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BRIEF REPORT

Risk of stroke the year following a delivery after using assisted reproductive technologies

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Abstract

Background: Studies indicate that individuals who deliver after assisted reproductive technologies (ART) may have an increased risk of cardiovascular disease (CVD). A recent large study from the U.S. showed a higher risk of stroke during the first year after delivery.

Objectives: To compare the risk of stroke during the first year after delivery according to the use of ART in the Nordic countries.

Methods: Registry-based cohort study using nationwide data from Denmark (1994–2014), Finland (1990–2014), Norway (1984–2015) and Sweden (1985–2015). Data on ART conception were available from ART quality registries and/or Medical Birth Registries (MBRs). National data on stroke were available from hospital and cause-of-death registries. The risk of stroke during the first year after delivery was estimated with Cox proportional hazard regression, adjusting for age, calendar year of delivery, multiple births, and country.

Results: A total of 2,659,272 primiparous individuals had a registered delivery in the MBRs during the study period, and 91,466 (4%) of these gave birth after ART. We observed no overall increased risk of stroke during the first year after delivery among individuals conceiving after ART (adjusted hazard ratio [HR] 1.10; 95% CI: 0.77, 1.57).

Similarly, there was no convincing evidence that the short-term risk of stroke was higher within 1, 2, 3, or 6 months after delivery, with adjusted HRs ranging between 1.23 and 1.33 and confidence intervals including the null value for all time periods. A secondary analysis also including multiparous individuals ($n = 3{,}335{,}478$) at the start of follow-up yielded similar findings.

Conclusions: We found no evidence of an increased short-term risk of stroke among individuals who delivered after using ART.

KEYWORDS
asisted reproductive technologies, stroke

1 | BACKGROUND

It has been hypothesized that individuals undergoing assisted reproductive technologies (ART) may have a higher risk of certain chronic diseases, including cardiovascular disease (CVD).[1,2] Proposed explanations include a contribution from underlying conditions related to both infertility and CVD, a mediating role of pregnancy complications, in addition to potential direct effects of aspects related to ART treatments and procedures on endothelial function and coagulation.[3–7]

A recently published U.S. study using the Nationwide Readmissions Database (NRD) found a higher risk of stroke during the first year after delivery following ART.[8] It was not possible to follow individuals in this database across calendar years, meaning that only deliveries occurring in January had a full year of follow-up, and data on parity were not available, possibly representing uncontrolled confounding. Our objective was to replicate the analyses in a large Nordic registry linkage on an unselected population in countries with universal health care. We have previously studied the long-term risk of CVD in this population.[2]

Synopsis

Study question

Do individuals who deliver using assisted reproductive technologies (ART) have an increased risk of stroke during the first year after delivery?

What is already known

Studies indicate that individuals who deliver after ART may have an increased risk of cardiovascular disease (CVD). A recent large study from the U.S. further showed a substantially higher risk of stroke during the first year after delivery.

What this study adds

In this large Nordic study including nationwide data from four countries, we found no robust evidence of a short-term increase in the risk of stroke among individuals who delivered after using ART.

2 | METHODS

2.1 | Committee of Nordic ART and safety

This study included national registry data linkage in four Nordic countries as part of the Committee of Nordic ART and Safety (CoNARTaS) collaboration.[9] The linkage includes data on all deliveries registered in the Medical Birth Registries (MBRs) in Denmark from 1994 to 2014, Finland from 1990 to 2014, Norway from 1984 to 2015, and Sweden from 1985 to 2015, depending on when the countries started registration of ART (in total 4,149,279 women). Follow-up information was available through national patient registries and cause-of-death registries. Hospital data were available from January 1987 for Sweden and Finland; January 1994 for Denmark; and January 2008 for Norway. We followed 2,659,272 primiparous individuals with no history of CVD (as defined previously[2]) who could be followed for 1 year after their first delivery (hereafter referred to as the index delivery). We restricted the main analysis to primiparous individuals to increase the homogeneity of the population and reduce the potential impact of selective fertility.[1]

2.2 | Assisted reproductive technologies

We defined each index delivery as conceived with or without ART (yes vs. no) based on information provided in the MBRs for Norway and Finland and in national ART quality registries for Denmark and Sweden.[3] ART included in vitro fertilisation with and without intracytoplasmic sperm injection and with autologous or donated gametes. We were unable to identify non-ART medically assisted reproduction, such as intrauterine insemination or ovulation induction. Thus, these patients were included in the non-ART population.

