Long-term consequences of polycystic ovary syndrome

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UNIVERSITY OF ZAGREB
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Long-term Consequences of Polycystic Ovary Syndrome

GRADUATE THESIS

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This graduate thesis was completed at University Hospital Petrova Gynecological Clinic – Human Reproduction Unit, mentored by assistant Professor Lana Škrgatić and was submitted for evaluation in 2016/1017.

Abbreviations

A: Androstenedione
BMI: Body Mass Index
CRP: C-reactive Protein
CV: Cardiovascular
CVD: Cardiovascular Disease
EE-CA: Ethinyl Estradiol-Cyproterone Acetate
HDL-C: High Density Lipoprotein Cholesterol
HOMA-IR: Homeostatic Model Assessment Of Insulin Resistance
IR: Insulin Resistance
LDL-C: Low Density Lipoprotein Cholesterol
OCP: Oral Contraceptive Pill
OR: Odds Ratio
PCOS: Polycystic Ovary Syndrome
SHBG: Steroid Hormone Binding Globulin
TG: Triglycerides
TNF-α: Tumor Necrosis Factor-α
Total-C: Total Cholesterol
WHR: Waist-Hip Ratio

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1. Summary

Title: Long-term Consequences of Polycystic Ovary Syndrome
Author: Monika Elisabeth Crumbach

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. It shares many features with the metabolic syndrome (insulin resistance, an increase in body mass index, changes in lipidogram, increases in C-reactive protein due to chronic inflammation). As a long-term consequence, development of cardiovascular disease (CVD) is likely.

The purpose of this retrospective observational study was to explore if cardiometabolic risk factors (BMI, HOMA-IR, total cholesterol, TG, LDL-C, HDL-C, CRP) worsen over time in PCOS patients. The data of 36 PCOS patients aged 26.5 ± 6.4, in whom the diagnosis was made according to the Rotterdam criteria, was included in the study. The metabolic parameters were taken from hospital records of University Hospital Petrova Gynecological Clinic in Zagreb, Croatia. We included laboratory values measured at the starting point of the study, in 2007, and after nine years, in 2016.

No significant worsening of cardiometabolic risk factors was found after the nine years. Only the percentage of PCOS patients with a BMI > 25 increased from 25.0% to 33.3% ($P = 0.002$).

Further studies should be conducted with a larger sample size and longer duration of observation.

Keywords: Polycystic ovary syndrome, cardiometabolic risk factors

2. Sažetak

Titula: Dugoročne Posljedice Sindroma Policističnih Jajnika
Autor: Monika Elisabeth Crumbach

Sindrom policističnih jajnika (PCOS) najčešći je endokrinološki poremećaj u žena reprodukcijske dobi. Ovaj sindrom dijeli mnoge karakteristike metaboličkog sindroma poput inzulinske rezistencije, povišenog indeksa tjelesne mase, poremećaja vrijednosti lipida, te povišenih vrijednosti C-reaktivnog proteina. S obzirom da ovi rizični metabolički parametri često prate PCOS, očekivana je veća vjerojatnost neželjenih kardiovaskularnih događaja kao dugoročna posljedica PCOS-a.

Cilj je ove retrospektivne opservacijske studije bio istražiti dolazi li tijekom vremena do pogoršanja kardiometaboličkih rizičnih čimbenika (BMI, HOMA-IR, ukupni kolesterol, trigliceridi, LDL-C, HDL-C,CRP). Analizirani su podaci 36 bolesnica, prosječne dobi 26.5 $\pm$ 6.4, kod kojih je dijagnoza PCOS-a postavljena prema Rotterdamskim kriterijima 2007 godine. Podaci o vrijednostima različitih metaboličkih parametara analizirani su iz bolničkog informacijskog sustava Klinike za ženske bolesti i porode KBC-a i Medicinskog fakulteta Sveučilišta u Zagrebu. U analizu smo uključili one laboratorijske nalaze koji su izrađeni 2007. godine i ponovno 2016. odnosno nakon vremenskog intervala od devet godina.

