivity analyses exploring treated vs untreated PCOS, we found that children born to mothers with untreated PCOS tended to have higher OR for ASQ failure than women under treatment for PCOS in adjusted analyses with exception of gross motor development (Table IV). Infertility treatment did not significantly modify the associations between PCOS and ASQ failure, nor did adjustment for infertility treatment or maternal mood disorder meaningfully affect results (data not shown).

Discussion

We found maternal diagnosis of PCOS was associated with developmental delays in offspring at early age. The magnitude of the associations was consistently higher among girls than boys. When examined by treatment status, children of women who reported untreated PCOS were at higher risk than those whose mothers reported receiving treatment. This is consistent with prior literature and represents the first study of PCOS and early childhood development. Further study of the offspring born to mothers with PCOS is necessary to confirm these findings.

While associations between maternal PCOS and offspring health during the perinatal period have been well-studied, few longitudinal studies have examined whether maternal PCOS has effects on early childhood development in offspring. Recent literature has reported associations between maternal PCOS and other offspring neurodevelopmental outcomes at ages 4 and older, and our results in younger children are largely in line with these findings (Palomba *et al.*, 2012; Kosidou *et al.*, 2015, 2016). Specifically, a large population-based case–control study using linkage data based on ICD-9 codes from healthcare registers in Sweden found offspring of mothers with PCOS at higher risk for ASD (Kosidou *et al.*, 2015). Another large Swedish study found associations between maternal PCOS and offspring diagnosis of ADHD (Kosidou *et al.*, 2016). A smaller longitudinal cohort study in Italy found offspring of women with PCOS had higher risk for pervasive developmental disorders (Palomba *et al.*, 2012). Children of women with PCOS had higher scores on total Autism-Spectrum Quotient (AQ-C)—a parent-report questionnaire of autistic traits in children aged 4–11 years—compared to offspring born to women without PCOS (Baron-Cohen *et al.*, 2001; Palomba *et al.*, 2012). This finding was stronger in daughters than sons (Palomba *et al.*, 2012). We also observed stronger associations among daughters as well as effects on communication, which is associated with ASDs. However, we did

Table I Characteristics of Upstate KIDS mothers and offspring by polycystic ovary syndrome status (*N* = 4453 mothers).

	Total	Polycystic ovary syndrome	No polycystic ovary syndrome	*P*-value*
No. (%)	4453 (100.0)	458 (10.3)	3995 (89.7)	
Age, mean (SD), year	30.4 (6.0)	31.2 (4.6)	30.3 (6.1)	0.277
Race				0.003
Non-Hispanic white	3629 (81.5)	389 (85.0)	3240 (81.3)	
Non-Hispanic black	204 (4.6)	6 (1.3)	198 (5.0)	
Non-Hispanic Asian	116 (2.6)	16 (3.5)	100 (2.5)	
Hispanic	243 (5.5)	19 (4.2)	224 (5.6)	
Mixed race or ethnicity/other	261 (5.9)	28 (6.1)	233 (5.8)	
Maternal education				<0.001
<High school	246 (5.5)	4 (0.9)	242 (6.0)	
High school or GED equivalent	562 (12.6)	34 (7.4)	528 (13.2)	
Some college	1363 (30.6)	157 (34.4)	1206 (30.2)	
College	990 (22.2)	112 (24.3)	878 (22.0)	
Advanced degree	1292 (29.0)	151 (33.0)	1141 (28.6)	
Private insurance	3354 (75.3)	409 (89.3)	2945 (73.7)	<0.001
Married/living as married	3880 (87.1)	432 (94.3)	3448 (87.4)	<0.001
Alcohol use while pregnant	552 (12.4)	49 (10.7)	503 (12.6)	0.479
Smoked during pregnancy	641 (14.4)	37 (8.1)	604 (15.1)	<0.001
Body mass index (pre-pregnancy)				<0.001
Underweight	115 (2.6)	5 (1.1)	110 (2.8)	
Normal weight	2003 (45.0)	126 (27.5)	1877 (47.0)	
Overweight	1138 (25.6)	101 (22.1)	1037 (26.0)	
Obese	1192 (26.8)	226 (49.3)	966 (24.2)	
Previous live birth	2383 (54.1)	206 (45.5)	2258 (55.3)	0.019
Gestational diabetes during pregnancy	433 (9.7)	103 (22.5)	330 (8.3)	<0.001
Pre-pregnancy diabetes	46 (1.1)	17 (3.8)	29 (0.8)	<0.001
Fertility treatment	1333 (29.9)	328 (71.6)	1005 (25.2)	<0.001
Birth weight, mean (SD), g				
Singletons	3379.7 (570.2)	3410.9 (630.2)	3376.3 (563.4)	0.289
Twins	2452.3 (591.7)	2487.5 (583.6)	2461.4 (592.5)	0.073
Infant sex				0.895
Female	2151 (48.3)	227 (49.6)	1924 (48.2)	
Male	2302 (51.7)	231 (50.4)	2071 (51.8)	
Gestational age, mean (SD), week				
Singletons	38.7 (1.9)	38.6 (1.9)	38.7 (1.9)	0.160
Twins	35.6 (2.8)	35.2 (3.0)	35.7 (2.8)	0.017
Age at last follow-up, mean (SD), month	26.4 (13.1)	27.5 (12.7)	26.2 (13.2)	0.024

