The association of PCOS and hypertensive disorders of pregnancy -a community based approach

Juhani Rantakallio[1], Jaana Nevalainen[1], Sammeli West[1], Meri-Maija Ollila[1], Katri Puukka[1], Aini Bloigu[1], Marjoriitta jarvelin[2], Juha Tapanainen[3], Stephen Franks[4], Terhi Piltonen[3], Marja Vääräsmäki [3], and Laure Morin-Papunen[1]

[1]Oulu University Hospital
[2]MRC-PHE Centre for Environment and Health
[3]University of Oulu
[4]Institute of Reproductive and Developmental Biology

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Abstract

OBJECTIVE To investigate the prevalence of hypertensive disorders of pregnancy (HDP), and the roles of polycystic ovary syndrome (PCOS), obesity, weight gain (WG) and hyperandrogenaemia in the development of HDP by age 46. DESIGN prospective population-based cohort. Setting and population The Northern Finland Birth Cohort 1966 (NFBC1966) METHODS Follow-up at ages 14, 31 and 46, including women with (n=408) and without (n=3373) HDP. HDP was combined from the questionnaire data at age 46, hospital discharge records and Finnish Medical Birth Registers. Women with both oligo-amenorrhea and hirsutism at age 31 and/or with PCOS diagnosis by age 46 (self-reported PCOS, srPCOS, n=279) were compared with women without symptoms or PCOS diagnosis (n=1577). Main outcome measures Association of PCOS and WG through life with HDP RESULTS Women with srPCOS had an increased HDP risk ([OR]=1.56 [95%CI:1.03-2.37]), but the association disappeared after BMI adjusting at age 31. Increase of BMI from age 14 to 31 was significantly greater in srPCOS (median [interquartile range]:5.94kg/m2[3.69;11.1], p<0.001) and non-PCOS (4.89kg/m2[3.21;7.57], p<0.001) women with HDP and in srPCOS women without HDP (4.59kg/m2[2.40;7.54], p=0.009) compared to non-PCOS without HDP. Among women with srPCOS, BMI increase was greater in women with than without HDP (5.94kg/m2 [3.69;11.1] vs 4.59kg/m2[2.40;7.54], p=0.015). Hyperandrogenaemia at 31 or 46 did not associate with HDP (OR=1.44[95%CI: 0.98-2.11]). CONCLUSION Obesity and weight gain from adolescence to age 46, but not srPCOS or hyperandrogenaemia, were associated with an increased risk of HDP.

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CONCLUSION Obesity and weight gain from adolescence to age 46, but not srPCOS or hyperandrogenaemia, were associated with an increased risk of HDP.

Keywords: Cohort study, hyperandrogenism, hypertensive disorders of pregnancy, PCOS, preeclampsia, obesity, weight gain

Tweetable abstract Self-reported PCOS or hyperandrogenaemia were not associated with an increased risk of HDP

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder affecting 5 to 15% of women at fertile age (1-3). PCOS is defined by the presence of two of the following criteria: (i) polycystic ovaries (PCO); (ii) oligo-amenorrhea (OA) or amenorrhea; and/or (iii) clinical or biochemical evidence of hyperandrogenism (4,5). The syndrome is associated with overweight and obesity in 20% to 80% of the women depending on the studied population and diagnostic criteria used (6,7).

Hypertensive disorders of pregnancy (HDP) complicate 5-10% of all pregnancies (9). Hypertensive disorders of pregnancy include chronic hypertension (blood pressure of at least >140/90 mmHg before pregnancy or before 20 weeks of gestation), preeclampsia (new onset of hypertension and proteinuria after 20 weeks of gestation), superimposed preeclampsia (chronic hypertension in association with preeclampsia) and gestational hypertension (defined according to the same criteria but without proteinuria) (10-12). All these disorders are associated with increased maternal and fetal morbidity and mortality during pregnancy and can also affect the future health of both the mother and child (13). Women with a history of HDP seem to be at higher risk of chronic hypertension, dyslipidemia, cardiovascular diseases (CVDs), type 2 diabetes mellitus and kidney disease in later life (9,13).

