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► To cite this version:

Anne-Laure Madika, Phenicia Nasserline, Sandra Langlet, Charlotte Lecerf, Guillaume Ledieu, et al.. Association between reproductive factors and carotid atherosclerosis in post-menopausal women. *Maturitas*, 2019, 126, pp.38 - 44. 10.1016/j.maturitas.2019.04.221 . hal-03485719

HAL Id: hal-03485719

<https://hal.science/hal-03485719>

Submitted on 20 Dec 2021

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Highlights

- A parity of 3 or more was associated with increased carotid atherosclerosis.
 - This association persisted after adjustment for anthropometric measures, traditional cardiovascular risk factors and pregnancy-related complications.
 - No other reproductive factor was significantly associated with carotid atherosclerosis.
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Association between reproductive factors and carotid atherosclerosis in post-menopausal women.

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Abstract

Objectives: Assessment of cardiovascular risk in women is specific and hormonal factors should be considered to avoid its underestimation. So far, studies on this issue are lacking and the impact of reproductive factors on cardiovascular risk has yet to be determined. We study the association between reproductive factors and carotid atherosclerosis, a non-invasive marker of cardiovascular diseases, in post-menopause.

Study design: In this cross-sectional study, data were analyzed from post-menopausal women with at least one cardiovascular risk factor followed through a dedicated healthcare pathway at the Lille University Hospital between January 1st, 2013 and December 31st, 2016.

Main outcome and measures: The primary outcome was the presence of plaque or stenosis at carotid ultrasound.

Results: We included 370 post-menopausal women with a mean age of 63.4 ± 0.5 years. Carotid atherosclerosis was found in 161 (43,3%) women. Women with 3 or more children had higher odds of having carotid atherosclerosis than women with fewer than 3 children after adjustment for age, OR 1,69 [CI 95% 1,09-2,61], $p = 0,019$, and after further adjustment for anthropometric measures, traditional cardiovascular risk factors and pregnancy-related complications: OR 1,65 [CI 95% 1,05-2,62], $p = 0,031$. No other reproductive factor was significantly associated with carotid atherosclerosis.

Conclusions: A higher parity was associated with higher odds of carotid atherosclerosis independently of age, traditional risk factors, anthropometric measures and gestational diseases among post-menopausal women at risk of cardiovascular diseases. This suggests the importance of considering the number of children when assessing cardiovascular risk in women.

Keywords : women ; risk factors ; atherosclerosis; parity; cardiovascular diseases

Introduction

Cardiovascular diseases remain the major cause of death worldwide. Recent epidemiological studies have shown that the proportion of deaths attributable to cardiovascular diseases in Europe is higher in women (51%) than in men (42%) (1). An increase in incidence of cardiovascular diseases, particularly acute coronary syndrome, has been observed in younger women, due to the modernization of life style over the past decades (2). Preventive measures must be implemented, and management approaches improved.

Women share traditional cardiovascular risk factors with men. However, their frequency and impact on cardiovascular risk differs according to gender. Prevalence of cardiovascular risk factors increase with age, especially in women. At the same age, women have a higher burden of cardiovascular risk factors than men (3). Moreover, relative weights on cardiovascular risk are different between men and women (4-6). Finally, women are exposed to reproductive factors during the life-span associated with a variety of hormonal and metabolic changes, which could impact their future cardiovascular health (7). Pregnancy-related complications have been linked to future maternal cardiovascular diseases (8,9). Other reproductive factors could influence cardiovascular risk such as parity (10-12), age at menarche (13) or duration of reproductive lifespan (14).

Assessment of cardiovascular risk in women is therefore specific and hormonal factors should be considered to not underestimated it (15,16). So far, studies on this issue are missing and the impact of reproductive factors on cardiovascular risk independently of traditional risk factors is still to determine.

Because of the usually long time interval between pregnancy and the onset of clinical cardiovascular events, surrogate markers of cardiovascular disease could be useful (17). Such noninvasive measures of total atherosclerotic burden include the presence of carotid plaques. It has a predictive value of subsequent myocardial infarction or stroke (18).

The aim of this study was to investigate whether there is an association between reproductive factors and carotid atherosclerosis in post-menopausal women.

