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Fetal growth, fetal development, and placental features in women with polycystic ovary syndrome: analysis based on fetal and placental magnetic resonance imaging*

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Abstract: Objective: Polycystic ovary syndrome (PCOS), a common endocrine-metabolic dysfunction in reproductive-aged women, may be involved in compromised pregnancy and offspring outcomes. This study aimed to investigate whether maternal PCOS affects fetal growth, fetal development, and placental features. Methods: This retrospective case-control study included 60 pregnant women with PCOS (PCOS group) and 120 healthy pregnant women without PCOS (control group). Fetal magnetic resonance imaging (MRI) was performed followed by an ultrasound examination and indications for imaging, including known or suspected fetal pathology, history of fetal abnormality in previous pregnancy or in a family member, and concern for placenta accreta. Fetal MRI images were analyzed for head circumference (HC), abdomen circumference (AC), lung-to-liver signal intensity ratio (LLSIR, a prenatal marker of fetal lung maturity), lengths of liver and kidney diameters in fetuses, and placental relative signal intensity on T2-weighted single-shot fast spin echo (SSFSE) imaging (rSI_{SSFSE}), and placental relative apparent diffusion coefficient value (rADC). Data on height and weight of offspring were collected through telephone follow-up. Results: Compared to the control group, the PCOS group showed the following characteristics: (1) smaller biparietal diameter and femur length in fetuses (P=0.026 and P=0.005, respectively), (2) smaller HC in fetuses (evident after 32 weeks; P=0.044), (3) lower LLSIR and smaller dorsoventral length of liver in fetuses (evident before 32 weeks; P=0.005 and P=0.019, respectively), and (4) smaller placental thickness (evident before 32 weeks; P=0.017). No significant differences in placental rSI_{SSFSE} or rADC were observed between the groups (all P>0.05). No significant differences in height and weight of offspring during childhood existed between the groups (all P>0.05). Conclusions: There exist alterations of fetal growth, fetal development, and placental features from women with PCOS.

Key words: Polycystic ovary syndrome (PCOS); Fetus; Magnetic resonance imaging (MRI); Growth and development; Placenta

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1 Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine-metabolic dysfunction in reproductive-aged women, with prevalence ranging from 5% to 13% depending on the population and applied criteria (Li et al., 2013; Bozdag et al., 2016; Skiba et al., 2018).

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PCOS is the leading cause of sub-fecundity and anovulatory infertility (Pan et al., 2018; Zhu and Qu, 2018). Even if being pregnant, women with PCOS have an increased prevalence of pregnancy complications, which may result in a compromised pregnancy and offspring outcomes (Palomba et al., 2015).

A strong genetic component, together with the suboptimal intrauterine environment provided by the PCOS status, was proposed to have detrimental impact on fetal programming and long-term health of PCOS offspring (Kosova and Urbanek, 2013; Dumesic et al., 2014; Cesta et al., 2020). Intrauterine growth might provide indications of long-term development and health (Hales and Barker, 2001). Poor fetal and infant growth has been associated with type 2 diabetes and cardiovascular diseases (Hales and Barker, 2001; Risnes et al., 2011), whereas large fetal size has been suggested to increase risk of cancer, obesity, and impaired glucose tolerance (Ahlsson et al., 2007; Paltiel et al., 2015; Pan et al., 2019). Although the growth of infant and prepubertal children born to women with PCOS has been studied, evidence for the effect of maternal PCOS on fetal characteristics in utero is scarce. It has been proposed that early embryos from PCOS women have different kinetics and development (Wissing et al., 2014); however, it is not clear whether differences in early development persist in the fetal period.

The placenta is suggested to play an important role in the development of pregnancy complications, especially of hypertensive disorders of pregnancy (HDP) and preeclampsia (PE) (Longtine and Nelson, 2011), which have been suggested to be common in women with PCOS who achieve a pregnancy (Yu et al., 2016). The placenta also is a key organ in supplying nutrients for fetal growth and programming the fetus for later disease (Thornburg et al., 2016). Women with PCOS were observed to have aberrant macroscopic and microscopic placental characteristics (Palomba et al., 2013; Koster et al., 2015). It is intuitive, therefore, that placental alterations seen in women with PCOS may predispose to adverse maternal, fetal, and birth outcomes (Kelley et al., 2019).

Fetal magnetic resonance imaging (MRI) enables good visualization and quantification of fetal growth and placental abnormalities (Pugash et al., 2008). In this study, we hypothesized that the impact of maternal PCOS on offspring growth may have existed in intrauterine life, and that fetuses of women with PCOS may have abnormal growth, development, and placental features. To test this hypothesis, we examined retrospectively whether differences in fetal growth and development exist between fetuses of women with PCOS and fetuses of healthy women without PCOS; we also compared the placental features detected by fetal MRI, including the occurrence of placental abnormalities, signal intensity of the placenta on T2-weighted MRI, and placental apparent diffusion coefficient (ADC) value on diffusion-weighted imaging (DWI).

2 Materials and methods

2.1 Study population

This retrospective study was performed at the Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, China. The hospital's Ethics Committee approved the study with ethical approval number 2019-006. Written informed consent was obtained before all fetal MRI procedures. Data were retrieved from the hospital's electronic medical record system and radiology database for the period 2013–2018. All referrals for fetal MRI followed an ultrasound examination. Imaging was performed for various clinical indications, including known or suspected fetal pathology, history of fetal abnormalities in a previous pregnancy or in a family member, and concern for placenta accreta (Committee on Obstetric Practice, 2012; Prayer et al., 2017). Eligibility criteria of participants in this study included: (1) pregnant women with diagnosed PCOS (PCOS group) and pregnant healthy women without PCOS (served as a control group), who underwent fetal MRI examination and to whom obstetric outcomes could be traced, (2) singleton pregnancies, and (3) deliveries with live birth infants. Exclusion criteria included the presence of pre-existing maternal diseases (including diabetes, chronic hypertension, and thyroid disease), maternofetal infection, abnormal fetal karyotype, and fetal malformation. Cases with poor MRI image quality were also excluded. For DWI analysis, cases for which DWI was non-diagnostic due to motion artifact degradation, which resulted in a blurred ADC map with poorly defined anatomical structures, were also excluded.

