”Natural Methods”
..and male contraception

Kristina Gemzell Danielsson, MD, PhD

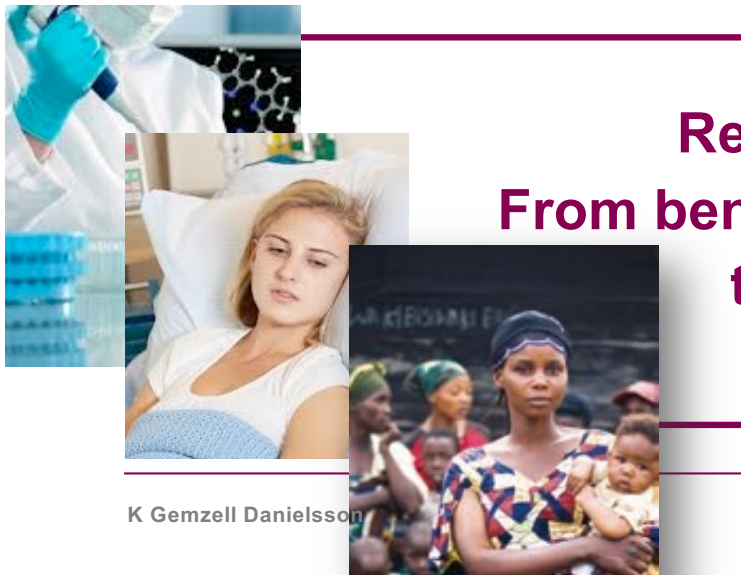
WHO Collaborating Centre for Research in Human Reproduction

Karolinska Universitetssjukhuset / Karolinska Institutet

UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, WHO,Geneva

Disclosures;

Gemzell-Danielsson has been ad hoc advisory board member or invited to give presentations for Merck (MSD), Bayer, Exelgyn, Actavis, Gedeon Richter, Mithra, Exeltis, Ferring, Natural Cycles, Gynuity, and HRA-Pharma



Reproductive Health Research
From bench - to bed - to the hands of women
to improve women's health

Overview of the presentation

Why is this important?

What do women want?

How do we address this?

Who are the users?

Effective contraceptive methods are prerequisite for Reproductive Health

”Sexual and reproductive health and rights
constitute fundamental human rights,
form a vital aspect of the women´s empowerment and
are a key to the achievment of gender equality”

Is there a need for new contraceptive methods?

Globally 270 mill women lack access to effective and acceptable contraception

>40%

Of all pregnancies are unplanned

50%

Results in aninduced abortion

Sedgh et al New York: Guttmacher Institute World Population Dashboard [Internet]. https://www.unfpa.org/data/world-population-dashboard (accessed August 20 2024).

Unmet need in contraception

- Improved (safe and “green”) methods with added health benefits
- “On demand” methods
- Methods for dual protection
- Long-acting, (non-hormonal) methods
- “Contragestion”
- Improved access/use of existing methods incl post abortion and post partum, removing barriers
- Reversible methods for men

Unmet Need
Contraceptive Preferences

- Fear of side effects, 2/3 discontinuing use due to health concerns [9,10].
- Infrequent or no sex is a common reason for not using contraception cited by 41% of unmarried and 24% of married women.

➔ 38% of US women say that whether a method of contraception is natural or does not contain hormones is important or very important to them[1]

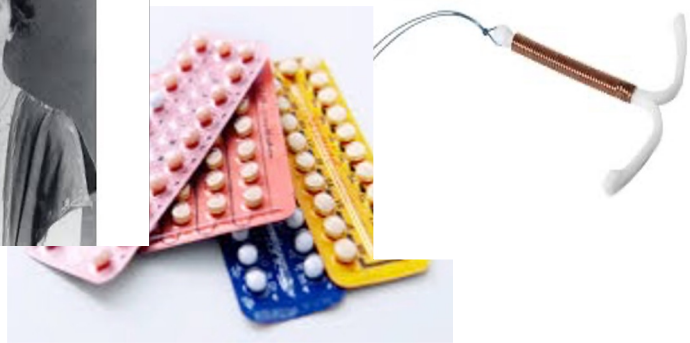
➔ For those not currently using contraception, the most common reason stated was that they don't want to take hormones (43%)

➔ 16.5M US women dont want to get pregnant but are doing nothing to prevent it

(Science and Society Picture Library)

3 A condom made of caecal membrane and silk, shown in its case (1880–1910).

Marie Stopes opened the UK's first family planning clinic in London 1921



Guttmacher contraceptive use report 2018, Bettizzi S, Mannava P, Nagai M, Sobel HL. Reasons for discontinuation of contraception among women with a current unintended pregnancy in 36 low and middle-income countries. *Contraception* 2020; **101**(1): 26-33.

Contraception: State of the Art

Table 1 Percentage of women experiencing an unintended pregnancy during the first year of typical use and the first year of perfect use of contraception and the percentage continuing use at the end of the first year. United States.

	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at One Year[3]
Method	**Typical Use[1]**	**Perfect Use[2]**	
No method[4]	85	85	
Spermicides[5]	21	16	42
Female condom[6]	21	5	41
Withdrawal	20	4	46
Diaphragm[7]	17	16	57
Sponge	17	12	36
Parous Women	27	20	
Nulliparous Women	14	9	
Fertility awareness-based methods[8]	15		47
Ovulation method[8]	23	3	
TwoDay method[8]	14	4	
Standard Days method[8]	12	5	
Natural Cycles[8]	8	1	
Symptothermal method[8]	2	0.4	
Male condom[6]	13	2	43
Combined and progestin-only pills	7	0.3	67
Evra patch	7	0.3	67
NuvaRing	7	0.3	67
Depo-Provera	4	0.2	56
Intrauterine contraceptives[9]			
ParaGard (copper T)	0.8	0.6	78
Mirena (52 mg LNG)	0.7	0.5	80
Skyla (13.5 mg LNG)	0.4	0.3	
Kyleena (19.5 mg LNG)	0.2	0.2	
Liletta (52 mg LNG)	0.1	0.1	
Nexplanon	0.1	0.1	89
Tubal occlusion	0.5	0.5	100

More options are needed for women seeking non-hormonal and self-controlled contraception

Methods to predict ovulation

NEXT cycle:

Menstrual Data /

Cycle length

calculate days ”safe periods”

