# Hormonal contraception and cardiovascular risks

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# Case study : High blood pressure



- 40 years old, she wants a prescription for the patch she has been taken since her last pregnancy (8 years ago)
- High blood pressure(HBP) during her last pregnancy but normal until now
- No smoking
- Family history of HBP
- BP: 160/100
- Do you prescribe the patch ?

# High blood pressure and hormonal contraception



- COCs Increase the risk of high BP in increasing synthesis of angiotensinogen
- Normalization of the BP in 50% of the cases when discontinue the COC

| Stroke risks | |
|---|---|
| Risks factors | 0R |
| Non smoking<br>Smoking | 2,5<br>5,5 |
| High blood pressure >160 and >100mmhg | 13,4 |

# High blood pressure



- Recommendation (WHO eligibility criteria 2009(

Stop COC(pill, patch, ring) if confirmation of high blood pressure (>16 and >10

No COC, even if blood pressure adequately controlled with a treatment

POC generally use

POI injectable not recommended

- Propose an other method:

  - IUD
  - Sterilization

- HBP during pregnancy is not a contraindication of COC/injectable but a risk factor.

# WHO

## Hypertension artérielle (HTA)

| | | |
|---|---|---|
| HTA bien contrôlée et mesurable ou HTA élevée (systolique 140-159 ou diastolique 90-99 mmHg) | | Méthodes progestatives (PMP, implant), DIU-Cu, DIU-LNG, méthodes barrières, naturelles |
| | | Progestatif injectable |
| | | Méthodes estroprogestatives (COC, patch, AIV) |
| HTA élevée (systolique ≥ 160 ou diastolique ≥ 100 mmHg) ou pathologie vasculaire | | DIU-Cu, méthodes barrières, naturelles |
| | | Méthodes progestatives (PMP*, implant*), DIU-LNG* |
| | | Progestatif injectable |
| | | Méthodes estroprogestatives (COC, patch, AIV) |
| Antécédent d'HTA gravidique (quand la tension artérielle mesurée est normale) | | Méthodes progestatives (PMP, injection progestatif, implant), DIU-LNG, DIU-Cu, méthode barrières, naturelles |
| | | Méthodes estroprogestatives (COC, patch, AIV) |

# Case study
# Obesity



30 years old, nulliparous

BMI  29/BP: 120/80

Familial history of obesity and high blood pressure

Wants (may be) a bariatric surgery

Need a contraception,  and don’t want an IUD or implant

No smoking

Blood lipid parameters normal

What prescription?

# Obesity (BMI >30)



Linked to an increased cardio vascular risk

BMC >25 multiply by 2 the thromboembolic risk
BMC >25 multiply by 4/5 the thromboembolic risk

Recommendations (WHO eligibility criteria 2009)

- POPs, implant  can be used in any circumstances
- COCs can generally be used but consider the other risk factors (age, smoking, diabetes)
- POI injectable +/-

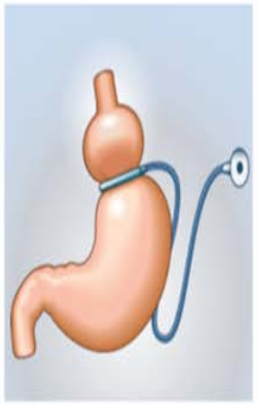
*Implant less effective if weight > 80 kg ????few data*

# Contraception et chirurgie

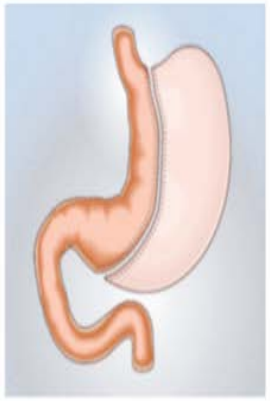
STOP COC before the intervention
Thrombo embolic risks ++

