Conflict of Interest

- Participation in clinical trials supported by Bayer Health Care, MSD, Pfizer, Procter/Gamble, Solvay, Grünenthal
- Member of Advisory Boards of BHC, MSD, Gedeon Richter, Lilly
- Lecturer during events sponsored by the above mentioned pharmaceutical companies

The focus on this collaboration was on counselling women and choices between different contraceptives and quality of life issues

«The new pill scare» the good and the bad pills

- Publications in BMJ claim an increased risk for CHC containing 3rd and 4th generation progestogens compared to those containing the second generation progestoge levenorgestrel
  - 3rd and 4th generation (Gestoden, Desogestrel, Drospirenone inkl Cyproteronacetat)

- **Media reports about severe complications in young women using yasmin**
  - Severe Handicap of 16 year old girl after reanimation in the context of a thromboembolic event
  - Other VTEs among young women

Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ 2009;339:b2890.
van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJ, Rosendaal FR. The venous thrombotic risk of oral contraceptives, effects of estrogen dose and progestagen type: results of the MEGA case-control study. BMJ 2009;339:b2921.

The «new pill scare» The good and the bad pill

- Additional publications report the same increased risk for CHCs containing 3rd and 4 th generation propestogens compared to levonorgestrel

- Other dramatic media reports
- Fatal complications in Diane users
- In France Diane 35 after almost 30 years is taken from the market by the authorities

- Van Vliet HAA, Winkel TA, Noort I, Rosing J, Rosendaal FR. Prothrombotic changes in users of combined oral contraceptives containing drospirenone and cyproterone acetate. J Thromb Haemost 2004;2:2060–2.
- Lidegaard Ø, Nielsen LH, Skovlund CW, Løkkegaard E. Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001–10. BMJ 2012;344:e2990.
- Lidegaard Ø, Milsom I, Geirssons RT, Skjeldestrad FE. Hormonal contraception and venous thromboembolism Acta Obstet Gynecol Scand 2012;91:769–78.

Previous studies found other results

- Publications in Contraception and Obstet Gynecol did not show significant differences between the different progestogens

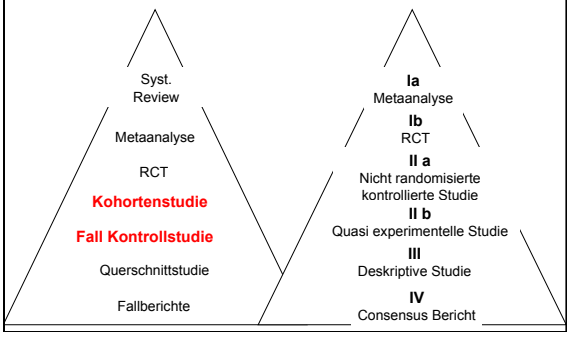
- **Nor reports in the media**
- **Studies sponsored by pharmaceutical company**

Dinger JC, Heinemann LAJ, Kuhl-Habich D. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance study on Oral Contraceptives based on 142,475 women-years of observation. Contraception 2007;75:344–54.
Seeger JD, Loughlin J, Eng PM, et al. Risk of thromboembolism in women taking ethinylestradiol/ drospirenone and other oral contraceptives. Obstet Gynecol 2007;110:587–93.
Skjeldestad FE. Increased number of induced abortions in Norway after media coverage of adverse vascular events from the use of third-generation oral contraceptives. Contraception 1997;55:11–4.
Goodyear-Smith A, Arroll B. Termination of pregnancy following panic-stopping of oral contraceptives. Contraception 2002;66:163–7.

The epidemiological controversy about the impact of different progestogens in combined hormonal contraceptives

- Type of studies and level of evidence
- Statistical significance versus clinical significance

Hierarchy of evidence



The epidemiological challenge

Weight FH

Age Smoking

Group 1 Group 2

Dosage Intake

Duration of uninterrupted use

Confirmed VTE, TEV

Consequence for research

- Randomized Clinical Trials will not be feasable
- Prospective observational studies with Starters of different CHC stratified according to age, weight, family history, smoking with the same type of surveillance and outcome evaluation developped and under supervision and control of a committee including representatives of health agencies, physicians, industry, epidemiologists, womens organisations, international bodies like WHO etc.
- In case that first prescription of LNG containing CHCs becomes obligatory prospective study looking into adverse outcomes, tolerability, satisfaction and continuation.

The «biological» controversy

Konsensus

- **Estrogen is the predominat factor in the pathophysiology of venous thrombosis**
- **Progestogens alone seem not to increase the risk for VTE**
- **If there is a risk between progestogens it has to be an indirect effect via Ethinylestradiol metabolism and/or EE action**

The «biological» controversy

- Progestogens differ in their androgenic or antiandrogenic partial effects

Progestogens with androgenic properties have an antiestrogenic action and this reduces the risk of VTE (less «estrogenicity»)
SHBG and APC Resistence are suitable surrogate markers for VTE risk

This mechanism has never been proven and the clinical importance is questionable
There are no suitable surrogate markers for VTE risk

Open questions and doubts

- Until now no epidemiological clear proof that 20 ug pills have a lower risk than 30 ug pills. but
  - How can a progestogen have a stronger pharmacodynamic action via EE than a dosage difference of more than 30% of EE.
- Norgestimate is metabolized to LNG which is considered the progestogen with the lowest risk but
  - Preprations with Norgestimate as a patch have a higher risk in the epidemiological studies
- Users of the vaginal ring have a very low exposure to EE but
  - The vaginal ring has an increased risk
- Mirena has only a small systemic action
  - The studies show a risk reduction compared to non users

The new public health debate

The new progestogens are more dangerous to the health of women than the LNG containing CHCs?
Evidence and clinical importance ?