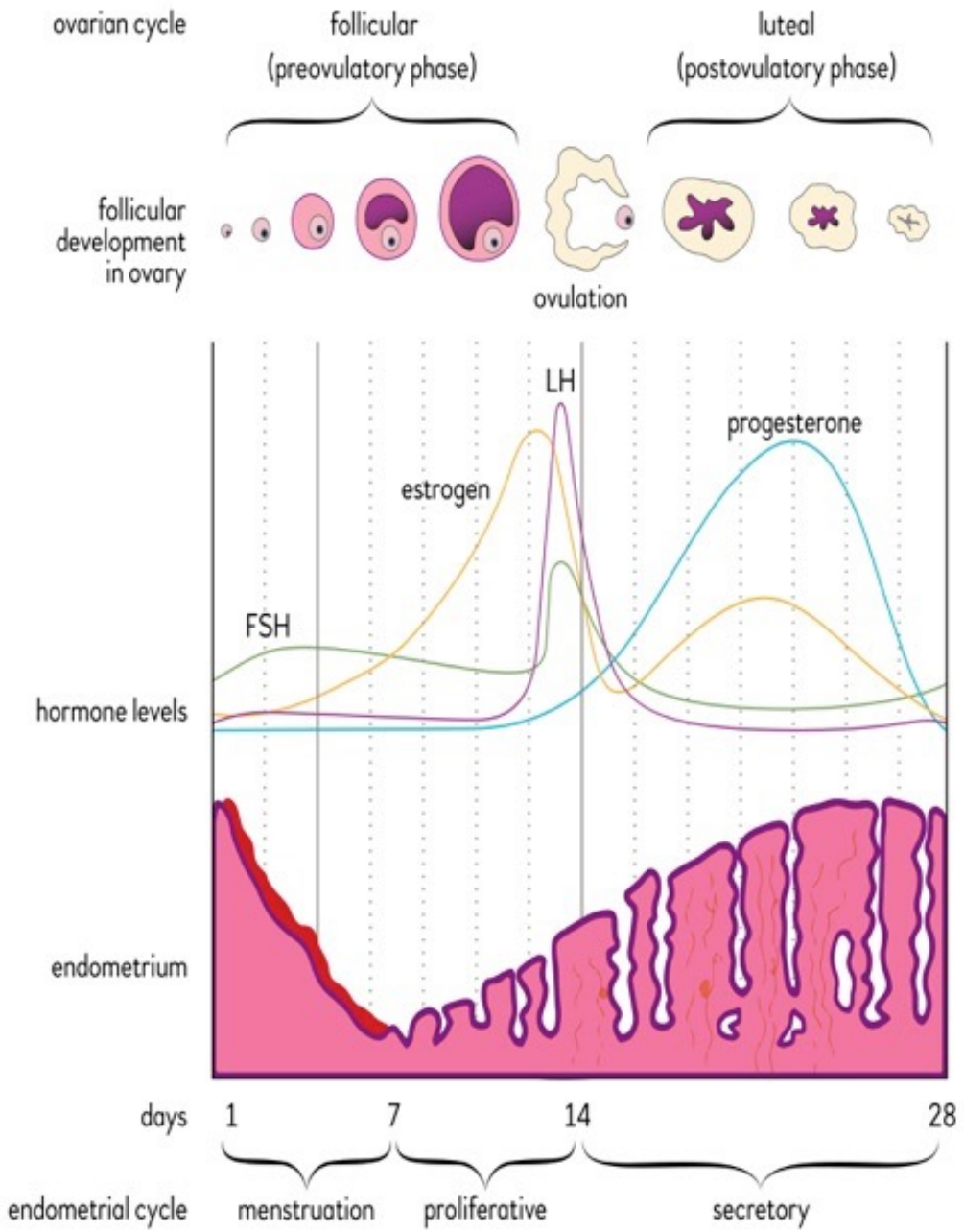
Rise in temperature - shows that ovulation has taken place

0,1-0,2 degrees C (induced by P4)

THIS cycle:

LH measure - shows when ovulation is expected (in this cycle)

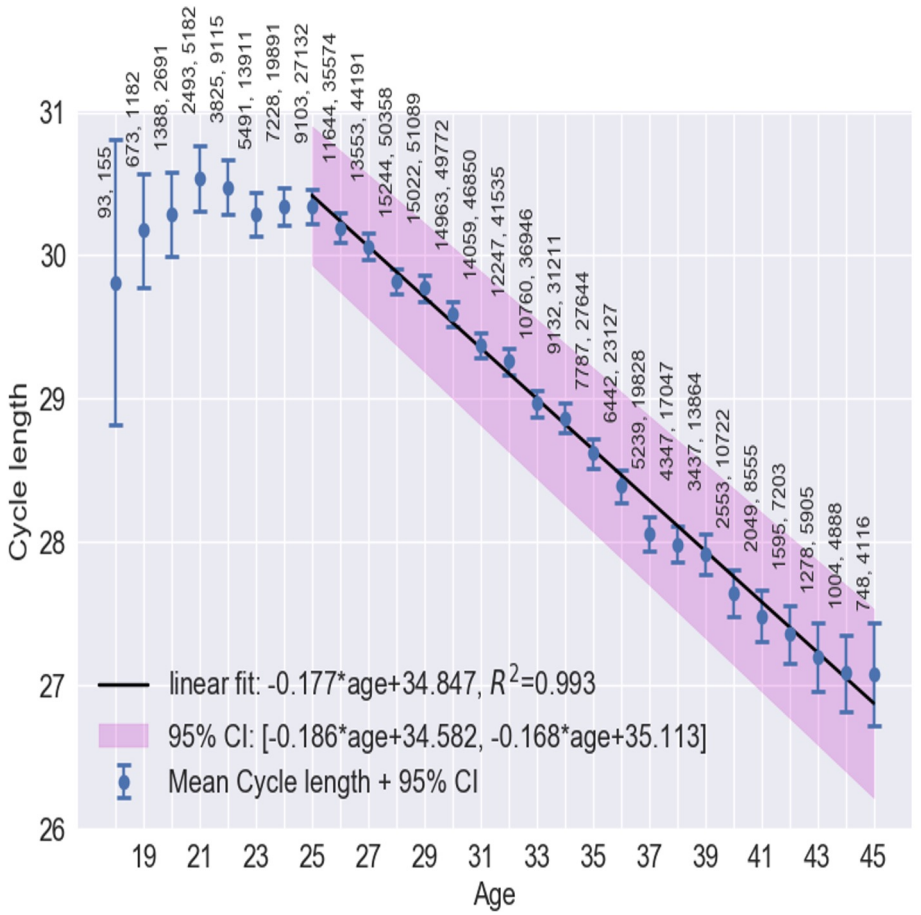
Plasma levels mirrored by Urine levels



The menstrual cycle. Modified from Wikimedia Commons and Encyclopedia Britannica 2008.

