Combined oral contraceptives and thromboembolic risks

A regulatory conundrum

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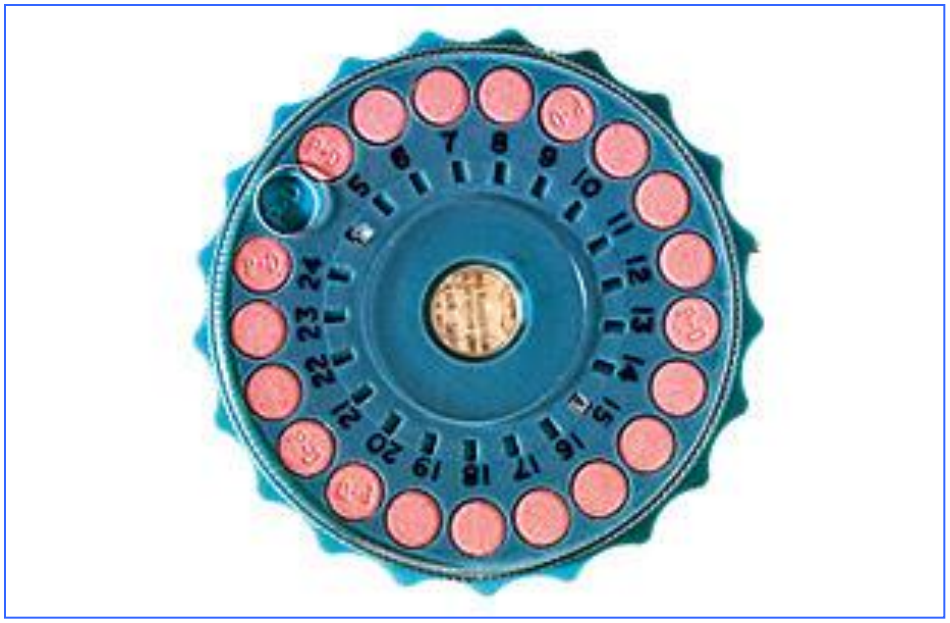
Long recognized adverse event

- First birth control pill approved May 9, 1960
- First case report of venous thromboembolism (VTE) in *the Lancet* Nov 18, 1961
- Higher estrogen dose; ↑ VTE, stroke & MI risk



Oral contraceptives and VTE risks

Most frequent cardiovascular risk

Non-pill users*	***Per 10,000/year***
Under 35	2
Aged 35-49	5
Pill users (all low-dose)*	***Per 10,000/year***
Under 35	6
Aged 35-49	15
Pregnancy (all ages)¶	7-27
Post-partum (all ages) ¶	40-65

*Lidegaard et al. BMJ 2011; 343:d6423

¶ www.fda.gov/Drugs/DrugSafety/ucm299305.htm

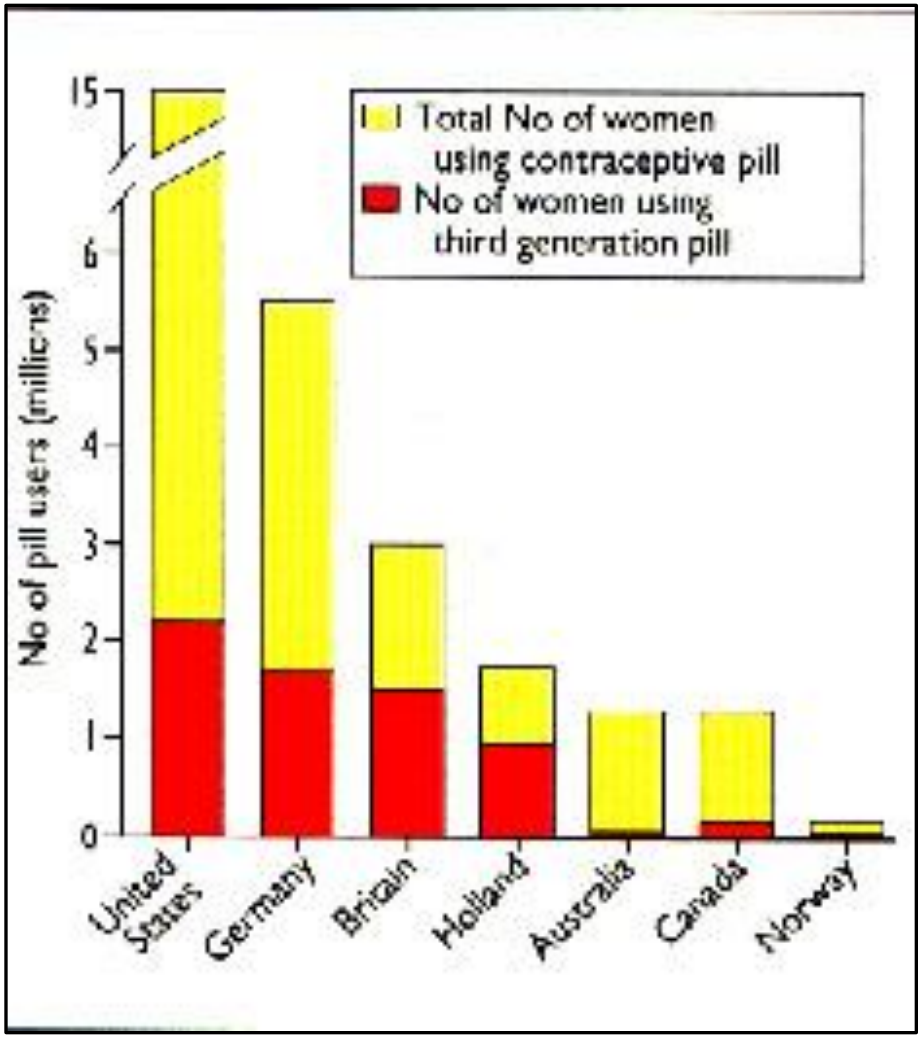
October 1995 – the UK "pill scare"

