PCOS AND BIRTH WEIGHT

Developmental origins of polycystic ovary syndrome (PCOS), a case control study comparing birth weight in women with PCOS and control group

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Abstract

Evidence from various epidemiological studies and experimental animal studies has linked adverse intrauterine circumstances with health problems in adult life. This field of investigation is known as Developmental Origins of Health and Disease (DOHaD). Studies investigating the relation between developing polycystic ovary syndrome (PCOS) in adulthood and birth weight have yielded inconsistent results: PCOS is described more often in women with low birth weight and high birth weight, while other studies have failed to establish any relation. In this retrospective case–control study, we evaluated whether women diagnosed with PCOS had lower birth weight compared to women with a regular menstrual cycle (controls). Binary logistic regression models were used to analyze the data and correct for known confounders. About 65 women with PCOS and 96 controls were recruited for this purpose. The average birth weight of PCOS women (3357 g) did not differ from the average birth weight of controls (3409 g). Mean age at menarche differed significantly between groups, 13.7 years and 12.8 years (p = 0.006), respectively, for PCOS women and controls. In conclusion, we could not confirm the effect of adverse intrauterine conditions, reflected in birth weight, on developing PCOS.

Introduction

Evidence from epidemiological studies and experimental animal studies has linked adverse intrauterine circumstances with health problems in adult life, recognized as Developmental Origins of Health and Disease (DOHaD) [1]. From an evolutionary biological point of view, a fetus growing in unfavorable intrauterine circumstances is known to permanently alter its’ organ growth and function possibly to adapt to its future environment [2,3]. Intrauterine growth restriction is known to affect organ structure and average organ weight in animal and human offspring [4–7].

Polycystic ovary syndrome (PCOS), a common fertility-related disorder associated with high levels of luteinizing hormone (LH) and subfertility has an estimated prevalence of up to 20% depending on the diagnostic criteria [8]. PCOS is often associated with metabolic disorders including insulin resistance, obesity and cardiovascular disease [9]. Insulin resistance and cardiovascular disease are also among the well-documented sequelae of intrauterine growth restriction [10]. Animal studies suggest that elevated prenatal testosterone levels during critical periods of gestation can cause a PCOS like phenotype and intrauterine growth restriction mediated through impaired placental function [11]. PCOS and insulin resistance have also been suggested to find their joint origin in fetal growth restriction mediated by excessive serine phosphorylation [12].

So far, reports on birth weight and PCOS have yielded inconsistent result. Some studies report an increased prevalence of PCOS in women born small for gestational age (SGA). In adolescent girls with a history of premature pubarche, impaired fetal growth is reported as an etiological contributor to PCOS [13,14]. On the other hand, a lower ponderal index and high birth weight also have each been associated with an increase in PCOS-related symptoms [15,16]. While other studies have failed to establish an association between PCOS and birth weight [17,18].

In this retrospective case–control study, we investigate if women with manifested impaired fertility due to PCOS indeed had a lower weight at birth compared to women showing no symptoms of PCOS.

Patients and methods

Study population

Subjects were patients from the department of Obstetrics and Gynecology VU Medical Center in Amsterdam. All patients were clinically diagnosed with PCOS, according to the Rotterdam criteria [19] based on the presence of at least two of the following...
clinical features: oligo/amenorrhea, polycystic ovarian morphology and hyperandrogenism and the absence of other common endocrinological disorders. Controls were recruited via advertising and from medical files of the department of Obstetrics and Gynecology of VU Medical Center. All controls had self-reported spontaneous regular menstrual cycles and no history of sub/infertility.

Patients and controls meeting any of the following criteria were excluded: history of ovarian disease or operation, abdominal radiation or chemotherapy or diagnosed with genetic abnormalities.

The ethical commission of the institute approved the study. Patients and controls receiving a letter informing them about the aim of the study and signed a consent form.

**Study design**

We used a retrospective case–control study design. Participants completed a written questionnaire addressing fertility and health issues. They were also asked to confirm their birth weight with a written record or if their birth mother was still alive to confirm the birth weight. Gestational age was reported as weeks or months of gestation. Education level was reported as: low (primary school or low vocational education), middle (high school or middle vocational education) or high (higher vocational education or academic education). Smoking was categorized as current smoker, former smoker or never smoked. Participants provided information on current height and weight, history of contraceptive use, hormone replacement therapy, history of gynecological treatment, age at menarche and age at menopause. We defined pre-term birth as birth before 37 weeks of gestation, and term birth as 38, 39, 40 weeks of gestation and post-term as above 41 weeks of gestation.

