OBSTETRICS

Pregnancy in advanced age and the risk of stroke in postmenopausal women: analysis of Women's Health Initiative Study

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BACKGROUND: The incidence of pregnancy in advanced age among women is increasing because of the availability of assisted reproduction, although the long-term health consequences are not known.

OBJECTIVE: The purpose of this study was to determine the effect of pregnancy in advanced age on the occurrence of cardiovascular events in a large cohort of postmenopausal women.

STUDY DESIGN: We analyzed the data for 72,221 women aged 50-79 years who were enrolled in the observational arm of the Women's Health Initiative study. We determined the effect of pregnancy in advanced age (last pregnancy at age ≥40 year) on the risk of ischemic stroke, hemorrhagic stroke, myocardial infarction, and cardiovascular death over a mean period (±standard deviation) of 12±1 years using Cox Proportional Hazards analysis after adjusting for potential confounders.

RESULTS: A total of 3306 of the 72,221 participants (4.6%) reported pregnancy in advanced age. Compared with pregnancy in normal age, the rates of ischemic stroke (3.8% vs 2.4%), hemorrhagic stroke (1.0% vs 0.5%), and cardiovascular death (3.9% vs 2.3%) were significantly higher among women with pregnancy in advanced age. In multivariate analysis, women with pregnancy in advanced age were 50% more likely to experience a hemorrhagic stroke (hazard ratio, 1.5; 95% confidence interval, 1.0−2.1) after adjustment for age, race/ethnicity, congestive heart failure, systolic blood pressure, atrial fibrillation, alcohol use, and cigarette smoking. There was no significant difference in the risk of ischemic stroke, myocardial infarction, and cardiovascular death among women with pregnancy in advanced age after adjustment for potential confounders.

CONCLUSION: Women with pregnancy at an advanced age have a higher risk for hemorrhagic stroke in the postmenopausal period.

Key words: cardiovascular death, hemorrhagic stroke, ischemic stroke, postmenopausal, stroke

There is an increasing number of women with pregnancy and childbirth in the fourth decade of life for different reasons.[1-3] In United States between 2007 and 2011, birth rates have decreased for all women aged <35 years, unchanged for women aged 35−39 years, and increased for women aged 40−44 years.[4] Several studies have found increased rates of stillbirth, perinatal death, preterm birth, low birthweight, and maternal complications such as gestational diabetes mellitus and hypertension, preeclampsia, and need for interventions such as cesarean delivery among women ≥40 years.[5-9] The rate of stroke and myocardial infarction during pregnancy and puerperium is higher among women with pregnancy in advanced age.[10-12] Preconception counselling regarding the short-term risks of pregnancy that are associated with advanced maternal ages is recommended for women >40 years.[13] However, the long-term health consequences in women with pregnancy in advanced age are not known.

We performed this study to determine the effect of pregnancy in advanced age on long-term occurrence of cardiovascular events in a large cohort of postmenopausal women.

Materials and Methods

We analyzed the data for 93,676 women aged 50−79 years who were enrolled in the observational arm of the Women's Health Initiative Study.[14,15] Study participants were enrolled at 40 centers throughout the United States between October 1, 1993, and December 31, 1998. All participants provided informed consent using materials approved by Institutional Review Boards at each center. Women who had never been pregnant were excluded from the analysis.

Baseline evaluation

Standardized questionnaires were used at baseline assessment to assess demographic and clinical data and data regarding family and medical history. Data were acquired based on self-report with the use of standard questionnaires. For other data, certified staff members took physical measurements that included blood pressure, height, and weight and collected blood samples at the clinic visit.[16] The participants were asked how old they were at the end of the last pregnancy; response was sought in following age groups: <20, 20−24, 25−29, 30−34, 35−39, 40−44, and ≥45 years. Use of oral anticoagulant was ascertained from the Medication and Supplement Inventory, which was collected once at baseline and subsequently at year 3. We categorized the participants into 2 groups based on the response: those aged <40 years and those aged ≥40 years at the time of the last pregnancy.

