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Association of PCOS with offspring morbidity: a longitudinal cohort study

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STUDY QUESTION: Do children whose mothers have polycystic ovary syndrome (PCOS) have an increased risk of morbidity?

SUMMARY ANSWER: Maternal PCOS is associated with an increased risk of infection, allergy and other childhood morbidity.

WHAT IS KNOWN ALREADY: PCOS is associated with higher rates of gestational diabetes, pre-eclampsia and preterm delivery, but the long-term impact on child health is poorly understood.

STUDY DESIGN, SIZE, DURATION: We conducted a retrospective longitudinal cohort study of 1 038 375 children in Quebec between 2006 and 2020.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We included 7160 children whose mothers had PCOS and 1 031 215 unexposed children. Outcomes included child hospitalization for infectious, allergic, malignant and other diseases before 13 years of age. We estimated hazard ratios (HRs) and 95% CI for the association of PCOS with childhood morbidity in adjusted Cox proportional hazards regression models.

MAIN RESULTS AND THE ROLE OF CHANCE: Children exposed to PCOS were hospitalized at a rate of 68.9 (95% CI 66.2–71.8) per 1000 person-years, whereas unexposed children were hospitalized at a rate of 45.3 (95% CI 45.1–45.5) per 1000 person-years. Compared with no exposure, maternal PCOS was associated with 1.32 times the risk of any childhood hospitalization (95% CI 1.26–1.40), 1.31 times the risk of infectious disease hospitalization (95% CI 1.25–1.38) and 1.47 times the risk of allergy-related hospitalization (95% CI 1.31–1.66). Risk of hospitalization was also elevated for childhood metabolic (HR 1.59, 95% CI 1.16–2.18), gastrointestinal (HR 1.72, 95% CI 1.53–1.92), central nervous system (HR 1.74, 95% CI 1.46–2.07) and otologic disorders (HR 1.34, 95% CI 1.26–1.43). Subgroup analyses suggested that there was little difference in the association of PCOS with hospitalization among boys (HR 1.31, 95% CI 1.24–1.39) and girls (HR 1.34, 95% CI 1.26–1.43).

LIMITATIONS, REASONS FOR CAUTION: We analyzed severe childhood morbidity requiring hospitalization, not mild diseases treated in ambulatory clinics. We lacked data on ethnicity, education and physical activity, and cannot rule out residual confounding.

WIDER IMPLICATIONS OF THE FINDINGS: Our findings suggest that maternal PCOS is associated with an increased risk of childhood morbidity.

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Key words: allergic diseases / cardiovascular diseases / central nervous system diseases / childhood morbidity / epidemiology / infectious diseases / metabolic diseases / neoplasms / polycystic ovary syndrome / PCOS

Introduction

Polycystic ovary syndrome (PCOS) is a common reproductive disorder, characterized by ovarian dysfunction, hyperandrogenism, polycystic ovary morphology and metabolic complications (Witchel *et al.*, 2019). PCOS affects up to 10% of women of reproductive age (Bozdag *et al.*, 2016). Women with PCOS are at risk of obesity, type 2 diabetes and cardiovascular disease, and a number of studies suggest that there may be associations with adverse pregnancy outcomes such as gestational diabetes, pre-eclampsia and preterm birth (Palomba *et al.*, 2015; McDonnell and Hart, 2017). Although an impact on birth outcomes has been documented, the long-term health of children whose mothers have PCOS has received limited attention.

Owing to elevated circulating androgen levels, metabolic dysfunction and the potential for a suboptimal intrauterine environment in women with PCOS, researchers have raised concern over the somatic and neurodevelopmental health of children who are exposed to these conditions *in utero* (Palomba *et al.*, 2015; Bell et al., 2018a). Hyperandrogenism and insulin resistance may affect fetal neuroendocrine and immune programming, possibly impacting the long-term health of offspring (Cardoso and Padmanabhan, 2019). Studies have found that maternal PCOS is associated with faster catch-up growth and greater BMI in childhood (Recabarren *et al.*, 2008; Finnbogadóttir *et al.*, 2017). Children of women with PCOS are more likely to have insulin resistance, abnormal lipid profiles and diabetes (Wilde *et al.*, 2018; Gunning *et al.*, 2020; Chen *et al.*, 2021), as well as attention deficit disorders (Kosidou *et al.*, 2017), autism spectrum disorder (Kosidou *et al.*, 2016; Cherskov *et al.*, 2018; Chen *et al.*, 2020) and developmental delay (Bell *et al.*, 2018b). We assessed the association between maternal PCOS and risk of child morbidity requiring hospitalization before 13 years of age.

