Nelson: What’s in the Pipeline for Contraception?

What’s in the Pipeline for Contraception?

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Learning Objectives

At the end of this presentation, the participants will be able to
- List the new developments in long acting reversible methods.
- Describe the new combined hormonal and barrier methods under development.
- Explain how these new methods may help reduce unintended pregnancies.

New Encouraging Developments

- Utilization of implants and IUDs increased among contracepting women from 8.5% in 2009 to 11.6% in 2012.\(^1\)
- Unintended pregnancy rates dropped from 51% in 2008 to 45% in 2011.\(^2\)
- Providers hope that newer options may provide women the tools they need for contraceptive success


Other IUD Possibilities: Progestin

- Etonogestrel (ENG) IUDs
  - 3 different doses tested
  - May go into US clinical trials soon
- Ulipristal acetate (UPA)
  - To suppress endometrial growth
- Other progesterone antagonists – improved bleeding patterns

**VeraCept: A new Intrauterine Copper Contraceptive**

- 175 mm² of copper
- At cervix and cornua
- Nitinol frame
  - Used in stents & Essure
  - Shape memory allows pre-loading
  - Allows 3.7 mm diameter inserter
- Novel design
  - Compliant arms
  - Fundus seeking
- Pre-cut strings

**Early Results of Trial in Dominican Republic**

<table>
<thead>
<tr>
<th></th>
<th>VeraCept</th>
<th>Copper T</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Total follow-up time</td>
<td>2029</td>
<td>827</td>
<td>0.02</td>
</tr>
<tr>
<td>(woman-months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuation at 12 months</td>
<td>167 (84%)</td>
<td>68 (68%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Verified at 12 months</td>
<td>144 (73%)</td>
<td>64 (64%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Discontinuations</td>
<td>31 (16%)</td>
<td>32 (32%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Expulsion</td>
<td>10 (5%)</td>
<td>12 (12%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Tolerability</td>
<td>7 (4%)</td>
<td>17 (17%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Other</td>
<td>14 (7%)</td>
<td>3 (3%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Adverse Events (all)</td>
<td>85 (43%)</td>
<td>59 (59%)</td>
<td>0.009</td>
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</tbody>
</table>

**Other Copper IUD Possibilities**

- New copper matrix
  - Cross-linked composite-like polyvinyl alcohol (PVA) containing copper ions
- IUDs coatings
  - Coating with poly (DL-lactide-co-glycolide)(PLGA) film
  - Coating with low-density polyethylene (LDPE) film
  - Pretreatment with organic inhibitors
  - Coating with NSAIDs
- Ultra-fine grained copper + single copper crystal

**Other IUD Possibilities: Shapes**

- Frameless copper IUDs: 5 year devices
  - 4 copper sleeves (200 IUD)
  - 6 copper sleeves (330 IUD)
- Threaded on polypropylene suture thread
- Single knot at top inserted 1cm into fundal myometrium to anchor system
- New version knot more visible on ultrasound
- Potential for frameless LNG IUD

**GyneFix-VIZ**

- Made of shape memory alloy wire
  - Tolerates flexion, but returns to its preset shape
- Wire covered with thin white polymer coating
  - Applied to improve visibility
- 17 pure copper sphere threaded over wire
- 300 mm² or 380mm² copper surface area
- 20cm double-tailed uncolored nylon monofilament thread
- Preloaded into tube (3.2mm) with rod inserter

**Intrauterine Ball**

- Made of shape memory alloy wire
  - Tolerates flexion, but returns to its preset shape
- Wire covered with thin white polymer coating
  - Applied to improve visibility
- 17 pure copper sphere threaded over wire
- 300 mm² or 380mm² copper surface area
- 20cm double-tailed uncolored nylon monofilament thread
- Preloaded into tube (3.2mm) with rod inserter
Nelson: What’s in the Pipeline for Contraception?

