14th ESC Congress
4-7 May 2016, Basel

Adding DHEA to a contraceptive pill

Androgen Restored Contraception

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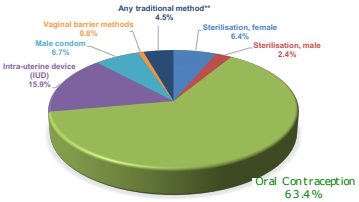
PANTARHEI BIOSCIENCE

Disclosures

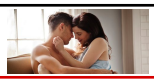
- Yvette Zimmerman is an employee of Pantarhei Bioscience, the company developing the clinical concept of Androgen Restored Contraception

Prevalence of contraceptive methods
Overall rate in Western Europe: 72%*



*Percentage using contraception among women aged 20-45, married or in a union
**Including prolonged abstinence, breastfeeding, douching, various folk methods and traditional methods not reported separately
Source: World contraceptive use 2011. United Nations

Effect contraceptive pill on sexual function and mood



- Effect of COC use on sexual function and mood is inconsistent, both positive and negative[1]
- Diminished sexual function and mood disturbances have been reported as side effect of COCs[2]
- Studies have also been investigating the effects of COCs on side effects in relation to androgen levels; these studies report conflicting results[3]

1 Kahn & Halbreich (2001); Davis & Castaño (2004); Burrows et al. (2012); Poromaa & Segebladh (2012); Pastor et al. (2013)
2 Sanders et al. (2001); Moreau et al.(2007); Wallwiener et al. (2010); Elaut et al. (2012); Gingnell et al. (2013); Smith et al. (2014)
3 Bancroft et al. (1991); Graham et al. (1995);Graham et al. (2007); Greco et al. (2007); Strufaldi et al. (2010); Schaffir et al. (2010); Caruso et al. (2011); Battaglia et al. (2012) ; Elaut et al.(2012); Battaglia et al. (2014)

Effect of combined oral contraceptives on testosterone and SHBG

- Systematic review & meta-analysis
- 42 studies; n=1,495 healthy young women

- Significant (P<0.0001) decrease T levels:
  - Total T: ↓31%
  - Free T: ↓ 61%
  - No differences between various COC types
  - No relationship with SHBG increase (which ranged from 50-250%)
- Significant (P<0.0001) increase SHBG levels:
  - Dose-dependent estrogen (EE) effect
  - Differently antagonised depending on the androgenicity of the progestin

Zimmerman et al. Hum Reprod Update (2014);20:76-105

Does it matter? Yes or No

- Symptoms female androgen insufficiency[1]:
  - Diminished sexual function
  - Reduced well-being and quality of life (mood, affect, energy)
  - Negative effects on bone and muscle mass
- Endocrine society recommends against making a diagnosis and treatment[2]
  - Lack of well-defined clinical syndrome of androgen insufficiency
  - Absence of normative data of total and free T levels
  - Lack of long-term safety data

1 Bachmann et al. Fertil Steril (2002);2 Wierman et al. JCEM (2006)

Difficulties investigating effects androgen deficiency on sexual function and mood

- Effects of androgens on sexuality are too subtle to measure with questionnaires like the FSFI measuring "dysfunctions"
- There are large inter-individual differences in the effects of androgens on sexual processing
- Some women are more sensitive to *changes in T* than others[1]
- Linking levels of endogenous sex steroids with sexual functioning is difficult due to individual variability in biosynthesis, enzymatic intracrine conversion, receptor binding, absorption rate, bioavailability, elimination, etc.

[1]Bancroft & Graham Hormones Behavior (2011); 59:717-729

Androgen Restored Contraception (ARC)

- The ARC concept refers to a combined oral contraceptive (COC) containing dehydroepiandrosterone (DHEA) with the objective to preserve sexual function by maintaining normal androgen levels, in particular free testosterone
- Why DHEA?
  - DHEA is a natural precursor hormone for androgens
  - Oral DHEA is metabolised to T and increases T levels dose dependently[1]
  - 50 mg DHEA increases T by about 1 nmol/L, is safe and does not increase estradiol[1]
  - Allows oral-only product

[1]Legrain, Baulieu et al. JCEM(2000)

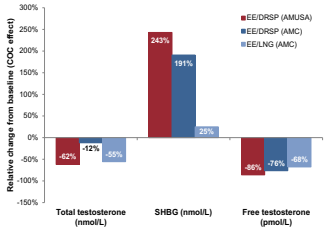
Two large prospective, randomised, double-blind, placebo-controlled studies

ARC-AMC study *van Lunsen and Laan, Amsterdam, NL*	***ARC-AMUSA study*** *Foidart and Pintiaux, Liège, B*
• Participants: 81 healthy COC users (20-35 yrs) and in steady relationship • Treatment (cross-over design): – One (1) month no hormonal contraception – Two COCs investigated: both 30 µg EE and either 150 µg levonorgestrel (LNG) or 3 mg DRSP – Five (5) cycles with placebo followed by 5 cycles with 50mg DHEA or the reverse	• Participants: 99 healthy and new COC users (18-35 yrs) • Treatment: – Three (3) months no hormonal contraception – Three (3) cycles 30µg EE/3 mg drospirenone (DRSP) – Six (6) cycles EE/DRSP with 50mg DHEA or placebo

