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Cerebrovascular disease at young age is related to mother's health during the pregnancy – the Northern Finland Birth Cohort 1966 study

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Abstract

Background and Purpose: For prevention of cerebrovascular diseases at younger age, it is important to understand the risk factors occurring early in life. We investigated the relationship between mothers' general health during pregnancy and the offspring's risk of cerebrovascular disease in age of 15 to 52 years.

Methods: Within the population-based prospective Northern Finland Birth Cohort 1966, 11,926 persons were followed from antenatal period to 52 years of age. Information on their mother's ill health conditions, i.e., hospitalizations, chronic diseases, medications, vitamin or iron supplement, fever, anemia, mood, and smoking was collected from 24th gestational week onwards. Ischemic and hemorrhagic cerebrovascular diseases of the offspring were identified from national registers in Finland. Cox proportional hazard models were used to estimate the association of mother's health conditions with incidence of cerebrovascular disease in the offspring, with adjustments for potential confounders.

Results: During 565,585 person-years of follow-up, 449 (2.8%) of the offspring had a cerebrovascular disease. Hospitalization during pregnancy was associated with an increased risk of cerebrovascular disease in the offspring (hazard ratio (HR)=1.49; 95% confidence interval (CI) 1.06-2.08) after adjustment for confounders, as was having more than three ill health conditions (HR=1.89; CI 1.14-3.11). Not using vitamin or iron supplement associated with increased risk for cerebrovascular disease in the offspring (HR=1.39; CI 1.01-1.89).

Conclusions: The results suggest that the risk of cerebrovascular disease may start as early as during the antenatal period, and the health characteristics of mothers during pregnancy may play a role in cerebrovascular disease risk of the offspring.

Key words: Cerebrovascular disease, stroke, risk factors, offspring, pregnancy, birth cohort

Introduction

It has been suggested that cerebrovascular diseases (CVD) among people under 55 years have different risk factors and etiologies than among older people[1, 2]. While the overall incidence of CVD is declining in developed countries, the incidence among people under 55 years of age is increasing[3]. To reduce the burden of CVD at younger age, it is important to understand the life course perspective of their risk factors and investigate risk factors occurring early in life.

It is known that mother's health during the pregnancy affects the whole life-course of the offspring from intrauterine environment, and the health of the newborn, to the general health in adulthood[4]. Previous studies have identified several antenatal risk factors for ischemic stroke of the newborn, such as maternal smoking, gestational hypertension, diabetes, bleeding, infections and primiparity[5, 6]. However, only few studies have investigated the relationship between maternal health conditions during pregnancy and offspring's CVD risk in adulthood[7-11]. We hypothesized that ill maternal health could start an accumulation of increased risk for a CVD in adulthood.

In this large population-based birth cohort study we set up to investigate mother's general health and health-related behaviors during the pregnancy and the risk of CVD of offspring during 52 years of follow-up. We were able to identify previously unknown risk factors for the incidence of CVD at young age.

Methods

The Northern Finland Birth Cohort 1966 (NFBC1966) is an unselected population-based birth cohort containing data on 12,055 mothers and all their 12,058 babies born alive in the Finnish provinces of Oulu and Lapland with an expected date of birth in 1966. Permission to gather data was obtained from the Ministry of Social Affairs and Health, and the study was approved by the Ethical Committee of Northern Ostrobothnia Hospital District in Oulu, Finland. Data protection was scrutinized by the Privacy Protection Agency of Finland.

Collected data of mothers were linked to Finnish nationwide registers of offspring with personal, pseudonymized identification numbers. Informed consent was inquired from all the participants. Excluded from sample were: mothers who reported information on less than half of used variables (n=65), offspring who did not give permission (n=59), and offspring who had CVD under the age of 15 years (n=8) (Figure 1). The sample included 11,926 offspring who were born alive and followed from mothers' mid-pregnancy to age of 52 years, and their mothers. The follow-up was based on complete nationwide registers and lasted until their first CVD, death, moving permanently abroad, or December 31st, 2018. There was no loss to follow-up. The 84 persons whose moving date abroad was unknown were censored at birth.

