Effects of Peroral Hormonal Contraception on Cardiovascular System: Analysis of Selected Cardiovascular Parameters in an Adolescent Cohort; a Pilot Project

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Summary

Oral contraceptive pills (OCPs) have some strong advantages over more traditional types of contraception, including their consistently high contraceptive effect as well as multiple additional positive side effects. OCPs went through decades of intense pharmaceutical development and current formulas are well optimized – however, a handful of their negative side effects remain, including some that affect cardiovascular system, for example higher risk of hypertension, venous thromboembolism and increased arterial stiffness. The gold standard for arterial stiffness assessment is currently applanation tonometry, a method that relies on arterial pulse wave velocity measurement (PWV). Another possible method for arterial stiffness measurement is the use of the VaSera device, which measures cardio-ankle vascular index (CAVI). The aim of this study was to discover the effect of OCPs use on selected cardiovascular parameters related to arterial stiffness. We measured these cardiovascular parameters in the OCPs using group (OCP) and in the control group (CTRL) using applanation tonometer Sphygmocor and the VaSera device. Comparison of the data from both groups showed us significantly increased diastolic blood pressure (DBP) and carotid-radial pulse wave velocity (crPWV) as well as significantly lower subendocardial viability index (SVI) in the OCP. These results imply a negative effect of hormonal contraceptives on the cardiovascular system with most of the negative changes affecting the peripheral arteries. Despite this evidence supporting the hypothesis of OCPs having a negative effect on cardiovascular health, further research is necessary.

Key words

Oral contraceptive pills • Arterial stiffness • Pulse wave velocity • Subendocardial viability index

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Introduction

First hormonal contraceptive drugs, oral contraceptive pills (OCPs) sold under the brand name Enovid, were placed on the market in 1960, after receiving approval from The United States Food and Drug Administration (FDA) [1]. What followed was a period of extensive pharmaceutical development, which led to newly synthetized hormonal analogs and related adjustments of doses and dosage forms [2]. In 2019, over 900 million women were reportedly using any form of contraception, with more than 150 million women using OCPs regularly [3]. According to this United Nations (UN) report, OCPs are one of the most prevalent types of contraception, especially in European and Northern American countries [3].

The popularity of OCPs stems from multiple factors, including their high reliability, relatively easy dosage, and various other side effects of treatment which result in health benefits, such as positive effect on period pain and reduction of acne [4]. Other advantages of OCPs use include their atheroprotective effect in cardiovascular system, while other peer-reviewed data shows reduced risks of several types of cancer in OCPs users [5,6].

However, ever since the 1960s, the undisputable advantages of OCPs have been seen together with and sometimes overshadowed by their negative effects on multiple organ systems of the human body [2,7]. Some of

the most notorious side effects of OCPs therapy are linked to the cardiovascular system and include hypertension, venous thromboembolism, dyslipidemia and increased arterial stiffness [8,9]. Contemporary data propose metabolic alterations leading to increased oxidative stress as a likely mechanism of these cardiovascular complications [5]. The number of publications in this field grew significantly in the last few years as novel approaches were used for experimental assessment of cardiovascular system [10]. There is, however, a persistent lack of scientific evidence regarding the molecular effect of OCPs on the cardiovascular system, and further research is therefore necessary.

Cardiovascular health of an individual can be assessed by a spectrum of different methods, with every method providing specific cardiovascular parameters. One of the more usual experimental approaches to assess the condition of the cardiovascular system is to determine the arterial stiffness. Arterial stiffness is a quantity describing the rigidity of the arterial wall and is in direct relation with its structure and mechanical properties. It can be used as a reliable marker of vascular aging and serve as an independent predictor of the risk of cardiovascular events [11,12]. Even though arterial stiffness cannot be measured directly, the increased arterial wall rigidity leads, besides increased systolic blood pressure (SBP) and diastolic blood pressure (DBP), to increased pulse wave velocity (PWV). PWV is therefore the optimal parameter for the assessment of arterial stiffness. Applanation tonometry also allows pulse wave analysis, which can yield several other cardiovascular parameters: augmentation pressure (AP), augmentation index (AI) and subendocardial viability index (SVI). Currently, the sphygmoplethysmomanometer VaSera can also be used for the assessment of arterial stiffness. This device allows measurement of the cardio-ankle vascular index (CAVI), as well as measurement of the ankle-brachial index (ABI) [13].