Nije nađeno značajno pogoršanje kardiometaboličkih rizičnih čimbenika u periodu od devet godina. Zabilježeno je povećanje udjela pacijentica s ITM > 25 kg/m^2 (P = 0.002).

Potrebne su daljnje studije koje će uključiti veći broj bolesnica s PCOS-om sa dužim vremenskim periodom praćenja.

Ključne riječi: Sindrom policističnih jajnika, kardiometabolički rizici

2. Preface

This graduate thesis is based on data collection of women with Polycystic ovary syndrome (PCOS), over the course of nine years, from 2007 to 2016. The sample of women consists of patients who have been followed by Assoc. Prof. Dinka Pavičić Baldani and Assist. Prof. Lana Škrgatić over this time period. The thesis is concerned with certain parameters of cardiometabolic risk associated with PCOS, their change over this nine-year period, due to their association with development of cardiovascular disease (CVD) over the years. The parameters associated with an increased risk of developing CVD considered in this text are increased body mass index (BMI) and waist-hip ratio (WHR), homeostatic model assessment of insulin resistance (HOMA-IR), changes in lipidogram (total cholesterol [total-C], triglycerides [TG], low density lipoprotein cholesterol [LDL-C], and high density lipoprotein cholesterol [HDL-C]), and C-reactive protein (CRP) as a strong independent predictor for development of CVD.

This thesis was a prerequisite for the completion of the Medical Studies in English Program at the University of Zagreb, School of Medicine. The author of the thesis is Monika Elisabeth Crumbach, who wrote it with the assistance of her mentor, Assist. Prof. Lana Škrgatić.

3. Hypothesis

Cardiometabolic risk factors (BMI, HOMA-IR, total cholesterol, TG, LDL-C, HDL-C, CRP) worsen over time in PCOS patients.

4. Objectives

The aim of the present study was to evaluate whether there is a worsening of various cardiometabolic risk factors in PCOS patients in the time frame of nine years. The data was collected from the hospital records of the University Hospital Petrova Gynecological Clinic in Zagreb, Croatia. Determining the changes in different cardiometabolic risk parameters could help in the development of preventive measures for this large group of affected women and would be of great help in their screening, treatment, and improvement of morbidity and mortality.

5. Introduction

PCOS, also known as Stein-Leventhal syndrome, is the most common endocrine disorder in women of reproductive age.

As defined by the Rotterdam criteria [1, 2], for the diagnosis of PCOS, more than two of the following are required: oligo-/anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries on ultrasound, after exclusion of other diseases that manifest similarly, such as congenital adrenal hyperplasia, hyperprolactinemia, androgen secreting tumors, thyroid dysfunction, and Cushing syndrome.

PCOS is often associated with an increased risk in developing CVD as a long-term consequence. The disorder shares many features with the metabolic syndrome (insulin resistance [IR], an increase in BMI, changes in lipidogram, increase in CRP due to chronic inflammation), and is therefore associated with an increase in cardiometabolic risk factors [3, 4]. These risk factors are closely interconnected and an understanding is essential for evaluating the overall risk.

Obesity and an increased BMI is a common but non-essential feature of PCOS. Even in non-obese patients with PCOS, an increased BMI and increase in WHR is evident [3]. It is well-known that women with PCOS tend to have a centripetal fat distribution, with an accumulation of visceral fat in the abdominal region [5]. Increased intra-abdominal obesity, leads to an increase in lipolysis of the metabolically more active visceral fat, and therefore in an increase of free fatty acids which further contributes to IR in said patients. Insulin signaling is inhibited by increased serine phosphorylation induced by the cytokine tumor necrosis factor-α (TNF-α) produced by the released free fatty acids. This leads to IR, which is a common feature in obese and in a smaller proportion of lean patients with PCOS [3, 6]. The present visceral fat does not only contribute to the development of IR, but also produces a state of chronic low-grade inflammation. An increase in BMI and WHR are well-recognized risk factors for developing CVD. Both obesity and PCOS contribute independently to the arterial stiffness connecting PCOS to CVD [7]. Ketel et al. [7] concluded that obesity has a stronger association with increased arterial stiffness than PCOS, and the focus in prevention of CVD should lie in central fat mass reduction in obese women with PCOS. Yusuf et al. [8] compared the odds ratio (OR) for developing a myocardial infarction

(MI) in patients with a WHR in the upper tertile with those in the lower tertile. He found that those in the upper tertile have an OR of around 2.