Information on the mothers' general health and health-related behaviors was collected by the local midwives in the antenatal clinics using a structured questionnaire between 24th and 28th gestational weeks in 1965-1966. The data were complemented during the pregnancy and after the delivery from maternity clinic cards. The prespecified variables measuring health of the mother included mother's

age, hospitalizations, chronic diseases, hypertension, medication use, fever, antibiotic use, use of vitamin or iron supplement, anemia, low mood, and smoking. These were chosen based on available data and study hypotheses (Supplement Figure 1). Covariate variables included sex of the child, mother's age and smoking, and occupational status of mother and father. Information on variable collection is provided in Supplements 1-2.

CVDs of offspring were identified from national Causes of Death Register based on death certificates and Care Register for Health Care (CRHC) based on medical records. CVDs were classified by primary diagnosis: subarachnoid hemorrhages (SAH), intracerebral hemorrhages (ICH), ischemic strokes, transient ischemic attack (TIA), and other CVDs. More detailed information is found in Supplement 1 and Supplement Table 1. Ischemic stroke and TIA were studied combined, as well as SAH and ICH. For analyses of 'any CVD' ischemic stroke, TIA, SAH, ICH, and other CVDs were combined.

Statistical analyses

To address missing values at baseline we used multiple imputation using 5 datasets. Overall rate of missing data before multiple imputation was 3.4%. Variables used in multiple imputation and their rates of missing data are shown in Supplement Table 2. Results of pooled analyses are reported. In cross-tabulations the pooled numbers of cases are rounded to 1, the percentages, means, and standard deviations (SD) to 0.1, and hazard ratios (HR) and 95% confidence intervals (CI) to 0.01.

First, baseline characteristics, i.e., mean age of mothers, CVD incidences, and mean age of CVD onset among offspring, were calculated. Second, we used Cox proportional hazard models to estimate the associations between mothers' health conditions during the pregnancy and incidence of any CVD, ischemic stroke or TIA, and SAH or ICH, respectively, in the offspring during follow-up. The models were adjusted for the sex of the child, mother's age and smoking, and socioeconomic status of the family. Participants were censored at the time of death or permanent move to abroad. As sensitivity analyses, we repeated the models excluding the offspring that got a TIA or other CVD as an outcome to study only ischemic strokes, SAH and ICH. Third, presence of hospitalization, chronic disease, hypertension, medication, fever, anemia, low mood, smoking, and non-use of vitamin or iron supplement were summed up to study the effect of several ill health conditions on the CVD risk of offspring. Duration of follow-up was calculated from date of birth until diagnosis of the first CVD, death, permanent move abroad, or the end of follow-up 31st of December 2018, whichever came first.

IBM SPSS Statistics, version 25.0, for Windows (IBM Corp., Armonk, NY, USA) was used for multiple imputation and statistical analyses.

Results

Characteristics of study population

Characteristics of male and female offspring and their mothers are shown in Supplement Table 3. Mean age of mothers at the beginning of the pregnancy was 27.8 years (SD 6.7 years). Of 11,926 offspring, 309 (2.6%) were born alive in multiple delivery, i.e., were twins.

The follow-up period from cohort members' birth date until 31st of December 2018 was in total 565,585 person-years (average 47.4 years per individual). During follow-up, 767 (6.4%) offspring died and 449 (3.8%) offspring had a CVD resulting in an incidence of 79.4 / 100,000 person-years. Of all CVDs, 142 were ischemic strokes, 163 were TIAs, 58 were SAHs, 36 were ICHs, and 50 were other CVDs. There were 29 CVD related deaths. The numbers of CVDs and incidences were similar between men and women (p=0.81 for difference): 227 (3.7%) vs. 222 (3.8%); incidence 78.8 / 100,000 vs. 80.0 / 100,000, respectively. The mean age of onset was 44.1 (SD 7.7) years for any CVD; 45.3 (SD 6.2) years for ischemic stroke or TIA, and 41.0 (SD 9.5) years for SAH or ICH.

Mother's health during the pregnancy and CVD risk of offspring

Mother's age, known chronic disease, hypertension, use of any medication, use of antibiotics, anemia, depressed mood, or smoking were not associated with increased CVD risk of offspring (Table 1). Offspring whose mothers were hospitalized during the pregnancy had an increased risk for any CVD (HR 1.49, 95% CI 1.06-2.08). The risk of any CVD in offspring whose mothers

reported not using vitamin or iron supplement during the pregnancy was increased (HR 1.39; 95% CI 1.01-1.89). In sensitivity analyses, offspring of hospitalized mothers had increased risk for ischemic stroke (HR 1.86; 95% CI 1.09-3.18), but the risk associated with not using vitamin or iron supplement did not remain, when TIA and other CVDs were excluded from the outcomes (Supplement Table 4). Mother having any type of hypertension during the pregnancy was not associated with increased CVD risk in the offspring in the original analyses (Table 1). However, offspring whose mothers had chronic hypertension had increased HR of 1.48 (95% CI 1.03-2.13) for any CVD in the sensitivity analyses with classified hypertension types (Supplement Table 5).