The aim of this study was to measure the above-mentioned cardiovascular parameters in young women and find any significant differences of these parameters following OCPs use.

Methods

Subjects

The study was approved by the Ethical committee of the Faculty of Medicine, Masaryk University Brno, Czech Republic. It was conducted in accordance with the principles stated in the Declaration of Helsinki. All respondents were informed about the aim and purposes of the study, and they signed the informed consent that was archived.

In this pilot study we included 24 females, who were divided into two groups: control group (CTRL, 10 women; age: 21.4±1.5 years; BMI: 22.08± 3.05 kg/m^2), and OCPs using group (OCP, 14 women; age: 20.6±1.3 years; BMI: 20.16±1.46 kg/m^2; duration of OCPs use: 3.6±1.2 years). All OCP respondents were using monophasic combined hormonal contraception (ethinylestradiol 0.02/0.03 mg, and progestogens with androgen neutral 0.075/0.15 mg, antiandrogen 2 mg, or antiandrogen and antimineralocorticoid 3 mg activity), while none of the CTRL respondents have taken OCPs in the past. CTRL respondents were measured only in the follicular or the luteal phase of the cycle, OCP respondents were measured in the corresponding phases of the contraceptive cycle. Parameters of the cardiovascular system were measured for all respondents.

Data collection

Vascular parameters

VaSera device (Fukuda Denshi, Tokyo, Japan) was used for the estimation of Cardio Ankle Vascular Index (CAVI) and Ankle Brachial Index (ABI). The electrocardiography (ECG), phonocardiography (PCG) and blood pressure measurements (SBP, DBP) on brachial and ankle arteries were performed by the VaSera device. CAVI and ABI values were automatically calculated by the VaSera:

$$CAVI = a\,(\ln SBP/DBP)\,(2\rho/\Delta P)\,PWV^2 + b$$

Where SBP is systolic blood pressure, DBP is diastolic blood pressure, ΔP is pulse pressure, PWV is pulse wave velocity between aortic valve and ankle, ρ is blood density and a, b are constants.

ABI is defined as the ratio of the SBP at the ankle and the SBP in the upper arm (brachium).

PWV (in m/s) was measured by applanation tonometry. The measurements were performed on the radial artery of respondents' dominant hand and on their ipsilateral carotid artery (carotid-radial PWV, crPWV). PWV was calculated as a ratio of the distance traveled by the pulse wave in both directions and the difference of transit times in radial and carotid arteries. The distance was measured from the suprasternal notch to the common

carotid artery and from the suprasternal notch to the radial artery. Transit times were calculated as the interval from the R wave on the ECG curve to the steep increase of the pulse wave curve in both arteries. All the measurements were calibrated using blood pressure values obtained by the oscillometric automated measurement on the ipsilateral brachial artery (Omron HEM, 907).

Peripheral pulse wave curve was obtained and SBP and DBP [mm Hg] were estimated using the aforementioned applanation tonometry. Using the SphygmoCor Px system, the measured peripheral pulse wave was further converted to the central aortic pulse wave, and following parameters were calculated from this central (aortic) curve (as shown in Fig. 1): augmentation pressure (AP, [mm Hg]) as a difference between the blood pressure at the peak of the reflected flow (P2, [mm Hg]) and the blood pressure at the peak of the systolic flow (P1, [mm Hg]), and augmentation index (AI, [%]) as a ratio of the AP and the aortic pulse pressure). These parameters were standardized to the heart rate of 75/min and to the pulse height.