not see a significant effect on the ASQ personal–social domain, which is more typically associated with ASDs. We found associations between PCOS and developmental delay in different domains in singletons and twins. The biological mechanisms underlying this difference are unclear and warrant further study.

It has been hypothesized that the poor outcomes in children of mothers with PCOS are related to exposure to excess levels of prenatal androgens (Doherty *et al.*, 2015; Kosidou *et al.*, 2015, 2016). Many women with PCOS are hyperandrogenic, and their elevated androgen concentrations persist into pregnancy (Sir-Petermann *et al.*, 2002). The placental tissue of women with PCOS displays increased androgen generation capacity and modified steroidogenesis, and newborns of mothers with PCOS have higher levels of umbilical vein androgens (Barry *et al.*, 2010; Maliqueo *et al.*, 2013). Higher amniotic testosterone levels have negatively correlated with cognitive development in offspring (Palomba *et al.*, 2012). The relationship between exposure to higher levels of male sex hormones in utero and developmental delay may occur through several biological mechanisms. Androgens can act as a fetal programming mechanism on the brain, affecting changes in multiple regions through reorganization of synaptic

Table II Odds ratios for polycystic ovary syndrome (ASQ) failures comparing mothers with polycystic ovary syndrome (PCOS) to mothers without PCOS in children from 4 to 36 months in the Upstate KIDS Study (2008–2010, *N* = 5388 offspring)

	Model 1				Model 2			
Total	**OR**	**Lower 95% CI**	**Upper 95% CI**	***P*-value**	**OR**	**Lower 95% CI**	**Upper 95% CI**	***P*-value**
All children								
Any fail	1.62	1.17	2.25	<0.01	1.36	0.97	1.89	0.07
Fine motor	2.30	1.61	3.29	<0.01	1.69	1.16	2.44	<0.01
Gross motor	1.57	1.08	2.30	0.02	1.27	0.86	1.87	0.24
Communication	1.80	1.26	2.57	<0.01	1.39	0.96	2.01	0.08
Personal–social	1.64	1.16	2.33	<0.01	1.18	0.82	1.70	0.37
Problem solving	1.68	1.14	2.50	<0.01	1.36	0.88	2.11	0.17
Singletons								
Any fail	1.26	0.81	1.96	0.31	1.19	0.74	1.90	0.47
Fine motor	1.79	1.14	2.81	0.01	1.77	1.09	2.89	0.02
Gross motor	1.31	0.78	2.21	0.30	1.38	0.79	2.42	0.26
Communication	1.19	0.75	1.88	0.45	1.21	0.74	1.99	0.45
Personal–social	1.06	0.65	1.73	0.83	1.05	0.63	1.76	0.84
Problem solving	1.37	0.81	2.32	0.24	1.45	0.81	2.58	0.21
Twins								
Any fail	1.54	1.04	2.28	0.03	1.37	0.91	2.07	0.13
Fine motor	1.51	0.98	2.34	0.06	1.24	0.74	2.07	0.39
Gross motor	0.95	0.62	1.46	0.81	0.74	0.44	1.24	0.26
Communication	1.79	1.15	2.79	0.01	1.94	1.19	3.18	<0.01
Personal–social	1.69	1.11	2.58	0.01	1.76	1.12	2.77	0.02
Problem solving	1.40	0.90	2.17	0.14	1.47	0.94	2.29	0.09