PCOS was defined according to the Rotterdam criteria (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). Data on previous PCOS diagnosis, or PCOS phenotypes including oligomenorrhea (menstrual cycles of ≥35 d), hyperandrogenism, and polycystic ovaries, were collected from medical records. If a PCOS diagnosis could not be determined for the women with isolated PCOS phenotypes, these women would be included in the PCOS group if they replied yes to the question, "Has a doctor ever told you that you have PCOS?" in a telephone visit. Women in the control group had a history of regular menstrual cycles and no hyperandrogenism, with a similar gestational age (GA) at the time of MRI examination to the women in PCOS group. For each woman with PCOS, two controls fulfilling the above criteria were randomly selected during the same period from our computerized database.

2.2 MRI

All prenatal MRI images were obtained with a 1.5-T unit (Signal HDxt, General Electric Company, CT, USA) and an eight-element phased array body coil. The mothers were placed in a supine or left lateral decubitus position without sedative or contrast medium. After a localizing gradient echo sequence, we randomly selected single-shot fast spin echo (SSFSE: short repetition time/echo time (TR/TE), 3100 ms/90 ms; bandwidth, 32 kHz; field-of-view (FOV), 30 cm×32 cm; matrix, 256×192; slice thickness, 3 to 5 mm; gap, 0 to 1 mm; number of excitations (NEX), 1) T2-weighted imaging and fast imaging employing steady-state acquisition (FIESTA: TR/TE, 3.6 ms/1.7 ms; bandwidth, 80 Hz; FOV, 32 cm×32 cm; matrix, 256×224; slice thickness, 4 to 5 mm; gap, 0 to 0.5 mm; flip angle, 55°) in the axial, coronal, and sagittal planes. DWI images were acquired in the axial plane using the single-shot echo planar imaging (EPI) technique with parallel imaging and fat suppression (TR/TE, 4200 ms/69 ms; FOV, 36 cm×36 cm; slice thickness, 4 mm; b-value, 600 s/mm^2). In our study, the specific absorption rate (SAR) values of all sequences were lower than 2.0 W/kg.

2.3 Data collection

All the following data were collected by patient medical records from electronic medical record system: maternal demographic and clinical data including age, body mass index (BMI), employment status, educational level, number of previous children, GA at MRI examination, and pregnancy complications; birth data including mode of delivery, GA at birth, neonatal gender, anthropometric measurements of newborn, and need for neonatal intensive care unit (NICU) admission; and ultrasound data from the ultrasound scan closest to the date of fetal MRI examination, including GA at ultrasound, biparietal diameter, femur length, and systolic-diastolic ratio (S/D) of umbilical artery. A telephone follow-up for the growth of offspring during childhood (2 to 7 years of age) was conducted in September 2020, and the height and weight of the children measured within a month of the phone call were collected. The World Health Organization (WHO) 2007 Reference and AnthroPlus (WHO, Geneva, Switzerland) were used to calculate the height, weight, and BMI z-scores for age.

Measurements and analyses of MRI images were conducted independently by two radiology research fellows, and confirmed by a radiologist with ten years of clinical experience. For the fetuses, head circumference (HC), abdomen circumference (AC), lengths of the liver including craniocaudal length (L_{CC}), transverse length (L_{TR}), and dorsoventral length (L_{DV}), and kidney diameters including anteroposterior (AP) and bipolar diameters of the bilateral kidneys, were measured by SSFSE or FIESTA acquisition. The methodology used to acquire these measurements was based on that of previous studies (Cannie et al., 2007; Hamabe et al., 2013; Kiserud et al., 2017) and detailed in Fig. 1. Signal intensity assessment of fetal lung and liver was measured with T2-weighted SSFSE imaging, at three regions of interest (ROIs) in both right lung and liver, in the same cut in one axial or coronal image based on the plane and image with the fewest artifacts (Fig. 2a). Fetal lung-to-liver signal intensity ratio (LLSIR), a prenatal marker of fetal lung maturity, was calculated as the average of the three right lung measurements divided by the average of the three-hepatic measurement (Yamoto et al., 2018).

For the placenta, presence or absence of placental abnormalities (irregular placental shape, abruptio placentae, placenta previa, placental hematoma), placental thickness, signal intensity of placenta, and placental ADC value were analyzed. Placental

