Belgian Menopause Society
Saturday October 8, 2016

"Post IMS Prague:
Update on menopause hormone therapy (MHT)"

UMC Sint-Pieter – CHU Saint-Pierre
Rue Haute 322 Hoegaartstaat
Bâtiment FOKUM Gebouw
1000 BRUXELLES

08.45 Coffee and registration

Following topics will be discussed:

Breast Cancer: Risk factors and Menopause Hormone Therapy

News on Osteoporosis, metabolism, Cardiovascular and
cognitive diseases and MHT

Presented by a.o.

Mieke Hendrickx (Aalst)
Caroline Antoine (ULB)
Evelyna Markowicz (ULB)
Herman Depypere (RUG)
Axelle Piniaux (ULG)
Serge Raazenberg (ULB-VUB)

There will be a coffee break and visit of the Boots at 10.15

12.00 General discussion and Conclusion

Price: free for members and assistants, 30€ for non members
A request of Accreditation has been made
ANDROGENS AND MENOPAUSE
CARDIOVASCULAR EFFECTS OF THE TESTOSTERONE
BACKGROUND

• FEW TESTOSTERONE PREPARATIONS LICENSED FOR WOMEN
• LACK OF LONG TERM SAFETY DATA
• EFFECTS OF ANDROGEN ON CVS POORLY UNDERSTOOD
• RECENT DATA SUGGEST THAT LOW ENDOGENOUS T IS DELETERIOUS ON ENDOTHELIAL FUNCTION
• BOTH LOW AND HIGH LEVELS OF T ARE ASSOCIATED WITH CV EVENTS
• VERY LIMITED DATA ON CV EFFECTS OF PHYSIOLOGICAL TRANSDERMAL REPLACEMENT

Rech 2016, Laughlin 2010
ENDOTHELIAL DYSFUNCTION IS AN EARLY MARKER OF CVD

• ENDOTHELIAL FUNCTION CAN BE ASSESSED BY BASELINE BLOOD FLOW IN THE BRACHIAL ARTERY, AFTER REACTIVE HYPEREMIA (ENDOTHELIIUM DEPENDENT)

• BLOOD FLOW CHANGE AFTER ADMINISTRATION OF GLYCERYL TRINITRATE IS ENDOTHELIIUM INDEPENDENT

• LOW E AFTER MENOPAUSE IMPAIRS REACTIVE HYPEREMIA BUT NOT GTN INDUCED BLOOD FLOW
CARDIOVASCULAR EFFECTS OF THE TESTOSTERONE PATCH

Aim:
To validate a protocol designed to investigate the effects of postmenopausal transdermal testosterone in conjunction with HRT on:
1. Cardiovascular system - arterial stiffness, endothelial function and insulin resistance
2. Libido

Hypotheses:
1. Transdermal testosterone will not have any adverse effects on insulin resistance and vascular function
2. Transdermal testosterone significantly improves sexual desire
Methodology

Active treatment pilot study, using 300µg TTP (Intrinsa®) for 12 weeks in conjunction with HRT. Aiming to recruit 20 women

Inclusion Criteria:
- Healthy postmenopausal women
- 45 to 70 years of age
- Reporting low libido
- On stable HRT regimen
- In stable relationship >6/12
- Give informed consent

Exclusion Criteria:
- Dyspareunia
- T implants <12 months or other androgen therapy <3 months
- Medications which may interfere (SSRI, antiandrogens, PDE5 inhibitors, DHEA, SERMS, tibolone)
- Significant psychiatric disorder
- History of breast cancer, DM, CVD, VTE, uncontrolled BP or hyperlipidaemia

Primary Outcomes:
1) Arterial stiffness – Pulse Wave analysis
   - Augmentation Index (Aix)
2) Endothelial function – EndoPAT*
   - Reactive hyperaemia index (RHI)
3) Insulin resistance
   - HOMA-IR

