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 each of these new methods may help reduce unintended pregnancies.

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


New IUDs

“LNG-16” 5 year IUD

- Smaller device, intermediate LNG levels
- Before FDA now
- LNG-20 Medicines 360 version
  - Modified introducer
  - Lower cost in developing countries
- Nanopaz – smaller cervical device
- Releases LNG 20 mcg/day

Other IUD Possibilities: Progestin

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


Other IUD Possibilities: Copper

- New copper matrix
  - Cross-linked composite like polyvinyl alcohol (PVA) containing copper ions
  - Reduce early copper burst and bleeding
  - Copper IUDs with NSAID coating
  - Tested in simulated uterine fluid ≥250 days
  - Cupric ion release more constant
  - Sustained release seen of indomethacin
- Ultra-fine grained copper + single copper crystal
  - Lower burst, less corrosion, high efficiency release
  - Lower dose IUD

4. Guaiti M, ASRM Boston 2013

Silicone Rubber/Nano-Copper Nanocomposite

- Material developed for use in IUDs
- Uniform dispersion of nano-copper in silicone matrix
- Release rate of Cu ions can be stabilized for months


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
- Potential for frameless LNG IUD


Other IUD Possibility: Shapes

- SCu300A Intrauterine ball (IUB) 12 mm in diameter takes a 3-dimensional spherical form
  - 12 mm in diameter
  - 5 year lifetime
- Potential benefits
  - Reduced perforation
  - Reduced malposition, expulsion rates
  - Reduced dysmenorrhea, menorrhea


GyneFix 200
Nelson: Future Developments in Contraception: What’s on the Horizon

**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 380 mm² copper surface area
- 20 cm double-tailed uncolored nylon monofilament thread
- Preloaded into tube (3.2 mm) with rod inserter


**Intrauterine Uterine Ball (IUB)**


**3-DRIUD**
- 3-dimentional, reticular intrauterine device
  - Nickel-titanium (Ni-Ti) covered with silicone rubber
  - Reticular spiral shape – expands to fill uterine horn
- Tested only in rats with laparotomy placement
  - 0 pregnancies with large IUD in place
  - Smaller devices less effective
- 90% rapid return to fertility


**Possible New Approaches to Control Copper IUD Bleeding**
- Randomized, double blind trial
  - 110 women
  - Enrolled into study if bleeding increased 1 month after IUD placement
- Vitamin B₁, 100 mg daily for 3 months vs. placebo
  - Significant reduction (vs. placebo) seen in:
    - Duration of bleeding
    - Number of sanitary pads
    - Amount of spotting


**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 worldwide¹
- Sold to Sun Pharmaceutical Industries (Mambi, India)
- PK and PD studies completed for US reintroduction²

New Progestin Injection Developments

- Levonorgestrel butanoate
  - 50 mg suppresses ovulation 5-6 months
  - 12.5 mg suppresses another 2-4 months
  - May have fewer progestin-related adverse effects
- Unject self injection system


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 17beta-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 Combined Oral Contraceptives: Extended Cycle Formulations

- Quartette: Increasing estrogen doses over time for cycle control with LNG (TEVA)
- YAZ Flex: 20 mcg EE/3 DRSP (Bayer)
  - Withdrawal bleed Q25-120 days determined by unscheduled bleeding pattern

Flexible Extended Regimen

- 20 mcg EE/3 DRSP: 3 regimens tested
  - Cyclic 24/4
  - Flexible (1): if 3 days bleeding/spotting days 25-120, stop for 4 days
  - Flexible (2): stop for 4 days anytime days 25-120
  - All women required to stop for 4 days at day 120

Flexible Extended Regimen Bleeding Patterns

- 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)
- 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


Low-Doses Contraceptive Patch Compared to Ortho Evra


Low-Does Contraceptive Patch

- EE/Gestodene “FC low” patch
  - 21/7 pattern of use
  - 1 patch per week X 3 weeks, 1 week off
- Transparent, smaller size
- 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
- Potential for women with contraindication to estrogen


Potential Transdermal Contraceptives

- Matrix type patch EE + MPA
  - Hormones released rapidly into skin
  - Skin acts as reservoir for slow systemic absorption
  - Tested in rats postcoitally
  - 100% anti implantation activity
  - ? Interceptive
- Other hormone candidate
  - Trimegestone – very potent
  - Ovulation suppression, strong endometrial activity

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 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 E2?


