GREEN CONTRACEPTIVE RESEARCH AND DEVELOPMENT

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Contraceptive Discovery and Development Branch
NICHD, NIH, DHHS

MISSION AND GOALS
♦ Green Working Group – Initial Meeting - November 2011
♦ Goal – to develop an agenda for Sustainable Contraceptive Research & Development
  Included representatives from:
  ♦ Reproductive Health Technologies Project
  ♦ Population Council
  ♦ NIH
  ♦ EPA
  ♦ USAID
  ♦ PATH
Outcome summarized in publication in Contraception 2013 Mar;87:347-51
A Greenprint for Sustainable Contraceptive Research and Development.
  Moore K, Townsend J, Spieler J, Coffey PS, Blithe D, Arndorfer E, Daws E.

WHAT IS GREEN CONTRACEPTION?
Redundant?

GOALS: Prevent unintended pregnancy! Minimize harm to the environment!

GREEN CONTRACEPTION LIFE CYCLE

CONCEPT & DESIGN
Discussion points:
♦ Can products be designed to be longer acting?
  ▪ Maximize effectiveness and minimize the number of times a consumer needs to use the product?
♦ Can we increase bioavailability of active drug and use lower amount?
Need to involve manufacturers, suppliers and consumers in the process.

RESOURCES & MATERIALS
♦ Can we encourage innovation in material design and production?
  ♦ Create biodegradable materials?
  ♦ Use recycled and recyclable materials?
  ♦ Minimize potential for waste during and after use?
♦ We need to review each step in the process to see if improvements can be made.
MANUFACTURING

What would encourage manufacturers to adopt greener practices?
Could there be a market advantage to producing greener products?
Would public awareness help motivate companies?

What can we do to help foster this culture?

PACKAGING & TRANSPORT

Is this "Low Hanging Fruit"?

- Reduce the size and complexity of the packaging or "final product". (example - EC pills)
- Use fewer layers to get to the product
- Minimize package inserts and use recycled materials
- Include only necessary info? Font? Refills?
- Reduce waste in leftover products (bottles, tubes, insertion equipment, etc)
- Promote environmentally-friendly shipping, storage and shelf life
- Coordinate supply chains with customer demand to avoid expired products

CONSUMER UTILIZATION

What do consumers expect?
- If we make them aware of green products, will there be a demand?

How can we improve uptake and continuation?
- Encourage transition to longer acting methods
- Can we improve access?
- Minimize side effects?

Cost - would procurement officials or consumers be willing to pay more for a green product?

WASTE & DISPOSAL

Multiple Issues:

Disposal of materials:
- Recycle materials from production and packaging
- Minimize unused and expired products
- Develop strategies for solid leftover waste
  - condoms, bottles, syringes, sharps, tubes, silicone rings

Excretion of active hormones or other drugs

- Improve Wastewater treatment?

Environmental Impact of Ethinyl Estradiol

Landfill of Vaginal Rings?

Environmental exposure assessment of EE from a combined hormonal vaginal contraceptive ring after disposal; leaching from landfills.

Geurts et al., 2007 Sci Total Environ 377:386-70

Visual approximation of landfill of rings

Conclusions: Few rings per cubic meter
Minimal leaching of EE from landfills in the Netherlands.

What if there are many more rings?
They are under development for many applications.
Not easy to destroy.
What about regions where disposal and wastewater treatment is not well controlled?

POTENCY OF ETHINYL-ESTRADIOL COMPARED WITH ESTRADIOL

<table>
<thead>
<tr>
<th>Potency relative to E2</th>
<th>E2</th>
<th>E1</th>
<th>EE</th>
</tr>
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<tr>
<td>Human assays a</td>
<td>E2</td>
<td>E1</td>
<td>EE</td>
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<tr>
<td>Serum FSH</td>
<td>1</td>
<td>0.8</td>
<td>150</td>
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<tr>
<td>Serum Angiotensinogen</td>
<td>1</td>
<td>1.4</td>
<td>330</td>
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<tr>
<td>Serum SHBG</td>
<td>1</td>
<td>0.5</td>
<td>500</td>
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<tr>
<td>Serum CBG</td>
<td>1</td>
<td>1.0</td>
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</tr>
</tbody>
</table>

Fish Assays b

| Serum FSH              | 1  | 0.8| 31 |
| Serum CBG              | 1  | 1.0| 33 |

Caldwell et al. Predictive effect concentrations in the steroid estrogens... 2012 Environ Toxicol Chem 31:1335-46
Hypothetical Green Score Factors for Contraceptives