Materials and methods

Study design and population

We performed a longitudinal cohort study of children born between 1 April 2006 and 31 March 2019 in Quebec, Canada. We used data from the Maintenance and Use of Data for the Study of Hospital Clientele repository, which contains discharge records for all inpatient hospitalizations in the province (Auger *et al.*, 2021). Diagnostic variables in the repository are coded by professional archivists who apply algorithms to verify data quality. The dataset is validated and previous studies have found high sensitivity and specificity for child outcomes (Brisson *et al.*, 2003; Nakhla *et al.*, 2019). Children are matched with their mothers. We used unique identification numbers to follow the children from birth until 31 March 2020 to identify morbidities that led to admissions before 13 years of age.

Exposure

The main exposure measure was maternal PCOS. We identified PCOS using *International Classification of Disease* codes (9th version before 31 March 2006; 10th version beginning 1 April 2006) (Supplementary Table SI). We identified women who had a diagnosis of PCOS in their prenatal chart or were hospitalized for the treatment of PCOS either before or after pregnancy. The comparison group included children whose mothers did not have PCOS.

Outcomes

The main outcome measure comprised childhood hospitalizations up to 13 years of age. There were three primary outcomes, categorized as infectious, allergic and malignant diseases. Infectious diseases included upper respiratory tract, bronchitis, bronchiolitis, pneumonia, infectious enteritis, nephritis, septicemia, otitis media, eye infection, meningitis and other infectious conditions. Allergic diseases included allergic asthma, anaphylaxis, atopic dermatitis, urticaria and other allergic disorders. Malignant diseases included leukemia, lymphoma, neuroblastoma, retinoblastoma, sarcoma and other solid tumors. We used *International Classification of Diseases-10* codes to classify all outcomes. We additionally used morphology and topography codes in the *International Classification of Diseases for Oncology-3* for childhood cancer (Steliarova-Foucher *et al.*, 2005).

Secondary outcomes included morbidities categorized by system: respiratory (respiratory infections, asthma, other respiratory disorders), cardiovascular (arrhythmia, cardiomyopathy, heart valve disorder, hypertension, heart failure, pulmonary vascular disease, stroke), metabolic (type 1 and 2 diabetes, obesity, metabolic syndrome, hypertension, dyslipidemia), gastrointestinal (esophageal, gastric and duodenal disorders, enteritis and colitis, other), urinary (nephritis, pyonephrosis, renal tubulointerstitial disorders, renal failure, cystitis, urethritis, urethral syndrome), genital (hydrocele, spermatocele), musculoskeletal (inflammatory arthropathies, kyphoscoliosis), central nervous system (cerebral palsy, epilepsy, hydrocephalus, other), ophthalmologic (eyelid/lacrimal/orbit, conjunctival, retina/choroid disorders, lacrimal stenosis, ophthalmitis, strabismus, visual disturbances, blindness, other), otologic (suppurative and nonsuppurative otitis media, otalgia, otorrhoea, otorrhagia), and mental and behavioral disorders.

Covariates

We adjusted for maternal characteristics, including age (<30, 30–34, ≥35 years), parity (0, 1, ≥2), ART, maternal comorbidity (hypertension, type 1 and 2 diabetes, obesity, dyslipidemia, maternal mental disorders, allergy and asthma), substance use disorders (tobacco, alcohol, drugs), socioeconomic deprivation (yes, no, unspecified) and year of birth (2006–2010, 2011–2015, 2016–2019). Data for ART were missing for 2006 and 2007, which we placed in a separate category (Wei *et al.*, 2021). Socioeconomic deprivation was determined from Canada census data and defined as the most deprived fifth of neighborhoods for mean income, employment rate and education (Pampalon *et al.*, 2012).

