



COLUMBIA UNIVERSITY
MEDICAL CENTER

New Frontiers in Contraceptive Discovery

Carolyn L. Westhoff, MD, MSc

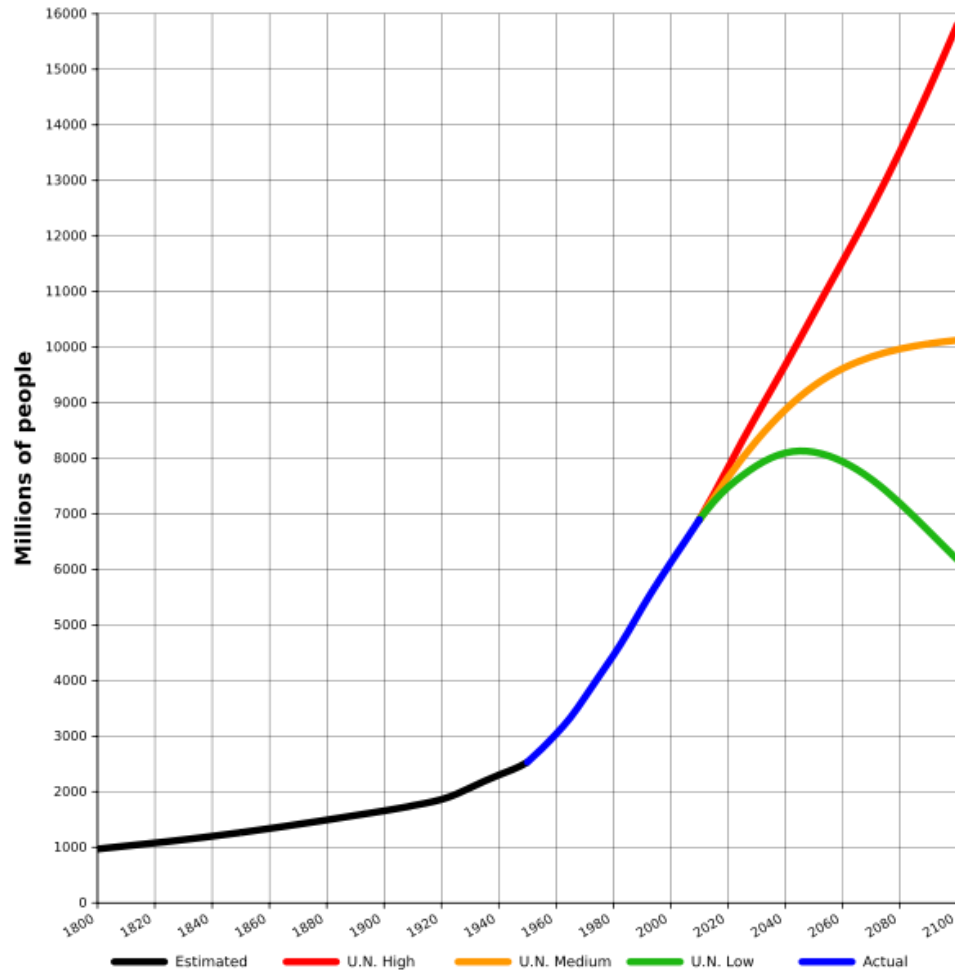
Research for a Lifetime: A Scientific Colloquium to
Commemorate the NICHD's 50th Anniversary

December 5, 2012



Discover. Educate. Care. Lead.

World Population Growth



Cairo, 1994 ICPD

International Conference on Population and Development



WE BELIEVE
THAT REPRODUCTIVE HEALTH
SHOULD BE A WOMAN'S RIGHT,
AND THAT MOTHERHOOD
SHOULD BE A WOMAN'S CHOICE.