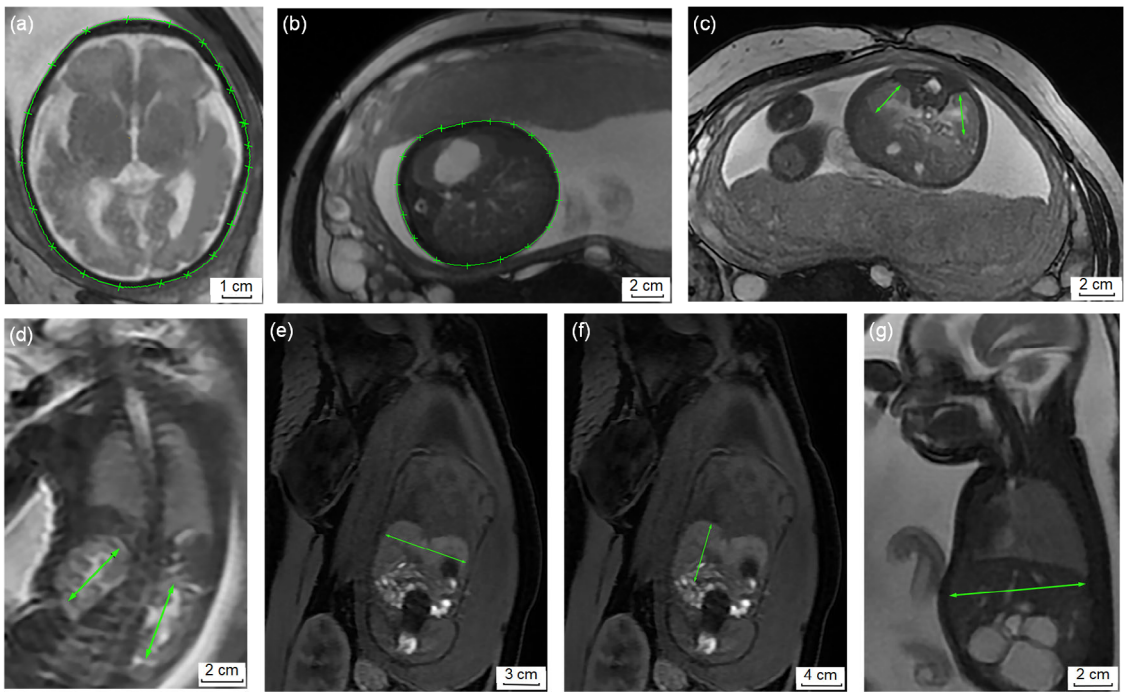

Fig. 1 Magnetic resonance imaging (MRI) slices showing fetal measurements

(a) Head circumference; (b) Abdomen circumference; (c) Anteroposterior diameters of bilateral kidneys; (d) Bipolar diameters of bilateral kidneys; (e) Liver transverse length; (f) Liver craniocaudal length; (g) Liver dorsoventral length

ADC values were calculated from DWI acquisition and the parametric maps of ADC were reconstructed using Advantage Workstation (AW) and FuncTool software (GE Healthcare, IL, USA). Three similarly-sized ROIs at different sites of placenta on the same slice were selected to measure ADC value. ROIs were positioned at the periphery and the center of placenta, avoiding cystic, calcific, hemorrhagic, and necrotic tissues. The mean value of three ROI measurements was calculated for placental ADC. The SSFSE sequence was used to assess signal intensity (SI_{SSFSE}) by averaging three ROIs within homogeneous regions of the placenta. An additional ROI in the vitreous humor of the fetal ocular globe was selected to measure SI_{SSFSE} and ADC value, separately. The fetal ocular globe was used as the reference tissue in the same series to calculate the ratio of placenta to fetal ocular globe, or placental relative SI_{SSFSE} (rSI_{SSFSE}) and relative ADC (rADC) values (Figs. 2b and 2c):

placental rSI_{SSFSE}=placental mean SI_{SSFSE}/SI_{SSFSE} of fetal ocular globe;

placental rADC=placental mean ADC/ADC of fetal ocular globe.

2.4 Statistical analysis

Statistical analysis was conducted using IBM SPSS (Version 21.0, IBM Corp., Armonk, NY, USA). Prior to analysis, the Kolmogorov-Smirnov test was used to assess data distribution. To compare quantitative data, we used the Student's *t* test for normally distributed data and the Mann-Whitney *U* test for non-parametric data. χ^2 test or Fisher exact test was used for comparisons of qualitative data. To analyze inter-group differences in fetal growth, development of fetal lung, liver and kidneys, and placental features, *P*-values resulting from univariate analyses were adjusted for potential confounding variables. Multivariate analyses were carried out using multiple regression linear models. First, baseline characteristics, including maternal age, BMI, nulliparity, GA at examination (ultrasound, MRI, or telephone follow-up), and neonatal gender were included in the multiple regression analyses. Second, we adjusted for pregnancy complications as well, including the presence of gestational diabetes mellitus, HDP/PE, thyroid diseases in pregnancy, and preterm birth. For all analyses, two-sided *P*-values of <0.05 were considered statistically significant.

3 Results

3.1 Population characteristics

A total of 60 pregnant women with diagnosed PCOS and 120 controls were included in this study. Demographic and clinical characteristics are presented in Table 1. Notably, mothers with PCOS have a significantly higher pre-pregnancy BMI than controls (P=0.020). No significant difference was found between PCOS and control groups in maternal age, employment status, educational level, gravidity, GA at ultrasound, or GA at time MRI examination (all P>0.05).

3.2 Obstetrical and neonatal outcomes

Comparison of obstetrical and neonatal outcomes between groups is shown in Table 2. Mothers in the PCOS group had a significantly higher incidence of gestational diabetes mellitus (GDM) than the controls (P=0.034). The incidence of HDP/PE, intrahepatic cholestasis of pregnancy (ICP), thyroid diseases in pregnancy, instrumental delivery, cesarean section or postpartum hemorrhage did not differ between groups (all P>0.05). Preterm births (GA at birth <34 weeks and <37 weeks) and NICU admissions were more frequent among newborns in the PCOS group (P=0.012, P=0.004, and P=0.004, respectively). No significant differences were found in GA at birth, neonatal gender, birth weight, Apgar score, or incidence of neonatal hyperbilirubinemia and respiratory distress (all P>0.05).