Menstrual cycle length and ovulation day vary

- Analysis of 1.5 million cycles, recorded by 183,445 users
- Cycle lengths varied between 15 and 50 days, with the average being 29.3
- Age is negatively correlated with cycle length (slope = -0.177, 95% CI: -0.168 to -0.186, R2 = 0.993)
- BMI was not correlated to differences in cycle length



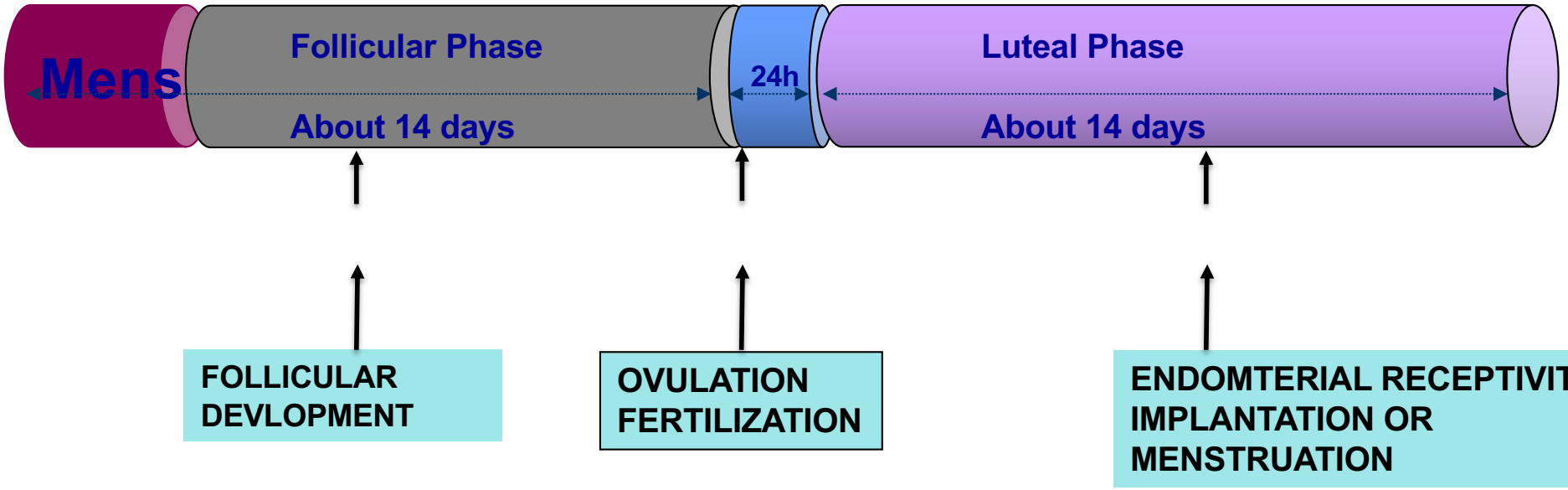
Age versus mean cycle length (95% CI). Linear regressions are fitted in the age range 25 - 45 with 95% CI shaded in pink. Points are labelled with the number of users followed by the number of cycles.

The knowledge about fertility

From prediction of ovulation to prediction of the fertile window

Probability of pregnancy increases until a maximum (30%) LH+0

Sharp decline immediately post ovulation, to 0% for any act of intercourse



The calendar or rhythm method

- In the 1920s and 30s, Hermann Knaus and Kyusaku Ogino independently described that the time between ovulation and the next menstruation to approx 14 days
- This allowed the development of a mathematical formula to determine the fertile window, known as the calendar or rhythm method
- Before the fertile window can be calculated and consequently use of this method for contraception, at least 6 cycles have to be recorded.
- To determine the first and last fertile day, subtract 18 days from her shortest cycle length and 11 days from her longest cycle length, respectively
- Pregnancy probabilities with typical-use of this traditional method have been estimated at 15 - 18.5% ,

  WHO reports numbers as high as 25%

The Standard Days Method (SDM)

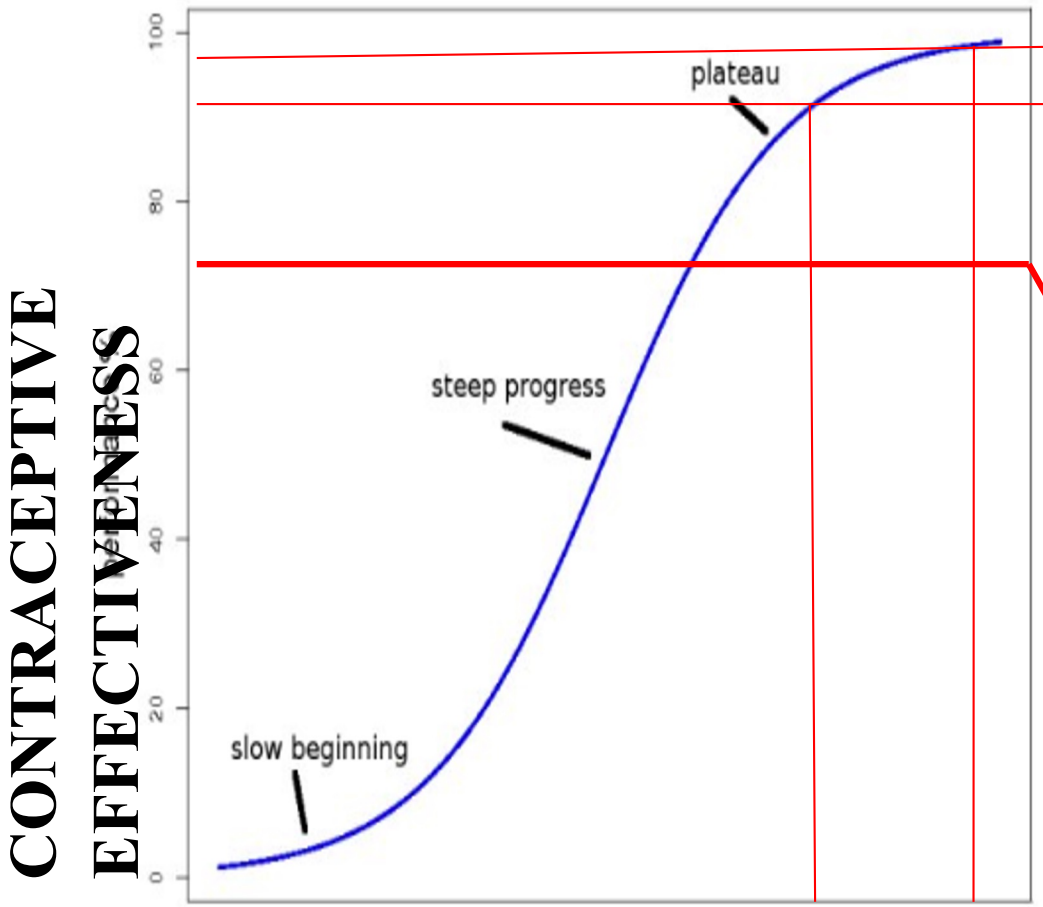
- Developed by the Georgetown University based on a dataset of over 7500 menstrual cycles gathered by the WHO
- Considered a modern method of contraception (in contrast to the calendar rhythm method)
- Requires typical cycle lengths within the range of 26-32 days.
- The fertile window is set to cycle day 9 to 18.
- To avoid a pregnancy, abstain from intercourse or use barrier methods for contraception during these 12 days
- Contraceptive effectiveness determined as
  4.75% with perfect-use, defined as abstinence during the fertile days, and 11.96% with typical-use

Can we improve effectiveness?

- Shift from ovulation to detection of the “fertile window”
- Use of technical support?
  - Tracking of menstrual periods
  - Algorithms
  - What should be included ?

- Will more data improve effectiveness? Or adversely affect compliance?
- Can improved compliance balance input of less information?