**Statistics**

Data available from other studies relating birth parameters to adverse fertility outcome were used as a guideline to estimate an appropriate sample size [20]. To demonstrate a clinically relevant difference of 200 g in birth weight using an independent Student’s t-test, the minimal sample size for each group was calculated to be 60 with alpha 0.05 and power 0.8.

IBM SPSS Statistics 21 (Chicago, IL) was used for all statistical analyses. An independent Student’s t-test was used when data were continuously and normally distributed. Continuous data are presented as mean and 95% confidence interval and significance level (p value) is presented. Nonparametric data were tested with a Chi-square test. Binary logistic regression models were computed adjusting for categorical as well as continuous independent variables.

**Results**

The study group consisted of 65 women diagnosed with PCOS according to the Rotterdam criteria. 96 women with regular menstrual cycles were included in the control group. Baseline characteristics and study parameters of continuous data are summarized in Table 1, categorical data are presented in Table 2.

| Table 1. Comparison of continuous variables of women diagnosed with polycystic ovary syndrome (PCOS) and control group. |
|---|---|---|---|
| | Control Mean (n = 96) | PCOS Mean (n = 65) | p Values | Lower | Upper |
| Age at interview, years (n) | 45.2 (96) | 39.8 (65) | 0.000 | 3.67 | 7.05 |
| BMI, kg/m² (n) | 24.5 (92) | 26.4 (63) | 0.021 | −3.55 | −0.297 |
| Age at menarche, years (n) | 12.8 (94) | 13.7 (62) | 0.006 | −1.57 | −0.265 |
| Birth weight, g (n) | 3409 (96) | 3357 (65) | 0.618 | −154 | 253 |
| Gestational age, wk (n) | 40 (64) | 39 (21) | 0.337 | −0.542 | 1.56 |

*Preterm birth is defined as birth before 37 weeks of gestation, term birth as 38, 39, 40 weeks of gestation and post-term as above 41 weeks of gestation.

| Table 2. Comparison of categorical variables of women diagnosed with polycystic ovary syndrome (PCOS) and control group. |
|---|---|---|---|
| | Control Mean (n = 96) | PCOS Mean (n = 65) | p Values |
| Birth weight categories | | | |
| <1.5 kg n (%) | 0 (0%) | 0 (0%) | – |
| <2 kg n (%) | 5 (5.2%) | 1 (1.5%) | 0.403 |
| <2.5 kg n (%) | 11 (11.5%) | 8 (12.3%) | 1.00 |
| >4 kg n (%) | 20 (20.8%) | 9 (13.8%) | 0.301 |
| Term* | n = 95 | n = 62 | |
| Preterm n (%) | 8 (8.4%) | 6 (9.7%) | 0.426 |
| Term n (%) | 67 (70.5%) | 48 (77.4%) | |
| Post-term n (%) | 20 (21.1%) | 8 (12.9%) | |
| Smoker | n = 96 | n = 65 | |
| Former or current n(%) | 56 (58.3%) | 42 (64.6%) | 0.511 |
| Never n (%) | 40 (41.7%) | 23 (35.4%) | |
| Education level | n = 92 | n = 65 | |
| Low (%) | 35 (38%) | 38 (58.5%) | 0.006 |
| Middle (%) | 11 (12%) | 11 (16.9%) | |
| High (%) | 46 (50%) | 16 (24.6%) | |

Chi-square test was used for categorical data.

An independent Student’s t-test was used for continuous data with a normal distribution. *BMI, body mass index defined as weight (kg)/height (m)².
Birth weight, gestational age, premature or post-term delivery did not differ significantly between women with PCOS and women with a regular menstrual cycle. To investigate a possible U-shaped or threshold effect, we also analyzed birth weight in categorical categories. We found no evidence for a difference in distribution between the birth weight categories according to PCOS diagnosis. Age at the time of investigation, age at menarche, BMI and education level however differed significantly between groups. Women diagnosed with PCOS were significantly younger, had an older age at menarche, a higher BMI and lower education levels compared to the control group. Using binary logistic models, we investigated whether the fact that we failed to find an association between birth weight and PCOS in our dataset was due to these differences in baseline characteristics. Confounders were added in a step forward manner. Odds ratio, 95% confidence interval and $p$ values of the final stage of the models are presented in Table 3. None of these analyses revealed any associations between early life determinants, including birth weight and gestational age at birth, after adjusting for confounders. A higher BMI and a later age of menarche remained positively associated with PCOS (data not shown).

| PCOS versus control | Odds ratio | 95%CI | p Value |
|---------------------|------------|-------|---------|
| Birth weight (g)*   | 1.0        | 0.999–1.00 | 0.78    |
| Categorical birth weight (>2 kg/<2 kg)* | 0.514 | 0.046–5.77 | 0.59    |
| Categorical birth weight (>2.5 kg/<2.5 kg)* | 1.12 | 0.286–4.41 | 0.87    |
| Categorical birth weight (<4 kg/<4 kg)* | 1.24 | 0.373–4.10 | 0.73    |

*Corrected for (stepwise): gestation age categories, age at menarche, BMI, smoking categories, education categories, age at time of interview.