Offspring whose mothers had more than three ill health conditions during the pregnancy had HR of 1.89 (95% CI 1.14-3.11) for any CVD compared to those with no ill health conditions when adjusted for the sex of the child, mother's age and smoking, and socioeconomic status of the family (Table 2). Compared to offspring whose mothers did not have any ill health conditions, the offspring whose mothers had one ill health condition had increased risk to have a SAH or ICH (HR 2.10; 95% CI 1.15-3.83). In sensitivity analyses where TIA and other CVDs were excluded from the outcomes, risk of any CVD (HR 1.75; 95% CI 1.11-2.77) and SAH or ICH (HR 2.11; 95% CI 1.12-3.96) in the offspring were increased if the mother had one ill health condition (Supplement Table 4). The association with more than three ill health conditions did not remain.

Post hoc analyses

The characteristics of hospitalized mothers, mothers not taking vitamin or iron supplement, and mothers with more than three ill health conditions are found in Supplement 3 and Supplement Tables 6-8.

Discussion

In this population-based birth cohort we observed that offspring of mothers who were hospitalized during the pregnancy had an increased risk of CVD in adulthood. Furthermore, the risk of CVD was increased for offspring whose mothers were not taking vitamin or iron supplement. Finally, presence of more than three ill health conditions during the pregnancy was associated with increased risk among the offspring.

A strength of this study is the use of a large, unselected, population-based birth cohort containing almost 12,000 mothers and their children with nearly 600,000 person-years of follow-up. The data prospective collection started from the second trimester of cohort members' antenatal period and follow-up lasted up to 52 years of age. The questionnaire and clinical examination data were combined with comprehensive, prospective nationwide registers based on medical records. The information on CVD diagnoses from nationwide registers was complete for the entire cohort. The incidence of CVD at young age was 80/100,000 that is similar to previous studies[3,12]. Finally, multiple imputation was used to complete the missing data.

Relatively small number of persons with incident CVD, especially hemorrhagic stroke, may have underpowered this study to detect small associations. Due to the limited number of cases, for example different subtypes of ischemic or hemorrhagic strokes as well as different chronic diseases were not studied separately. Another limitation is the lack of data in the first 24 weeks of pregnancy, as this is an important time in fetal development. Additionally, although the cohort was designed to study pregnancy risk factors for later diseases, we were restricted to the risk factors that

were collected in 1960s. Information on all chronic diseases that may affect pregnancy and its outcome were not available. Furthermore, due to prospective nature of data collection and use of timely ICD classifications, there are some discrepancies between CVD outcomes in different ICD versions. CVD outcomes of the study are heterogenous as they represent the morbidity of general population. Finally, we did several analyses, and the findings should be interpreted with caution. Not being able to obtain all exposure information during pregnancy might raise the potential for residual confounding.

We found that mother's hospitalization during the pregnancy associated with increased CVD risk of offspring in adulthood, which is in line with a previous study[11]. The sensitivity analyses without TIA or other CVDs as outcomes showed an association especially for ischemic stroke. Although it is unlikely that mother's hospitalization has a causal relationship with the CVD risk of offspring, it may represent an underlying ill health condition that increases the risk. Interestingly, mother being in sickbed at home was not associated with offspring's CVD risk in our study. It should be noted that the reason for mother's hospitalization was not known. Post hoc analyses showed that mothers who were hospitalized were more likely to be older and to have ill health conditions. However, none of these health factors was associated with CVD risk of the offspring when studied separately, except for not using vitamin or iron supplement. An explanation may be that these factors affect the risk of offspring's CVD only when added together. Supporting the additive effects, we found that presence of more than three ill health conditions associated with increased CVD risk of the offspring. Furthermore, the hospitalization of mother might also present severity of underlying ill health conditions, interactions between them, or risk of birth complications.