IR causes hyperinsulinemia, which contributes to hyperandrogenism through a resulting increase in androgen production by the ovaries, and inhibition of steroid hormone binding globulin (SHBG) production in the liver. This mechanism further aggravates the syndrome [3]. There is an overall prevalence of IR in women with PCOS, partly independent of the presence of obesity. According to Randeva et al. [9] both lean (30%) and obese (70%) women with PCOS show decreased insulin sensitivity, compared to a control group of women of equal age. Women with PCOS of all ages commonly suffer from IR, hyperinsulinemia and diabetes [4]. Dunaif et al. [6] found that IR is caused by excessive serine phosphorylation of insulin receptors, which leads to decreased protein kinase activity. Serine phosphorylation of the regulatory enzyme P450c17 involved in androgen metabolism further contributes to hyperandrogenism present in women with PCOS [3, 9]. Free fatty acids excessively released by lipolysis in obese patients is a stimulant factor for serine phosphorylation [3, 9].

Dyslipidemia is the most common metabolic abnormality in PCOS [10]. Both lean and obese women with PCOS present with dyslipidemia [9]. The lipidogram shows an increase in TGs and LDL-C, while HDL-C is decreased [3 ,9, 10]. The change in lipid profile is associated with the presence of hyperinsulinemia and IR [3], similar to the changes found in type 2 diabetes [9]. IR causes an increase in very-low-density-lipoproteins, chylomicrons, TG, and an increased clearance of apolipoprotein-A, which leads to a general decrease of the cardioprotective HDL in the circulation [5]. Randeva et al. [9] observed that there is a 1.8-fold increase in risk of developing dyslipidemia in women with PCOS in comparison to their relatives. Particularly increased LDL-C and low HDL-C levels predict the development of coronary artery disease according to the Framingham study [11].

A powerful independent risk factor for the development of CVD is CRP, a marker of chronic inflammation [12]. As mentioned above, visceral obesity leads to a state of chronic low-grade inflammation. CRP also acts as a mediator in the atherosclerotic process itself [13]. Therefore, high CRP levels in women with PCOS also correlate with an increased risk of developing early CVD in these patients. Amongst others reasons for high CRP levels in women with PCOS is its production by pro-inflammatory cytokines, such as Interleukin-6 and TNF-α. The association of cardiometabolic

syndrome with PCOS is already well established and has also been the subject of other studies. Its importance is growing, especially in the light of the increased incidence of sedentary lifestyles and obesity demographics [14, 15]. Only a few studies have looked into the long-term changes of cardiometabolic risk parameters over time. Therefore, the aim of the present study was to evaluate whether there is a difference between various cardiometabolic risk factors in PCOS patients in the time frame of nine years.

6. Patients and Methods

To examine the association between various cardiometabolic risk factors and PCOS, we performed a retrospective observational study. The data of 36 PCOS patients aged 26.5 ± 6.4 in whom the diagnosis was made according to the Rotterdam criteria [1, 2] was included in the study. The patient data was only included if they contained measurements of BMI, HOMA-IR, total-C, TG, LDL-C, HDL-C, and CRP in the years 2007 and 2016, respectively. The data on FSH, LH, total testosterone, free testosterone, A, DHEA-S, and SHBG was only extracted from the medical records when it was used for the diagnosis of PCOS in 2007. The data was obtained from the hospital records of the Human Reproduction Unit Outpatient Clinic of the Gynecological Hospital Petrova in Zagreb, Croatia.