Progestin-Only Vaginal Ring

- Progering® for breastfeeding women
  - Ring 58 mm diameter with cross-section 8.4mm
  - Release progestin over 3 months (? 4 months)
  - Initial 33.7 nmol/L → 10 nmol/L
  - Available in Chile, Peru, Bolivia, Dominican Republic, Ecuador, Guatemala, Panama
  - Unlikely to affect infant when in breast milk
  - Prolongs lactational amenorrhea
  - Pregnancy rate 1.5/100 women years
  - Vaginal problems 25.8%
  - Under study in India


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


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


Other Delivery Systems for Nesterone

- Metered dose transdermal system
  - Nesterone + estrogen
  - Fast drying liquid formulation – non-occlusive spray
    - Serum levels Nesterone 285-290 pmol/L
    - Blocks ovulation
  - Spray formulation Nesterone + (EE or E2)
    - Currently in initial PK studies

Male Condoms

- New sizes: up to 91 needed
- Waiting for approval by international testing authorities
- ORIGAMI Male Condom™
  - Non-rolled condom — rapid application
  - Link to video demo: http://bcove.me/ivd4s8h9
  - No current development activity

SILCS Diaphragm

- PATH and CONRAD
- Single-use disposable diaphragm
  - Contoured spring and soft pliability
  - No fitting needed
  - May be available over-the-counter
  - Tested in combination with N-9 and Buffer Gel
  - Licensed to Kissel (Frankfurt, Germany)
  - May apply for FDA approval

Anita L. Nelson, MD

Woman's Condom from PATH

- Condom is packed into thin, soft capsule
  - Packaged and placed like a tampon
  - Capsule dissolves – releases condom
  - Foam dots on outer surface of condom adhere to vaginal wall
  - Phase III clinical trials
  - Licensed to Dahua Medical Apparatus Company (Shanghai, China)

Other Female Condoms

- VA w.o.w.® (worn of women)
- 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

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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, disposable bag

More Female Condoms: Cupid FC®

- Natural rubber latex sheath
- Open end attached to octanol frame
- Sponge at leading edge
- Pre-lubricated with silicone
- Scented, natural color and pink
- Available in India and some EU countries


Origami Female Condom

- Telescoping design
- Small silicone cap expands during intercourse
- No current development activity

Spermicides Available Elsewhere

- Benzalkonium chloride (BZK) gel
  - Spermicide as effective as N9 and thickens cervical mucus
- Current products in Canada and some EU countries
  - Suppository 18.9 mg
  - Sponge 60 mg
  - Cream 60 mg
  - “Optimized” BZK gel 18 mL (0.429%)
  - 6 month pregnancy rate 5.11%
Spermicidal Compounds: Early Testing

- HerbOshield™ vaginal gel 100 mg/mL dose
  - Complete sperm immobilization in 20 seconds
- Submicron-particle-size, lipophilic gel-microemulsion
  - In vitro more effective than N-9


On Demand – Occasional Use: Vaginal Gels

- LNG 750 mcg/4mL in Carraguard® 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)


Non-Hormonal Contraceptives: COX-2 Inhibitors

- Meloxicam 30 mg x 5 days in late follicular phase suppresses follicular rupture
  - Meloxicam 15 mg combined with LNG EC increased proportion of cycles with no follicular rupture
  - Meloxicam 30 mg/day given days 5-22 > 20% ovulation
- Rofecoxib 25 mg given when dominant follicle reached 14-16 mm
  - Delayed follicular rupture > 48 hours after LH peak in 4 of 8 women


Novel Nonhormonal Approaches

- Oocyte maturation studies
  - Phosphodiesterase-3 inhibitor ORG 9935
    - Inhibits meiosis
  - Genes involved in meiosis
  - Cumulus expansion inhibition
  - Molecules antagonist to PGE2 receptor
  - Follicle rupture
  - Matrix metalloprotease inhibitors
  - Maintained luteinized follicle unruptured with progesterone production


Novel Nonhormonal Contraceptives: Blocking Oocyte Maturation

- Reinitiation of oocyte meiotic maturation
  - Provides and oocyte in metaphase II available for ovulation
  - Triggered by decrease in intracellular cAMP
  - Triggered by pre-ovulatory gonadotropin surge
  - Phosphodiesterase (PDE) causes decline in cAMP
  - What if we could block PDE????