Hypertensive disorders, occurring in 10% of pregnancies, are one of the most common causes for hospitalizations during pregnancy worldwide[13]. Previous studies have shown that hypertensive disorders during pregnancy are associated with increased cardiovascular risk factors and CVD risk in the offspring[9]. In this study, maternal hypertension in general was not associated with increased risk of CVD in the offspring. Mother having chronic hypertension associated with increased CVD risk in offspring. It is possible that shared risk factors between mother and child, e.g., hypertension, could influence both the risk of pregnancy hospitalization and offspring's risk. Especially shared genetic and environmental characteristics between mother and offspring may account for the relationships found in this study. We have attempted to account for shared environmental characteristics by adjusting for family socioeconomic status and mother's smoking. One potential mechanism by which ill health of the mother might impact the offspring's risk of CVD is the ill health of the newborn. A previous study from the same birth cohort found that small birth weight, height and ponderal index at birth were associated with an increased risk of later ischemic event[14].

In Finland in 1965 the use of vitamin D, folic acid and iron was usually recommended for pregnant women. In this study, offspring of mothers who were not taking vitamin or iron supplement during pregnancy had increased risk for CVD. The type of vitamin or iron supplement was not asked. Previous studies have found associations between prenatal exposure to famine and poor nutrition and increased CVD risk in midlife[15]. Also, vitamin D deficiency during pregnancy is related to adverse pregnancy outcomes[16], and adverse birth outcomes[17]. In addition, iron supplementation during pregnancy associates with lower incidence of adverse birth outcomes[18]. Previous studies have found associations between adverse birth outcomes and offspring's increased CVD risk[7, 10], which may explain findings of this study. However, non-use of vitamin or iron supplement may

also be a proxy of poor lifestyle habits associated with CVD risk of offspring. Poor lifestyle factors are usually transmitted from parents to offspring[19], which might contribute to the increased risk in later life. There is no consideration of intermediate risk factors or CVD etiology in this study and those topics require further investigation.

Conclusion

In this population-based birth cohort, mother being hospitalized, not taking vitamin or iron supplement, and having more than three ill health conditions during the pregnancy associated with increased cerebrovascular disease risk in the offspring. The results suggest that the risk of cerebrovascular disease may start as early as during the antenatal period, and the health characteristics of mothers during pregnancy may play a role in the development of the risk in the offspring.

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Figure 1. Selection of participants

Table 1. Associations between ill health conditions during pregnancy and offspring's risk for CVD.

	Any CVD		**Ischemic stroke or TIA**		**SAH or ICH**	
	No. (%)	HR (95%CI)	No. (%)	HR (95%CI)	No. (%)	HR (95%CI)
All (N=11,926)	449 (3.8%)		305 (2.6%)		94 (0.8%)	
Age of mother						
<20y (n=1199)	47 (3.9%)	Ref	34 (2.8%)	Ref	9 (0.8%)	Ref
20-24.99 (n=3511)	143 (4.1%)	0.98 (0.70-1.37)	88 (2.5%)	0.82 (0.55-1.23)	31 (0.9%)	1.13 (0.54-2.38)
25-29.99 (n=3208)	108 (3.4%)	0.83 (0.58-1.17)	77 (2.4%)	0.80 (0.53-1.20)	19 (0.6%)	0.79 (0.35-1.76)
30-34.99 (n=1998)	78 (3.9%)	0.96 (0.66-1.38)	56 (2.8%)	0.93 (0.61-1.44)	17 (0.8%)	1.13 (0.50-2.56)
>=35 (n=2001)	72 (3.6%)	0.88 (0.61-1.29)	49 (2.5%)	0.82 (0.53-1.28)	18 (0.9%)	1.18 (0.53-2.69)
Mother in sickbed						
No (n=10,651)	395 (3.7%)	Ref	268 (2.5%)	Ref	87 (0.8%)	Ref
In hospital (n=770)	40 (5.2%)	1.49 (1.06-2.08)*	27 (3.5%)	1.46 (0.96-2.21)	5 (0.6%)	0.82 (0.33-2.03)
At home (n=505)	14 (2.7%)	0.74 (0.43-1.28)	11 (2.2%)	0.84 (0.45-1.56)	2 (0.4%)	0.49 (0.12-1.99)
Chronic disease						
No (n=11450)	432 (3.8%)	Ref	291 (2.5%)	Ref	92 (0.8%)	Ref
Yes (n=476)	17 (3.6%)	0.99 (0.59-1.68)	14 (2.9%)	1.15 (0.65-1.04)	2 (0.4%)	0.52 (0.13-2.14)
Hypertension						
No (n=7545)	276 (3.7%)	Ref	199 (2.6%)	Ref	54 (0.7%)	Ref
Yes (n=4381)	173 (3.9%)	1.07 (0.88-1.30)	106 (2.4%)	0.90 (0.70-1.14)	40 (0.9%)	1.23 (0.81-1.90)
Any medication						
No (n=8581)	320 (3.7%)	Ref	214 (2.5%)	Ref	72 (0.8%)	Ref
Yes (n=3345)	129 (3.9%)	1.03 (0.83-1.29)	91 (2.7%)	1.09 (0.83-1.42)	22 (0.7%)	0.78 (0.47-1.32)
Fever during pregnancy						

