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Insulin resistance in pregnant women with and without polycystic ovary syndrome, and measures of body composition in offspring at birth and 3 years of age

Running headline: maternal PCOS and offspring obesity

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Conflict of interest statement:

None of the authors of this article have any conflict of interest in connection with this article.

Abstract

Introduction: Polycystic ovary syndrome (PCOS) is associated with obesity and insulin resistance in the non-pregnant state, but little is known about insulin sensitivity in the pregnant state. Our objective was to compare insulin resistance in pregnant women with and without PCOS and explore the impact of PCOS on body composition in offspring at birth and at 3 years of age. Material and methods: A prospective cohort study including 2548 live born singleton mother-child pairs residing in Odense municipality, Denmark, during 2010-2013. Of the 2548 women, 241 (9.4%) had PCOS. Results: Homeostatic model assessment for insulin resistance (HOMA-IR) assessments were comparable in women with and without PCOS. However, the subgroup of overweight women with PCOS had significantly higher levels of HOMA-IR than overweight women without PCOS (mean ±2SD): 4.4 (3.1) vs. 3.6 (3.4), p = 0.004. Maternal PCOS did not affect offspring birthweight after accounting for age. PCOS, adjusted for maternal BMI, was however, associated with increased BMI at 3 years of age (mean ±2SD): 16.0 (2.2) vs. 15.7 (2.1) kg/m², p = 0.04. Conclusion: In our cohort, maternal PCOS was not associated with insulin resistance after correcting for BMI and was not an independent predictor of offspring birthweight. However, both PCOS and high maternal BMI may increase risk of childhood obesity at 3 years of age.

Keywords

Polycystic ovary syndrome, insulin resistance, HOMA-IR, PCOS, pregnancy, offspring

Abbreviations:

PCOS: polycystic ovary syndrome

HOMA-IR: homeostatic model assessment for insulin resistance

BMI: body mass index

IR: insulin resistance

GDM: gestational diabetes mellitus

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BW: birthweight
GA: gestational age
AC: abdominal circumference
CV: coefficient of variation

Key message
HOMA-IR assessments in our cohort were comparable between women with and without PCOS, although in the subgroup of overweight women, the difference was significant. Maternal PCOS did not affect offspring birthweight, but was associated with increased offspring BMI at 3 years of age.

Introduction
Polycystic ovary syndrome (PCOS) is a common endocrine disorder, affecting about 12-18% of women of reproductive age (1). PCOS is associated with an over 75% prevalence of insulin resistance (IR) (2) and a 5 - 10-fold increased risk of developing type-2 diabetes mellitus (3). Additionally, over 50% of women with PCOS are overweight (body mass index (BMI) ≥25) (4) compared to 30% of Danish women in the general population (5). Increasing BMI is closely associated with PCOS (6), although it is unknown whether obesity is a result of, or a contributing factor to PCOS.

In pregnancy, maternal insulin sensitivity changes to accommodate fetal glucose needs, with IR prevailing in the third trimester (4). When insulin secretion fails to compensate for IR, maternal hyperglycemia can result in gestational diabetes mellitus (GDM), complicating 2-3% of pregnancies in Denmark (7). Maternal hyperglycemia is associated with maternal, fetal and obstetric complications (4), such as excessive fetal growth (8) and increased need for cesarean delivery (9). High maternal BMI is associated to adverse pregnancy outcome, such as high birthweight (BW) (10) and cesarean sections (11). The intrauterine environment in women with PCOS is influenced by maternal obesity, hyperinsulinemia and androgen excess, possibly causing elevated fat mass in the offspring at birth (12) and increased risk of cardiovascular disease later in life (13). Studies in pregnant women without PCOS suggest that measures of maternal IR could be a better marker of BW and pregnancy outcome than maternal BMI (14), but data for women with PCOS are lacking. Animal studies in rhesus monkeys showed that a hormonal environment similar to human PCOS resulted increased lifetime risk of IR and type-2 diabetes mellitus in offspring (15). Meta-analyses reported association between maternal PCOS and adverse
pregnancy outcomes such as GDM, and high and low BW in offspring (9, 16), but included studies were either small in scale, retrospective, or reported a very low PCOS prevalence (9, 16). The best predictor of pregnancy outcome and offspring health in PCOS therefore remains to be established.