How much do we need to add?
The Effectiveness / Learning Curve



Multiple tests/ hormones/ symptoms

- Intelligent algorithms
- BBT

NATURAL CONTRACEPTION

Increase in cost, decrease in patient compliance

FDA Cleared software application for contraception

Mechanism of Action

Natural Cycles Detects Ovulation Based on User Data

Data input by the user

- Daily temperature readings
- Monthly menstruation data
- LH/ovulation tests*
- Collected/input individual cycle data

Includes
- Previous use of hormonal contraception
- Recent pregnancy
- Cycle length/frequency
- Last menstruation date

In-app calculations

- Recent temperature vs luteal phase temperature
- Luteal vs follicular phase temperature
- Current stage of cycle
- Time point when ovulation usually occurs
- LH level*
- Recent use of hormonal contraception

The Natural Cycles app computes uncertainties around these parameters to accurately detect ovulation

Assessment: has ovulation occurred?

Yes/No

*Optional
LH, luteinising hormone

Fertile (Red) and Non-Fertile (Green) Days

The Natural Cycles algorithm determines fertility status on a specific day

Green day = Not fertile

Red day = At risk

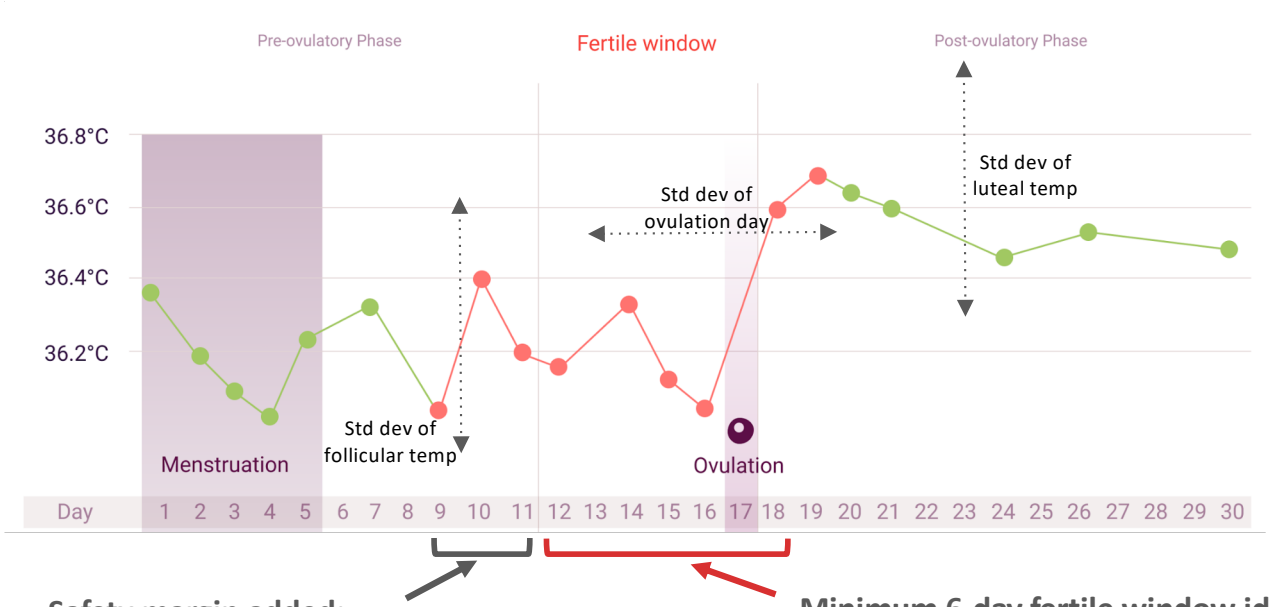
In order to prevent conception, women must abstain or use protection (e.g. condoms)

Mechanism of Action

How Natural Cycles Maps out the Fertile Window

The algorithm predicts ovulation using weighted averages of previous ovulation days

As more of an individual's cycles are known, the SD becomes smaller, leading to fewer days indicated as 'fertile days'



Safety margin added:

- Allows for uncertainty in ovulation day prediction (based on individual's variance)

Minimum 6-day fertile window identified:

- 5 days pre-ovulation (sperm survival)
- 1 day post ovulation (viability of ovum)

- Green = non-fertile days
- Red = fertile days

SD, Std Dev, standard deviation

Natural Cycles Mechanism of Action (internal data on file)

Reasons for switching to a ”Natural Method”

What method of contraception did you use before the Natural Method?	Number of Women*
Pill (oral contraceptive)	46.2%
Injection, Implant, Patch or Ring	7.9%
Hormonal IUD (hormonal coil)	5.4%
Hormonal contraception (All)	**59.5%**
Male condom	17.7%
No sex or Withdrawal method	8.7%
Copper IUD (non-hormonal coil)	4.6%
Nothing	4.5%
Natural Family Planning	2.6%
Female condom or Diaphragm	0.4%
Non hormonal contraception (All)	**38.5%**
Other	2.0%
Total	**100%**

*Total US women

Reason for choosing a Natural Method? (Previous Hormonal Contraception)

41% I want to understand better my body and my cycle

32% I was suffering from side effects

15% Worried about long term health risks of hormonal contraception

Reason for choosing (Previous Non-Hormonal Contraception)

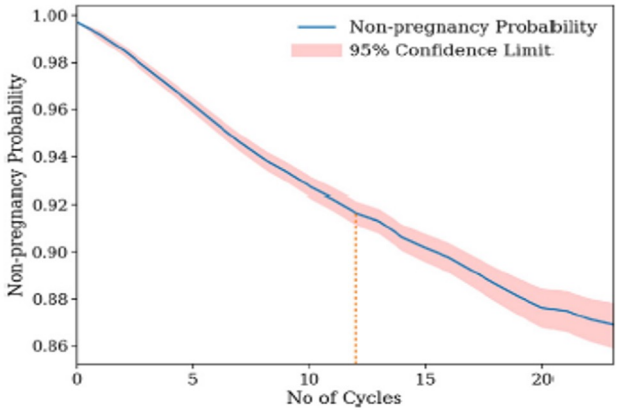
26% I want to understand better my body and my cycle

22% I want to reduce my risk of unintended pregnancy

18% I want to use less condoms

Real-World Effectiveness Study

- N=22,785 users and 18,548 woman-years, published in Contraception 2017[1]
- Inclusion Criteria: Women 18+ years who had registered to use Natural Cycles (Aug 2014–Aug 2016) and recorded data for ≥20 days; women used Natural Cycles for an average of 9.8 months[1]
- Life table analysis calculated a 13-cycle pregnancy probability of 8.3% (95% CI: 0.5–1.5) with typical use



