

Oral contraceptives intake may be inversely correlated with varicose veins and chronic venous insufficiency

Analysis of sex related and lifestyle risk factors in women

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Keywords

Oral contraception, varicosis, chronic venous insufficiency, risk factors

Schlüsselwörter

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Mots clés

Contraception orale, varicose, insuffisance veineuse chronique, facteurs de risque

Summary

Aim: Determination of lifestyle and sex related risk factors that contribute to higher prevalence of varicose veins (VV) and chronic venous insufficiency (CVI) in women and establishment of a possible link between reported exposure to oral contraceptives (OC) and prevalence of VV and CVI. **Methods:** The Warsaw Brodno Venous Population Survey was a cross-sectional study, conducted on a group of 2530 women. On the basis of a targeted questionnaire, medical records and clinical investigation, sex, and lifestyle related risk factors were identified. **Results:** In women the prevalence of VV was 15.9% and of CVI (C1-C6) 40.15%. Open ulceration and healed ulceration were diagnosed in 0.51% and 0.75%, respectively. Analysis of lifestyle and job related risk factors for VV showed OR = 0.52 for sitting and OR = 1.56 for vertical lifestyle, and for CVI for office workers OR = 0.53 versus physical workers OR = 1.88. Women taking ever oral contraceptives and those who took them for more than 5 years had a decreased risk of CVI: OR = 0.44 and OR = 0.36 respectively. For VV risk OC intake demonstrated OR = 0.30 and OR = 0.27, respectively. **Conclusions:** Oral contraception may be inversely correlated with the prevalence of varicose veins and chronic venous insufficiency, although the reasons for this finding require further elucidation. We have confirmed that vertical life style and physical work, pregnancy, family history of varicose veins increase the risk of VV and CVI.

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Zusammenfassung

Ziel: Bestimmung von Risikofaktoren, die zu einer höheren Prävalenz von Varizen und chronisch-venöser Insuffizienz (CVI) bei Frauen beitragen, in Bezug auf Lebensstil und Geschlecht sowie Erstellung eines möglichen Zusammenhangs zwischen der angegebenen Exposition mit oralen Kontrazeptiva (OK) und der Prävalenz von Varizen und CVI. **Methoden:** Der Warsaw Brodno Venous Population Survey war eine Querschnittsstudie, die bei 2530 Frauen durchgeführt wurde. Auf der Basis eines gezielten Fragebogens, medizinischer Fakten und einer klinischen Untersuchung wurden die mit Geschlecht und Lebensstil zusammenhängenden Risikofaktoren identifiziert. **Ergebnisse:** Bei Frauen betrug die Prävalenz von Varizen 15,9% und der CVI (C1-C6) 40,15%. Offene und abgeheilte Ulzera wurden in 0,51% bzw. 0,75% der Fälle diagnostiziert. Eine Analyse von Risikofaktoren für Varizen bezogen auf Lebensstil und Arbeitsplatz ergab bei vorwiegend sitzenden bzw. stehenden Aktivitäten eine OR (odds ratio) von 0,52, bzw. 1,56. Für CVI-Risikofaktoren ergab sich für im Büro tätige Frauen eine OR = 0,53 im Vergleich zu OR = 1,88 für körperlich Tätige. Frauen, die jemals orale Kontrazeptiva eingenommen hatten und solche, die sie länger als 5 Jahre eingenommen hatten, hatten ein geringeres Risiko für eine CVI: OR = 0,44 bzw. OR = 0,36. Für Varizen ergab sich mit der Einnahme oraler Kontrazeptiva: OR = 0,30 bzw. OR = 0,27. **Schlussfolgerungen:** Die orale Kontrazeption steht möglicherweise in umgekehrtem Zusammenhang zur Prävalenz von Varizen und chronisch-venöser Insuffizienz. Die Ursachen hierfür bedürfen der weiteren Klärung. Mit dieser Studie wurden bestätigt, dass ein Leben mit vorwiegend im Stehen durchgeführten Aktivitäten und körperlicher Arbeit, Schwangerschaft und Varizen in der Familienanamnese das Risiko für Varizen und CVI erhöht.

