

Parity as predictor of early hypertension during menopausal transition

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Objectives: Studies regarding the effects of parity on blood pressure in later life produced conflicting results. The aim of our study is to analyse whether parity influences the prevalence of hypertension in perimenopausal and postmenopausal women.

Methods: One thousand perimenopausal and postmenopausal women (mean age 55.2 ± 5.4 years) were enrolled with a median follow-up of 63.0 months. The study sample consisted of patients who self-referred, in 1998–2009, to the BenEssere Donna Clinic, dedicated to menopause-related disorders.

Results: One hundred and twenty-two (12.2%) women were nulliparous and 878 (87.8%) had at least one child. Thirty-four (27.9%) women among nulliparous and 326 (37.1%) among parous were hypertensive at baseline ($P=0.046$) and 812 women (81.2%) were in their postmenopausal period. Univariate analysis showed that women with one or more children were at higher risk of being hypertensive [odds ratio (OR): 1.529; 95% confidence interval (CI): 1.006–2.324; $P=0.047$]. Likewise, multivariate analysis revealed that parity (OR: 2.907; 95% CI: 1.290–6.547; $P=0.010$), BMI (OR: 1.097; 95% CI: 1.048–1.149; $P<0.001$) and family history of hypertension (OR: 3.623; 95% CI: 2.231–5.883; $P<0.001$) were independently related to hypertension at baseline. In a subanalysis of 640 initially normotensive women, 109 (17.0%) patients developed hypertension after follow-up, without a statistically significant association with parity (13.6% in nulliparous versus 17.6% in parous; $P=0.362$). Consistently, parity showed no relationship with the incidence of hypertension during follow-up (OR: 1.350; 95% CI: 0.707–2.579; $P=0.363$).

Conclusion: For the first time in a population of White perimenopausal and postmenopausal women, parity was demonstrated to be independently associated with early hypertension during menopausal transition. Conversely, postmenopausal hypertension was not related with parity.

Keywords: early hypertension, menopausal transition, parity, white women

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; DXA, dual-emission X-ray absorptiometry; HDL, high density lipoprotein; HRT, hormonal replacement therapy; LDL, low density lipoprotein; NO, nitric oxide; OR, odds ratio

INTRODUCTION

Hypertension is the most common cardiovascular risk factor for women [1] and both SBP and DBP are continuously and independently related to cardiovascular morbidity and mortality [2]. Blood pressure is affected by a number of traditional cardiovascular risk factors such as age, family history and BMI, but also those parameters related to reproductive history may play a role in hypertension development [3]. Pregnancy produces marked alterations in vascular physiology [4–6] and may be considered as a temporary dip into the metabolic syndrome [7]. It may result in permanent and not just temporary detrimental effects on the body and promote weight gain, insulin resistance and dyslipidemia in later life [8,9]. Hemodynamic adaptations during pregnancy include increases in cardiac output and blood volume and decreases in perfusion pressure and total systemic vascular resistance [4]. Several studies have considered the association between parity and the prevalence of hypertension in later life and results were conflicting [3,4,10,11]. One study reported significant effects of parity on decreases in both SBP and DBP [12], whereas other studies showed no significant association or a clinically small negative relationship between reproductive history and blood pressure or hypertension [10,11,13,14]. Additionally, some studies suggested a protective effect of parity only for younger subgroups of women [10]. Conversely, a study conducted on 126 African-American women demonstrated that as parity increased, SBP increased; however, DBP decreased after three to four children [3]. Similarly, the Trabzon Hypertension Study demonstrated a linear association between parity and the prevalence of hypertension [15]. Finally, considering the association of multiparity with increased BMI in later life [14], it is plausible to hypothesize a relationship between multiparity and hypertension.

The aim of our study is, therefore, to investigate such relationship between parity and hypertension for the first

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time in a population of perimenopausal and postmenopausal women. In addition, our purpose is to analyze the role of parity and compare it with traditional cardiovascular risk factors, such as BMI, family history, dyslipidaemia, previous oral contraceptive use and age at menopause.

METHODS

Population

We retrospectively enrolled all women who presented at the BenEssere Donna Clinic from 1998 to 2011, who reached at least 2 years of follow up in the period from October 2009 to April 2011.

