Biodegradable implants

Matthew Reeves, MD, MPH
October 31, 2011

Overview

• The need
  — Arriving at a logical target product profile
• The technology
  — Capronor
  — Injectable microspheres
• The goal
  — Meeting the target product profile
  — Rapid development - before 8 billion

Injectables as a proportion of modern contraception in Africa

Holy Family Hospital

Phalombe, Malawi
• 500,000 people
• 2 doctors
• 4 clinical officers
• Tubal ligation at Cesarean
• Sharp D&C for “incomplete ab”
• DMPA (only)
• Coke & Beck

Women’s choices

Contraceptive uptake in Bangladesh in 1978-1980

Depo-Provera

• “Real medicine” is injected
• Discrete methods are popular
• Easy to give (I.M. injection)
• Irregular bleeding → amenorrhea
• Weight gain & hair loss
• E2 suppression: vaginal epithelial thinning and other effects
• “Enough hormone for a village”

Lesson learned

• Discrete
• No provider limitations → access
• Return to fertility is rarely an issue
• Irreversibility not limiting
**Implanon**
- Single rod: 68mg etonogestrel
- Approved by FDA July 2006

**Lessons learned:**
- Counseling: No one likes to feel things in their arms (even small things)
- Successful private sector development
- Target serum levels well quantified for ENG
- Training is limiting even in US
- A better implant is unlikely

**Capronor**
- Poly-caprolactone capsule
- Levonorgestrel 21.6 mg
- 4 cm rod promising
- No problems with removal in two Phase II studies
- Rods loose strength
- Rods broken is dog studies

**Providers**
- Any provider can perform a subcutaneous injection
  - Not just family planning
- Injections are fast
- Dedicated training limits access
- Removal problematic for implants

**Contraceptive landscape**

<table>
<thead>
<tr>
<th>Oral</th>
<th>IUDs</th>
<th>Implants</th>
<th>Injectable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (users)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Providers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manufacturers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Researchers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Policymakers</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**An idea before its time**

Biodegradable systems for the sustained release of fertility-regulating agents

Just 9 years after first paper on synthetic resorbable sutures

**An idea whose time has come**

- Biodegradable technology
- Target serum levels known for LNG & ENG
WomanCare Global’s Target Product Profile

- Simple to use for women
- Simple to initiate/continue
- Discrete/undetectable
- Low-dose
- Effective 6-12 months
- No removal
- Acceptable side-effect profile
- Near 0-order release
- Quick return to fertility
- Rapid development timeline

Development landscape

<table>
<thead>
<tr>
<th>Oral</th>
<th>Intrauterine</th>
<th>Implanted Rods</th>
<th>Injectable, Progestin-only</th>
<th>Vaginal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enovid</td>
<td>Silkworm gut</td>
<td>Norplant</td>
<td>DMPA</td>
<td>LNG 20</td>
</tr>
<tr>
<td>50-mcg EE</td>
<td>Plastic</td>
<td>Jadelle</td>
<td>NET-EN &amp; combined P/E</td>
<td>Nuvaring</td>
</tr>
<tr>
<td>30-mcg EE &amp; phasic pills</td>
<td>Copper</td>
<td>Implanon</td>
<td>LNG-But</td>
<td>Progesterone</td>
</tr>
<tr>
<td>20-mcg EE &amp; extended regimens</td>
<td>Progestin</td>
<td></td>
<td>Progestin + biodegradable polymer</td>
<td>NES/EE ring</td>
</tr>
</tbody>
</table>

A discrete implant

- Implants needs to be smaller than Implanon
- Injection needle needs to be smaller

Solution: Microcapsules
- Break up the implant into particles

Biodegradable polymers

- Polymers degraded within the body
  - Hydrolysis
  - Enzymatic degradation
- Many types in use
  - Short-chain hydroxy acids
    - Lactate & pyruvate
    - ε-Caprolactone
  - Sugars
  - Amino acids
  - Other small organic monomers

Poly lactic (co)-glycolic acid

- Poly lactic co-glycolic acid (PLGA)
  - Lactate slows degradation
  - Degrades to lactate & pyruvate
- Microspheres used in several successful injectables
  - GNRH agonists
  - Depot Lupron (3-4 months)
  - Trelstar Depot (6-12 months)
**Progestins**

- Levonorgestrel
- Etonogestrel
- Gestodene
- Nestorone

**NET in PLGA microspheres**


**Norethindrone microcapsules**

Serum levels with 106-150 µm capsules 5mg/kg in rabbits

**Progestins**

- Levonorgestrel
- Etonogestrel
- Gestodene
- Nestorone

**NET in PLGA microspheres**


**Norethindrone microcapsules**

Serum levels with 106-150 µm capsules 5mg/kg in rabbits

**LNG serum levels from Jadelle**


**LNG-PLGA microcapsules**


**LNG-PLGA microcapsules**

LNG release from 106-150 µm microcapsules in rabbits

Injectable polylactate-NET

Cumulative $^{14}$C-NET release in vitro (%)

180-250 µm
90-180 µm
180-250 µm coated

One particle type

Multiple particle types

Injection Site

• Intramuscular vs. Subcutaneous
  — Less vascular = slower release

• Cervical injection?
  — More local hormonal effect is good
    • Lessons learned from Mirena
    — Same/lower skill levels than STD screening

The ideal result

• An injectable micro-implant of a potent progestin
  — Volume of < 2 mL
  — Via a needle ≥ 20 gauge

• 12-month efficacy approaching 100%

• Fertility return by 18 months

• Side-effect profile similar to Jadelle
  — approaching Mirena with cervical injection

Three pathways

Donor funding

• Public access is priority
• Rarely expedient
• Needs oversight
  — Control by entity invested in rapid development

Private funding

• IP to protect investment
• ROI keeps project moving
• Needs oversight
  — Control by entity invested in creating access

Public-Private partnership

• Profit motivation for rapid progress
• Guaranteed access a priori
• Oversight by entity invested in rapid development AND creating access
Thank you