Relations between combined oral contraceptive therapy and indices of autonomic balance (baroreflex sensitivity and heart rate variability) in young healthy women

Doustna antykoncepcja hormonalna a równowaga autonomiczna i wrażliwość baroreceptorów tętniczych u młodych, zdrowych kobiet

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Abstract

Introduction: *There are structural and functional links between autonomic nervous and endocrine systems. Derivatives of estrogens and gestagens applied in combined oral contraceptives (COC) reduce the production of endogenous sex steroids, but their effect on autonomic nervous system remains unknown.*

Aim: *To compare indices of heart rate variability (HRV) and baroreflex sensitivity (BRS) among young healthy women taking vs. non-taking COC.*

Material and methods: *We performed a cross-sectional study in a group of 53 healthy women (age: 23±3 years, BMI: 22.3±2.8 kg/m^2) taking COC for ⩾ 3 months (COC-group) and in a group of 113 healthy women (age: 24±4 years, BMI: 22.0±3.1 kg/m^2) not taking COC for ⩾3 months (n-COC-group). All examined women were between the 4th and the 8th day of menstrual (or pill-driven) cycle lasting from 21 to 35 days. Indices of autonomic balance was assessed based on the time- and frequency- domains of heart rate variability (HRV, very low (VLF), low (LF), high (HF) frequencies and total HRV spectrum). BRS was evaluated using the sequence (BRS-Seq) and the controlled breathing (BRS-CtBr) methods.*

Results: *There were no differences in: age, weight, height, measures of adiposity and fat distribution, the menstrual (or pill-driven) cycle day on the day of examination, heart rate and HRV parameters between the two studied groups (all p>0.1). BRS-CtBr was higher among n-COC-group as compared to COC-group (20.00±6.28 vs. 18.07±6.57 ms/mmHg, p<0.05). There was a trend towards higher BRS-Seq in the n-COC-group as compared to the COC-group (19.47±7.85 vs. 16.95±5.76 ms/mmHg, p=0.12). In the n-COC-group, BRS-CtBr and RMSSD were inversely related to age (r=-0.23, r=-0.19, p<0.05). In the COC-group, SDNN was inversely related to waist circumference and WHR (respectively r=-0.34 and r=-0.35, both p<0.05).*

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Conclusions: *COC impair the reflex regulation of cardiovascular system based on baroreflex, which may indicate unfavorable influence of COC use on women`health. The exact mechanism of BRS impairment caused by COC remains unknown, also in the context of the different composition of various COC. Thus, it needs to be studied further.*

Key words: **combined oral contraceptives / autonomic nervous system / cardiovascular reflex regulation / baroreflex sensitivity / heart rate variability /**

Streszczenie

Wstęp: *Autonomiczny układ nerwowy łączy się z układem endokrynnym zarówno strukturalnie jak i funkcjonalnie. Syntetyczne pochodne androgenów i gestagenów zawarte w doustnych środkach antykoncepcyjnych (COC) zmniejszają produkcję endogennych steroidów płciowych. Wpływ COC na układ autonomiczny pozostaje nieznany.*

Cel: *Celem badania było porównanie zmienności rytmu serca (HRV) i wrażliwości baroreceptorów tętniczych (BRS) wśród młodych, zdrowych kobiet przyjmujących vs. nieprzyjmujących COC.*

Materiał i metody: *Zbadano 53 zdrowe kobiety (wiek: 23±3 lata, BMI: 22,3±2,8 kg/m^2) przyjmujące COC ⩾3 miesiące (grupa-COC) oraz 113 zdrowych kobiet (wiek: 24±4 lata, BMI: 22,0±3,1 kg/m^2) nieprzyjmujących COC od ⩾3 miesięcy (grupa-n-COC). Wszystkie badane kobiety były między 4. a 8. dniem cyklu, który trwał nie krócej niż 21 dni oraz nie dłużej niż 35 dni. Zbadano następujące wskaźniki równowagi autonomicznej: czasowe i częstotliwościowe domeny zmienności rytmu serca (w trzech zakresach częstotliwości: bardzo niskiej VLF, niskiej LF i wysokiej HF). BRS oceniano metodami: sekwencyjną (BRS-Seq) i kontrolowanego oddychania (BRS-CtBr).*

