Drug use in population screening. Pharmacoepidemiological and pharmacoeconomical aspects

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CHAPTER 5

The impact of hormonal contraceptives on blood pressure, urinary albumin excretion and glomerular filtration rate

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ABSTRACT

Introduction

In short-term studies, hormonal contraceptives (HC) suggested to induce a rise in blood pressure (BP) and urinary albumin excretion (UAE), while the effect of HC in renal function (GFR) is still debate. Data on long-term and withdrawal effects of HC-use on these outcomes are however, not available. We therefore studied whether start and cessation of HC induce changes in BP, UAE and GFR.

Methods

We used data from the PREVEND-Study, a prospective cohort of subjects aged 28-75 years. Eligible were women aged ≤ 45 years old with complete clinical and pharmacy data on baseline and follow-up screening (4-yrs later). Multivariate regression analysis was used to estimate the effects of HC on BP, UAE and GFR in those who started (*n*=73), stopped (*n*=117) or continued (*n*=183) with those who never used (*n*=286) as reference group.

Results

BP increased among starters and fell in stoppers. These changes were statistically significant compared to never-users, also after adjustment for relevant variables. UAE increased 14.2% in starters (p=0.074) and fell 10.6% in stoppers (p=0.021), while GFR fell 6.3% in starters (p<0.001) and did not change in stoppers. The effects of stopping HC on UAE and GFR were significantly different compared to changes among never-users, also after adjustment for other variables (p=0.023 and 0.036, resp).

Conclusions

The start of HC is independently associated with worsening of BP, UAE and GFR, while stopping HC-use resulted in an improvement. These data suggest that long-term HC-use (aged 28-45) may be deleterious from cardiovascular and renal point of view, but stopping may result in correction of these effects.

INTRODUCTION

Hormonal contraceptives (HC) have been used for more than three decades. Much attention has been drawn to the thrombo-embolic and cardiovascular adverse events associated with these agents. It is generally acknowledged since 1978 [1] that HC may increase blood pressure. The activation of renin angiotensin system (RAS) which is recently suggested play a role on this mechanism of HC in elevated BP, however, are still in debate [2-5]. Although the association between the use of HC and BP elevation has been repeatedly demonstrated [5-7], few studies showed the beneficial effect on blood pressure after cessation of HC [8-9].

Epidemiological and patophysiological data on HC use and the renal outcome e.g. albuminuria and renal function are limited. Interestingly, some studies have recently described an association between the use of HC and albuminuria [3,5,10]. Higher levels of albuminuria are considered an early marker of vascular endothelial damage [11-12] and are related to an increased risk for progressive renal failure and excess cardiovascular morbidity and mortality [12-17]. The mechanism of HC on UAE is still unknown. Although there are some studies showing that it may be related to a systemic haemodynamic effect, that is a rise in BP [1,9,18] or a specific renal effect [4,19] .

There is currently no evidence suggest that hormonal contraceptives use predispose women to renal disease. However, studies on the association between HC and renal outcome so far have been conducted in a hypertensive [5] or diabetic populations [3]. In the general population data are scarce. Two studies described previously that the use of HC may be associated with an increased risk for microalbuminuria, independent of blood pressure [5,10]. The subjects included in our previous cross sectional study [10] have now been followed for more than 4 years. Participants have been seen for a second screening, and their drug use has been monitored. We now present a prospective, observational study, performed in this cohort of women, investigating whether the long-term use of HC has an effect on BP, albumin loss and glomerular filtration rate.