The aim of the present study was to compare IR in pregnant women with and without PCOS and explore the impact of PCOS on body composition in offspring at birth and at 3 years of age. We hypothesized that obesity and IR in PCOS could be associated with offspring growth. We have used data from the Odense Child Cohort (17) and compared IR in women with and without PCOS in the 28th week of pregnancy. We examined the influence of maternal PCOS diagnosis on offspring weight, BMI, and abdominal circumference (AC) at birth and 3 years of age, and fat percentage at 3 years.

Material and methods

The study was a single-center prospective cohort study including pregnant women residing in Odense municipality, as recently described (17). Of 6707 pregnant women, 2874 chose to participate in the cohort. Women pregnant more than once during the study period were enrolled separately each time (6 women with PCOS, and 94 women without PCOS were included in the cohort with two or more children), due to the fact that modifiable risk factors, especially weight, could change considerably between pregnancies.

The exclusion criteria were abortions and miscarriages (n = 103), multiple pregnancy (n = 55), stillbirths (n = 10) and missing birth data (births at unaffiliated hospitals, moving out of the municipality before birth (n = 158)).

PCOS was defined according to the Rotterdam criteria (18). Data on previous PCOS diagnosis and hirsutism were collected from a questionnaire on the mothers’ health during the second trimester (n = 1902). Women were classified as having PCOS if they replied yes to the question ‘has a doctor ever told you that you have PCOS?’ (n = 96) or they reported both facial hair, and oligomenorrhea (menstrual cycles of ≥ 35 days) (n = 9). We included women with only self-reported facial hirsutism as cases as well (n = 96), as around 80% of women presenting with hirsutism have PCOS (19). Data on PCOS status in non-responders were extracted from medical records, adding 40 cases. Cohort staff was unaware of maternal PCOS diagnosis.

Women with GDM risk factors (glycosuria, previous GDM diagnosis, BMI ≥ 27 kg/m², disposition to diabetes, previous birth of child with BW ≥ 4500 g, multiple pregnancies) had fasting glucose and insulin measured at around 28 weeks of gestation. Women without risk factors were asked to donate fasting blood samples. In total 1529 women donated fasting blood samples.
Maternal anthropometric data (age, height, pre-pregnancy weight, parity, prior diabetes diagnosis), birth data (gestational age (GA) at delivery, mode of delivery, pregnancy complications, gender, anthropometric measurements of offspring) and GDM diagnoses were extracted from hospital records by using maternal social security numbers.

Children were invited to a physical examination within 2 weeks of their 3rd birthday (attendance on average 10 days after (interquartile range: -5; 20)). Three trained laboratory technicians measured offspring anthropometric data (height to the nearest millimeter (SECA 213) and skin fold thicknesses to the nearest 0.1 mm (Harpender skin folder) as the average of three measurements, weight to the nearest 10 grams (SECA 701/877), and AC (n = 1421). Fat percentage was calculated using Slaughter et al’s formula for triceps and subscapular skin folds according to gender (20). After two missed appointments, the 3-year examination was skipped.

Data on weight and BMI was missing in 5/2548 (0.2%) women. Weight and length at birth was missing in 10/2548 (0.4%) neonates. By the time of this study, 1421 children had attended 3-years examinations (participation rate 74.4%). BMI was missing in 92/1421 (6.5%) children, skin fold thicknesses in 107/1421 (7.5%) children, and AC in 49/1421 (3.4%) children.

Laboratory analyses

Assays were performed by the Clinical Biochemical Unit at Odense University Hospital, Denmark. Glucose levels were measured by the hexokinase method (Architect, Abbott), the intra-assay coefficient of variation (CV) was 5.2-5.4% and the inter-assay CV was 1.2-1.7%. Serum insulin was analyzed by an electro-chemiluminescence immunoassay (ECLIA, Cobas e411, Roche), the intra-assay CV was 0.8-3.7% and the inter-assay CV was 2.5-4.9%. Insulin was entered into a formula for the homeostasis model assessment for IR (HOMA-IR: (fasting glucose mmol/L x fasting insulin mU/L)/22.5 (n = 1527)).