Cardiovascular events ascertainment

The participants were followed for 8−12 years. Annual mailed follow-up forms updated information on hormone treatment and other selected risk factor information and facilitated structured

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initial reporting of clinical events.[17] Specific details of myocardial infarction (MI) and stroke-related hospitalizations were obtained if applicable via a standardized questionnaire that was administered by phone, in-person interview, or self-completed form.[17] Portions of the medical record (discharge summary and results of relevant diagnostic and laboratory tests) were reviewed by a designated local adjudicator for conformation of event.

The local adjudicator classified incident stroke events into ischemic stroke and hemorrhagic stroke (included both intracerebral and subarachnoid hemorrhages) based on the results of neuroimaging tests. Central oversight was provided by review of a fraction of the stroke events in the observational study by central neurologists to ensure quality of stroke event classification.[17] An incident cardiovascular heart disease event during follow-up period was defined as the first-time occurrence of either (1) acute MI that required overnight hospitalization, (2) coronary revascularization procedures, which included percutaneous transluminal coronary angioplasty, stent placement, and coronary artery bypass graft surgery, or (3) coronary death. MI was identified if the level of any cardiac enzyme (creatine kinase, lactate dehydrogenase, troponin, or myoglobin) was $\geq$2 times the upper limit when participant had ischemic symptoms or if the level were 1−2 times the upper limit of normal with Q waves or ST segment or T wave abnormalities that were suggestive of an MI or if enzymes were normal or absent; however, evolving Q-wave and evolving St segment or T wave abnormalities were documented. For any death event, information was obtained on any outcomes that occurred between the participant's last routine contact and her date of death. Data linkage with the National Death Index of the National Center for Health Statistics was used to ascertain survival and cause of death for all Women's Health Initiative study participants. Women's Health Initiative study participants who are lost to follow up or who were known to be dead were matched to the National Death Index to search for otherwise unreported deaths and to ascertain causes of death.

Statistical analysis

Cox proportional hazards analysis was used to estimate the hazard ratio (HR) for ischemic stroke, hemorrhagic stroke, MI, and cardiovascular death using the IBM SPSS statistical software (IBM Corp, Armonk, NY). The time-to-event variable was calculated from time enrolled in the study to time of endpoint occurrence. For those subjects without the event, the follow-up period was censored at last known follow-up or death. We calculated the HR for last pregnancy at maternal age of $\geq$40 years using last pregnancy at age <40 years as reference. The potential confounders were identified from univariate analysis of demographic and clinical variables between women with last pregnancy at age of $\geq$40 years compared with those at age <40 years. We used chi-square and analysis of variance tests for categoric and continuous variable comparisons, respectively. The Cox proportional hazards model were adjusted for differences in age, ethnicity (American Indian/Alaskan native, Asian/Pacific islander, black/African American, Hispanic/Latino, white [not Hispanic Origin], others), systolic blood pressure (<140 or $\geq$140 mm Hg), cigarette smoking (never, past, <1 pack per day, $\geq$1 pack per day), congestive heart failure, atrial fibrillation, alcohol use (nondrinker, past drinker, <1 drink per day, $\geq$1 drink per day), anticoagulant use recorded at baseline or 2 subsequent ascertainments (mentioned earlier), and other variables that were significantly different in univariate analysis. We adjusted for age as a time-dependent covariate in the model. We calculated 95% confidence intervals (CI) using a Taylor series approximation for the standard error of the HR. In an exploratory analysis, we entered oral anticoagulant use (at baseline or at follow-up ascertainment as mentioned earlier) to the model to adjust for any confounding effect on the relationship between last pregnancy at age of $\geq$40 years and hemorrhagic stroke. In another exploratory analysis, we also performed another Cox proportional hazards analysis to evaluate the effect of last pregnancy at maternal age of $\geq$40 years on a combined endpoint of cardiovascular death with ischemic stroke, hemorrhagic stroke, or MI.