METHODS

Study design and population

This study is part of the PREVEND (Prevention of REnal and Vascular ENd-stage Disease) study, an ongoing, prospective study which is designed to investigate the impact of urinary albumin excretion on renal and cardiovascular disease progression in the general population. The formation of this cohort study has been previously described in detail elsewhere [10,20]. Briefly, in 1997 a cohort of subjects aged 28-75 years enriched for an elevated urinary albumin excretion was drawn from the population of the city of Groningen. Overall 8592 subjects gave written informed consent and were included in 1997 in the the observational cohort for extensive baseline screening (baseline screening). The 8592 subjects identified of whom 95% caucasians were followed up for cardiovascular and renal morbidity and mortality details since the time of their baseline screening. They were invited for a second screening after a mean follow-up period of 4.2 years (range 2.8-6.1). By then 246 subjects had died, 130 were lost to follow up and 1322 declined participation, leaving 6894 subjects who completed the second screening. Of these 6894 subjects, we only included women in our analysis (*n*=3450). We excluded those subjects who aged >45 years old (*n*=1880) and those for whom no complete information on drug use during follow-up study period (4.2 years) was available (*n*=1129). Thus, 751 subjects are available for further analysis. The shanges in BP, UAE and GFR from baseline compared with the second screening were studied in relation to the use of HC.

Measurement of the study

The methodology used in the PREVEND cohort study has been described previously in elsewhere [10,20]. The screening examinations included two visits to an outpatient clinic, at the first visit an interview is held on demographics, medical history and smoking habits. During a physical examination, weight, height and BP were measured. Body weight was mesured to the nearest 0.5 kg, using a balance scale (seca Vogel & Halke GmbH & C0, Hamburg, Germany) after removal of shoes and heavy clothing. Height was measured to the nearest 0.5 cm using stationer measuring board with right angle. Body mass index (BMI) was calculated as weight in kilogram divided by the square of height in meters. In the supine position, BP in the right arm was measured at 2 visits, every minute for 10 minutes using an automatic blood pressure monitoring device (Dinamap XL Model 9300; Johnson-Johnson Medical Inc, Tampa, Florida). Systolic and diastolic BP was calculated as the mean of the last two measurements at both visits. Fasting blood

samples was drawn for direct measurement of total cholesterol, glucose and serum creatinine. Furthermore urine was also collected during two days for measurement of UAE.

Plasma glucose, serum cholesterol and serum and urinary creatinine were recorded based on findings of an automated dry chemistry analyzer system (Kodak Etachem; Eastmen Kodak, Rochester, NY). Urinary albumin concentration was determined by nephelometry with a threshold of 1.8 to 2.3 mg/l and intra- and interassay coefficients of variation of less than 2.2% and 2.6% respectively (Dade Behring Diagnostic, Marburg, Germany). UAE is given as the mean of the two 24-hour urine excretions. GFR (ml/min/1.73 m2) was estimated using the Modification of Diet in Renal Disease (MDRD) formula: 186 x (serum creatinine) $^{-1.154}$ x (age) $^{-0.203}$ x (0.742 if female) [21].

Information on drug use

Information on drug use was obtained from the InterAction Database (IADB), containing pharmacy-dispensing data from community pharmacies in the city of Groningen. Dutch patients usually register at a single community pharmacy and therefore this pharmacy can provide an almost complete listing of subject's prescribed drugs [22]. Pharmacy data contain, among others, information on the name of the drug dispensed, ATC (Anatomical Therapeutical Chemical) classification, date of prescription and number of days the drug was prescribed and the number of defined daily dose (DDDs) based on definition of WHO [23]. The use of over the counter (OTC) drugs and in-hospital prescriptions are not included. Information on drug use was collected from at least one year prior to the date of the first screening until at least the second screening.

Exposure definitions

Hormonal contraceptives (HC) were defined as preparations containing ethinyl estradiol and/or a progestin, either oral, injection or subcutaneus implant. The Intra Uterine Devices (IUD) and the progestagen-only oral preparations (mini-pill contains low potency progesteron)) are not considered HC in this study.

