Can we believe epidemiologists?

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First global conference in contraception, reproductive and sexual health
Copenhagen, May 23, 2013

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Introduction

- Epidemiology is a relatively new discipline
- The knowledge about epidemiological methods is limited among many clinicians
- This makes it difficult to assess the validity of methodological criticism
- There are, however, epidemiologic baseline criteria which make it possible to evaluate the quality of epidemiologic studies.

Evaluation criteria

These criteria include:

- Validity exposure data
- Validity of end points
- Inclusion of relevant confounders
- Adequate regression analysis
- Transparency in data and data analysis
- A sufficient statistical power
- Publication in journals with critical review

Introduction

- Generally, epidemiological studies have a worse reputation than justified
- Generally, studies coming up with new unexpected results are more critically evaluated than studies confirming our prejudices
- Epidemiological studies are rarely randomised (for good reasons)
- Randomisation is for many clinicians the gold standard

VT and drospirenone

	VT	IR	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[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

Critique

Risk of venous thromboembolism among users of oral contraceptives: a review of two recently published studies

Samuel Shapiro, Jürgen Dinger

J Fam Plann Reprod Health Care 2010; **36**(1): 33–38
(Accepted 25 November 2009)

Combined oral contraceptives, venous thromboembolism, and the problem of interpreting large but incomplete datasets

Jürgen Dinger,[1] Samuel Shapiro[2]

J Fam Plann Reprod Health Care (2011). doi:10.1136/jfprhc-2011-100260

Combined hormonal contraceptives and the risk of venous and arterial thromboembolism and cardiovascular death: misuse of automated databases

Samuel Shapiro

Family Planning and Reproductive Health Care 2013;39:89–96.

VT and drospirenone

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Dinger versus Lidegaard

	Dinger	Lidegaard
Design	Cohort	Hist. Cohort
Exposure		
Exposure period	few years	15 years
Update interval	6-12 mo	Daily
Source of inf.	Questionnaire	Registry
Case finding		
Case identification	Questionnaire	Hosp diagn
Confirmation	GP	Anticoag.
Predefined criteria	No	Yes

Dinger versus Lidegaard

	Dinger	Lidegaard
Exclusion of predisposed		
Pregnant women	No	Yes
Puerperal women	No	Yes
Previous VTE	No	Yes
Previous arterial thromb	No	Yes
Known thrombophilia	No	Yes
Previous cancer	No	Yes
Hysterectomy	No	Yes
Oophorectomy (bilat)	No	Yes

Dinger versus Lidegaard

Inclusion of potential confounders	Dinger	Lidegaard
Age	Yes	Yes
Education	No	Yes
Length of use	Yes	Yes
Oestrogen dose	No	Yes
Ovarian stimulation	No	Yes
Major surgery	No	Yes
BMI	Yes	No
Family disposition	No	No

VT and drospirenone

	VT	IR^{4th}	Rate ratio	
Dinger^{07}	118	9.1	1.0 (0.6-1.8)	4th/2nd*
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Dinger versus Lidegaard

	Dinger	Lidegaard
Statistical power		
Included women	58,674	1,296,120
Womenyears	142,475	7,937,565
Years on 2nd gen	15,428	477,885
Years on 3rd gen	na	1,781,704
Years on 4th gen	28,621	309,914
Events on 2nd gen	25	242
Events on 3rd gen	Na	1,229
Events on 4th gen	26	212

Dinger vs Lidegaard; Conclusion

Conclusion

No objective reason to consider the Danish cohort studies as less valid than the much smaller German study.

On the contrary, several methodological aspects point to the opposite conclusion

A recent statement

Statement on combined hormonal contraceptives containing third- or fourth-generation progestogens or cyproterone acetate, and the associated risk of thromboembolism

Johannes Bitzer

Cosignatories

Jean-Jacques Amy,[1] Rob Beerthuizen,[2] Martin Birkhäuser,[3] Teresa Bombas,[4] Mitchell Creinin,[5] Philip D Darney,[6] Lisa Ferreira Vicente,[7] Kristina Gemzell-Danielsson,[8] Bruno Imthurn,[9] Jeffrey T Jensen,[10] Andrew M Kaunitz,[11] Ali Kubba,[12] Medlard M Lech,[13] Diana Mansour,[14] Gabriele Merki,[15] Thomas Rabe,[16] Katarina Sedlecki,[17] David Serfaty,[18] Jacques Seydoux,[19] Lee P Shulman,[20] Regine Sitruk-Ware,[21] Sven O Skouby,[22] Anne Szarewski,[23] James Trussell,[24] Carolyn Westhoff[25]

A recent statement

SUMMARY OF THE CURRENT EVIDENCE CONCERNING THE RISK OF VTE

Several registry-based case-control studies have come to the conclusion that the use of third- and fourth-generation CHCs is associated with a higher risk (RR 1.6–2.4) of VTE than that related to the use of CHCs containing LNG. Two large cohort studies did not find such a difference.

Many factors contribute to VTE risk (e.g. age, duration of use, weight, family history, etc.), which makes epidemiological studies vulnerable to bias and confounders, and may explain contradictory results.[21] Additional prospective well-controlled studies are needed.