Therefore, we obtained a homogenous and representative sample of white perimenopausal and postmenopausal women. All participants gave their written informed consent to participate in this study and for the processing of personal data. The study protocol was approved from our internal research board.

Study protocol and data collection

We collected personal and anthropometric data of all women and performed a clinical examination, including a 12-lead electrocardiogram. The questionnaire consisted of questions regarding family history (for hypertension, diabetes and cardiovascular disease), clinical history, reproductive life (menarche, menopause, parity and miscarriages) and current drug therapy. In order to allow an adequate cardiovascular risk assessment, women were requested to have recent blood tests containing high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides and glycemia. After anamnestic and clinical evaluation, the cardiologist gave advice regarding lifestyle modifications and prescribed a pharmacologic therapy when indicated. Also bone mineral density, measured with dual-emission X-ray absorptiometry (DXA), and information about use of vitamin D/calcium supplements or bisphosphonates were collected.

Follow-up

All patients were followed up in our outpatient clinic with a clinical examination after at least 2 years. In addition, a telephone interview was done for those patients who failed to present during follow-up in the clinic. Events recorded were incidence of hypertension, hypertensive urgencies and emergencies, myocardial infarction, angina pectoris, transient ischemic attack, stroke, paroxysmal atrial fibrillation, and all other heart diseases that required cardiac surgery.

BenEssere Donna Clinic

The BenEssere Donna Clinic can be considered as the first example of a women's clinic in Italy and it is dedicated to the study, prevention and treatment of cardiovascular menopause-related disorders. Since 1996, this service is open to all perimenopausal and postmenopausal women up to 65 years. Women are initially drawn to the clinic through local media advertising, have free access and can make queries about particular symptoms by taking appointments beforehand. The interconnection with other institutions and services of the hospital makes the BenEssere Donna

a multidisciplinary center dedicated to the identification of key risk factors that arise especially in the postmenopausal period. For example, women at high cardiovascular risk or with metabolic syndrome can be addressed to the cardio-metabolic clinic or to further investigation. These preferential pathways ensure a targeted and complete assessment of the women.

Definitions

Family history of hypertension or diabetes was defined as the presence of hypertension or diabetes diagnosis, respectively, in parents, brothers or sisters, sons or daughters of the patient. Family history for cardiovascular disease was considered positive only when a cardiovascular event occurred in a first-degree relative younger than 56 years old if man and younger than 66 years old if woman [16].

Hypertension was defined through serial blood pressure measurements and in accordance with current guidelines [17–20].

Natural menopause was defined as the permanent cessation of menses as a result of the loss of ovarian follicular activity. It was diagnosed retrospectively after 12 consecutive months of amenorrhea, for which there were no other pathological or physiological cause [21]. Induced menopause was defined as the cessation of menstruation, which follows either surgical removals of both ovaries (with or without hysterectomy) or iatrogenic ablation of ovarian function, for example, by chemotherapy or radiation [21]. According to the Staging of Reproductive Aging Workshop Staging System, the perimenopausal period was divided into early and late menopausal transition. Early menopausal transition begins when cycles remain regular, but their length changes by 7 day or more and the late perimenopausal transition ends 1 year after menopause [22].

The diagnosis of diabetes was made in accordance to the recommendations of American Diabetes Association [23,24].

In order to define the presence of the metabolic syndrome, we adopted the criteria of the American Association of Clinical Endocrinologists [25].

Statistical analysis

We compared two cohorts of patients based on parity (nulliparous women versus women with at least one child). Continuous data are reported as mean \pm SD unless otherwise specified. Categorical data are presented as absolute values and percentages. Comparison of continuous variables was performed by the use of Student's *t*-test or Kruskal–Wallis test in case of nonnormal distribution. Levene test was performed for testing equality of variances. Either Pearson χ^2 test or Fisher's exact test were used as appropriate for comparison of categorical variables.

Variables predictive of events were calculated through univariate analysis by logistic regression and presented with odds ratios (OR) and 95% confidence intervals (CI). Moreover, data were adjusted through a backward stepwise logistic regression.