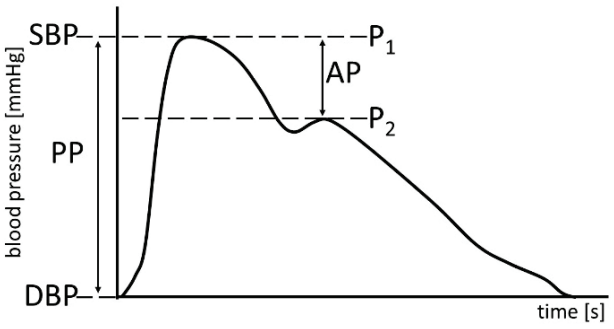

Fig. 1. Central pulse curve: systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), pressure at the peak systolic flow (P1), pressure at the peak of reflected flow (P2), augmentation pressure (AP).

Parameters of cardiac function

Following heart function parameters were estimated from the central pulse wave curve (as shown in Fig. 2): tension time index (TTI, [s]) as the area under the systolic part of the pulse curve, diastolic time index (DTI, [s]) as the area under the diastolic part of the pulse curve), and subendocardial viability index (SVI, [%]) as the ratio of diastolic time index and tension time index).

Statistical analysis

We used the program Statistica 13.2 (StatSoft) for the statistical analysis. Given the non-Gaussian distribution, we used the median and lower-upper quartile. Nonparametric Mann-Whitney U test was used to provide the comparison of OCP and CTRL, as well as follicular and luteal subgroups.

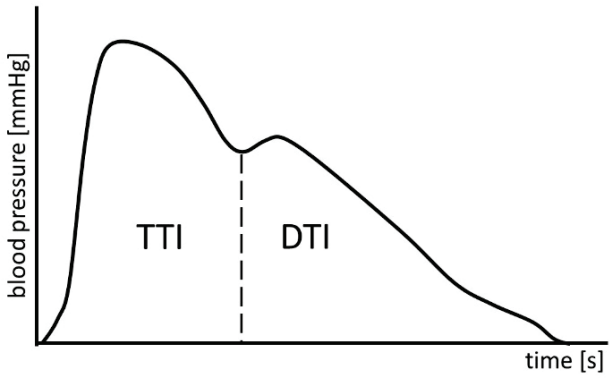

Fig. 2. Central pulse curve: tension time index (TTI), diastolic time index (DTI).

Results

Vascular parameters

The values of all measured vascular parameters lie within their physiological range. Results for all measured parameters are represented in Table 1. Statistically significant differences between OCP and CTRL were observed in the following parameters: DBP, crPWV. Comparison of other parameters between the main groups yielded no significant results.

In respondents measured in follicular phase (resp. corresponding phase of the contraceptive cycle), we found statistically significant increase of the DBP in the OCP (77 mm Hg vs. 59 mm Hg; $p<0.05$). The same comparison of vascular parameters in luteal phase does not show significant difference, except DBP, where the difference was at a border level of significance (75 mm Hg vs. 65 mm Hg; $p=0.06$).

Cardiac function parameters

The values of cardiac function parameters are shown in Table 2. While comparing respondents in the OCP and CTRL in the luteal and corresponding contraceptive phase, we found significantly decreased SVI in the OCP (153 % vs. 170 %; $p<0.05$). Other cardiovascular parameters used in this OCP vs. CTRL comparison did not show any statistically significant differences.

We also did the comparison of respective cardiovascular parameters between the follicular and

luteal subgroups inside both OCP and CTRL as a part of this statistical analysis, which showed no significant differences in cardiovascular parameters between follicular and luteal subgroups of both OCP and CTRL.

Table 1. Comparison of vascular parameters.

Parameter	OCP	CTRL	p-level
SBP [mm Hg]	120 (118 - 122)	117 (115 - 129)	NS
DBP [mm Hg]	75.5 (71 - 77)	62 (56 - 69)	p<0.01
AP [mm Hg]	2.3 (-0.5 - 3.5)	2.5 (1 - 6.5)	NS
AI [%]	108.5 (98.5 - 114)	110 (104 - 124)	NS
crPWV [m/s]	7.0 (6.8 - 7.5)	6.5 (5.8 - 6.7)	p<0.05
$CAVI_r$	5.3 (4.8 - 5.6)	5.2 (4.9 - 5.7)	NS
$CAVI_l$	5.4 (5.1 - 5.8)	5.4 (4.7 - 5.8)	NS
ABI_r	0.9 (0.9 - 1.0)	1.0 (0.9 - 1.0)	NS
ABI_l	0.9 (0.9 - 1.0)	0.9 (0.9 - 1.0)	NS