Möglicher umgekehrter Zusammenhang zwischen der Einnahme oraler Kontrazeptiva mit Varizen und chronisch-venöser Insuffizienz: Analyse von Risikofaktoren bei Frauen bezogen auf Geschlecht und Lebensstil

Résumé

Objectif: Détermination des facteurs de risque associés au style de vie et au sexe contribuant à une prévalence plus élevée de veines variqueuses (VV) et d'insuffisance veineuse chronique (IVC) chez les femmes et établissements d'un lien possible entre l'exposition rapportée à des contraceptifs oraux (CO) et la prévalence de VV et d'IVC. **Méthodes:** La « Warsaw Brodno Venous Population Survey » était une étude transversale, réalisée sur un groupe de 2530 femmes. Des facteurs de risque associés au sexe au style de vie ont été déterminés sur la base d'un questionnaire ciblé, de données médicales et d'essais cliniques. **Résultats:** Chez les femmes, la prévalence des vv était de 15,9% et celle des IVC (C1-C6) de 40,15%. Des ulcères ouverts et guéris ont été diagnostiqués dans 0,51% et 0,75% des cas respectivement. Une analyse des facteurs de risque pour les VV associés au style de vie ou à la profession a montré un OR de 0,52 pour un style de vie en position assise et un OR de 1,56 pour la station debout, et pour l'IVC, un OR de 0,53 pour les personnes travaillant dans un bureau contre 1,88 pour les personnes exerçant un travail physique. Les femmes ayant pris des contraceptifs oraux dans leur vie et celles les ayant pris durant plus de 5 ans ont présenté un risque plus faible d'IVC : OR = 0,44 et OR = 0,36 respectivement. Le risque de VV associé à la prise de CO était de OR = 0,30 et OR = 0,27 respectivement. **Conclusions:** La contraception orale peut être inversement corrélée à la prévalence de veines variqueuses et de l'insuffisance veineuse chronique, même si les raisons de ces résultats nécessitent des investigations plus approfondies. Nous avons confirmé que la station debout et le travail physique, la grossesse et les antécédents familiaux de veines variqueuses provoquent une hausse du risque de VV et d'IVC.

La prise de contraceptifs oraux pourrait être en corrélation inverse avec les veines variqueuses et l'insuffisance veineuse chronique: analyse des facteurs de risque associés au sexe féminin et au style de vie

Varicose veins (VV) are one of the most common disease of mankind (2, 13). They represent, however, only a part of the broad spectrum of symptoms producing a condition known as chronic venous insufficiency (CVI). Despite tremendous efforts to study the epidemiology of VV and CVI as documented by a significant number of papers (1, 5, 6, 12), the data presented are often incoherent and the estimated prevalence differs significantly. Nevertheless, with the exception of two studies published in the first half of last century, all authors point out the significantly higher prevalence of varicose veins and CVI among women, sex ratio ranging from 1.3 to 4.0 (2). Quite recently, some debate questioning the significant intersex difference in VV prevalence arises (5, 7). Interestingly, sex related and lifestyle risk factors (obstetric history, genetic factors, lifestyle, work, oral contraception) that could be considered at least partially responsible for that situation despite numerous trials, still requires further elucidation (6).

Up to now, only little attention was paid to the relation between risk of varicose veins and/or CVI and long exposure to orally taken hormonal contraceptives (OC). Although the increased risk of OC in relation to venous thromboembolism is reasonably well known, and with introducing of

new generations of OC has subsequently decreased (15, 17), it is anticipated that VV are potential source of deep venous thrombosis. Considering epidemiological scales of OC intake and VV or CVI, a possible link between them would be of significant clinical importance.