A subject was defined as using HC at the first screening, if she had used at least one prescription of the drug in the year prior to the first screening. Women who had used HC at the first screening, but stopped its use more than one year before the second screening, were classified as "stopper" (n=117) and those who continued to use it until the second screening (with a mean prescribed daily dose (PDD) during the observation period $\geq$0.75), were defined "continuer" (n=183) (the PDD was calculated from the total amount of DDDs divided by the number of

days exposured). The women who did not use HC at the first screening but started to use it at least a year prior to the second screening, were defined "starter" (*n*=73). Women who had used the hormone for a short period in between the two screenings (intermediate use, *n*=92) were not taken into account in this study. Women who had never used HC in the entire observation period were defined "non users" (*n*=286). We similarly registered the use of antihypertensive medication with a split up in agents interfering in the renin angiotensin system (RAS), such as ACE inhibitors or angiotensin II receptor blockers, and other antihypertensives. Also the use of lipid lowering and glucose-lowering drugs was registered.

Second, we studied subgroups of oral HC users according to their progestin classified as second generation (levonorgestrel, lynestrel, and norethindrone) or third generation (desogestrel, gestodene, and norgestimate) [24]. Subjects who received only one type of HC generation during the study period were included in the subgroup analyses for the type of generation of HC. Subjects who switched from one type HC generation to another were excluded for subgroup analysis for the type of HC generation.

The statistical analysis

Baseline characteristics are reported as mean and standard deviation for continuous variables and as percentage for categorical variables. Because of its skewed distribution, logarithmic transformation of UAE was applied for further analyses and reported values are transformed back to the original scale (geometric means). Differences in population characteristics at baseline between the various groups under investigation were tested for continuous variables by Student's t-test for non-paired data and for categorical variables by a Chi-square test.

We compared the percentage change in BP, UAE and GFR between the first and second screening for each category of HC-user with Student's t-test for paired data. One way ANOVA was applied to test for changes in blood pressure, UAE and GFR between groups with never users as reference. Multivariate linear regression models were built to adjust the baseline parameters that are known to influences changes in BP, UAE and GFR such as age, systolic and diastolic BP, body mass index, cholesterol, glucose, UAE and GFR. Similar analyses were performed to study the association between the various generations of HC and outcome. All calculations were performed with SPSS version 12.0.1 software (SPSS, Chicago, IL, USA). A *p*-value <0.05 was considered statistically significant.

RESULTS

Of the 751 women 342 used HC at the time of the first screening, while 409 women did not. Among the 342 women who used HC at baseline, 117 (34.2%) stopped using the drug before the second screening (*stoppers*), while 183 (53.5%) women were still using it at the time of the second screening (*continuers*) and 42 women used HC less than 0.75 of DDD (*intermediate*). Of the 409 subjects who did not use HC at the baseline examination, 73 (17.8%) started use of HC before the second screening (*starters*), while 286 (69.9%) women never used HC during the entire follow up period (*never users*) and 50 women used HC only for a short period in between the two screenings (*intermediate*). Intermediate users (n=92) were not included for further analysis.

The characteristics of these subjects at baseline according to their HC use at second csreening are presented in Table-1. Women who never used HC were older and had a lower systolic BP and higher GFR compared with those who used or had used HC. Other factors such as diastolic BP, plasma cholesterol, glucose, smoking status, previous myocardial infarction, use of lipid or blood pressure lowering drugs and antidiabetic were not significant different among groups.

The effect of HC on SBP, DBP, UAE and GFR is shown in Table-2. The start of HC was associated with a rise in SBP and DBP, while SBP and DBP fell in *stoppers*. The percentage change in blood pressure among *starters* and *stoppers* was statistically different from the change in the *never users* for both systolic and diastolic BP, also after adjustement for relevant variables.

A similar pattern is also found for UAE. Compared to the first screening, UAE at second screening increased by +14.2% (p=0.074) in *starters* compared to +5.9% (p=0.081) in those who *never used* HC, although the difference between these two groups did not reach statistical significance after adjustment for confounders (p=0.201). In contrast, stopping HC use resulted in a decrease of 10.6% in UAE (p=021). This decrease was significantly different compared to never users, also after adjustment for others variables (p=0.023).