Methods

Study design and population

We undertook a cross-sectional study based on data of post-menopausal women followed through a dedicated healthcare pathway for women at risk of cardiovascular diseases at the Lille University Hospital between January 1st, 2013 and December 31st, 2016. Women were referred by private or hospital physicians (general practitioners, gynecologists, cardiologists, or diabetologists) based on a diagnosis of an increased risk of cardiovascular disease (i.e. the presence of at least one cardiovascular risk factor).

All women underwent carotid ultrasound through the care pathway. They were all in post-menopause defined as 12 months of amenorrhea or hysterectomy with oophorectomy. Women with early menopause (<40 years old), no menopause or decline of carotid ultrasound were excluded.

This study was authorized by the Commission nationale de l'informatique et des libertés (CNIL) for the treatment of personal health data. All patients were informed in writing of the collection of their data for analysis.

Assessment of cardiovascular risk factors and reproductive factors

Cardiovascular risk factors, reproductive factors and medical history were retrieved from self-reports on a standardized questionnaire administered by face-to-face interviews. These data were then checked with medical records if available.

It allowed to determine medical history, smoking status (categorized as never smokers or current smokers including ex-smokers who quit within the previous 3 years), presence of high blood pressure, diabetes mellitus (defined as self-report accompanied by use of anti-hyperglycemic medication or by elevated serum glucose twice (fasting >126 mg/dl [7.0 mmol/l]) and/or serum hemoglobin A1C (HbA1C) $>7.0\%$), hypercholesterolemia (defined as known high blood cholesterol and/or use of lipid-lowering drugs for high blood cholesterol) and family history of cardiovascular diseases (defined as a first-degree relative who developed stroke and/or myocardial infarction before 55 years in men and 65 years in women) (16).

A dedicated questionnaire interview and medical reports were used to determine gynecological history. Parity was assessed as the number of births. Gestational hypertension was defined as isolated hypertension after 20 weeks of amenorrhea or in immediate postpartum without known hypertension before pregnancy and preeclampsia as hypertension associated to significant proteinuria ($> 0,3$ g/24h) after 20 weeks of amenorrhea. Gestational diabetes was defined as diabetes beginning or first diagnosed during pregnancy. Ever use of hormone replacement therapy (HRT) was determined by self-report and the current list of medications for each participant; preparations with just progesterone were excluded. Hysterectomy and oophorectomy were also assessed. Time since menopause was categorized in three groups: <5 years, 5 to 10 years, and ≥ 10 years.

Body mass index (BMI) was calculated from measured height and weight. Waist circumference was measured 1 cm above the iliac crest and hip circumference at the widest circumference of the buttocks at the area of the greater trochanters. Obesity was defined as a BMI over 30 kg/m² and abdominal obesity as a waist circumference over 88 cm (16).

Blood pressure was measured in seated subjects after a 5-minute rest period using an automatic sphygmomanometer with a cuff adapted to the arm circumference. The average of 3 readings was used in the analyses.

Assessment of global cardiovascular risk according to ESC-SCORE classification was collected (16).

Study outcome

The primary outcome was the presence of plaque or stenosis of the extracranial portion of the carotid arteries at carotid ultrasound. Ultrasounds were performed by trained and certified physicians in vascular echography. They examined the extracranial carotid arteries bilaterally with B-mode ultrasound using a linear array transducer and a high-resolution instrument (GE Vivid E9). Presence or absence of arterial plaques was assessed in the distal portion of the common carotid artery, the carotid bulb, and the proximal portion of the internal carotid artery. Carotid plaque was defined as the presence of focal wall thickening that is at least 50% greater than that of the surrounding vessel wall or an intima-media thickness (IMT) over 1.5 mm (19). Significant carotid stenosis was defined using both morphological and hemodynamic criteria. Equivalence to a stenosis of 50% as defined by NASCET (North American Symptomatic Carotid Endarterectomy Trial) was chosen as threshold (20).