Physiology of Dominant Follicle

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
Phosphodiesterase (PDE) Inhibitors

- Treatment with PDE3 inhibitors causes ovulation of non-fertilizable immature oocyte
- No adverse impact on CLC or menses
- Tested in macaques
  - Only worked when levels > 300 nmol/L
  - Side effects potentially serious


Non Hormonal Agents Block Embryo Implantation

- Proprotein convertase 5/6 (PC6) critical for endometrial epithelial receptivity and stromal cell decidualization
- C1239-PEG-Poly R: potent PC6 inhibitor
  - Administered vaginally daily x 3 days
  - Starting 6 days after mating
  - Dose-dependent response
  - 60% reduction in pregnancy


Non Hormonal Agents to Block Rat Embryo Implantation

- Serine protease inhibitor:
  - 4-(2-aminoethyl) benzenesulfonyl fluoride hydrochloride (AEBSF)
- Day 3 administered in endometrial cavity or in tail vein
  - Intrauterine dose response 42% reduction in implantation at 5 mg and 90% at 10 mg
  - Tail vein injection 41% reduction in implantation


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


Zona Pellucida-Based Contraceptive Vaccines

- Considerable cross reactivity across species
- Current versions result (in pig, mouse, rabbit) in oocyte destruction and severe depletion of resting follicles
- Monkey trials- females ovulated but no pregnancies when titers high
  - No oocyte destruction
- Human: recombinant zona protein-based vaccine. Worked in Indian street dogs, Australian marsupials


"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.

US Report Card

- 49% unintended pregnancy rate constant for a decade
  - Since before IUDs, implants were introduced
- Maternal mortality highest in 20 years
  - More high risk women conceiving
- Additional 34,000 near misses occur each year
- No statistics on planned and prepared pregnancies
- No coverage for preconceptional care
- No coverage for contraception at delivery except South Carolina, Colorado, New York...

US Challenges

- Appalling mistruths in letters to editors go unanswered
- Sex education stripped from the curriculum or gutted of any scientific accuracy
  - Don’t need to teach contraception to teach reproduction facts
- Women are given FDA, lawyer-written lists of risks of contraception. Nowhere are women told of risks of pregnancy
- Pregnancy is a medical condition – not a magical experience where the laws of health are suspended

Reality Check 2014: How Many of You Know

- Hospitals where women cannot get tubal sterilization?
- Pharmacies that will not dispense EC?
- Pharmacies that lock up male condoms?
- Pharmacies that refuse to carry any contraception?
- Providers who will not prescribe IUDs because they are abortifacients?
- Legislators eager to defund contraception and even outlaw it?

Why Do These Problems Persist?

- No concept that pregnancy is something a woman should prepare for
- High rates of ambivalence
- Under-appreciation of the health risks of pregnancy
- Over-estimation of risks of contraception


Women With Unintended Pregnancy: Reasons for Unprotected Intercourse

- 33% thought they could not get pregnant at that time
- 10% thought they or partner were sterile
- 30% ambivalent
- 22% partner did not want to use contraceptives
- 16% side effects
- 10% access problems
- 18% other

Reasons for Unprotected Intercourse

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- 30% ambivalent
- 22% partner did not want to use contraceptives
- 16% side effects
- 10% access problems
- 18% other

Women’s Knowledge of Pregnancy Risks

- Survey of 248 English speaking women
  - 13.7% correctly identified all the listed health risks of pregnancy
  - 30% did not know VTE risk rise in pregnancy
  - 49% know risks of VTE, DM and HTN rise in pregnancy
  - 76% rated pill more hazardous than pregnancy

Reproductive Life Plans

- 250 English speaking women asked about their pregnancy plans
  - Virtually the only women who answered rapidly were seeking pregnancy or had completed family
  - All other women – slow, hesitant, vague answers
  - When asked if women should plan for pregnancy, virtually all said “yes”
  - Only 22% mentioned anything about health or medical preparation for pregnancy.