Statistical analyses

Baseline characteristics were expressed as arithmetic mean (±SD), median (interquartile range), or number (percentage), as appropriate. Differences in means were analyzed using unpaired t-tests for normally distributed data, and for non-normally distributed data after ln-transformation (maternal and offspring BMI, offspring skin folds, fasting glucose and insulin, HOMA-IR). Offspring outcomes included: Weight, ponderal index, and AC at birth, and BMI, fat percentage and AC at three years. Multiple linear regression was applied in four models to examine associations between PCOS and offspring outcomes, and between HOMA-IR and offspring outcomes. The first model was unadjusted.

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The second model was adjusted for maternal age, parity, smoking status, child sex, and maternal BMI. The third model was adjusted for maternal age, parity, smoking status, child sex, and GA. The fourth model was similar to the third model, but additionally adjusted for maternal BMI. Additionally, regressions with BW and BMI at three years of age were performed within maternal BMI categories (BMI < 24.9 kg/m² (lean, n = 1660), 25-29.9 kg/m² (overweight, n = 596) and ≥ 30 kg/m² (obese, n = 287)). Regression results were presented as change in β-coefficients for one BMI-unit increase (95% confidence interval). Tests were two-sided, results with p <0.05 were considered statistically significant and denoted with an asterisk. All statistical analyses were performed with STATA Statistical Software version 14 (StataCorp., College Station, TX, USA).

Outliers were defined as maternal insulin, and offspring fat percentage at 3 years that were more than 5 SD above the previous value (n = 6, and n = 1, respectively). HOMA-IR was calculated with and without outlying insulin values. No significant changes in mean differences were seen between the two groups when outliers were excluded in each analysis (data not shown).

Ethical approval

All participants gave written consent for participation and the project was approved by the Danish Data Protection Agency (j.no. 2008-58-0035), and Regional Scientific Ethical Committees for Southern Denmark (application no. S-20090130).

Results

Maternal data

The study included 2548 live-born singleton mother-child pairs (Figure 1). A total of 241 women were included as cases, a prevalence of 9.4%. Maternal age, parity, smoking habits, and percentage of cesarean sections were similar between women with and without PCOS (Table 1). The cohort was ethnically homogenous: 95% of the women were of Scandinavian descent. Overall, women with PCOS had significantly higher pre-pregnancy BMI than women without PCOS, explained by significantly higher BMI in overweight women with PCOS compared to overweight non-PCOS women: 30.8 (26.9-32.5) vs. 29.2 (26.3-30.9) kg/m², p < 0.01. In the subgroup of lean women (BMI < 25 kg/m²), there was no significant difference in BMI according to PCOS status: 21.8 (21.5-22.1) in women with PCOS vs. 21.8 (21.7-21.9) kg/m² in women without PCOS, p = 0.87. GDM was diagnosed in 6/241 (2.5%) women with PCOS and 31/2307 (1.3%) women without PCOS, p = 0.15.
Maternal fasting insulin, glucose and HOMA-IR levels were comparable between women with and without PCOS (Table 1). However, in the subgroup of overweight women, women with PCOS had significantly higher median insulin: 123 (92-151) vs. 92 (68-125) pmol/l, \( p = 0.005 \), fasting glucose: 5.4 (5.0-5.6) vs. 5.2 (4.9-5.5) mmol/l, \( p = 0.04 \), and HOMA-IR: 4.7 (3.6-5.9) vs. 3.6 (2.5-5.0), \( p = 0.005 \). These differences were attenuated and became non-significant after correcting for BMI.

**Offspring at birth**

Offspring of women with PCOS were born on average 92 grams lighter than non-PCOS offspring: 3398 (2319-4979) vs. 3490 (2529-4815) grams, \( p = 0.02 \) (Table 2). After adjusting for GA (Table 3, model 3), this difference was attenuated to 24 grams and no longer statistically significant. In the PCOS group, \( 4/241 \) (1.7%) of the children had a BW \( \geq \) 4500 grams compared to \( 76/2307 \) (3.3%) of the children from the non-PCOS group, \( p = 0.66 \) (Table 2). Similarly, \( 3/241 \) (1.2%) had low BW (< 2500 grams after 37 weeks of gestation) in the PCOS group, compared to \( 16/2307 \) (0.7%) in the non-PCOS group, \( p = 0.63 \). Mothers with PCOS gave birth to a slightly higher percentage of preterm infants: 5.4% vs. 3.7%, \( p = 0.19 \). We found no differences in ponderal index, AC or sex between children born to women with and without PCOS.