All tests were two-tailed, and probability was considered to be statistically significant at 0.05. All analyses were performed using SPSS software, version 18.0 for Windows (SPSS Inc., Chicago, Illinois, USA) and STATA/SE software,

version 10.0 for Windows (STATA Corp., College Station, Texas, USA).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

RESULTS

The study population consisted of 1000 patients, with a mean age of 55.2 ± 5.4 years. Mean age at menarche resulted 12.3 ± 1.9 years; the number of deliveries was 1.45 ± 0.85 and the number of miscarriages 0.38 ± 0.75 .

Eight hundred and twelve (81.2%) women were in postmenopausal status at baseline (mean age at menopause 49.5 ± 4.6 years), whereas 188 (18.8%) patients were in their premenopausal period. Of these 188 (fertile) premenopausal women, 167 (88.8%) experienced menopause during follow-up; thus, at the second examination 979 (97.9%) women were in postmenopausal status (mean age at menopause 49.7 ± 4.6 years) and 21 (2.1%) in premenopause. One hundred and one (10.3%) of these 979 postmenopausal women experienced an induced menopause.

Three hundred and sixty (36.0%) patients presented at the BenEssere Donna Clinic with a history of hypertension, diagnosed at a mean age of 50.7 ± 8.4 years, whereas 109 (10.9%) developed hypertension during follow-up. Twenty-one (2.1%) patients had a diagnosis of hypertension at baseline, but after lifestyle modifications and increased physical activity, reported normal blood pressure at the end of follow-up. The prevalence of hypertension in

our population was, therefore, 44.8%, diagnosed at a mean age of 52.6 ± 8.4 years. The median follow-up period was 63.0 months (25–75° percentiles: 42.7–104.0 months).

The study population was divided into two groups, according to parity. One hundred and twenty two (12.2%) women were nulliparous and 878 (87.8%) have had at least one child. Basal characteristics did not differ between the two groups. Conversely, the prevalence of hypertension was significantly higher among parous women: 34 (27.9%) nulliparous versus 326 (37.1%) parous women resulted hypertensive at baseline ($P = 0.046$). Moreover, 107 (87.7%) among nulliparous and 705 (80.3%) among parous women were in their postmenopausal period at baseline ($P = 0.050$) and consistently, nulliparous women showed younger age at menopause (47.6 ± 5.3 versus 49.7 ± 4.4 ; $P < 0.001$). Comparisons between groups are shown in Tables 1 and 2.

Univariate analysis confirmed the relationship between parity and hypertension, pointing out that parous women had a statistically significant increase of estimated risk of hypertension at baseline (OR: 1.529; 95% CI: 1.006–2.324; $P = 0.047$). As expected, results showed that age (OR: 1.040; 95% CI: 1.015–1.065; $P = 0.001$), weight (OR: 1.043; 95% CI: 1.032–1.054; $P < 0.001$), BMI (1.129; 95% CI: 1.097–1.163; $P < 0.001$) and diabetes (OR: 2.360; 95% CI: 1.024–5.438; $P = 0.044$) were related to hypertension at baseline. Metabolic syndrome (OR: 19.764; 95% CI: 11.429–34.178; $P < 0.001$) and family history of hypertension (OR: 2.848; 95% CI: 2.120–3.826; $P < 0.001$) appeared to have the strongest associations with hypertension. Conversely, no relation was evidenced between hypertension and