2.3 | Stroke

Stroke was defined based on any registrations of International Classification of Diseases (ICD) version 8 or 9 codes 430–438, or ICD version 10 codes I60–69, in the patient registries and cause-of-death registries after delivery. In secondary analyses, we defined ischemic stroke as ICD-8 and 9 codes 433–437; ICD-10 codes I63, I65–I67and haemorrhagic stroke as ICD-8 and 9 codes 430–432; ICD-10 codes I60–I62 and I69. The outcome definitions are in line with Sachdev et al.[8]

2.4 | Covariates

We obtained information from the MBRs on age and year at birth (i.e. start of follow-up, continuous) and whether the index delivery was a multiple birth. In addition, we obtained information on pre-pregnancy diabetes mellitus (yes vs. no), pre-pregnancy chronic hypertension (yes vs. no), stillbirth (yes vs. no), delivery by caesarean (yes vs. no) and whether there were complications such as pre-eclampsia (yes vs. no), preterm birth (<37 completed gestational weeks; yes vs. no) and small-for-gestational age (based on Marsál equations[10]; yes vs. no). We only included descriptive information on pregnancy outcomes and did not adjust for these, as they could be potential intermediates, similar to what the U.S. study did.[8]

2.5 | Statistical analysis

We used Cox proportional hazard regression to compare the risk of stroke across the first year after delivery among individuals by use of ART. The start of follow-up was the date of the index delivery, and the end of follow-up was the date of stroke, death from any cause, emigration or 1 year after the index delivery. Data from all countries were pooled, and the multivariable analysis adjusted for age (linear and squared term) and year at the start of follow-up, country, and multiple birth, similar to the adjustment strategy in the study by Sachdev and colleagues.[8] In addition, we explored adjustment for chronic hypertension and diabetes mellitus. We do not show country-specific estimates due to small numbers. We subsequently investigated the risk during the first month, and the first 2, 3, and 6 months, separately. For the secondary analysis of haemorrhagic and ischemic stroke, we censored individuals if they experienced the other type of stroke or if their stroke could not be further classified (18%). Finally, we conducted an analysis including multiparous individuals at the start of the follow-up.

All analyses were conducted using Stata version 17 (StataCorp).

2.6 | Ethics approval

This study was approved by regional ethical committees in Norway and Sweden. In Denmark and Finland, ethical approval is not required for medical research solely based on registry data.

3 | RESULTS

A total of 2,659,272 primiparous individuals without any history of CVD were available for analysis (Figure S1). Of these, 91,466 were delivered following ART conception. Background characteristics were very similar across the Nordic countries (Table S1). Characteristics of individuals who delivered with or without ART conception are shown in Table 1.

The rate of stroke during the first year after delivery was 2.4 per 10,000 person-years ($n = 634$), which was similar across the countries. There were only 36 cases among those who delivered after using ART. We observed no increased risk of stroke during this period for those who delivered following ART, with an adjusted HR of 1.10 (95% CI 0.77, 1.57; Table 2). The results were similar after adjustment for pre-existing chronic hypertension and diabetes (Table 2). Overall, the rate of stroke during the first month was 11.4 per 10,000 person-years, while the rate was 6.6 during the first 2 months, 5.1 during the first 3 months, and 3.3 during the first 6 months. Individuals who delivered after using ART had no increased risk of stroke during any of these time periods (Table 2). Using random-effects analysis to account for potential heterogeneity between the countries yielded a similar estimate for the risk of stroke the first year after delivery (HR 1.11, 95% CI 0.78, 1.58).

The rate of haemorrhagic stroke was 1 per 10,000, while the rate of ischemic stroke was 0.9 per 10,000. We observed no increased risk of either of these types of stroke, although there was great uncertainty due to a few events (Table 3). The analysis including multiparous individuals showed estimates which were slightly farther away from the null value (Tables S2 and S3). These estimates were attenuated after adjustment for parity, while additional adjustment for history of pre-eclampsia did not impact the results.