Results

Of the 93,676 participants in the Women's Health Initiative observational study, 72,221 reported $\geq$1 pregnancy; 21,455 women were excluded because they either did not report age at last pregnancy or were never pregnant. A total of 3306 of the 72,221 participants (4.6%) reported last pregnancy at age $\geq$40 years. The mean age of women at baseline evaluation with last pregnancy at age $\geq$40 years was greater than those with last pregnancy at <40 years (68.1±7.1 vs 63.3±7.2). The proportion of white women was lower among women with last pregnancy at age $\geq$40 years. The mean systolic blood pressure (mm Hg±SD) of women at baseline evaluation with last pregnancy at age $\geq$40 years was greater than those with last pregnancy at <40 years (130.3±19 vs 126.7±17.8). The proportion of women with diabetes mellitus, congestive heart failure, atrial fibrillation, and any alcohol use was higher among those with last pregnancy at age $\geq$40 years (Table 1). The proportion of women in all categories of cigarette smoking was lower (those who never smoked cigarettes were used as reference) among participants with last pregnancy at age $\geq$40 years. The proportion of women in all categories of alcohol use was lower (those who never used alcohol were used as reference) among participants with last pregnancy at age $\geq$40 years, except for past drinkers, which was higher in women with last pregnancy age $\geq$40 years. The use of oral anticoagulants was higher among women with last pregnancy at age $\geq$40 years.

Compared with women with last pregnancy at <40 years, the rate of ischemic stroke (3.8% vs 2.4%), hemorrhagic stroke (1.0% vs 0.5%), and cardiovascular death (3.9% vs 2.3%) was significantly higher among women with last pregnancy at age $\geq$40 years. There was a trend towards a higher rate of MI among women with last pregnancy at age $\geq$40 years (3.0% vs 2.5%).

TABLE 1
Baseline characteristics of study participants: Women's Health Initiative observational study

Variable	Last pregnancy at <40 years of age	Last pregnancy at ≥40 years of age	Relative risk (95% confidence interval)
Overall, n	68,915	3306	
Mean age, y[a]	63.3±7.2	68.1±7.1	1.1 (1.1–1.1)
Race/ethnicity, n (%)			
American Indian/Alaskan native	271 (0.4)	20 (0.6)	1.5 (0.9–2.4)
Asian/Pacific islander	1,838 (2.7)	119 (3.6)	1.4 (1.1–1.6)
Black/African American	4,980 (7.2)	313 (9.5)	1.3 (1.2–1.5)
Hispanic/Latino	2,205 (3.2)	162 (4.9)	1.6 (1.3–1.8)
White (not Hispanic origin)	58,708 (85.2)	2638 (79.8)	0.7 (0.6–0.7)
Other	736 (1.1)	43 (1.3)	1.2 (0.9–1.7)
Body mass index, kg/m^2[a]	27.3±5.7	27.4±5.6	1.0 (1.0–1.0)
Systolic blood pressure, mm Hg[a]	126.7±17.8	130.3±19.0	1.0 (1.0–1.0)
Cardiovascular risk factors, n (%)			
Diabetes mellitus	3741 (5.4)	247 (7.5)	1.4 (1.2–1.6)
High cholesterol	10,020 (14.5)	483 (14.6)	1.0 (0.9–1.1)
Congestive heart failure	749 (1.1)	52 (1.6)	1.5 (1.1–1.9)
Atrial fibrillation	3,215 (4.7)	199 (6.0)	1.3 (1.2–1.5)
Anticoagulation use[b]	1,490 (2.2)	108 (3.3)	1.5 (1.3–1.9)
Cigarette smoking status, n (%)			
Never	34,181 (49.6)	1853 (56.0)	Reference
Past	29,626 (43.0)	1220 (36.9)	0.8 (0.7–0.8)
<1 Pack/d	2,853 (4.1)	114 (3.4)	0.7 (0.6–0.9)
≥1 Pack/d	466 (0.7)	14 (0.4)	0.6 (0.3–0.9)
Alcohol use, n (%)			
Nondrinker	7,431 (10.8)	455 (13.8)	Reference
Past drinker	12,680 (18.4)	651 (19.7)	1.1 (1.1–1.3)
<1 Drink/d	39,802 (57.8)	1828 (55.3)	0.8 (0.7–0.8)
≥1 Drink/d	8,632 (12.5)	347 (10.5)	0.7 (0.6–0.8)