GFR was lower at follow-up visit in *starters* (p<0.001) and *continuers* (p=0.002), but also fell in subjects who never used HC (p<0.001), while GFR in *stoppers* did not change significantly. The fall in GFR was greatest in those who started HC compared to never users and was smallest in those who stopped HC. The percentage reduction in GFR between *stoppers* versus *never users* was significantly different (p=0.036) after adjustment for other variables.

Table-1. Baseline characteristics of the study cohort according to use of hormonal contraceptives (HC)

	Never users n= 286	Starters n= 73	Continuers n= 183	Stoppers n= 117	p-value
Age (years)	39.1 (+/- 4.3)	37.4 (+/- 4.6) *	37.6 (+/- 4.6) *	36.5 (+/- 4.5) *	< 0.001
Body mass index (kg/m^2)	25.0 (+/- 4.4)	24.3 (+/- 3.6)	24.7 (+/- 3.8)	24.2 (+/- 4.3)	0.34
Systolic blood pressure (mmHg)	114.0 (+/- 13.3)	114.8 (+/- 10.5)	117.7 (+/- 13.3) *	114.6 (+/- 12.7)	0.02
Diastolic blood pressure (mmHg)	67.4 (+/- 8.0)	67.8 (+/- 7.5)	69.1 (+/- 7.7)	68.1 (+/- 7.4)	0.17
Glucose (mmol/l)	4.4 (+/- 1.0)	4.4 (+/- 0.6)	4.3 (+/- 0.7)	4.4 (+/- 0.6)	0.71
Cholesterol (mmol/l)	5.1 (+/- 1.3)	5.0 (+/- 1.0)	5.0 (+/- 1.5)	5.0 (+/- 0.9)	0.88
Urinay albumin excretion (mg/24hr)	8.4 (3.9-18.4)	8.3 (4.4-15.4)	9.7 (4.1-23.0)	8.9 (4.5-17.9)	0.23
e-Glomerular filtration rate (ml/min/1.73m^2)	82.1 (+/- 11.9)	81.1 (+/- 13.2)	78.3 (+/- 11.4) *	81.7 (+/- 10.0)	0.01
Smoking (%)	46.8	52.1	52.7	53.8	0.48
History of myocardial infarction (%)	0.7	0.0	0.5	0.0	0.74
Use of lipid lowering drug (%)	0.3	2.7	1.6	1.7	0.29
Use of statins (%)	0.0	2.7	1.6	1.7	0.11
Use of anti-hypertensive (%)	5.9	4.1	5.5	3.4	0.73
Use of renin-angiotensin system inhibitors (%)	1.4	0.0	1.1	1.7	0.74
Use of anti-diabetic (%)	0.3	0.0	0.0	0.0	0.73

*Continuous variables are presented as mean and standard deviation; categorical variables are presented as percentage; urinary albumin excretion is presented as geometric mean and 95%comfidence intervalI; p-value indicates whether mean or prevalence of a certain variable differs between groups (using one way ANOVA for mean and Pearson chi-square for percentage); *p value < 0.05 indicates mean of a certain variable differs between this group compareed with never users using the Tukey test.*

Table-2. Use of hormonal contraceptives in relation to blood pressure urinary albumin excretion and glomerular filtration rate

