PCOS, hormonal contraception and thrombotic disease

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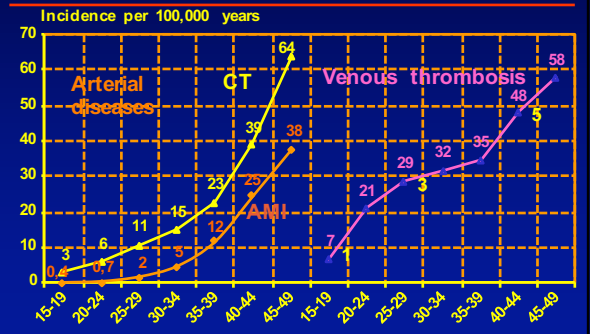
Background

- Women with PCOS have risk factors of cardiovascular diseases: diabetes, adiposity and hypertension
- 1st choice treatment: Oral contraceptives and weight loss.
- Studies have shown that hormonal contraception increases the risk of venous and arterial thrombosis.
- We found no study assessing the risk of arterial thrombosis in young women with PCOS.

CT, AMI and VT in DK 2001-2010

Pregnant and puerperal women excluded



Lidegaard et al NEJM 2012 and BMJ 2011

Objectives

- To assess the risk of
  - venous thrombosis
  - thrombotic stroke, and
  - myocardial infarction

  in women of reproductive age with PCOS.
- To quantify how much adiposity and use of hormonal contraception contribute to the increased risk of thrombotic disease in women with PCOS

Danish infrastructure

National Health Registry (>1977)
VT diagnoses,
Previous CaVD/canc.
Pregnancies, surgery

Prescription Registry (>1995): HC use
Anticoagulation therapy
hypertension, DM,
Hyperlipidaemia

1995 → 2015

Cause of Deaths Registry (>1977)
Lethal VT

Statistics Denmark
PIN-codes, education
vital status, emigration

Material

- Inclusion: Women 15-49 years during the period January 2001-December 2012
- Exclusion: Previous CaVD, cancer, thrombophilia, and women with hysterectomy, sterilisation or bilateral oophorectomy.
- Censoring: Death, emigration.
- Temporary exclusion: Treatment of infertility and pregnancy.

Methods

- Data source: National Danish Health Registries
- Exposure: HC, adiposity, and PCOS
- Outcome: First ever thrombotic disease.
- Reference: Women without diagnosed PCOS
- Poisson regression with adjustment for age, BMI, hormonal contraception and education.
- Sensitivity analysis restricted to women with known BMI.

Results

Number of included women:	1,427,113
Number of exposure years:	11,332,675
Women with PCOS:	9,640
Exposure years on PCOS:	90,038
Women with thrombotic stroke:	2,029
Women with myocardial infarction:	1,674
Women with venous thrombosis:	4,184

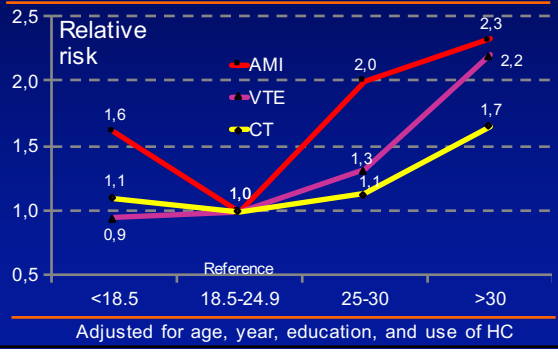
Results

	CT	AMI	VTE
Fold increase by age"	25	100	8
+PCOS vs –PCOS*	2.2	2.5	1.9
% reduc. with BMI adj.	11%	19%	26%
Risk with adj. for bmi	2.0	2.0	1.4

") from age 15 to 49

*) adjusted for age, year, education, and use of hormonal contraception

Influence of BMI on risk of thrombosis



Adjusted for age, year, education, and use of HC

Strengths

- All Danish women included
- >11 million observation years
- 12 years complete follow-up.
- National Health Registry stores discharge codes for other purposes than research=>reduces selection bias
- Information on hormonal contraception from prescription registry => no recall bias
- Adjustment for the most important confounder: use of hormonal contraceptives.

Limitations

- BMI not available before 2005
- The definition of PCOS has changed through the study period.
- The prevalence of PCOS was 0.7%
- Only women referred to hospital were recorded with a PCOS diagnosis code.
- No information about exercise and smoking.

Conclusion

- Young women with PCOS have a doubled risk of thrombotic stroke which is not explained by a higher BMI or use of hormonal contraception.
- Other studies have confirmed an increased risk of venous thrombosis in young women with PCOS
- and of myocardial infarction in older women with PCOS.

