OBSTETRICS

Cerebral white matter lesions and perceived cognitive dysfunction: the role of pregnancy

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OBJECTIVE: Women who suffered eclampsia or preterm preeclampsia are twice as likely to demonstrate cerebral white matter lesions (WML) on magnetic resonance imaging compared with age-matched women who had normotensive pregnancies, and they report more cognitive dysfunctions in everyday life. We aimed to determine whether pregnancy in and of itself has a relationship with the presence of WML and subjective cognitive dysfunction.

STUDY DESIGN: Eighty-one parous women who had a normotensive pregnancy were matched for age with 65 nulliparous women and all underwent cerebral magnetic resonance imaging. Presence of cerebral WML was rated and blood pressure was measured. Subjective cognitive functioning was assessed using the Cognitive Failures Questionnaire.

RESULTS: There was no difference in the presence (22% vs 19%) of WML between parous and nulliparous women. Age was a predictor for the presence of WML, whereas the presence of current hypertension was not. Average score on the Cognitive Failures Questionnaire was not different between both groups, nor related to WML.

CONCLUSION: A history of pregnancy in and of itself is not related to the presence of cerebral WML and the perception of cognitive dysfunction. Because of the relationship with preterm preeclampsia and eclampsia, future research should focus on the clinical importance and development throughout the years of such cerebral WML in young women and focus on risk factors for cardiovascular disease.

Key words: cerebral white matter lesions, cognitive functioning, preeclampsia, pregnancy, young adulthood

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With the aging population, diseases such as dementia and stroke will become major health issues in the near future. A feature of such conditions is that preclinical structural cerebral changes, such as white matter lesions (WML), may be present years before a clinically recognizable disease. The presence of such WML may be an important risk marker for the development of cognitive impairment, vascular dementia, Alzheimer's disease and stroke.[1-4] In individuals in their 50s and 60s, WML are especially seen in combination with risk factors for small vessel disease such as hypertension and diabetes.[3-5]

WMLs are a frequent neuroimaging finding in elderly individuals, but their prevalence as well as their relationship with cognitive dysfunction in younger asymptomatic populations is unknown.[6] The prevalence of WML and perceived cognitive dysfunction in women who experienced (pre)eclampsia has recently been investigated by our group.[7-11] Women who had (pre)eclampsia report cognitive problems years following the index pregnancy, which appear to be related to memory, concentration, and vision-related tasks of everyday life.[9-11] In addition, women who had eclampsia, or preterm preeclampsia (<37 weeks), appeared twice as likely to demonstrate WML compared with age-matched women who had normotensive pregnancies.[7,8] The relationship between WML and perceived cognitive dysfunction in women who had preeclampsia/eclampsia is the focus of our ongoing work. Although a direct causal relationship remains to be elucidated, we hypothesize that an underlying predisposition for vascular disease contributed to both the development of (pre)eclampsia as well as WML. However, in our previous studies, we found that 1 in 5 women who experienced a normotensive pregnancy also had WML at an average age of 37. This raises the question whether pregnancy and parity in and of itself have a relationship with the presence of such lesions and the perception of cognitive difficulties.

Therefore, the aim of this study was to compare the prevalence of cerebral WML in women who had normotensive

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pregnancies compared to nulliparous women and to determine the relationship with self-perceived cognitive dysfunction.

MATERIALS AND METHODS

Participants

Participants who had a normotensive pregnancy formed the control group in follow-up studies assessing cerebral long-term consequences of preeclampsia. Recruitment and selection criteria have been published previously.[7-9,12] This project was approved by the University Medical Center Groningen Institutional Review Board and all women signed informed consent.

Seventy-five parous controls from our previous studies that underwent magnetic resonance imaging (MRI) and 6 additional parous controls were included, leaving 81 controls for analysis. Nulliparous women were recruited between March 2012 and June 2013 by means of an invitation in local newspapers, on the Internet and among hospital personnel. Nulliparous women willing to participate were matched for age (± 2 years) and level of education to 1 of the parous women. A total of 65 women of 134 eligible nulliparous women who responded to the recruitment advertisement could be matched and did not have MRI contraindications. There were 20 parous women who did not complete the Cognitive Failures Questionnaire (CFQ), (n = 60).