TABLE 1. Basal parameters of subgroups according to parity

| Parameter | Nulliparous <i>N</i> = 122 | Parous <i>N</i> = 878 | <i>P</i> |
|------------------------------------|----------------------------|-----------------------|----------|
| Personal and anthropometric data | | | |
| Age (years) | 54.5 ± 5.6 | 55.3 ± 5.4 | 0.102 |
| BMI (kg/m^2) | 26.0 ± 5.3 | 26.3 ± 4.7 | 0.438 |
| Reproductive history and menopause | | | |
| Age at menarche (years) | 12.2 ± 1.8 | 12.3 ± 2.0 | 0.358 |
| Miscarriages | 0.4 ± 0.9 | 0.4 ± 0.7 | 0.336 |
| Menopause | 107 (87.7%) | 705 (80.3%) | 0.050 |
| Induced menopause | 18 (16.8%) | 83 (11.8%) | 0.140 |
| Age at menopause (years) | 47.6 ± 5.3 | 49.7 ± 4.4 | <0.001 |
| OC | 59 (48.4%) | 407 (46.4) | 0.677 |
| OC (months) | 62.5 ± 71.1 | 52.0 ± 61.6 | 0.234 |
| HRT | 47 (43.9%) | 296 (42.0%) | 0.705 |
| HRT (months) | 61.5 ± 46.4 | 62.5 ± 50.6 | 0.894 |
| Cardiovascular risk assessment | | | |
| Framingham risk score (%) | 2.3 ± 0.3 | 2.6 ± 0.1 | 0.320 |
| Family history | | | |
| Family history of CVD | 28 (23.0%) | 215 (24.5%) | 0.711 |
| Family history of diabetes | 46 (37.7%) | 290 (33.0%) | 0.306 |
| Family history of hypertension | 77 (63.1%) | 563 (64.1%) | 0.828 |
| Modifiable risk factors | | | |
| Smoking status | 25 (20.5%) | 152 (17.3%) | 0.389 |
| Total cholesterol (mg/dl) | 226.0 ± 38.4 | 227.8 ± 39.9 | 0.664 |
| HDL cholesterol (mg/dl) | 64.9 ± 20.3 | 62.5 ± 14.9 | 0.308 |
| LDL cholesterol (mg/dl) | 145.3 ± 38.3 | 146.6 ± 36.8 | 0.776 |
| Triglycerides (mg/dl) | 98.5 ± 51.1 | 104.3 ± 54.6 | 0.319 |
| Blood glucose (mg/dl) | 93.1 ± 12.5 | 94.1 ± 17.4 | 0.560 |
| Diabetes | 2 (1.6%) | 21 (2.4%) | 0.603 |

CVD, cardiovascular disease; HDL, high density lipoprotein; HRT, hormone replacement therapy; LDL, low density lipoprotein; OC, oral contraceptive. Parameters are expressed as mean value \pm 1 SD or as percentages.

TABLE 2. Prevalence of hypertension at baseline and incidence of hypertension during follow-up according to parity

| Parameter | Nulliparous | Parous | P |
|---|-------------|-------------|-------|
| | N=122 | N=878 | |
| Hypertension at baseline | 34 (27.9%) | 326 (37.1%) | 0.046 |
| Hypertension after FU | 44 (36.1%) | 404 (46.0%) | 0.038 |
| Incidence of hypertension | 12 (9.8%) | 97 (11.0%) | 0.687 |
| Subanalysis of initially normotensive women (N=640) | | | |
| | N=88 | N=552 | |
| Incidence of hypertension during FU | 12 (13.6%) | 97 (17.6%) | 0.362 |

FU, follow-up.

menopause ($P=0.777$) or hormone replacement therapy ($P=0.282$). On the contrary, LDL/HDL ratio (OR: 1.423; 95% CI: 1.202–1.684; $P<0.001$), triglycerides (OR: 1.009; 95% CI: 1.006–1.012; $P<0.001$) and blood glucose (OR: 1.017; 95% CI: 1.006–1.027; $P=0.001$) were related to hypertension. Finally, as expected, the higher Framingham Risk Score, the higher risk of being hypertensive. Results are shown in Table 3.

Backward multivariate logistic regression analysis confirmed results with regard to parity, indeed it showed an independent association with hypertension (OR: 2.907; 95% CI: 1.290–6.547; $P=0.010$), even stronger compared with the univariate. Consistently, metabolic syndrome (OR: 17.252; 95% CI: 7.057–42.178; $P<0.001$) and family history of hypertension (OR: 3.623; 95% CI: 2.231–5.883; $P<0.001$) remained the strongest predictors of being hypertensive at baseline. Results are shown in Table 4 and Fig. 1.

Comparisons between groups according to parity revealed that parous women had higher prevalence of hypertension not only at baseline, but also after follow-up: 404 (46.0%) women among parous versus 44 (36.1%) women among nulliparous were hypertensive after follow-up. Despite this, the incidence of hypertension did not differ between groups ($P=0.687$). Results are shown in Table 2.