Inform and educate patients
Shared decision making and counselling

The new progestogens are more dangerous to the health of women than the LNG containing CHCs
Evidence given
Clinically important

Obligatory first prescription with LNG containing CHC
New progestogens only with limited indication as second choice
Prohibit new progestogens

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[1].
- 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 for an increase in VTEs.
- Medical Eligibility Criteria (WHO, 2010) indicates that women with history of deep venous thrombosis (VT) or pulmonary embolism (PE), acute DVT/PE, DVT/PE and established on anti-coagulant therapy, or women who have been through a major surgery with prolonged immobilization are not eligible to uptake oral contraceptive pills.

IPPF Bulletin
Februar 2013

Recommendations

- Member Associations can advise women to continue using the third and fourth generation pills as currently there is no clinical evidence of increased risk for VTE. Member Associations should open the space to discuss clients' concerns regarding third and fourth generation pills. Counselling women about the potential risk is appropriate, if they are informed about what signs, symptoms and risk markers they should pay attention to.
- Member Associations may continue providing third and fourth generation pills as part of their contraceptives method mix. However, It is recommended that providers follow closely the criteria stated on the Medical Eligibility Criteria (WHO, 2010) to assess women's eligibility to take any contraceptive including oral contraceptives.
- Member Associations should support information, communication and education activities to overcome the negative messages around oral contraceptives spread as a result of the recent public alarm in Europe.

Conclusions and practical consequences

- Contraceptive methods should protect women against untimed pregnancies with their negative medical and psychosocial consequences
- Until now there is no method available which is 100% effective, free from any possible health risk, and well tolerated by all women
- The choice of a contraceptive method must therefore be always based on a thorough, individual assessment of risks and benefits, advantages and disadvantages.

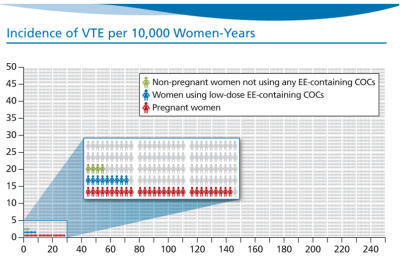
Conclusions and practical consequences

- In this process of balancing different characteristics of contraceptive methods have to be taken into account and discussed with women
  - Efficacy and ease of use
  - Health risks
  - Side effects
  - Health benefits
  - Additional therapeutic potential
- The women have to attribute the importance and weight of this different characteristics in a process of shared decision making with their health care professional.

Conclusions and practical consequences

- Combined hormonal contraceptives are highly efficient when properly used.
- In relation to their composition CHCs are well tolerated by most women, and have additional health benefits as well as specific therapeutic actions
- The main health risk of CHCs is the increased risk of thromboembolic events. The absolute risk increase is small and considerably lower than the risk associated with a pregnancy or the postpartum period.
- This risk is mainly linked to the action of the estrogen component in CHC.
- There are studies indicating that there is a difference in risk related to the progestogen component in CHCs. It seems that levonogestrel containing CHCs have the lowest risk among CHCs and that the other progestogens lead to an relative risk increase of about 1.4-2.2 in comparison to levonorgestrel. There are however conflicting data and other studies have not confirmed this risk. The difference in risk should be further elucidated. Women have to be informed about these findings
- Women should also be informed about the possible health benefits for users of combined hormonal contraceptives

Risk Counselling

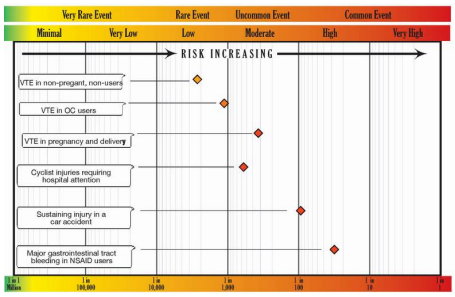


- Risk of VTE is highest in the post-partum period[1]

http://www.peervoice.com/o1/pvr72

PeerVoice

Putting the risk into perspective

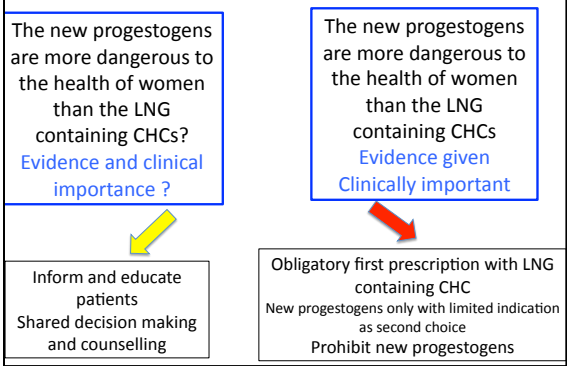


Adapted from Stallings SP and Paling JE: Obstet Gynecol 2001
Data on VTE incidence: Dinger JC, et al. Contraception. 2007

Conclusions and practical consequences

- The most important measure to reduce the incidence of DVT in users is to look for risk factors in potential users (Personal history, Family history, Weight, Smoking, Age).
- By using Medical Eligibility Criteria (WHO MEC or UK MEC) in women with these risk factors a thorough risk- benefit evaluation should be made and the use of progestogen only contraceptives or non hormonal contraceptives should be advised in those women where the risk outweighs the benefit.

The new public health debate



Evaluate a public health intervention in the context of family planning

Do a prospective study with starters monitoring the following outcomes during 1 year or if possible 2 years

- **VTE**
- **Side effects (tolerability)**
- **Positive effects**
- **Compliance**
- **Discontinuation**
- **Unplanned pregnancy**