Recent meta-analyses have suggested that PCOS is associated with an increased risk of pregnancy induced hypertension (PIH) and pre-eclampsia (3,15-17), although conflicting results have also been obtained (18-20). Of note, in some studies, the association between PCOS and HDP has been confounded by multiple factors such as a higher multiple pregnancy rate, parity, age and body mass indexes (BMI) (16,21). It has also been suggested that the increased risk of HDPs in PCOS may be linked mainly to obesity or hyperandrogenaemia, but not specifically to the syndrome itself.

This study has two main aims: firstly, to investigate whether women with self-reported PCOS experience an increased prevalence of HDP during their reproductive life. Secondly, to identify the impact of factors associated with PCOS, particularly obesity and hyperandrogenaemia, on the development of HDP. More specifically, to explore the significance of weight gain from adolescence to adulthood regarding the emergence of HDP both in PCOS and in non-PCOS women.

Methods

Data collection and study population

The study population consisted of the Northern Finland Birth Cohort 1966 (NFBC1966), a unique population-based, follow-up cohort of subjects (12058 born alive during 1966 in two northernmost provinces of Finland, of these 5889 females). Collection of this database began at the 24th gestational week and was supplemented

by data collected at ages 14, 31 and 46. At age 14, in 1990, the adolescent females (n=5455, 94.6%) answered a postal questionnaire, with the help of their parents, including questions about weight and height. In 1997, at age 31, a postal questionnaire, including questions about health, behavior, work and social background, was sent to 5608 women and 4523 (81%) of them responded. In addition, those living in Northern Finland or in the Helsinki metropolitan area (n=4074) were invited to a clinical examination. Of these, 3127 (77%) women participated in a clinical examination including anthropometric measurements and blood samples for hormonal and metabolic parameters. Again, at age 46, a new large questionnaire including all main health issues and an invitation to clinical examination was sent to 5123 women. Of these, 3706 (72.3%) answered the questionnaire and 3280 women (64.0%) participated in the clinical examinations, including also blood samples. (Figure 1). When gathering the final study population women without deliveries (n=638) were excluded from the analyses.

In all clinical examinations, participants' weight (kg) was measured with a regularly calibrated, digital scale. Height (cm) was measured twice by using standard and calibrated stadiometer and the average of the measurements was calculated. Body mass index (BMI) was calculated (kg/m^2) and women who were overweight (BMI [?]25 kg/m^2) or obese (BMI >30 kg/m^2) were identified. BMI values at ages 31 and 46 from clinical examination and postal questionnaire were combined to create a variable where clinically measured BMI was primarily used and self-reported BMI used if measured BMI was not available. The clinically measured and self-reported BMIs did not differ (22,23). Weight changes (median ±SD) between ages 14-31, 31-46 and 14-46 as well as increase in waist circumference between ages 31 and 46 were calculated in each study group.

Definition of HDP diagnosis

The diagnosis of HDP had to be assessed at least in two of the three following sources to be considered as reliable: the Finnish Medical Birth Register (FMBR), the hospital discharge register (HDR) or the questionnaire at age 46. The process is described in more detail in Figure S1.

Data on women´s pregnancies and deliveries until the end of 2013 was obtained from the FMBR. The FMBR, active since 1987, is currently run by the National Institute for Health and Welfare. For each delivery in Finland, a structured form for FMBR is completed by the delivery hospital, including demographic and health data of the mother, the course and complications of the pregnancy (including HDP diagnosis) and the delivery, and the perinatal health of the newborn until the age of seven days. The FMBR is supplemented with data compiled by the Population Register Centre on live births and by Statistics Finland on stillbirths and deaths during the first week of life. After these additions, the registration of birth is 100%.

The HDR was checked for the data available (years 1972-2017) and the ICD-8, ICD-9 and ICD-10 diagnostic codes for HDPs were identified.

In the NFBC1966 46-year postal questionnaire questions about HPD (chronic hypertension, PIH and preeclampsia) were asked as follows: If you have been pregnant, have you been diagnosed during pregnancy with 1) hypertension (including preexisting chronic hypertension and PIH) 2) hypertension and proteinuria (=pre-eclampsia)?