No contraindication of COC or POP

Anneau gastrique

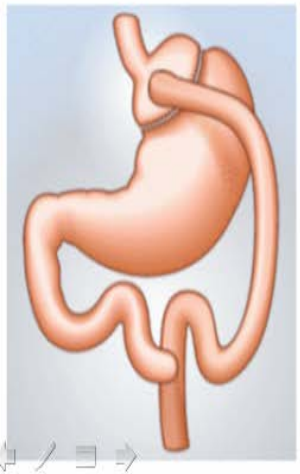


Sleeve gastrectomy

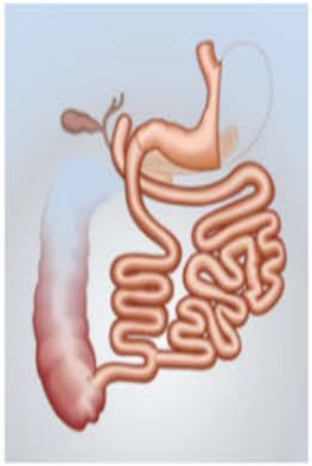


= restrictive
réduction gastrique

By Pass gastrique



Dérivation bilio-pancréatique



= mixte
réduction gastrique +
malabsorption par
court-circuit digestif

Contraindication of all oral contraception Decrease of effectiveness of oral contraception by malabsorption

# Case study
# Contraception and lipids parameters



She is 32 years old, 2 children

Takes COC for 5 years.

BP:130/80 60kg/1,60

Family history of hyperlipidemia

No family history of CVD before 50 years

Cholesterol is 2,60g

LDL : 1,30

# Contraception and lipids parameters



- CHCs increase total cholesterol, VDRL , LDL

- Recommendation (WHO criteria eligibility)
- CHCs can generally be use
- Consider the other risks factors (age, weight, smoking, blood pressure)

Routine screening is not appropriate because of the rarity of the conditions

- French Recommendation

Screening every 5 years

NO CHC when Triglyceridemia > 2- 2g 50

Cholesterol >3g

LDL Cho > 1.90 g-2.20 g/l

# Case study
# Diabetes



- 28 years old
- diabetes since age 9, adequately controlled
- No complication of the diabetes
- One abortion 2 years ago
- No smoking
- 60 kg/1,62
- Uses condom but has now a stable partner and wants an other contraception

# Diabetes (insulin and non insulin dependent)



- COCs are responsible of a decrease of carbohydrate tolerance (the androgenic action of the progestin ) but biological parameters remain normal

- Slightly less decrease with the more recent progestin

# Diabetes (insulin and non insulin dependent)



Recommendations (WHO eligibility criteria 2009)

- Combine methods, POP, POI generally use method **if diabetes is adequately controlled and no vascular complications** Consider the other risks factors (age, weight, smoking, blood pressure)
  - Vascular complications (kidney, eye, diabetes >20 years) : **absolute contraindication for estrogen**
  **but** POPs generally use
- Others methods (IUD)

Gestational diabetes during pregnancy is not a contraindication of COC/injectable but a risk factor.

# Case study headaches/migraines



- 21 years old, nulliparous ; 50kg/1,70
- COC for 1 year
- No smoking
- Since few months, headaches during the free interval

- 23 year old has migraine with aura for 3 years
- Came after an abortion
- Wants a contraception

# Headaches/migraines



Recommendations (WHO eligibility criteria 2009)

- Nonmigrainous headaches
  - Hormonal methods can be used in any circumstances

- Migraines without aura
  - <35 yo Combined method generally used but switch to progesterone seems to be better
  - >35 yo Progestérone method

- Migraines with auras at any age :
  - Combined methods: **Not to be us**
  - POP can generally be used

| Stroke risks for migraine + aura | |
|---|---|
| Hormonal contraception non users | × 6 |
| COC users | × 14 |
| COC+ smoking | × 34 |

*Others contraception…..*

# Céphalées et OMS



## Céphalées

| | | |
|---|---|---|
| Céphalées non migraineuses (légères ou sévères) | | Méthodes estroprogestatives (COC, patch, AIV) (si déjà sous contraception, catégorie 2)<br>Méthodes progestatives (PMP, progestatif injectable, implant),<br>DIU-Cu, DIU-LNG, méthodes barrières, méthodes naturelles |
| Migraines, sans aura, femme < 35 ans | | PMP (si déjà sous contraception, catégorie 2), DIU-Cu, méthodes barrières, méthodes naturelles |
| | | Méthodes estroprogestatives (COC, patch, AIV) (si déjà sous contraception, catégorie 3), méthodes progestatives (progestatif injectable, implant), DIU-LNG |
| Migraines, sans aura, femme ≥ 35 ans | | PMP (si déjà sous contraception, catégorie 2), DIU-Cu, méthodes barrières, méthodes naturelles |
| | | Méthodes progestatives (progestatif injectable, implant), DIU-LNG, |
| | | Méthodes estroprogestatives (COC, patch, AIV) (si déjà sous contraception, catégorie 4) |
| Migraines avec aura | | DIU-Cu, méthodes barrières, méthodes naturelles |
| | | Méthodes progestatives (PMP, progestatif injectable, implant) (si déjà sous contraception, catégorie 3), DIU-LNG* (si déjà sous contraception, catégorie 3) |
| | | Méthodes estroprogestatives (COC, patch, AIV) |