Lack of clarity and consistency in defining varicose veins and chronic venous insufficiency are important obstacles in comparing results of epidemiological investigations (6). To address this issue, the former author has routinely used duplex ultrasound assessment of venous reflux. However, the majority of authors prefer as basic reference the use of the worldwide accepted CEAP classification.

The aim of this paper is to present sex and life style related risk factors of varicose veins and CVI, with particular reference to oral hormonal contraceptives intake. It is based upon a randomly selected urban community population consisting of 2530 women tested within Warsaw Brodno Venous Population Survey.

Study population and methods

The Warsaw Brodno Venous Population Survey was conducted between March 1,

1998 and December 30, 2000. For this epidemiological study ca. 140 000 residents (mainly of the urban type) of Warsaw's Brodno district characterized by a low migration rate (<0.8%/a) were recruited. 2000 men and 3000 women (age: 35-75 years) were randomly selected from the Mayor's Office Register. An invitation to participate in the study was sent to them. They were also asked to present all available medical documentation. In order to avoid bias of non-responders, they were invited by letter up to three times. 3656 turned in, corresponding to a total response rate of 73.1% (56.3% men, 84.3% women). Local ethics committee approval was obtained, each candidate signed informed consent to participate in the study.

Participants were asked directly, and further assessed by medical staff according to the general questionnaire consisting of 32 items on demographic and general vascular disease data, and the specific one with 49 items targeted on venous diseases.

Questions specifically addressed to sex and lifestyle related risk factors addressed predominant life and work mobility. The sitting lifestyle was defined as preference of sitting activities (e. g. during working hours) and the vertical one as standing and predominant lifestyle or professional activities in vertical position. Further questions aimed at type of work (dichotomous – predominantly manual or physical work, predominantly office/static work), parity, duration of orally taken hormonal contraception (<12 months, 1-5 years, 6-10 years, >10 years), family history of varicose veins and venous diseases.

All participants underwent general examination, with particular attention to chronic venous insufficiency signs. Standard examination was initially performed in supine position, in a well lit area. Then they were supposed to stand for a minute. All skin changes and other findings were documented on a scheme, clinical tests (Trendelenburg and Perthes) were performed to assess superficial and perforating veins reflux, as well as deep system patency. In doubtful cases pocket size continuous wave Doppler probe was available, whilst duplex scan investigation remained reserved for selected cases.

C	clinical signs (grades 0 to 6)
E	aetiologic classification (congenital, primary, secondary)
A	anatomic distribution (superficial, deep, perforator, alone or in combination)
P	pathophysiological dysfunction (reflux or obstruction, alone or in combination)

Tab. 1
CEAP: classification of chronic venous insufficiency

class	clinical description
0	no visible or palpable signs of venous disease
1	teleangiectases or reticular veins
2	varicose veins
3	oedema
4	skin changes ascribed to venous disease (e. g. pigmentation, venous eczema, lipodermatosclerosis)
5	skin changes as defined here with healed ulceration
6	skin changes as defined here with active ulceration

Tab. 2
CEAP: clinical classification, variable C

Diagnostic criteria of chronic venous insufficiency and varicose veins were based upon internationally accepted CEAP criteria, published previously also in Polish (14). Particular emphasis was put on C (clinical) criteria, as shown in table 1 and table 2 (13).

According to criteria mentioned above, chronic venous insufficiency was diagnosed when any of the C1-C6 (including teleangiectases and reticular veins) criteria was met. The aim of such a broad scope was to analyze the whole symptomatic spectrum. Varicose veins were diagnosed clinically with help of continuous portable Doppler device.

All data were entered into computer database in order to perform computerized statistical analysis with use of Epi Statcalc software. Statistical analysis was done by use of Fisher exact test and Mantel-Hanszel test. Univariate analysis, across age strata was performed. Odds ratio (OR) for each risk factor analyzed was extracted.