Higher maternal HOMA-IR scores in 28th week of pregnancy, in all women irrespective of PCOS status, predicted higher BW, higher ponderal index, and a larger AC at birth in the crude model and after adjusting for maternal factors (age, parity, smoking, BMI), offspring sex and GA (Table 4).

**Offspring at 3 years of age**

Children born to mothers with PCOS had a significantly higher BMI at three years, compared with non-PCOS offspring: 16.0 (15.2-16.8) vs. 15.8 (15.0-16.3) kg/m\(^2\), \( p = 0.02 \), even after adjusting for maternal BMI (Table 3). The difference was on average 0.2 BMI point, or 200 grams for a 1-meter tall 3-year-old. There was no significant difference in fat percentage or AC between the two groups. Children of overweight mothers had significantly higher BMI than children of normal weight mothers, regardless of maternal PCOS status; 16.4 (15.4-17.4) vs. 15.9 (15.2-16.6) kg/m\(^2\), \( p = 0.005 \).

HOMA-IR, in all women, was significantly associated with offspring BMI and fat percentage at 3 years. The association remained significant after adjusting for maternal age, parity, smoking, offspring sex and GA, but not after adjusting for maternal BMI (Table 4, models 1, 3, and 4).
Discussion

In this prospective single-center study, overweight women with PCOS had increased IR during pregnancy, compared to overweight women without PCOS. However, after adjustment for pre-pregnancy BMI, IR in the 28th week of gestation was comparable in women with and without PCOS. To our knowledge, this is the first study that prospectively assessed IR in pregnant women with and without PCOS. Furthermore, the prevalence of PCOS in the present study was 9.4%, which is close to the estimated population prevalence (1), and therefore likely included both mild and severe cases.

We lower BW in offspring of women with PCOS compared with non-PCOS offspring, but this difference dissipated after adjusting for GA. In accordance, three meta-analyses reported that the difference in BW between PCOS and non-PCOS offspring was marginal, if at all significant after adjusting for GA (9, 16, 21). Women with PCOS in our study cohort gave birth on average one day earlier, with a slightly higher percentage of premature births than women without PCOS, but neither difference was statistically significant. Some previous meta-analyses reported a higher risk of premature birth in pregnant women with PCOS (9, 16, 21). A possible explanation for the discrepancy may be the low number of premature births in our cohort. The induction rate was similar in women with and without PCOS, thus a shorter gestation did not reflect a propensity to intervene in a PCOS pregnancy.

Importantly, in the clinical setting of the present study, the diagnosis of PCOS was not an indication for more clinical controls or biochemical investigations during pregnancy.

GDM prevalence was not increased in PCOS in the present study, and our results supported that BMI and not PCOS status predicted the degree of IR in pregnancy. The adverse effects of obesity on pregnancy outcomes are well established (22) and preterm delivery, macrosomia and GDM were more prevalent in overweight women with PCOS compared with normal weight women with PCOS (23). We found that 40% of women with PCOS were overweight before gestation, which was lower than observed in other studies (6, 24). The inclusion of the whole spectrum of PCOS phenotypes including more mild PCOS could have affected our study outcomes. The women participating in Odense Child Cohort were less overweight than the background population and ethnically homogenous, likely associated with a decreased risk of GDM, but the prevalence of GDM in Odense Child Cohort was comparable to the Danish general population (7). Our findings of unchanged GDM risk in PCOS contrast a large Swedish register study where the risk of GDM, pre-eclampsia and pregnancy induced hypertension was significantly higher in women with PCOS (25), but the authors reported a PCOS prevalence of only 0.3%, likely including only the most severe PCOS phenotypes. In recent meta-analyses, the risk of GDM was three-fold increased in PCOS, but the heterogeneity of included studies was high and not adjusted for BMI (9, 21).
Increased testosterone levels in combination with high fat diet may be especially unfavorable for IR in PCOS. In female monkeys treated with testosterone therapy and randomized to normal or high fat diet, the addition of high fat diet to testosterone treatment significantly impaired glucose metabolism (26). The present study design did not allow for differentiation between PCOS phenotypes, but we previously reported comparable incidence of adverse obstetric outcomes and anthropometric measures in newborns across different phenotypes of PCOS (27). Future studies should investigate possible associations between testosterone levels in the PCOS pregnancy, and pregnancy outcomes.