<table>
<thead>
<tr>
<th>Product</th>
<th>Mechanical effectiveness</th>
<th>Chemical effectiveness</th>
<th>Safety</th>
<th>Bioactivity</th>
<th>Sustainability</th>
<th>Biodegradability</th>
<th>Market potential</th>
<th>Hypothetical Green Score</th>
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<tbody>
<tr>
<td>Implant - Implanon</td>
<td>99.9</td>
<td>plastics</td>
<td>master</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>93</td>
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<tr>
<td>IUS - Mirena</td>
<td>99.8</td>
<td>plastics</td>
<td>master</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>++</td>
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<tr>
<td>IUD - Cu 380</td>
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<td>+++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
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<tr>
<td>DMPA</td>
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<td>plastics</td>
<td>master</td>
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<td>++</td>
<td>98</td>
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<tr>
<td>Nuvaring</td>
<td>92</td>
<td>plastics</td>
<td>dio</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>76</td>
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<tr>
<td>Pills</td>
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<td>plastics</td>
<td>dio</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
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<td>POPs</td>
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<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
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<td>Intrauterine Contraceptive</td>
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<td>+</td>
<td>++</td>
<td>++</td>
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<tr>
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<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
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<tr>
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<td>+++</td>
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<td>Barrier methods</td>
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<td>+++</td>
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<td>+++</td>
<td>++</td>
<td>75</td>
</tr>
<tr>
<td>No Method</td>
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<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>15</td>
</tr>
</tbody>
</table>

**CONTRACEPTIVE EFFECTIVENESS**

- **Implant - Implanon**: 99.9% effectiveness, 5 years of use, LARC Hormonal Method
- **IUS - Mirena**: 99.8% effectiveness, 5 years of use, LARC Hormonal Method
- **IUD - Cu 380**: 99.2% effectiveness, 10 years of use, LARC Hormonal Method
- **DMPA**: 93.97% effectiveness, 5 months of use, LARC Hormonal Method
- **Nuvaring**: 92% effectiveness, 1 month of use, LARC Hormonal Method
- **Pills**: 92% effectiveness, 1 month of use, LARC Hormonal Method
- **OOCs**: 92% effectiveness, 6 months of use, LARC Hormonal Method
- **POP**: 92% effectiveness, 12-3 months of use, LARC Hormonal Method

Hormonal Contraceptives:

- **Implant - Implanon**: 99.9% effectiveness, 5 years of use, LARC Hormonal Method
- **IUS - Mirena**: 99.8% effectiveness, 5 years of use, LARC Hormonal Method
- **IUD - Cu 380**: 99.2% effectiveness, 10 years of use, LARC Hormonal Method
- **DMPA**: 93.97% effectiveness, 3 months of use, LARC Hormonal Method

Barrier Contraceptives:

- **Condoms - male**: 85% effectiveness, 1 month of use
- **Condoms - female**: 79% effectiveness, 1 month of use
- **Spermicides**: 71% effectiveness, 1 month of use

**UNINTENDED PREGNANCY IN THE USA (~49%)**

- **Use of Method**
  - Correct: 19
  - Incorrect: 65
  - None: 16

- **Unintended Pregnancies**
  - 52
  - 43

**MISSION AND GOALS**

- **Green Working Group** – Developed a “Greenprint for Sustainable Research & Development”
  - Devise a Green Score?

**NIH**

- **Eunice Kennedy Shriver National Institute of Child Health and Human Development**
- **NICHD Mission** - to ensure that every person is born healthy and wanted, that women suffer no harmful effects from reproductive processes, and that all children have the chance to achieve their full potential for healthy and productive lives...
- **Contraceptive Discovery & Development Branch Goal** - to promote contraceptive research and development for preventing or reducing unintended pregnancies...

**FACTS ON UNINTENDED PREGNANCY IN THE UNITED STATES - GUTTMACHER INSTITUTE 2012**

- **Use of Method**
  - Correct: 19
  - Incorrect: 65
  - None: 16

- **Unintended Pregnancies**
  - 52
  - 43
**CHARACTERISTICS FOR NEW CONTRACEPTIVES?**

Need products that are:

- Easier to use – better compliance
- Less reliant on health care provider and need for new prescription
- Fewer side effects, better satisfaction with method
- Environmentally friendly
- Safe for women with health conditions, including obesity, diabetes, hypertension, etc.

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**NEW HORMONAL PRODUCTS FOR WOMEN (on the horizon)**

**Nes-EE Contraceptive Vaginal Ring**

- **Nestorone®** - 150 ug - new progestin - not orally active
- **Ethinyl Estradiol (EE)** - 15 ug - synthetic estrogen – (in most COCs)

- **One ring for 1 year (13 cycles)**
- **One Rx per year, better compliance**

*The Nes-EE CVR is a Greener alternative to monthly rings.*

- Even lower EE or no EE thought to be safer but POPs may be less effective
- Obesity and age are also risk factors for VTE
- Risk of VTE with pregnancy is much higher than any method!