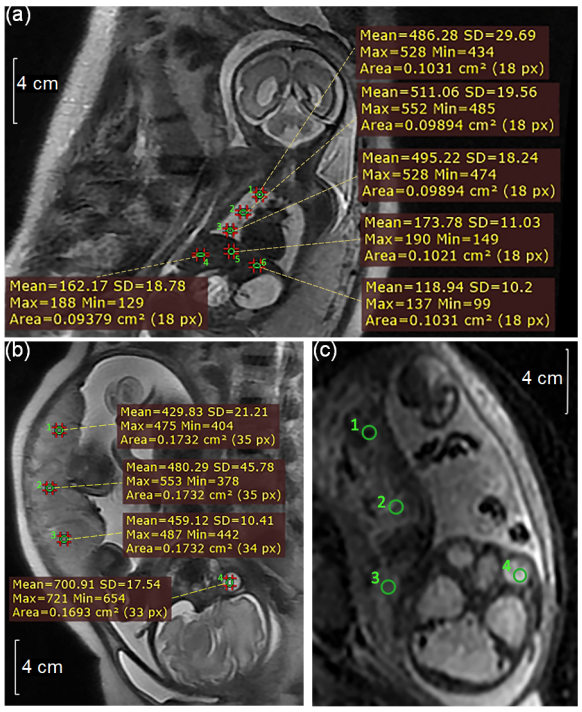

Fig. 2 MRI slices showing ROIs

(a) Signal intensity assessment of fetal lung and liver with T2-weighted imaging. The regions of interests (ROIs) for pulmonary (1–3) and hepatic (4–6) fetal measurements are shown. (b) ROIs for signal intensity assessment of placenta (1–3) and fetal ocular globe (4) on T2-weighted imaging. (c) ROIs for apparent diffusion coefficient measures in placenta (1–3) and fetal ocular globe (4) on diffusion-weighted imaging. MRI, magnetic resonance imaging

3.3 Fetal growth

Fetal growth as measured by ultrasound and fetal MRI is shown in Table 3. Biparietal diameter and femur length in fetuses assessed by ultrasound were significantly smaller in the PCOS group than in the control group, and these differences were still significant after adjustment for potential confounding variables (P=0.026 and P=0.005, respectively). Fetuses in the PCOS group had a smaller HC compared with fetuses in the control group; however, this was not statistically significant after adjustment for potential confounding variables. However, fetuses in the PCOS group had a smaller mean HC at GA>32 weeks compared to those in the control group after adjustment for potential confounding variables (P=0.044).

3.4 Development of fetal lung, liver, and kidneys

Development of fetal lung, liver, and kidneys measured by fetal MRI is shown in Table 4. Fetuses at GA≤32 weeks in the PCOS group had significantly smaller LLSIR and liver L_{DV} than those in the control group after adjustment for potential confounding variables (P=0.005 and P=0.019, respectively). Overall, liver L_{DV}, left and right AP kidney diameters of fetuses were significantly smaller in the PCOS group than in the control group; however, this difference was still significant only for liver L_{DV} after adjustment for potential confounding variables (P=0.001).

3.5 Placental features

Table 5 shows the placental characteristics of both groups, measured by placental MRI or by direct measurement after delivery. Mean placental thickness

Table 1 Population characteristics

Item	PCOS group (n=60)	Control group (n=120)	P-value[a]
Maternal age (year)	30.8±3.8	30.2±3.9	0.337
Age>35 years	5 (8.3)	11 (9.2)	0.853
Pre-pregnancy BMI (kg/m^2)	21.7±2.6	20.6±2.9	0.020
BMI<25 kg/m^2	52 (86.7)	111 (92.5)	0.207
BMI≥25 kg/m^2	8 (13.3)	9 (7.5)	
Maternal employment status			
Full-time employment	49 (81.7)	100 (83.3)	0.434
Part-time employment	5 (8.3)	8 (6.7)	
Registered unemployed	6 (10.0)	8 (6.7)	
Others	0 (0.0)	4 (2.0)	
Maternal educational level			
No college education	25 (25.0)	28 (23.3)	0.888
College education	39 (65.0)	82 (68.3)	
Higher than college education	6 (10.0)	10 (8.3)	
Parity			
Nulliparity	39 (65.0)	77 (64.2)	0.912
Multiparity	21 (35.0)	43 (35.8)	
GA at ultrasound (week)[b]	32.0±3.7	32.4±3.4	0.541
GA≤32 weeks	31 (56.4)	69 (58.5)	0.793
GA>32 weeks	24 (43.6)	49 (41.5)	
GA at MRI (week)	31.8±3.9	32.6±2.8	0.210
GA≤32 weeks	33 (55.0)	66 (55.0)	1.000
GA>32 weeks	27 (45.0)	54 (45.0)	

Data are presented as mean±standard deviation (SD) or number (percentage). [a] Student's t test or χ^2 test. [b] n=55 in PCOS group and n=118 in control group. PCOS, polycystic ovary syndrome; BMI, body mass index; GA, gestational age; MRI, magnetic resonance imaging