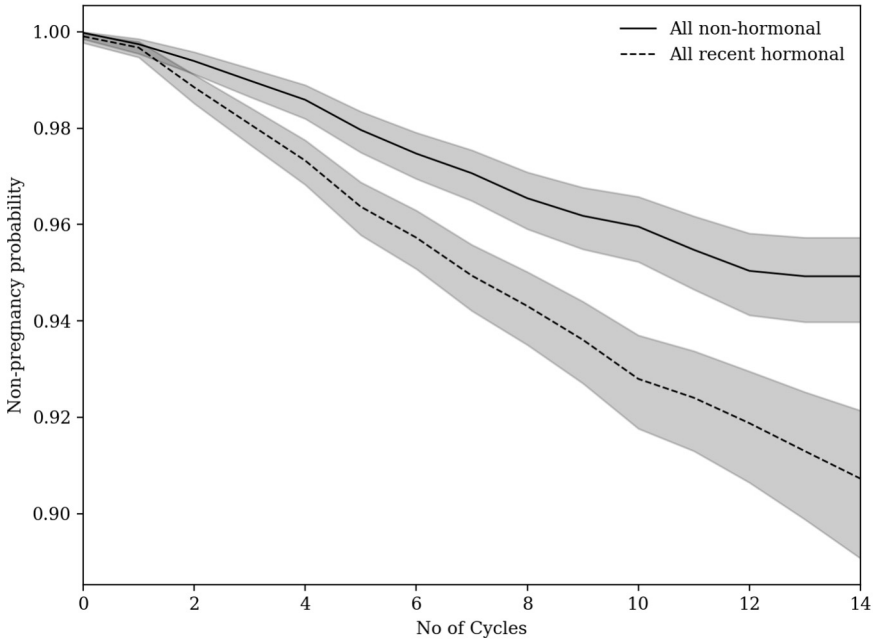
	Pearl Index*	Pregnancies	Woman-years	Cycles
Perfect Use	1.0	17	1,661	21,597
Typical Use	6.9	1,273	18,548	224,563

1. Berglund Scherwitzl E, et al. *Contraception* 2017;96:420–5.

Natural Cycles°

Impact of previous method of contraception

- n=16,331 Natural Cycles users from Sweden[1]
- Women who had previously used any non-hormonal method (n=6,147) had a 13-cycle failure rate of 4.8% ± 0.9%
- Women who had recently used any hormonal method (n=5,218) had a 13-cycle failure rate of 8.2% ± 1.0%



Natural Cycles

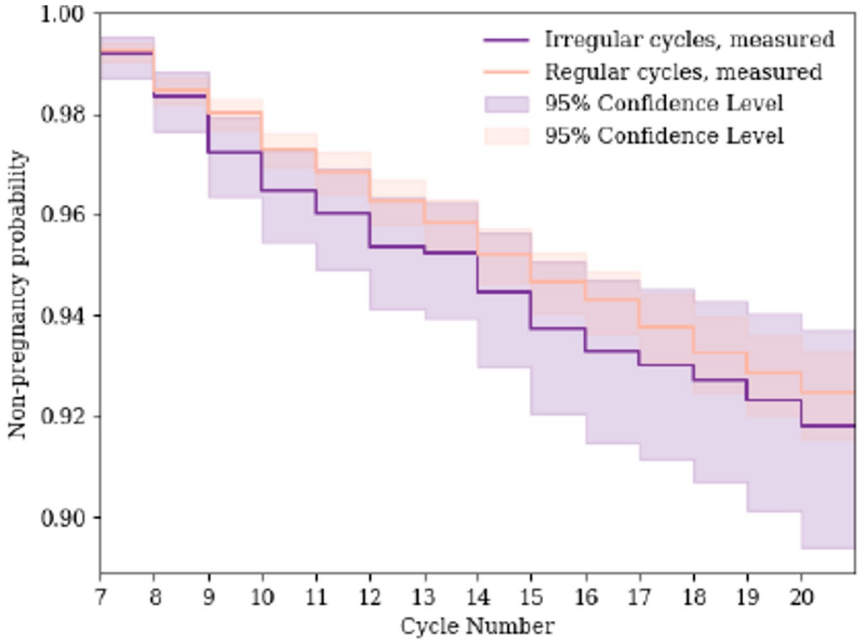
Bull J. et al. *BMJ Open*. 2019

Natural Cycles

Natural Cycles Effectiveness in Women With Irregular and Short Cycles

- Prospective observational study (women 18–45 years; data for ≥20 days; 30% of users contributed >1 year of data)
- Cycle length had no significant effect on the contraceptive effectiveness of Natural Cycles
- Cycle-by-cycle effectiveness of Natural Cycles is not reduced for women with irregular menstrual cycles

Right: Non-pregnancy probability irregular vs regular users (6 months observation)



Lundberg O, *et al*. *Eur J Contracept Reprod Health Care* 2018;23(Supl 1):94 (A-103)

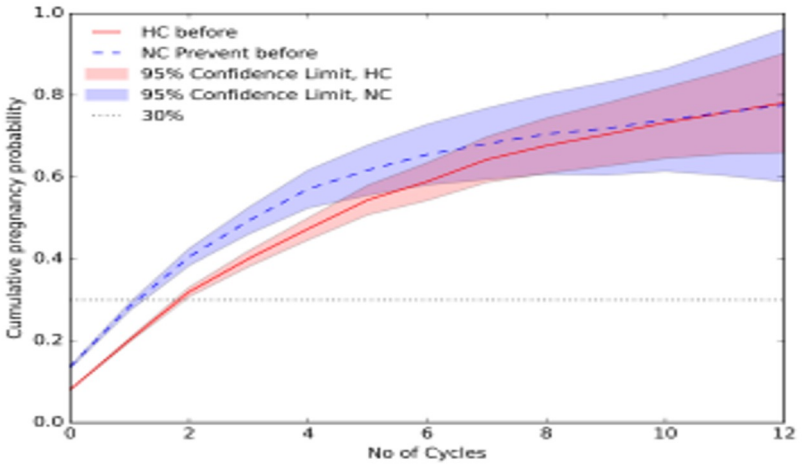
Natural Cycles

Prior Natural Cycles Contraceptive Use Reduces Time to Pregnancy

Study design	• Real-life prospective observational study of women using Natural cycles to plan pregnancy • **Time to conception compared for women previously using Natural Cycles (n=1,284) vs hormonal contraceptive (n=1,590) methods**
Results	• Short-term average time to conception was reduced for women previously using Natural Cycles vs hormonal contraceptives • No significant differences between the groups in 13-cycle cumulated pregnancy probability was observed
Conclusion	• Use of Natural Cycles contraceptive app potentially increases fertility awareness and reduces short-term time to pregnancy for women actively trying to conceive

	Previous contraceptive method	
	Natural Cycles (738 pregnancies)	**Hormonal (918 pregnancies)**
Time to pregnancy, cycles	2.3 (95% CI: 2.1–2.4)	3.7 (95% CI: 3.4–3.9)

Time to 30% cumulated pregnancy probability was 1.6 times longer for women previously using hormonal vs Natural Cycles contraception



Unmet need in contraception

- Improved (safe and “green”) methods with added health benefits
- “On demand” methods
- Methods for dual protection
- Long-acting, (non-hormonal) methods
- “Contragestion”
- Improved access/use of existing methods incl post abortion and post partum, removing barriers
- **Reversible methods for men**

Would women trust their partners to use a male pill?