Statistical analysis

We calculated hospitalization rates per 1000 person-years and the cumulative incidence at 13 years of age. We estimated hazard ratios (HRs) with 95% CI for the association of maternal PCOS with childhood hospitalization using Cox proportional hazards regression. Models were adjusted for maternal age, parity, ART, maternal comorbidity, substance use disorders, socioeconomic deprivation and year of birth. We defined the follow-up time as the number of days between birth and the first hospitalization for each outcome, or the study end

on 31 March 2020. We used robust sandwich estimators to account for children with the same mother. Children who were never hospitalized or died before the end of the study were censored. As prenatal exposure to hyperandrogenism may influence boys and girls differently, we carried out subgroup analyses stratified by child sex. We also examined if the association of PCOS with hospitalization varied during infancy (<2 years), early childhood (2 to 4 years) and later childhood (5 to 13 years).

In sensitivity analyses, we examined models that were not adjusted for maternal comorbidity, and excluded children who were conceived by ART, were multiple births, had mothers with comorbidity, or were born preterm, to rule out an effect of these factors. Analyses were performed in SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics approval

We obtained an ethics waiver from the institutional review board of the University of Montreal Hospital Centre, as data from hospital discharge abstracts are anonymized.

Results

Population characteristics

We followed 1 038 375 children from birth up to 13 years of age, for a total of 7 719 940 person-years under study (Table I). The cohort included 7160 children whose mothers had PCOS and 1 031 215 children who were unexposed. Mothers with PCOS were more likely to be older (≥30 years: 60.7% versus 51.8%), nulliparous (55.4% versus 49.0%) and have comorbidities including obesity, type 1 and 2 diabetes, hypertension and dyslipidemia (24.8% versus 8.5%) compared with no PCOS. Mothers with PCOS were more likely to have used ART than mothers without PCOS (14.7% versus 1.8%). The percentage of substance use disorders and socioeconomic deprivation was comparable among mothers with and without PCOS.

Table I Characteristics of children exposed to maternal PCOS.

	PCOS n = 7160	No PCOS n = 1 031 215
Maternal age, years[a]		
<30	2813 (39.3)	497 217 (48.2)
30–34	2783 (38.9)	347 870 (33.7)
≥35	1564 (21.8)	186 128 (18.1)
Parity		
0	3965 (55.4)	505 610 (49.0)
1	2285 (31.9)	357 935 (34.7)
≥2	910 (12.7)	167 670 (16.3)
ART		
Yes	1056 (14.7)	18 418 (1.8)
No	5152 (72.0)	784 144 (76.0)
Maternal comorbidity[a]		
Yes	1776 (24.8)	87 945 (8.5)
No	5384 (75.2)	950 430 (91.5)
Substance use disorder[b]		
Yes	112 (1.6)	20 107 (2.0)
No	7048 (98.4)	1 011 108 (98.0)
Socioeconomic deprivation		
Yes	1285 (18.0)	207 057 (20.1)
No	5875 (82.0)	824 158 (79.9)
Year of birth		
2006–2010	1845 (25.8)	387 059 (37.5)
2011–2015	3050 (42.6)	403 005 (39.1)
2016–2019	2265 (31.6)	241 151 (23.4)

[a]Hypertension, type 1 and 2 diabetes, obesity, dyslipidemia, mental disorders, allergy and asthma.
[b]Tobacco, alcohol and drug use disorders.
PCOS, polycystic ovary syndrome.

Childhood hospitalization rates

A total of 275 354 children were hospitalized during follow-up, including 2314 (0.8%) children whose mothers had PCOS (Supplementary Table SII). Hospitalization rates were higher for children exposed to PCOS (68.9 per 1000 person-years, 95% CI 66.2–71.8) than unexposed children (45.3 per 1000 person-years, 95% CI 45.1–45.5). Children exposed to PCOS had a higher cumulative incidence of hospitalization at 13 years (39.0 per 100) compared with unexposed children (31.8 per 100).

Association of PCOS with childhood hospitalization

In adjusted Cox models, PCOS was associated with 1.32 times the risk of any childhood hospitalization compared with no PCOS (95% CI 1.26–1.40) (Table II). PCOS was associated with 1.31 times the risk of infection hospitalization (95% CI 1.25–1.38) and 1.47 times the risk of allergy hospitalization (95% CI 1.31–1.66), but the risk of cancer was not elevated (HR 1.17, 95% CI 0.67–2.05). PCOS was associated with 1.32 times the risk of respiratory (95% CI 1.23–1.41), 1.59 times the risk of metabolic (95% CI 1.16–2.18), 1.72 times the risk of gastrointestinal (95% CI 1.53–1.92), 1.74 times the risk of central nervous system (95% CI 1.46–2.07), 1.46 times the risk of ophthalmologic (95% CI 1.27–1.67) and 1.34 times the risk of otologic hospitalization (95% CI 1.26–1.43). PCOS was also associated with hospitalization for mental and behavioral disorders (HR 1.68, 95% CI 1.42–1.99). PCOS was not associated with cardiovascular, malignancy or musculoskeletal hospitalization.