Model 1 unadjusted.
Model 2 adjusted for maternal age, body mass index, race/ethnicity, marital status, private insurance, education, smoking during pregnancy, drinking during pregnancy, any diabetes and plurality (in 'All Children' models).

patterning via cell apoptosis and differentiation during sensitive developmental periods (McCarthy and Arnold, 2011; Lombardo *et al.*, 2012). Sex hormones play a role in organization of dendritic spine synapses, which are involved in numerous neuropathologies (McCarthy and Arnold, 2011). There is also evidence that sex hormones are involved in the epigenetic modulation of histones and differential cell death in some brain regions (McCarthy and Arnold, 2011). It is possible that the hyperandrogenic uterine environment in a mother with PCOS-like phenotype may have a greater impact on female offspring than male offspring given the contra-sexual hormonal exposure. This finding has been observed in some studies of offspring, but not all (Palomba *et al.*, 2012; Doherty *et al.*, 2015; Hu *et al.*, 2015; Kosidou *et al.*, 2015, 2016; Puttabyatappa *et al.*, 2016). Female offspring born to mothers with PCOS are at higher risk of developing PCOS themselves, and it has been hypothesized that this may be due to a combination of genetic factors and perinatal programming (Puttabyatappa *et al.*, 2016). Females exposed to higher levels of androgens in utero, such as those with congenital adrenal hyperplasia, have been shown to have higher risk of a range of psychiatric disorders, supporting the hyperandrogenic programming hypothesis (Engberg *et al.*, 2015).

PCOS is associated with a constellation of other metabolic abnormalities, such as hyperinsulinemia, obesity, and insulin resistance (Dumesic *et al.*, 2015). These conditions have also been associated with risk of developmental delay in offspring (Doherty *et al.*, 2015). In our study the association between maternal PCOS and risk of ASQ failure persisted even after adjusting for pre-pregnancy BMI and diabetes, suggesting possible effects of PCOS on offspring beyond associated metabolic disturbances (Doherty *et al.*, 2015). Whether PCOS causes these metabolic risk factors or whether they cause PCOS remains unclear. Adjustment for potential mediators may underestimate the true association, particularly since obese women with PCOS tend to have more severe hyperandrogenemia (Hirschberg, 2009). PCOS is also the most common cause of infertility, and in this study women with PCOS were much more likely to use fertility treatments compared to women without PCOS (Dumesic *et al.*, 2015). We found no evidence of interaction between fertility treatment and ASQ failure. This finding is supported by previous analyses from this cohort that demonstrate no association between fertility treatment and ASQ failure (Yeung *et al.*, 2016). Since women who did not report PCOS may include undiagnosed women, we performed an analysis excluding women who reported use of fertility treatment and those who reported hirsutism, both markers for PCOS, from the non-PCOS group. This analysis did not result in a meaningful difference from our primary results.

Our study found that women who reported receiving no treatment for PCOS had higher risks of having children with developmental delay

Table III Odds ratios for Ages and Stages Questionnaire (ASQ) failures comparing mothers with polycystic ovary syndrome (PCOS) to mothers without PCOS in children from 4 to 36 months by infant sex in the Upstate KIDS Study (2008–2010, *N* = 5388 offspring).