Table I. Demographic characteristics, current contraceptive use and response to the idea of hormonal contraception for men

	Edinburgh (n = 450)	CapeTown (n = 544)			Hong Kong (n = 450)	Shanghai (n = 450)
		Black (n = 286)	Coloured (n = 151)	White (n = 107)		
Mean age (years)	27.6	30.0	29.2	28.0	31.3	30.9
% ⩽20	18	15	14	4	11	2
% >40	4	11	9	4	14	12
% with higher qualifications	42	13	32	69	3	19
% married/co-habiting	49	35	61	56	71	96
% with regular partner	44	58	27	25	25	3
% with children	31	80	72	25	67	65
Contraceptive method						
% using oral contraception	72	9	47	72	28	4
% using injectable	4	90	48	22	7	0
% using IUD	3	0	1	0	10	36
% using condom	15	0	1	4	40	34
Other including NFP	2	1	2	1	7	11
None	5	0	2	1	8	15
% happy with methodb	64	93	84	79	59	44
% unhappy	18	7	9	8	21	23
Male contraception a good idea (%)	**94**	**93**	**91**	**97**	**71**	**87**

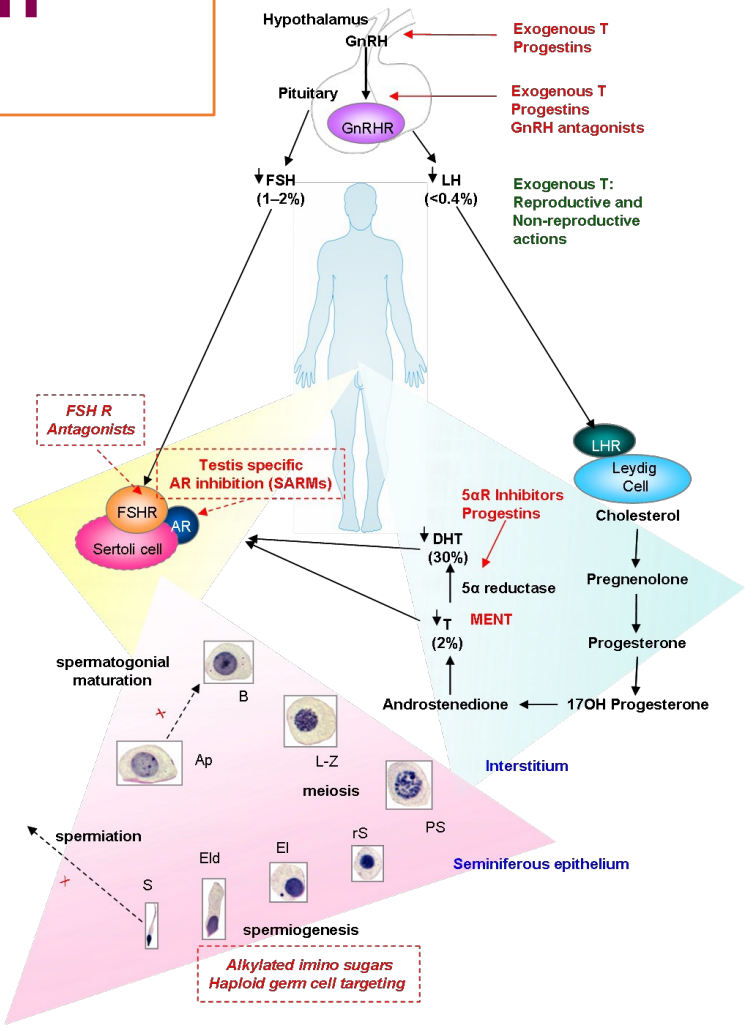
Glasier et al. Human Reproduction, Volume 15, Issue 3, March 2000

How does it work?