Compared with no exposure, children whose mothers had PCOS were at risk of hospitalization for several diseases (Supplementary Table SIII). PCOS was associated with 1.30 times the risk of otitis media (95% CI 1.22–1.38), 1.21 times the risk of pneumonia (95% CI 1.08–1.34), 1.43 times the risk of gastroenteritis (95% CI 1.25–1.64), 1.54 times the risk of asthma (95% CI 1.36–1.76) and 1.71 times the risk of metabolic syndrome hospitalization (95% CI 1.27–2.30).

Association according to child sex

Subgroup analyses stratified by child sex suggested that there was little difference in the association of PCOS with hospitalization among boys

Table II Association of maternal PCOS with childhood hospitalization.

	No. children		Hospitalization rate per 1000 person-years (95% CI)		Hazard ratio (95% CI)	
	PCOS	No PCOS	PCOS	No PCOS	Unadjusted	Adjusted[a]
Type of hospitalization						
Any	2314	273 040	68.9 (66.2–71.8)	45.3 (45.1–45.5)	1.35 (1.30–1.42)	1.32 (1.26–1.40)
Infection	2051	240 220	59.2 (56.7–61.8)	38.9 (38.7–39.0)	1.34 (1.28–1.41)	1.31 (1.25–1.38)
Allergy	289	28 727	6.5 (5.8–7.3)	3.8 (3.8–3.9)	1.57 (1.40–1.77)	1.47 (1.31–1.66)
Cancer	12	1659	0.3 (0.1–0.5)	0.2 (0.2–0.2)	1.15 (0.65–2.03)	1.17 (0.67–2.05)
Physiological system						
Respiratory	1070	122 443	27.0 (25.4–28.6)	17.8 (17.7–17.9)	1.33 (1.24–1.42)	1.32 (1.23–1.41)
Cardiovascular	50	5215	1.1 (0.8–1.4)	0.7 (0.7–0.7)	1.48 (1.11–1.96)	1.31 (0.99–1.74)
Metabolic	40	3921	0.9 (0.6–1.2)	0.5 (0.5–0.5)	1.68 (1.23–2.29)	1.59 (1.16–2.18)
Gastrointestinal	333	29 885	7.6 (6.8–8.5)	4.0 (4.0–4.1)	1.78 (1.59–1.99)	1.72 (1.53–1.92)
Urinary	172	18 333	3.8 (3.3–4.5)	2.4 (2.4–2.5)	1.40 (1.20–1.63)	1.43 (1.23–1.66)
Genital	38	4194	1.6 (1.2–2.2)	1.1 (1.0–1.1)	1.40 (1.02–1.92)	1.36 (0.99–1.87)
Musculoskeletal	11	2024	0.2 (0.1–0.4)	0.3 (0.3–0.3)	0.89 (0.49–1.60)	0.85 (0.47–1.53)
Central nervous system	141	11 407	3.1 (2.6–3.7)	1.5 (1.5–1.5)	1.97 (1.66–2.34)	1.74 (1.46–2.07)
Ophthalmologic	222	22 929	5.0 (4.4–5.7)	3.0 (3.0–3.1)	1.52 (1.33–1.73)	1.46 (1.27–1.67)
Otologic	1160	128 177	29.3 (27.7–31.1)	18.6 (18.5–18.7)	1.40 (1.32–1.50)	1.34 (1.26–1.43)
Mental and behavioral	145	13 196	3.2 (2.7–3.8)	1.7 (1.7–1.8)	1.87 (1.58–2.21)	1.68 (1.42–1.99)

[a]Hazard ratio for PCOS relative to no PCOS, adjusted for maternal age, parity, ART, maternal comorbidity, substance use disorder, socioeconomic deprivation and year of birth.
PCOS, polycystic ovary syndrome.