The IUD in its free form (left) and loaded into the insertion tube (right)


Contraception Implants
- In use elsewhere
  - Jadelle - 2 implant system with LNG
    - Approved in US as Norplant II
  - Sino-Implant II – LNG releasing
    - Made in People’s Republic of China

New Contraceptive Implants
- Potential Progestins
  - Nomegestrol acetate
    - 1 year study pregnancy rate 0.94%¹
  - Nesterone – for breastfeeding women
    - Lactational amenorrhea lasted 1 year
    - 2 year pregnancy rate 1.7%
    - Less effective in non-lactating women


Long-Acting Injectable Contraceptives
- Need for products to fill in gap between 3 month injection and 3 year implant or IUD
- Older: DMPA 300/400mg IM Q6 months
- Active pharmaceutical ingredient approach
  - LNG-butanoate
  - LNG-cyclopropyl-carboxylate
  - LNG-cyclobutyl-carboxylate
- Delivery system approach
  - Biodegradable polymers – microspheres
    - Polymer matrix
    - Hollow polymer structure


New Progestin Injection Developments
- Levonorgestrel butonate
  - 50 mg suppresses ovulation 5-6 months
  - 12.5 mg suppresses another 2-4 months¹
  - May have fewer progestin-related adverse effects²
  - Uninject self injection system


Microspheres - Past
- Synthetic polyesters
  - Poly (glycolide) PLG
  - Poly (lactide) PLA
  - Poly-lactic-co-glycolic acid PLGA
- PLGA used for slow release for treatment endometriosis, alcohol dependence, acromegaly
- PLG, PLA, PLGA – LNG release
- PLGA microspheres – nesterone
- PLGA NE up to 6 months

Microsphere Materials-Future

- Polyanhydrides used for local anesthesia, antibiotics, growth hormones
  - Can adjust release and degradation
- Porous silicon with precise pore size and distribution
- Precision particle fabrication uses acoustic excitation to get uniform size droplets
  - Narrows size distribution


Combination Monthly Injection

- Previously marketed in US as Lunelle
  - 5 mg estradiol cypionate/104 mg DMPA
  - Administered every 28 days sub-Q
  - Used by 2.5 million women worldwide
- Sold to Sun Pharmaceutical Industries (Mumbai, India)
- PK and PD studies completed for US reintroduction


Drospirenone-Only Oral Contraceptive: Efficacy

- 4.0mg DRSP in 24/4 formulation
  - No back-up needed if <24 hours since missed pill
- Tested in 41 European centers for 13 cycles
- Pregnancies corrected for sexual activity and other method use

<table>
<thead>
<tr>
<th></th>
<th>All Subjects</th>
<th>Women &lt; 35</th>
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<tbody>
<tr>
<td>Number cycles</td>
<td>7191</td>
<td>5530</td>
</tr>
<tr>
<td>Pearl index</td>
<td>0.5423</td>
<td>0.7052</td>
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</table>


New Combined Oral Contraceptives: Monthly Cyclic Formulation

- E2/Nomegestrol (NOMAC) monophasic 24/4 (Merck)
  - 2.5 mg NOMAC
    - Potent antiestrogenic effects on endometrium
    - 1.5 mg 17β E₂ (estradiol)
    - Pearl index 0.38% (Europe), 1.13% (USA)
    - Scheduled bleeding shorter, lighter than EE/DRSP
    - 30% no scheduled bleeding at 12 months
    - Available in EU
    - Application at FDA


New Molecules for Oral Contraception

- Estetrol (E4) – from fetal liver
  - Combined with ENG or LNG
  - 18 times less potent than EE
  - No hepatic conversion

- Progesterone antagonist (PAs), progestin receptor modulators (PRMs)
  - Block ovulation and prevent follicular rupture

Ulipristal Acetate

- Selective progesterone receptor modulator (SPRM)
- 2nd generation compound used in ella
- Binds to progesterone receptor to block progesterone-mediated DNA transcription
  - Blocks or delays LH surge
- Being investigated as potential estrogen-free, daily pill
  - NIH phase II trials of 5 and 10 mg doses (21/7, 24/4) completed
- PRM-associated endometrial changes (PAEC)

**New Transdermal Contraception**
- EE/LNG patch AG200-15 Agile Patch (Twirla®)
  - 7 day patch 21/7
- Active matrix core in perimeter adhesive system
  - Bulkier patch but softer with good adhesion
- Systemic EE levels ~ 30 mcg COC
  - Absorption from abdomen lower
- Equally effective in suppressing ovarian activity in non-obese and obese women
  - Comparative trial conducted vs. COC
  - Failed to earn FDA approval initially
- Phase III trial underway