Wyniki: *Badane kobiety nie różniły się wiekiem, wzrostem, masą ciała czy wskaźnikami dystrybucji tkanki tłuszczowej (wszystkie p>0,1). W obu grupach rozkład odsetków kobiet badanych w każdym z 5 dni (4, 5, 6, 7 lub 8) był taki sam (p>0,1).*

Badane grupy nie różniły się także pod względem parametrów HRV (wszystkie p>0,1). Wartość BRS-CtBr była wyższa wśród kobiet z grupy n-COC w porównaniu z kobietami przyjmującymi środki hormonalne (20,00±6,28 vs. 18,07±6,57 ms/mmHg, p<0,05). Podobny trend zaobserwowano w przypadku BRS-Seq (kobiety z grupy n-COC 19,47±7,85 vs. kobiety z grupy COC 16,95±5,76 ms/mmHg, p=0,12). Ponadto w grupie n-COC, BRS-CtBr oraz RMSSD były odwrotnie proporcjonalne do wieku badanych kobiet (odpowiednio r=-0,23, r=-0,19, oba p<0,05). W grupie COC, SDNN było odwrotnie proporcjonalne do obwodu talii oraz wskaźnika WHR (odpowiednio r=-0,34 i r=-0,35, oba p<0,05).

Wnioski: *COC upośledza regulację układu sercowo-naczyniowego, opartą na odruchu z baroreceptorów tętniczych. Może to sugerować niekorzystny wpływ stosowania COC na zdrowie kobiet. Mechanizm działania COC na BRS jest nieznany (również w kontekście preparatów o różnym składzie), stąd opisane zjawisko wymaga dalszych badań.*

Słowa kluczowe: **dwuskładnikowe środki antykoncepcyjne / autonomiczny układ nerwowy / regulacja odruchowa układu krążenia / / wrażliwość baroreceptorów / zmienność rytmu serca /**

Introduction

Hormonal fluctuation occurring during the physiological menstrual cycle has an effect on autonomic nervous system activity of women [1-3]. For instance, baroreflex sensitivity (BRS) is higher in the second (luteal) phase of the cycle, probably due to an elevated level of natural estrogens and progesterone [1, 3].

Combined oral contraceptives (COC) contain derivatives of estrogens and gestagens, and markedly reduce the natural production of endogenous sex hormones due to e.g. the interference with the regular cyclic hormone activity of the hypothalamic-pituitary-gonadal axis [4-7]. Using COC leads to the constant lowering of sex hormones blood concentration as compared to the physiological level, typical for the luteal phase [5-11]. Taking into consideration close links between steroid hormones and the functioning of autonomic system [12-14], we have presumed that COC might affect the functioning of ANS. Indices of heart rate variability (HRV) and BRS are physiological measures reflecting the efficiency of reflex regulatory mechanisms within cardiovascular system [15, 16].

Therefore, the aim of the present study was to compare HRV and BRS among young healthy women taking and non-taking COC.

Methods

2.1 Studied subjects

The study was performed in Cardiology Department, Military Hospital (Wroclaw, Poland).

The criteria for the inclusion of the study comprised:

1) age between 18 and 35 years,

2) female sex,
3) physiological length of a menstrual cycle among women not taking COC (i.e. from 21 to 35 days),
4) no evidence of any chronic/acute disease and related treatment.

The exclusion criteria included:
1) pregnancy or breast feeding;
2) lack of written informed consent.

The study was approved by the local ethics committee and was conducted in accordance with the Helsinki Declaration.

2.2 Study protocol

Participants of the reported study were recruited among 200 women who simultaneously participated in another project regarding the female preferences for male morphology. The project was advertised at several universities in Wroclaw Universities, via the project web-site and local newspapers. All appointments were scheduled between 8 a.m. and 12 a.m., and were performed between the 4th and 8th day of menstrual (or pill-driven) cycle of each woman. The participants were advised to refrain from drinking coffee and smoking on the day of examination.

Basic anthropometric parameters (i.e. body weight [kg], body height [cm], waist and hip circumferences [cm]) were measured before the physiological assessments, and were used to calculate a body mass index (BMI; the individual's body weight [kg] divided by the square of his/her height [m^2]) and a waist-to-hip ratio (WHR; the individual's waist circumference [cm] divided by his/her hip circumference [cm]).

Participants were also asked to complete a short questionnaire regarding: (a) general health status (b) the average length of their menstrual (or pill-driven) cycle, and (c) therapy with COC.

