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Research Article

Polycystic Ovary Syndrome, Hormonal Contraception and Thrombotic Stroke: A Historical Cohort Study

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Keywords

- Polycystic ovary syndrome
- Thrombotic stroke
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Abstract

Introduction: Women with polycystic ovary syndrome (PCOS) have an increased long-term risk of thrombotic stroke (TS). Combined hormonal contraception increases the same risk moderately in young women. The aims of this study were to assess the risk of TS in women of reproductive age with PCOS and to explore how obesity and use of hormonal contraception influence that risk.

Material and methods: This historical cohort study followed all Danish non-pregnant women 15-49 years old who were free of previous thrombotic disease or cancer from January 2001 through December 2012. Women were identified in four national registries for having a PCOS discharge diagnosis, use of hormonal contraception, and a first-ever TS diagnosis. Risk estimates were calculated by Poisson regression and adjusted for age, year, education, use of hormonal contraception, and Body Mass Index (BMI).

Results: Within 11,332,675 observation years, 2,029 women were recorded with a first TS, of which 90,038 women-years and 25 TS were in women with PCOS. The risk of TS increased 20 times with increasing age, more than halved with increasing education, and increased 58% (95% CI 12-122%) with increasing BMI. Women with PCOS had an adjusted 2.2 (95%CI 1.5-3.2) times increased risk of TS. In a sub-analysis on women with known BMI, (n=301,514), adjustment for BMI reduced the risk estimate of TS non-significantly by 11%.

Conclusion: Women of reproductive age with PCOS have a doubled risk of thrombotic stroke, which is not explained by increased obesity or use of hormonal contraception by these women.

ABBREVIATIONS

BMI: Body Mass Index; **TS:** Thrombotic stroke; **HC:** Hormonal contraception; **PCOS:** Polycystic Ovary syndrome.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women, with a prevalence of 6-10 % [1-3]. It has in Europe since 2003 been defined by at least two out of three Rotterdam criteria; Oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries on ultrasound examination [4]. The causes of PCOS are not yet established [5]. Many studies have demonstrated more prevalent risk factors of cardiovascular disease in women with PCOS, such as diabetes II [6,7], obesity, and hypertension [8]. Previous studies have assessed the risk of cardiovascular events in women of reproductive age with PCOS, but with inconclusive results [9-11]. The association of PCOS with ischemic stroke is of substantial interest, and data are limited and were cited as an area of needed research in the recent AHA Guidelines on "Prevention of Stroke in Women" 2014.

First line treatment of PCOS is oral contraceptives, which reduce the ovarian steroid production [12]. Several studies have shown an elevated risk of thrombotic stroke in current users of combined hormonal contraception [13-17]. Although thrombotic stroke is not very frequent in women of reproductive age, the consequences of these events are generally more serious as compared to the more frequent venous thrombosis.

The objective of this study was to assess the risk of thrombotic

stroke in women of reproductive age with and without PCOS, and to assess the contribution of obesity and use of hormonal contraception for any such risk.

MATERIALS AND METHODS

Data for this historical cohort study were retrieved from four national Danish registries. A ten-digit personal identification code given to all Danish citizens at birth or immigration made a merge between these registries possible. All female residents of Denmark aged 15-49 years old during the period January 1, 2001 to December 31, 2012 were initially included.

We excluded all women previously (1977-2000) diagnosed with a cardiovascular disease, cancer, thrombophilia, or had undergone a hysterectomy, bilateral oophorectomy, or sterilization before the study period. Included women were censored if any such events happened during the study period, and in case of death or emigration.

End point data were collected from The National Health Registry, which stores discharge diagnoses from all public and private hospitals classified according to the International Classification of Diseases (ICD-8 1977-1993 and ICD-10 from 1994). To ensure a high validity of the included cases women with first-ever thrombotic stroke were identified by the ICD-10 diagnosis I63 (which include both cerebral thrombosis and cerebral embolism). Transient cerebral ischemic attack, unspecified apolexia, hemorrhagic stroke, and cerebral venous thrombosis were not included.

Death by thrombotic stroke without hospitalization was achieved from the National Cause of Death Registry.

Pregnant women were temporarily excluded during pregnancy and during the puerperal period defined as 12 weeks or during four weeks after an abortion. Due to a possible increased risk of cardiovascular diseases during infertility treatment, women were temporarily excluded during ovarian stimulation and four weeks thereafter [18].

Women with PCOS were identified by the ICD-8 code 256, 90 (1977-1993) or ICD-10 code E282 (1994-2012). Since PCOS is a chronic disease, we presumed the condition, once recorded, to be present throughout the study period.