Discussion

We found no relation between PCOS and a low birth weight or any other perinatal determinant. Literature on this subject is inconsistent. Some studies report an association between a low birth weight and PCOS [13,14]. However, these studies seem to have described a specific phenotype of women with SGA, an early age at puberty, hyperandrogenism and PCOS. Furthermore, impaired catch up growth, small adult stature and a low adult BMI were hallmarks of the phenotype described by Ibanez et al in contrast to the majority of women with PCOS described in other studies, who have an average height with a higher BMI and a later age at menarche [21]. There might therefore be a specific group of women in which SGA is the offset or the first manifestation of endocrine dysfunction or that in these cases SGA is an added symptom in a more complex disease system.

In other studies, low birth weight was not associated with PCOS [15,17,20]. A large Danish study, by Mumm et al., found that women whose birth weight was in the highest percentiles were more likely to develop PCOS, as were women born to mothers with gestational diabetes. As gestational diabetes and macronomic offspring are more common in women with PCOS, while PCOS also has a high heritability these findings more likely indicates a genetic or epigenetic common pathway. Recent studies have suggested various genetic and epigenetic plausible pathways associated with PCOS although the exact mechanism underlying PCOS is still unclear [22–25].

It seems that low and high birth weight per se, as parameters for possible intrauterine nutritional disorders are not relevant for PCOS. Investigations in the field of DOHaD shift from size at birth to focusing on the timing of malnutrition during pregnancy. An increasing body of evidence from experimental animal studies indicates that the timing of malnutrition during and even before gestation has a profound effect on adult health while not resulting in a low birth weight [26–28]. The Dutch hunger winter presented an exceptional situations in history to study the effect of malnutrition in different gestational periods [29]. Adults affected by famine during their early gestation had a higher incidence of coronary heart disease and a higher BMI. Their birth weight, however, did not differ significantly [30,31].

The highest peak of oocyte production and oocyte apoptosis in humans is in early, up to mid gestation. One, therefore, would not expect adverse environmental influences late in gestation, affecting birth weight, negatively influencing the oocyte reserve. On the other hand, in humans temporary placental dysfunction or temporary food restriction besides hyperemesis gravidarum is extremely rare.

Primate animal models prenatally exposed to exogenous androgen develop a PCOS-like reproductive and metabolic phenotype in adulthood. Primate animal models, unlike rodent and sheep animal models, show no signs of intra uterine growth restriction [31]. To our knowledge, there are no studies experimenting with maternal nutritional or placenta function during different periods of gestation in PCOS animal models to investigate the effect of intrauterine growth restriction in PCOS predisposed animals on PCOS severity or birth weight.

Obviously, our study also has a few shortcomings. First of all, the retrospective design of our study presents a potential recall bias. The possibility of recall bias cannot be excluded, but we see no reason why women with PCOS would be more or less likely to be in possession of a written document confirming their birth weight. The fact that all information, other than PCOS diagnosis in the patient group, is self-reported can also introduce an additional information bias.

Another issue is that the control group was significantly older than the patients were. Although there is no evidence that the prevalence of PCOS changed over the years [9], we eliminated any potential confounding effects by adding age to the binary logistic models.

The PCOS patients in our study had a significantly lower education level compared to the control group. Even though we did not find any correlation between PCOS and education level in the literature, this might explain the difference in BMI between groups. A lower social economic level is indeed related to a higher BMI [32]. Though, when correcting BMI for education level, BMI remained significantly related to PCOS.

In conclusion, our study findings were not consistent with the hypothesis that intrauterine growth is a determinant of PCOS. Meanwhile other studies point in the direction of adverse environmental conditions acting only in specific developmental windows during gestation and negative lifestyle effects during infancy and puberty. Animal studies focusing on environmental effects during different stages of gestation, the effect of hyperemesis gravidarum and lifestyle intervention during infancy and puberty should shed more light on these issues.

Acknowledgements

Authors thank all the participants who volunteered for this study. We also thank Ted Korsens, research nurse, who helped recruiting participants and setting up the database.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.
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