Table 2 Obstetrical and neonatal outcomes

Item	PCOS group (n=60)	Control group (n=120)	P-value[a]
Obstetric outcomes			
GDM	15 (25.0)	15 (12.5)	0.034
HDP/PE	8 (13.3)	6 (5.0)	0.094
ICP	3 (5.0)	3 (2.5)	0.402
Thyroid diseases in pregnancy	6 (10.0)	3 (2.5)	0.062
Instrumental delivery	2 (3.3)	3 (2.5)	1.000
Cesarean section	31 (51.7)	54 (45.0)	0.398
Postpartum hemorrhage	2 (3.3)	3 (2.5)	1.000
Neonatal outcomes			
GA at birth (week)	39 (37, 40)	39 (38, 40)	0.678
FGR	1 (1.7)	3 (2.5)	0.721
Preterm birth (<34 weeks)	4 (6.7)	0 (0.0)	0.012
Preterm birth (<37 weeks)	10 (16.7)	5 (4.2)	0.004
Gender			
Male	31 (51.7)	74 (61.7)	0.200
Female	29 (48.3)	46 (38.3)	
Birth weight (g)	3228.7±688.5	3269.5±554.2	0.668
Birth weight<10th centile (SGA)	3 (5.0)	7 (5.8)	0.818
Birth weight>90th centile (LGA)	4 (6.7)	6 (5.0)	0.733
Birth height (cm)	49.0±3.7	49.6±2.5	0.222
1 min Apgar score<7	1 (1.7)	2 (1.7)	1.000
5 min Apgar score<7	0 (0.0)	1 (0.8)	1.000
Neonatal hyperbilirubinemia	15 (25.0)	19 (15.8)	0.139
Respiratory distress	8 (13.3)	10 (8.3)	0.292
NICU admission	15 (25.0)	11 (9.2)	0.004

Data are presented as number (percentage), mean±standard deviation (SD), or median (quartiles). [a] χ^2 test, Student's t test, or Mann-Whitney U test. PCOS, polycystic ovary syndrome; GDM, gestational diabetes mellitus; HDP/PE, hypertensive disorders of pregnancy or preeclampsia; ICP, intrahepatic cholestasis of pregnancy; GA, gestational age; FGR, fetal growth restriction; SGA, small-for-gestational-age; LGA, large-for-gestational age; NICU, neonatal intensive care unit

Table 3 Fetal growth

Item	PCOS group		Control group		PCOS vs. control		
	Number	Mean±SD	Number	Mean±SD	*P*-value[a]	Adjusted *P*-value[b]	Adjusted *P*-value[c]
Ultrasound data							
Biparietal diameter (cm)							
GA≤32 weeks	31	7.7±0.9	67	8.1±0.6	0.017	0.022	0.148
GA>32 weeks	24	8.6±0.5	45	8.8±0.6	0.067	0.051	0.107
Overall	55	8.1±0.9	112	8.4±0.7	0.017	0.002	0.026
Femur length (cm)							
GA≤32 weeks	31	5.4±0.7	67	5.9±0.5	0.001	<0.001	0.002
GA>32 weeks	23	6.5±0.4	44	6.7±0.5	0.309	0.115	0.323
Overall	54	5.9±0.8	111	6.2±0.6	0.017	<0.001	0.005
S/D value of umbilical artery							
GA≤32 weeks	30	2.8±0.6	47	2.7±0.4	0.690	0.804	0.636
GA>32 weeks	21	2.4±0.3	30	2.6±0.2	0.152	0.227	0.175
Overall	51	2.6±0.5	77	2.7±0.5	0.624	0.570	0.300
Fetal MRI data							
HC (mm)							
GA≤32 weeks	33	291.1±34.8	66	306.3±43.3	0.083	0.859	0.827
GA>32 weeks	27	323.7±18.5	54	335.3±21.1	0.017	0.024	0.044
Overall	60	305.8±32.7	120	319.4±37.8	0.019	0.079	0.327
AC (mm)							
GA≤32 weeks	33	261.0±41.7	66	285.4±24.7	0.003	0.021	0.144
GA>32 weeks	27	316.3±27.9	54	314.7±45.5	0.862	0.904	0.390
Overall	60	285.9±45.4	120	298.6±38.3	0.066	0.125	0.828

[a] Student's *t* test. [b] Multivariate analysis adjusted for maternal age, BMI, nulliparity, GA at ultrasound or MRI, and neonatal gender. [c] Multivariate analysis adjusted for maternal age, BMI, nulliparity, GA at ultrasound or MRI, neonatal gender, GDM, HDP/PE, and thyroid diseases in pregnancy and preterm birth (<37 weeks). PCOS, polycystic ovary syndrome; SD, standard deviation; GA, gestational age; S/D, systolic-diastolic ratio; MRI, magnetic resonance imaging; HC, head circumference; AC, abdomen circumference; BMI, body mass index; GDM, gestational diabetes mellitus; HDP/PE, hypertensive disorders of pregnancy or preeclampsia

in fetuses in the PCOS group at GA>32 weeks was significantly lower than that in the control group after adjustment for potential confounding variables (P=0.017). No significant differences in rADC or rSI_{SSFSE} were observed between groups (all P>0.05). There were no significant differences in weight, maximum and minimum diameter, or the incidence of placental abnormalities between the groups (all P>0.05).

3.6 Follow-up assessments of childhood growth

Follow-up assessments of childhood growth were carried out in 58 of the 60 (96.7%) offspring of women with PCOS and 107 of the 120 (89.2%) offspring of women without PCOS. Growth data during childhood are shown in Table 6. No significant differences were found in height, weight, BMI, or height, weight, and BMI z-scores for age after adjustment for potential confounding variables (all P>0.05).

4 Discussion

With an original design providing a global vision of fetal MRI measurements and follow-up assessments of childhood growth, our study offers novel insights on fetal growth, fetal development, and placental features in women with PCOS. After adjustment for potential confounding variables, our results indicate decreased biparietal diameter, femur length, HC, LLSIR, and liver length in fetuses, and smaller placental thickness from women with PCOS, compared with controls, suggesting that maternal PCOS affects fetal growth and placental development.