Information on redeemed prescriptions of hormonal contraception was retrieved from the National Registry of Medical Product Statistics. Data were retrieved from 1995 in order to categorize women correctly according to duration of use as of January 1, 2001.

Information about length of schooling and level of education was retrieved from Statistics Denmark and used as a proxy of social class. Educational level was divided into four groups; a: Elementary school education, b: Ongoing or completed high school education, c: High school with additional ongoing, or completed middle length education (3-4 years), and d: High school with additional ongoing or completed long education (≥5 years). A last category (unknown) with no information about education included mainly the youngest women.

Sensitivity analysis

As Body Mass Index (BMI) could be a potential confounder for the influence of PCOS on the risk of thrombotic stroke, a sensitivity analysis restricted to women with this information was conducted. Since 2004, BMI has been routinely recorded in the National Health Registry for all pregnant women in the early pregnancy. BMI was categorized into groups BMI <18.5, 18.5-24.9, 25-30, >30 and unknown.

Statistical analysis

In a multiple Poisson regression analysis, data were categorized into five-year age groups. The absolute and relative risk of thrombotic stroke in women with different exposures was calculated with control for age, calendar year, BMI, hormonal contraception, and education. The control for calendar year ensured control for changes in BMI over time.

We calculated 95% confidence limits, and p-values below 0.05 were considered significant.

Approval of this study was obtained from The Danish Data Protection Agency (J no. 2013-331-0354) and The State Serum

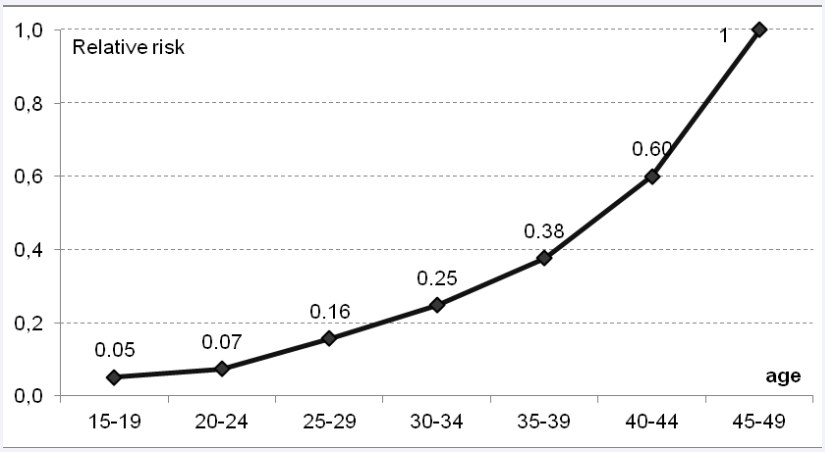

Figure 1 **) Adjusted for calendar year, education, use of hormonal contraception, and body mass index.*
Adjusted* relative risk of first ever thrombotic stroke among non-pregnant women according to age.

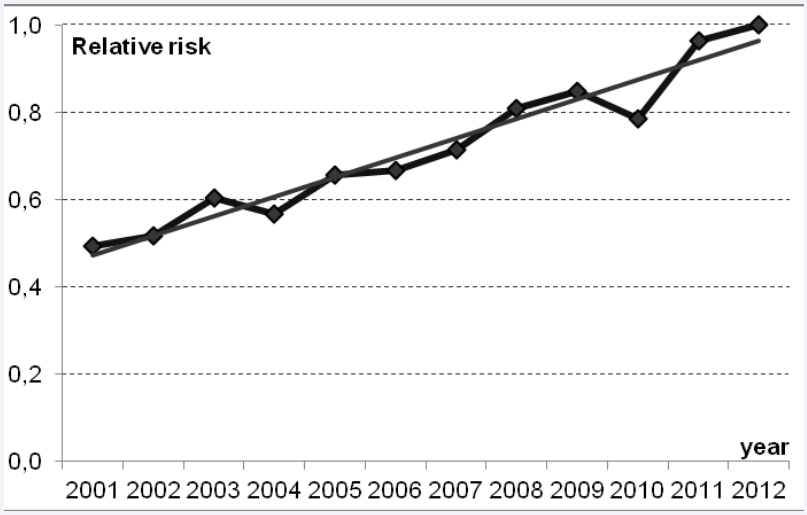

Figure 2 **) Adjusted for age, education, use of hormonal contraception, and body mass index.*
Relative risk of first ever-thrombotic stroke among non-pregnant Danish women, 15-49 years old, with 2012 as reference. Best linear fit indicated.