Unintended Pregnancies (US, 2006)

~50% of US pregnancies are unintended (> 3 million per year)

- **52/1,000 women 15-44 yrs**
 - 80/1,000 women < HS education
 - 78/1,000 Hispanic women
 - 91/1,000 Black women
 - 132/1,000 women < 100% FPL
 - 17/1,000 higher income white women

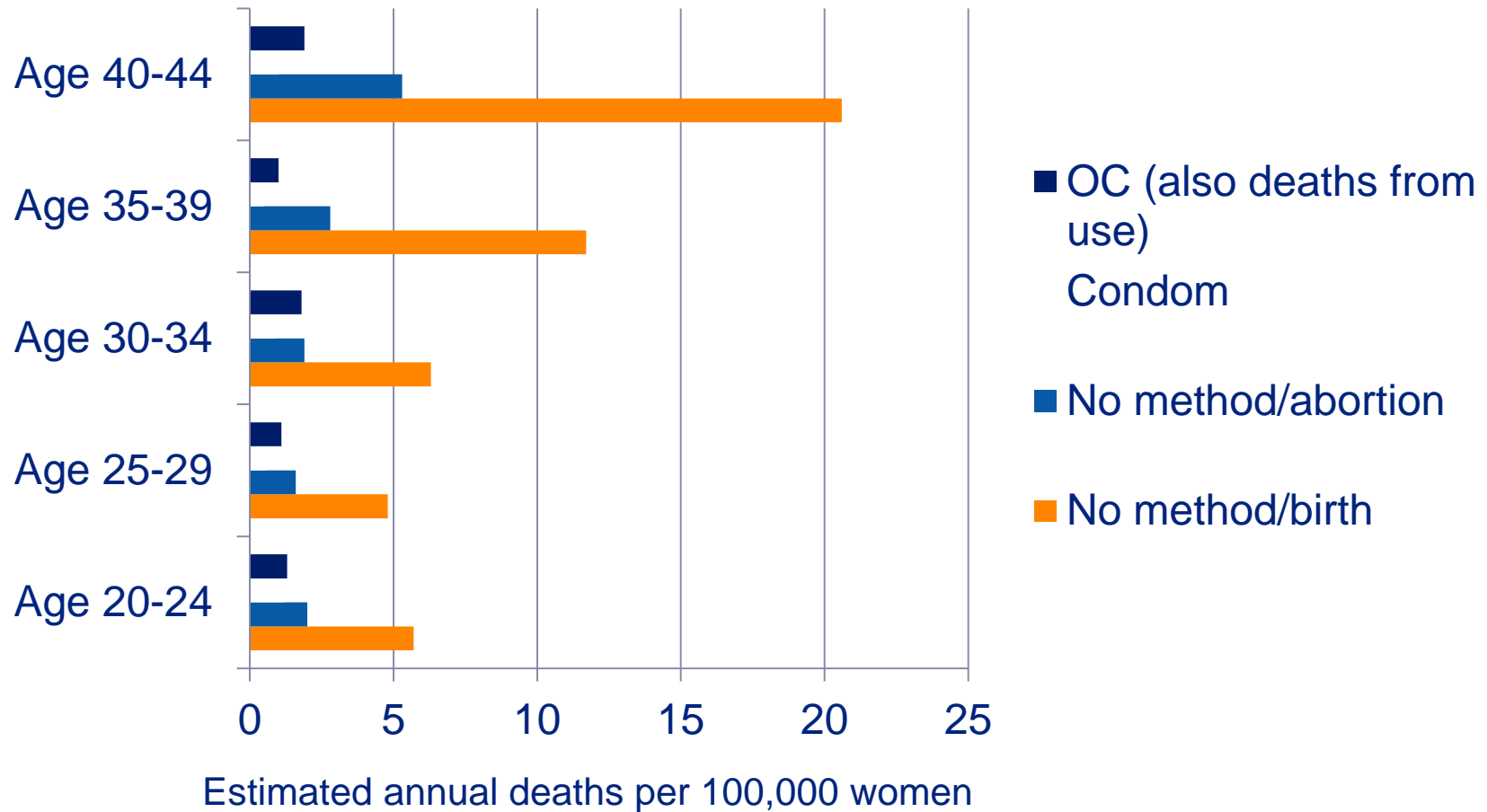


Maternal Mortality and Morbidity (US, 2007)

- 4.2 million births
- 600 maternal deaths
- 34,000 near misses
- >1,000,000 hospitalizations for complications
- Maternal deaths worldwide ~360,000 annually



Preventing Pregnancy=Preventing Death



Contraceptive Methods by effectiveness (WHO)

Most Effective
Sterilization
IUDs
Implants
Effective
Pill
Patch/Ring
Injection
Less Effective
Diaphragms, Caps Spermicides
Condoms Withdrawal