Published data on the relationship of maternal PCOS and fetal growth are inconclusive. An earlier meta-analysis reported an almost 2.6-fold increased risk of small-for-gestational-age (SGA) at birth (Kjerulff et al., 2011), whereas a later meta-analysis found

Table 4 Development of fetal lung, liver, and kidneys

Item	PCOS group		Control group		PCOS vs. control		
	Number	Mean±SD	Number	Mean±SD	*P*-value[a]	Adjusted *P*-value[b]	Adjusted *P*-value[c]
LLSIR							
GA≤32 weeks	33	2.46±0.53	66	2.70±0.88	0.158	0.007	0.005
GA>32 weeks	27	3.06±0.92	54	2.67±0.46	0.013	0.077	0.145
Overall	60	2.73±0.79	120	2.68±0.71	0.715	0.778	0.718
Liver L_{CC} (mm)							
GA≤32 weeks	33	49.7±7.7	66	50.1±7.1	0.803	0.343	0.223
GA>32 weeks	27	55.1±6.4	54	57.3±8.0	0.229	0.127	0.231
Overall	60	52.2±7.6	120	53.3±8.3	0.355	0.847	0.889
Liver L_{TR} (mm)							
GA≤32 weeks	33	69.4±11.2	66	71.9±8.2	0.259	0.696	0.300
GA>32 weeks	27	78.8±6.6	54	80.3±6.6	0.344	0.078	0.229
Overall	60	73.6±10.4	120	75.7±8.6	0.193	0.209	0.789
Liver L_{DV} (mm)							
GA≤32 weeks	33	46.3±10.9	66	54.0±7.4	0.001	0.003	0.019
GA>32 weeks	27	55.0±10.5	54	60.0±9.4	0.038	0.075	0.166
Overall	60	50.2±11.5	120	56.7±8.8	<0.001	<0.001	0.001
Left AP kidney diameter (mm)							
GA≤32 weeks	33	19.9±3.9	66	21.7±3.1	0.026	0.427	0.913
GA>32 weeks	27	21.4±2.8	54	22.2±2.6	0.236	0.218	0.347
Overall	60	20.6±3.5	120	21.9±2.8	0.007	0.013	0.070
Right AP kidney diameter (mm)							
GA≤32 weeks	33	20.0±3.7	66	22.3±3.6	0.003	0.102	0.265
GA>32 weeks	27	22.4±2.4	54	22.2±2.6	0.733	0.658	0.428
Overall	60	21.1±3.4	120	22.3±3.2	0.021	0.039	0.136
Left bipolar kidney diameters (mm)							
GA≤32 weeks	33	31.7±5.2	66	33.8±3.3	0.037	0.570	0.696
GA>32 weeks	27	35.9±3.9	54	35.3±3.4	0.477	0.208	0.098
Overall	60	33.6±5.1	120	34.5±3.4	0.219	0.724	0.898
Right bipolar kidney diameters (mm)							
GA≤32 weeks	33	31.6±5.1	66	33.4±3.3	0.068	0.583	0.815
GA>32 weeks	27	35.5±3.4	54	34.8±3.8	0.467	0.383	0.197
Overall	60	33.3±4.8	120	34.1±3.6	0.307	0.677	0.702

[a] χ^2 test or Student's *t* test. [b] Multivariate analysis adjusted for maternal age, BMI, nulliparity, GA at MRI, and neonatal gender. [c] Multivariate analysis adjusted for maternal age, BMI, nulliparity, GA at MRI, neonatal gender, GDM, HDP/PE, and thyroid diseases in pregnancy and preterm birth (<37 weeks). PCOS, polycystic ovary syndrome; SD, standard deviation; LLSIR, lung-to-liver signal intensity ratio; GA, gestational age; L_{CC}, craniocaudal length; L_{TR}, transverse length; L_{DV}, dorsoventral length; AP, anteroposterior; MRI, magnetic resonance imaging; BMI, body mass index; GDM, gestational diabetes mellitus; HDP/PE, hypertensive disorders of pregnancy or preeclampsia

that PCOS in pregnancy had little or no effect on SGA or fetal growth restriction (FGR) (Yu et al., 2016). However, the degree of correlation between maternal PCOS and fetal outcomes may differ according to study design and confounding factors, and most fetal outcomes could not be assessed in previous studies. The present study found that fetuses of women with PCOS had shorter biparietal diameter and femur length and smaller HC, suggesting delayed fetal growth. This finding is consistent with one previous study suggesting that maternal PCOS per se has a "growth restrictive" effect on fetal growth, yielding offspring with smaller biparietal diameter at GA of 32 weeks and shorter body length at birth (Hjorth-Hansen et al., 2018). As decreased biparietal diameter, femur length, and HC were previously reported to be associated with a subsequent delivery of SGA offspring (Mailath-Pokorny et al., 2015; Kim et al., 2019), the results in

our study also support the finding that newborns of women with PCOS are more likely to be born with SGA (Sir-Petermann et al., 2005; Han et al., 2011; Palomba et al., 2014b).

T2-weighted MRI measurements of fetal LLSIR can be used as a prenatal marker of fetal lung maturity (Yamoto et al., 2018). In the present study, fetal LLSIR at GA≤32 weeks was lower in fetuses of women with PCOS, indicating slower rate of early lung development that correlates with postnatal functioning. This finding reflects an earlier critical review that reported an almost 1.3-fold increased risk of respiratory distress or other pulmonary problems in neonates with maternal PCOS (McDonnell and Hart, 2017). Liver length is correlated with fetal body wight and has been used as an assessment method for fetal growth and nutrition (Hamabe et al., 2013). Our study found a shorter dorsoventral length in livers of fetuses of women with PCOS. As the liver is involved in numerous metabolic processes (Roberts et al., 1994), and an increased risk of metabolic disorders was found in adult PCOS offspring (Doherty et al., 2015), our findings may contribute not only to understanding fetal growth in fetuses with maternal PCOS, but also to the long-term well-being of these offspring.