Results

All of the 3656 responders (2530 women, 1126 men) to the questionnaire gave their informed consent and thus were included into the study. For women varicose veins were diagnosed in 404 cases (15.9% versus 8.7% in men), and chronic venous insufficiency C1-C6 in 1016 women (40.15% versus 26.82% in men). Advanced stage of CVI C6 (open ulceration) was diagnosed in 19 women (0.75% versus 0.71% in men), and C5 (healed ulceration) in 13 women (0.51% versus 0.35% in men).

Basic demographic age structure is shown in table 3 together with the prevalence of chronic venous insufficiency and varicose veins. Figure 1 presents percentual prevalence of VV veins and CVI in age groups compared to average for the female population. In the age group of 35-45 years, prevalence of varicose veins is 7.17%, in that of 65-75 years it is more than three times higher: 23.26%. Similarly, symptoms of CVI rise dramatically with age: from 14.34% in youngest age group up to 63.62% in the oldest. Fortunately, the most serious grades C5 and C6 contribute only

Tab. 3
Varicose veins, chronic venous insufficiency and age group distribution (n = 2530 women)

parameter/age group (years)	35-44	45-54	55-64	65-75
total no participants	251	763	914	602
percentage age group distribution (%)	9.92	30.16	36.13	23.79
varicose veins n = 404	18	87	159	140
prevalence of varicose veins in age strata (%)	4.45	21.5	39.3	34.6
chronic venous insufficiency n = 1016	36	240	357	383
prevalence of chronic venous insufficiency in age strata (%)	14.34	31.45	39.05	63.62

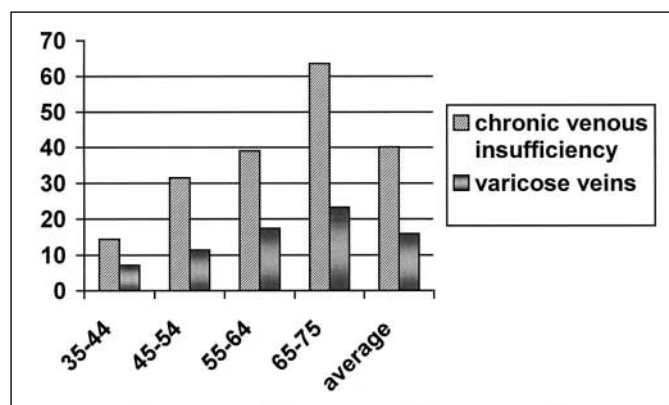


Fig. 1
Prevalence (%) of chronic venous insufficiency and varicose veins in women (n = 2530) stratified by age

3.1% of all the CVI C1-6 cases (no age stratification was done for this group).

A sitting lifestyle reported 1337 persons, out of them varicose veins were reported in 159 cases, which results in a prevalence in this group of 11.89%. Vertical lifestyle reported 1149 persons, out of them varicose veins were diagnosed in 221 cases, resulting in prevalence of 19.23%. That means OR (odds ratio) = 0.52 with 95% CI (confidence interval) 0.42-0.65 for sitting lifestyle and OR = 1.56 (95% CI 1.25-1.94) for vertical lifestyle.

Analogically to lifestyle, within the professionally active group (retirement age for women in Poland is 60) we found 1279 women representing 50.55% of our population sample. Out of 730 office workers CVI was diagnosed in 185, prevalence 25.34%, and out of 549 physical workers CVI was reported in 214 cases corresponding to a prevalence of 38.98%. OR for office workers was 0.53 (95% CI 0.42-0.68) compared to OR for physical workers 1.82 (95% CI 1.47-2.41).

Out of 404 women with varicose veins 73.7% (n = 298) were parous. 47.65% out of them (n = 142) reported, that varicose veins appeared during pregnancy. Family history of varicose veins reported 78% (316/404).