# Case study
# Varicose veins



- 32 years old, 2 children, 1 abortion
- COC since 6 years
- Complaining of increase varicose veins and pain in the legs
- Family history of varicose veins but no family history of deep venous thrombosis (DVT)
- Does not want IUD.

# Superficial venous thrombosis



Recommendations (WHO eligibility criteria 2009)

- Varicose thrombosis is not a risk factor of DVT

All hormonal contraception can be used in any circumstances

- Superficial thrombophlebitis

COCs can generally be used but be sure of the diagnosis of “superficial”

POCs can be used  in any circumstances

# Case study
# Deep venous thrombosis (DVT)



- 40 years old , 2 children , 1 abortion
- Took COC few years ago
- Uses condom but want to take pills now
- Has been treated for a DVT last year (when she had a cast for a leg fracture)
- The test for the thrombogenic mutations was negative.
- 55kg /1,60
- BP: 120/80

# Thromboembolic risks and COC



- Regardless the type of pill, there is an Increase risk of venous thrombosis because of negative changes in hemostasis parameters linked mainly to estrogen

Progestin intervenes in decreasing the estrogenic level

| Age | Incidence of DVT for COC non users Per 10 000 women-years | OR (95% IC) | Incidence of DVT for COC users Per 10 000 women-years |
|---|---|---|---|
| < 30 years old | 1.2 | 3.2 (2.2-4.6) | 3.7 |
| 30-40 years old | 2.0 | 5.0 (3.8-6,7 | 10.0 |
| 40-50 years old | 2.3 | 5.8 (4.6-7.3) | 13.3 |

A van Hylckama Vieg.BMJ 3009

# 3rd , 4th generation progestin, acetate de cyprotérone and thromboembolic risks



Danish and Nederland survey published in 2009 in BMJ

- 10 millions Danish women cohort 15-49 years old between1995-2005.
- Thromboembolic risk x 2 with COC
- Decrease of the risk if 20/30ug EE pill (gestodène, désogestrel)
- Increase risk with G3
- Increase risk for acetate de Cyproterone acetate and Drospirone (x 2 to 3)
- Decrease with the duration of exposure

- MEGA: cases control survey 1524/1760 women<50years old
- Thromboembolic risk x 3 à 5 with COC with G3/G4
- Decrease of the risk if 20/30ug EE pill
- LNG: RR 3,9 à 4,6
- Increase rik with G3 and G4
  - gestodene (OR: 5 à 8),
  - desogestrel (OR: 7,3)
  -Acétate de Cyprotérone (OR :6,8)
  - Drospirénone (OR: 6,3)
- Increase risk mainly when start

# POP and risk of thrombosis



## Contraception micro-progestative et thrombose

| Auteurs | Type | RR (IC à 95%) |
|---|---|---|
| Lewis 1996 | Cas-tem | 1.28 (O.66-2.50) |
| Lidegaard 1998 | Cas-tem | 2.61 (0.69-9.80) |
| WHO 1998 | Cas-tem | 1.74 (0.80-3.99) |
| Vassilakis 1999 | Cohorte | 1.30 (0.30-6.80) |
| Heinemann 1999 | Cas-tem | 0.68 (0.30-2.60) |
| Lidegaard 2002 | Cas-tem | 2.00 (0.80-5.10) |
| | **Méta-analyse** | **1.45 [0.92-2.26]** |

Bergendal 2009

Pas de modifications des paramètres de la coagulation

D'après Geneviève Plu-Bureau

# Deep venous thrombosis (DVT)/pulmonary embolism



Recommendations (WHO eligibility criteria 2009)

- **Absolutes contraindication of all hormonal methods with estrogen**

- Whatever the circumstances of the DVT
- Whatever the doses , the type of estrogen or progestin
- With or without thrombogenic mutations

- Progestin only methods generally use ( but not in acute situation)
- And others contraception…..

