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Polycystic ovary syndrome, body mass index and hypertensive disorders in pregnancy

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ABSTRACT

Objective: Some studies of women with polycystic ovary syndrome (PCOS) report increased prevalence of hypertensive disorders in pregnancy, while others do not. Several of these studies do not control for obesity. We aimed to study whether PCOS is associated with hypertensive disorders in pregnancy and whether it is dependent on body mass index (BMI).

Study design: We present a cross-sectional analysis of 3732 women from Denmark, Estonia, Iceland, Norway and Sweden, born in 1945–72, who participated in the Respiratory Health In Northern Europe (RHINE) study and answered an extensive women's health questionnaire on menstruation, PCOS, infertility, pregnancy history and childbirth. The main outcome measurement was hypertensive disorders of pregnancy. We adjusted for smoking, age, infertility treatment and study center. Effect modification by BMI was assessed.

Results: PCOS was related to hypertensive disorders in pregnancy with a relative risk (RR) of 1.62 (95% CI 1.09–2.42). This relationship was found among underweight women with a BMI of $< 18.5\,kg/m^2$ [RR = 5.2 (95% CI 1.66–16.5)] and obese women with a BMI of $\geq 30\,kg/m^2$ [RR = 2.36 (95% CI 1.29–4.31)], but not among normal-weight women, BMI 18.5–25 kg/m^2 [1.08 (0.53–2.20)], or overweight women, BMI 25–30 kg/m^2 [1.24 (0.50–3.08)] (p-interaction = 0.041).

Conclusion: Polycystic ovary syndrome is associated with hypertensive disorders in pregnancy. This association only occurs among underweight and obese women and not among normal-weight and slightly overweight women.

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common cause of hormonal disorders in women [1]. The estimated prevalence varies from 6 to 17%, depending on the diagnostic criteria used and the population studied [2–4]. According to the 2003 Rotterdam criteria [5], PCOS is characterized by a combination of any two or all three of the following: irregular menstruation, hyperandrogenism and polycystic ovaries [1,2,4]. Women with PCOS are often obese and some studies report that these women run an increased risk of hypertensive disorders

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during pregnancy [6–8] while others do not [9,10]. Many of these studies did not, however, control for obesity, or take the potential modifying effects of body mass index (BMI) into consideration. The disorder is complex and heterogeneous and ranges from a mild form in some women to severe disturbances of reproductive, endocrine and metabolic functions in others [1,11,12].

Hypertensive disorders during pregnancy, including preeclampsia, are a major public health concern for women and their infants [13]. They complicate up to 10% of pregnancies worldwide and increase the risk for preterm delivery and fetal growth restriction, but the etiology is still unknown [14–17]. Obesity and features of the metabolic syndrome, including insulin resistance, central obesity and hypertension, are associated with hypertensive disorders during pregnancy [15,18,19].

We aimed to study whether PCOS among women from the population is associated with hypertensive disorders during pregnancy, and whether it is dependent on BMI.

2. Materials and methods

Eligible women were randomly selected from the population in Bergen in Norway; Umeå, Gothenburg and Uppsala in Sweden; Aarhus in Denmark; Reykjavik in Iceland and Tartu in Estonia born in 1945–72, who participated in the Respiratory Health In Northern Europe (RHINE) study II in 1999–2001 and III 2010–2012 (www.rhine.nu) [20]. The study included a women's questionnaire on menstruation, PCOS, infertility, menopause, premenstrual syndrome, use of exogenous sex hormones, gynecologic conditions and operations, pregnancy history and childbirth. Women were asked to state whether they developed hypertension, proteinuria or diabetes in any of their pregnancies. In all, 5300 of 7195 participants (74%) responded to the women's questionnaire. Included in the analyses were 3732 women who had ever given birth and responded with complete answers to questions on hypertensive disorders in pregnancy, menstrual regularity, height and weight (Fig. 1). All available survey data were included in the analysis.

The main outcome measurement was hypertensive disorders in pregnancy. It was defined by the question "During this pregnancy, did you have high blood pressure and/or protein in your urine?" with the first child and up to the sixth child (response alternatives Yes/No). According to the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy [13] hypertensive disorders in pregnancy are defined as 1) preeclampsia-eclampsia, 2) chronic hypertension (of any cause; hypertension that predates pregnancy), 3) chronic hypertension with superimposed preeclampsia, and 4) gestational hypertension (BP elevation after 20 weeks of gestation in the absence of proteinuria).