Total	Model 1				Model 2			
	OR	Lower 95% CI	Upper 95% CI	*P*-value	OR	Lower 95% CI	Upper 95% CI	*P*-value
Female								
Any fail	2.23	1.40	3.57	<0.01	1.86	1.17	2.96	0.01
Fine motor	3.00	1.80	5.02	<0.01	2.04	1.24	3.36	0.01
Gross motor	2.10	1.24	3.54	0.01	1.64	0.97	2.78	0.06
Communication	2.19	1.31	3.66	<0.01	1.78	1.09	2.91	0.02
Personal–social	1.69	1.02	2.80	0.04	1.33	0.81	2.17	0.26
Problem solving	1.86	0.84	4.10	0.13	1.68	0.94	3.01	0.08
Male								
Any fail	1.17	0.70	1.93	0.55	1.73	0.94	3.16	0.08
Fine motor	1.80	1.00	3.23	0.05	1.31	0.71	2.41	0.38
Gross motor	1.20	0.66	2.16	0.55	0.76	0.39	1.50	0.43
Communication	1.33	0.74	2.39	0.34	1.04	0.57	1.90	0.90
Personal–social	1.48	0.80	2.71	0.21	1.10	0.58	2.10	0.77
Problem solving	1.37	0.70	2.67	0.35	1.08	0.53	2.20	0.83

Model 1 unadjusted.
Model 2 adjusted for maternal age, body mass index, race/ethnicity, marital status, private insurance, education, smoking during pregnancy, drinking during pregnancy, any diabetes and plurality.

compared to women who received treatment. Treatment of PCOS through medications such as metformin can have direct effects on ovarian steroidogenesis independent of effects on insulin sensitivity (Kurzthaler *et al.*, 2014). Studies of PCOS treatment in pregnancy have reported beneficial effects: meta-analyses and a large, multi-center trial have shown metformin use in pregnancy can reduce gestational diabetes risk, as well as risk of preterm delivery in observational studies and clinical trials (Rowan *et al.*, 2008; Kumar and Khan, 2012; Feng *et al.*, 2015; Zeng *et al.*, 2016). Meta-analyses in mothers without PCOS also suggests reduced risks of a variety of pregnancy complications with metformin use (Palomba *et al.*, 2009; Kumar and Khan, 2012; Cassina *et al.*, 2014; Feng *et al.*, 2015). No data was collected in our study regarding whether PCOS mothers discontinued treatment before or after pregnancy, but current evidence indicates no association between treatment with medication in early pregnancy and major birth defects (Cassina *et al.*, 2014). Only a few studies have assessed the teratogenicity of PCOS medications, and larger studies are needed to confirm these findings, but use of metformin during pregnancy is generally considered safe, and results of our study are consistent with prior studies suggesting no harm to the developing fetus, and likely benefits in reducing complications (Cassina *et al.*, 2014; Palomba *et al.*, 2009; Syngelaki *et al.*, 2016).