Statistical analysis

Continuous variables are described as the mean \pm SD. Categorical variables are presented as absolute numbers and/or percentages. For comparisons of baseline characteristics, we used the

χ^2 test or the Fisher's exact test for categorical variables and the Student unpaired t test or Wilcoxon's non-parametric test when needed for continuous variables. Logistic regression analyses were performed to study the association between reproductive factors and carotid atherosclerosis. Two models were used: a model controlling for age and a second model adjusting for age, anthropometric measures (body mass index and abdominal perimeter), cardiovascular risk factors (smoking, hypertension, diabetes mellitus, dyslipidemia and family history of stroke or myocardial infarction, serum creatinine), pregnancy-related complications (preeclampsia, gestational hypertension and gestational diabetes) and time since menopause. Results of logistic regression models are presented as odds ratio and 95% confidence intervals (CI). Parity was categorized into two groups according to its median value and a cutoff determined by Receiver Operating Characteristic (ROC) curves. A p value < 0.05 was considered statistically significant. The statistical analysis was performed using SAS software (release 9.3: SAS Institute, Cary, NC, USA).

Results

We included 370 post-menopausal women with a mean age of 63.4 ± 0.5 years. Flow diagram of the population is represented in Figure 1.

Carotid atherosclerosis was found in 161 (43,3%) women. It was mainly carotid plaque as only 11 women had a significant carotid artery stenosis.

Initial characteristics of the population stratified by presence or absence of carotid atherosclerosis are described in Table 1. Women with carotid atherosclerosis were older ($p < 0.0001$) and more likely to have diabetes ($p = 0.014$). Time since menopause was greater in women with carotid atherosclerosis ($p = 0.006$). Evaluation of cardiovascular risk according to ESC-SCORE classification was similar in case of absence or presence carotid atherosclerosis: 61,7% of women at high or very high cardiovascular risk and 67,7% respectively ($p = 0,23$).

Parity according to presence or absence of carotid atherosclerosis is represented in Figure 2. Modal number of children was 3. A parity of 3 or more occurred in 51,2% of patients with no carotid atherosclerosis and 65,8% of patients with carotid atherosclerosis. Women with carotid atherosclerosis had a higher number of children than women with no carotid atherosclerosis : mean parity $3,2 \pm 2,2$ versus $2,8 \pm 1,9$ respectively ($p=0.005$). Women with no children were more likely to have no carotid atherosclerosis ($p=0,04$).

Association between reproductive factors and prevalence of carotid atherosclerosis are shown in Table 2. After adjustment for age, a parity of 3 or more was associated with higher odds of having carotid atherosclerosis compared to a parity of 0,1 or 2: OR 1,69 [CI 95% 1,09-2,61], $p= 0,019$. In multivariate logistic regression analysis, women with 3 or more children had significantly more carotid atherosclerosis than women with 2 children or less after adjustment for age, anthropometric measures, traditional cardiovascular risk factors, pregnancy-related complications and time since menopause: OR 1,65 [CI 95% 1,05-2,62], $p= 0,031$.

No other reproductive factor was significantly associated with carotid atherosclerosis.

Discussion

Our study demonstrates that a higher parity (over 2 children) is associated with higher odds of carotid atherosclerosis independently of age, traditional risk factors, anthropometric measures and gestational diseases.

Because carotid plaque has predictive value for myocardial infarction and stroke (18), our findings suggest an association of the childbearing history of women with risk of later-life CVD. This is consistent with some previous studies reporting a higher mortality (10) and a higher incidence of coronary heart disease (CHD), stroke and

heart failure with increasing number of pregnancies (11,12). A J-shape relationship and a nadir of 2 children was observed in two studies.

Only few studies focused on the relationship between parity and subclinical atherosclerosis. It is yet crucial to better understand underlying mechanisms. In an American study, the association between parity and markers of subclinical atherosclerosis, coronary artery calcium (CAC) measured by computed tomography and aortic wall thickness (AWT) by magnetic resonance imaging (MRI), was investigated in 1644 women. It was found that the number of live births is associated with subclinical coronary and aortic atherosclerosis, with an apparent U-shaped relationship and a nadir of 3 births, after adjustment for traditional risk factors (21). A smaller study also found an increase of coronary calcium score in post-menopausal women with 4 children or more (22). The association between carotid intima-media thickness and number of live births was also assessed in some studies with non-consistent results. Some studies found a positive association between parity of 4 or more and carotid atherosclerosis (17, 23, 24). In another study, this association disappeared after adjustment for age (25). In contrast, in our study, the association between parity of 3 or more and carotid atherosclerosis remained significant after adjustment for age. Moreover, none of these analyses were adjusted for pregnancy-related complications which have been linked to an increased future cardiovascular risk (8,9). In our analysis, the positive association between parity and carotid atherosclerosis was significant after adjustment for gestational diseases suggesting that other mechanisms could be involved.