Out of 2530 women 692 (27.35%) were ever taking oral contraceptives. 184 of these demonstrated signs of CVI (26.59%) and 47 varicose veins (11.63%). Comparing prevalence in women ever practising hormonal contraception we found, that oral intake is linked with OR = 0.44 (95% CI 0.36-0.53) for CVI and OR = 0.30 (95% CI 0.22-0.42) for VV, respectively.

Similar comparisons for women taking oral contraceptives for a period longer than 5 years 512/2530 (20.23%) showed, that CVI symptoms were demonstrated by 116/512 (22.65%), and VV by 30/404 (7.42%). Compared to the total number, women taking oral hormonal contraceptives for more than 5 years were at decreased risk of

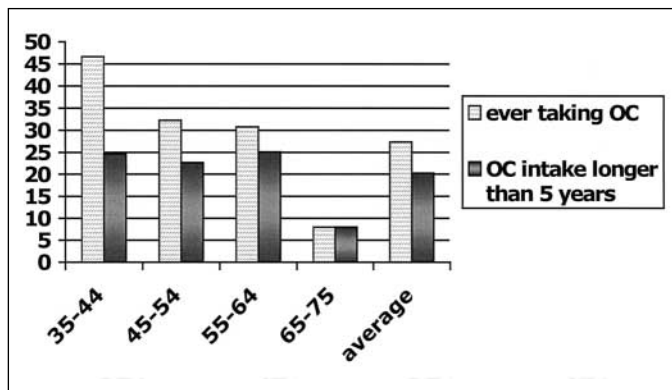


Fig. 2
Distribution (%) compared to total sample) of reported oral contraceptives (OC) intake in age groups

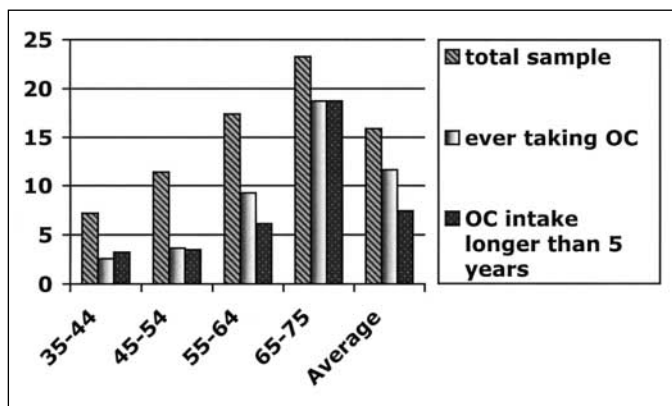


Fig. 3
Prevalence (%) of varicose veins among women taking oral contraceptives (OC) in comparison to average in sample, stratified by age groups

- CVI: OR = 0.36 (95% CI 0.29-0.46) and
- VV: OR = 0.27 (95% CI 0.18-0.41).

Figure 2 shows the distribution of reported orally taken hormonal contraceptives in age groups. Figure 3 depicts the prevalence of varicose veins in women taking oral contraceptives in comparison to the average in the sample, stratified by age. In each strata VV prevalence is lower, than in total sample. All these age stratified relations are statistically significant ($p < 0.005$), except from oldest age strata ($p = 0.59$ and $p = 0.41$ for women taking OC ever and longer than 5 years, respectively), and young women taking OC for a period longer than 5 years.

Discussion

This paper specifically focusses on the relation between long term oral hormonal contraception intake and the prevalence of varicose veins and chronic venous insufficiency

C1-6 according to CEAP classification. This study firstly demonstrates for all age groups the consistently lower prevalence of VV and CVI in women exposed to oral contraceptives, regardless of long or short term intake. Secondly, it addresses the prevalence of varicose veins and chronic venous insufficiency in Polish women aged 35 to 75 years. We thus confirmed previous reports of lower incidence of VV related to sitting (as opposed to vertical) lifestyle and office-like type of work (as opposed to manual or physical) (6). We further confirmed the important role of genetic (i. e. family history) and previous pregnancy risk factors.

