The International Committee for Contraceptive Research Pioneered Modern Long-Acting Methods of Contraception

<table>
<thead>
<tr>
<th>Method</th>
<th>Duration (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper T 200 IUD</td>
<td>4</td>
</tr>
<tr>
<td>Copper T 380A IUD</td>
<td>10</td>
</tr>
<tr>
<td>Norplant® 6 capsules</td>
<td>5</td>
</tr>
<tr>
<td>Jadelle® 2-rod implant</td>
<td>5</td>
</tr>
<tr>
<td>Mirena® levonorgestrel IUS</td>
<td>5</td>
</tr>
</tbody>
</table>
Newly Approved Contraceptives

Orals: New Pills with E2 instead of Ethinyl Estradiol
- Oral: Qlaira®/Natazia® (dienogest+E2V 1-3mg)
- Oral: Zoely® (nomegestrol Ac + E2 1.5mg 24/4)

Non-orals: (semi-long acting methods)
- Transdermal: Evra ® (norelgestromin+EE 20)
- Vaginal: Nuvaring ® (etonogestrel+EE15)
- Implant: Implanon ® (etonogestrel)
## The Future: Meeting the Unmet Needs

<table>
<thead>
<tr>
<th>Targets</th>
<th>Projects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better birth spacing</td>
<td>Progesterone vaginal ring</td>
</tr>
<tr>
<td>Mid-acting methods</td>
<td>NES/EE one-year ring, new injectables</td>
</tr>
<tr>
<td>Methods used privately</td>
<td>NES/E2 transdermal gel</td>
</tr>
<tr>
<td>Methods acceptable to younger population</td>
<td>Vaginal gels on demand</td>
</tr>
<tr>
<td>Dual protection</td>
<td>Dual protection Ring</td>
</tr>
<tr>
<td>Methods for men</td>
<td>MENT implants, NES gel</td>
</tr>
</tbody>
</table>

*Adjudin, sperm targets*
New Contraceptive Rings

- One-year vaginal ring*
- Progesterone 3-month
- Progesterone receptor modulator vaginal ring
- Dual-protection ring with anti-retroviral agents and contraceptive steroids

* Delivers NES/EE 150/15µg /day, 13 cycles 3 weeks on followed by 1 week off

Developed by the Population Council
Sponsored by USAID, NICHD, WHO
New Molecules with added benefit

• Ulipristal Acetate, A PRM with antiovulatory effect and which does not stimulate breast cells

• Progesterone and Nestorone (NES) show positive effects on myelin repair both *in vitro* and *in vivo* models (Hussain et al, Endocrinology 2011)

• Effects of 19nor-P and NES on neuro-regeneration (Liu et al Endocrinology, 2010)
Transdermal Contraceptives

- Transdermal patch (Ortho Evra)
- Two other TDS in development
  - (gestodene or LNG +EE)

- Transdermal spray and gel
  Progestin (Nestorone®)
  - and Estradiol (E2)
Metered Dose Transdermal System

MDTS® Applicator
Used for simple, accurate & flexible dosing
US Pat. appl.no. 10/442,323

ACROSS® Enhancers
Allow drugs to pass through skin more rapidly
US Pat. no. 6,299,900

Patchless Patch® Reservoir
Forms an invisible reservoir within the skin
US Pat. no. 6,818,226
Nestorone – Steady State

Steady State PK results following dosing for 5 days (n=6)

Fraser et al  Contraception, Dec 2007
METHODS ACCEPTABLE TO YOUNG PEOPLE

Pericoital use: Vaginal Gels “On Demand”

• Concept: use vaginal gel as a vehicle

• Deliver a progestin, levonorgestrel (LNG), known to be absorbed from the vagina

• Determine doses based on plasma levels of LNG, which is known to block ovulation

• Use the gel BEFORE intercourse

Percentage of Anovulation in 5-day post-LNG Gel, 0.75 mg/4 mL or LNG oral 0.75 mg x 2

Higher efficacy with vaginal delivery of LNG

MENT for Male Contraception

A TISSUE-SELECTIVE ANDROGEN

- No effect on prostate
- Maintains libido, muscle mass, bone
- Implants for one-year contraception
New non-hormonal targets for Contraception

Prevent entry of Spermatozoid in the zona pellucida
Prevent motility of Spermatozoid by targeting enzymes or proteins involved in sperm movement

Population Council
A Few Promising Leads for Men

- **Adjudin** [Adherens Junction Disruption] *(Cheng)*
- **CatSper:** Cation channel Sperm *(Clapham)*
- **Epididymal Protease Inhibitor (EPPIN)** *(O’Rand)*
- **Glyceraldehyde 3-phosphate dehydrogenase-S** *(GAPDHS)* *(O’Brien)*
- **Retinoic Acid Receptor Antagonists** *(Wolgemuth)*

Antagonists to prevent sperm maturation, activation, motility.
Targets in the Ovary

• Inhibition of oocyte maturation
• **PDE3** inhibitors: impaired oocyte maturation (MarcoConti, UCSF)
• **Wee1B** KO: oocytes remain arrested in metaphase II, not activated and cannot be fertilized
• **Wee1B** an oocyte-specific meiosis inhibitor (Hanna C…Jensen JBIol Reprod 2010)
Targets in the Ovary

• Inhibition of cumulus-oocyte expansion /follicle rupture

• **PGE2** induced expansion of the complex: PGE2-R antag to block event

• **GM 6001** (MMP inhibitor) blocks follicle rupture, and maintain luteinized follicle unruptured with secretion of P levels.

Jon Hennebold, OHSU, Portland, OR
Meloxicam Oral or Vaginal

- Cyclooxygenase-2 (COX-2) inhibitor
- COX-2 inhibitors are accessible over-the-counter in many countries
- Potential CV concerns
- Oral use 5 days for EC
- Vaginal ring proposed for continuous contraception (H Croxatto, Chile)
NICHD's Vision: The Next Decade
Scientific Opportunities for Contraception Research

• Improve understanding of the risk factors for unintended pregnancy and the social and cultural behaviors that facilitate or detract from the correct and consistent use of contraceptive methods.
• Improve existing contraceptive methods
• Develop new methods with added benefits

http://www.nichd.nih.gov/vision
Acknowledgments

- USAID
- NICHD
- CONRAD, UNFPA
- Bill & Melinda Gates Foundation
- Mellon Foundation
- Hewlett Foundation
- Collaborative country governments
Acknowledgments

- **Program Committee**: Irwin R. Merkatz, Daniel R. Mishell Jr, Regine Sitruk-Ware
- **Unrestricted grants** from Teva, HRA Pharma, Merck
- **CME Accreditation** from Einstein Medical College, Dr Irwin R. Merkatz, Vincene Aquilato
- **Organizational help**: Yvonne O’Neal, Naquan Davis, Chris Carhart, Elena Hoskin, Barbara Nee, Evan Read, Naomi Rijo, Monica Ruse, Jared Stamm, Debra Warn