Contraception Methods

Method	1962
Most Effective	
Sterilization	Laparotomy
IUDs	Inert
Implants	∅
Effective	
Pill	2 pills
Patch/Ring	∅
Injection	∅
Less Effective	
Female Barriers Spermicides	Diaphragm
Male Barriers Withdrawal	Condoms



Contraceptive Methods

Method	1962	2012
Most Effective		
Sterilization	Laparotomy	Laparoscopic Hysteroscopic Vasectomy
IUDs	Inert	Copper Hormonal
Implants	∅	Capsules Rods
Effective		
Pill	2 pills	~40 pills
Patch/Ring	∅	Patch Ring
Injection	∅	DMPA Net-En Cyclofem
Less Effective		
Female Barriers Spermicides	Diaphragm	Condoms Diaphragm Sponge
Male Barriers Withdrawal	Condoms	Condoms

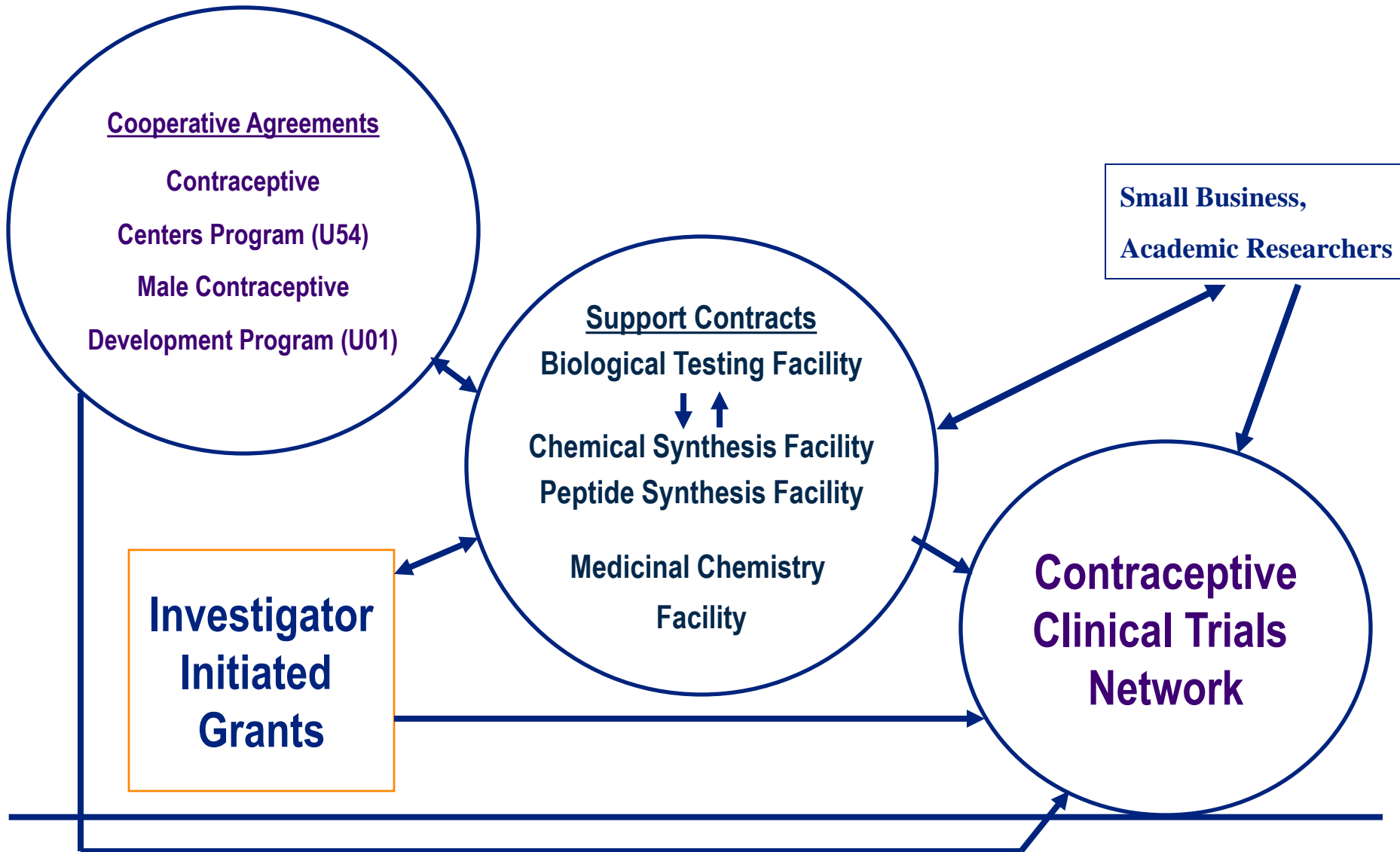


Contraceptive Methods

Method	1962	2012	Pipeline
Most Effective			
Sterilization	Laparotomy	Laparoscopic Hysteroscopic Vasectomy	Transvaginal
IUDs	Inert	Copper Hormonal	Phase 2, 3
Implants	∅	Capsules Rods	Phase 1, 2
Effective			
Pill	2 pills	~40 pills "EC"	Many
Patch/Ring	∅	Patch Ring	Phase 1, 2, 3
Injection	∅	DMPA Net-En Cyclofem	Phase 2
Less Effective			
Female Barriers Spermicides	Diaphragm	Condoms Diaphragm Sponge	PATH Condom Microbicides
Male Barriers Withdrawal	Condoms	Condoms	Hormonal Contraceptives Novel targets



Contraceptive Research and Development



New Products for Women

New Hormonal Products:

- **Ella (emergency contraception) - approved by FDA in 2010**
- **Esmya (fibroid treatment) – approved in Europe, NDA application pending in USA**
- **Nestorone EE vaginal ring - one ring for 1 year (13 cycles) - NDA application preparation**
- **Levonorgestrel Patch** - weekly patch - safe for obese women
- **Levonorgestrel butanoate** - long acting injectable (4+ months) – long-acting & safe for obese women
- **Nestorone Estradiol vaginal ring** - continuous use for 3 months – long-acting & safe for obese women
- **Low dose ulipristal acetate** - estrogen independent contraception - safe for obese women & may have breast-protective properties.

Non-hormonal products (dual protection):

- **Path Woman's Condom - Phase III trial completed – Preparing Clinical Study Report for FDA review**
- C31G spermicidal gel - Phase III trial – completed – pending commercial partner development
- Buffer Gel – Phase III trial – completed - pending commercial partner development
- Silcs diaphragm with antimicrobial gel – Phase I trial

– New initiative to identify targets for non-hormonal products for women:

- Follicular development - potential preservation of fertility
- Oocyte maturation -WEE2, WEE1B, INSL3, LGR8, NALP
- Follicular rupture - Prostaglandin E2 Synthesis/Signaling Inhibitors, TRP1 Protease, Metalloproteinase, ADAMS, Endothelin