Secondary Outcomes:
- Libido
  - B-PFSF
- Anthropometry
  - Waist/hip circ, weight, BMI, BP
- Lipids and hormone
  - Estradiol, testosterone, SHBG, lipids
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>53.0 (6.7)</td>
</tr>
<tr>
<td>Smokers (n)</td>
<td>1 (4.8%)</td>
</tr>
<tr>
<td>HRT route</td>
<td>Oral 2 (9.5%), transdermal 19 (90.5%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.2 (11.1)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.5 (4.7)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>85.6 (11.4)</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>101.6 (8.5)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>114.6 (11.8)</td>
</tr>
<tr>
<td>B-PFSF</td>
<td>15.3 (9.1)</td>
</tr>
<tr>
<td>Estradiol (pmol/L)</td>
<td>332.0 (296.0)</td>
</tr>
<tr>
<td>FAI</td>
<td>0.56 (0.40)</td>
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Data shown as mean (SD) or n (%)
EFFECTS ON ANTHROPOMETRIC AND METABOLIC CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>Mean difference</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>0.443</td>
<td>-0.18 to 1.07</td>
<td>0.211</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.159</td>
<td>-0.38 to 0.07</td>
<td>0.218</td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td>-0.262</td>
<td>-1.38 to 0.86</td>
<td>0.661</td>
</tr>
<tr>
<td>Hip Circumference (cm)</td>
<td>-0.738</td>
<td>-1.42 to -0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>-2.52</td>
<td>-7.02 to 1.98</td>
<td>0.265</td>
</tr>
<tr>
<td>Fasting Glucose (mmol/L)</td>
<td>0.053</td>
<td>-0.12 to 0.23</td>
<td>0.533</td>
</tr>
<tr>
<td>Fasting Insulin (pmol/L)</td>
<td>5.809</td>
<td>-10.66 to 22.27</td>
<td>0.5</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.106</td>
<td>-0.20 to 0.41</td>
<td>0.705</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>-0.0053</td>
<td>-0.24 to 0.23</td>
<td>0.954</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>-0.251</td>
<td>-0.51 to 0.0071</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total chol: HDL</td>
<td>-0.774</td>
<td>-0.54 to 0.38</td>
<td>0.089</td>
</tr>
<tr>
<td>Lipoprotein (a) (mg/L)</td>
<td>-3.11</td>
<td>-76.32 to 13.75</td>
<td>&lt;0.05</td>
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</tbody>
</table>
Sexual function

B-PFSF scores improved significantly by a mean of 3.7 points by 6 weeks (p=0.012) and 5.05 points by 12 weeks (p<0.0001).
EFFECT ON VASCULAR FUNCTION

Primary Outcomes

- No significant change in:
  1. RHI (endothelial function)
  2. Aix (arterial stiffness)

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<th>p</th>
</tr>
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<tr>
<td>RHI</td>
<td>0.06</td>
<td>-0.19 to 0.31</td>
<td>0.61</td>
</tr>
<tr>
<td>Aix</td>
<td>1.07</td>
<td>-3.85 to 1.72</td>
<td>0.43</td>
</tr>
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</table>
CHANGE IN VASCULAR PARAMETERS

Data suggestive of improvement in endothelial function:

- 11.3% increased in EFI (i.e., improved endothelial function) but did not reach statistical significance
- Significant improvement in salbutamol mediated vasodilatation (endothelial dependent)
IN SUMMARY

• OPEN LABEL PILOT STUDY, 12 WEEKS
• NO ADVERSE EFFECT ON ARTERIAL STIFFNESS
• MAY IMPROVE ENDOTHELIAL FUNCTION
• REDUCED HDL CHOLESTEROL AND LIPOPROTEIN A
• NO EFFECT ON GLUCOSE METABOLISM
Proliferative effects of progesterone in the breast

- Two stages in post-natal breast development
  - First one occurs at the onset of puberty: ductal elongation and branching
  - The second in response to pregnancy: proliferation of the epithelial compartment and differentiation to generate alveoli and prepare for lactation

- Mouse genetics:
  - Mammary ductal outgrowth under the control of estrogen (ERαKO)
  - PR is required to observe ductal side branching and alveolar budding in nulliparous mice, and alveologenesis in parous mice
  - At the cellular level PRKO epithelial cells unable to undergo proliferation in response to E+P treatment

Soyal et al. 2002
Risque de cancer du sein ?
progestérone, dydrogestérone ≠ progestatifs

WHI 2002
■ CEE + MPA

WHI 2004
■ CEE seul

MWS 2003
• E (oral/ cutané) ou CEE + Progestatifs (MPA, NETA, LNG)
• E seuls

E3N 2008
△ E cutanés + Progestérone
△ E + Dydrogestérone
△ E + autres Progestatifs
△ E (oral/cutané) seuls

E = estradiol ; CEE = Conjugated Equine Estrogen ; MPA = Acétate de Médroxy Progestérone ;
NETA = Acétate de Noréthistérone ; LNG = Levonorgestrel

Progesterone receptor is essential for tumorigenesis in mice (2/2)

- DMBA-induced mammary tumor incidence: 15% in PRKO compared to 60% in WT mice

Lydon et al. 1999
SPRMS AND BREAST

• **MIFEPRISTONE** ADMINISTRATED TO BRCA1/P53 DEFICIENT MICE: INHIBITION OF TUMORIGENESIS BY DECREASING DUCTAL BRANCHING AND ALVEOLAR PROLIFERATION + INCREASED SURVIVAL  *POOLE 2006*

• RATS RECEIVING **UPA** HAD DECREASED INCIDENCES OF FIBROADENOMAS AND ADENOCARCINOMAS IN THE MAMMARY GLAND IN ALL TREATED GROUPS.
	*POHL O, CURR DRUG SAF 2013*
Carcinogenicity and Chronic Rodent Toxicity of the Selective Progesterone Receptor Modulator Ulipristal Acetate.

- Carcinogenic properties of Ulipristal Acetate (UPA), a selective progesterone receptor modulator developed for the treatment of benign gynecological conditions such as uterine fibroids, were assessed in a 26-week carcinogenicity study in Transgenic TGRash2 mice and a 104-week study in Sprague Dawley rats. Dose levels used in the mouse study were 15, 45, or 130 mg/kg/day and for the rat study the doses used were 1, 3, or 10 mg/kg/day. Vehicle and water controls were part of both studies and a positive control, N-nitroso-N-methylurea intraperitoneally, was included in the transgenic mouse assay. Survival at all dose levels was similar to vehicle controls in both sexes of both species and there was no evidence of any UPA-induced carcinogenicity in either species. Rats receiving UPA had decreased incidences of fibroadenomas and adenocarcinomas in the mammary gland in all treated groups.

A Tg-rash2 mouse is an innovative transgenic mouse, developed in the Central Institute for Experimental Animals (CIEA), carrying the three copies of human prototype c-Ha-ras oncogenes with endogenous promoter and enhancer in tandem.
This study compares the proliferation level (Ki67) and the expression of ER, PR, and of the PR target gene, fatty acid synthase (FASN), in histologically normal breast tissues from women with BRCA1 mutations (BRCA1+/mut, n=23) or without BRCA1 mutations (BRCA1+/+, n=28). BRCA1+/mut tissues showed an increased proliferation and impaired hormone receptor expression with a marked loss of the PR isoform, PR-B. Responses to estradiol and progesterone treatments in BRCA1+/mut and BRCA1+/+ breast tissues were studied in a mouse xenograft model, and showed that PR and FASN expression were deregulated in BRCA1+/mut breast tissues. Progesterone added to estradiol treatment increased the proliferation in a subset of BRCA1+/mut breast tissues. The PR inhibitor, ulipristal acetate (UPA), was able to reverse this aberrant progesterone-induced proliferation. This study suggests that a
Figure 4: A significant reduction in the Ki-67 index is evident, $P = 0.012$ in the mifepristone-treated group at the end of treatment (right) compared with the baseline value (left). The individual variations are also reduced during treatment. The median value is displayed as a horizontal line, and 50% of subjects are within the box and 80% within the whiskers. The dots represent individuals over the 90th percentile or below the 10th percentile.
ANTI-TUMORAL EFFECTS OF ANTI-PROGESTINS IN A PATIENT-DERIVED BREAST CANCER XENOGRAFT MODEL

NATHALIE ESBER1,2,3 & CLÉMENT CHERBONNIER4 & MICHELÈ RESCHE-RIGON3
&
ABDALLAH HAMZE5 & MOUAD ALAMI 5 & JÉRÔME FAGART1,2 & HUGUES
LOOSFELT 1,2 &
MARC LOMBÈS1,2,6 & NATHALIE CHABBERT-BUFFET7,8,9

HORM CANC (2016) 7:137–147
ulipristal acetate (UPA)  
“APR19” a new selective PR antagonist

As opposed to P4 that slightly reduces tumor volume, UPA and APR19 treatment for 42 days led to a significant 30 % reduction in tumor weight, accompanied by a significant 40 % retardation in tumor growth upon UPA exposure while a 1.5-fold increase in necrotic areas was observed in APR19-treated tumors.
PR expression was upregulated by a 2.5-fold factor in UPA-treated tumors while APR19 significantly reduced expression of both PR and estrogen receptor α, indicating a potential distinct molecular mechanism among PR antagonists.
Cell proliferation was clearly reduced in UPA group compared to vehicle conditions, as revealed by the significant reduction in Ki-67, Cyclin D1, and proliferating cell nuclear antigen (PCNA) expression. Likewise, an increase in activated, cleaved poly(ADP-ribose) polymerase (PARP) expression was also demonstrated upon UPA exposure.
CONCLUSIONS
SPRMS= NEW TOOLS

• TO TREAT EXCESS BLEEDING
• TO TREAT MYOMAS
• TO PROVIDE A FREE ESTROGEN CONTRACEPTION
• TO PROTECT THE BREAST