Women were excluded if they had MRI contraindications, neurologic disorders such as epilepsy, demyelinating disorders, a known cerebrovascular accident, intracranial infections or a history of any intracranial surgery, or were currently pregnant. Nulliparous women were excluded if they had experienced a pregnancy of >12 weeks duration, or if they had recent contact with a hospital concerning fertility treatment or diagnostic procedures.

All patients completed a short questionnaire about their current and past medical health. At the time of imaging, weight, and blood pressure (manually, using an aneroid sphygmomanometer) were measured. Current hypertension was defined as a blood pressure of ≥140/90 mm Hg and/or current antihypertensive medication use.

MRI protocol

Participants were invited to the 3-T MRI facilities (Philips Intera; Philips Medical Systems, Best, The Netherlands) of the Neuro-Imaging Center of the School for Behavioral and Cognitive Neurosciences in Groningen. The MRI protocol has been previously published by our group.[7,8]

An experienced neuroradiologist rated the prevalence, size, and number of WML and other structural brain abnormalities. WML were considered to be present if hyperintense on fluid-attenuated inversion recovery, proton density-weighted, and T2-weighted images and not as hypointense as liquor on T1-weighted images. A correction for inclusion of partial volume misclassification was made as described previously.[8]

Subjective cognitive functioning

The CFQ evaluates the number of errors committed in the completion of daily tasks.[13] Subjects were asked to complete the questionnaire based on their experiences in the past 6 months. The CFQ consists of 25 items, each scored on a 5-point scale (0-4). The total scale ranges from 0−100, with higher scores indicating more cognitive failures. A cutoff point for high CFQ total scores based on the Dutch population was set at ≥44, indicating cognitive problems.[14]

The CFQ was developed as a valid self-report instrument to measure the tendency to make mistakes in everyday life.[13] In a healthy population, the CFQ is a valid measure of a stable cognitive resource that is involved in attention, memory, and action in daily life, with good test-retest reliability for groups of individuals and good internal reliability.[15]

Statistical analysis

To achieve sufficient statistical power with α of .05 and β of .20, a total sample size of 150 women was needed to detect a difference in prevalence of WML of 20% (1-sided test), based on the difference found in our previous studies in eclamptic/preeclamptic women (41/37%) as compared with controls (21%).[7,8] In addition, with α of .05 and β of .20, we estimated that a total sample size of 100 women was needed to detect a difference in CFQ score (1-sided test) of 7 with a standard deviation of 14.[9]

Statistical analysis was performed using IBM SPSS Statistics for Windows version 20 (IBM Corp., Chicago, IL). All data were checked for normality of distribution using Shapiro-Wilk test and Levene's test for homogeneity of variance. Demographic data were compared using χ^2 test for categorical data or Student t test for normally distributed data. The presence of WML was compared between groups using χ^2 test. CFQ total score was analyzed using Student t test, χ^2 test was used for cutoff scores. Univariate and multivariate regression analyses were used to identify possible determinants related to the presence of WML (binary logistic regression) and CFQ score (linear regression), ie, age, current hypertension, migraine, smoking, and weight. A determinant was selected for the multivariate analysis if $P < .25$ in the univariate regression.

RESULTS

Participants

In total, 81 parous and 65 nulliparous women with an average age of 37 years underwent cranial MRI. Groups were not significantly different as to weight, current hypertension, and smoking (Table).

White matter lesions

WML were present in 18 (22%) parous and 12 (19%) nulliparous women ($P = .58$). Small lesions were present in 10 (12%) parous and 10 (15%) nulliparous women ($P = .61$). Medium or large lesions were present in 11 (14%) parous and in 7 (11%) nulliparous women ($P = .60$). Presence of WML within the parous group was not different between women who experienced 1 (8; 20%) vs multiple pregnancies (10; 24%) ($P = .64$). Univariate regression analysis revealed that age, odds ratio (OR), 1.07; 95% confidence interval, 1.01−1.13; $P = .03$, was a significant predictor for the presence of WML. The Figure shows the distribution of WML according to age in parous and nulliparous women.