PCOS defined by the 2003 Rotterdam criteria, requires two of the following three features: irregular menstruation, hyperandrogenism or polycystic ovaries [5]. The following five questions from the women's questionnaire were used to define women with PCOS.

1. Do you have regular periods? (response alternatives: Yes; *No, they have never been regular*; No, they have been irregular for a few months; No, my periods have stopped).
2. What is the usual interval between your periods or what was the usual interval between your periods before they became irregular or stopped (from the first day of one period, to the first day of the next)? (response alternatives: < 24 days, 24–26 days, 27–29 days, 30–32 days, 33–35 days, *> 35 days*).
3. Have you ever had excessive growth of body hair (hirsutism)? (response alternatives: No/*Yes*).
4. Has a doctor or health professional ever told you that you have polycystic ovaries or polycystic ovary syndrome? (response alternatives: No/*Yes*).
5. Have you ever taken hormonal contraceptives because of polycystic ovary syndrome? (response alternatives: No/*Yes*).

We defined PCOS as having irregular menstruation and hirsutism, *or* cycles longer than 35 days and hirsutism, *or* having had PCOS diagnosed by a doctor, *or* contraception prescribed by a doctor because of PCOS.

BMI was calculated from self-reported height and weight. We used BMI from RHINE II, which was closest to childbearing age. BMI was analyzed as either a continuous variable, or as a categorical variable according to the World Health Organization (WHO) classification as underweight ($< 18.5\ kg/m^2$), normal weight ($18.5–24.9\ kg/m^2$), overweight ($25–29.9\ kg/m^2$) and obese ($\geq 30\ kg/m^2$) [21]. Smoking was categorized as never, current or former. Reported age was used as an adjusting covariate. Infertility treatment was defined by a positive answer to the following statement "I have only been pregnant following fertility treatment."

Continuous variables were summarized as means. Categorical variables were reported as percentages. Pearson's chi-square test was used to assess the likelihood of differences between categorical variables and PCOS. For continuous variables, a *t*-test was used. P-values of $< .05$ were considered statistically significant for main analyses.

Associations of PCOS and BMI with hypertensive disorders in pregnancy were analyzed by relative risk estimation using Poisson regression with robust error variance in unadjusted and adjusted models. The adjusted analysis included study center and smoking by convention, together with variables that were significantly different in the unadjusted analysis. The association of PCOS and hypertensive disorders in pregnancy was stratified by BMI categorized according to WHO classification. The differences in associations of PCOS with hypertensive disorders in pregnancy ever, with the first child and with the second child, according to BMI, were analyzed by including interaction terms between BMI and PCOS in a regression model. Margin plots visualize the added effect of BMI on the risk of hypertensive disorders in pregnancy in women with and without PCOS. Contrast plots illustrate the difference in the probability of hypertensive disorders ever according to BMI in pregnancy among women with PCOS vs. women without PCOS. All statistical analyses were performed with STATA version 14.0.

3. Results

A hypertensive disorder during a pregnancy was reported by 13% of the women, and ranged from 10% to 16% at the centers. PCOS was reported in 111 women (3%) and differed from 0.9% in Gothenburg, Sweden, to 8.5% in Tartu, Estonia (Table A1, online material). Women with PCOS were younger and were more often pregnant after treatment for infertility (Table 1).

Women with PCOS ran a significantly higher risk of hypertensive disorders in pregnancy compared with women without PCOS, p = .02 (Table 2). The risk of hypertensive disorders in pregnancy increased with increasing BMI (Fig. 2a). PCOS was independently associated with hypertensive disorders in pregnancy, ever and with the first child, after adjustments for age, BMI, smoking, infertility treatment and study center (Table 2). When stratifying by BMI, a significant association between PCOS and hypertensive disorders in pregnancy was found among underweight ($BMI < 18.5\ kg/m^2$) and obese ($BMI \geq 30\ kg/m^2$) women but not among normal-weight and slightly overweight women (Table 3). The interaction was significant for hypertensive disorders during the first pregnancy ($p_{interaction} = 0.041$, Table 3). Characteristics of the study population according to BMI categories are shown in Table A2 (supplementary online material).

The margins plot in Fig. 2a visualizes the fact that underweight women with PCOS ran a 40% risk of hypertensive disorder in pregnancy, while underweight women without PCOS ran a 9% risk. It also illustrates that obese women with PCOS ran a 59% risk of hypertensive disorder in pregnancy vs. a 25% risk in obese women without PCOS. Contrast plots in Fig. 2b illustrate that underweight women with PCOS had a 31% greater probability of hypertensive disorders ever in