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Maternal Polycystic Ovary Syndrome and Risk for Attention-Deficit/Hyperactivity Disorder in the Offspring

Kyriaki Kosidou, Christina Dalman, Linnea Widman, Stefan Arver, Brian K. Lee, Cecilia Magnusson, and Renee M. Gardner

ABSTRACT

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) is the most common childhood neurodevelopmental disorder, and boys are two to three times more likely to develop ADHD. Maternal polycystic ovary syndrome (PCOS), a common metabolic disorder associated with excess circulating androgens, has been associated with increased risk for autism spectrum disorder in the offspring. In this study, we aimed to investigate whether maternal PCOS increases the risk for ADHD in the offspring.

METHODS: We conducted a matched case-control study using health and population data registers for all children born in Sweden from 1984 to 2008. Maternal PCOS was defined by ICD-coded register diagnosis. The outcome of ADHD was defined as an ICD-coded register diagnosis of ADHD and/or registered prescription of medications to treat ADHD. A total of 58,912 ADHD cases (68.8% male) were identified and matched to 499,998 unaffected controls by sex and birth month and year.

RESULTS: Maternal PCOS increased the odds of offspring ADHD by 42% after adjustment for confounders (odds ratio [OR], 1.42; 95% confidence interval [CI], 1.26–1.58). Exclusion of ADHD cases with comorbid autism spectrum disorder attenuated but did not explain the relationship (OR, 1.34; 95% CI, 1.18–1.52). The risk was somewhat elevated for ADHD with comorbid autism spectrum disorder (OR, 1.76; 95% CI, 1.37–2.26). The risk for ADHD was higher among obese mothers with PCOS (OR, 1.68; 95% CI, 1.31–2.17) and was highest among obese mothers with PCOS and other features of metabolic syndrome (OR, 2.59; 95% CI, 1.02–6.58).

CONCLUSIONS: This study provides evidence that maternal PCOS may subtly influence the neurodevelopment of the offspring, resulting in increased risk for neurodevelopmental disorders such as ADHD.

Keywords: Attention-deficit disorder with hyperactivity, Autism spectrum disorder, Comorbidity, Epidemiology, Matched case-control study, Polycystic ovary syndrome, Prospective study

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Attention-deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed psychiatric disorder in childhood, with a prevalence of 4% to 12%, though symptoms often persist into adulthood (1–3). Though there is a substantial genetic component to ADHD risk, multiple environmental factors and gene–environment interactions have been identified (4–6). ADHD is a sexually dimorphic condition, with boys being two to three times more likely to receive a diagnosis (7). Sex hormones can modify brain development (8) and may explain the male-skewed risk for certain neurodevelopmental disorders. Brain regions involved in ADHD, such as the hippocampus, prefrontal cortex, striatum, and amygdala, are influenced by sex hormone signaling during development (9,10). ADHD often co-occurs with autism spectrum disorder (ASD), another male-skewed disorder, and the two conditions may share causal pathways (11). Although increased exposure to prenatal androgens has been noted in ASD (12), the relationship between prenatal hormones and ADHD risk has not been explored.

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of childbearing age, affecting 5% to 15% of women and characterized by hyperandrogenism, ovarian dysfunction, and polycystic ovarian morphology (13). The causes of PCOS are not clear, but there is evidence for a genetic susceptibility to the disorder (14). Some studies support an interaction between genetic susceptibility and the influence of maternal environment, including in utero exposure to excess androgens, in the etiology of PCOS (15,16). Furthermore, weight gain and obesity are of importance for the development of PCOS. Obesity is closely related to the hyperinsulinemia that enhances hyperandrogenemia in women with PCOS (17). Hyperandrogenism in turn contributes to the adiposity, insulin resistance, and hyperinsulinemia that are common in PCOS (13,18). PCOS often emerges during puberty, but it may also develop later in reproductive years, for instance, as a result of weight gain (13,19). Maternal PCOS is a potential source of excess androgen exposure for the

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fetus (20,21). Maternal diagnosis of PCOS is associated with increased risk for ASD in the offspring, particularly in obese mothers (22). We hypothesized that maternal PCOS may also influence the offspring's risk for ADHD.

Here, we test this hypothesis by examining the relationship between maternal diagnosis of PCOS and risk for clinically diagnosed ADHD in the offspring in a Swedish nationwide case-control study using prospectively collected health register data. We explored whether high levels of comorbidity between ADHD and ASD could explain this relationship.