We found that children of mothers with PCOS had significantly higher BMI at three years compared to offspring of non-PCOS mothers, after adjusting for maternal factors including BMI. These findings along with normal BW in PCOS could indicate a faster catch-up growth in early life. Furthermore, BMI in children of overweight mothers was significantly higher compared to children of normal weight mothers, regardless of maternal PCOS status. Maternal HOMA-IR was an independent predictor of offspring BMI and fat percentage at 3 years. The association between PCOS and offspring health after birth has, to our knowledge, not previously been studied. In non-PCOS populations, pre-pregnancy maternal BMI and hyperglycemia at week 28 in pregnancy were positively associated with offspring BMI in school-aged children (28, 29). Our GDM prevalence was low, but Catalano et al. found that maternal pre-pregnancy BMI was a more important factor for predicting obesity in American 8-year-olds than maternal hyperglycemia and IR (28). Thaware et al. reported that maternal BMI explained both maternal hyperglycemia and high offspring BMI in a subgroup of the HAPO study population, and concluded that offspring needs to be exposed to an obesogenic environment both in fetal life and postnatally for obesity to develop (29). Future studies are needed to study the impact of pre-pregnancy weight loss on offspring health in PCOS.

This prospective study included 241 women with PCOS. We used a combination of self-reported PCOS and medical records, as PCOS cannot be diagnosed during pregnancy. Adding self-reported PCOS allowed us to identify cases diagnosed and treated by a general practitioner or private gynecologist. This results in a PCOS cohort including relatively healthy women, but is arguably more applicable to the general population. In accordance, Glintborg et al. recently showed that the birthrates of Danish women with and without PCOS were comparable (3), most likely due to a combination of a low overall birthrate in Denmark, a relatively lean PCOS population in our study, and subsidized infertility treatment. We did, unfortunately, not have access to complete data on participants’ infertility treatments. Another major strength of the study were standardized physical examinations at 3 years of age, performed by the same three laboratory technicians in the same setting.

The cohort was more ethnically homogenous than the background population, more educated and lean and less likely to smoke (17). This is a prevalent problem in cohort studies, as minorities and people of lower social status tend to drop out. However, it is unlikely that such differences should bias
associations between PCOS and offspring anthropometry, as a Danish study on pregnant women showed that associations were fairly non-biased, and compared well to initial non-participants (30).

HOMA-IR was used as a marker for IR in the present study, as a less invasive and time consuming substitute for the gold-standard euglycemic hyperinsulinemic clamp. Oral glucose tolerance testing was only performed in a subset of study participants.

In conclusion, maternal PCOS was not associated with IR after correcting for BMI and was not an independent predictor of offspring BW. However, both PCOS and high maternal BMI may increase risk of childhood obesity at 3 years of age.

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Legends

Table 1. Baseline characteristics by maternal polycystic ovary syndrome (PCOS) status.

Table 2. Offspring data at birth and 3 years of age, by maternal polycystic ovary syndrome (PCOS) status.

Table 3. Changes in offspring anthropometric measurements at birth and three years of age by maternal polycystic ovary syndrome (PCOS) status.

Table 4. Changes in offspring anthropometric measurements at birth and 3 years of age by changes in maternal HOMA-IR scores at 28th week of pregnancy.

Figure 1. Flowchart of mother-child pairs included in the study.

**Table 1. Baseline characteristics by maternal polycystic ovary syndrome (PCOS) status.**

<table>
<thead>
<tr>
<th></th>
<th>PCOS</th>
<th>Non-PCOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 241</td>
<td>n = 2,307</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>31 (22-39)</td>
<td>30 (21-39)</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)$^b$</td>
<td>25.4 (19.3-37.8)*</td>
<td>24.3 (18.9-32.9)</td>
</tr>
<tr>
<td>Obesity (BMI ≥25 kg/m$^2$)</td>
<td>96 (39.8%)*</td>
<td>768 (33.3%)</td>
</tr>
<tr>
<td>Primipara</td>
<td>129 (53.5%)</td>
<td>1284 (55.7%)</td>
</tr>
<tr>
<td>Smokers</td>
<td>14 (5.8%)</td>
<td>132 (5.7%)</td>
</tr>
</tbody>
</table>