In total, 200 women were questioned. Based on the acquired data, these women were divided in 2 groups: those who did not take COC for >3 months (n=113) and those who were taking COC for >3 months (n=53). Women, who did not meet these criteria, were excluded from the further study regarding the autonomic status (n=34, 17% of all questioned women). Finally, 166 healthy women were enrolled in the proper study described below.

The proper recordings were performed in a horizontal position and were preceded by 10 minutes of resting. Afterwards, the digital non-invasive recording of synchronized systolic blood pressure (BP) and heart rate (HR, R-R intervals) was acquired continuously (PORTAPRES, FMS, Finapres Medical Systems BV, Amsterdam, The Netherlands, with a sample frequency of 200 Hz) during 30 minutes of resting and 5 minutes of breathing with a speed of 6 breaths per minute, according to the instructions presented on the computer's monitor.

2.3 Measures of HRV and BRS

For the analysis, a 10-minute fragment of an acceptable quality was selected from the whole resting recording in order to calculate indices of HRV and BRS using the sequence method (BRS-Seq). In order to calculate BRS using controlled breathing method (BRS-CtBr) a 200-second fragment of an acceptable quality from the recording performed during breathing with a speed of 6 breaths per minute was selected.

HRV was calculated using:

• time domain measures:

mean RR – mean duration of R-R intervals (ms); SDNN – standard deviation of average R-R intervals (ms); RMSSD – the square root of the mean of the sum of the squares of differences between adjacent R-R intervals (ms); and TRIANG – number of all RR intervals divided by the height of the histogram of the distribution of all RR intervals [17];

• frequency domain measures:

2 main spectral components distinguished in HRV spectrum at: low (LF): 0.04 to 0.15 Hz, and high (HF): 0.15 to 0.4 Hz frequencies and within the whole frequency spectrum (0-0.5 Hz) (total power, HRV_{total}). Power components were expressed in absolute values (ms^2) as well as a LF/HF ratio in order to describe the balance between sympathetic and parasympathetic drive within ANS [17, 18].

Calculation of BRS-Seq was based on the selection of 3 heart beats sequences with a change in systolic BP of ≥1.0 mmHg accompanied by a change in a R-R interval of ≥5.0 ms, which occurred during the whole analyzed spectrum segment. BRS-Seq was interpreted as an averaged regression slope of all these sequences relating systolic BP to R-R intervals [ms/mmHg] [19-22].

BRS-CtrBr was calculated as a ratio of the average amplitude of R-R interval oscillations to the average amplitude of systolic BP oscillations (ms/mmHg) [20].

2.4 Statistical analysis

Normality of the continuous variables distribution was tested using the Kolmogorov-Smirnov test. Continuous variables with a normal distribution were presented as means ± standard deviation (x±SD). Continuous variables with a skewed distribution were log transformed which enabled to normalize their distribution. The inter-group differences for continuous variables were tested using the Student's t-test. The inter-group differences in categorized variables were analyzed using the chi-square test (χ^2). Correlations between continuous variables were assessed using a Pearson's correlation coefficient.

A value of $p<0.05$ was considered statistically significant.

Statistical analysis was performed using Statistica 9.0 software (StatSoft, Tulsa, USA).

Results

There were no differences in age, weight, height, BMI, waist circumference and WHR, between women from the COC-group as compared to those from the n-COC-group (all $p>0.2$) (Table I).

Women from the COC-group used oral contraceptives containing ethinylestradiol, combined with the following components: etonogestrel (in 6% of women from the COC-group), gestodene (in 4%), desogestrel (in 23%), drospirenone (in 40%), levonogestrel (in 6%), norgestimate (in 13%) and cyproterone (in 8%).

There were no differences in indices of HRV between these two studied groups (all $p>0.4$) (Table II).

BRS-CtBr was higher in women from the n-COC-group ($p=0.04$) as compared to those from the COC-group. (Figure 1). There was also a trend towards higher BRS-Seq in women in a non-COC-group as compared to those from COC-group ($p=0.12$) (Table II).

Among women not taking COC, RMSSD and BRS-CtBr were inversely related to age ($r=-0.19$, $p<0.05$; $r=-0.23$, $p=0.02$, respectively). (Figure 2).

Table I. Clinical characteristics of healthy women non taking oral contraceptives (n=113) and taking oral contraceptives (n=53) .