Table 1: *Relative risk (RR) of thrombotic stroke (TS) in women, with and without polycystic ovary syndrome and according to different potential confounders. Significant results bolded.*

	Women	TS	Crude	Adjusted[1]			Adjusted[2]		
	years	N	RR	RR	95% CI		RR	95% CI	
Age									
15-19	1,712,477	51	0.06	**0.05**	0.03	0.07	**0.05**	0.04	0.07
20-24	1,459,558	66	0.09	**0.06**	0.05	0.08	**0.07**	0.06	0.10
25-29	1,343,258	111	0.17	**0.13**	0.10	0.16	**0.16**	0.13	0.20
30-34	1,505,711	175	0.24	**0.21**	0.18	0.25	**0.25**	0.21	0.30
35-39	1,779,092	299	0.36	**0.34**	0.30	0.39	**0.38**	0.33	0.43
40-44	1,819,101	511	0.59	**0.58**	0.52	0.65	**0.60**	0.54	0.67
45-49	1,713,478	816	1	1	Reference		1	Reference	
Year									
2001	998,673	125	0.43	**0.53**	0.39	0.72	**0.49**	0.36	0.67
2002	984,200	130	0.45	**0.55**	0.41	0.74	**0.52**	0.38	0.70
2003	969,250	151	0.53	**0.64**	0.48	0.86	**0.61**	0.45	0.81
2004	960,534	141	0.49	**0.60**	0.45	0.81	**0.57**	0.42	0.76
2005	947,534	161	0.57	**0.69**	0.52	0.93	**0.66**	0.49	0.88
2006	938,342	162	0.58	**0.70**	0.52	0.94	**0.67**	0.50	0.89
2007	930,635	171	0.61	0.75	0.56	1.00	**0.71**	0.53	0.95
2008	927,580	192	0.69	0.84	0.63	1.12	0.81	0.61	1.08
2009	921,356	199	0.72	0.87	0.66	1.16	0.85	0.64	1.13
2010	1,530,181	314	0.64	0.80	0.61	1.05	0.78	0.60	1.03
2011	906,773	218	0.80	0.97	0.73	1.28	0.96	0.73	1.28
2012	317,616	65	1	1	Reference		1	Reference	
PCOS									
Yes	90,038	25	**2.18**	**2.16**	1.46	3,21	**2,15**	1.45	3.20
No	11,242,637	2,004	1	1	Reference		1	Reference	
Education									
a (low)	2,430,973	757		**1.41**	1.18	1.69	**1.47**	1.22	1.76
b	1,186,888	126		**0.57**	0.45	0.73	**0.63**	0.49	0.80
c	2,508,468	622		0.85	0.70	1.02	0.88	0.73	1.07

d (high)	1,566,495	280		**0.59**	0.48	0.73	**0.63**	0.51	0.77
Unknown	3,639,852	244		1	Reference		1	Reference	
Ratio a/d				2.39			2.33		
Hormonal contraception*									
Yes	4,274,152	718		**1.62**	1.47	1.79	**1.62**	1.47	1.78
No	7,058,523	1,311		1	Reference		1	Reference	
BMI									
<18.5	108,098	8	-				1.10	0.54	2.25
18.5-24.9	1,763,896	128	-				1.00	Reference	
25-30	614,167	52	-				1.11	0.81	1.53
>30	360,131	45	-				**1.58**	1.12	2.22
unknown	8,486,383	1,796	-				**1.70**	1.40	2.06

Adjusted 1: Adjusted for age, year, education and hormonal contraception
Adjusted 2: Additionally adjusted for BMI) Includes also progestin only contraception*

Table 2: *Relative risk (RR) of thrombotic stroke in women with versus without polycystic ovary syndrome and according to different potential confounders. Only women with known BMI included. Significant results bolded.*