According to the questionnaire, 665 women were diagnosed with HDP by age 46. Of those women, 358 were not given a formal diagnosis of HDP according to the HDR or the FMBR. Their medical records were checked, and for 51 of those 358, the diagnosis of HDP was confirmed in the patients' records. The remaining women whose diagnosis could not be confirmed were excluded from further analyses (n=307). After exclusion of the women with a diagnosis of HDP from only one source (n=522), the final study group therefore comprised 408 women with a confirmed diagnosis of HDP. The women without diagnosis of HDP from any of these three sources were considered as control women (n=3373, Figure S1).

Definition of PCOS diagnosis

At age 31, the questionnaire included two questions on hirsutism (H) and oligo-amenorrhoea (OA): 1) is your menstruation cycle over twice a year more than 35 days? and 2) do you have excessive body hair? Of

the women who responded to the questionnaire (excluding women using hormonal contraception, n=1459 and not permitting the use of their data for data analysis, n=41), 10.4% (n=321) reported isolated H, 10.2% (n=330) isolated OA and 3.4% (n=125) both OA and H (24-26). Women with only one PCOS symptom were excluded from the analyses. At age 46, the question on self-reported PCOS was inquired as follows: Have you been diagnosed with polycystic ovaries (PCO) and/or PCOS? Women with either both symptoms at age 31 and/or self-reported PCO/PCOS diagnosis by age 46 were classified as cases (self-reported PCOS, srPCOS, n=279), which is consistent with both the National Institutes of Health and the Rotterdam criteria for diagnosis of PCOS (4,27). Women without any PCOS symptoms at age 31 and without self-reported diagnosis of PCOS by age 46 were classified as "non-PCOS controls" (n=1577, Figure 1).

Final study population

The study population was further divided into four groups: women with srPCOS with HDP (n=36), women with srPCOS without HDP (n=154), non-PCOS women with HPD (n=161) and non-PCOS women without HDP (n=1045) (Figure 1).

Laboratory methods

Biochemical assays and laboratory methods used at age 31 have been detailed previously (28). Sex hormone binding globulin (SHBG) at the age of 46 years was analyzed by chemiluminometric immunoassay (Immulite 2000, Siemens Healthcare, Llanberis, UK). Analytical sensitivity of method was 0.02 nmol/l. Serum samples for assay of total testosterone (T) at ages 31 and 46 were analyzed by using Agilent triple quadrupole 6410 liquid chromatography mass spectrometry LC-MS equipment with an electrospray ionization source operating in positive-ion mode (Agilent Technologies, Wilmington, DE, USA).

A woman was considered as having an elevated T levels if T was over 2.3 nmol/l at age 31 (upper limit in our accredited laboratory in fertile age women) or over 1.7 nmol/l at age 46. The cut-off value for T at age 46 was determined according to the upper limit of 97.5% reference range in non-PCOS women in the study population. The free androgen index (FAI) was calculated by using the equation 100×T (nmol/l)/SHBG (nmol/l).

Statistical methods

The differences in distributions of clinical characteristics were tested by using nonparametric Mann-Whitney U test, when appropriate, otherwise a t -test was used. The p-values were further adjusted for BMI at ages 31 and 46 using univariate general linear modelling (ANCOVA). Categorical data were analyzed using cross-tabulation and Pearson's Chi-squared (χ^2) test. Continuous data are presented as medians with lower (25^{th}) and upper quartiles (75^{th}) (interquartile range, IQR).

The whole study population was also stratified into quartiles regarding serum total T level and free androgen index (FAI) at age 31 and 46. Chi-squared (χ^2) test's Linear-by-Linear association was used to identify the trend of HDP prevalence across these quartiles. The p-values were further adjusted for BMI at age 31 and 46 using a binary logistic regression model.

Binary logistic regression models were employed to estimate the factors associated with HDP. The models were adjusted for the consumption of alcohol, smoking and education status at age 46. The results are reported as odds ratios (ORs) with 95% confidence intervals (95% CIs). A p-value <.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics 23.0 (SPSS Inc., Chicago, IL, USA).