Type of HC user		1st-screening	2nd-screening	p value*	% change	p-value†
	N	**Systolic Blood Pressure (mmHg)**				
Never users	286	114.0 (± 13.3)	113.9 (± 12.7)	0.838	+ 0.3 (± 8.5)	reference
Starters	73	114.8 (± 10.5)	117.7 (± 12.3)	0.023	+ 2.8 (± 9.1)	0.002
Continuers	183	117.7 (± 13.3)	117.4 (± 14.2)	0.664	- 0.02 (± 8.4)	0.162
Stoppers	117	114.6 (± 12.7)	111.7 (± 12.6)	0.001	- 2.3 (± 7.2)	0.041
	N	**Diastolic Blood Pressure (mmHg)**				
Never users	286	67.4 (± 8.0)	68.1 (± 7.6)	0.035	+ 1.4 (± 8.0)	reference
Starters	73	67.8 (± 7.5)	70.0 (± 7.1)	0.002	+ 3.6 (± 8.5)	0.008
Continuers	183	69.1 (± 7.7)	70.0 (± 8.6)	0.041	+ 1.6 (± 8.6)	0.152
Stoppers	117	68.1 (± 7.4)	67.0 (± 7.5)	0.020	- 1.4 (± 7.5)	0.015
	N	**Urinary Albumin Excretion (mg/ 24hr)**				
Never users	286	8.4 (3.9-18.4)	8.9 (4.0-20.0)	0.081	+ 5.9 (-0.7 / 12.8)	reference
Starters	73	8.3 (4.4-15.4)	9.5 (3.7-23.9)	0.074	+ 14.2 (-1.0 / 31.9)	0.201
Continuers	183	9.7 (4.1-23.0)	9.9 (4.1-24.3)	0.580	+ 2.3(-5.7 / 11.0)	0.809
Stoppers	117	8.9 (4.5-17.9)	8.0 (4.3-14.8)	0.021	- 10.6 (-18.7 / -1.8)	0.023
	N	**e-Glomerular Filtration Rate (ml/min/1.73m2)**				
Never users	286	82.1 (± 11.9)	78.7 (± 13.1)	<0.001	- 4.0 (± 10.7)	reference
Starters	73	80.8 (± 13.2)	75.0 (± 13.2)	<0.001	- 6.3 (± 13.0)	0.074
Continuers	183	78.3 (± 11.4)	76.2 (± 13.2)	0.002	- 2.4 (± 10.9)	0.409
Stoppers	117	81.7 (± 10.0)	80.5 (± 11.0)	0.167	- 1.0 (± 11.3)	0.036

U**rinary **albumin excretion** (UAE) are presented in geometric mean and 95%confidenc einterval; **% change systolic and diastolic blood pressure (SBP and DBP) and estimated glomerular filtration rate (e-GFR)** are presented in mean and standard deviation; **p-value indicates whether UAE, SBP, DBP and e-GFR differs between first and second screening (using paired sample t-test); **p-value†** associated with dummy variable for group, adjusted for baseline age, SBP, DBP, cholesterol, glucose, UAE, and body mass index (using multivariate linear regression analysis); included the use of antihypertensives at baseline in the model did not change the result*

Table-3. Change in blood pressure, urinary albumin excertion and glomerular filtration rate according to different generation of hormonal contraceptives