METHODS AND MATERIALS

Study Population

We used similar methods for the population selection and statistical methods as in our recent study that examined the relationship between maternal diagnosis of PCOS and risk for offspring ASD (22). All data are derived from linkages held by Statistics Sweden and the National Board of Health and Welfare, containing routinely collected health and sociodemographic data on the entire population of Sweden and cross-linked by each resident's unique national registration number (23). The eligible study population consisted of all individuals born in Sweden from 1984 to 2011 and followed until December 31, 2011. We matched all cases of ADHD (see below) in the study population with up to 10 living controls who were without an ADHD diagnosis at the end of the follow-up period. Controls were matched by sex and birth month and year. After exclusion of children not born in Sweden, born after 2008, from a multiple birth, adopted, and those with missing covariate data (Figure 1), the final sample consisted of 58,912 ADHD cases matched to 499,998 controls, with a case to control ratio between 1:2 and 1:10. This study was approved by the regional ethical review board at Karolinska Institutet. Informed consent was not required for the analysis of anonymized register data.

ADHD Case Ascertainment

We used a previously validated two-step approach for identifying cases of ADHD (24). First, ADHD case status as of December 31, 2011, was defined as a recorded diagnosis of ICD-10 code F90 or ICD-9 code 314 within the National Patient Register (NPR). The NPR provides data on inpatient care since 1973 and outpatient specialist physician care since 2001. The coverage of the NPR is approximately 99% of all somatic discharge diagnoses, and the validity of the diagnoses is generally high (25). As a second step, we searched the Prescribed Drug Register (PDR) for anyone recorded as receiving prescriptions for ADHD medications (methylphenidate [Anatomical Therapeutic Chemical (ATC) Classification System code N06BA04] or atomoxetin [ATC code N06BA09]). The PDR contains data on medications dispensed to the entire population in Sweden since July 1, 2005. Receipt of a prescription for ADHD medications is a useful proxy for an ADHD diagnosis because Swedish medical guidelines mandate that ADHD medications should only be prescribed by a psychiatric specialist and after other (nonpharmacological) interventions have failed.

Exposure

Maternal PCOS status was classified according to any lifetime recorded diagnosis (ICD-8 code 256.90, ICD-9 code 256E, and ICD-10 code E28.2) within the NPR, supplemented by diagnoses in the Medical Birth Register (MBR). The MBR includes information on pregnancy, delivery, and the neonatal period for approximately 98% of births in Sweden since 1973. We used lifetime diagnoses of PCOS as the exposure because PCOS is a longitudinal disorder with hormonal and metabolic manifestations through the life span (26,27).

Covariates

Covariates were identified a priori as potential confounding factors and/or risk factors for ADHD. Maternal and paternal ages at the time of birth were categorized as $<$25, 25 to 29, 30 to 34, 35 to 39, and $\geq$40 years. Data on family income after deduction of taxes were obtained from the Integrated Database for Labor Market Research, adjusted for family size, and categorized into quintiles according to birth year. The highest education of either parent at the time of birth was classified as years of completed formal education ($\leq$9, 10–12, or $\geq$13 years). Parental history of psychiatric inpatient and outpatient treatment before the birth of the index child (yes/no) was defined as any psychiatric diagnosis (chapter V of ICD-8 and ICD-9 or chapter F of ICD-10) recorded in the NPR. Maternal migrant status was categorized as born in Sweden or not.

We explored whether obstetric complications influenced the findings of our main analysis due to reports of increased obstetric complications in mothers with PCOS (28) and associations of obstetric complications with ADHD (29). Apgar score at 5 minutes was categorized as $<$7 or $\geq$7 and supplemented by Apgar score at 1 minute when data on Apgar score at 5 minutes were not available. Size for gestational age was categorized as small for gestational age or not. Preterm birth was categorized as $<$37 weeks or not. Preeclampsia was classified according to ICD-8 codes 637.03 to 637.04 and 637.09 to 637.10, ICD-9 codes 642E to 642H, and ICD-10 codes O14 to O15 for diagnoses recorded within the MBR or in the NPR during the 9 months before and 1 month after birth of the index child. Birth order was categorized as first born or not according to the MBR.

Obesity and other features of metabolic syndrome are common in PCOS and are related to more severe hyperandrogenemia in women with PCOS (30,31). Furthermore, elevated maternal body mass index (BMI) has been associated with risk for ADHD (32). Thus, we explored the influence of prepregnancy BMI and metabolic syndrome on the relationship between maternal PCOS and offspring ADHD.

To calculate maternal baseline BMI (in kg/m^2), we used weight and height data recorded at the first visit to a maternal health clinic (33). Data were available on 71% of the mother-child pairs in our analytical sample (Figure 1). Maternal baseline BMI was categorized by standard convention (34): underweight (BMI $<$ 18.5 kg/m^2), normal (18.5 $\leq$ BMI $<$ 25 kg/m^2), overweight (25 $\leq$ BMI $<$ 30 kg/m^2), and obese (BMI $\geq$ 30 kg/m^2). Mothers were classified as having a prior diagnosis of diabetes mellitus according to the codes ICD-8 250; ICD-9 250, 648A, and 790C; and ICD-10 E10 to E11 and O24.0 to O24.1 if at least one diagnosis was recorded prior to and including the birth year