MENT: ICCR’s contribution to male contraception

E. Nieschlag,
Center for Reproductive Medicine and Andrology
University of Münster

N. Kumar, R. Sitruk-Ware
Center for Biomedical Research
Population Council, New York
Hypothalamus -> GnRH -> Pituitary
- LH, FSH
- DHT, Estradiol, Testosterone

Testes
- Leydig cells: Testosterone, DHT
- Sertoli cells: Spermatogenesis, Estradiol, Testosterone

Androgen effects, Fertility

Hypothalamus

Testosterone

Pituitary

GnRH

LH

FSH

Testes

Sertoli cells

Leydig cells

DHT

Estradiol

Androgen effects

Fertility

Nieschlag, Behre, Nieschlag „Andrology“ 3rd ed, Springer 2010
Clinical trials for hormonal male contraception 1972 – 2011

- 60 surrogate trials counting sperm
- 8 real contraceptive efficacy trials
- 71 reviews
Phase II-b trial of TU i.m. and ENG implants for male contraception (Schering-Organon trial, 2008)

- Assessed for eligibility (n=589)
  - Excluded (n=235)
    - Not meeting inclusion/exclusion: n=158
    - Refused to participate: n=53
    - Other reasons: n=24
  - Randomized (n=354)
    - Low release ENG implant (n=149)
      - 1 withdrew IC
      - Treated (n=148)
        - TU 1: n=47
        - TU 2: n=50
        - TU 3: n=51
        - Discontinued treatment (n=36)
          - Due to (S)AE: n=24
          - Other reason: n=12
        - Completed treatment (n=112)
          - Did not start follow up (n=7)
            - Discontinued follow up (n=5)
              - Due to (S)AE: n=1
              - Other reason: n=4
          - Completed follow up (n=136)
    - High release ENG implant (n=152)
      - 2 withdrew IC, 1 switch
      - Treated (n=149)
        - TU 1: n=50
        - TU 2: n=50
        - TU 3: n=49
        - Discontinued treatment (n=15)
          - Due to (S)AE: n=6
          - Other reason: n=9
        - Completed treatment (n=134)
          - Did not start follow up (n=2)
            - Discontinued follow up (n=3)
              - Due to (S)AE: n=0
              - Other reason: n=3
          - Completed follow up (n=144)
    - Placebo (n=53)
      - 1 switch
      - Treated (n=52)
        - Discontinued treatment (n=3)
          - Due to (S)AE: n=3
          - Other reason: n=0
        - Completed treatment (n=49)
          - Did not start follow up (n=0)
            - Discontinued follow up (n=3)
              - Due to (S)AE: n=0
              - Other reason: n=3
          - Completed follow up (n=49)

- Completed follow up (n=144)
  - Completed follow up (n=136)
  - Completed follow up (n=144)
  - Completed follow up (n=49)
Sperm concentration (mill/ml) in 23 normal and 18 subnormal volunteers under testosterone undecanoate
Male contraceptive efficacy trials based on hormones

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Treatment</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PopCouncil</td>
<td>1977</td>
<td>TE + DMPA</td>
<td>100</td>
</tr>
<tr>
<td>WHO I</td>
<td>1990</td>
<td>TE</td>
<td>271</td>
</tr>
<tr>
<td>WHO II</td>
<td>1996</td>
<td>TE</td>
<td>225</td>
</tr>
<tr>
<td>Gu et al</td>
<td>2003</td>
<td>TUch</td>
<td>305</td>
</tr>
<tr>
<td>Gu et al</td>
<td>2009</td>
<td>TUch</td>
<td>898</td>
</tr>
<tr>
<td>Soufir et al</td>
<td>2011</td>
<td>Tgel + MPA</td>
<td>35</td>
</tr>
<tr>
<td>Turner et al</td>
<td>2003</td>
<td>TI + DMP</td>
<td>53</td>
</tr>
<tr>
<td>WHO/CONRAD</td>
<td>2011</td>
<td>TUeu + NETE</td>
<td>(440)</td>
</tr>
</tbody>
</table>

TUch = TU chinese = TU in tea seed oil
TUeu = TU european = TU in castor oil
Multicenter clinical trial of DMPA and TE or TI for male contraception: Sperm concentrations (million/ml) in 9 / 100 men around the time their wives became pregnant.