(HR 1.31, 95% CI 1.24–1.39) and girls (HR 1.34, 95% CI 1.26–1.43) (Table III). PCOS was associated with infection, allergy, respiratory, gastrointestinal, urinary, central nervous system, ophthalmologic, and mental and behavioral hospitalization among both boys and girls. However, PCOS was associated with metabolic disorders in boys (HR 1.76, 95% CI 1.19–2.62), but not girls (HR 1.37, 95% CI 0.82–2.28).

Association according to child age

The association between PCOS and hospitalization was slightly stronger earlier in childhood (Table IV). Compared with no exposure, PCOS was associated with 1.36 times the risk of any hospitalization before 2 years (95% CI 1.29–1.43), 1.24 times the risk at 2 to 4 years (95% CI 1.13–1.35) and 1.28 times the risk at 5 to 13 years (95% CI 1.10–1.49). Associations with allergy, respiratory, gastrointestinal, central nervous system, ophthalmologic, and mental and behavioral hospitalization persisted after 5 years. Associations with infection and otologic hospitalization were, however, attenuated after 5 years of age.

Sensitivity analyses

In models not adjusted for maternal comorbidity, maternal PCOS was slightly more strongly associated with adverse offspring outcomes (Supplementary Table SIV). Excluding children who conceived with ART, were multiple births, or were born preterm did not affect the results. However, excluding mothers with comorbidity resulted in an elevated risk of child mental and behavioral disorders (HR 1.92, 95% CI 1.58–2.33).

Table III Association between maternal PCOS and childhood morbidity stratified by child sex.

	Hazard ratio[a] (95% CI)	
	Boys (n = 532 876)	Girls (n = 505 499)
Type of hospitalization		
Any	1.31 (1.24–1.39)	1.34 (1.26–1.43)
Infection	1.31 (1.23–1.38)	1.32 (1.24–1.41)
Allergy	1.52 (1.32–1.76)	1.38 (1.13–1.68)
Cancer	0.91 (0.38–2.20)	1.46 (0.69–3.08)
Physiological system		
Respiratory	1.30 (1.20–1.40)	1.34 (1.22–1.48)
Cardiovascular	1.39 (0.97–1.99)	1.21 (0.77–1.88)
Metabolic	1.76 (1.19–2.62)	1.37 (0.82–2.28)
Gastrointestinal	1.74 (1.51–2.01)	1.68 (1.43–1.99)
Urinary	1.57 (1.27–1.93)	1.31 (1.05–1.62)
Genital	1.36 (0.99–1.88)	–
Musculoskeletal	0.46 (0.15–1.42)	1.24 (0.62–2.49)
Central nervous system	1.70 (1.36–2.12)	1.79 (1.39–2.32)
Ophthalmologic	1.49 (1.25–1.78)	1.42 (1.16–1.73)
Otologic	1.31 (1.22–1.42)	1.37 (1.25–1.50)
Mental and behavioral	1.73 (1.41–2.12)	1.58 (1.20–2.10)

[a]Hazard ratio for PCOS relative to no exposure, adjusted for maternal age, parity, ART, maternal comorbidity, substance use disorder, socioeconomic deprivation and year of birth.
PCOS, polycystic ovary syndrome.

Table IV Association of maternal PCOS with hospitalization according to child age.

	Hazard ratio[a] (95% CI)		
	<2 years	2–4 years	≥5 years
Type of hospitalization			
Any	1.36 (1.29–1.43)	1.24 (1.13–1.35)	1.28 (1.10–1.49)
Infection	1.34 (1.27–1.42)	1.27 (1.15–1.39)	1.14 (0.93–1.38)
Allergy	1.54 (1.31–1.82)	1.40 (1.15–1.70)	1.40 (1.02–1.93)
Cancer	1.49 (0.67–3.32)	1.52 (0.69–3.36)	0.00 (0.00–0.00)
Physiological system			
Respiratory	1.30 (1.22–1.40)	1.30 (1.13–1.49)	1.37 (1.06–1.76)
Cardiovascular	1.37 (0.98–1.91)	1.26 (0.62–2.54)	1.05 (0.43–2.53)
Metabolic	1.45 (0.88–2.38)	1.77 (1.00–3.15)	1.66 (0.94–2.93)
Gastrointestinal	1.87 (1.63–2.14)	1.44 (1.06–1.97)	1.39 (1.05–1.83)
Urinary	1.42 (1.20–1.68)	1.45 (0.93–2.25)	1.45 (0.77–2.70)
Genital	1.29 (0.79–2.11)	1.35 (0.82–2.21)	1.63 (0.73–3.67)
Musculoskeletal	1.09 (0.45–2.66)	0.58 (0.19–1.79)	0.92 (0.30–2.87)
Central nervous system	1.73 (1.30–2.30)	1.56 (1.20–2.03)	2.20 (1.55–3.12)
Ophthalmologic	1.49 (1.23–1.80)	1.34 (1.05–1.70)	1.59 (1.15–2.20)
Otologic	1.37 (1.26–1.48)	1.30 (1.17–1.45)	1.16 (0.89–1.50)
Mental and behavioral	1.81 (1.38–2.38)	1.90 (1.26–2.87)	1.52 (1.13–2.04)