Ella® - Emergency Contraception



CDP – 3940



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PATH - Female Condom



Agile Contraceptive Patch



AG 200-15 EE2 + LNG

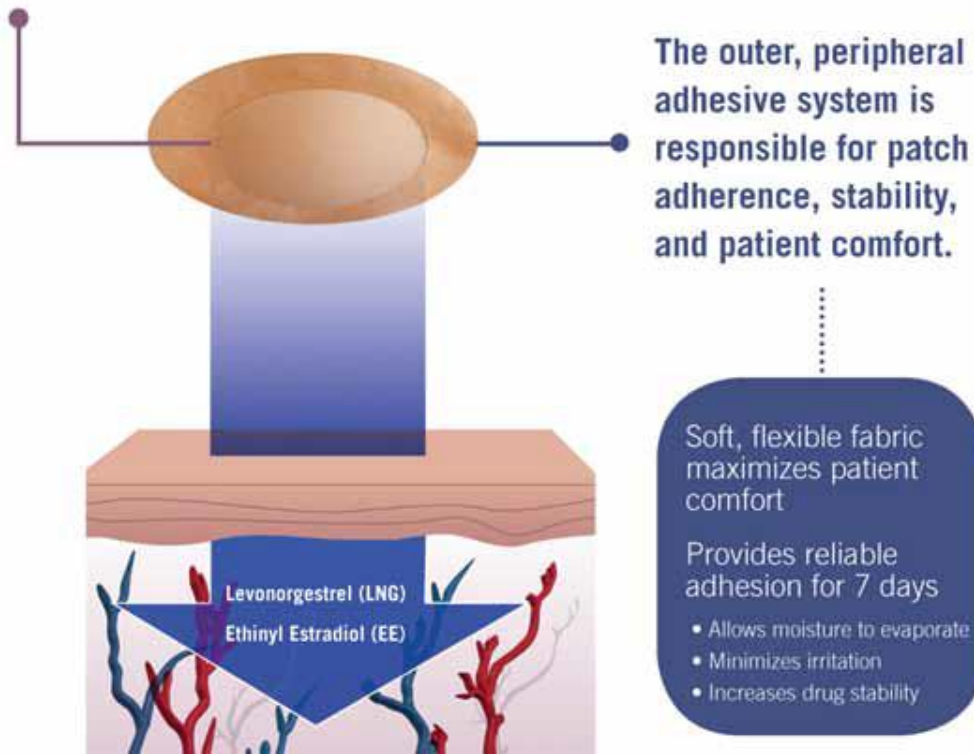
AG 890 LNG only



Agile Combination Patch

Technology

The TCDS technology is composed of an inner, active matrix adhesive system that delivers both EE and LNG at unique, targeted levels through the skin.



New Ring

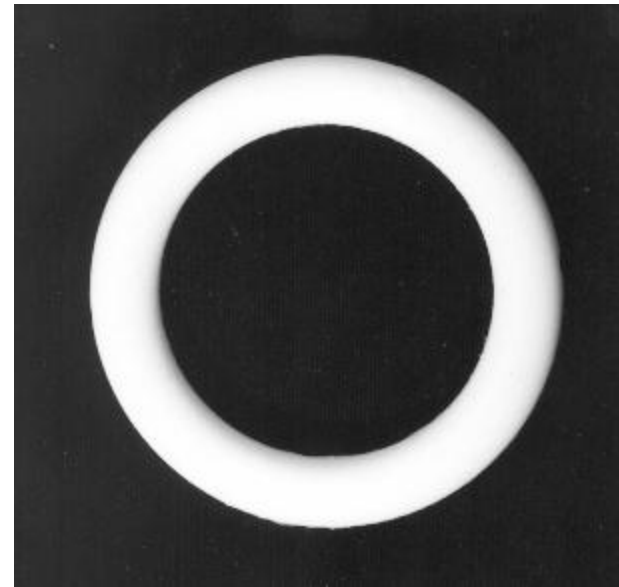
Population Council

EE2/Nesterone for 12 months – 3 weeks in/ 1 week out.

- 2,277 women, highly effective
- Europe, Australia, Latin America, and the United States
- 56 mm diameter
- 8.4 mm cross-section

FDA review in progress.

Phase 2 – three month ring w E2
and NES



The Road to a Male Contraceptive Product

Start



Finish



Basic research – supported by grants, contracts, Pharma

- Identify and validate target
- Identify drug(s)
- Demonstrate efficacy in several species (reversible and safe)



Translational research – very difficult for academic investigators

- Synthesis – GMP for clinical trials
- Formulation and delivery
- Toxicology – very high bar of safety for long-term use in healthy subjects

Clinical research

- Investigational New Drug Application
- Clinical trials in normal volunteers...
 - How many subjects? How long?



Hormonal Approach to Male Contraception

2-Step Process - Searching for the Best Regimen

Step 1 - Suppress gonadotropins using:

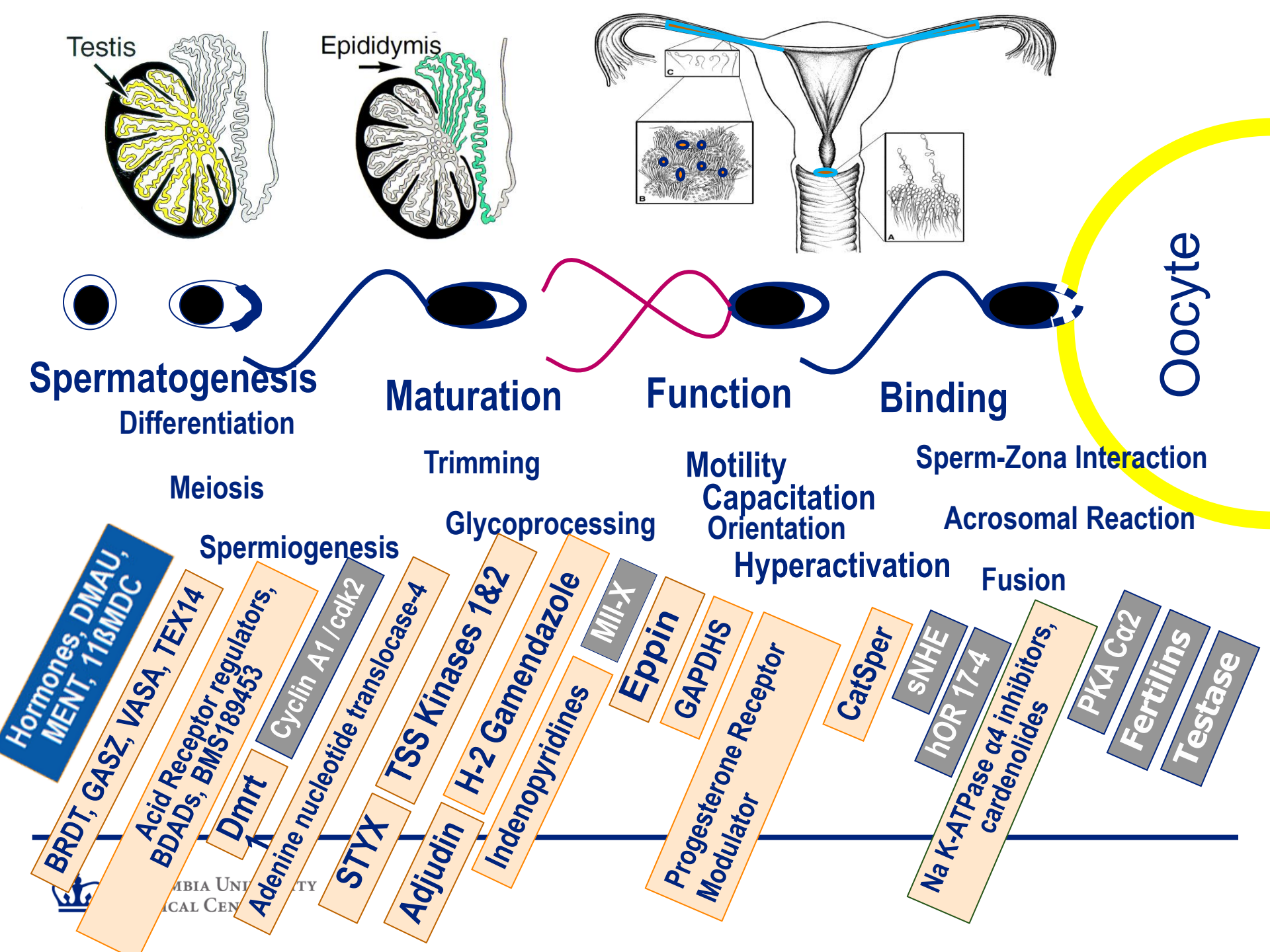
Progestins – commercially available as oral, injection, implant
» --- but NOT labeled for use in men - not likely to be

New progestins:

- Levonorgestrel butanoate – long-acting injection (~ 3-4 months)
- Nestorone Gel - (daily) – Phase 1 trials in men are ongoing

Step 2 – Replace androgen to restore serum levels

- ❖ No oral **Testosterone** formulation yet
- ❖ **Testosterone** gel is commercially available
 - Combine with **Nestorone** Gel for effective contraceptive method
- Phase 2 trials in men are ongoing
- *Dual progestin and androgen activity (in animal models)*
 - ❖ **DMAU** - oral (daily) – Phase 1 trials in men are ongoing
 - long acting injectable also possible



A Few Promising Leads for Men

Adjudin [Adherens Junction Disruption] (*Cheng*)

CatSper: Cation channel Sperm (*Clapham*)

Epididymal Protease Inhibitor (EPPIN) (*O'Rand*)

Glyceralaldehyde 3-phosphate dehydrogenase-S (GAPDHS) (*O'Brien*)

Retinoic Acid Receptor Antagonists (*Wolgemuth*)

Antagonists to prevent sperm maturation, activation, motility.