(Barfield et al Contraception 20: 121-127, 1979)

<table>
<thead>
<tr>
<th>Monthly Treatment</th>
<th>Months Before Conception</th>
<th>Months After Conception</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>150 DMPA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>500 TE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 DMPA</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>250 TE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>150 DMPA</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>250 TE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 DMPA</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>250 TE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 DMPA</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>250 TE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 DMPA</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>250 TE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>250 TE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>150 DMPA</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>250 TE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Treatment (month following injection)
- Two sperm: nonprogressive motility
- One sperm: slow, coordinated zigzag motility
Contraceptive efficacy of testosterone enanthate (200 mg biweekly) in 346 men: pregnancy rates per 100 person-years in relation to sperm concentration.

(WHO, Fertil. Steril. 65; 821, 1996)
The search for long-acting testosterone preparations

Testosterone

19-Nortestosterone

enanthate
implants
buciclate
undecanoate
Phase III trial of TU in tea seed oil in 10 Chinese centres

Design: 1000 mg TU loading, 500 mg TU / month
If sperm < 1 million/mL, efficacy phase for 2 years

Volunteers: 1045 men recruited, 733 men completed efficacy and recovery phase

Pregnancies: F 2143/1
Phase III trial of TU in tea seed oil in 10 Chinese centres

The changes in sperm concentration with log scale during the study period
Phase III trial of TU in tea seed oil in 10 Chinese centres

Design: 1000 mg TU loading, 500 mg TU / month
If sperm < 1 million/mL, efficacy phase for 2 years

Volunteers: 1045 men recruited,
733 men completed efficacy and recovery phase

Pregnancies: 1.1 in 100 men years
(6 with sperm between 2-8 million/mL
3 with sperm < 1 million/mL)
Testosterone undecanoate
Injectable testosterone undecanoate alone or with oral levonorgestrel or injectable norethisterone enanthate in a controlled clinical trial for male contraception (Kamischke, Nieschlag et al. 2001 & 2002)
SPERM SUPPRESSION AND CONTRACEPTIVE PROTECTION PROVIDED BY NORETHISTERONE ENANTATE (NET-EN) COMBINED WITH TESTOSTERONE UNDECANOATE (TU) IN HEALTHY MEN

A WHO and CONRAD Multicentre Phase IIb clinical trial

UNDP/UNFPA/WHO/WORLD BANK Special Programme of Research, Development and Research Training in Human Reproduction (HRP)
Department of Reproductive Health and Research (RHR)

and

CONRAD

Treatment schedule:

1000 mg testosterone undecanoate (TU) plus 200 mg norethisterone enanthate (NETE) intramuscular every 8 weeks in 440 male partners of fertile couples
10 centers worldwide
487 couples screened since July, 2008
321 couples enrolled
260 entered efficacy phase
   6 failed to suppress
   55 discontinued before suppressing
114 couples completed efficacy

No further injections after April 6, 2011
Testosterone

19-Nortestosterone

MENT (7α-Methyl-19-nortestosterone)

The search for long-acting testosterone preparations
"Anabolic, androgenic and myotropic activities of derivatives of
7α-methyl-19-nortestosterone"

(Lyster & Duncan [Upjohn]
Acta endocrinol
43: 399 - 411, 1963)
Myotropic-androgenic activity in the immature castrate rat of 7α-methyl-19-nortestosterone acetate and T. P. following repeated daily injection at single dose levels.

(Lyster & Duncan (Upjohn) Acta endocrinol 43: 399 - 411, 1963)
7α-Methyl-19-nortestosterone: An Ideal Androgen for Replacement Therapy

Kalyan Sundaram, Narender Kumar, and C. Wayne Bardin

Center for Biomedical Research, The Population Council, New York, New York 10021
Development of MENT by the Population Council

1963  MENT first described by Lyster & Duncan (Upjohn)
1988  C.W. Bardin and B. Monder identified MENT as suited for replacement therapy and male contraception
1990  RIA for MENT by Kumar et al.
1990-  Pharmacology, modes of application and toxicology since 1995
1995  by Kumar & Sundaram
since 2000
1995  Clinical trials for treatment of hypogonadism since 2000
2001-
2004
2006
Serum androgen levels, prostate volumes and lumbar bone density in 2 x 8 hypogonadal men receiving one (group 1) or two (group 2) MENT implants