Abnormal fetal growth could be attributed to maternal characteristics of PCOS status and pregnancy complications, which are more prone to develop in

Table 5 Placental features

Item	PCOS group		Control group		PCOS vs. control		
	Number	Percentage (%) or mean±SD	Number	Percentage (%) or mean±SD	*P*-value[a]	Adjusted *P*-value[b]	Adjusted *P*-value[c]
Placental MRI data							
Placental thickness (mm)							
GA≤32 weeks	33	39.0±7.9	66	39.8±10.9	0.679	0.536	0.533
GA>32 weeks	27	39.7±7.5	54	43.1±8.8	0.069	0.131	0.017
Overall	60	39.3±7.7	120	41.3±10.1	0.169	0.218	0.174
rSI_{SSFSE}							
GA≤32 weeks	33	0.63±0.14	66	0.58±0.09	0.034	0.059	0.054
GA>32 weeks	27	0.53±0.12	54	0.53±0.09	0.904	0.702	0.742
Overall	60	0.58±0.14	120	0.55±0.09	0.093	0.085	0.061
rADC							
GA≤32 weeks	26	0.72±0.13	56	0.68±0.11	0.159	0.209	0.179
GA>32 weeks	20	0.70±0.13	44	0.66±0.13	0.373	0.378	0.922
Overall	46	0.71±0.13	100	0.67±0.12	0.100	0.147	0.216
Placental findings at delivery							
Weight (g)	28	490.0±67.4	58	506.2±59.7	0.261	0.559	0.519
Maximum diameter (cm)	59	18.8±2.1	117	18.8±1.8	0.782	0.841	0.774
Minimum diameter (cm)	59	17.5±1.9	117	17.4±1.8	0.722	0.513	0.551
Irregular placental shape							
No	58	96.7	117	97.5	1.000	0.653	0.828
Yes	2	3.3	3	2.5			
Abruptio placentae							
No	58	96.7	115	95.8	1.000	0.959	0.774
Yes	2	3.3	5	4.2			
Placenta previa							
No	59	98.3	115	95.8	0.665	0.468	0.663
Yes	1	1.7	5	4.2			
Placental hematoma							
No	59	98.3	120	100.0	0.333	0.989	1.000
Yes	1	1.7	0	0.0			

[a] χ^2 test or Student's *t* test. [b] Multivariate analysis adjusted for maternal age, BMI, nulliparity, GA at MRI or at delivery, and neonatal gender. [c] Multivariate analysis adjusted for maternal age, BMI, nulliparity, GA at MRI or at delivery, neonatal gender, GDM, HDP/PE, and thyroid diseases in pregnancy and preterm birth (<37 weeks). PCOS, polycystic ovary syndrome; SD, standard deviation; MRI, magnetic resonance imaging; GA, gestational age; rSI_{SSFSE}, relative signal intensity on half-Fourier acquisition single-shot turbo spin-echo; rADC, relative apparent diffusion coefficient; BMI, body mass index; GDM, gestational diabetes mellitus; HDP/PE, hypertensive disorders of pregnancy or preeclampsia

Table 6 Growth during childhood

Item	PCOS group (n=58)	Control group (n=107)	PCOS vs. control		
			P-value[a]	Adjusted P-value[b]	Adjusted P-value[c]
Boy	n=30	n=70			
Age (year)	3.3±1.2	4.4±1.6	0.000		
Height (cm)	100.2±10.2	107.4±11.6	0.004	0.979	0.752
Height for age (z-score)	0.4 (−0.7, 1.3)	0.5 (−0.0, 1.1)	0.381	0.585	0.715
Weight (kg)	16.0±3.6	18.3±4.0	0.009	0.229	0.995
Weight for age (z-score)	0.1 (−0.2, 1.2)	0.2 (−0.3, 1.1)	0.955	0.627	0.828
BMI (kg/m^2)	15.9±1.9	15.8±1.8	0.807	0.821	0.843
BMI for age (z-score)	0.2 (−0.7, 1.0)	0.1 (−0.9, 1.3)	0.874	0.282	0.373
Girl	n=28	n=37			
Age (year)	4.0±1.4	4.5±1.6	0.188		
Height (cm)	102.4±10.9	106.2±11.5	0.173	0.802	0.583
Height for age (z-score)	0.2 (−0.1, 0.7)	0.2 (−0.4, 0.9)	0.979	0.772	0.569
Weight (kg)	16.1±3.1	17.6±3.9	0.091	0.557	0.445
Weight for age (z-score)	0.1 (−0.0, 0.4)	−0.1 (−0.4, 0.6)	0.368	0.430	0.995
BMI (kg/m^2)	15.4±1.8	15.5±1.8	0.750	0.375	0.332
BMI for age (z-score)	0.1 (−0.7, 0.6)	−0.2 (−0.8, 0.7)	0.812	0.484	0.423