The data values were expressed as the means ± standard deviation, and categorical data as percentages. The non-parametric Wilcoxon Signed Rank Test was used to test the differences between continuous variables, while Pearsons χ^2-test was used for categorical variables. Categorical data was also presented graphically. All statistical analyses were done using the SPSS for Windows (version 22.0; SPSS Inc., Chicago, IL, USA). A *P*-value < 0.05 was considered statistically significant.

7. Results

The hormonal parameters which aided in the diagnosis of PCOS patients from the year 2007 are presented in table 1. The table shows that 25% (9 out of 36) of the patients had a BMI above 25 kg/m^2, and were therefore overweight per definition. Almost 85% of patients had hyperandrogenism.

Table 1. Basic characteristics of PCOS patients included in the observational study. Data extracted from medical records in 2007.

	N = 36
Age (years)	26.5 ± 6.4
BMI (kg/m^2)	23.5 ± 2.3
BMI > 25 (kg/m^2) (%)	25
FSH (IU/L)	3.4 ± 1.0
LH (IU/L)	8.3 ± 4.2
tT (nmol/L)	2.3 ± 0.9
tT > 2.0 (nmol/L) (%)	52.8
freeT (pmol/L)	44.4± 28.3
freeT > 26.0 (pmol/L) (%)	83.3
A (nmol/L)	10.8±4.5
DHEA-S (µmol/L)	6.5±2.6
SHBG (nmol/L)	43.7±37.5

We found no statistically significant differences in cardiometabolic risk factors in the year 2007 compared to 2016 using the Wilcoxon Signed Rank Test ($P < 0.05$), except in BMI values, which are presented in table 2. The percentage of PCOS patients with a BMI > 25 increased from 25.0% to 33.3% (N = 36, $P = 0.002$). IR was present in 10 (27.8%) PCOS patients in 2007, and in 11 (30.6%) patients in 2016. Hence, the changes were not statistically significant ($P = 0.611$). In 2007 hypercholesterolemia was measured in only four patients out of 36, while in 2016 the number increased to seven out of 36 patients ($P = 0.163$). The number of patients with hypertriglyceridemia increased from 12 patients in 2007 to 13 patients in 2016 ($P = 0.447$). In 2007, six

women with PCOS had an HDL-C < 1.2 nmol/L, while in 2016 the number only increased to seven (*P* = 0.671). In a similar manner, LDL-C values > 3nmol/L were measured in 2007 in five PCOS patients, and in 2016 in six patients (*P* = 0.550). CRP levels in 2007 were measured to be 2.0 ± 0.4 mg/L and until 2016 barely increased to 2.1 ± 0.6 mg/L (*P* = 0.574).

Table 2. Differences between concentrations of various metabolites in PCOS patients in 2007 compared to 2016.

	PCOS (N = 36) 2007.	PCOS (N = 36) 2016.	*P*-value[1]
BMI (kg/m^2)	23.5 ± 2.3	24.47 ± 2.8	<0.001
BMI > 25 (kg/m^2) (%)	25.0	33.3	0.002
glucose (mmol/L)	4.4±0.5	4.5 ± 0.5	0.900
insulin (mIU/L)	12.7±10.0	11.9 ± 9.5	0.928
GIR	8.9±6.0	9.6 ± 6.5	0.550
HOMA-IR	2.6±2.3	2.5 ± 2.2	0.967
HOMA-IR > 2.5 (%)	27.8	30.6	0.611
Total-C (nmol/L)	4.5±0.3	4.5 ± 0.4	0.644
Total-C > 5 nmol/L	11.1	19.4	0.163
TG (nmol/L)	1.4±0.4	1.4 ± 0.3	0.905
TG >1.7 nmol/L (%)	33.3	36.1	0.447
HDL – C (nmol/L)	1.6±0.3	1.5 ± 0.2	0.726
HDL-C < 1.2 nmol/L	16.7	19.4	0.671
LDL-C (nmol/L)	2.3±0.5	2.4 ± 0.6	0.550
LDL-C > 3 nmol/L	13.9	16.7	0.378
CRP (mg/L)	2.0±0.4	2.1 ± 0.6	0.574

[1]Wilcoxon Signed Rank Test, Chi square test

Figure 1 graphically presents the values listed in table 2, showing an increasing trend in all measured cardiometabolic parameters, but this did not reach statistical significance. BMI shows the only significant change with an increase over time (*P* =

0.002). The biggest change observed among metabolic parameters was in serum levels of total-C, but also insignificant (P = 0.163).