[a] Data are given as mean±standard deviation; [b] Use of oral anticoagulant was ascertained at baseline and at year 3.
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In multivariate analysis, women with last pregnancy at age ≥40 years were 50% more likely to experience a hemorrhagic stroke (HR, 1.5; 95% CI, 1.0–2.1) after adjustment for age, race/ethnicity, congestive heart failure, systolic blood pressure, atrial fibrillation, alcohol use, and cigarette smoking (Table 2). Adjustment for anticoagulant use in the multivariate model for hemorrhagic stroke did not have any significant effect on the HR (HR, 1.4; 95% CI, 1.0-2.1). There was no significant difference in the risk of ischemic stroke (HR, 1.0; 95% CI, 0.8–1.2), MI (HR, 0.8; 95% CI, 0.7–1.0), and cardiovascular death (HR, 1.0; 95% CI, 0.8–1.2) among women with last pregnancy at age ≥40 years after adjustment for potential confounders. Compared with women with last pregnancy at <40 years, there was no difference in the rates of combined endpoint of cardiovascular deaths with ischemic stroke, hemorrhagic stroke, or MI among women with last pregnancy at age ≥40 years in age-adjusted or multivariate adjusted analysis.

Comment

We observed a higher rate of ischemic and hemorrhagic stroke and cardiovascular death in the postmenopausal years among women with last pregnancy at age ≥40 years compared with those women with last pregnancy at age <40 years. In the multivariate analysis, there was a trend towards higher adjusted risk of

TABLE 2
Multivariate adjusted[a] risk of cardiovascular endpoints in women in age strata based on age at last pregnancy: Women's Health Initiative observational study

Age at last pregnancy	Events, n	Age-adjusted hazard ratio (95% confidence interval)	Multivariate-adjusted hazard ratio (95% confidence interval)
Ischemic stroke			
<40 Y	1654	Reference	Reference
≥40 Y	126	1.1 (0.9–1.3)	1.0 (0.9–1.3)
Hemorrhagic stroke			
<40 Y	342	Reference	Reference
≥40 Y	32	1.4 (1.0–2.0)	1.5 (1.0–2.1)
Any cerebrovascular event (ischemic or hemorrhagic stroke, transient ischemic attack)			
<40 Y	2681	Reference	Reference
≥40 Y	126	1.0 (0.9–1.2)	1.0 (0.9–1.2)
Myocardial infarction			
<40 Y	1704	Reference	Reference
≥40 Y	98	0.9 (0.7–1.1)	0.7 (0.7–1.0)
Cardiovascular death			
<40 Y	1576	Reference	Reference
≥40 Y	129	1.0 (0.8–1.2)	1.0 (0.8–1.2)

[a] Adjusted for age, ethnicity, congestive heart failure, systolic blood pressure, atrial fibrillation, alcohol use, and cigarette smoking.
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hemorrhagic stroke among women with last pregnancy at age ≥40 years. There was no difference in the risk of ischemic stroke and cardiovascular death among women with last pregnancy at age ≥40 years and those at age <40 years after adjustment for differences in cardiovascular risk factors. However, the magnitude of any association that was observed in the analysis was small, and the cause-effect relationship between age at last pregnancy and any of the cardiovascular endpoints was unclear. We chose to evaluate the differential risk of long-term risk of stroke and cardiovascular disease using pregnancy at age of ≥40 years as the "at risk" group. The risk of adverse maternal and pregnancy outcomes starts increasing at approximately 35 years, with a more pronounced effect at age ≥40 years.[18] Women with age ≥40 years at pregnancy have become the focus of research regarding short- and long-term health consequence because of a sharp increase in prevalence over the last 2 decades.[19] We used the women with last pregnancy at age <40 years as the reference group instead of those who were never pregnant to identify the effect of maternal age separate from pregnancy that was consistent with previous studies.[18-20]