TABLE 3. Univariate analysis for hypertension at baseline

| Parameter | OR | 95% CI | P |
|--------------------------------|--------|---------------|--------|
| Age | 1.040 | 1.015–1.065 | 0.001 |
| Weight | 1.043 | 1.032–1.054 | <0.001 |
| BMI | 1.129 | 1.097–1.163 | <0.001 |
| Metabolic syndrome | 19.764 | 11.429–34.178 | <0.001 |
| Diabetes | 2.360 | 1.024–5.438 | 0.044 |
| Parity | 1.529 | 1.006–2.324 | 0.047 |
| Menopause | 1.049 | 0.753–1.462 | 0.777 |
| HRT | 0.865 | 0.663–1.127 | 0.282 |
| Family history of hypertension | 2.848 | 2.120–3.826 | <0.001 |
| Family history of diabetes | 0.926 | 0.703–1.218 | 0.581 |
| Family history of CVD | 1.306 | 0.971–1.757 | 0.077 |
| Total cholesterol | 1.000 | 0.997–1.004 | 0.961 |
| LDL cholesterol | 1.002 | 0.998–1.006 | 0.413 |
| HDL cholesterol | 0.969 | 0.959–0.980 | <0.001 |
| LDL/HDL cholesterol | 1.423 | 1.202–1.684 | <0.001 |
| Triglycerides | 1.009 | 1.006–1.012 | <0.001 |
| Blood glucose | 1.017 | 1.006–1.027 | 0.001 |
| Framingham risk score | 1.650 | 1.478–1.842 | <0.001 |

CVD, cardiovascular disease; HDL, high density lipoprotein; HRT, hormone replacement therapy; LDL, low density lipoprotein.

Prospective analysis

We performed a subanalysis of our population, considering 640 initially normotensive women, stratified for parity into two groups. Eighty-eight (13.8%) women were nulliparous and 552 (86.2%) have had at least one child. Basal characteristics did not differ between nulliparous and parous women, respectively, with the exception of age (53.7 ± 5.0 versus 55.0 ± 5.3 ; $P=0.030$), menopause [78 (88.6%) versus 440 (79.7%); $P=0.048$] and age at menopause (47.9 ± 4.6 versus 49.5 ± 4.4 ; $P=0.003$).

Analysing the incidence of hypertension during follow-up within these groups, there were no differences with regard to parity ($P=0.362$). Results are shown in Table 2.

At univariate analysis parity did not show any association with the incidence of hypertension during follow-up (OR: 1.350; 95% CI: 0.707–2.579; $P=0.363$). Conversely, BMI (OR: 1.074; 95% CI: 1.027–1.124; $P=0.002$), family history of hypertension (OR: 1.667; 95% CI: 1.083–2.567; $P=0.020$) and Framingham-risk score at baseline (OR: 1.183; 95% CI: 1.016–1.378; $P=0.030$) resulted related with the incidence of hypertension during follow-up.

Finally, after backward stepwise adjustment, parity was excluded from being a significant predictor of hypertension. Results of multivariate analysis are shown in Table 5. Those parameters associated with the incidence of hypertension during follow-up were age (OR: 1.067; 95% CI: 1.012–1.125; $P=0.016$), BMI (OR: 1.090; 95% CI: 1.027–1.158; $P=0.005$) and family history of hypertension (OR: 2.193; 95% CI: 1.208–3.979; $P=0.010$), as well as total (OR: 1.039; 95% CI: 1.013–1.067; $P=0.003$), HDL (OR: 0.970; 95% CI: 0.944–0.996; $P=0.026$) and LDL cholesterol (OR: 0.963; 95% CI: 0.938–0.990; $P=0.007$).

DISCUSSION

Our study, for the first time in a population of white perimenopausal and postmenopausal women, demonstrated the association of parity with early hypertension during menopausal transition; particularly, women with at least one child had almost three-fold risk of being hypertensive compared with nulliparous women. Conversely, the incidence of hypertension during follow-up was not related with parity, so that the influence of parity seemed to play its role within perimenopause and not after menopause.

Our results are consistent with other studies indicating a linear association between parity and the prevalence of hypertension [15] or showing increased SBP with increased parity [3]; conversely, Gunderson *et al.* [4] stated that a first birth may be accompanied by persistent lower levels of