(Anderson et al. JCEM 88: 2784, 2003)
MENT (12 ug/day) vs. testosterone implants (72 ug/day) over 4 months for hypogonadal osteoporosis: a preclinical study in the aged orchidectomized rat model

(Sinnesael et al Int J Androl 34: e601-e611, 2011)

Trabecular microstructure

Trabecular bone volume  Trabecular bone number  Trabecular thickness
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since
1995  Clinical trials for treatment of hypogonadism
since
2000  Clinical trials for male contraception
2001-
2004
2006
Effect of 100 µg MENT/day Silastic implants on sperm counts in Bonnet monkeys: no pregnancy

Clinical trials using MENT Silastic implants for suppression of spermatogenesis

MENT applied to bonnet monkeys
(Ramachandra et al. 2002)

MENT applied to 35 volunteers in 3 centres
(Münster, Santiago de Chile, Santo Domingo)
(von Eckardstein et al. 2003)
MENT Ac™ Subdermal Implant

Lot No. 980304  Implant No. m-g1

Implant Length: 4.5 cm

Population Council
1230 York Avenue
New York, NY 10021

Caution: New Drug. Limited by Federal (U.S.) Law to Investigational Use
Suppression of spermatogenesis and LH, FSH in 34 men treated with 1, 2 or 4 MENT implants

Clinical trials using MENT Silastic implants for suppression of spermatogenesis

MENT applied to bonnet monkeys

(Ramachandra et al. 2002)

MENT applied to 35 volunteers in 3 centres
(Münster, Santiago de Chile, Santo Domingo)

von Eckardstein et al. 2003

Etonogestrel combined with MENT or testosterone implants in 29 volunteers (Edinburgh)

(Walton et al. 2007)
Serum hormone concentrations in men receiving 2 etonogestrel implants either with testosterone (closed circles) or MENT implants (open circles)

Sperm concentrations in 29 men receiving 2 etonogestrel implants either with testosterone (closed circles) or MENT implants (open circles)
Blood pressure in 29 men receiving 2 etonogestrel implants either with testosterone (closed circles) or MENT implants (open circles) (Walton et al. J Androl 28: 679-688, 2007)
Clinical trials using MENT Silastic implants for suppression of spermatogenesis

MENT applied to bonnet monkeys

(Ramachandra et al. 2002)

MENT applied to 35 volunteers in 3 centres
(Münster, Santiago de Chile, Santo Domingo)

von Eckardstein et al. 2003

Etonogestrel combined with MENT or testosterone implants in 29 volunteers (Edinburgh)

(Walton et al. 2007)

MENT plus levonorgestrel implants in 72 volunteers in 3 centres (Los Angeles, Münster, Santiago de Chile)

(Wang et al. in preparation)
Development of MENT by the Population Council

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1995  Clinical trials for treatment of hypogonadism since
2000  Clinical trials for male contraception
2001-  MENT licensed to Schering AG:
2004  eF-MENT gel in phase I studies
2006  MENT back to Population Council for contraception
Most promising testosterone/progestin combinations

- Transdermal T + Oral MDP (Paris)
- T implant + DMPA (Sydney / Melbourne)
- T undecanoate + NETE (Münster / Bologna WHO-CONRAD Schering)
- T undecanoate + NETA (Schering-Organon)
- T undecanoate + ETN (Popul. Council)
- MENT implant + LNG / DMPA (Edinburgh / Organon / PopCcl)
- T implant + DSG
- T implant/MENT + ETN
MENT for male contraception: key messages

- MENT has high androgenic potency (5 – 10 times T).
- Suited for long-lasting implants (one year and longer).
- However, implantation & removal require minor surgery.
- Needs to be combined with progestin for contraception in Caucasian men.
- No 5α-reduction i.e. little effect on prostate.
- At adequate doses bone mass is maintained.
- Minor effect on blood pressure needs to be resolved.
- MENT and eF-MENT has potential for substitution therapy.
- A male contraceptive is still a long way off.
The End