4 | COMMENT

In this Nordic study, we did not find convincing evidence of an increased risk of stroke among individuals who delivered following ART. Hence, our results do not support the findings in the recent study from the U.S,[8] but are in line with previous studies indicating no long-term risk of stroke among individuals who had used ART/fertility medications.[1,2,11,12]

We accounted for changes in ART procedures over time by adjusting for the year at the start of follow-up. However, with the small number of exposed cases, we could not reliably assess whether associations changed across calendar time. Future studies with more contemporary datasets would be useful. An important limitation of our study, and the published study that we aimed to validate, is that pregnant individuals who experienced a miscarriage or abortion were not included. However, for this selection to substantially influence the associations of interest, miscarriage or abortion would need to be strongly associated with the risk of stroke. We had no information on potential confounding factors (particularly lifestyle characteristics) measured

TABLE 1 Characteristics of included individuals according to use of assisted reproductive technologies (ART).

Background characteristics	No use of ART ($n = 2,567,806$)	Use of ART ($n = 91,466$)
Age at start of follow-up, mean (SD)	27.9 (4.9)	33.3 (4.3)
Chronic hypertension, *n* (%)	21,206 (0.8)	1139 (1.3)
Diabetes mellitus, *n* (%)	13,440 (0.5)	646 (0.7)
Multiple birth, *n* (%)	32,649 (1.3)	12,784 (14.0)
Stillbirth, *n* (%)	10,387 (0.4)	601 (0.7)
Pre-eclampsia, *n* (%)	162,329 (6.3)	8136 (8.9)
Preterm birth, *n* (%)	166,923 (6.5)	13,144 (14.4)
Small for gestational age birth, *n* (%)	133,552 (5.2)	7149 (7.8)

TABLE 2 Short-term risk of stroke after delivery using assisted reproductive technologies among primiparous individuals at the start of follow-up.

Time period	Exposure group	Rate per 10,000 person-years	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[c]
First year	Unexposed to ART	2.3	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Exposed to ART	3.9	1.15 (0.81, 1.63)	1.10 (0.77, 1.57)	1.11 (0.78, 1.58)
First month	Unexposed to ART	11.0	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Exposed to ART	22.6	1.24 (0.75, 2.07)	1.22 (0.73, 2.05)	1.23 (0.73, 2.07)
First 2 months	Unexposed to ART	6.4	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Exposed to ART	14.0	1.40 (0.88, 2.22)	1.32 (0.83, 2.12)	1.33 (0.83, 2.13)
First 3 months	Unexposed to ART	4.9	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Exposed to ART	10.2	1.33 (0.85, 2.06)	1.27 (0.80, 1.98)	1.27 (0.81, 2.00)
First 6 months	Unexposed to ART	3.2	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Exposed to ART	6.2	1.27 (0.86, 1.89)	1.23 (0.82, 1.85)	1.24 (0.83, 1.86)

[a]Adjusted for age and year of start of follow-up.

[b]Adjusted for age, year of start of follow-up, country, and multiple birth.

[c]Adjusted for age, year of start of follow-up, country, multiple birth, pre-existing chronic hypertension, and diabetes mellitus.

TABLE 3 Short-term risk of stroke during the first year after delivery using assisted reproductive technologies among primiparous individuals at the start of follow-up stratified by type of stroke.

Type of stroke	Exposure group	Rate per 10,000 person-years	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[c]
Haemorrhagic stroke	Unexposed to ART	1.0	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Exposed to ART	1.7	1.18 (0.70, 2.00)	1.17 (0.69, 1.99)	1.18 (0.70, 2.00)
Ischemic stroke	Unexposed to ART	0.9	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Exposed to ART	1.3	0.90 (0.50, 1.63)	0.81 (0.44, 1.48)	0.81 (0.44, 1.49)

[a]Adjusted for age and year of start of follow-up.

[b]Adjusted for age, year of start of follow-up, country and multiple birth.

[c]Adjusted for age, year of start of follow-up, country, multiple birth, pre-existing chronic hypertension and diabetes mellitus.

at the time of conception, which could have resulted in residual confounding.