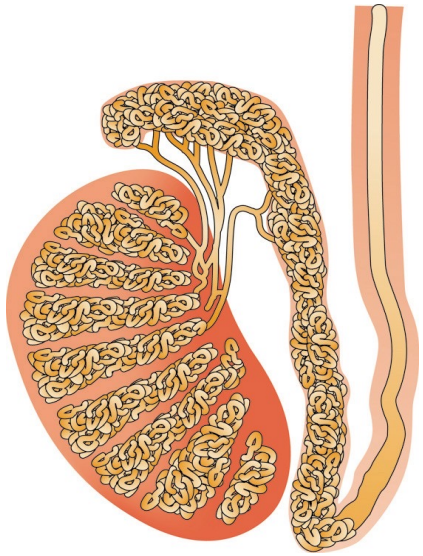
Potential approaches in the male

Endocrine control

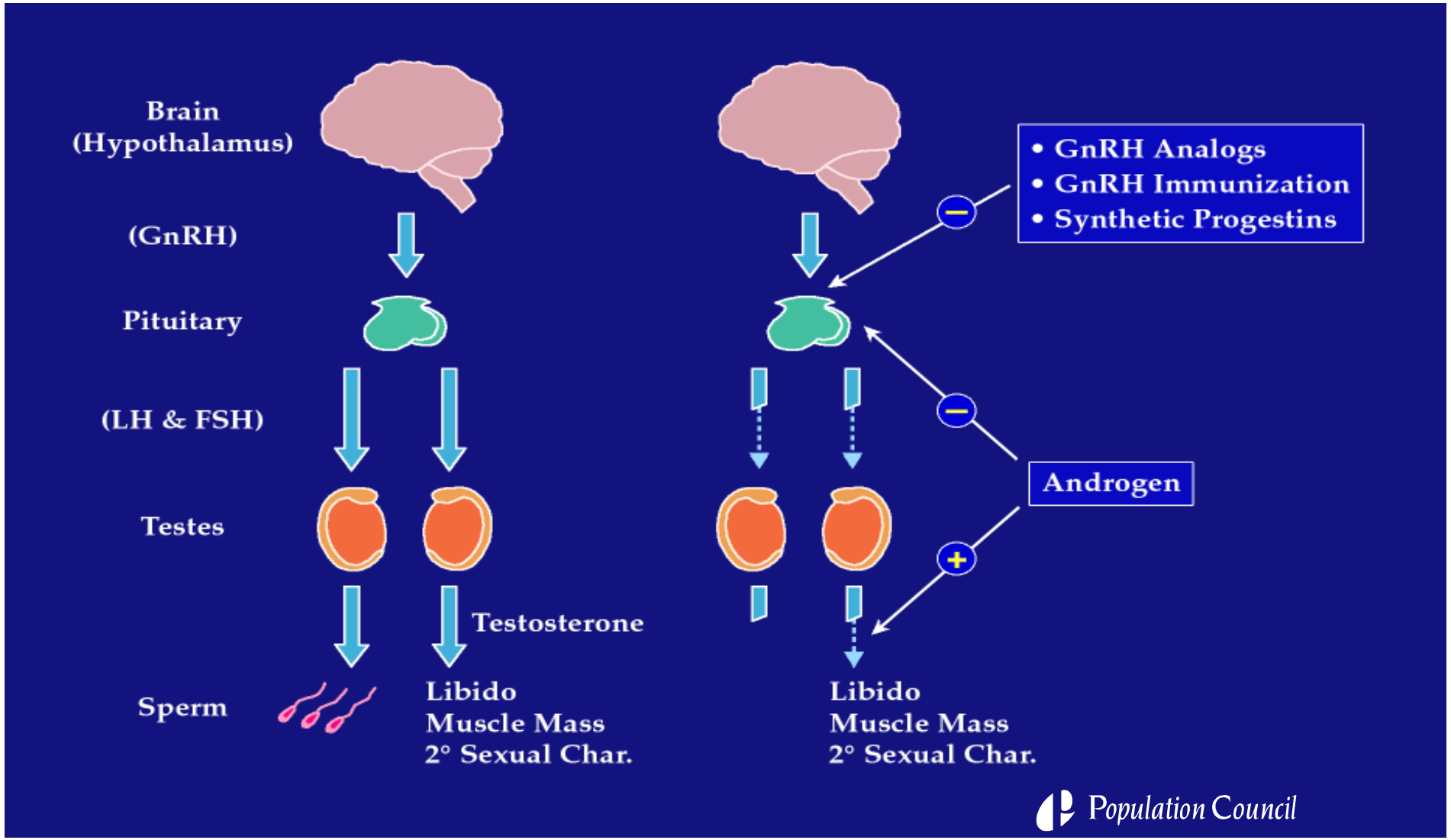
Spermatogenesis



Post-testicular



Matthiesson KL et al. Hum Reprod Update 2006 12:463



T+P suppress GnRH, Gonadotropins, intratesticular and circulating T, and sperm production-

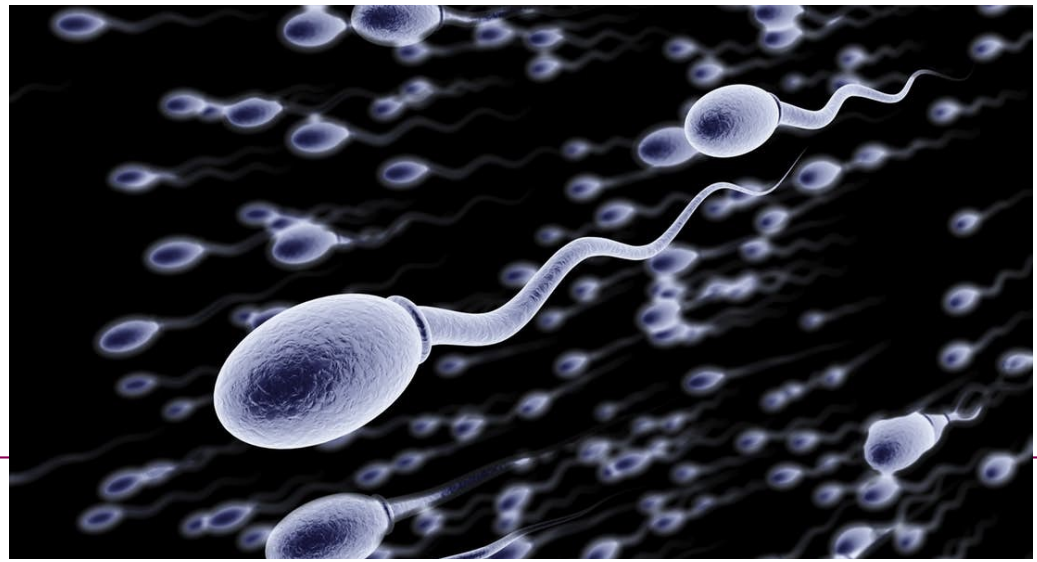
Replacing T doesn't restart sperm production.

How low do you need to go?
Effect of Sperm Count on Fertility.

- Following ejaculation/insemination sperms can be retrieved from the endocervix within 90 seconds and from the Fallopian tube in 5 min

- The usual quantity of semen : 3.5 ml, and an average count 120 million sperm/ml (35 million to 200 million).
  15-20 million/ml (the person is likely to be infertile).

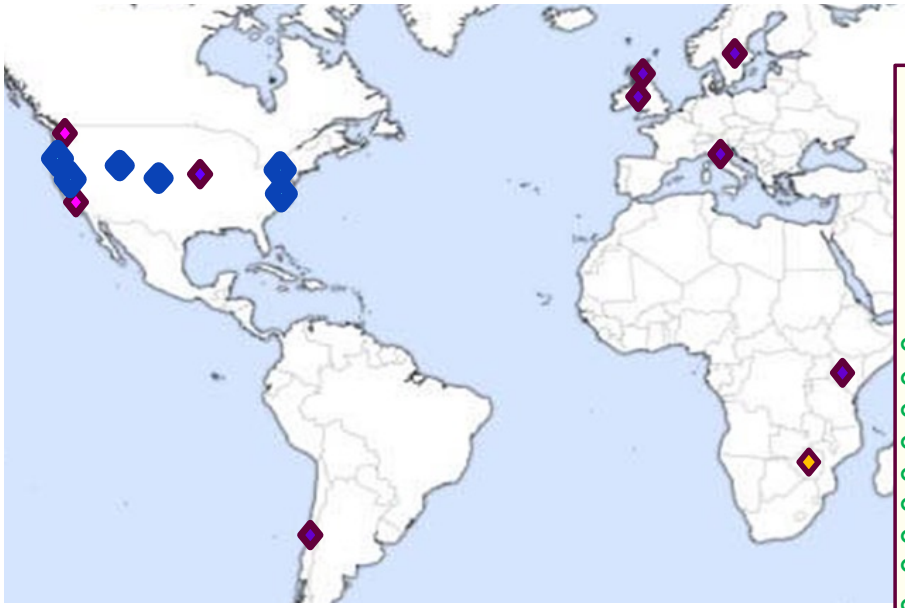
- <1 million /ml - contraception



Study Rationale

- Limited contraception options for men – condoms and vasectomy
- International surveys indicate a large number of men would use a new contraceptive method if one were available and female partners support male involvement in family planning
- Successful hormonal male contraception depends on near complete suppression of spermatogenesis without producing untoward effects on libido or other androgen-dependent functions
- No safety concerns to date based on previous studies in humans

CCN017 - Contraceptive Clinical Trials Network Sites (17) - Male Methods



University of Washington

- Stephanie Page
- William Bremner
- John Amory
- Brad Anawalt
- Arthi Thirumalai

The Lundquist Institute at Harbor-UCLA Medical Center

- Christina Wang
- Ronald Swerdloff
- Peter Liu
- Fiona Yuen
- Brian Nguyen

CCTN Partner Investigators & Institutions

- Richard Anderson, University of Edinburgh, Scotland, UK
- Cheryl Fitzgerald, University of Manchester, UK
- Kristina Gemzell Danielsson, Karolinska Inst, Sweden
- John Kinuthia, University of Nairobi, Kenya
- Cristina Meriggiola, University of Bologna, Italy
- Ajay Nangia, University of Kansas, USA
- Gabriela Noe, ICMER, Chile
- Jose Vinay, University of Chile, Chile
- David Archer, Eastern Virginia Medical School, USA
- Kurt Barnhart, University of Pennsylvania, USA
- Mitch Creinin, University of California, Davis, USA
- Alison Edelman, Jeff Jensen, Oregon Health & Science University, USA
- Aaron Lazorwitz, University of Colorado, USA
- David Turok, University of Utah, USA
- Felix Mhlanga, University of Zimbabwe, Zimbabwe