Our study has numerous strengths. We used a large, population-based prospective cohort study to examine our question of interest. Detailed information was also collected on confounding variables at numerous points in time improving our ability to adjust for potential confounders. Though our outcome is a screening instrument, it was specifically designed to maximize specificity and limit overdiagnosis of developmental delay (Gollenberg *et al.*, 2010; Schonhaut *et al.*, 2013; Veldhuizen *et al.*, 2015; King-Dowling *et al.*, 2016). Untreated delays can persist into the school years and are associated with diminished school performance and behavioral issues (Berkman *et al.*, 2015). Our study also examines the offspring development at an early age (under 3 years) more proximal in time to the in utero exposure than other studies. Associations found in our study, while not always attaining statistical significance, were nearly all in the same direction. Our study also collected data on infertility treatment, which is strongly correlated with maternal PCOS. Our study also has several potential limitations. As in most studies, there was some attrition in the study population over time, however missing data was addressed through use of generalized linear effects models and multiple imputation. While our study used sampling weights to account for a study design powered to examine infertility treatment, higher socioeconomic status (SES) groups may have agreed to participate compared to those who did not. Our analysis adjusted for SES, however, the results may be less generalizable to a lower SES population. Another limitation is that measurement of PCOS was provided by maternal self-report of a provider's diagnoses of PCOS, which may not be clinically robust. It is likely that there are undiagnosed cases of PCOS among the mothers in the study, as women may have polycystic ovaries without overt symptoms of the syndrome (Polson *et al.*, 1988). Women may have also erroneously reported a diagnosis of PCOS. This would likely add non-differential measurement error in the exposure, which in most cases would bias estimates towards the null. Our point estimates generally pointed in the direction of increased risk of delay among children born to mothers with PCOS, however, not all results were statistically significant at the traditional 0.05 level, and should be interpreted with caution. Longer follow-up is needed to assess whether these delays are

Table IV Odds ratios for ASQ failures by treatment comparing mothers with PCOS to mothers without PCOS in children from 4 to 36 months in the Upstate KIDS Study (2008–2010, *N* = 5388 offspring).

	Model 1			
Total	**OR**	**Lower 95% CI**	**Upper 95% CI**	***P*-value**
All children				
Any fail				
No PCOS	1.00	REF	REF	
Untreated PCOS	1.62	0.95	2.75	0.08
Treated PCOS	1.16	0.79	1.73	0.45
Fine motor				
No PCOS	1.00	REF	REF	
Untreated PCOS	2.07	1.21	3.53	0.01
Treated PCOS	1.53	0.97	2.40	0.06
Gross motor				
No PCOS	1.00	REF	REF	
Untreated PCOS	0.93	0.47	1.83	0.83
Treated PCOS	1.49	0.96	2.32	0.08
Communication				
No PCOS	1.00	REF	REF	
Untreated PCOS	2.02	1.17	3.47	0.01
Treated PCOS	1.05	0.68	1.64	0.81
Personal–social				
No PCOS	1.00	REF	REF	
Untreated PCOS	1.24	0.74	2.07	0.42
Treated PCOS	1.18	0.75	1.88	0.47
Problem solving				
No PCOS	1.00	REF	REF	
Untreated PCOS	1.78	0.92	3.44	0.09
Treated PCOS	1.10	0.67	1.80	0.72

Model 1 adjusted for maternal age, body mass index, race/ethnicity, marital status, private insurance, education, smoking during pregnancy, drinking during pregnancy, any diabetes and plurality.

merely transient and assess if risks of permanent disorders such as autism and ADHD differ as children reach older age. Given these limitations, further study is needed to determine the clinical impact of these findings. However, the large sample size and multiple development data collections over time remain strengths.

Conclusion

Overall, we found evidence that maternal PCOS is associated with higher risk of developmental delays in offspring through 3 years of age. Risks appeared somewhat higher among female offspring. Offspring of women who reported receiving no treatment for their PCOS were also at mildly higher risk compared to offspring women who had received treatment. Our study suggests more research is needed on treatment of PCOS in pregnant mothers, as these gynecologic conditions may have implications for offspring health. Longer term follow-up is necessary to understand the impact of PCOS exposure on ADHD or autism in this population. Our findings are consistent with prior literature and represent the first study of maternal PCOS and developmental delay in children under 3 years of age.

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Authors' roles

G.B. conceptualized and designed the study, carried out the initial analyses, drafted the initial article, and reviewed and revised the article. S. L.M., M.B., H.P. and J.M. conceptualized and designed the study, made substantial contributions to analysis and interpretation of data, and critically revised the article. E.B., E.H.Y. and R.S. collected data, designed the data collection instruments, and coordinated and supervised data collection, and critically reviewed the article. All authors approved the final article as submitted and agree to be accountable for all aspects of the work.

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Conflict of interest

None declared.

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