Results

Association of srPCOS with HDP

The prevalence of HDP was 14.1% (n=197/1396) in the whole population. Women with srPCOS presented more often HDP compared with the non-PCOS controls 18.9% vs 13.3%, respectively, (p=0.044, Figure 2) and displayed also a slightly increased risk of HDP (OR=1.56 [95% CI: 1.03-2.37]). The risk between the

groups, however, was abolished after adjustment for BMI at age 31 (Figure 3A). The results were similar when replacing BMI at age 31 by BMI at age 46.

Waist circumference is well known to be strongly associated with insulin resistance and metabolic risks. After adjustment with waist circumference at age 31 or 46 instead of BMIs, the results did not change (data not shown).

When obese (BMI [?]30 kg/m^2 vs BMI[?]30kg/m^2) women with srPCOS were compared with the non-PCOS controls, the association with HDP was significant in obese srPCOS women at ages 31 (OR=6.40 [95%CI:3.10-13.23]) and 46 (OR=3.91 [95%CI:2.15-7.10]) (Figure 3A).

Comparison of women with srPCOS with and without HDP (Table 1, Figures 4A and 4B)

When comparing women with srPCOS with or without HDP, BMI was significantly higher at ages 14 (p=0.022), 31 (p=0.001) and 46 (p<0.001) and waist circumference was significantly greater at age 46 (p=0.003) in srPCOS cases with HDP. They also had greater weight gain from adolescence to late adulthood (Table 1, Figure 4A). However, the increase of waist circumference (age 31-46) did not significantly differ between the two groups (Figure 4B).

At ages 31 and 46, FAI was significantly higher in women with srPCOS and HDP (p=0.015 and p=0.020, respectively), but statistical significance was lost after adjustment for BMI.

Comparison of women with HDP with and without srPCOS (Table 1 and Figures 4A and 4B)

When comparing HDP women with srPCOS to those without srPCOS, BMI was significantly higher in the srPCOS group at ages 14 (p=0.018), 31 (p<0.001), and 46 (p=0.003) and their weight gain was greater from age 14 to 31 (p=0.033). (Table 1 and Figure 4A). Waist circumference was significantly greater at ages 31 (p=0.021) and 46 (p=0.011). The increase of waist circumference between ages 31 and 46 did not differ and the pattern of this increase was very similar between the two groups (Figure 4B).

Further, in HDP women with srPCOS, the serum levels of T were significantly higher (p=0.011) at age 31, and FAI was significantly higher at age 31 (p=0.002) and 46 (p=0.007) than in HDP women without srPCOS. After BMI adjustments, statistical significance was lost regarding serum levels of T (p=0.061) but the difference in FAI remained significant at both ages 31 (P=0.012) and 46 (p=0.037).

Comparison of non-PCOS women with and without HDP (Table 1, Figure 3B)

In the non-PCOS women with HDP, BMI was significantly higher at ages 14 (p=0.011), 31 (p<0.001) and 46 (p<0.001), and waist circumference was significantly greater at ages 31 (p=0.005) and 46 (p<0.001) compared to the non-PCOS women without HDP. Weight gain was significantly greater between ages 14-31 (p<0.001) and 14-46 (p<0.001) in the HDP group. In the non-PCOS women at age 31, the risk of HDP increased along BMI class (Table 1, Figure 3B).

Association of hyperandrogenaemia with HDP in the whole population (Figure S2)

In the whole population, women with elevated serum T (>2.3nmol/l at age 31 or >1.7nmol/l at age 46) did not have a significantly greater risk of HDP compared to non-hyperandrogenic controls (data not shown). The levels of FAI expressed as medians were significantly higher at ages 31 (4.53 [2.62; 7.63] vs. 3.76 [2.43; 5.72], p=0.009) and 46 (1.72 [1.25; 2.46] vs. 1.52 [1.06; 2.16], p<0.001) in women with HDP compared with women without HDP and the significance remained at age 46 after adjustment for BMI (p=0.042). The prevalence of HDP in the T quartiles was not significantly linearly associated at age 31 (p=0.337) or at age 46 (p=0.895). In the FAI quartiles, the prevalence of HDP were significantly linearly associated at age 31 (p=0.019), and at age 46 (p<0.001), but overall significance was lost after adjustment for BMI (Figure S2).