Type of HC user	2nd-generation of hormone contraceptives			3rd-generation of hormone contraceptives		
	N	**% change SBP**	**p value***	**N**	**% change SBP**	**p-value†**
Never users	286	+ 0.3 (± 8.5)	reference	286	+ 0.3 (± 8.4)	reference
Starters	45	+ 0.4 (± 7.3)	0.379	17	+ 5.3 (± 12.0)	0.004
Continuers	100	- 0.7 (± 7.6)	0.519	30	+ 0.7 (± 7.1)	0.733
Stoppers	67	- 2.5 (± 7.2)	0.045	26	- 0.2 (± 7.9)	0.896
	N	**% change DBP**	**p value***		**% change DBP**	**p-value†**
Never users	286	+ 1.4 (± 8.0)	reference	286	+ 1.4 (± 8.0)	reference
Starters	45	+ 2.1 (± 7.8)	0.282	17	+ 6.1 (± 10.2)	0.010
Continuers	100	+ 1.3 (± 8.6)	0.171	30	+ 0.5 (± 6.6)	0.437
Stoppers	67	- 1.2 (± 7.7)	0.093	26	+ 0.2 (± 7.7)	0.658
	N	**% change UAE**	**p value***		**% change UAE**	**p-value†**
Never users	286	+5.9 (-0.7 / 12.8)	reference	286	+ 5.9 (-0.7 / 12.8)	reference
Starters	45	+14.3 (-7.1 / 40.5)	0.188	17	+19.6 (-6.2 / 52.6)	0.465
Continuers	100	- 5.6 (-15.1 / 4.9)	0.663	30	+ 33.2 (6.4 / 66.6)	0.032
Stoppers	67	- 16.9 (-28.0 / -4.2)	0.011	26	+ 7.5 (-7.0 / 24.3)	0.788
	N	**% change e-GFR**	**p value***		**% change e-GFR**	**p-value†**
Never users	286	- 4.0 (± 10.7)	reference	286	- 4.0 (± 10.7)	reference
Starters	45	- 6.7 (± 13.9)	0.052	17	- 9.2 (± 9.2)	0.058
Continuers	100	- 1.0 (± 11.4)	0.057	30	- 4.8 (± 10.0)	0.422
Stoppers	67	- 1.4 (± 10.0)	0.183	26	- 1.3 (± 14.5)	0.195

HC (hormonal contraceptives); UAE(urinary albumin excretion; mg/24-hr) *are presented in geometric mean and 95% confidence interval;* ***%change SBP and DBP (systolic and diastolic blood pressure; mmHg) and e-GFR (estimated glomerular filtration rate; ml/min/1.73m2)*** *are presented in mean and standard deviation;* ***p-value†*** *associated with dummy variable for group, adjusted for baseline age, SBP, DBP, cholesterol, glucose, UAE, and body mass index (using multivariate linear regression analysis); included the use of antihypertensives at baseline in the model did not change the result.*

When studying the 2nd and 3rd generation contraceptives seperately (Table-3), start of a 3rd-generation HC resulted in an increase in systolic and diastolic BP compared to *never users*. This was not the case among starters of a 2nd-generation HC (*n*=45). On the other hand, subjects who stopped a 2nd-generation HC showed lowering of systolic BP, while stoppers of a 3rd-generation HC had no difference in BP change compared to *never users*. Starting use of either a 2nd- or 3rd-generation HC resulted in an increase in UAE, although these increases were not significant after adjustment compared with *never users*. The rise in UAE was greatest among women who continued the use of 3rd-generation HC (+33.2%) whereas the fall in UAE was most pronounced among subjects who stopped a 2nd-generation HC (-16.9%) and both were significant compared to *never users* after adjusting confounding factors. The changes in GFR among *starters, continuers* or *stoppers* of HC, either a 2nd- or 3rd-generation, were not significant different compared to *never users* (Table-3).

DISCUSSION

We found that the start of HC may induce a rise in SBP and DBP with an albeit insignificant rise in UAE, and fall in GFR. Cessation of the use of HC was associated with a statistically significant fall in SBP, DBP and UAE, and a preservation of kidney function.

This study is the first that evaluates the effect of HC-use on BP and renal outcome in the general population during long-term follow-up and pays attention also to the effect of the withdrawal of HC. Short term studies showed previously that the administration of HC is associated with a rise in BP [5-7]. Ribstein *et al* [5] reported that both in normotensive and hypertensive subjects, HC users had a significantly higher BP compared with non-users. Activation of the renin-angiotensin system (RAS) is considered as an important factor leading to the increase in blood pressure since estradiol administration stimulates the hepatic synthesis of angiotensinogen [2,25]. In another study, Lubianca *et al* [8] reported a significant decrease in SBP and DBP in women who stopped the use of contraceptives compared with those who did not stop. Thus our long-term observational data on blood pressure confirm the findings found in short-term intervention studies.