TABLE 4. Multivariate backward regression analysis for hypertension at baseline

| Parameter | OR | 95% CI | P |
|--------------------------------|--------|--------------|--------|
| BMI | 1.097 | 1.048–1.149 | <0.001 |
| Metabolic syndrome | 17.252 | 7.057–42.178 | <0.001 |
| Diabetes | 0.170 | 0.030–0.952 | 0.044 |
| Parity | 2.907 | 1.290–6.547 | 0.010 |
| Family history of hypertension | 3.623 | 2.231–5.883 | <0.001 |
| Family history of diabetes | 0.547 | 0.340–0.880 | 0.013 |
| Total cholesterol | 0.952 | 0.929–0.975 | <0.001 |
| LDL cholesterol | 1.034 | 1.011–1.059 | 0.004 |
| HDL cholesterol | 1.058 | 1.030–1.087 | <0.001 |
| Framingham risk score | 1.945 | 1.651–2.290 | <0.001 |

HDL, high density lipoprotein; LDL, low density lipoprotein.

blood pressure from preconception to years after delivery. It is well known that pregnancy leads to increased blood volume and decrease in systemic vascular resistance, together elevating utero-placental blood flow without compromising maternal circulation [5,6]. Thus, the issue is whether these physiologic cardiovascular adaptations leave a lasting imprint on arterial compliance and endothelial function. Dhawan *et al.* [26] found greater pressure responses to phenylephrine and acute stress in repeatedly bred versus virgin rats and speculated that this augmented response of multiparous rats may be ascribed to a greater increase in total peripheral resistance. Indeed, they hypothesized that repeated pregnancy may blunt the activity of the vasodilatory NO system and enhance the productions of vasoconstrictive prostaglandins. Another study conducted on female rats by Reckelhoff *et al.* [27] suggested that pregnancy might leave the vessels with some degree of endothelium damage, which could be responsible for subsequent endothelium dysfunction. These evidences are consistent with our results and also propose possible mechanisms by which parity may be related with higher prevalence of hypertension in later life. Our study has the peculiarity of analysing the prevalence of hypertension through menopausal transition, intended as a period of

potential vulnerability across women's life span. Our main findings suggest that the association between parity and hypertension is already evident during menopausal transition and not after menopause. Conversely, when high blood pressure develops after menopause, there is no association with parity. It is the first time this relationship between parity and hypertension has been investigated specifically through menopausal transition and early postmenopause. Several studies analyzed the impact of childbearing on BMI and the incidence of the metabolic syndrome. The Coronary Artery Risk Development in Young Adults study showed that parity was associated with future development of the metabolic syndrome independent of prior obesity and pregnancy-related weight gain [28]. Similarly, the Guangzhou Biobank Cohort Study stated that higher parity was related to a consistent increase in the risk of metabolic syndrome in Chinese women [14]. Given this and considering that pregnancy may have detrimental effects on fat distribution and insulin resistance, it might be plausible that parity increases women's risk of hypertension in terms of higher BMI and incidence of the metabolic syndrome. Despite this, in our population there is no difference in terms of BMI in nulliparous versus parous women. Indeed, the relationship between parity and

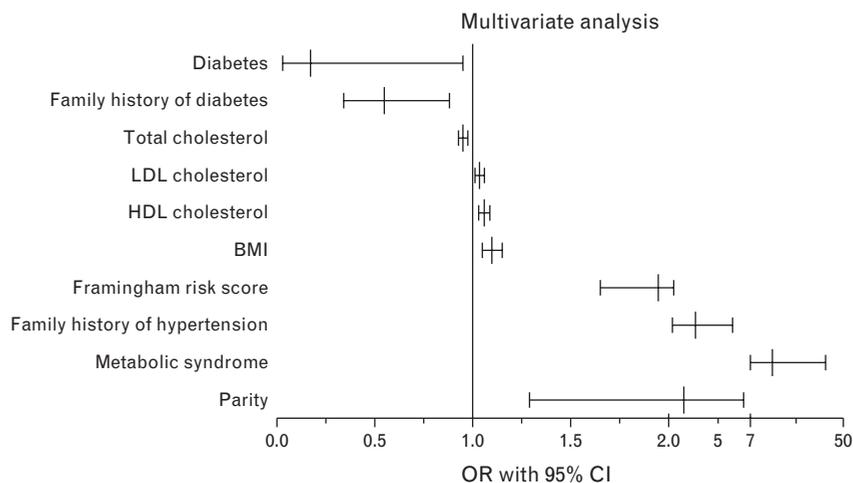
**FIGURE 1** Multivariate analysis for hypertension at baseline.