Variables	non – COC (n=113)	COC (n=53)	*p* values
Age (years)	24 ± 4	23 ± 3	0.43
Menstrual cycle length (days)	29 ± 2	28	-
Body weight (kg)	60 ± 10	61 ± 8	0.31
Height (cm)	165 ± 5	166 ± 5	0.24
BMI (kg/m^2)	22.0 ± 3.1	22.3 ± 2.8	0.56
WHR	0.72 ± 0.04	0.73 ± 0.04	0.26
Waist circumfence (cm)	71 ± 7	72 ± 6	0.32
Heart rate (beats per minute)	69±11	69±9	0.58
Percentage of women examined during 5 consecutive cycle days (4/5/6/7/8;%)	(9/15/19/23/34)	(13/9/34/25/19)	0.11

Data are presented as a mean±SD or percentage where appropriate;
COC – combined oral contraceptives;
BMI – body mass index;
WHR – waist-to-hip ratio

Table II. Time and frequency domain measures of HRV and BRS in healthy women non taking oral contraceptives (n=113) and taking oral contraceptives (n=53) .

Variables	non – COC (n=113)	COC (n=53)	p values
Heart Rate Variability - time domains			
Mean RR (ms)	896 ± 132	876 ± 94	0.43
SDNN (ms)	61 ± 32	61 ± 27	0.79
RMSSD (ms)	52 ± 34	52 ± 31	0.83
TRIANG (ms)	217 ± 60	219 ± 58	0.80
Heart Rate Variability - frequency domains			
HRV_{VLF} (ms^2)	6305 ± 12327	4955 ± 3936	0.43
HRV_{LF} (ms^2)	4432 ± 5299	3821 ± 2955	0.92
HRV_{HF} (ms^2)	3439 ± 3078	3141 ± 2273	0.94
HRV_{total} (ms^2)	14237 ± 17247	17058 ± 40253	0.69
Baroreflex Sensitivity			
BRS-Seq (ms/mmHg)	19.47 ± 7.85	16.95 ± 5.76	0.12
BRS-CtBr (ms/mmHg)	20.00 ± 6.28	18.07 ± 6.57	0.04

Data are presented as a mean±SD;
COC – combined oral contraceptives; HRV – heart rate variability; RR – RR interval; SDNN – standard deviation of average RR intervals; RMSSD – the square root of the mean of the sum of the squares of differences between adjacent RR intervals; TRIANG – number of all RR intervals divided by the histogram height distribution of all RR intervals; VLF – very low frequency; LF – low frequency, HF – high frequency; BRS-Seq – baroreflex sensitivity calculated using sequence method; BRS-CtBr – baroreflex sensitivity calculated using control breathing method.

Among women taking COC, SDNN was inversely related to WHR (r=-0.35, p=0.01) (Figure 3) and to waist circumference (r=-0.34, p=0.01). Additionally in this subgroup, TRIANG was negatively related to waist circumference (r=-0.28, p<0.05).

There were no other relations between BRS, indices of HRV and other parameters analyzed separately in women taking versus not-taking COC (all p>0.2).

Discussion

The major finding of the present study was lower BRS during the follicular phase of the menstrual cycle in women taking COC as compared to those who do not use hormonal contraception.

Sex hormones have numerous effects on the cardiovascular system [12-14]. For instance, natural estrogens enhance NO synthesis [23] and stimulate opening of the calcium-activated potassium channels [24], which finally leads to vasodilatation. Intravenous injection of estrogen results in dose-dependent increase of BRS in ovariectomized female rats [25, 26]. On the other hand, there is evidence on the negative effect of natural and synthetic sex hormones on the blood coagulation [27-29]. Synthetic estrogens contained in COC are more than 200-fold more potent than natural ones [4]. They stimulate the coagulation pathways [28], which has been shown also in the study on hormone replacement therapy, where synthetic estrogens caused susceptibility to thrombosis [30]. Also, progesterone included in COC has an influence on coagulation, however the risk of thrombosis differs between various preparations [31]. Moreover, COC impair endothelial function [32] and disturb blood flow.

Other studies revealed the negative influence of COC on lipid metabolism, resulting in changes, which were similar to those associated with an increased risk of coronary heart disease. Moreover, this effect was related to both the dose and the type of used synthetic hormone [33,34]. However, there are some modern preparations, which do not induce any adverse changes within the metabolism of lipids [35].