One of the questions is what potentially can mediate the increased risk of stroke and cardiovascular deaths among women with last pregnancy at age ≥40 years. Recent studies have emphasized long-term health consequences of pregnancy with a higher burden on those with pregnancy at advanced age. Certain maternal conditions such as preeclampsia during pregnancy are seen more frequently among women with advanced maternal age and are associated with a higher risk of ischemic heart disease and stroke in subsequent years.[21,22] Similarly, gestational diabetes mellitus, which is observed more frequently in women with pregnancy in advanced age, is associated with higher atherosclerotic disease in subsequent years.[23] The results of the multivariate analysis suggests that part of the increased risk is probably attributable to age differences, higher systolic blood pressure, and higher rates of diabetes mellitus, congestive heart failure, and atrial fibrillation among women with last pregnancy at age ≥40 years. It should be noted that the ascertainment of these cardiovascular risk factors was performed several years after the last pregnancy. Therefore, whether pregnancy at advanced age led to higher frequency of such cardiovascular risk factors in subsequent years cannot be excluded. The mechanism of a higher risk of hemorrhagic stroke in later life in women with last pregnancy at age ≥40 years appears to be independent of known cardiovascular risk factors. The higher risk of hemorrhagic stroke during pregnancy and puerperium (not studied in subsequent follow up) has been identified in previous reports.[24,25] Another interesting observation was the higher use of oral anticoagulants among women with last pregnancy at age ≥40 years during follow-up examinations.

Part of the increased risk of hemorrhagic stroke may be explained by the higher use of oral anticoagulants among women with the last pregnancy at age ≥40 years. However, the trend towards higher risk of hemorrhagic stroke was seen after adjustment for oral anticoagulant use in the model. However, whether oral anticoagulants were used actively before the occurrence of hemorrhagic stroke cannot be determined reliably because the information regarding use of oral anticoagulants was not ascertained regularly.

There are issues that need to be considered before interpretation of the data. The ascertainment of outcomes of interest in our analysis followed a standardized procedure that was used in the Women's Health Initiative study. There were no data regarding pregnancy-related factors that were acquired as part of data collection in the study. Therefore, our ability to identify the underlying mechanism and contribution of pregnancy-specific factors was limited. The number of hemorrhagic stroke events was too small for further analysis in subgroups of subarachnoid and intracerebral hemorrhages. We also acknowledge that confounding variables being adjusted for hemorrhagic stroke may not include all relevant parameters, unlike ischemic stroke where established parameters are better known because of a detailed understanding of risk factors.[26] The accuracy of primary outcomes in the study is expected to be high.[27] In a previous validation study, 94.5% of stroke events that were identified by a local adjudicator were confirmed on central review; 93.8% of centrally adjudicated strokes had been classified as strokes by local adjudicators who used similar methods as in the Women's Health Initiative clinical trial.[28] However, the adjudication was based on investigations that were performed as part of clinical care without a standard investigative protocol. The differentiation between ischemic and hemorrhagic stroke requires a computed tomographic scan, which is almost always performed in any patient with a suspected stroke. The variations in investigative tests, such as cardiac evaluation and vascular imaging, are likely to affect the accuracy of diagnosis of ischemic stroke subtypes.[29] We did not enter risk factors such as congestive heart failure and atrial fibrillation as time-dependent variables in the model, which may obscure the confounding effect of new diagnoses. The follow-up period was too short to use an approach like the pooled repeated measures method, which divides the follow-up period into multiple observation periods and reclassifies the risk factors and event status of every person at the beginning of new observation period.[30]

The practical implications of the current findings need to be determined. Preconception counselling regarding the risks of pregnancy with advanced maternal age, promotion of optimal health and weight, and screening for concurrent medical conditions such as hypertension and diabetes mellitus is recommended for women aged >40 years.[13] Whether information regarding the long-term increased risk of cardiovascular diseases should be included in the preconception counselling must be considered further. The higher prevalence of certain cardiovascular risk factors in later life among women with the last pregnancy at age ≥40 years would suggest that a targeted cardiovascular assessment at regular intervals may be considered. Further studies may be necessary to confirm the magnitude and mediators of increased hemorrhagic stroke risk that is conferred by pregnancy at age ≥40 years. Studies that focus on the identification of protracted changes in the cerebrovascular system in experimental models of pregnancy may be considered. ■

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