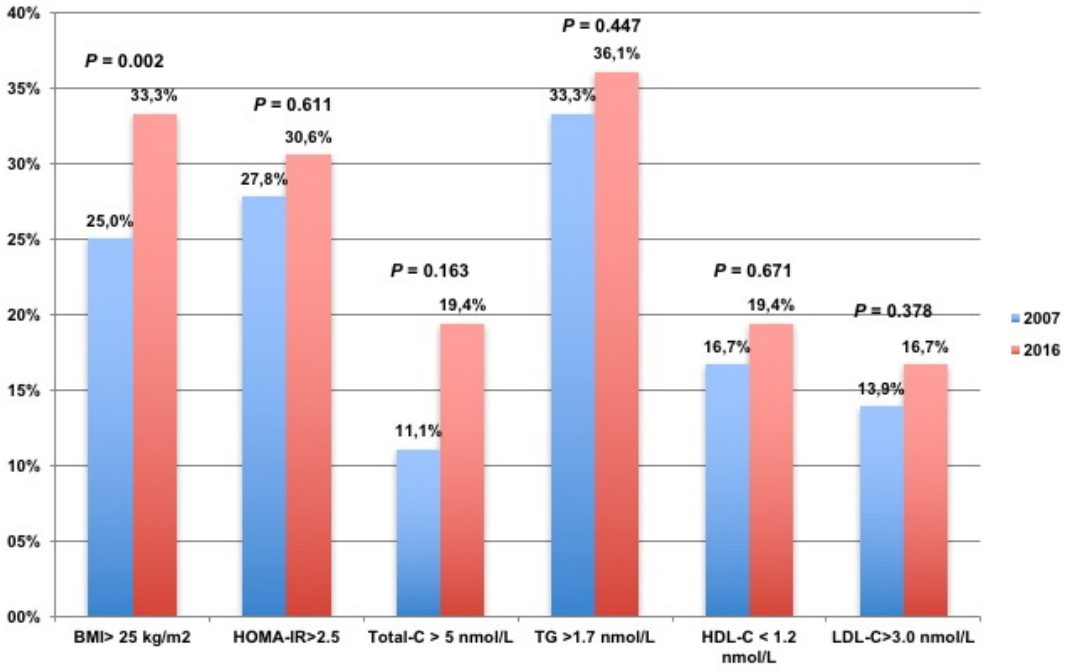

Figure 1. Graphic presentation of the differences in metabolite concentrations in 2007 compared with 2016.

8. Discussion

This retrospective observational study followed up different cardiometabolic parameters (BMI, HOMA-IR, total-C, TG, LDL-C, HDL-C, CRP) of 36 PCOS patients of the Human Reproduction Unit of the Gynecological Hospital Petrova in Zagreb, Croatia. The parameters were recorded and re-assessed after a time period of nine years from 2007 to 2016. Only a few studies have examined the changes of cardiometabolic risk factors over time so far. Our results showed that there was no significant difference in cardiometabolic parameters after that time. Therefore, our hypothesis that the cardiometabolic risk changes over time was not supported.