# Case study
# Deep venous thrombosis (DVT)



- 40 years old , 2 children , 1 abortion
- Took COC few years ago
- Uses condom but want to take pills now
- Has been treated for a DVT last year (when she had a cast for a leg fracture)
- The test for the thrombogenic mutations was negative.
- 55kg /1,60
- BP: 120/80

The 16 years old daughter needs a contraception

# Family history (first degree relatives and < 60 years old) of deep venous thrombosis (DVT)/pulmonary embolism



Recommendations (WHO eligibility criteria 2009)

- Progestin only methods can be used in any circumstances
- Combined methods can be used generally
- Others contraception …..

Do we need to ask for a thrombogenic mutation check up before prescribing hormonal contraception?

- Only if there is a mutation in the first degree family
- Not useful (and very expensive) in other cases.

# Screening for thrombogenic mutation when family history of DVT/pulmonary embolism less than 60 years



- TCA, TQ, NFS
- Anti Thrombine,Protéine C, Protéine S
- Recherche un déficit quantitatif ou une anomalie qualitative
- Facteur V de Leiden G1691A
- Facteur II de Leiden G20210 A

# Case study
# hormonal contraception and smoking



- 34 years old, 1 child
- Smoking 10 to 15 cig/days since she is 17
- BP:120/70
- 60kg/1,75
- No personal or family history of CV disease
- Takes pill since the adolescence

# hormonal contraception and smoking



## Recommendations (WHO eligibility criteria 2009)

- <35 years old, COC can be used in any circumstances but consider the other risks factors
- >35 years old, COC not be used
- PO methods can be used in any circumstances

Tabac

| | Méthodes estroprogestatives | | | Méthodes progestatives pures | | | Dispositifs utérins implantables | | Méthodes barrières (préservatif, spermicide, diaphragme, cape vaginale) | Méthodes naturelles |
|---|---|---|---|---|---|---|---|---|---|---|
| | contraception orale combinée | patch | anneau intravaginal | pilule micro-progestative | progestatif injectable | implant progestatif | au cuivre | au lévonorgestrel | | |
| Âge < 35 ans | | | | | | | | | | |
| Âge ≥ 35 ans | Si < 15 cigarettes/jour | | | | | | | | | |
| | Si ≥ 15 cigarettes/jour | | | | | | | | | |

