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.