TABLE
Overview of participant characteristics

Characteristic	Parous women (n = 81)	Nulliparous women (n = 65)	*P* value
Age (total range, 21–59), y	37 (6.9)	37 (7.9)	.81
White ethnicity	75 (93%)	63 (97%)	.25
Weight, kg	72 (10.8)[a]	73 (17.3)	.59
Current hypertension	8 (10%)[b]	8 (13%)[c]	.60
Smoking	13 (16%)	8 (12%)	.52
History of migraine	17 (21%)	15 (24%)	.69
Elapsed time since index pregnancy, y	6 (4.9)		
Primipara	40 (49)		

Results are expressed as mean (SD) or number (percentage).

[a] n = 80; [b] n = 78; [c] n = 61.

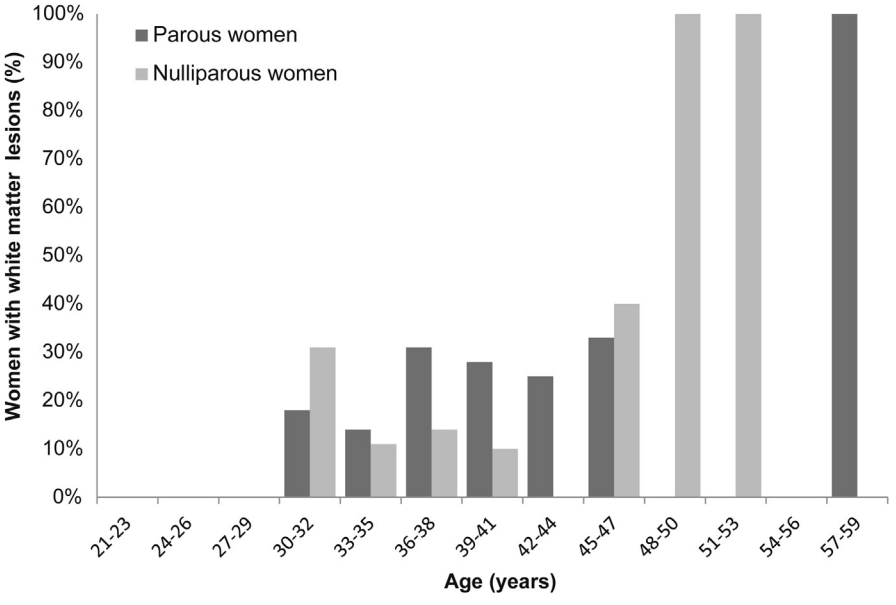
Postma. Cerebral white matter lesions following pregnancy. Am J Obstet Gynecol 2014.

Subjective cognitive functioning

A total of 125 women (60 parous and 65 nulliparous women) completed the CFQ. There was no significant difference in CFQ total score between the groups (36 ± 11.0 for parous women and 33 ± 9.6 for nulliparous women, $P = .16$). No difference was found in the percentage of women scoring higher than the cutoff score ≥44 (indicating cognitive problems): 11 (18%) parous women and 8 (12%) nulliparous women, $P = .35$.

The presence of WML was not related to subjective cognitive function (CFQ score 34 ± 7.5 for women with WML and 35 ± 10.9 for women without WML), $P = .77$. Subjective cognitive function was not significantly different within the parous group between women who experienced 1 vs multiple pregnancies (CFQ score of 36 ± 11.2 and 35 ± 11.1, respectively), $P = .75$. Univariate regression analysis revealed that none of the determinants in the equation were a significant predictor for CFQ scores.

FIGURE
White matter lesions and age distribution



Percentage of white matter lesions according to age in parous and nulliparous women.

Postma. Cerebral white matter lesions following pregnancy. Am J Obstet Gynecol 2014.

Comment

This study demonstrates that approximately 1 in 5 women in a population-based cohort with an average age of 37 have WML independent of pregnancy in and of itself. Furthermore, this study confirms that the prevalence of WML is associated with increasing age. Neither the prevalence of WML in this age category nor a history of pregnancy on average 6 years prior had any relationship with perceived cognitive failures in daily life.

Previous studies demonstrated brain WML twice as often in formerly eclamptic women and women with preterm preeclampsia compared with women following normotensive pregnancies.[7,8] An increased propensity for vascular disease in women with a history of preeclampsia may be an associated factor in the development of such lesions even though their pathogenesis has not become clear to date.[16] The present study shows that the presence of WML seems independent of pregnancy and parity.