	TS	Crude	Adjusted[1]			Adjusted[2]		
	n	RR	RR	Low	High	RR	Low	High
Year								
2001	10	0.33	0.50	0.21	1.19	0.49	0.21	1.16
2002	6	0.18	**0.28**	0.10	0.75	**0.27**	0.10	0.73
2003	10	0.30	0.44	0.19	1.02	0.44	0.19	1.01
2004	10	0.31	0.44	0.19	1.01	**0.44**	0.19	0.99
2005	17	0.49	0.69	0.34	1.41	0.68	0.34	1.39
2006	13	0.36	0.49	0.23	1.04	0.49	0.23	1.03
2007	13	0.34	**0.46**	0.22	0.96	**0.46**	0.22	0.95
2008	24	0.60	0.79	0.42	1.50	0.79	0.42	1.49
2009	20	0.48	0.62	0.32	1.19	0.62	0.32	1.19
2010	46	0.62	0.82	0.46	1.44	0.81	0.46	1.43
2011	47	0.95	1.17	0.67	2.05	1.17	0.67	2.05
2012	17	1.00	1.00	Reference		1.00	Reference	
PCOS								
yes	5	1.75	1.80	0.74	4.36	1.61	0.66	3.93
no	228	1.00	1.00	Reference		1.00	Reference	
Education								
a (low)	79		1.08	0.70	1.68	1.08	0.70	1.69
b	40		0.62	0.36	1.04	0.65	0.38	1.10
c	44		0.78	0.45	1.35	0.79	0.46	1.38
d (high)	24		0.56	0.30	1.06	0.60	0.32	1.14
Unknown	46		1.00	Reference		1.00	Reference	
Ratio a/d			1.93			1.80		
Hormonal contraception*								
Yes	131		**1.97**	1.50	2.59	**1.98**	1.51	2.60
No	102		1.00	Reference		1.00	Reference	
Body mass index								
<18.5	8					1.10	0.54	2.25
18.5-24.9	128					1.00	Reference	
25-30	52					1.13	0.82	1.56
>30	45					**1.65**	1.17	2.33

Adjusted 1: Adjusted for age, year, education and hormonal contraception
Adjusted 2: Additionally adjusted for BMI
**) Includes also progestin only contraception*
***Abbreviations:PCOS:** Polycystic Ovary syndrome; **TS:** Thrombotic stroke.*

Institute (FSE ID 421). All statistical results were analyzed by a statistician.

RESULTS AND DISCUSSION

After exclusion of 88,624 women with previous thrombosis, cardiovascular disease, cancer, thrombophilia, or who had undergone hysterectomy, bilateral oophorectomy, or sterilization, the final study population of 1,439,547 women contributed 11,332,675 women-years of observation.

The number of women included with PCOS was 9,640 (0.7 %), contributing 90,038 women-years. Among women with PCOS, 41.1 % had recorded BMI.

During the study period, 2,029 women experienced a thrombotic stroke, and of these 25 were diagnosed PCOS. Among women with PCOS the incidence rate of thrombotic stroke was 27.8 per 100,000 women years, compared to 17.8 per 100,000 in women not diagnosed with PCOS, or one more per 10,000 women per year. The incidence thrombotic stroke increased by more than 100% throughout the study period after adjustment for age, education, hormonal contraceptive use, and BMI (Figure 1).

The adjusted relative incidence rate of thrombotic stroke increased 20 times with increasing age (Figure 2) and about 2.3 fold with decreasing educational length (Table 1).

Current users of hormonal contraception (including progestin only contraception) had an average adjusted relative risk of thrombotic stroke of 1.62 (CI 95% 1.47-1.78) as compared with non-users (Table 1).

With increasing BMI, the relative risk of thrombotic stroke increased to 1.58 (CI 95% 1.12-2.22) in the obese group (BMI>30) as compared to women with normal weight (BMI 18.5-24.9) (Table 1).

The sensitivity analysis restricted to only women with known BMI insignificantly reduced the relative risk of thrombotic stroke in women with PCOS from 1.80 (CI 95% 0.74-4.36) to 1.61 (CI 95% 0.66-3.93) with adjustment for BMI, suggesting the increased risk of thrombotic stroke in women with PCOS only to a little degree is explained by more obesity in women with PCOS (Table 2).

The adjusted 2.39 fold increased risk of thrombotic stroke in women with the shortest education, was reduced to a 1.93 fold increased risk when the analysis was restricted to women with known BMI (Table 1 and 2). In both analyses the ratio did not change significantly when additionally adjusting for BMI.

Use of hormonal contraception, on the other hand, further increased the relative risk of thrombotic stroke to 1.97 (CI 95% 1.50-2.59) when the analysis was restricted to women with known BMI, and control for BMI did not change the estimates (Table 2).

This study was performed to assess the risk for thrombotic stroke in women of reproductive age with PCOS. According to our study PCOS confers a doubled risk of thrombotic stroke, an increase that was only slightly modified after adjustment for use of hormonal contraceptives and BMI. This result also held when the analysis was restricted to women with known BMI.

In a recent meta-analysis, women with PCOS were found to have a two-fold increased risk of coronary heart disease or stroke (in all ages). That relative risk was reduced to 1.6 (95% CI 1.3-1.9) with adjustment for BMI [9]. The meta-analysis and the original studies behind the analysis did not provide separate estimates for coronary heart disease and stroke, and it included mainly end points beyond menopause. Whereas BMI according to Danish data contributed significantly to the increased risk of venous thrombosis in women with PCOS, (S. Thranov, unpublished data, 2013) we found only a weak confounding influence from obesity on the risk of thrombotic stroke in women of reproductive age with PCOS.