# Myocardial infarction (MI), smoking and COC

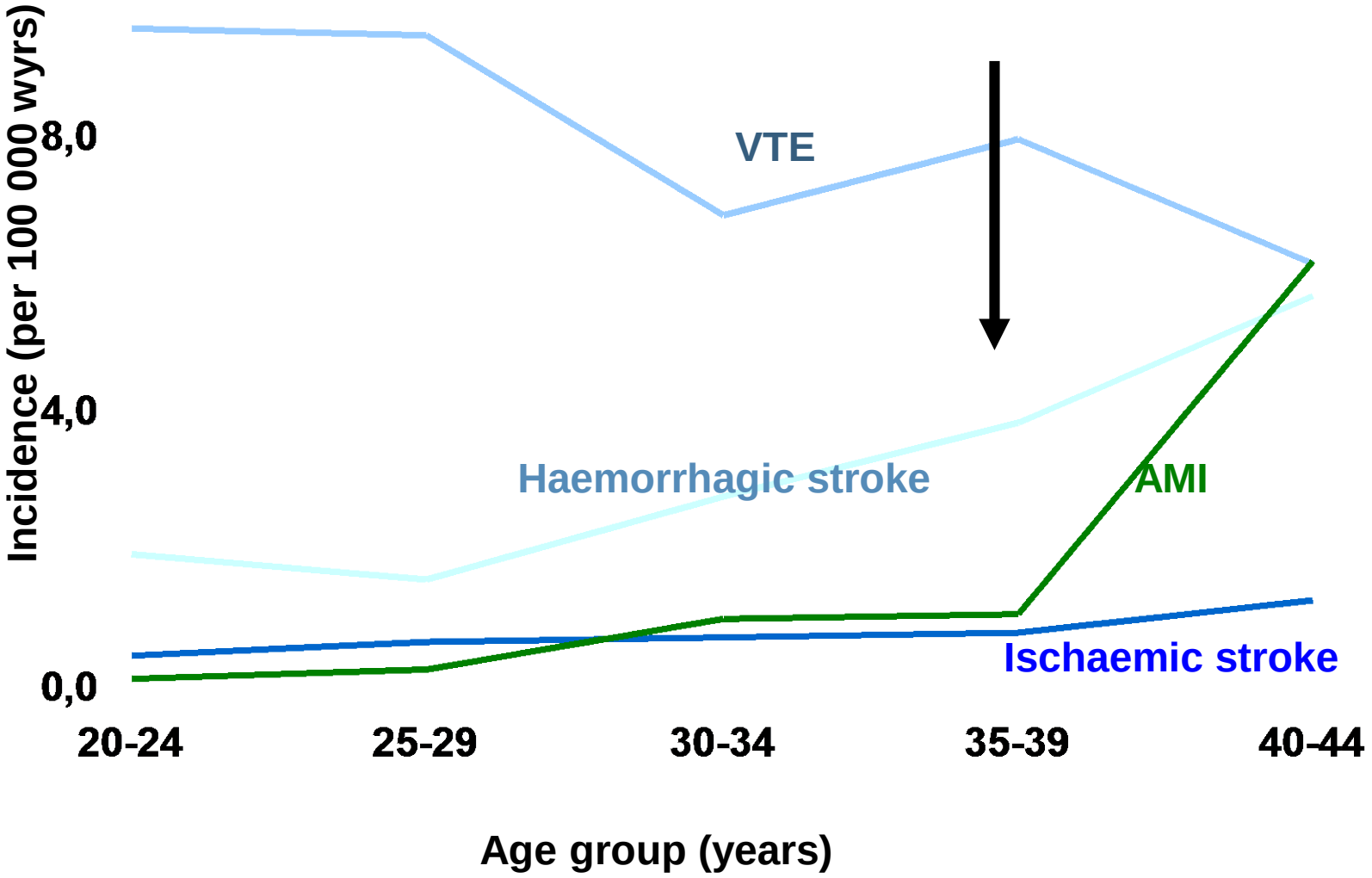


- Increase risk with age and number of cig/day but **the risk under 35 years old is very low**

| | < 35 years old per 100.000 | >35 years old per 100.000 |
|---|---|---|
| Non smoker | 0,06 | 3 |
| Smoker | 1,73 | 19,4 |

# Hormonal contraception and cardiovascular risks

# Observed CVD Incidence Oxford




*J Epidemiol Comm Health* 1998; **52**: 775

# CV risks of Combined method

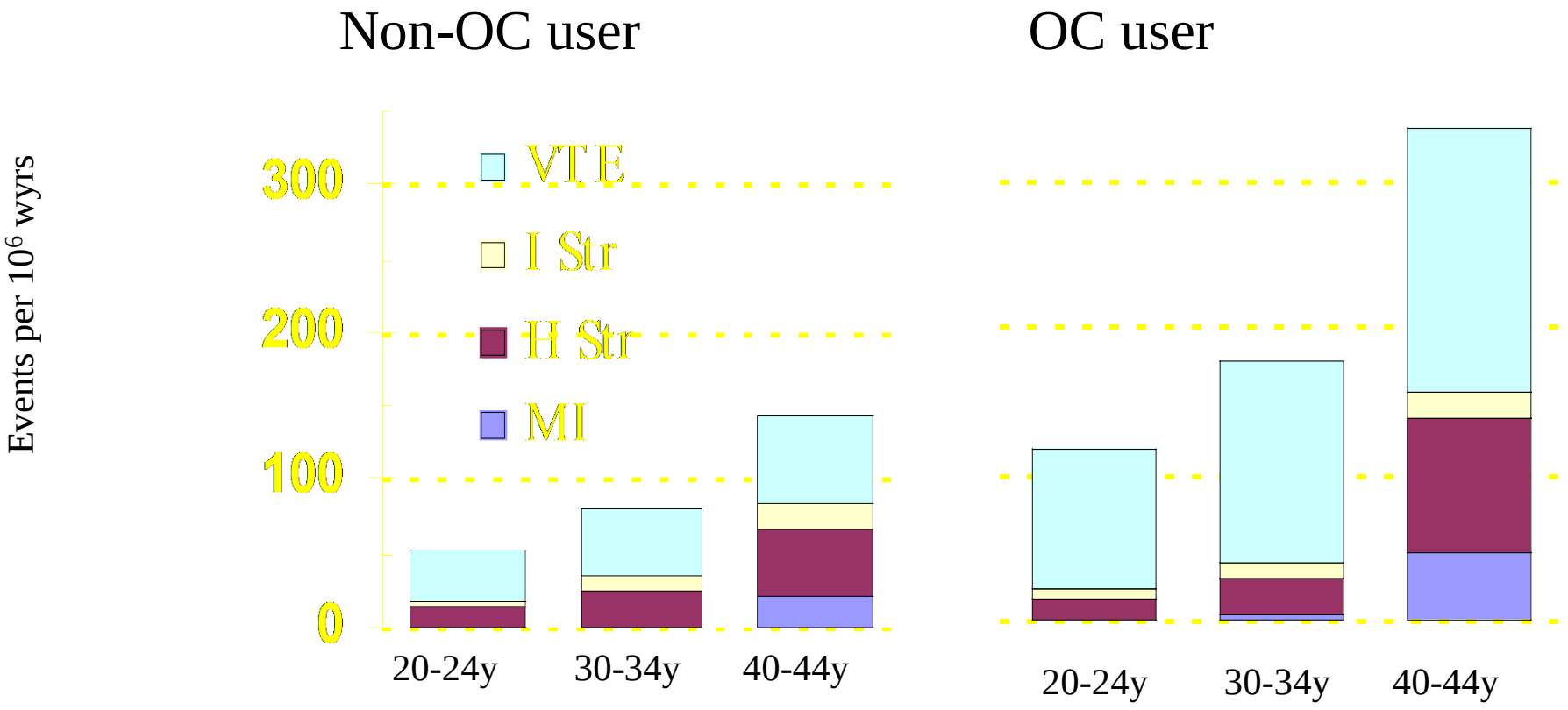
## WHO survey (case study
## 17 countries (5 Europe /12 DC



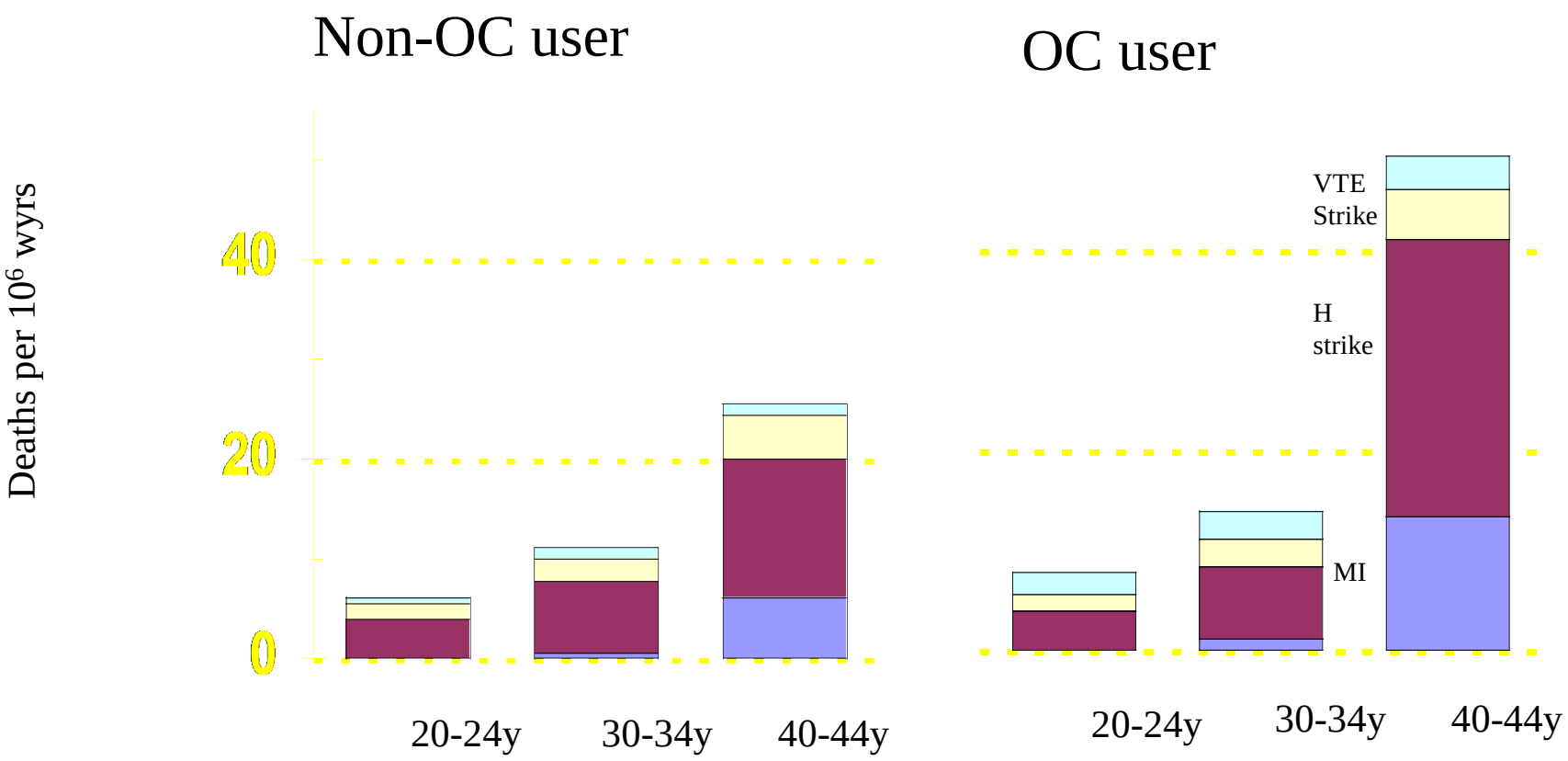
| | OR | Risk factors |
|---|---|---|
| **Deep venous thrombosis**<br>**Pulmonary embolism** | 4,1<br>20 per100 000 women year<br>30-40 per 100 000 women year for 3rd generation progestin | Weight<br>HBP during pregnancy |
| **Myocardial infarction** | 4,9 | + smoking : 44, 9<br>+ HBP : 12,8 |
| **Stroke** | 2,9 | + Smoking : 5,5<br>+ HBP : 13, 4 |

# CVD Incidence - Non-smoker





# CVD Mortality - Non-smoker



# Absolute Cardio vascular contraindications of combined methods



- Age >35 years old and smoking ( > 15 cig/j)
- High blood pressure ( S > 160 mm Hg or D > 100 mm Hg )
- Diabetes with vascular complication or  > 20 years
- Deep venous thrombosis whatever the circumstances
- Pulmonary embolism
- Known thrombogenic mutations

WHO  medical eligibility criteria for contraceptive use 2009

# Absolute Cardio vascular contraindications of combined methods



- Major surgery with prolonged immobilization
- Ischemic cardiopathy
- Complicated valvular heart disease
- Stroke
- Migraine with aura
- Systemic lupus erythematosus with (or unknown antiphospholipid antibodies)

WHO medical eligibility criteria for contraceptive use 2009

# Progestin-only methods CV contraindications



- Acute deep venous thrombosis (DVT)
- Active CVD disease
- Systemic lupus erythematosus with positive or unknown phospholipid antibodies

+ High blood pressure for Progestin only injectable

# Conclusion



- All combined methods have increased cardio-vascular risks whatever the dose of Estrogen or the type of progestin or the routes.
- The risk is very low and lower than pregnancy and delivery.
- Routine screening for lipid parameters or thrombogenic mutations is not appropriate because of the rarity of the conditions
- Plurality of risk factors may lead to not to prescribe or to discontinue
- Absolute contraindications are rare but has to be respected whatever the composition of the drug.
- benefit/risk balance has to be assessed for each woman and each time she is coming

# Mortality among contraceptive pill users



Cohort of 46112 femmes follow up since 1968

and121000 with a follow up of 36 years

- No increase of mortality compared to COC non users (nurse study)
- Decrease of the risk of mortality whatever the causes are RR=0,88 ( RCGP)
- Increase of violent death (2 studies)
- Decrease of the ovarian cancer incidence
- More often associated with beast cancer (nurse study)

BMJ. 2010 Mortality among contraceptive pill users: cohort evidence from Royal College of General Practitioners' Oral Contraception Study. .Hannaford PC, Iversen L, Macfarlane TV, Elliott AM, Angus V, Lee AJ.

BMJ 2014 ***Oral contraceptive use and mortality after 36 years of follow-up in the Nurses' Health Study: prospective cohort study.*** Charlton BM et all