The prevalence of WML in one-fifth of participants in this study with an average age of 37 years (range, 21–59 years) is remarkable. Many studies have reported a high prevalence of WML in the elderly from 22.7% up to 100% in individuals aged 60 and over.[1,6,17-23] Few studies have been performed in younger cohorts; the reported prevalence at <40 years of age is 0.5%-32%.[19,24-29] Differences in prevalence in the abovementioned studies might be due to different MRI field strengths and scanning sequences, different methods of WML rating, presence or absence of cardiovascular risk factors and differences in age range. For instance, 2 studies that found lower prevalence rates excluded patients with cardiovascular risk factors.[20,29] Higher prevalence in females compared with males has been reported in some, but not all studies.[5,6,23,29,30] The

present study showed that WML presence was related to increasing age (OR, 1.06), which is comparable to the OR found in the study of Chowdhury et al,[20] however, lower than in some other studies,[21,29] which may be due to inclusion of different age ranges. The present study failed to show a significant effect of blood pressure on the presence of WML, although this relationship has been often described in the literature as well as in prior studies of our own group.[8,31,32] This might be due to the relatively young and healthy population in the cohort now reported and, subsequently, the small number of women with hypertension, which is similar to the prevalence in the general Dutch population.[33] In this study, we found no effect of parity on WML presence. Parity seems associated to cardiovascular disease in later life,[34] however, this association may be due to socioeconomic variables and may only hold true for women with $\geq$4 pregnancies, which were not present in our study.

The clinical implications of WML in young women are only speculative so far and are subject of further investigation. In the elderly, WML are related to cognitive decline and dementia.[35] Although perceived cognitive failures in formerly eclamptic and preeclamptic women have been previously reported,[9,10,36] minor neurocognitive impairment was found on neurocognitive tests.[37-39]

Up to several months postpartum, women frequently report cognitive deficits, which are clustered under the terms 'mommy brain' or 'maternal amnesia'.[40] Postpartum women indeed show a small, but significant, impairment on some measures of cognition that place relatively high demands on executive cognitive control.[40] The animal literature views cognitive changes occurring during pregnancy and postpartum from an adaptive perspective. Rather than being a negative consequence of pregnancy, these cognitive changes may be seen as cognitive reorganization based on structural changes in the form of neuronal plasticity, in which social cognition that is relevant to maternal or fetal well-being is enhanced to the cost of other cognitive tasks.[40] In humans, fMRI studies investigating the parental response to infants show increased gray matter volumes in large regions of the prefrontal cortex, parietal lobe, and midbrain suggesting similar neuronal plasticity in humans.[41,42] Prenatal hormone levels seem to play a role in these changes.[43]

Although such adaptations have not been assessed longitudinally, one could expect these postpartum cognitive changes to have subsided 6 years following pregnancy and indeed, we did not find significant differences in CFQ scores between parous and nulliparous women. In this study, we found no effect of parity on CFQ scores. Glynn[44] found that adverse effects of pregnancy on memory function are compounded with successive pregnancies. However, these measurements were only performed during gestation and at 3 months postpartum, but not more than 1 year postpartum.

To our knowledge, this is the first study to assess the long-term relationship between pregnancy and WML as well as subjective cognitive function. Moreover, it is one of the few studies in the literature to date to report on the relationship of WML and subjective cognitive dysfunction in such a young cohort in general. There are some methodologic limitations to this study; no imaging data of the parous participants are available before their index pregnancy. Whether WML were present before pregnancy is therefore unknown. Second, determinants related to cardiovascular disease other than included in this study may play a role, such as blood glucose, family history, physical activity, and hyperlipidemia. Even though the current study used a state of the art 3-Tesla MRI scanner, we cannot exclude that pregnancy does induce long-term structural brain changes. If so, such changes likely develop on a micro level and below a threshold for detection by the current state of the art neuroimaging techniques.

The examination of WML and their possible neurocognitive sequelae in younger individuals is important for a variety of reasons. It may help to understand the pathogenesis of such lesions and identify potentially modifiable factors in the early stages of their development. Moreover, because the presence of neuropsychiatric syndromes like Alzheimers, vascular dementia, and depression have been related to WML the functional consequences of these lesions in midlife are of utmost interest.[1,3,4,31] This age group should therefore be the focus of further work to identify risk and protective (modifiable) factors as it may prove to be the age at which preventive strategies need to be introduced to have an optimal impact on brain health in the future. ■

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