There are several potential reasons why we did not observe the same findings as the recent study. One is that the U.S. study could not follow individuals across calendar years. This means that only individuals who delivered in January could be followed up for a whole year. Also, this might have led to an underestimation of the number of individuals with pre-existing CVD. They also had limited opportunity to adjust for comorbid conditions, such as pre-existing hypertension and diabetes mellitus. Another potential explanation is that in the U.S. study, they were unable to account for parity in their analyses, which could have led to overestimation of the associations.

Finally, there were several differences in exposure classification between the studies, with the U.S. study capturing a larger range of fertility treatments.

5 | CONCLUSIONS

We observed no robust evidence of a short-term increased risk of stroke among individuals who delivered after using ART.

AUTHOR CONTRIBUTIONS

Maria C. Magnus analysed the data and performed statistical analyses. All authors contributed to manuscript writing, assisted with data interpretation, and critically reviewed the manuscript.

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CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data cannot be shared publicly owing to restrictions by law. Data are available from the CoNARTaS server at Statistics Denmark, after approval by the Ethics Committees and registry keeping authorities in each country, as described in the following publication: Opdahl S, Henningsen AA, Bergh C, Gissler M, Romundstad LB, Petzold M, Tiitinen A, Wennerholm UB, Pinborg AB. Data Resource Profile: Committee of Nordic Assisted Reproductive Technology and Safety (CoNARTaS) cohort. Int J Epidemiol. 2020 Apr 1;49 (2):365-366f. doi: 10.1093/ije/dyz228. Contact information for Statistics Denmark: Division of Research Services Statistics Denmark Sejrøgade 11 DK-2100 Copenhagen Denmark Email: forskningsservice@dst.dk Phone: +45 39 17 31 30.

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REFERENCES

1. Dayan N, Filion KB, Okano M, et al. Cardiovascular risk following fertility therapy: systematic review and meta-analysis. *J Am Coll Cardiol*. 2017;70:1203-1213.
2. Magnus MC, Fraser A, Håberg SE, et al. Maternal risk of cardiovascular disease after use of assisted reproductive technologies. *JAMA Cardiol*. 2023;8:837-845.
3. Farland LV, Grodstein F, Srouji SS, et al. Infertility, fertility treatment, and risk of hypertension. *Fertil Steril*. 2015;104:391-397.
4. Henriksson P, Westerlund E, Wallén H, Brandt L, Hovatta O, Ekbom A. Incidence of pulmonary and venous thromboembolism in pregnancies after in vitro fertilisation: cross sectional study. *BMJ*. 2013;346:e8632.
5. Sealey JE, Itskovitz-Eldor J, Rubattu S, et al. Estradiol- and progesterone-related increases in the renin-aldosterone system: studies during ovarian stimulation and early pregnancy. *J Clin Endocrinol Metab*. 1994;79:258-264.
6. Tan J, Taskin O, Iews M, et al. Atherosclerotic cardiovascular disease in women with endometriosis: a systematic review of risk factors and prospects for early surveillance. *Reprod Biomed Online*. 2019;39:1007-1016.
7. Wekker V, van Dammen L, Koning A, et al. Long-term cardiometabolic disease risk in women with PCOS: a systematic review and meta-analysis. *Hum Reprod Update*. 2020;26:942-960.
8. Sachdev D, Yamada R, Lee R, Sauer MV, Ananth CV. Risk of stroke hospitalization after infertility treatment. *JAMA Netw Open*. 2023;6:e2331470.
9. Opdahl S, Henningsen AA, Bergh C, et al. Data resource profile: Committee of Nordic Assisted Reproductive Technology and Safety (CoNARTaS) cohort. *Int J Epidemiol*. 2020;49:365-366f.
10. Marsál K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr*. 1996;85:843-848.
11. Ge SQ, Tao X, Cai LS, Deng XY, Hwang MF, Wang CL. Associations of hormonal contraceptives and infertility medications on the risk of venous thromboembolism, ischemic stroke, and cardiovascular disease in women. *J Invest Med*. 2019;67:729-735.
12. Udell JA, Lu H, Redelmeier DA. Long-term cardiovascular risk in women prescribed fertility therapy. *J Am Coll Cardiol*. 2013;62:1704-1712.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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