Several mechanisms are discussed to explain association between parity and atherosclerosis. One hypothesis is the role of socioeconomic or lifestyle factors related to child-rearing. Some studies have reported a similar association between number of children and cardiovascular risk in women and men (26). Authors then conclude that the increase CVD risk seen in women may be more likely to be explained by social, cultural, psychological and behavioral

factors related to parenthood and childrearing than by biological processes related to pregnancy and childbearing. However, these results are not consistent with other studies showing a residual independent risk only in women (11,23). This suggests that biological changes during pregnancies may also play a role.

Pregnancy results in physiologic changes in several biological cardiovascular pathways such as activation of renin-angiotensin-aldosterone system, increase in insulin resistance, modification of lipid profile, hemostasis, immune modulation and endothelial function (27-29). Association between parity and subclinical atherosclerosis found in our study supports the hypothesis of an accelerated development of atherosclerosis by a prolonged exposure time to pregnancy changes. It is possible that these alterations cumulating over successive pregnancies may lead to increased cardiovascular risk by promoting atherosclerosis via a prothrombotic effect or greater plaque vulnerability. A previous study supports similar hypothesis as gravidity and parity were associated with lower carotid artery distensibility, suggesting the role of arterial remodeling that lasts beyond childbirth (30). However, the role of endogenous sex hormones in the development of atherosclerosis remains debated. Repeated pregnancies may also lead to chronic metabolic alterations, such as increased dyslipidemia, adiposity, and type 2 diabetes (31-33). These factors are generally associated with carotid atherosclerosis and thus may at least partly mediate the association between parity and atherosclerosis observed among women. However, in our study, the association between parity and carotid atherosclerosis was maintained even after adjustment for pregnancy-related complications that can lead to onset of hypertension or diabetes, and after adjusting for waist circumference, BMI and

traditional CV risk factors, notably hypertension, cholesterol, diabetes, and smoking. These results are in accordance with other studies (10-12). As such, increased parity appears to be an additional risk factor for atherosclerosis among women, beyond the presence of conventional risk factors.

In our study, compared to ever parity, nulliparous was not associated with carotid atherosclerosis after adjustment for age and other confounders. Most of studies showed no association or a slight increase of cardiovascular risk in case of nulliparity (10-12, 34). A U-shape relationship rather than a linear one between parity and cardiovascular risk is described in some studies but is still debated. Infertility or decrease in fertility through pathologies such as polycystic ovary syndrome may be involved (35). Reasons for the lack of association in our study may be that adjustment for pregnancy-related complications was performed unlike most studies. However, potential confounders such as socioeconomic factors and age at 1st birth, not considered in our study, can also explain the inconsistent results in literature. Further research is needed to precise this complex relationship.

No other reproductive factors were found to be associated with carotid atherosclerosis in our study. It has been demonstrated that pregnancy-related complications such as gestational diabetes or preeclampsia are associated with the future risk of cardiovascular diseases (8,9,16). However, results concerning its association with subclinical atherosclerosis are conflicting. A meta-analysis found an increase in carotid IMT at diagnosis and at 10 years among women with an history of preeclampsia (36). However, in another study, no association was found between preeclampsia and IMT at 20 years (37). These results may be explained by the high prevalence of cardiovascular risk factors with ageing, particularly during menopausal transition. Considering pregnancy-related complications may therefore be

useful mainly for early identification of women at cardiovascular risk to optimize prevention in pre-menopause. Recent studies suggest that women with history of miscarriage are more likely to develop cardiovascular disease, especially coronary heart disease (38,39). The risk was particularly greater in women with multiple miscarriages. In our study, we did not find such association, but it may be due to the small number of women with recurrent miscarriage. In these studies, the same relationship was found between stillbirths and cardiovascular risk after adjusting for traditional cardiovascular risk factors. Stillbirths could therefore participate to the increased cardiovascular risk with the number of pregnancies. Hypertensive disorders during pregnancy could lead to stillbirths and were taken into account in our study. Further study should investigate mechanisms such as other medical conditions, age at pregnancy and psychological factors related to pregnancy loss.