The inherent inability of database studies to adequately control for baseline confounders render this design less suitable for providing further clarification.

Some epidemiologists question whether the RR increase of around 2 described in the aforementioned case-control studies reflects a clinically relevant difference.

Several studies have shown that the risk of VTE during pregnancy and the postpartum period is considerably higher (29–300 per 10 000 users) than during use of a CHC.[21]

A recent statement

SUMMARY OF THE CURRENT EVIDENCE CONCERNING THE RISK OF VTE

Several registry-based case-control studies have come to the conclusion that the use of third- and fourth-generation CHCs is associated with a higher risk (RR 1.6–2.4) of VTE than that related to the use of CHCs containing LNG.

- Eight of 10 studies have demonstrated a higher risk of VT with use of 4th vs 2nd generation hormonal contraception.
- Of these eight studies, six were cohort studies, two were case-control studies

A recent statement

Two large cohort studies did not find such a difference

- Of the two studies demonstrating no difference, one was a cohort study, the other a case-control study. Both by Dinger et al. and both sponsored by the marketing holder.
- The “large” Dinger cohort study included 118 events, while the Danish cohort study included 4,246 or 35 times as many events.

Validity of statement

Many factors contribute to VTE risk (e.g. age, duration of use, weight, family history, etc.), which makes epidemiological studies vulnerable to bias and confounders, and may explain contradictory results.

- Those with the most effective confounder control found the highest rate ratios of venous thrombosis between users of 3rd/4th versus 2nd generation hormonal contraceptives

A recent statement

Additional prospective well-controlled studies are needed.

- How many well controlled cohort studies are needed before we accept a difference?
- So far we have seven independent studies.
- Nothing in these studies supports the assertion that the results were due to bias or uncontrolled confounding

Validity of statement

The inherent inability of database studies to adequately control for baseline confounders render this design less suitable for providing further clarification.

- The database studies actually had better confounder control than those based on questionnaires.
- The database studies have far more precise exposure and end point data

Validity of statement

Some epidemiologists question whether the RR increase of around 2 described in the aforementioned case-control studies reflects a clinically relevant difference.

- If you are in doubt about the clinical relevance of a doubled risk of venous thrombosis, then ask the one half of women who could have avoided their thrombosis just by using a safer product, whether this is a clinically relevant difference.

Validity of statement

Several studies have shown that the risk of VTE during pregnancy and the postpartum period is considerably higher (29–300 per 10 000 users) than during use of a CHC.

- If a woman goes through a pregnancy and a puerperal period in a year, her relative risk of venous thrombosis will on average be increased about eight times.
- A woman on a 3rd or 4th generation pill has a six times increased risk – roughly the same
- Pregnancy is not the alternative to high risk pills. That is low risk pills.

Validity of statement

Conclusion:

- Not a single one of the ”summary of the current evidence” statements holds true.
- So much for a multi-author statement

IPPF

From choice, a world of possibilities

February 2013

IMAP= International Medical Advisory Panel

IPPF Medical Bulletin

IMAP Short Statement on the Safety of Third and Fourth Generation Oral Contraceptives

Based on the analysis conducted by the United States Food and Drugs Administration (FDA) (2013) and the recommendations contained on the publications "Family Planning: a Global Handbook for Providers" by WHO (2011) and Medical Eligibility Criteria (WHO, 2010),[i] IMAP Members provide guidance to IPPF's Member Associations on the safety of third and fourth generation oral contraceptives. This statement is developed in response to recent public alarm in European countries, where women sued manufacturers for potential fatal blood clots (Venous Thromboembolism) as a result of using Meliane (Gestodene-containing oral contraceptive pill). The conclusions presented below do not apply to implants, IUS or other products containing the active components in third and fourth generation oral contraceptives.

What are third and fourth generation

What is Venous Thromboembolism

The term venous thromboembolism (VTE) refers to both deep vein thrombosis (DVT) – a blood clot in one of the deep veins of the body; and pulmonary embolism – a blood clot that travels through the bloodstream and lodges in one of the lungs.