Discussion

Main findings

This large follow-up, cohort study indicates that the increased risk of HDP in srPCOS can mostly be attributed to overweight or obesity and that normal weight women with srPCOS seem not to be at increased risk for developing HDP. More specifically, our study revealed also that weight gain from adolescence until the end of reproductive life was the most significant parameter associated with HDP both in srPCOS women and in non-PCOS women. Lastly, our results could not confirm any significant association of hyperandrogenaemia with the development of HDP.

Interpretation

The total prevalence of HDP was 14.1% in our study population, which is relatively high when compared to other studies which report a prevalence of HDP between 5 and 10% (9,29,30). However, direct comparison of HDP prevalence across populations from different countries is challenging, given the considerable heterogeneity in screening approaches, diagnostic criteria, and underlying population characteristics. Moreover, it seems that the prevalence of HDP is increasing widely due to the rising burden of obesity in women of reproductive age (29).

In the whole group of women with srPCOS, the risk of HDP was significantly increased but in overweight/obese women with srPCOS the risk was more than three-fold compared to normal weight non-PCOS women. These findings are in line with the conclusions of recent meta-analyses, suggesting that women with PCOS have an increased risk of developing PIH and preeclampsia (3,15-17). In the present study, however, the difference disappeared when comparing overweight/obese srPCOS women with overweight/obese non-PCOS women, and the prevalence of HDP was not increased among normal-weight srPCOS women compared to their normal weight non-PCOS counterparts. These findings suggest that srPCOS was not associated with an increased risk of HDP. Similar results were found in the non-PCOS groups when comparing the risk of HDP in obese or overweight with their normal weight counterparts, suggesting that the risk of HDP is mostly attributable to overweight/obesity, in line with some earlier data (31,32). The diverging conclusions of the aforementioned meta-analyses could be explained by the fact that the majority of the eligible studies either did not take into account confounding factors such as BMI or were of retrospective study design and included a relatively small sample size. Only few previous studies have addressed the possible interaction of BMI with PCOS regarding the risk of HDP. Lonnebotn et al also reported an increased risk of HDP in obese but not in normal weight or overweight women with PCOS (33). However, that study reported also increased risk in underweight (BMI <18.5 kg/m^2) women, whereas there were no underweight women with both srPCOS and HDP in our study. All in all, the results of the present study indicate that the increased risk of HDP in srPCOS can mostly be attributed to overweight/obesity and that normal weight women with srPCOS were not at increased risk for developing HDP.

In previous literature, there is a lack of long-term follow up studies investigating the association of lifelong increase of weight or of waist circumference with the risk of HDP. In this study, both srPCOS and non-PCOS women with HDP experienced a significantly greater increase in weight from adolescence to late adulthood compared with women without HDP. Interestingly, the pattern of increase in waist circumference between ages 31 and 46 was mostly associated with HDP, but not with PCOS status. These findings further strengthen the role abdominal obesity and insulin resistance, as a pivotal factor associated with the development of HDP. The existence of a complex synergistic interrelationship between PCOS, abdominal obesity and weight gain are most likely risk factors for these alterations.

In the whole study population, the risk of HDP was not significantly increased in the group of women with elevated serum T levels compared with controls. However, hyperandrogenaemia assessed by FAI was significantly associated with HDP, and both srPCOS and non-PCOS women with HDP had higher values of FAI compared with non-PCOS women without HDP. Again, after adjusting for BMI, the effect of hyperandrogenaemia lost its statistical significance. Some previous studies have suggested that the hyperandrogenic PCOS phenotypes are associated with higher prevalence of HDP, especially preeclampsia, compared to normoandrogenic phenotypes (34,35) but other studies have produced conflicting results (21). Hyperandrogenism has been associated with preeclampsia also in the absence of PCOS (36-39). A possible explanation for these observations may be that placental aromatase (the enzyme responsible for the conversion of androgens to

estrogens) is deficient in placental ischemia and preeclamptic pregnancy (37), thus explaining the observed elevation of maternal androgens during preeclampsia. Elevated androgens have also been postulated to play an important role in the aetiology of preeclampsia, although the mechanism is not clear (38). In the present study, the lack of association between hyperandrogenaemia and HDP may be partly due to the fact that we were not able to differentiate the diagnosis of pre-eclampsia from the other causes of HDP. Based on the present and earlier results, the role of hyperandrogenaemia in the pathogenesis of HDP remains therefore under debate and needs further research to be clarified.