Study objective

To investigate the endocrine and clinical effects of the pill with and without co-administration of DHEA

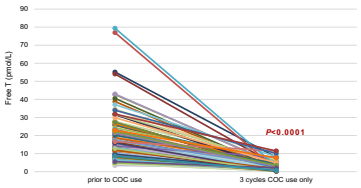
Significant change ($P<0.05$) in total T, SHBG and free T after use of 3-5 cycles of a COC containing 30 µg ethinylestradiol (EE) and 3 mg drospirenone (DRSP) or 30 µg EE and 150 µg levonorgestrel (LNG)



Zimmerman et al. ESHRE (2014)

Free T levels during the normal menstrual cycle and COC use

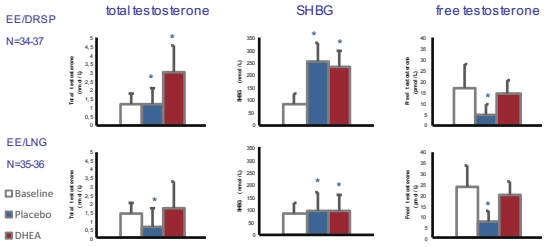
1. Huge variation of free T levels during the normal menstrual cycle
2. COC reduces free T significantly and in all 99 women



Zimmerman et al. ESHRE (2014)

Effect adding DHEA/placebo to COC on total T, SHBG and free T

* Significant difference between baseline and after 5 cycles with DHEA or placebo ($P< 0.05$)



Outcome measures for clinical effects

➢ **ARC-AMUSA study:**
- Questionnaires: McCoy Female Sexuality Questionnaire (MFSQ), Moos Menstrual Distress Questionnaire (MDQ), Quality of Life (Q-LES-Q)

➢ **ARC-AMC study:**
- Questionnaires: FSFI, FSDS-R
- SexLab: genital sexual arousal (VPA) & subjective sexual arousal (SSAQ)
- At home setting with Sexual Function Diary (SFD; 1 week prior to SexLab):
  - self-reported sexual arousal and desire
  - frequency of sexual activities per week
  - sexual response to these activities

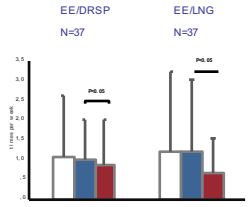
Women taking an EE/LNG and EE/DRSP COC reported a significant decline in sexual function

- FSFI:
  - Three FSFI domains indicated worse sexual function with EE/LNG use compared to baseline ($P<0.05$)
  - Lower FSFI scores during COC use with 33.3% of women below the cut-off dysfunctional FSFI score of 26.55 compared to 24.4% of women not using COC
- SFD (diary): Significant worsening of sexual desire and arousability ($P<0.05$) after 5 cycles COC; no difference found between LNG or DRSP
- SFDS-R: No difference
- Laboratory setting: No differences in genital response to erotic fantasy and film)
- MFSQ: Significant worsening for global score, sexual interest and orgasm ($P<0.001$)

Zimmerman et al. Contraception (2015); Van Lunsen et al. (2016; *submitted*)

Effect adding DHEA/placebo to COC on frequency of sexual activity

* Significant reduction to sexual initiatives of the partner with DHEA compared to placebo

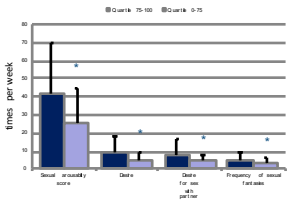


Receptiveness to sexual encounters initiated by partner was higher when women were taking COC with DHEA compared to COC with placebo

Baseline
Placebo
DHEA

Van Lunsen et al. (2016; *submitted*)

Effect adding DHEA/placebo to COC on levels of sexual desire and arousability measured by SFD (diary)



Sexual arousability, desire and fantasies significantly higher in women with highest levels of free testosterone with DHEA compared to placebo
* $P<0.02$

In this group (Q4):
14 women were using EE/LNG/DHEA and 4 women EE/DRSP/DHEA

Van Lunsen et al. (2016; submitted)

Conclusions

- COCs significantly suppress androgen concentrations, especially free T (decrease of 68-86%)
- COC use has unfavourable effects on sexual function
- Addition of 50 mg DHEA restores total and free testosterone when combined with an LNG pill, but this dose is too low for a DRSP pill
- Maintenance of androgen levels by adding DHEA to a COC preserves sexual arousability and desire, particularly in those women with a strong free T response to DHEA
- Co-treatment with DHEA for 5 cycles was safe and did not cause symptoms of hyperandrogenicity (except for a few single cases, both during DHEA and placebo)

Acknowledgements

UNIVERSITE DE LIEGE
DEPARTEMENT DE GYNECOLOGIE OBSTETRIQUE

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Thank you for your attention