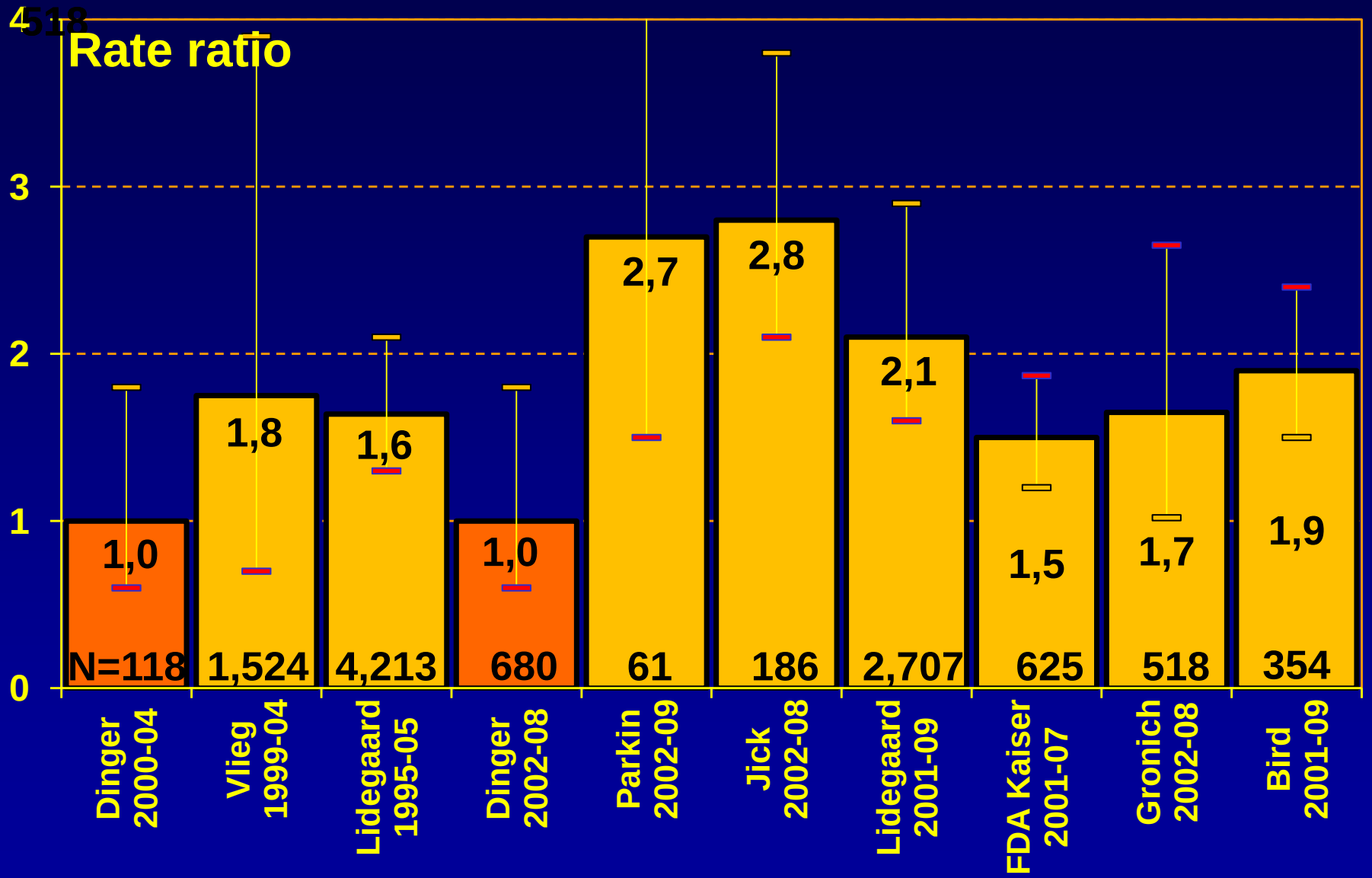
Evidence on third and fourth generation pills

- Recent epidemiological studies reviewed by the FDA have not shown the magnitude of increased risk of Venous Thromboembolism (VTE) reported in earlier studies as a result of using third and fourth generation oral contraceptives[ii].
- Earlier studies reporting increased risk of VTE produced conflicting results and had methodological limitations that call into question the validity of their findings and conclusions about the magnitude of the additional risk associated with using these products.
- Changes in the results of coagulations tests as a result of using third and fourth generation oral contraceptives suggested in earlier studies have not been shown to be directly responsible

Evidence on third and fourth generation pills

- Recent epidemiological studies reviewed by the FDA have not shown the magnitude of increased risk of Venous Thromboembolism (VTE) reported in earlier studies as a result of using third and fourth generation oral contraceptives[ii].
- Earlier studies reporting increased risk of VTE produced conflicting results and had methodological limitations that call into question the validity of their findings and conclusions about the magnitude of the additional risk associated with using these products.

COC with DRSP vs LNG



BMJ Editorial Nov 2011

This new study has tackled many of the concerns expressed about the earlier investigation. Although unpalatable to some, it is difficult not to conclude that combined oral contraceptives with desogestrel, gestodene, or drospirenone confer a higher risk of venous thromboembolism than those with levonorgestrel.

Philip Hannaford. BMJ 2011; 343: d6592

Human weaknesses

One of the most widespread human weaknesses is our readiness to accept claims that fit our beliefs and reject those that clash with them. We demand impossible standards of proof when confronted with something we don't want to hear, but will believe any old cobblers if it confirms our prejudices:

The Guardian, November 22, 2011

Conclusion

- The majority of epidemiological studies fulfilling basic scientific rules for such studies are valid.
- The interpretation of epidemiological studies by people without epidemiological knowledge is often non-valid.
- The evaluation of epidemiological studies by company sponsored experts is generally non-valid.

Hormonal contraception and venous thrombosis

- George Monbiot, Guardian, March 2010

”In fighting for science, we subscribe to a comforting illusion: That people can be swayed by the facts”

http://www.monbiot.com/2010/03/08/the-unpersuadables/

Hormonal contraception and venous thrombosis

Thanks for your attention

www.lidegaard.dk/slides