Body Mass Index

As presented in the results, BMI was the only cardiometabolic parameter with a statistically significant change over the nine years. The number of women with PCOS with a BMI > 25kg/m^2 increased from nine to 12 out of 36 (P = 0.002). Even though the number increased as we predicted, we expected an even bigger increase associated with PCOS. The changes observed here could also be purely related to increases of BMI commonly associated with aging. According to a Norwegian study [16] which started in the mid-80s women aged 20-29 increased their weight on average by 7.3kg over a period of 11 years. Another Norwegian study [17] examined increases in BMI by level of income and education in the time frame from 1990 to 2001. This study also found an increase in the percentage of overweight individuals from 27% to 40% (N=1169 adults). Reas et al. [17] concluded that accelerated weight gain occurs due to lifestyle changes (diet, energy expenditure), especially in younger adulthood. At the start of our study in 2007, the PCOS patients followed up were aged 26.5 $\pm$ 6.4, thus falling in the category of younger adults. Therefore, the possibility that the weight gain is solely associated with aging would be conclusive with the aforementioned Norwegian studies [16, 17].

Insulin Resistance

HOMA-IR values were used to assess IR. Our study did not show any statistically significant changes in HOMA-IR over the evaluated nine years (P = 0.967). The number of women with PCOS with HOMA-IR > 2.5% only increased by one until the year 2016 (P = 0.611). According to other studies there is evidence of clustering of

metabolic risk factors in metabolic syndrome and therefore the development of CVD [18, 19]. A Framingham Offspring Study with 2616 nondiabetic participants found that an increase in BMI, which is also present in our study, is especially strongly related to similar changes in other metabolic risk factors, especially IR [18]. With the presence of this correlation among all the metabolic parameters, a slightly more impressive change in IR could have been expected. This is also supported by the already well-known role of abdominal obesity in the development of IR [3, 6]. An even bigger change in IR would have probably been seen with an even greater increase in BMI. Additionally, Rutter et al. [18] found that changes in IR played an important role in the clustering of metabolic risk factors as well. On the other hand, this could explain why there was only a small change in our measured parameters over time.

Lipids

As previously mentioned, dyslipidemia is the most common metabolic abnormality in women with PCOS [10], even though it is also true that many patients have entirely normal lipid profiles [3]. The parameters of the lipidogram considered in this study were total-C, TG, and LDL-C which represent known risk factors of CVD, and the cardioprotective HDL-C. The results of our study showed that the respective values did not change in a statistically significant way.

According to Diamanti-Kandarakis et al. [20] it is exceedingly difficult to establish a cause-effect relationship between the different cardiometabolic risk factors present in PCOS, even though obesity seems to be a major risk factor for developing dyslipidemia. This was supported by Robinson et al. [21] who observed in a different study that obesity is not the only inherent risk factor in PCOS predisposing to dyslipidemia. In their study, Diamanti-Kandarakis et al. [20] tested the influence of the antiandrogen receptor blocker flutamide on dyslipidemia in PCOS and found an improvement, hence supporting evidence of the role of hyperandrogenism in the development of dyslipidemia.

CRP

Our study did not show a significant increase in CRP levels, similar to the other metabolic parameters observed.

A Finnish randomized clinical trial [22] examined the influences of therapy with metformin versus ethinyl estradiol-cyproterone acetate (EE-CA) oral contraceptive pills

(OCPs) in 20 non-obese and 32 obese women diagnosed with PCOS and increased CRP values over six months. A significantly higher CRP level was observed in obese compared to non-obese women. This difference remained during both treatments. The study showed a significant correlation (Pearson's correlation) of CRP levels and BMI, WHR and waist circumference, as well at baseline as at six months of respective treatment. At six months, treatment with metformin resulted in a 31% decrease of CRP levels in non-obese subjects and a 56% decrease in obese subjects, proving its beneficial effects on metabolic and hormonal parameters, and implying a possible decrease in chronic inflammation. On the other hand, treatment with the EE-CA OCP lead to an increase in CRP levels after six months. This increase suggested it to be an unfitting treatment in especially obese women with IR diagnosed with PCOS. These results suggest that a lack of change in CRP levels could be due to the long-term treatment of our population.