Strengths and limitations

The main strength of this study is the prospective population-based cohort design with the longest follow-up time compared with previous studies. The participation rates for the clinical examinations and questionnaires at ages 31 and 46 were remarkably high and anthropometric parameters were mostly clinically measured. By taking advantage of FMBR, HDR and the questionnaire data we were able to have an accurate estimate of HDP in our study population as HDP diagnosis was set only if it was found in at least two out of the three sources. Moreover, our study included careful adjustments for possible confounders allowing us to identify the respective effects of srPCOS and other risk factors, such as obesity, hyperandrogenaemia and weight gain from adolescence to late adulthood, on risk of having developed HDP during reproductive life.

A potential limitation of our study is that documenting symptoms of PCOS at age 31 and PCOS diagnosis at age 46 was based on questionnaires. Hirsutism might be over-reported by self-estimation and ovarian ultrasonography was not available to aid the diagnosis of PCOS. However, we have previously shown that co-existence of self-reported oligo-amenorrhoea and hirsutism can identify women with the typical endocrine, metabolic and psychological profiles of PCOS (26,28,40). It was not possible to differentiate between the diagnosis of chronic hypertension, PIH and preeclampsia, as all these conditions were included as one identity into the HDP diagnosis. We excluded from the analyses 522 women with only one source of diagnosis, which may result in underestimation of the incidence of HDP. Finally, even though BMI values were collected at ages 31 and 46 from clinical examination and postal questionnaire, BMI data during pregnancy were not available.

Conclusions

The increased risk of HDP in srPCOS can mostly be attributed to overweight/obesity and weight gain through life. Importantly, normal weight women with srPCOS were not at increased risk for developing HDP. The present results emphasize the importance of weight management prior pregnancy to reduce the incidence of HDP, an important factor cause of postnatal morbidity. The role of hyperandrogenaemia in the pathophysiological process of HDP could not be confirmed, remaining under debate with further research being needed to clarify its role.

Disclosure of interests

None

Contribution to authorship

L.C.M.-P., S.I.W., J.N and J.S.S.R conceived and designed the study. A.H.B. and J.S.S.R. analysed the data and L.M.C.-P., J.N. and M.S.V contributed to its interpretation. J.S.S.R. and J.N drafted the manuscript. M.-M.E.O, K.P, M.-R.J, J.S.T, S.F and T.T.P participated in the revision process and have approved this submission for publication.

Details of ethics approval

The study followed the principles of the Declaration of Helsinki. The Ethics Committee of the Northern Ostrobothnia Hospital District (EETTMK decision number 94/2011) has approved the research on Sebtember 17th, 2012. All participants took part on a voluntary basis and signed an informed consent to use all data.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flowchart of the HDP diagnosis.

Figure S2. Prevalence of hypertensive disorders of pregnancy (HDP) in different total level of testosterone (A) and free androgen (B) quartiles at ages 31 and 46

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Table 1 Clinical characteristics of non-PCOS women and women with srPCOS, sorted according to status of hypertensive disorder of pregnancy.

Clinical Non-PCOS Non-PCOS P-value[a] srPCOS P-value[b] srPCOS P-value[c]P-value[d] P-value[e]

Characteristics without HDP with HDP (BMI-adj. without HDP (BMI-adj. with HDP (BMI-adj. (BMI-adj. (BMI-adj.