It is known that BRS is decreased during pregnancy [36]. The studies based on animal model (with female rats) showed that3-OH-dihydroprogesterone (3 -OH-DHP; the major metabolite of progesterone elevation occurring during pregnancy), is involved in this changes, due to its' influence on CNS GABA A receptor function [37-39]. Pregnant female rats were characterised by attenuated arterial baroreflex sympathoexcitation. However, sympathoinhibitory responses remained maintained or even potentiated [38].

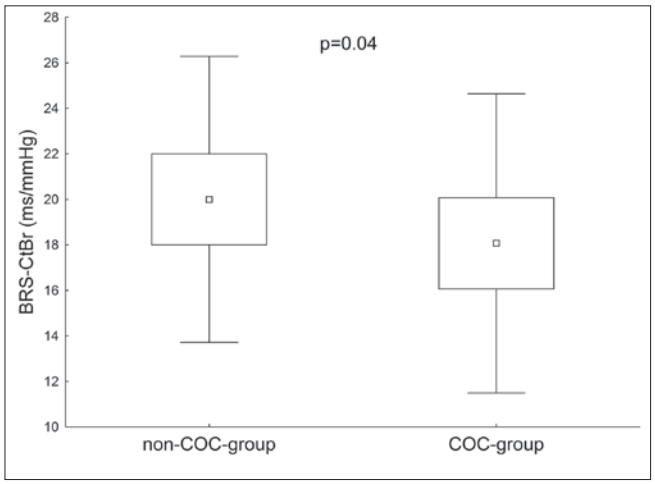

Figure 1. Baroreceptor sensitivity as assessed with the controlled breathing methods (BRS-CtBr) for the non-COC-group and COC-groups.
The ends of the whiskers represent one standard deviation above and below the mean, which is presented as the middle point of the box.

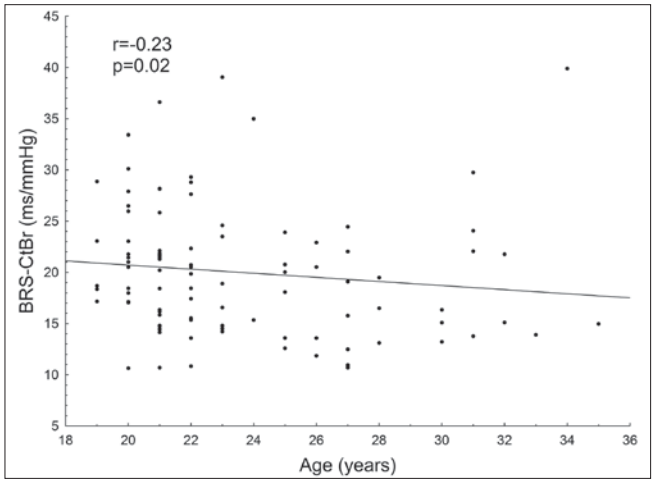

Figure 2. The inverse relationship between BRS-CtBr and age in the n-COC-group.

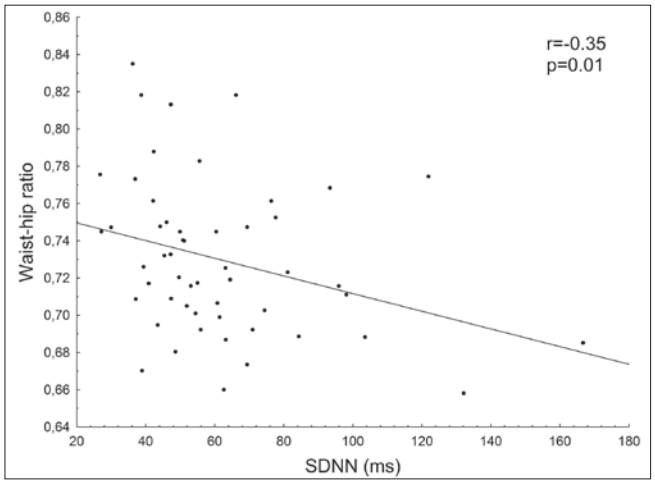

Figure 3. The inverse relationship between WHR and heart rate variability expressed as SDNN in the COC-group.