The rate ratio of thrombotic stroke between women with short and long education was changed from a ratio of 2.33 to a ratio of 1.80, when restricted to women with known BMI (Table 1+2). However the estimates did not change significantly when additionally adjusting for BMI. Therefore, we conclude that length of education implies a higher impact on the risk of cerebral thrombosis than obesity. Women with limited education more often smoke cigarettes, which could contribute to the increased risk among these women [19].

The low PCOS prevalence of 0.7 % is an underestimation of the true prevalence because only women admitted to hospital with PCOS (primary fertility treatment) were categorized as having PCOS. Many women with PCOS are treated in general practice. This underestimation implies that some of our “controls”, categorized as women without PCOS, indeed had this disorder. On the other hand, women with PCOS referred to hospital probably represent a sample of women with more severe PCOS. These two biases tend to underestimate and overestimate the impact of PCOS, respectively.

In the 12-year study period we found more than a doubling of the incidence rate of thrombotic stroke (Figure 1), probably due to improvements in the diagnostic equipment making it possible to detect also small infarctions. Another contributing factor is an increase in the specificity of stroke diagnoses, with an increasing discrimination between hemorrhagic and thrombotic stroke. This study only considered strokes specified as thrombotic.

We found 20-times increase in first thrombotic stroke with increasing age (45-49 years vs. 15-19 years). The increase has been demonstrated in several previous studies [17,20-22].

The 1.6 times increased risk of thrombotic stroke in users of hormonal contraception also included users of progestin-only contraception, which does not confer an increased risk of thrombotic stroke [17]. The analysis restricted to women with known BMI, confirms that BMI, although being a risk factor for thrombotic stroke [23], is not a confounder, because the proportion of adipose women is approximately the same among users and non-users of hormonal contraception. A recent Danish cohort study found a 1.5 to 2 times increased risk of thrombotic stroke among women on combined oral contraceptives, without consistent differences in risk according to the progestin type [17]. The incidence of thrombotic stroke is less frequent than venous thrombosis in young women, but the former has more serious consequences for the survivors.

Traditionally women with PCOS have been treated with combined oral contraceptives with low androgen activity, meaning 3rd and 4th generation pills with desogestrel, gestodene or drospirenone. Considering the increased risk of both venous thrombosis [24-26] and thrombotic stroke in women with PCOS, a careful consideration on the choice of hormonal contraception is advisable. Despite the well-documented clinical benefits of low androgen hormonal contraceptives, these benefits should be weighted against the thrombotic risks in women already at an increased risk.

Strengths and limitations

The national coverage of women in the National Health Registry and the Prescription Registry ensured both valid exposure data and an almost complete follow-up of women with PCOS through the 12-year study period. All prescriptions were transferred electronically from the pharmacies by bar codes linked to the personal identification number. This eliminated recall bias, an issue of concern in retrospective studies.

The validity of the thrombotic stroke diagnosis was enhanced by including only the specific cerebral infarction diagnosis (I63). Almost all women suspected for thrombotic stroke undergo CT-scan or MR scan in Denmark.

Since 2005 information on BMI has been recorded in the National Health Registry. We had complete information on 21% of the study population and on 41% of women with PCOS, and had the opportunity to conduct sensitivity analyses restricted to those with recorded BMI with similar results.

The definition of PCOS has changed over time. Before the introduction of the "Rotterdam criteria," in 2003, elevated levels of androgens or clinical signs of hyperandrogenism and amenorrhea/oligomenorrhea defined PCOS. Thus the definition of women with PCOS broadened by time.

Another limitation was the inclusion of only hospitalized women with PCOS Thus some of our women anticipated not to have PCOS had in fact PCOS, a circumstance slightly underestimating the risk of thrombotic stroke in women with PCOS. We did not have information on some potential confounders such as family disposition, exercise, smoking, blood pressure and dietary habits. In Denmark there is a strong correlation between smoking and short education. By adjusting for educational level we have probably controlled for some of the possible confounding influence from smoking. We have no reason, however, to believe, that women with PCOS differ according to smoking habits as compared to women without PCOS, so residual confounding from smoking is expected to be limited.

CONCLUSION

We found a doubled risk of thrombotic stroke in women with PCOS. More obesity and more users of hormonal contraception in these women did not explain their increased risk.

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Conflict of Interest

Lidegaard declares that he has received honoraria for speeches in pharmacoepidemiological issues, and has been an expert witness for plaintiff in US legal cases in 2011 and 2012. The other authors declare not to have any conflicts of interest.

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