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Caucasian ethnicity 229 (95.0%) 2203 (95.5%)
Gestational diabetes mellitus 6 (2.5%) 31 (1.3%)
Spontaneous birth 151 (64%) 1421 (62%)
Cesarean section 52 (21.6%) 495 (21.5%)
Questionnaire return rate 203 (84.2%) 1699 (73.6%)

\[
\begin{array}{ll}
\text{Insulin (pmol/l)} & a,b \\
71.5 (50.0-106.0) & 68.0 (49.0-96.0) \\
\text{Glucose (mmol/l)} & a,b \\
5.0 (4.8-5.4) & 5.0 (4.8-5.3) \\
\text{HOMA-IR} & a,b \\
2.8 (1.8-4.4) & 2.5 (1.8-3.7) \\
\end{array}
\]

\(^a\) ln-transformed data.
\(^b\) Data presented as mean (±2SD), median (quartiles), or number (%).

\(^*\) \(p < 0.05\) PCOS vs. non-PCOS

**Table 2. Offspring data at birth and 3 years of age, by maternal polycystic ovary syndrome (PCOS) status.**

<table>
<thead>
<tr>
<th></th>
<th>PCOS</th>
<th>Non-PCOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>At birth</td>
<td>n = 241</td>
<td>n = 2,307</td>
</tr>
<tr>
<td>Birth weight (grams)(^a)</td>
<td>3398 (2319-4979)*</td>
<td>3490 (2529-4815)</td>
</tr>
<tr>
<td>Ponderal index (kg/m(^3))</td>
<td>25.1 (20.3-30.0)</td>
<td>25.1 (20.3-30.0)</td>
</tr>
<tr>
<td>Abdominal circumference (cm)</td>
<td>33.2 (28.4-38.0)</td>
<td>33.4 (28.9-37.9)</td>
</tr>
<tr>
<td>Prematurity (&lt;37 weeks)</td>
<td>13 (5.4%)</td>
<td>85 (3.7%)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Gestational age (days)</th>
<th>280 (273-286)</th>
<th>281 (274-287)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>131 (54.4%)</td>
<td>1220 (52.9%)</td>
</tr>
</tbody>
</table>

**At 3 years of age**

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>14.8 (11.7-18.6)</th>
<th>14.7 (11.9-18.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>16.0 (13.5-18.9)*</td>
<td>15.7 (13.6-18.2)</td>
</tr>
<tr>
<td>Fat Mass (%)</td>
<td>14.5 (8.9-20.0)</td>
<td>14.2 (8.9-19.5)</td>
</tr>
<tr>
<td>Abdominal circumference (cm)</td>
<td>50.4 (44.5-56.3)</td>
<td>50.0 (44.6-55.5)</td>
</tr>
<tr>
<td>Days from 3rd birth day</td>
<td>3 (-4-16)</td>
<td>3 (-5-20)</td>
</tr>
<tr>
<td>Male gender</td>
<td>80 (55.9%)</td>
<td>671 (52.5%)</td>
</tr>
</tbody>
</table>

*ln-transformed data.

Data presented as mean (±2SD), median (quartiles), or number (%).

*p< 0.05 PCOS vs. non-PCOS.

Table 3. Changes in offspring anthropometric measurements at birth and three years of age by maternal polycystic ovary syndrome (PCOS) status.

<table>
<thead>
<tr>
<th>Birth data n = 2,548</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (grams)</td>
<td>-82.4*</td>
<td>-106.5*</td>
<td>-24.2</td>
<td>-42.2</td>
</tr>
<tr>
<td></td>
<td>(-153.4; -11.3)</td>
<td>(-175.2; -37.8)</td>
<td>(-79.9; 31.5)</td>
<td>(-97.5; 13.1)</td>
</tr>
<tr>
<td>Ponderal index (kg/m³)</td>
<td>0.02</td>
<td>-0.03</td>
<td>0.09</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>(-0.3; 0.3)</td>
<td>(-0.3; 0.3)</td>
<td>(-0.2; 0.4)</td>
<td>(-0.3; 0.4)</td>
</tr>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
<td>Model 3</td>
<td>Model 4</td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Abdominal circumference (cm)</td>
<td>-0.19</td>
<td>-0.3</td>
<td>0.02</td>
<td>-0.03</td>
</tr>
<tr>
<td></td>
<td>(-0.5; 0.1)</td>
<td>(-0.6; 0.04)</td>
<td>(-0.2; 0.3)</td>
<td>(-0.3; 0.2)</td>
</tr>
<tr>
<td>3 years of age</td>
<td>n = 1,421</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m$^3$)</td>
<td>0.24*</td>
<td>0.21*</td>
<td>0.26*</td>
<td>0.23*</td>
</tr>
<tr>
<td></td>
<td>(0.04; 0.45)</td>
<td>(0.01; 0.42)</td>
<td>(0.05; 0.46)</td>
<td>(0.02; 0.43)</td>
</tr>
<tr>
<td>Fat percentage (%)</td>
<td>0.31</td>
<td>0.27</td>
<td>0.32</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>(-0.16; 0.77)</td>
<td>(-0.20; 0.75)</td>
<td>(-0.16; 0.81)</td>
<td>(-0.21; 0.75)</td>
</tr>
<tr>
<td>Abdominal circumference (cm)</td>
<td>0.36</td>
<td>0.31</td>
<td>0.41</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>(-0.13; 0.84)</td>
<td>(-0.18; 0.79)</td>
<td>(-0.08; 0.90)</td>
<td>(-0.12; 0.85)</td>
</tr>
</tbody>
</table>