Our study has several limitations. First, our cohort is based on a single center with a population of women with at least 1 risk factor for cardiovascular disease and as such with an increased risk of cardiovascular disease. However, average number of children in this cohort is similar to that of the French population. Second, the cross-sectional design of this study does not allow drawing conclusions on the causality of the link between parity and later atherosclerosis. Third, some of the data collected were self-reported and this could result in a non-differential classification bias. However, declarations of women were systematically checked in medical records if available. Finally, no information was available on potential confounders such level of education or precarity and age at pregnancy (40). Moreover, despite numerous known confounders considered in our analyses, we cannot exclude some other possible residual confounding factors because of the observational design of our study and limited measured variables. Other reproductive risk factors, which are associated with cardiovascular disease such age at menarche (13) and reproductive life-span (14) could also be interesting to study.

In conclusion, a higher parity (more than 2 children) was associated with higher odds of carotid atherosclerosis independently of age, traditional risk factors, anthropometric measures and gestational diseases among post-menopausal women at risk of cardiovascular diseases. This supports the accelerated development of atherosclerosis as a potential mechanism of such association and suggest the potential interest in considering the number of children, a relatively easy data to collect, when assessing cardiovascular risk in women for a more effective and targeted cardiovascular prevention. Further investigations are needed to better understand links between reproductive factors and cardiovascular risk, their underlying mechanisms and their impact in specific cardiovascular risk assessment in women.

Contributors

Anne-Laure Madika was responsible for the methodology of the study, statistical analysis, and writing of the manuscript.

Phénicia Nasserline was responsible for recruitment of patients.

Sandra Langlet was responsible for recruitment of patients.

Charlotte Lecerf was responsible for recruitment of patients.

Guillaume Ledieu was responsible for recruitment of patients.

Patrick Devos was responsible for statistical analysis.

Claire Mounier-Vehier was responsible for the methodology of the study, and writing of the manuscript.

All authors saw and approved the final version of the manuscript.

Conflict of interest

Claire Mounier-Vehier has given talks and attended conferences sponsored by Astra-Zéneca, Bayer Pharma, BMS, Boeringher-Ingelheim, Daichi-Sankyo, Ardix-Therval -Euthérapie - Servier, Novartis Pharma, Ménarini, Merck Serono, Microlife, Resmed, MSD.

The other authors have no conflict of interest to declare.

Funding

No funding was received for this study.

Ethical approval

This study was approved by the Commission nationale de l'informatique et des libertés (CNIL), reference DEC2015-9, for the treatment of personal health data. All patients were informed in writing of the collection of their data for analysis.

The collection and analysis of the data comply with French regulations.

Provenance and peer review

This article has undergone peer review.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request.

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Figure 1. Flow diagram of the population