TABLE 5. Multivariate backward stepwise analysis for hypertension development in prospective subpopulation

| Parameter | OR | 95% CI | P |
|--------------------------------|-------|-------------|-------|
| Age | 1.067 | 1.012–1.125 | 0.016 |
| BMI | 1.090 | 1.027–1.158 | 0.005 |
| Family history of hypertension | 2.193 | 1.208–3.979 | 0.010 |
| Total cholesterol | 1.039 | 1.013–1.067 | 0.003 |
| LDL cholesterol | 0.963 | 0.938–0.990 | 0.007 |
| HDL cholesterol | 0.970 | 0.944–0.996 | 0.026 |

HDL, high density lipoprotein; LDL, low density lipoprotein.

hypertension remains significant after adjustment for other confounding effects, especially BMI, and these evidences refute the hypothesis that higher blood pressure among parous women is due to a worse metabolic profile. Moreover, there are no differences regarding lipid and glucose profile according to parity.

Demonstrating that parous women are at higher risk of being hypertensive, our study also supports the hypothesis that pregnancy may influence future cardiovascular risk profile of the mother. Nevertheless, it is the first study identifying this increased risk due to higher blood pressure. In fact, other studies suggested adverse lipid profile and diabetes as responsible for increased coronary heart disease [8] or carotid artery plaques in elderly women [29].

Nulliparous women were more likely to be postmenopausal at baseline and menopause occurs 2 years later among women with at least one child: this is coherent with the evidence that during pregnancy ovarian follicles are preserved. Despite this difference in age at menopause according to parity, no relation has been highlighted with the prevalence of hypertension. Our study agrees with those indicating no association between menopause and hypertension and showing high blood pressure after menopause is due to increasing age and BMI [30].

Apart from parity, also traditional cardiovascular risk factors such as metabolic syndrome, BMI and diabetes showed an independent relationship with hypertension at baseline. Family history of hypertension was found to be the strongest predictor of estimated hypertension risk, increasing it more than three-fold.

Our study has some limits. First of all, it is an observational study, only partially prospective; therefore, it is able to provide associations, but not to prove a causal relationship between parity and hypertension. This study design, however, allow us to explore the specific issue of parity impact across menopausal transition. As it is a retrospective study, data regarding pregnancy-induced hypertension that resolved with the end of pregnancy and gestational diabetes are lacking. On the contrary, we gathered data regarding the age of hypertension development. Indeed, in our database are reported cases of women who developed pregnancy-induced hypertension and remained hypertensive after pregnancy. Moreover, we collected data regarding previous hormonal replacement therapy and the duration of treatment, although information about the timing of treatment are lacking.

Although the majority of the studies analyzed SBP and DBP levels, we took into consideration only hypertensive or normotensive status. SBP and DBP, indeed, vary greatly according to the time of the day and emotional status,

making the prevalence of hypertension a much more reliable parameter. Hormonal measurements, such as FSH, have not been performed. Hormone assays would have been helpful for the identification of the stages of reproductive aging and it would be appropriate and interesting to investigate these parameters in the comparison between groups. Nevertheless, biomarker criteria are only supportive for identification of the stages of reproductive aging [22] and considering that the main target of BenEssere Donna Clinic is cardiovascular prevention, such tests are not routinely performed, according to current guidelines [31]. A limitation of our study is that marriage status has not been taken into account, as well as data regarding the age of the first pregnancy and whether parity was due to choice or infertility. We did not take into account thyroid function, although it is well known that any type of thyroid dysfunction may reduce the likelihood of pregnancy, so that it would be very interesting to investigate this issue in relation with hypertension in future. Finally, a strength of our study is the relatively large and homogeneous sample, representative of a real-life population of women around menopause, which are still underrepresented in clinical trials [32].

In conclusion, parity is associated with early hypertension during menopausal transition in white perimenopausal and postmenopausal women, so that women with at least one child had almost three-fold risk of being already hypertensive compared with nulliparous women. Conversely, newly diagnosed hypertension after menopause is not related with parity.

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Conflicts of interest

There are no potential conflicts of interest that relate to the manuscript, and there were no extramural sources to support this research.

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Reviewer's Summary Evaluations

Referee 1

Strengths: The results are based on a large-scale study and describe a relatively novel finding, associating parity with

hypertension. Weaknesses: retrospective analysis based on patient records, lack of information on possible confounders.