- '3rd generation' pills: with desogestrel and gestodene
- Marketed from 1980's; claim = less androgenic
- Case-control studies ↑ risk
  - Farley et al. (WHO) Lancet 1995; 346: 1582-8
  - Jick et al. Lancet 1995; 346: 1589-93
  - Spitzer et al. BMJ 1996; 312: 83-8
  - Bloemenkamp et al. Lancet 1995; 1593-6

Regulatory response in mid 1990's

- UK advises doctors and public of risk
- Germany limits use: not first time, < age 30
- Norway: limits use; not first time, not first line
- Netherlands, U.S., Canada, Australia: no action
- European Union: advises of risk
- World Health Organization: advises of risk

Women using oral contraceptives - 1995



BMJ 1995;311:1589-1590

Aftershocks of the "pill scare" in Europe

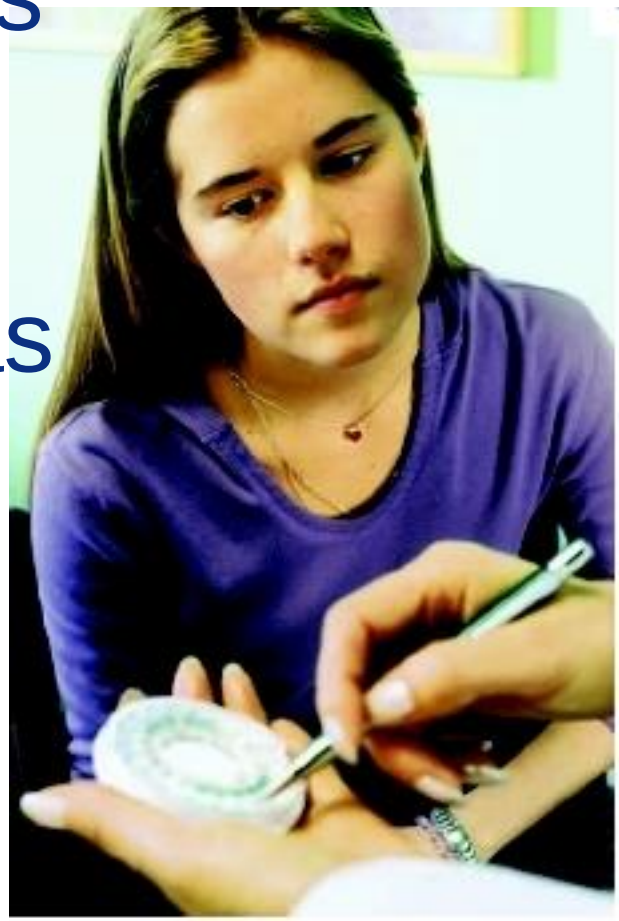
- Lead Canadian pharmacoepidemiologist, author of Schering study – UK press conferences
- Re-analysis of UK GPRD study by Farmer et al., opposite conclusions; journal later apologizes
- Claimed increase in unwanted pregnancies not supported by evidence*

**Jick et al. Lancet 1998;351:1404-5*

Selection bias

New user bias

Confounding



Attrition bias

Referral bias

Minor effect

The aftermath of this controversy…

- Meta-analysis: RR = 1.7 (95% CI 1.4-2.0)*
  - RR= 1.3 (1.0-1.7) if industry funded
  - RR= 2.3 (1.7-3.2) not industry funded
- New delivery modes – patch, ring
- New progestin – drospirenone (Yaz, Yasmin)
- Many more studies – refined methods

**Kemmeren et al. BMJ 2001;323:1-9*

To get a new contraceptive to market

- Randomized controlled trials of effectiveness ‘open-label’ or uncontrolled
- 2000 to 3000 women exposed, 1-2 years
- Inadequate data to characterize VTE risk