Data presented as β-coefficients (95% confidence interval) for PCOS vs. non-PCOS.

*p < 0.05 PCOS vs. non-PCOS.

Model 1: Crude model.

Model 2: Adjusted for maternal age, parity, smoking, BMI, and sex of the offspring.

Model 3: Adjusted for maternal age, parity, smoking, sex of the offspring and gestational age.

Model 4: Adjusted for maternal age, parity, smoking, BMI, sex of the offspring and gestational age.
Table 4. Changes in offspring anthropometric measurements at birth and 3 years of age by changes in maternal HOMA-IR scores at 28th week of pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (grams)</td>
<td>30.78* (13.65; 47.91)</td>
<td>22.80* (3.46; 42.15)</td>
<td>46.79* (33.43; 60.15)</td>
<td>35.35* (19.64; 51.05)</td>
</tr>
<tr>
<td>Ponderal index (kg/m³)</td>
<td>0.12* (0.04; 0.20)</td>
<td>0.12* (0.03; 0.21)</td>
<td>0.16* (0.08; 0.23)</td>
<td>0.14* (0.05; 0.23)</td>
</tr>
<tr>
<td>Abdominal circumference (cm)</td>
<td>0.08* (0.008; 0.15)</td>
<td>0.06 (-0.03; 0.14)</td>
<td>0.14* (0.07; 0.20)</td>
<td>0.10* (0.02; 0.17)</td>
</tr>
<tr>
<td>BMI at 3 years (kg/m²)</td>
<td>0.06* (0.01; 0.11)</td>
<td>-0.01 (-0.07; 0.04)</td>
<td>0.06* (0.02; 0.12)</td>
<td>-0.01 (-0.07; 0.05)</td>
</tr>
<tr>
<td>Fat percentage at 3 years (%)</td>
<td>0.15* (0.04; 0.26)</td>
<td>0.07 (-0.05; 0.20)</td>
<td>0.17* (0.06; 0.27)</td>
<td>0.07 (-0.05; 0.20)</td>
</tr>
<tr>
<td>Abdominal circumference (cm)</td>
<td>0.08 (-0.04; 0.19)</td>
<td>-0.06 (-0.20; 0.08)</td>
<td>0.09 (-0.02; 0.21)</td>
<td>-0.05 (-0.19; 0.09)</td>
</tr>
</tbody>
</table>

Data presented as β-coefficients (95% confidence interval) for changes in maternal HOMA-IR in 28th week of pregnancy. * p < 0.05 PCOS vs. non-PCOS

Model 1: Crude model.

Model 2: Adjusted for maternal age and parity, smoking, sex of offspring and maternal BMI.

Model 3: Adjusted for maternal age and parity, smoking, sex of offspring and gestational age.

Model 4: Adjusted for maternal age and parity, smoking, sex of offspring, gestational age and maternal BMI.

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Figure 1. Flowchart of mother-child pairs included in the study

Registered pregnancies in Odense municipality
n = 6,707

Enrolment material accepted
n = 3,605

Inclusion into cohort
n = 2,874

103 abortions/miscarriages
10 stillbirths
55 multiple pregnancies
158 missing birth data

Live born singleton children
n = 2,548

9.4% PCOS prevalence

Women with PCOS
n = 241
3 year examination
n = 143

Controls
n = 2,307
3 year examination
n = 1,278