The main limitation of this study is the cross-sectional design, which only permits general conclusions. It allows to establish a hypothesis of inverse correlation between varicose veins and orally taken hormonal contraceptives, which should be confirmed in case control design study. Because of the large sized sample, and interesting results, we consider our data warrant discussion.

Obviously, statistical strength of associations observed and conclusions are therefore limited. We hoped, that reminding up to three times potential subjects to attend the study increased response rate and validity of studied sample.

As mentioned before, despite efforts towards an exact definition of chronic venous insufficiency, classification, and unification (13) obstacles in comparing the prevalence of CVI of different trials still exist. CVI definition as used in this study was very generous, thus encompassing all forms of CVI including teleangiectases and reticular veins as well. The rationale was to demonstrate wide scope of venous problems affecting a significant part of the population. Serious stages of CVI (C5-6) were found in 1.26% of women. This figures are close to results cited by Fowkes (8) and of San Valentino Vascular Screening Project from Central Italy (5), where CVI prevalence was reported as 0.86%, and open ulcers 0.48% in comparison to the prevalence of VV of 7%.

In contrary to our findings Cesarone et al. did not found significant differences in the prevalence of VV between sexes. The former findings should be, however, considered as a local Italian variability, as prevalence of VV in Southern Italy Campania region (3) in elderly women (35.2%) was twice as much as in men (17%).

Epidemiological survey in Portugal showed CVI prevalence of 40%, and trunk reticular varices of 10 to 22%, with average sex ratio $w : m = 2 : 1$. This is very similar in level as compared to our findings, though in Portugal the prevalence of C5-6 appears to be higher (3.9%) (4).

Epidemiological survey from Germany, performed before CEAP classification had been introduced (21) showed, that varicosities of all grades affect 48.7% of district population, though considerable varices affect 13% of population. Sex distribution was similar.

A study from former Czechoslovakia reported similar proportions of hyphenwebs (30.7%), trunk (14.4%) and reticular varices (15.4%) in a group of 696 women working at a large department store (19).

In our investigation, we noticed a significantly higher prevalence of VV in women,

although not as high as in mini-Finland health survey (8000 persons, VV prevalence in women up to 25%, in men 7%) (18). A prevalence study in Brazil (12), a developing country, demonstrated presence of CVI (excluding teleangiectases) in non-pregnant women ranging up to 50.9%, and VV of 21.2%. The population sample consisted, however, of patients attending clinic for routine examination or disease complaints, which rather disqualifies sample as representative for the whole population.

In previous comparable epidemiological studies risk of varicose veins is supposed to increase proportionally to economical factors being significantly lower in developing countries (2). Nevertheless, this point of view seems disputable, as despite significant economical differences between Poland and Western Europe prevalence profiles of CVI and VV do not differ considerably.

Age stratified prevalence of VV and CVI showed trend to increase in older age groups. This is confirmed by others (8, 16, 19). Interestingly, prevalence of CVI symptoms in age groups increased faster than prevalence of varicose veins. Does it represent the fact, that so-called venous disorders are subsequently blamed for troubles caused by coexisting e. g. musculoskeletal complaints? Or perhaps varicose veins tend to appear earlier, whereas symptoms of CVI occur later in life. Other studies confirm this tendency (10), even if CVI group had been restricted to C6 cases (16).

Similarly to our findings (vertical lifestyle OR = 1.82) standing at work is linked with higher prevalence of VV in a number of studies (19, 20), some of them with OR reaching 2.63. Gourgou et al. in France (9) found, that standing at work (OR = 1.4/ OR = 2.7) is positively associated with VV risk, but in his paper it was rather low physical activity (OR = 1.6) that positively correlated with prevalence of VV.