[a]Hazard ratio for PCOS relative to no PCOS, adjusted for maternal age, parity, ART, maternal comorbidity, substance use disorder, socioeconomic deprivation and year of birth. There were 1 038 375 children at risk before 2 years, 791 129 children at risk between 2 and 4 years and 533 831 children at risk at ≥5 years.
PCOS, polycystic ovary syndrome.

Discussion

In this study of 1 038 375 children followed from birth to 13 years of age, children exposed to maternal PCOS had a higher risk of hospitalization compared with unexposed children after adjusting for maternal comorbidities and other confounders. PCOS was associated with elevated risks of hospitalization for infectious, allergic and other disorders, but not malignant diseases. Risks of specific disorders, including otitis media, pneumonia, asthma, nephritis and metabolic syndrome, were all elevated. The associations were stronger earlier in childhood but persisted after 5 years of age for allergy, gastrointestinal, central nervous system, and mental and behavioral disorders. There was little evidence of a difference between boys and girls. Moreover, the associations were not explained by ART, multiple birth, maternal comorbidity or preterm birth. Overall, the findings suggest that maternal PCOS may have a negative impact on offspring development, enough to lead to a measurable increase in the risk of childhood hospitalization.

Few studies have investigated the long-term impact of maternal PCOS on offspring outcomes. Our findings suggest that children exposed to maternal PCOS may be at risk of infectious and allergic hospitalization. In the only other cohort study of infectious outcomes, maternal PCOS was associated with an increase in the number of hospitalizations for upper and lower respiratory tract infections and asthma among 38 028 Australian children (Doherty *et al.*, 2015). A cross-sectional study from the Netherlands found that maternal PCOS was associated with elevated inflammatory cytokines in offspring, suggesting a propensity toward chronic inflammation and risk of infection (Daan *et al.*, 2016).

An emerging body of evidence suggests that maternal PCOS may be linked with the cardiometabolic profiles of offspring. A recent systematic review and meta-analysis reported that children of women with PCOS are more likely to have insulin resistance and hypertriglyceridemia (Gunning *et al.*, 2020). Studies have found that children exposed to PCOS have higher concentrations of triglycerides and low-density lipoprotein cholesterol, and greater carotid intima-media thickness (Wilde *et al.*, 2018), as well as faster catch-up growth and greater BMI at 3 years of age (Finnbogadóttir *et al.*, 2017). A cohort study of 24 682 children in Finland concluded that children of women with PCOS had an increased risk of obesity and diabetes (Chen *et al.*, 2021). Our results align with much of this body of evidence as we found a consistent association between maternal PCOS and metabolic disorder hospitalization, including metabolic syndrome and type 1 and 2 diabetes.

Recent studies suggest that maternal PCOS may impact offspring neurodevelopment (Kosidou *et al.*, 2016, 2017; Cherskov *et al.*, 2018; Bell *et al.*, 2018b; Chen *et al.*, 2020). Children exposed to PCOS appear to have increased risks of attention deficit hyperactivity disorder (Kosidou *et al.*, 2017; Chen *et al.*, 2020), autism spectrum disorder (Kosidou *et al.*, 2016; Cherskov *et al.*, 2018; Chen *et al.*, 2020) and intellectual disability (Chen *et al.*, 2020) compared with unexposed children. A cohort study of 5388 children in the USA found that exposure

to maternal PCOS was associated with a higher risk of developmental delay before 3 years of age (Bell et al., 2018b). Another cohort study suggested that PCOS was associated with neuropsychiatric disorders after accounting for genetic and environmental confounders (Cesta et al., 2020). Our findings accord with previous studies that suggest that exposure to maternal PCOS increases the risk of central nervous system, and mental and behavioral, disorders in children.