The Future of Contraceptive Development

Expand current program to emphasize development of non-hormonal male and female contraception.

Take advantage of advances in areas such as genomics, proteomics and bioinformatics.

- Target identification
- Target characterization (structural analysis of binding sites)
- Target validation (? blocking = contraception)
- Target specificity (w/ sensitive expression assays)
- Lead identification (High Throughput Screening)
- Lead optimization (molecular modeling)

The Dream Pipeline

Effective and acceptable MALE contraceptives

Combination pills/patch/rings with NO VTE

Universal coverage for all contraceptives

OTC status for Pills

Unlimited refills

Self-administered DMPA injections

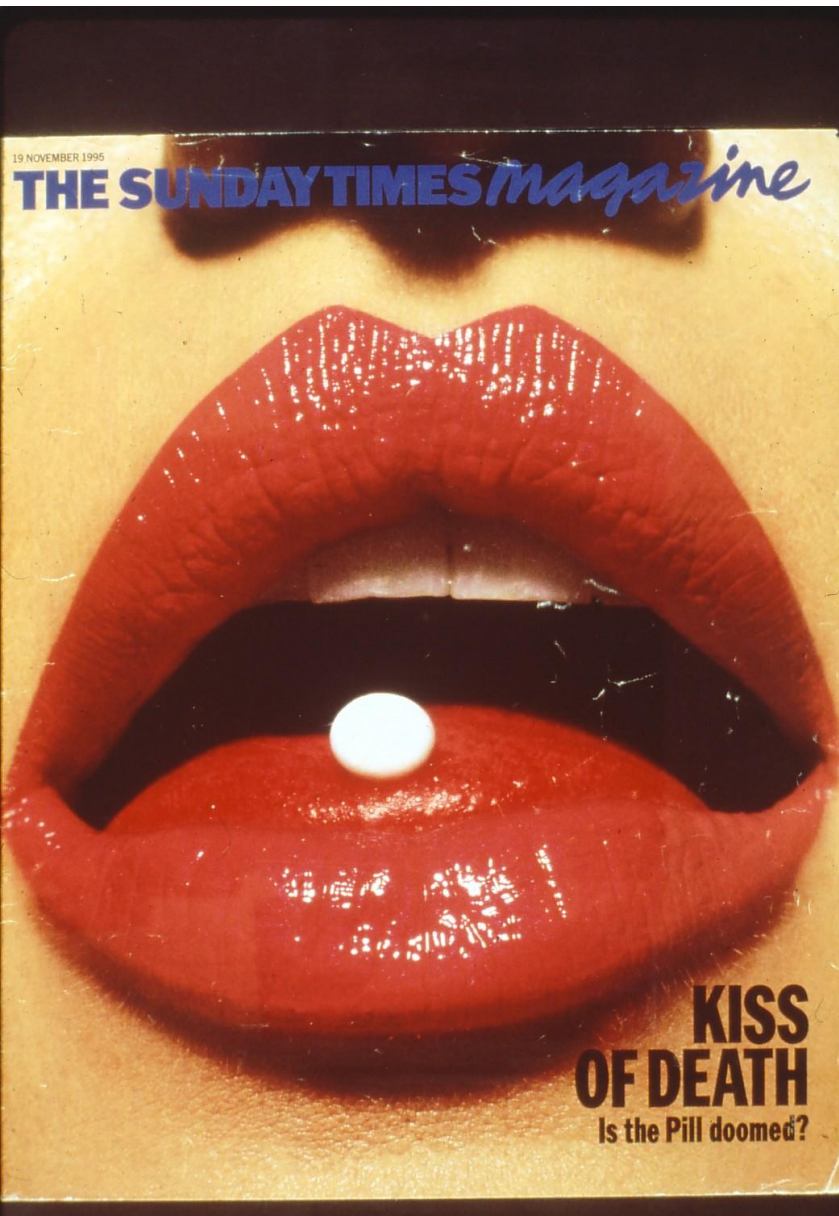
No more side effect mythology

Additional non-contraceptive benefits





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