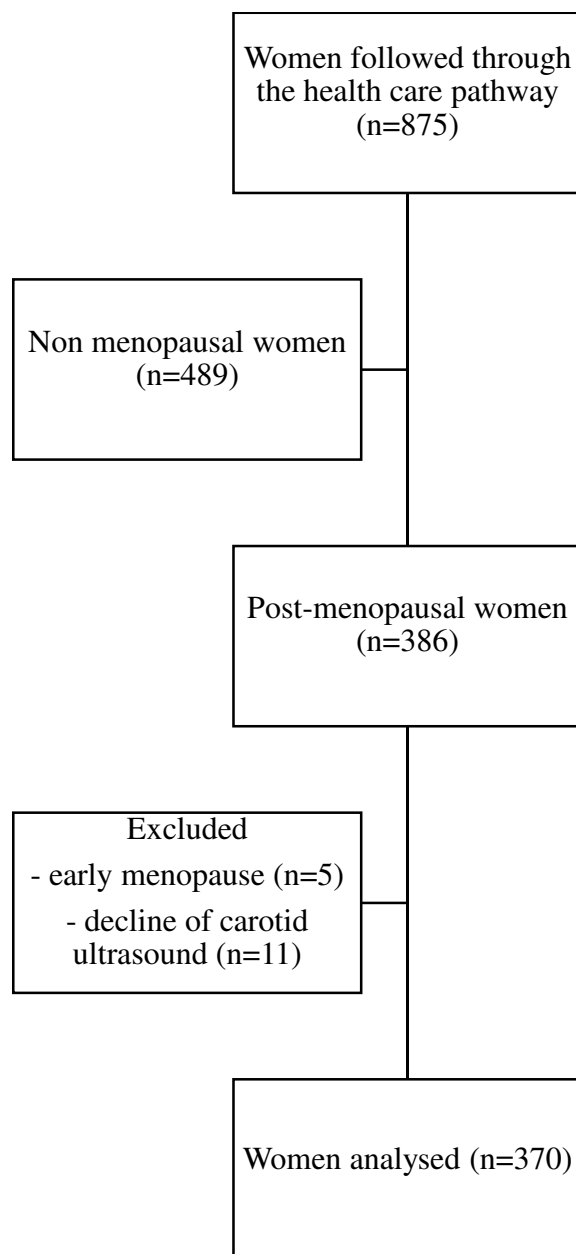


Figure 2. Distribution of parity according to the absence or presence of carotid atherosclerosis

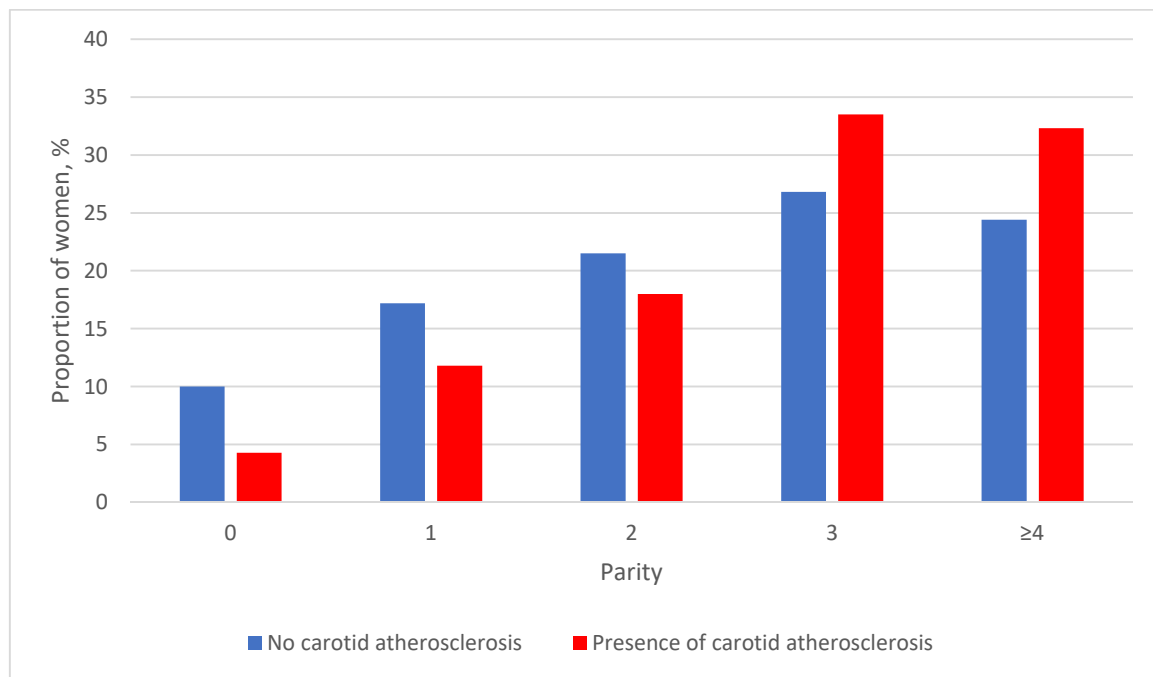


Table 1. Baseline characteristics of the study population by presence or absence of carotid atherosclerosis