Recent studies indicated that the occurrence of premenstrual syndrome is related to the activity of progesterone (endogenous metabolites in CNS) and COC can reduce these symptoms effectively[40-42]. While using COC the level of progesterone is lower as compared to the normal value[5-10], and its' natural synthesis is inhibited [4-7], which suggest the potential positive effect of COC on AUN regulation.

We have demonstrated that healthy women taking COC have also reduced BRS, the latter being associated with several unfavourable consequences [43, 44]. Reduced BRS is accompanied by other cardiovascular risk factors, such as diabetes and dyslipidaemia [45]. Impaired BRS is a significant predictor of cardiovascular disease in a general population [44], and the predictor of poor outcome in patients with established heart disease [46]. There is no available literature concerning the direct comparison of BRS in women taking COC for ≥3 months versus women who do not take COC. However, there is evidence that COC have an acute effect on BRS. Namely, Minson et al. examined 9 young (mean age 30±2 years) healthy women who received COCs during 21 days and then placebo for the remaining 7 days of their cycle. BRS (assessed using microneurography and test with nitroprusside and phenylephrine) was lower on the days when COC was used [47].

In our cross-sectional study women from the COC group have lower BRS-CtBr as compared to those from the non-COC group, but also a similar borderline pattern is observed regarding BRS-Seq. It is known that both of these non-invasive BRS measures are closely related to each other [48], and correspond to invasive measures (e.g. the phenylephrine method) [44]. However, the physiological interpretation of these 2 applied non-invasive measures of BRS is slightly different. BRS-Seq reflects the spontaneous parallel changes in systolic BP and heart rate, which are rather smaller in their magnitude [49]. BRS-CtrBr is determined during the baroreceptor stimulation by an additional stimulus, i.e. induced by slow and deep breathing [50], and changes in systolic BP and heart rate are more rapid and greater in their magnitude [51]. BRS-CtBr method is also characterized by the best reproducibility among all BRS measures and the lowest failure rate in controls and in patients with heart failure [52].

The exact mechanism associated with reduced BRS in COC group is unknown and requires further studies. However, the inhibition of NO synthesis has been shown to decrease BRS in rats [53]. NO is being synthesised in the endothelium [12] thus it is possible that COC can affect NO synthesis, by their negative effect on endothelial function [32, 54]. However, the exact influence of COC on NO production requires more detailed studies.

Recent studies showed that the severity of subclinical coronary atherosclerosis in healthy asymptomatic subjects was related to the lower BRS [55]. The negative effect of COC on lipid metabolisms can also be responsible for lower BRS in COC group. The thrombosis susceptibility occurring during using COC can affect BRS by unfavourable influence on blood flow. However, the data proving this theory is unavailable. COC contain substances with pleiotropic effect on the organism [4]. Negative effect of COC on ANS cannot be definitely excluded, although lower level of progesterone could have some positive effect [40-42].

Studied groups did not differ in HRV, which is in accordance with previous studies [56]. It was proved that HRV is constant during both phases of menstrual cycle [1,2]. Among women using COC, those with higher body weight had lower indices of HRV. Estrogens are being synthesised within the fat tissue [57] and the concentration of estradiol is correlated with BMI [58]. It has been shown that obese women taking COC have higher hypothalamic-pituitary-ovarian activity [59]. It can be suggested that women with higher body weight in COC group have higher sex hormones concentration than those with lower body weight.

The revealed inverse relation between HRV and both WHR and waist circumferences in COC group remains unclear. This can be linked to the above mentioned pleiotropic influence of COC on the whole organism.

BRS was inversely related to age within the non-COC group, which is consisted with the previous findings [44, 60, 61] suggesting that BRS decreases with age.

Our study indicates that COC therapy impair the control of cardiovascular system based on baroreflex, however exact mechanisms leading to this situation are unknown and require further studies. Such an unfavourable effect of COC (especially the therapy is chronic) may lead to negative long-term consequence within cardiovascular system. Further studies regarding various COC-components are needed in order to establish which substances are linked to the particular effects (e.g. endocrine derangements).

Limitations of the study:

There are some limitations of the present study that need to be acknowledged. Firstly, we did not measure the concentrations of sex hormones in the blood of studied women. Secondly, as it has been mentioned within the discussion section, we did not analyse the potential differences related to various COC components within the COC-group. This was related mainly to low number of women within the COC-groups, which was the crucial limitation of the presented study.

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