Regarding the effects of HC on UAE, various short-term studies and cross sectional epidemiological studies have shown an association of HC use and urinary albumin loss [3,5,10]. Our previous study for instance, using data of the first screening of the PREVEND cohort showed that women receiving HC had a 90%

increased risk for microalbuminuria (UAE 30-300 mg/d) compared to non-users [10]. Ribstein *et al* [5] found a significant increase in 24-hour UAE in normotensive as well as hypertensive women using oral contraceptives when compared with non-users. Similar results were observed in a recent study in diabetic population by Ahmed *et al* [3]. These authors reported that in this population 18% of contraceptive users developed macroalbuminuria (UAE > 300 mg/d) compared with 2% in non-users (RR=8.90). Interestingly, in our study a significant reduction in UAE is observed among women that stopped the use of HC, suggesting a reversible effect after discountinuation of HC. This fall in albuminuria was seen in stoppers of 2nd-generation HC but not in women who stopped 3rd - generations HC.

It is of interest that our study is able to give information on age-related changes in renal function over time. It is well known that renal function will decrease with age. We found that, compared to women who never used HC, those who started to use HC tended to have a greater decline in GFR over time, while those who stopped HC had less decline in GFR. At first glimpse this seems in contrast with data from literature that showed that HC users have similar [5] or a higher [3] GFR than non-users. This led to these authors to suggest that HC use may be associated with glomerular hyperfiltration, thus also explaining the risk for microalbuminuria. Our data suggest long term use of HC to induce a fall in GFR. The reassuring finding of our data is however, that these unfavourable effects of HC are reversible after withdrawal, even after many years.

We separetely studied whether these renal effects of HC were seen more in second versus third generation OC. Our data do not permit to draw firm conclusions on this issue, partly because there were only few women on third generation agents. If any conclusion can be drawn, there maybe a tendency that stopping HC use results in an improvement in BP, UAE and GFR in women using second generation HC, while there were no changes observed in stoppers of third generation HC. This may suggest that 3rd-generation HC may be more deleterious than 2nd-generation HC from a renal point of view. This may be in agreement with the data that there is a relationship between HC use and inflammatory markers in particular in women taking 3rd-generation agents. The latter has been argued to contribute to an increased risk for athero-thrombotic [6] and peripheral arterial disease [26]. A recent prospectives cross-over randomized study found no association between second and third generation HC with inflammation marker such as level of serum c-reactive protein [27]. A recent meta analysis conducted by Baillargeon *et al* [28] reported an increased risk of both cardiac and vascular events among 2nd and 3th generation OC users, however, the risk in 3th generation users seems less than in 2nd generation users.

Several potential limitations of the present study have to be considered. Firstly, we could only analyse half of the women who had participated in the previous screening, because approximately 20% of the women withdrew consent and from participating women only 60% had complete information on pharmacy data for the entire study period. However, the baseline characteristics of the women who were lost to follow-up did not differ statistically significant from those who remained in the study, suggesting that loss to follow-up will not be an important source of bias. Second, this study did not include women under 28 years old and a high percentage of our population was current or past smoker at baseline. Third, bias may have been introduced through confounding by indication or contraindication for HC use. This may apply in particular women on 3rd-generation agents, since these preparations were originally introduced to protect against myocardial infarction due to their favourable effect on the lipid profile [29] . The major strength of this study is that we were able to provide the long term prospective follow-up with monitoring of pharmacy records in a large sample of the general population. Furthermore, the design of our study enabled us to compare the effect of HC in women who used HC at first screening but stopped it afterwards, versus subjects who never used these agents, used them continuously, or started the use.

In conclusion, the use of HC on women aged 28 to 45 years old is independently associated with a worsening of BP, UAE and GFR, while stopping HC-use resulted in an improvement. With respect to the generation of HC, our data suggest that third generation agents might be more deleterious than second generation of HC. These data suggest that long-term use of HC may be deleterious from a cardiovascular and renal point of vies, but that stopping may result again in correction of these effects.

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