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**NEW HORMONAL PRODUCTS FOR WOMEN (in development)**

**Nestorone Estradiol Vaginal Ring**

- substituting estradiol (E2) for EE
- continuous use for 3 months

- Natural hormone estradiol should be safer for all women
- E2 is absorbed vaginally better than orally
- E2 has benefits for bone health and other estrogen-dependent activities in the body

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**NEW PROGESTIN-ONLY PRODUCTS (in development)**

**Levonorgestrel Butanoate**

- No EE
- long acting injectable (4+ months)  
  - better compliance
- safe for obese women

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**NOVEL PRODUCTS FOR WOMEN**

**Low dose Ulipristal Acetate**

- No EE!
- Safe for women with obesity, diabetes, other health issues?
- May have breast-protective properties?

*Effects of the progestosterone receptor modulator VA2914 in a continuous low dose on the hypothalamic-pituitary-ovarian axis and endometrium in normal women: a prospective, randomized, placebo-controlled trial.*

Collaborations on Family Planning/Reproductive Health R&D
Contraceptive Technology Supporting Agency Working Group (CT-SAWG)

ORGANIZATIONS
• Bill & Melinda Gates Foundation (BMFG)
• US NIH / National Institute of Child Health & Human Development (NICHD)
• USAID, Office of Population & Reproductive Health

Goal: Maximize communication and available resources for effective contraceptive development

NEW MPT PRODUCTS FOR WOMEN
Multipurpose Prevention Technologies (MPTs) - to prevent unintended pregnancy as well as infection by HIV or other STIs

ORGANIZATIONS
• Association of Reproductive Health Professionals
• AVAC: Global Advocacy for HIV Prevention
• Bill and Melinda Gates Foundation
• Brown University
• Coalition Advancing Multipurpose Innovations
• CONRAD
• FHI360
• Guttmacher Institute
• Indian Council of Medical Research
• Kenya Medical Research Institute
• Mapp Biopharmaceutical
• Nanjing University
• NIH / National Institute of Child Health and Human Development
• NIH / National Institute for Allergies and Infectious Diseases
• NIH / Office of AIDS Research
• PATH
• Population Council
• Public Health Institute
• UK Department for International Development (DFID)
• University of California Berkeley
• University of California San Francisco
• University of Witwatersrand
• US Agency for International Development
• World Health Organization

Beginning…
Organizations need to take a multipronged approach to determine the most effective and feasible methods for women.

NEW MPT PRODUCTS FOR WOMEN
(Multipurpose Prevention Technologies)

Non-hormonal products (dual protection):
➢ PATH Woman’s Condom
  -Phase III trial completed in the NICHD CCTN
➢ Spermicides – for use with diaphragm or alone
  ➢ C31G spermicidal gel – Phase III contraceptive trial completed
  ➢ Buffer Gel spermicidal gel – Phase III contraceptive trial complete

NON HORMONAL OPTIONS FOR WOMEN
If a woman cannot take hormonal methods, her effective, reversible options are limited to:
➢ Copper IUD
➢ Condoms
➢ Spermicides +/- Diaphragm

New NICHD program will solicit ideas for targets for non-hormonal methods for women –
Funding Opportunity: Request for Applications - 2014
Alternatively...
The best option for some women may be a male contraceptive!

Goal of Male Contraception
➢ Inhibit spermatogenesis (production of sperm)
  ➢ Hormonal – clinical trials ongoing or completed
  ➢ Non-hormonal – preclinical stage
    - Targets and drugs identified
➢ Inhibit sperm function (motility, binding, fusion)
  ➢ Non-hormonal – preclinical
    - Potential targets and drugs identified

Nestorone/Testosterone Gel Study
Percent of Men with Sperm Suppression

T + Nes 8 mg

Treatment
Recovery
Week
0
20
40
60
80
100

-8
-6
-4
-2
0
8
16
24
32
40
CHALLENGES AND NEXT STEPS
- Expand the Circle: Contraception, 2013
  - Product developers, providers, consumers
- Conduct cost-benefit Landscape Analysis
- Encourage green chemistry and manufacturing
- Manufacturers, Environmental Regulatory Agencies
- Influence current Research & Development
- Seek quick wins and long-term impacts for sustainability

New Ideas? What can you do to help?

GREEN CONTRACEPTION LIFE CYCLE

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