**New Transdermal Contraception**
- EE/Gestodene “FC low” patch
  - 21/7 pattern of use
  - 1 patch per week X 3 weeks, 1 week off
  - Transparent, smaller size (10 cm²)
  - Systemic levels EE ~ 20 mcg EE
  - Suppressed ovulation and follicle growth
  - Applying for license in EU


**Progestin-Only Patch**
- Levonorgestrel patch
  - In Phase 2 trials
  - Cervical mucus, follicle growth, ovulation
- Norethindrone acetate patch
  - In Phase III trial


**New Contraceptive Ring**
- EE/Nesterone: Population Council
  - 13 cycles of hormones in one ring
  - Releases 15 mcg EE and 150 mcg nesterone per day
  - Placed monthly: 3 weeks/1 week out
  - Nesterone potent nonandrogenic progesterone derivative
    - Not orally absorbed
    - Phase 3 trials completed


**Nesterone/EE Vaginal Ring**
- E2/Etonogestrel vaginal ring
  - E2 may be substituted for EE in ring because constant release does not require long acting estrogen for cycle control
  - Cyclic use in Phase III clinical trials now

Clinicaltrials.gov.
NuvaRing with Estradiol

Levonorgestrel Vaginal Ring
- 3 month ring releasing 20 mcg/day
- WHO clinical trial 8,176 women years
  - Pregnancy rate 4.5%
- Menstrual disturbance lead to discontinuation in 17% of subjects
- Rim on early model: erythema seen at vault

Nesterone-Only Vaginal Ring
- Population Council dose finding study
  - 3 prototypes: 50, 75, 100 mcg/day
- All 3 doses
  - Inhibited ovulation
  - Caused menstrual irregularities
  - Lower doses more so
- May be used in breastfeeding women or with $E_2$?

New Vaginal Rings
- UPA
  - 3 month silicone rubber ring with ulipristal acetate 600-800 mcg/d
    - Ovulation suppression seen in only 68%
  - Higher doses of UPA (6-7 ng/mL)
    - 80-90% ovulation suppression
- Dual rings
  - Antiretroviral agents + contraceptive steroids

New Contraceptive Ring Accessories: Applicator
- Trial of performance and safety of vaginal ring applicator
- Testing placebo vaginal ring with single-use, non-sterile applicator
- Study design:
  - Open-label, randomized, 2-period crossover study on insertion of NuvaRing placebo with and without use of NuvaRing Applicator
- Study outcomes
  - % successful insertions – immediately
  - % successful insertions – 48 hours after insertion

Clinical Trials.gov (MK-8342A-063)
Nesterone/E₂ Transdermal Gel
- Randomized, open-label, 3 treatment period crossover dosing study
- 18 women: 21 days exposure to abdominally administered gel

<table>
<thead>
<tr>
<th>Dose</th>
<th>Median NES Cmax (pmol/L)</th>
<th>Median maximum follicular diameter (mm)</th>
<th>Ovulation suppressed with correct use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 mg NES</td>
<td>318.6</td>
<td>8.5-23.0</td>
<td>100%</td>
</tr>
<tr>
<td>0.5 mg E₂</td>
<td>783.0</td>
<td>10.2</td>
<td>93.3%</td>
</tr>
<tr>
<td>3.0 mg NES</td>
<td>1063.8</td>
<td>6.5-19.4</td>
<td>100%</td>
</tr>
<tr>
<td>1.0 mg E₂</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.5 mg NES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5 mg E₂</td>
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Male Condoms
- New sizes: up to 91 needed
  - Waiting for approval by international testing authorities
- Gates Foundation announced funding to develop male condoms that are easier or more pleasurable to use


Galactic Cap
- 2-piece prophylactic device fits only over the tip of the penis
  - Polyurethane adhesive film that fits around the meatus above the coronal ridge
  - Man able to wear for hours to days?
  - Able to urinate, showering
- Reservoir cap attaches by adhesive to base film
  - Thick reservoir tip emerges to capture ejaculate
- May be adopted by adult video industry