A saturated market – same pregnancy rate

Min-Ovral, Portia, Seasonale/nique	EE 30 µg/ LNG (levonorgestrel) 150 µg
Alesse, Aviane	EE 20 µg/ LNG 100 µg
Brevicon 1/35, Ortho 1/35	EE 35 µg/ NET (norethindrone) 1mg
Brevicon 0.5/35, Ortho 0.5/35	EE 35 µg/ NET 0.5 mg
Loestrin 1.5/30	EE 30 µg/ NET 1.5 mg
Minestrin 1/20	EE 20 µg/ NET 1mg
Ortho	EE 35 µg/ NET 0.5mg
Cyclen	EE 35 µg/ NGM (norgestimate) 250 µg
Marvelon, Ortho-Cept, Apri	EE 30 µg/ DSG (desogestrel) 150 µg
Demulen	EE 30 µg/ Ethynodiol 2mg
Yasmin	EE 30 µg/ DRSP (drospirenone) 3mg
Yaz	EE 20 µg/ DRSP 3mg (24 days on/ 4 off)
Diane-35	EE 35 µg/ cyproterone 2 mg
Linessa	EE 25 µg/ DSG 0.1mg; 0.125 mg; 0.15mg
Ortho 7/7/7	EE 35 µg/ NET 0.5 mg: 0.75 mg; 1 mg
Synphasic	EE 35 µg/ NET 0.5 mg; 1 mg; 0.5 mg
Tri-Cyclen	EE 35 µg/NGM 0.18 mg; 0.215 mg; 0.25 mg
Tri-Cyclen Lo	EE 25 µg/NGM 0.18 mg; 0.215 mg; 0.25 mg
Tri-Phasil, Triliquar	EE 30 µg/EE 40 µg/ EE 30 µg/ LNG 0.05 mg/ LNG 0.075 mg/ LNG 0.125 mg

Yaz and Yasmin (drospirenone / EE)

DROSPIRENONE IS A SPIRONOLACTONE ANALOGUE WITH ANTIMINERALOCORTICOID ACTIVITY (3 MG EQUIVALENT TO ~25MG SPIRONOLACTONE); CAN AFFECT POTASSIUM METABOLISM

Regulators require post-market studies

- FDA concerned about potassium; later VTE
- EMA concerned about VTE
  - Manufacturer sponsored studies show no extra risk* (~60,000 women-years/study)
  - Two independent studies, BMJ 2009 – riskier (Lidegaard et al.10.4 million women-years)
- Independent studies characterized as ‘weaker methods, poorer quality’

**Dinger et al Conteraception 2007; Seeger et al Obstet Gynecol 2007*

Contraceptives and VTE risks

Low estrogen dose pills	***versus non-use****
Levonorgestrel (LNG)	2.2 (1.7-2.8)
Desogestrel '3rd generation'	4.2 (3.6-4.9)
Drospirenone (Yasmin)	4.5 (3.9-5.1)
Drospirenone (Yaz)	4.8 (3.2-7.3)
Newer contraceptives	***versus LNG****
Drospirenone (Yasmin)	2.2 (1.6-2.8); NNH=1111/year§
Drospirenone (Yaz)	2.1 (1.3-5.5)
Patch (EVRA)	1.9 (0.9-4.0)**
Ring (Nuvaring)	1.8 (1.3-2.4)**

*Lidegaard et al. BMJ 2011; ** Lidegaard et al BMJ 2012 §Bjerre et al BMJ 2000

"Yaz is the best-selling oral contraception pill in the United States, with sales last year of about $616 million…"

– New York Times, Feb 10, 2009

FDA Warning letter – Yaz Oct 2008

"The TV ads are misleading because they broaden the drug's indication, overstate the efficacy of YAZ and minimize serious risks…"

Bloomberg BusinessWeek

Sunday March 14, 2010

HOME FINANCE TECHNOLOGY INNOV

Bloomberg

Bayer Accused in Canadian Lawsuit of Hiding Yaz Risks (Update1)

March 11, 2010, 12:54 AM EST

(Adds Bayer statement in fifth paragraph.)

By Joe Schneider

March 10 (Bloomberg) -- Bayer AG, Germany's largest drugmaker, was accused in a lawsuit of ignoring health risks of the contraceptive Yaz and advertising the drug as safe to boost sales.

The Yasmin family of birth-control pills, known as Yaz and Yasmin, carries a four times increased risk of deep vein thrombosis and pulmonary embolism compared with other contraceptives, according to the suit, filed today in St. Catharines, Ontario, by two women. They seek class-action, or group, status to represent all women who used the drugs.

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Pfizer Says Two Cancer D Fail in Clinical Trials (Upd

STORY TOOLS

What's wrong with this picture?

- Newer pills, patch, ring no more effective
- Tolerability no better
- Life-threatening risks (VTE) higher
- US FDA's own study confirms Yaz/Yasmin risks
- worse than existing options!

JAMA, May 2012

Recommended solutions

- Pre-market
  1. Require evidence of therapeutic advantage
  2. Require enough exposure for known SAE
  3. Conditional approval, access via trials
  4. Open, accountable decision-making
- Post-market
  1. Independent safety assessments (DSEN)
  2. Registered protocols, set scientific methods
  3. Full public access to data (+international reg)
  4. No direct-to-consumer or physician-oriented promotion allowed until safety profile known

Questions or comments?