(n=521-1039[d]) (n=85-160[d]) p-value [f]) (n=88-147[d]) p-value[f]) (n=21-35[d]) p-value[f]) p-value [f]) p-value[f])

BMI (kg/m^2) 14 yr 18.7 (17.4; 20.2) 19.2 (17.9; 20.9) .011 19.3 (18.0; 20.6) .006 20.4 (18.6; 22.8) <.001 .022 .018

BMI (kg/m^2) 31 yr 22.6 (20.7; 24.9) 24.0 (21.8; 26.7) <.001 24.1 (21.5; 27.2) <.001 28.0 (22.4; 33.9) <.001 .001 <.001

BMI (kg/m^2) 46 yr 25.2 (22.6; 28.6) 26.9 (23.9; 30.5) <.001 26.2 (23.7; 30.3) .002 31.4 (26.1; 37.3) <.001^t <.001^t.003^t

Waist (cm) 31 yr 76.0 (70.0; 83.0) 78.0 (72.5; 85.3) .005 81.0 (71.0; 92.0) <.001 83.5 (75.0; 98.0) <.001 .113 .021

Waist (cm) 46 yr 83.5 (77.0; 93.5) 90.0 (79.5; 99.0) <.001 86.5 (79.5; 97.8) .020 94.5 (83.6; 115.1) .001^t.003^t .011^t

Change in BMI (kg/m^2) 14-31 yr 3.83 (2.27; 5.74) 4.89 (3.21; 7.57) <.001 4.59 (2.40; 7.54) .009 5.94 (3.69; 11.1) <.001 .015 .033

Change in BMI (kg/m^2) 31-46 yr 2.40 (0.81; 4.19) 2.65 (0.97; 5.61) .068 2.19 (0.71; 4.60) .745 2.96 (0.14; 4.40) .895 .801 .479

Change in BMI (kg/m^2) 14-46 yr 6.33 (3.90; 9.33) 7.54 (5.32; 11.62) <.001 7.21 (4.16; 10.5) .151 9.82 (6.23; 14.6) <.001^t .001^t.073^t

Change in waist (cm) 31-46 yr 8.30 (2.60; 14.0) 8.80 (3.00; 16.0) .352 8.00 (3.00; 15.0) .692 11.0 (5.00; 19.9) .203^t.247^t .691^t

Total testosterone (nmol/l) 31 yr 1.80 (1.40; 2.30) 1.90 (1.40; 2.40) .527 (.979) 2.00 (1.70; 2.80) <.001 (.003) 2.60 (1.95; 3.10) .002^t (.083) .284^t (.558) .011^t (.061)

FAI 31 yr 3.75 (2.57; 5.44) 4.41 (2.67; 6.00) .097 (.985) 5.08 (3.14; 7.64) .002 (.372) 10.31 (4.55; 13.31) .001^t (.013) .015^t (.189) .002^t (.012)

Total testosterone (nmol/l) 46 yr 0.82 (0.62; 1.05) 0.80 (0.61; 1.07) .963 (.664) 0.86 (0.68; 1.05) .277 (.236) 0.97 (0.72; 1.13) .092^t (.066) .315^t (.232) .113^t (.063)

FAI 46 yr 1.53 (1.06; 2.22) 1.63 (1.17; 2.24) .324 (.727) 1.62 (1.29; 2.25) .064 (.347) 2.17 (1.43; 3.41) .001 (.037) .020 (.176) .007 (.037)

Data is expressed as medians (interquartile ranges). The significance test used was Mann-Whitney U test, when a rule |skewness/standard error of skewness|>1.96 was valid for the dependent variable, otherwise t-test was used (^{t}-sign).[a]P-value: non-PCOS with HDP compared to non-PCOS without HDP. [b]P-value: srPCOS without HDP compared to non-PCOS without HDP. [c]P-value: srPCOS with HDP compared to non-PCOS without HDP. [d]P-value srPCOS with HDP compared to srPCOS without HDP. [e]P-value: srPCOS with HDP compared to non-PCOS with HDP. [f]The numbers of women in separate analyses varies due to non-response to some items. [f]The results were adjusted for BMI at age 31 and 46 years using univariate general linear modelling (ANCOVA). BMI: body mass index; FAI: free androgen index; HDP: hypertensive disorder of pregnancy; srPCOS: self-reported polycystic ovary syndrome; SHBG: sex hormone binding globulin.

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