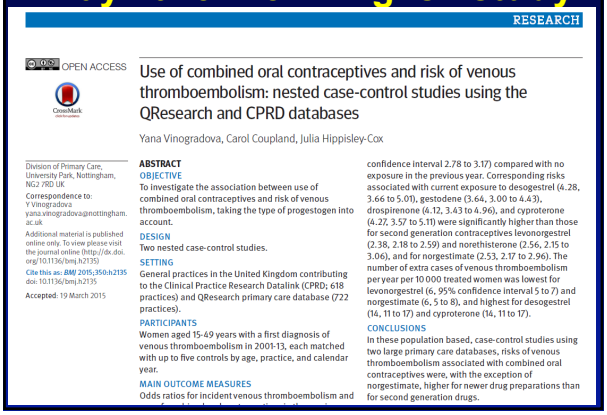
Clinical consequence

- First the evidence in women without PCOS

VT and drospirenone/LNG

	VT	IR[4]	Rate ratio	
Dinger[07]	118	9.1	1.0 (0.6-1.8)	4th/2nd
Vlieg [09]	1,524	na	1.7 (0.7-3.9)	4th/2nd
Lidegaard[09]	4,213	7.8	1.6 (1.3-2.1)	4th/2nd
Dinger[10]	680	na	1.0 (0.5-1.8)	4th/2nd
Parkin[11]	61	2.3	2.7 (1.5-4-7)	4th/2nd
Jick[11]	186	3.1	2.8 (2.1-3.8)	4th/2nd
Lidegaard[11]	4,246	9.3	2.1 (1.6-2.8)	4th/2nd
FDA Kaiser[11]	625	7.6	1.5 (1.2-1.9)	4th/2nd
Gronich[11]	518	8.6	1.7 (1.0-2.7)	4th/2nd
Bird[13]	354	18.0	1.9 (1.5-2.4)	4th/2nd
Dinger[14]	123	7.2	0.8 (0.5-1.6)	4th/2nd
Vinogradova[15]	10,562	na	2.1 (1.6-2.7)	4th/2nd
Dinger[16]	306	10.7	1.1 (0.8-1.7)	4th/2nd

May 2015: New English study



RESEARCH

OPEN ACCESS

Use of combined oral contraceptives and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases

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ABSTRACT

OBJECTIVE
To investigate the association between use of combined oral contraceptives and risk of venous thromboembolism, taking the type of progestogen into account.

DESIGN
Two nested case-control studies.

SETTING
General practices in the United Kingdom contributing to the Clinical Practice Research Datalink (CPRD; 618 practices) and QResearch primary care database (722 practices).

PARTICIPANTS
Women aged 15-49 years with a first diagnosis of venous thromboembolism in 2001-13, each matched with up to five controls by age, practice, and calendar year.

MAIN OUTCOME MEASURES
Odds ratios for incident venous thromboembolism and confidence interval 2.78 to 3.17) compared with no exposure in the previous year. Corresponding risks associated with current exposure to desogestrel (4.28, 3.66 to 5.01), gestodene (3.64, 3.00 to 4.43), drospirenone (4.12, 3.43 to 4.96), and cyproterone (4.27, 3.57 to 5.11) were significantly higher than those for second generation contraceptives levonorgestrel (2.38, 2.18 to 2.59) and norethisterone (2.56, 2.15 to 3.06), and for norgestimate (2.53, 2.17 to 2.96). The number of extra cases of venous thromboembolism per year per 10 000 treated women was lowest for levonorgestrel (6, 95% confidence interval 5 to 7) and norgestimate (6, 5 to 8), and highest for desogestrel (14, 11 to 17) and cyproterone (14, 11 to 17).

CONCLUSIONS
In these population based, case-control studies using two large primary care databases, risks of venous thromboembolism associated with combined oral contraceptives were, with the exception of norgestimate, higher for newer drug preparations than for second generation drugs.