Parameters are expressed as median (lower quartile – upper quartile). Hormonal contraceptive using group (OCP), control group (CTRL), systolic (SBP) and diastolic (DBP) blood pressure, augmentation pressure (AP), augmentation index (AI), carotid-radial pulse wave velocity (crPWV), cardio-ankle vascular index on right/left side of the body ($CAVI_{r/l}$), ankle-brachial index on right/left side of the body ($ABI_{r/l}$).

Table 2. Comparison of cardiac function parameters.

Parameter	OCP	CTRL	p-level
TTI	1656 (1561 - 1898)	1732 (1577 - 1919)	NS
DTI	3041 (2807 - 3119)	3065 (2934 - 3384)	NS
SVI [%]	160 (149 - 169)	177 (170 - 194)	p<0.05

Parameters are expressed as median (lower quartile – upper quartile). Hormonal contraceptive using group (OCP), control group (CTRL), tension time index (TTI), diastolic time index (DTI), subendocardial viability index (SVI).

Discussion

The impact of monophasic OCPs on the cardiovascular system is based on the exact composition of respective OCPs formula. While only ethinylestradiol is currently used as the estrogen component in the vast majority of OCPs, the situation is different with gestagens (progestogens), as multiple synthetic gestagens are used. These gestagens can be divided into subgroups based on their affinity to receptors other than progesterone receptors and their activity (androgenic, nonandrogenic, antiandrogenic, antimineralocorticoid etc.) [14].

The estrogen component is responsible for the stimulation of RAAS as well as for other metabolic processes that are in most cases the major cause of OCPs side effects. In naturally-cycling women, these effects are partially suppressed by progesterone, which has minor antimineralocorticoid activity, thus reducing the RAAS activation [15]. The gestagens used in OCPs, however, mostly do not possess the antimineralocorticoid activity, the only exception being drospirenone [16]. Cardiovascular side effects of rather high significance have been observed in women using a combination of an estrogen and a gestagen with strong androgenic activity, such as levonorgestrel [14].

Based on currently available information, it is safe to assume that the effects of different types of gestagens from the nonandrogenic (gestodene, desogestrel) and antiandrogenic (dienogest, chlormadinone acetate) groups on the body metabolism, as well as on blood pressure and lipid profile, are not significantly different between these two groups [17,18]. Drospirenone, as an antiandrogenic compound with extra antimineralocorticoid activity, also does not seem to have excessive effect on the compared parameters, although it might in some cases lead to reduced BMI and blood pressure, as well as to other significant changes in

comparison with nonandrogenic and antiandrogenic gestagens [18,19]. Except for gestagens with androgenic effect, none of the compounds seem to cause impairments of endothelial function or disrupt the vessel wall [19].

According to the currently available publications, long-term OCPs use has a negative effect on selected cardiovascular parameters, and in combination with other risk factors (age, obesity, smoking) leads to increased cardiovascular risk of the users [8,9,20]. As the majority of the risk factors were eliminated in this study thanks to the respondent selection, comparison of our cohorts should point towards changes determined mostly by the effect of hormonal contraception itself. Data from this study shows that OCPs use significantly affects some of the cardiovascular parameters related to cardiovascular health.

Hypertension is a leading risk factor for numerous cardiovascular diseases (CVD) and is at the same time one of the most prevalent lifestyle diseases [21,22]. It is a multifactorial disease in which one of the most important factors is increased stiffness of the arterial walls. Parameters of arterial stiffness obtained from the pulse wave analysis such as AP and AI are influenced by the speed of propagation of both forward and backward pulse waves; size of backwards pulse waves and their time of return to the ascending aorta in return depend on the rigidity of the arterial wall. Our measured values of AP and AI show no statistically significant differences between OCP and CTRL.