	No carotid atherosclerosis (n=209)	Presence of carotid atherosclerosis (n=161)	P value
Age, years \pm SD	61.5 \pm 8.6	65.8 \pm 9.1	<0,0001
Body mass index, kg/m² \pm SD	30,1 \pm 6,9	30,3 \pm 6,9	0,76
Abdominal perimeter, cm \pm SD	105,3 \pm 17,1	106,8 \pm 18,5	0,44
Hypertension, %	89,5	91,3	0,60
<i>treated</i>	97,8	99,4	0,31
Obesity (body mass index \geq30 kg/m²), %	48,3	47,2	0,90
Dyslipidemia, %	49,8	56,5	0,21
<i>treated</i>	61,3	56,1	0,49
Diabetes mellitus, %	37,8	49,1	0,014
Current smoker, %	20,1	24,2	0,38
Family history of stroke or myocardial infarction, %	32,1	37,9	0,27
ESC-SCORE classification, %			
Low risk	12,9	6,8	0,23
Moderate risk	25,4	25,5	
High risk	9,1	8,1	
Very high risk	52,6	59,6	
Systolic blood pressure, mmHg \pm SD	137 \pm 19	141 \pm 17	0,06
Diastolic blood pressure, mmHg \pm SD	80 \pm 11	84 \pm 12	0,18
Serum creatinine (mg/L)	8,1 \pm 2,4	8,2 \pm 2,6	0,74
Parity, %			
0,1 or 2	48,8	34,2	0,005
≥ 3	51,2	65,8	
Nulliparity, %	10,0	4,3	0,04
Miscarriage and/or abortion, %			
0	71,3	73,3	0,36
1	13,4	10,6	
≥ 2	15,3	13,2	
History of preeclampsia, or pregnancy-induced hypertension, %	15,8	15,5	0,90
History of gestational diabetes, %	6,7	7,5	0,84
Hysterectomy, %	19,6	24,8	0,25
Current or previous hormone replacement therapy, %	12,0	11,2	0,87

Time since menopause, %			
<5 years	43,1	25,5	
5-10 years	30,6	39,1	
≥ 10 years	26,3	35,5	0,006

SD: standard deviation

Table 2. Logistic regression analysis of the association between reproductive factors and carotid atherosclerosis

	Age-adjusted model		Multivariable-adjusted model	
	OR (CI 95%)	P value	OR (CI 95%)	P value
Parity				
≥ 3	1,69 (1,09-2,61)	0,019	1,65 (1,05-2,62)	0,031
0,1 or 2	Ref.		Ref.	
Nulliparity				
No children	0,40 (0,16-1,00)	0,051	0,45 (0,13-1,57)	0,21
At least 1 child	Ref.		Ref.	
Miscarriage and/or abortion				
0	Ref.			
1	1,44 (0,76-2,75)	0,27		
≥ 2	1,83 (0,81-4,14)	0,14		
History of preeclampsia, or pregnancy-induced hypertension				
Yes	1,26 (0,70-2,27)	0,4		
No	Ref.			
History of gestational diabetes				
Yes	1,55 (0,68-3,55)	0,3		
No	Ref.			
Hysterectomy				
Yes	0,65 (0,22-1,90)	0,4		
No	Ref.			
Current or previous hormone replacement therapy				
Yes	0,75 (0,38-1,47)	0,4		
No	Ref.			
Time since menopause				
<5 years	Ref.			
5-10 years	0,73 (0,40-1,38)	0,34		
≥ 10 years	1,04 (0,62-1,74)	0,90		

OR: odds ratio, CI: confidence interval

Multivariable-adjusted model adjusting for age, anthropometric measures (body mass index and abdominal perimeter), cardiovascular risk factors (smoking, hypertension, diabetes mellitus, dyslipidemia and family history of stroke or myocardial infarction, serum creatinine), pregnancy-related complications (preeclampsia, gestational hypertension and gestational diabetes) and time since menopause.