A meta-analysis of 26 studies matching for BMI established that the elevation of CRP is more notable in obese women with PCOS [23]. After adjusting the BMI, the elevation attributable to PCOS is relatively small. Therefore, there is a strong association between BMI and CRP elevation, and BMI reduction could help regulate CRP levels. This further supports results like those from our study, that even in long-term follow-up no significant CRP changes need to be present.

Other studies investigating cardiometabolic risk factors in PCOS and their correlation with mortality in a bigger population brought similar results. Iftikhar et al. [24] found few differences in cardiovascular (CV) risk factors and no overall difference in CV events in a retrospective cohort study comparing 309 women with PCOS to 343 women without PCOS during a mean follow-up of 23 years. Pierpoint et al. [25] concluded in another long-term follow-up of 786 women with PCOS in the United Kingdom that there is no increase in mortality from CVD, even though the disease is strongly associated with important cardiometabolic risk factors. Wild et al. [26] did a similar retrospective study of 319 women diagnosed with PCOS, based on the fact that there is an increase in cardiometabolic risk factors compared to age-matched controls. The result of this study was also that there is no significant increase in CV mortality [26]. This could lead to the assumption that there was no significant increase in cardiometabolic parameters, and Wild et al. [26] speculated that a different etiology for coronary heart disease should be considered in women diagnosed with PCOS. All

these studies compared women with PCOS to women without PCOS, and only Schmidt et al. [4] analyzed the risk in a similar set of patients. In their study, they compared the cardiometabolic risk factors in pre- and perimenopausal women with PCOS. Schmidt et al. [4] concluded after the 21-year follow-up that the only more frequently persistent cardiometabolic risk factors in women with PCOS were hypertension and triglyceridemia. Altogether they did not observe an obvious increase in cardiovascular events during the post-menopausal period in PCOS patients [4].

Generally, there are a few biases that could have largely influenced our results. Firstly, a relatively small population size was selected. Another factor that likely influenced our outcome was the duration of the study. Increasing the duration of follow up could increase the significance of our test results. Perhaps the outcome could be improved if we were to follow up the patients from diagnosis to the occurrence of a CV event, but this is difficult to accomplish, especially considering drop-out bias and other. Furthermore, it is important to mention that the metabolic parameters were not measured at the same laboratories in 2016. This could also have an influence on the precision of the test results.

9. Conclusions

In conclusion, our results showed that there is a trend observed towards worsening of all cardiometabolic risk factors present in PCOS which were considered in this stud, but the changes did not show any statistical significance. Our results could have been influenced by different biases (observational study, small sample size, metabolic parameters measured in different laboratories). BMI was the only metabolic parameter that changed significantly during the nine years observed in this study, although less than expected.

Further studies should be conducted and designed with larger sample sizes, longer time course of observation, more frequent follow ups and measurement in the same laboratories. Moreover, a comparison of pharmacological treatment of the PCOS patients and its relation to changes in metabolic parameters would be informative. Another idea to improve future studies would be to evaluate siblings and other family members of women with PCOS.

10. Acknowledgements

I would like to express my sincere gratitude to my mentor assistant Professor Lana Škrgatić for the inspiration to choose this topic and pursue my study of gynecology. Her teaching skills and expertise provided great help to guide me throughout this paper.

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12. Biography

Monika Elisabeth Crumbach was born on July 5th 1988 in Munich, Germany. After finishing her Abitur (the general school leaving examination and prerequisite for higher education) at Gymnasium der Benediktiner Schäftlarn in Germany, she enrolled into the University of Zagreb School of Medicine, Medical Studies in English.

During her studies Monika participated in several extracurricular activities and clubs, such as “Lege artis”, the choir of the medical school, and CROSS. Furthermore, she attended workshops to increase skills and knowledge in ALS and ECG organized by the Swedish Student Council. In her fifth and sixth year of study, Monika also got elected to be one of the student representatives for her class and was an active member in the student council. During this time, she won the Rector’s award together with eMed, the student council of the English program.

Monika’s interest lies in the fields of Gynecology, Family Medicine and Psychiatry. She hopes to practice in one of these in the future.