Data are presented as mean±standard deviation (SD) or median (quartiles). [a] Student's t test. [b] Multivariate analysis adjusted for maternal age, BMI, nulliparity, and offspring age. [c] Multivariate analysis adjusted for maternal age, BMI, nulliparity, offspring age, GDM, HDP/PE, and thyroid diseases in pregnancy and preterm birth (<37 weeks). PCOS, polycystic ovary syndrome; BMI, body mass index; GDM, gestational diabetes mellitus; HDP/PE, hypertensive disorders of pregnancy or preeclampsia; BMI, body mass index

women with PCOS (Palomba et al., 2015; Yu et al., 2016); our study showed a higher pre-pregnancy BMI, and higher incidence of GDM and preterm delivery in women with PCOS. However, after adjusting for variables of maternal characteristics and pregnancy complications, the observed abnormal fetal growth was still present, implying that the pathophysiology potentially originates from other factors. It is possible that poor oocyte and embryo quality, and in utero environment in pregnant women with PCOS account for the observed abnormalities in fetal growth and adverse neonatal outcomes (McDonnell and Hart, 2017). Moreover, a hyperandrogenic environment during gestation in women with PCOS may predispose their offspring to excess androgen exposure during fetal life (Mehrabian and Kelishadi, 2012; Daan et al., 2017), which may have negative impacts on fetal growth (Whitehouse et al., 2010).

Placental dysfunction is another possible explanation for abnormal fetal growth in fetus of women with PCOS. From macroscopic and microscopic examinations comparing women with and without PCOS, previous studies confirmed structural alterations and histopathological abnormalities of placentas in PCOS women (Palomba et al., 2013, 2014a; Koster et al., 2015). Increased levels of placental signal transducer and activator of transcription 3 (STAT3) signaling were seen in pregnant women with PCOS, and activation of STAT3 signaling would affect important pathways in the regulation of placental nutrient transport and indirectly affect fetal growth (Maliqueo et al., 2015). Higher 3β-hydroxysteroid dehydrogenase type 1 activity and lower P450 aromatase activity have been observed in placental tissue of PCOS women, suggesting altered function of placental steroidogenesis and increased androgen production (Maliqueo et al., 2013).

Consistent with previous studies (Palomba et al., 2013, 2014a), our study found decreased placental thickness in women with PCOS. This result was evident after GA of 32 weeks and adjustment for pregnancy complications, suggesting that the observed placental alteration seems not to be caused by increased incidence of pregnancy complications in women with PCOS. ADC is known to be reduced in placentas of growth-restricted fetuses (Bonel et al., 2010), and the placental SSFSE signal intensity can be used to evaluate placental function and risk of SGA (Himoto et al., 2016). However, our study found

no significant difference in placental ADC or SSFSE signal intensity between women with and without PCOS, suggesting that placental perfusion and tissue density may not be affected by PCOS.

5 Conclusions

In conclusion, there exist alterations of fetal growth, fetal development, and placental features in women with PCOS. However, this conclusion might be limited by the necessarily retrospective design of our study, which restricted our ability to identify different PCOS phenotypes, and by the lack of prospective follow-up for offspring outcomes. The data reflecting intrauterine status of fetuses and placenta in this study need to be more comprehensively reevaluated after delivery. As we found that children born to mothers with PCOS grew similarly compared to children born to mothers without PCOS, the association between growth in utero and after birth in offspring of mothers with PCOS needs to be further investigated by standardized anthropometrics and long-term follow-up. Moreover, the sample size was small, and ultrasound data and ADC maps were absent for some patients. However, the value of our findings is supported by the robust study design, comprehensive data collection, and high-quality MRI measurements. In addition, all data were adjusted for many potential confounding factors.

Contributors

Fan QU designed the research, reviewed and edited the manuscript. Qing ZHANG and Zhong-kun BAO wrote the manuscript and performed data analysis. Mei-xiang DENG, Qiong XU, Dan-dan DING, Man-man PAN, and Xi XI collected the data. Fang-fang WANG and Yu ZOU explained the data. All authors have read and approved the final manuscript and, therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Qing ZHANG, Zhong-kun BAO, Mei-xiang DENG, Qiong XU, Dan-dan DING, Man-man PAN, Xi XI, Fang-fang WANG, Yu ZOU, and Fan QU declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Written informed consent was obtained from all patients for being included in the study before all fetal magnetic resonance imaging procedures.

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中文概要

题　目：多囊卵巢综合征女性孕期的胎儿生长发育和胎盘特征：基于胎儿和胎盘磁共振成像分析

目　的：探讨母亲多囊卵巢综合征（PCOS）对子代胎儿期生长发育和胎盘特征的影响。

创新点：首次关注到 PCOS 女性孕期的胎儿和胎盘磁共振成像（MRI）特征，通过影像学和临床疾病的结合，对胎儿和胎盘 MRI 图像进行全面分析和测量，评估胎儿生长发育和胎盘特征，并追踪产科和子代随访结局，以期为 PCOS 对子代的潜在影响提供科学依据。

方　法：本研究对浙江大学医学院附属妇产科医院 2013～2018 年行胎儿 MRI 检查的妊娠女性病例行回顾性分析，根据鹿特丹诊断标准纳入 PCOS 妊娠女性 60 例，随机选取与其胎儿 MRI 检查孕周相匹配的非 PCOS 妊娠女性 120 例作为对照，收集胎儿和胎盘 MRI 图像信息，统计学分析比较 PCOS 妊娠女性与非 PCOS 妊娠女性影像学测量指标，包括胎儿的双顶径、头围、腹围、肝脏和肾脏各径线，胎儿肺和肝的信号强度，胎盘异常情况、胎盘厚度、胎盘信号强度和表观扩散系数值（ADC），并比较分析人口学数据、产科和新生儿结局，随访子代儿童期的生长情况。

结　论：母亲 PCOS 会造成子代胎儿期生长发育和胎盘特征的改变。因本研究为回顾性研究、样本量偏小及一些潜在的偏差，结论有待进一步证实。

关键词：多囊卵巢综合征；胎儿；核磁共振成像；生长发育；胎盘