No (n=11817)	327 (3.7%)	Ref	300 (2.5%)	Ref	90 (0.8%)	Ref
Yes (n=109)	10 (9.2%)	2.29 (0.45-11.63)	5 (4.6%)	1.73 (0.57-5.29)	4 (3.7%)	n.a.
Antibiotics						
No (n=10338)	383 (3.7%)	Ref	259 (2.5%)	Ref	84 (0.8%)	Ref
Yes (n=1588)	66 (4.2%)	1.15 (0.86-1.55)	46 (2.9%)	1.19 (0.82-1.71)	10 (0.6%)	0.75 (0.36-1.59)
Vitamin or iron supplement						
Yes (n=10958)	401 (3.7%)	Ref	273 (2.5%)	Ref	83 (0.8%)	Ref
No (n=968)	48 (5.0%)	1.39 (1.01-1.89)*	32 (3.3%)	1.33 (0.92-1.95)	11 (1.1%)	1.49 (0.75-2.94)
Anemia						
No (n=10141)	384 (3.8%)	Ref	261 (2.6%)	Ref	79 (0.8%)	Ref
Yes (n=1785)	65 (3.7%)	0.98 (0.75-1.27)	44 (2.5%)	0.97 (0.70-1.34)	15 (0.8%)	1.07 (0.62-1.87)
Mood						
Normal (n=10196)	381 (3.7%)	Ref	260 (2.5%)	Ref	82 (0.8%)	Ref
Depressed (n=1730)	68 (3.9%)	1.10 (0.85-1.43)	45 (2.6%)	1.08 (0.78-1.49)	12 (0.7%)	0.86 (0.46-1.58)
Smoking						
No (n=9640)	358 (3.7%)	Ref	247 (2.6%)	Ref	73 (0.8%)	Ref
Yes (n=2286)	91 (4.0%)	1.12 (0.89-1.43)	58 (2.5%)	1.03 (0.77-1.39)	21 (0.9%)	1.24 (0.75-2.05)
Number of ill health conditions						
None (n=2985)	103 (3.5%)	Ref	81 (2.7%)	Ref	15 (0.5%)	Ref
One (n=4227)	161 (3.8%)	1.09 (0.85-1.41)	100 (2.4%)	0.86 (0.64-1.17)	46 (1.1%)	2.10 (1.15-3.83)*
Two (n=3054)	108 (3.5%)	1.04 (0.78-1.38)	71 (2.3%)	0.87 (0.62-1.22)	22 (0.7%)	1.37 (0.68-2.75)
Three (n=1213)	50 (4.1%)	1.22 (0.84-1.77)	37 (3.0%)	1.14 (0.74-1.76)	8 (0.7%)	1.22 (0.39-3.79)

Four or more (n=447)	447 (6.1%)	1.89 (1.14-3.11)*	16 (3.7%)	1.47 (0.82-2.66)	4 (0.9%)	1.77 (0.53-5.89)

Cox regression adjusted for sex, mother's age, smoking, and socioeconomic status. Chronic disease=diabetes, thyroid disease, heart disease, chronic pulmonary disease, or chronic renal disease. Medication=diuretics, antibiotics, analgesics or sedatives. Ill health conditions=hospitalization, chronic disease, hypertension, medication, fever, anemia, low mood, smoking, and non-use of vitamin or iron supplement. CVD=cerebrovascular disease, TIA=transient ischemic attack; SAH=subarachnoid hemorrhage; ICH=intracerebral hemorrhage; No.=number; HR=hazard ratio; CI=confidence interval; n.a.=not applicable; Ref=reference group. *$p < 0.05$. Results are based on imputed data and numbers may not sum up.