Vinogradova 2015

VTE confirmed	Vinogradova
Non use	1 reference
COC levonorgestrel	3.0 (2.6-3.3)
COC norgestimate	3.5 (2.9-4.4)
COC desogestrel	6.2 (5.0-7.7)
COC gestodene	6.5 (5.0-8.4)
COC drospirenone	6.1 (4.7-7.8)
COC cyproterone	6.0 (4.7-7.7)

Vinogradova et al. BMJ 2015; 350: h2135

Li/15

Vinogradova vs Lidegaard

VTE confirmed	Vinogradova	Lidegaard
Non use	1 reference	1 reference
COC levonorgestrel	3.0 (2.6-3.3)	3.0 (2.2-4.0)
COC norgestimate	3.5 (2.9-4.4)	3.5 (2.9-4.3)
COC desogestrel	6.2 (5.0-7.7)	6.6 (5.6-7.8)
COC gestodene	6.5 (5.0-8.4)	6.2 (5.6-7.0)
COC drospirenone	6.1 (4.7-7.8)	6.4 (5.4-7.5)
COC cyproterone	6.0 (4.7-7.7)	6.4 (5.1-7.9)

Vinogradova et al. BMJ 2015; 350: h2135
Lidegaard et al. BMJ 2011; 343: d6423

Li/15

HC and RR of VTE: Conclusion

No/low risk <1.5	Middle risk 1.5-4	High risk >4	Few data	No data

EE dose	NETA Norethis-terone	LNG Levonor-gestrel	NGM Norges-timate	DGS Deso-gestrel	GSD Gesto-dene	DRSP Drospire-none	CPA Cyproterone-acetate
Combined products							
Middle	3	3		6	6		6
Low		2.5?'		5			
Nat oe	E2V-DNG 4.5*			E2 NOMAC"			
N-oral			Patch 7	Vaginal ring 6¤			
Progestogen only products							
Oral	POP 1			Cerazette 1			
N-oral	Depot 1	IUS 1§		Implant 1.4			

')Loette ")Zoely *)Qlaira ¤)NuvaRing §) Mirena

HC and thrombotic stroke

Low risk: <1.5	Middle risk: 1.5-4	High risk: >4	No data

EE dose	NETA Norethis-terone	LNG Levonor-gestrel	NGM Norges-timate	DGS Deso-gestrel	GSD Gesto-dene	DRSP Drospi-renone	CPA Cyproterone-acetate
Combined products							
Middle	2.2*	1.7*	1.5*	2.2*	1.8*	1.6*	1.4
Low				1.5*	1.7*	0.9	
Nat oe	E2V-DNG			E2 NOMAC			
N-oral			Patch 3.2	Vaginal ring 2.5*			
Progestogen only products							
Oral	POP 1.4			Cerazette 1.4			
N-oral	Depot	IUS 0.7		Implant 0.9			

Clinical consequence

- First the evidence in women without PCOS
- Risk of VTE is increased 3-fold in women on 2nd gen CHC and 6-fold in women on 3rd and 4th gen CHC.
- Risk of arterial thrombosis is increased 50-100% in women on CHC without consistent differences according to progestogen type.
- Risk of progestogen-only contraception is generally safe concerning thrombosis

Lidegaard, Expert Opinion Drug Safety 2014: 13: 1353-60

Clinical recommendations

Young women (<35 years)

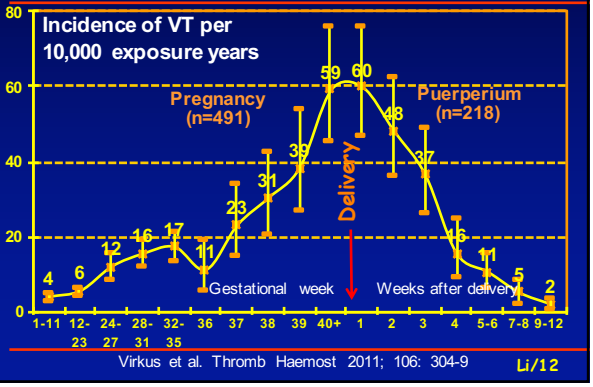
1st choice	Middle risk (2nd gen) COC
2nd choice	Low risk LNG-IUS (e.g Jaydess)
3rd choice	High risk 3rd or 4th gen COC

Women from 35 years or women at risk

1st choice	Low risk LNG-IUS
2nd choice	Middle risk 2nd gen. COC
3rd choice	Non hormonal contraception

Lidegaard, Expert Opinion Drug Safety 2014: 13: 1353-60

Venous thrombosis in pregnant and puerperal women, DK 1995-2005. N=709



Virkus et al. Thromb Haemost 2011; 106: 304-9 Li/12

1st myth: HC vs pregnancy

Age	Exposure	VTE/10,000 years
30	pregnancy, 1st trim	3
30	pregnancy, 2nd trim	4
30	pregn, birth, puerp:	8
30	low risk pill	9
30	high risk pill	18

Conclusion: The risk of VTE is *higher* with HC than with pregnancy.

PCOS, hormonal contraception and thrombosis

Thanks for your attention

www.lidegaard.dk/slides