In our study office work, which complies to predominantly sitting lifestyle appeared to be a factor leading to decreased risk of VV and CVI. This finding is conform with that of Fowkes et al. (6). We were very surprised to find out, that physical activity appeared to be a risk factor for varicose veins. Perhaps it was in fact an often strenuous physical effort.

Perhaps the risk factor "physical activity" should be defined more clearly.

Other authors confirmed that such factors as family history of venous insufficiency dramatically increases the risk for VV (OR = 7.7), though the impact of this factor differs significantly (9, 16). 78% of family history reported by the women examined by our team is well above most of reports, ranging from 49.4%, as reported by Kom-suoglu et al. (10) up to 63% (2).

Reproductive history seems to be important as risk factor in the prevalence of varicose veins. Canonico et al. (3) reported 40.5% of women noticed, that VV appeared following pregnancy compared to 47.6% in our study. Callam (2) quoted numerous studies dating as early as 1930, confirming that parity, and even the number of pregnancies increased the risk (12), whilst according to Gourgou et al. OR rises up to 3.4 for women reporting more than four pregnancies (9). Interestingly, multiparity may be linked with older age of multiparous women compared to uniparous, thus causing a bias (2).

Exposure to oral hormonal contraceptive agents is linked with increased risk for venous thromboembolism (VTE) (11, 15, 17). Some authors (17) consider OC of the third generation containing desogestrel generally as safer. Others (11) conclude, that VTE risk of the second and third generation estrogen component of oral contraceptives is similar, particularly among the women starting OC intake. Therefore it appears, that for initial assessment of VV or CVI risk factors, OC of different generations should be analyzed together. In general, the incidence of VTE episodes is declining over the preceding three decades (17).

The first who described the link between OC and (although not significantly) reduced prevalence of superficial venous reflux was Fowkes et al. (6). His concept of possible influence on venous wall components (elastin and collagen) by sexual hormones as an explanation for VV risk reduction seems very interesting.

The percentage distribution of OC intake in the different age groups (Fig. 2) showed a decline among elder women representing the rising OC intake in Poland within the preceding four decades. Ana-

lyzing Figure 3, a tendency to slow down incidence of VV among young women taking OC might be observed.

One of the confusing factors of the observed risk reduction in women taking OC could be the fact, that they – of course – thus avoided (multi)parity. It would be therefore advisable to test nullipari who never practised hormonal contraception (although such a group could be difficult to extract) against nullipari with prolonged OC use. On the other hand, parous women contributed to a significant amount of the studied sample (73%). Because average age of first pregnancy in OC takers versus others is unknown, it is difficult to assess, whether there was any bias influencing outcome.

Because this is a crosssectional survey it is subjected to the prevalence/incidence bias. It might be, that women with varicose veins were advised against hormonal contraception. On the other hand, the average reported latency period of varicose veins in studied population amounted to 4.5 years, which is a relatively short period in comparison to long lasting OC use.

If other epidemiological or observational surveys, possibly of case control design, would confirm that interesting relation, there would be an extra factor influencing sex ratio in VV and CVI prevalence. Such a factor most likely could be linked with both lifestyle and socioeconomic status, although the mutual influence of socioeconomic status and lifestyle on OC use has not been assessed here. Considering that OC are linked with higher incidence of VTE episodes, possibly by change in blood coagulation properties, it would be interesting if these drugs would also protect the venous walls. Perhaps uniformly negative influence of OC on the vascular system could be then perceived as more biased.

Conclusions

Varicose veins, chronic venous insufficiency and venous leg ulcer prevalence in the Warsaw Brodno population, as well as sex distribution are similar to that reported in other European epidemiological surveys.

We confirmed, that such risk factors as vertical lifestyle, physical or manual type of work, parity and family history are important risk factors. We found out as already emphasised by others (6) a consistent decrease in the prevalence of both VV and CVI symptoms among women taking oral hormonal contraceptives in all age strata. We are convinced, that this issue requires further research.

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