Fundamental Issues

- Contraception given to healthy women to prevent potentially life-threatening problems
  - Analogous to hypertension treatment
  - Technically pregnancy is not a disease
    - But it is still a health risk
      - Almost 50% of pregnancies ≥ 1 morbidity
      - Most severe complications at delivery and postpartum increased in last 10 years
  - Could we dare to consider unwanted pregnancy to be a disease?
  - Risks of contraception never measured against risks of pregnancy

Redefining the Issue

Let’s Admit That

- Unwanted pregnancy is a disease that
  - Kills women
  - Orphans children
  - Causes maternal diabetes, hypertension, stroke, heart attack, renal failure, paralysis, gallbladder disease, liver disease, cancer, incontinence, weight gain, permanent skin discoloration, tooth loss, bone loss, hemorrhoids, and stretches your-you-know-what
  - Causes sickly babies

“The mind-set that invites a couple to use contraception is an anti-child mind-set. So when a baby is conceived accidentally, the couple already have this negative attitude toward the child. Therefore, seeking an abortion is a natural outcome. We oppose all forms of contraception.”

Judie Brown
President, American Life League

What Happened?
We Used to be the Good Guys

- Women today do not have personal experience with maternal mortality and uncontrolled fertility as they did in the 1950s
- New methods introduced, used and attacked as soon as become popular and profitable
- Media frenzy over any bad news about contraception
- Lawsuits keep old issues in news for years
- Politicalization of family planning

Consequences
- Risks of contraception are never measured against the risks of pregnancy
  - Women can not possibly make informed decisions
  - Women are overly concerned about risks of contraception

Don’t Underestimate
The Power of Images
- Often we analytical types believe that the facts (should) speak for themselves
  - We spend our time gathering those facts
  - We feel guilty (dirty) trying to manipulate or influence people using commercial approaches
  - We counsel; we educate
- But are we effective? Are our customers really rational? Are we creating a vacuum?
What Does He Feel When He Drives It Off the Lot?
- Powerful:
  - The extra noise the engine makes draws attention to him
  - The outrageous price and the atrocious gas mileage demonstrate that he can afford it
- In control
  - An enormous engine throbs beneath him awaiting his commands
- Happy and fulfilled as a man:
  - He is alone in the sleek car - there is no extra space

What Would He Feel if Family Planners Had Named It?
- Being rational, factual folks, we would never have named that vehicle a sports car
  - He obviously is not an athlete
  - We would name it for what it really is a
    - Rapidly Accelerating Loud Car
- And we would refer to it economically by its abbreviation
  - RALC
- Maybe we would be surprised it did not sell

LARC
- What does that mean to a woman who does not have a decoder ring?
- Nothing at all -- with that spelling
- What about LARK?
  - Now that’s a sweet song bird

How Do We Want A Woman to Feel When She Uses Using a Top Tier Method?
- Confident
  - She has chosen a top-tier method
- In control
  - She can decide when to time her pregnancy
- Proud
  - She made an excellent, modern choice
- Happy
  - Her method is most convenient
- Relieved
Where Do We Start?

- Let’s put FAMILY back into Family Planning
  - We are the good guys helping women prepare for pregnancy to get healthy babies
  - We are the good guys helping women and their partners avoid pregnancy until they are ready to be a family
  - We are the good guys helping families stay okay by letting parents effectively choose how many children they want

What Do We Want to Say?

- Let’s shift from “natural” to “healthy”
  - Just because something is natural does not mean it is good for you
- Uncontrolled fertility is a health problem
- Unite all fertility disorders under one roof
  - Infertility for those desiring pregnancy but unable to achieve it spontaneously
  - Undesired fertility for those able to conceive but not desiring pregnancy now

Make the Most of Every Opportunity

- Provide contraceptive counselling when prescribing teratogenic drug
- 26% of women surveyed had been prescribed potential teratogenic
  - 40% of them did not receive any counselling about medication–induced birth defects or their need to contracept

New Terminology for Research Pregnancy Classification

- Eliminate old terms:
  - Intended pregnancy
  - Unintended pregnancy
- Use 3 terms to classify pregnancies:
  - Prepared for pregnancies
  - Accepted pregnancies
  - Unwanted pregnancies

What Else Can We Do?

- Use words we know
  - “Top tier contraception”
  - “Unwanted pregnancy”
  - “Healthy”
- Invent new terms
  - Not4Upreg
  - Pre-parent
  - Sex-up
- Harness the power of social marketing
  - Let people have fun with contraception
  - Gates Foundation Grand Challenge

References: