UNIVERSITÉ PARIS DESCARTES

COCHIN BROCA HÔTEL-DIEU

Safety of estradiol containing combined hormonal contraceptives in perimenopausal women

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COI

- Member of an advisory board MITHRA (Estetrol in Menopause)
- Participation without honorarium to symposia organised by Besins, Mylan
- indirect
  - Ex member of EMAS and IMS boards
  - Member of GEMVI board
  - Member of ESC board

Why an hormonal contraception in the perimenopause?

- Contraception is needed until the last menstrual period
- Bleeding is a common feature in perimenopausal women. WHO and ACOG recommend pills for that indication.
- Perimenopause is a situation with hyper/hypoestrogenic states which implies tailoring hormone treatment
- Climacteric symptoms start in 30% of women long before the last menstrual period.

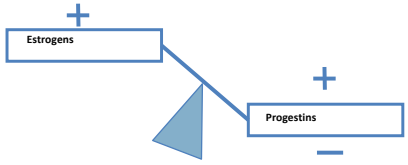
The evidence concerning estrogen/progestin and VTE

- Oral EE/ estradiol can activate the coagulation and increase the RR of VTE
- Transdermal estradiol at usual doses for MHT are not associated with activation of coagulation, VTE, stroke
- Type of progestin can modulate the estrogenic impact on coagulation

Composition of hormonal contraceptives

- EE and E2 (E2V)
  - Less hepatic impact
  - Rapid half life and metabolisation
  - Relative potencies: On the basis of hepatic protein synthesis, 10 mcg of EE was shown to be equivalent in potency to 1.25 mg of CEE (Mandel FP et al Obstet Gynecol 1982) >>2mg E2. E2 : 100-600 times less potent than EE → 20-30µg of EE>1-1.5mg E2
- Progestins: different profile: androgenic or antiandrogenic→ different impact on coagulation

Antiandrogen potency favorates estrogen-dependent activation of coagulation

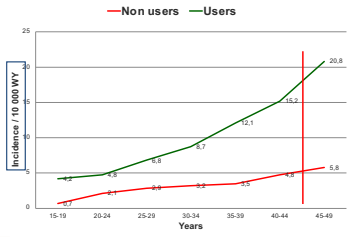


Antiandrogen/
Non androgenic
EE + 3rd Gén
EE+ DSP
EE+ CPA
EE+CMA
E2+DNG

VASCULAR EVENTS AND CANCER INCREASE WITH AGE

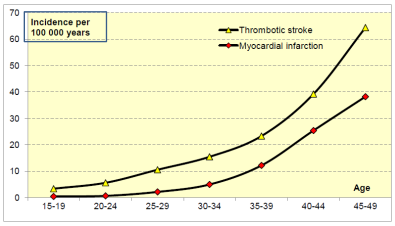
Age and VTE incidence

(Lidegaard O, BMJ 2011)



Incidence of T Stroke and MI according to age including women using COC

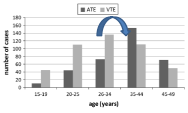
(Lidegaard et al NEJM 2012)



Age is a risk factor for VTE and > ATE under COC

(Gourbil M et al, Drug safety, 2014)

- **2966 cases** of arterial or venous thromboembolic events from a French drug safety surveillance database; 20% used any estrogen-progestin contraception
- More VTE for 3rd and 4rth generations (but younger women), equal numbers of ATE and VTE for 1rst and 2nd
- Risk factors for VTE: **age>40years (22%)**, obesity (15%), family history of VTE (13%), thrombophilia diag after VTE, long journey>5h, surgery <1 month
- Risk factors for ATE: **current smoking (50%!!), age>40 ans (47%!!),** dyslipemia (32%), HTA (10%),PFO/ASA diag after (19%), **migraine+ aura (17%)**



Estradiol containing pills

- Qlaira®:
  - 3mg E2V, days 1–2; 2mgE2V+2 mg DNG, days 3–7 ; 2mg E2V+3 mg DNG days 8–24; 1mg E2V , days 25–26: and placebo, days 27–28
- Zoely®
  - E2 **1.5 mg** + nomegestrol acetate 2.5 mg , 24 d/28

Pharmacological properties

- Dienogest has antiandrogen and antimineralocorticoid properties
- NOMAC is reported to be a pure ligand for PR and not androgenic
- Combination with E2→ relative equilibrium?, E2V+DNG more estrogenic than E2+NOMAC?

SCARCE DATA ON CARDIO-VASCULAR EVENTS

NO COMPARISON BETWEEN E2+DNG AND E2+NOMAC

Cardio-vascular endpoints

(Dinger et al, Contraception, 2016; 94:328–339)

- Prospective, non interventional cohort study conducted in the US and 7 European countries, 2 groups new users of DNG/EV and other COC, and LNG COC
- 50,203 new COC users were followed up for up to 5.5 years (mean value, 2.1 years), 20.3% used DNG/EV and 79.7%others including 11.7% LNG-COC

risk factors	DNG/EV	oCOC	LNG
Treated high blood pressure	2.6%	2%	2.4%
Family history of fatal ATE	2.7%	1.9%	1.8%
Family history of VTE	3.9%	2.9%	3.2%
obese	**6.8%**	**14.9%**	**10.8%**
smoking>15cig/day	4.1%	2.7%	3.5%
VTE	**n=23**	**n=39**	**n=6**

RESULTS

VTE	DNG/EV	oCOC	LNG	NO USE
n (PE)	9 (5)	58 (19)	10 (5)	9 (2)*
incidence/10,000 WY	**7.2**	**9.1**	**9.9**	3.5°

* 5 cases with pregnancy
° **1.6**/ 10000wy

18 Arterial events: 4 AMIs, 10 strokes, 2TIAs, 2 thromboses of a peripheral artery
N cases DNG/EV 1 case, oCOC 15 cases, LNG 1 case, no use 2 cases
Incidence/10,000 WY: DNG/EV:0.8 ATE, oCOC:2.4, LNG:1.0, no use:0.8

E2+DNG
HEPATIC IMPACT

Surrogate end points for E2/DNG

- **Equivalent or less hepatic impact than 30EE+150LNG or a triphasic with LNG**
  - A randomized, open label, parallel-group study in 74 women,18–35 years with E2V+DNG or **30µgEE+150µgLNG**, third cycle (Raps et al, J Thromb Haemost. 2013;11:855-61).
    - Mild increase in APCr
    - Increase in SHBG
    - → **No statistical difference between both pills**
  - 32 women 18-50 y randomized between Qlaira and **30EE+150LNG** 3 months (Klipping C, et al,Drugs R D. 2011;11:159-70)
    - Prothrombin 1 + 2: no change with DNG, small increase with LNG
    - smaller increase in D-dimers with DNG (37.3%±69.3%) than LNG (88.1%±99.3%)
    - No significant modifications in anticoagulant proteins
    - **APC sensitivity ratio levels :significant increase in both groups** 7.7 ± 25.7 and 39.3 ± 38.5%
    - **SHBG: 48 and 41%**
  - 58 women 18-50 years randomized to E2V/DNG or **Triphasic 30-40µg EE/LNG 50-75-125µg** 7 cycles(Junge W , Clin Drug Investig. 2011;31:573-584)
    - **SHBG: increase** by 62.7% and 111%
    - Fragment 1+2 prothrombin: x2 with LNG, **no change with DNG**
    - AT III, protein C and APCsr **small increase with DNG<LNG** NS
- Favorable effect in women without or with PCOS on insulin resistance (Grandi et al Gynecol Endoc, 2014; De Leo et al Contraception 2013;88 :364–368)

Surrogate endpoints for NOMAC/E2

- **Hepatic (estrogenic) impact of NOMAC/E2 is weaker than the comparators 20/100µg or 30µg EE/150µg on coagulation parameters, CRP**
- 121 **healthy** women, **18-50 years** of age RT compared with **LNG/EE (150 µg/30 µg)** (Ågren et al. Eur J Contracept Reprod Health Care.2011)
  - Significant differences in
    - ETP-based APC sensitivity ratio (**small increase with NOMAC, larger increase with LNG**)
    - Antithrombin III and total protein S (**increase with NOMAC,** decrease with LNG)
    - Protein C (increase with LNG)
    - CRP: + 67%NOMAC and +258% LNG (p<0.001)
    - SHBG: **+ 44% NOMAC and 22% LNG** (p=0.019)
- 90 healthy women 18-38 years of age three cycles LNG/EE 100/20 (Gaussem et al Thromb Haemost. 2011;105:560-7.)
  - prothrombin fragment 1+2 levels (primary endpoint) no increase with NOMAC/E2 compared with LNG/EE (-0.02 vs. +0.08 nM, p<0.01)
  - antithrombin (+0.3% vs. -4.4%, p<0.001APCr- normalised ratio (+0.20 vs. +0.46, p<0.01), D-dimer (-53 vs. +43 ng/ml, p<0.001), plasminogen (+6% vs. +30%, p<0.0001) and plasminogen activator inhibitor-1 (-3.1 vs. -8.0 ng/ml, p<0.001)
- No modification in insulin/glucose
- More increase in SHBG but to a limited extent

Cycle control with E2+DNG

(Ahrendt HJ et al Contraception 2009)

- 798 women **18-50 years** 7 cycles compared with 30EE/LNG
- **Fewer bleeding/spotting** days reported by women who received E2V/DNG than those who received EE/LNG
- **Fewer scheduled withdrawal** bleeding: 77.7-83.2% with E2V/DNG and 89.5-93.8% with EE/LNG (p<0.0001 per cycle)
- Similar intracyclic bleeding with E2V/DNG (10.5%-18.6%) and EE/LNG (9.9%-17.1%) (p>0.05 per cycle)

Clinical tolerance and efficacy NOMAC/E2

compared to DRSP/30EE

- **fewer bleeding/spotting days, shorter withdrawal bleeds, and a higher incidence of amenorrhea**
- **Higher acne** (15% vs 7%), withdrawal bleeding irregular (11.7% vs. 0.4%); weight increased (7.9% vs. 6.2% and 9.5% vs 5.2%);
- Pearl Index estimates: in women ≤ 35 years

0.40 (0.15 – 1.06) compared to 0.77 (0.25 – 2.39) for DRSP/EE (Mansour et al)

Or 1.27 (0.66–2.22) compared to 1.89 (0.69–4.11) (Westhoff et al)

Discussion

- Estradiol containing pills have a weaker impact on surrogate markers of C-V and VTE risk than EE in healthy women
- Increase in VTE with DNG/E2V, no data with NOMAC/E2
- However it is known from the E3N and Esther that norpregnanes are associated with a higher risk of VTE
  - HR=1.8(1.2 -2.7) E3N
  - OR=3.9(1.5-10.0) Esther
  - The doses of NOMAC was probably higher than in the pill (5 versus 2.5mg).
  - Women were older…
  - This suggests a potential increase risk in VTE with age with these pills
- Breast safety: increase RR of BC in the E3N study with NOMAC

Conclusions

- Scarce data on vascular events and only for EV/DNG, not in aged women; **RR VTE increased**
- The cycle control has not been specifically studied in these women but seems acceptable with less breakthrough and withdrawal bleeding
- There is no data on climacteric symtoms
- Breast safety has not been studied for DNG, only in vitro data suggesting that DNG is similar to other progestins, but BC increases with NOMAC +E2 TTS in postmenopausal women