The pathways linking PCOS with childhood morbidity have yet to be established. Circulating androgen levels and insulin resistance, the two hallmarks of PCOS, have been linked with oxidative stress, inflammation, endothelial dysfunction and placental abnormalities in pregnant women (Murri et al., 2013; Koster et al., 2015; Rudnicka et al., 2021). A recent systematic review found that women with PCOS had greater concentrations of oxidative biomarkers, including homocysteine (Murri et al., 2013). Hyperhomocysteinemia is associated with fetal growth restriction and low birthweight (Yajnik et al., 2014). Maternal PCOS may also impair immune function and lead to low-grade systemic inflammation in the child (Daan et al., 2016; Rudnicka et al., 2021).

Women with PCOS may have placental abnormalities, including chorioamnionitis, funisitis, villitis, thrombosis, infarction and impaired placental maturation, all of which are associated with a hypoxic state and a suboptimal intrauterine environment (Koster et al., 2015). Studies have consistently demonstrated that the intrauterine environment can influence fetal programming during critical developmental stages (Kwon and Kim, 2017). Suboptimal intrauterine environments owing to hyperandrogenism and metabolic dysfunction may affect fetal neuroendocrine and immune programming and metabolism, and impact health outcomes in childhood (Vanky et al., 2019). In addition, intrauterine PCOS exposure may affect DNA methylation patterns in the promoter regions of metabolic genes (Echiburú et al., 2020). Genome-wide studies have identified candidate genes related to the etiology of PCOS (Al-Khaduri et al., 2020). In addition, observational studies have found evidence of transgenerational effects in offspring (Risal et al., 2019).

Women with PCOS may be more likely to have comorbidities such as asthma, obesity and diabetes. Some studies suggest that maternal obesity and diabetes increase the risk of adverse offspring outcomes (Godfrey et al., 2017; Yu et al., 2019). Maternal asthma is associated with offspring asthma and allergic disorders (Morten et al., 2018; Sly, 2019). Although PCOS remained associated with childhood hospitalization after adjustment for maternal comorbidity in our data, it is possible that other unmeasured maternal morbidities contribute to our findings or that morbidity is a mediator.

This study has strengths. We used a longitudinal population-based cohort with a large sample size that allowed us to investigate a range of childhood disorders while controlling for a number of potential confounders. We followed the children over more than a decade with little possibility of recall or attrition bias. There are nevertheless limitations. We used a register-based cohort in which we captured severe cases of PCOS that required medical treatment but could not identify women with mild PCOS who were never diagnosed. We analyzed severe childhood morbidity requiring hospitalization, not mild diseases treated in ambulatory clinics. Exposures and outcomes in administrative hospital data may be misclassified, which may attenuate the associations without affecting the overall interpretations. We did not have data on genetic variants or phenotypes of PCOS. We lacked data on ethnicity, education, maternal pre-pregnancy BMI, gestational weight gain and physical activity, and cannot rule out residual confounding. We had no information on paternal age or medical conditions, and medications such as metformin. *E*-values suggested that a confounder would have to be associated with two times the risk of PCOS and child hospitalization to explain away the associations we observed (Supplementary Table SV) (VanderWeele and Ding, 2017). We cannot exclude the possibility of detection bias owing to a greater number of physician visits in women with PCOS.

In summary, we found that children exposed to maternal PCOS have a greater risk of hospitalization for infection, allergy and other childhood morbidity before 13 years of age. The association between PCOS and childhood morbidity is stronger earlier in childhood but persists after 5 years of age. The association is also independent of exposures such as advanced maternal age or ART. Further research is needed to determine if effective management of maternal PCOS may reduce childhood morbidity and improve long-term health.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

Code book and analytic code may be requested from the authors. Data described in the manuscript can be requested from the Quebec Ministry of Health and Social Services following standardized access procedures.

Authors' roles

S.Q.W. and N.A. conceived the study. S.Q.W., M.B.-B. and N.A. designed the study. S.Q.W. analyzed the data. S.Q.W., M.B.-B. and N.A. interpreted the data. S.Q.W. wrote the draft, and M.B.-B. and N.A. revised the manuscript. All authors approved the final version.

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Conflict of interest

None declared.

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