Other Female Condoms
- VA w.o.w.® (worn of women)
- Condom féminin®
- L’amour®
- Reddy FC®
  - Natural rubber latex
  - Medical grade sponge at closed end
  - Outer anchoring structure: triangular shaped frame
  - Pre-lubricated with silicone oil
- Approved EU and Brazil


More Female Condoms: Phoenurse™ FC
- Dumbbell-shaped device
- Polyurethane with inner and outer rings
- Shorter in length than current version
- Long plastic insertion tool
- Packaged with water based lubricant, sanitary towel, disposal bag

Spermicides Recently Tested

Buffer Gel

- Acid-buffering vaginal gel microbicidal/viricidal spermicide
- Used with diaphragms
  - 6 month pregnancy rate
    - Buffer Gel 10.1% vs. N-9 12.3%\(^1\)
- No protection seen against HIV infection\(^2\)


C31G

- Mixture of 2 surfactants
- Myristamine oxide + cetyl betaine
- Less toxic than N-9
  - Treatment related AE (35 vs. 41%)
- 6 month failure rates with diaphragm
  - C31G 10.1% vs. N-9 12.3%
- 12 month pregnancy rate
  - C31G: 13.8% vs. N-9:19.8% (NS)\(^2\)
- No reduction in HIV


Amphora

- Clear, water-based gel
- Acidifying, bioadhesive and viscosity-retaining properties
  - Forms long-lasting layer of gel over vagina and cervix
  - Continued acidification of ejaculate in vagina
- Recently completed Phase 3 clinical trials

\(^{1}\) Brache V, et al. Contraception. 2007;76(2):111-6

On Demand – Occasional Use: Vaginal Gels

- LNG 750 mcg/4mL in Carraguard\textsuperscript{\textregistered} vaginal gel
  - Administered once when follicle reached diameter of 12-14, 15-17, and >18 mm
  - 74%: no follicular rupture within 5 days
  - 4%: ovulation observed
  - 96%: prevented/delayed ovulation or caused ovulatory dysfunction (inadequate LH surge)

\(^{1}\) Brache V, et al. Contraception. 2007;76(2):111-6

Polidocanol Foam Infusion for Tubal Occlusion

- Polidocanol foam (PF) approved by FDA as treatment for varicose veins
- Animal models: baboons, macaques
  - Dose finding study +/- DMPA
- Complete tubal occlusion seen in
  - 3/8 1% concentration PF
  - 6/7 5% concentration PF
  - 5% PF eliminates epithelial lining
  - Occludes completely 1-2 months
- DMPA improved results


Non-Hormonal Contraceptives: COX-2 Inhibitors

- Meloxicam 30 mg x 5 days in late follicular phase suppresses follicular rupture\(^{1,3}\)
- Meloxicam 15 mg combined with LNG EC increased proportion of cycles with no follicular rupture\(^{1}\)
- Meloxicam 30 mg/day given days 5-22 > 20% ovulation\(^2\)
- Rofecoxib 25 mg given when dominant follicle reached 14-16 mm
  - Delayed follicular rupture > 48 hours after LH peak in 4 of 6 women

\(^{3}\) Pall M. Hum Reprod 2001;16(7):1523-8.
Nelson: What’s in the Pipeline for Contraception?

Physiology of Dominant Follicle

- Meiotic Maturation
- Egg Activation

PDE 3 Inhibitors prevent breakdown of Germinal Vesicle in Prophase I

GVBD = Germinal Vesicle Breakdown

David Greenstein, Department of Cell and Developmental Biology, Vanderbilt University School of Medicine

Antisperm Contraceptive Vaccines

- Novel sperm-specific antigens/genes
- Vaccination with these sperm antigens
  - Cause reversible effects in females and males of many species
  - Systemic and local antisperm antibody reaction
  - Only tested in one primate model
- Combination vaccine with peptides of various sperm proteins
- Once-a-month immuno-contraceptive


“Green Contraceptive” R&D Agenda

- Both hormone free and eco-friendly
- Current green methods
  - Latex condoms: sustainable growth rubber trees
  - Copper IUDs
- All elements must be considered
  - Resources and materials
  - Concept and decision
  - Manufacturing, packaging, transportation
  - Consumer utilization and disposal


What If We Got Them All?

- At the end of the day, we are still dealing with humans.