NICHD Program Director

DIANA BLITHE, PhD

Coordinating Center

Health Decisions (Premier Research)

PI: Clint Dart

Population Council

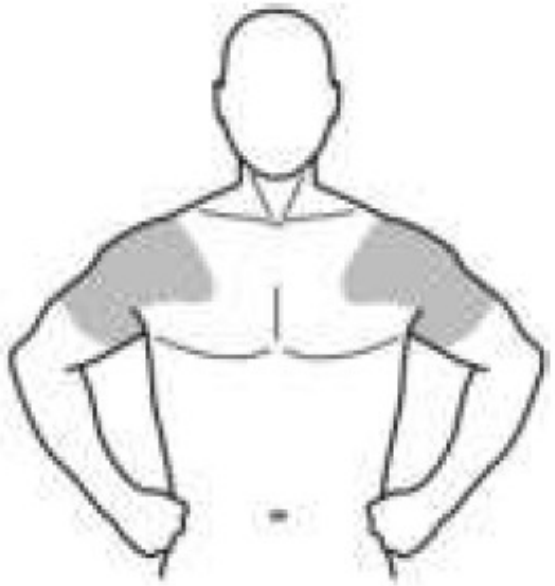
REGINE SITRUK-WARE-MD.

Co-Director

- Dan Loeven
- Rebecca Brodsky
- Lisa Haddad
- Jim Sailer

IP Application

- Study gel should be applied to clean dry skin at approximately the same time each morning (preferably in the morning after showering)
- Cover for 4 hours
- Subject should apply to the upper arms and shoulders



CCN017: Phase IIb Evaluation of NES / T Gel

Daily 5.0 ml dose contains 8 mg Nestorone + 74 mg Testosterone*

Target : Enrolling 420 couples of which 200 couples completing one year of efficacy

- **Primary Endpoint: Prevention of pregnancy**
- **Secondary Endpoints:**
  - **Safety, side effects**
  - **Acceptability to both partners**

Slide courtesy of NICHD Study Team

Comments from CCN017 Study Participants…

MEN

- "It was easy."
- "I wish we could keep using it."
- "When will this be available?"
- "… the control I was able to have over my own fertility felt empowering …."
- "…nice to be a part of something that gives women more freedom."
- "…easier to put on a gel than take a contraceptive pill..."

WOMEN

- "Better for my relationship… I'm much happier."
- "Wish I didn't have to go back on my old method."
- "It was a chance to get back to myself. On the pill, I had mood swings. I didn't feel like I was in the natural rhythm of my body."

Huge Media Interest

Petra & Gustav testar nytt preventivmedel – för män

KAROLINSKA UNIVERSITETSSJUKHUSET Publicerad 26 aug 2019 kl 04.30

För Petra Hattar, 27, och Gustav Karlsson, 32, var det självklart att delta i studien om p-gel för män. Foto: PRIVAT

PREMIUM Ett nytt preventivmedel för män testas nu på Karolinska institutet i Stockholm.

Gustav Karlsson, 32, och sambon Petra Hattar, 27, är ett av paren som deltar i studien.

– I alla relationer jag har haft så har min partner mått dåligt av sina preventivmedel. Därför känns det viktigt att vara med och ta fram ett alternativ, säger Gustav.

Här berättar paret och professor Kristina Gemzell Danielsson hur preparatet fungerar.

– Det känns så skönt att sluta med hormoner! Jag har haft preventivmedel i 12 år, jag har ingen aning om hur min kropp fungerar utan hormoner. Jag sörjer redan när det här året är över och jag kommer att behöva gå tillbaka till preventivmedel igen. Det är som att ha en godiskorg framför sig i ett år och sedan rycker de bort den, säger hon.

So why isn't a male 'pill' available? Is there a future for male contraception?

Past challenges

- Industry aren't convinced/involved
- No Advocacy group
- Regulatory issues – No guidelines available
  - one person takes a drug to prevent a condition in someone else
- Non-hormonal methods are largely pre-clinical

Today

- Some companies interested
- Advocacy groups: ICMC & Male Contraception Initiative (MCI)
- Expert Guidelines published: Wang et al, Andrology Sept 20, 2023

Npn-hormonal methods now in pipeline

Our goal

- We need to **increase contraceptive choice:**
  - → Make it possible for all women (and men), at different stages of life and with different needs, to find a contraceptive method
  - → To make it worth the effort!
  - → To make a difference to women themselves in their lives - their relations, the possibility to achieve education & for the benefit of their children
- Consider the **efficacy of agents** and what we can do to **minimise their risks & side effects**
- Aim to bring a **positive health impact** & to **improve patient motivation and compliance**

FABM

- Improved detection of the fertile wondow
- NaturalCycles, the first and only FDA cleared software application for contraception
- Improved feasibility with wearables

- →No randomised studies with hormonal methods or condom

”Conclusion - Male contraception“

- Shared responsibility – increased equality
- Globally huge unmet need for method used and controlled by women
- Consequenses of contraceptive failure/ ”forgotten pill”
- Increasing access and choices for men and women will reduce the burden of unintended pregnancies and decrease maternal mortality globally.

WHO Collaborating Centre for Research in Human Reproduction

Karolinska University Hospital/ Karolinska Institutet

- Research Group on Post-Ovulatory Methods for Fertility Regulation, UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, WHO,Geneva
- ICCR, Population Council, Regine Sitruk-Ware
- NICDH, Diana Blithe
- Swedish research council
- www.muvs.org

Reproductive Health Research

From bench- to bed- to the hands of women

to improve women's health

Acknowledgements

Contraceptive Development Program, NICHD, NIH

Program Director: Diana Blithe, PhD
Medical Monitor: Jeffrey Kroopnick, MD
Chemist: Min Lee, PhD

Population Council

Co-Director: Regine Sitruk-Ware, MD
Regulatory: Daniel Loeven
Medical Director, Safety: Lisa Haddad, MD

University of Washington

Investigators:
Stephanie Page, MD, PhD (Center Director & PI)
William J. Bremner, MD, PhD
Brad Anawalt, MD
John Amory, MD, MPH
Arthi Thirumalai, MD

The Lundquist Institute at Harbor-UCLA

Investigators:
Ronald S. Swerdloff, MD (Center Director)
Christina Wang, MD (PI)
Peter Liu, MBBS, PhD,
Brain Nguyen, MD, MPH (USC)
Fiona Yuen, MD

POPULATION COUNCIL
Ideas. Evidence. Impact.

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

THANK YOU!

Reproductive Health Research

From bench - to bed - to the hands of women

to improve women's health