Another feature of altered arterial stiffness are changes of the PWV. The most common approaches to measuring PWV using applanation tonometry are carotid-radial pulse wave velocity (crPWV), which characterizes mostly the peripheral part of arterial tree, and carotid-femoral pulse wave velocity (cfPWV), which is mostly determined by central parts of the arterial tree. In this pilot project the measured crPWV was significantly increased in OCP. Other research projects aimed at similar vascular parameters showed no significant changes in PWV, it is however necessary to mention that these projects utilized cfPWV instead of crPWV [20,23,24]. As both DBP and crPWV are mostly based on the state of the peripheral parts of the arterial tree, our significantly higher DBP and crPWV in OCP show impaired peripheral parts of the arterial system, leading to increased stiffness of the peripheral arteries. These negative changes could be due to the overactivity of the sympathetic nervous system, renin-angiotensin-aldosterone system, increased body weight or obesity, atherosclerotic processes, oxidative stress [5,10] and hypercholesterolemia, as all these factors are likely to be influenced by OCPs [25,26].

Even though AP, AI, and PWV generally describe arterial stiffness, the changes in these parameters have a different origin [27]. While crPWV reflects peripheral vascular resistance, AP and AI are influenced not only by the peripheral resistance, but also by the pattern of left ventricle ejection.

CAVI is a relatively novel parameter of arterial stiffness and is determined by the state of the central arteries. It allows the evaluation of almost all central and peripheral arteries in the whole body. Moreover, CAVI reflects both functional and structural changes [28] and is not dependent on the age of the measured person as well as on their blood pressure [29]. In this study, we did not find significant changes of CAVI between the groups.

Based on the significantly increased DBP and crPWV in OCP, together with unchanged AP, AI and CAVI, we assumed that the observed changes of vascular parameters were mostly caused by increased arterial stiffness in the peripheral parts of the arterial system.

Despite the low incidence of thromboembolism (8-10 events per 10 000 women) in OCP users, OCPs use is a factor which increases the risk of thromboembolism appearance [30]. Estrogen stimulation affects both arterial (AT) and venous (VT) thrombosis; unfortunately, we still do not know the exact mechanisms of this phenomenon, although there is a direct correlation with the dosage of estrogen and duration of OCPs usage [31]. ABI measurement is a non-invasive method, which detects the presence and severity of peripheral arterial disease (PDA), which could lead to AT, and it is reliable in non-symptomatic patients [32]. In our pilot project we did not find significant differences in ABI between OCP and CTRL.

SVI could be used as an indicator of the effectiveness of myocardial oxygenation and the subendocardial viability. It is an indirect parameter which determines the predisposition of the left ventricle to diastolic dysfunction as it is fully dependent on the diastolic function of the heart [33]. Although still used mostly experimentally, SVI can be used to predict even subclinical changes of the myocardial tissue. We observed significantly decreased SVI in the OCP. This could lead to severe cardiovascular complications if combined with other cardiovascular risk factors. Unfortunately, there is an insufficient number of publications considering OCPs effect on heart's function

as well as on systolic/diastolic dysfunction confirmed by echocardiography in young OCPs users.

While comparing the follicular subgroups of OCP and CTRL, we found a statistically significant increase in DBP; the increase of DBP in the luteal phase comparison was on the border level of significance. The luteal phase comparison also yielded a significantly lower SVI in OCP. These findings are in correlation with available data since the exogenous estrogen supplementation does not seem to provide protective cardiovascular effects[20].

The comparison of respondents in follicular and luteal phases within both OCP and CTRL showed no significant differences during the ovarian/contraceptive cycle. This result is consistent with our expectations since the variability of the chosen cardiovascular parameters during the ovarian/contraceptive cycle should not be statistically significant [23]. Although insignificant, the resulting differences of cardiovascular parameters during the cycles were given by interindividual variability.

Based on our results, we can conclude that OCPs use has a negative impact on the cardiovascular system, more specifically on the peripheral parts of the arterial tree, which may represent a risk factor for young women to develop CVD later in adulthood.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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