Presentation for Healthcare Professionals

1 Introduction:
Overview of the **Natural Cycles** application

2 The Algorithm:
How does **Natural Cycles** differ from fertility trackers?

3 Clinical Studies:
Accuracy and effectiveness of the method for contraception

4 Summary:
Key clinical findings

Natural Cycles

Introduction

The Founding Story

The idea for **Natural Cycles** came about when founders, **Elina** and **Raoul,** were searching for an **effective** but **natural** method of birth control

As physicists, they were able to utilise an advanced knowledge of mathematics and data analysis to develop a solution that would meet their needs

*The **Natural Cycles** algorithm was born and developed into an mobile app that can be easily accessed by other couples like Elina and Raoul*

"Natural Cycles plays a huge role in women's lives, which humbles us. So we always have their best interest at heart in every decision we make"

Elina Berglund, CTO & Co-founder of Natural Cycles

Natural Cycles

Increases contraceptive choice and fertility awareness for women and their partners

- The **Natural Cycles app** is a digital contraceptive that uses a sophisticated algorithm to accurately predict daily fertility

- Fertility indicators utilised include:
  - Temperature
  - Menstruation
  - LH (optional)

E. Scherwitzl *et al*, *European Journal of Contraception and Reproductive Health* 2015;20:403–408

LH, luteinizing hormones

Contraceptive Mode: Non-Fertile (Green) and Fertile (Red) Days

- The **Natural Cycles** algorithm determines whether there is a risk of conception on a specific day[1,2]
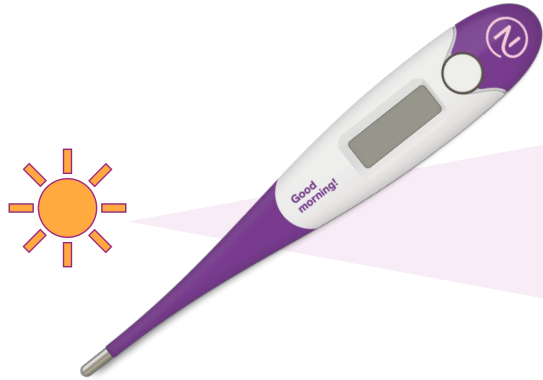
  ✔ **Green day = Not fertile**

  ✘ **Red day = Fertile**
  In order to prevent conception, women must abstain or use protection (e.g. condoms)
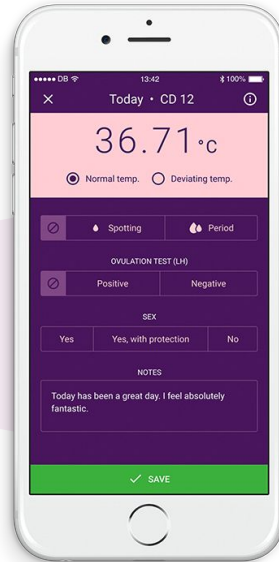
1. E. Scherwitzl *et al*, *European Journal of Contraception and Reproductive Health* 2015;20:403–408;
2. E. Scherwitzl *et al*, *European Journal of Contraception and Reproductive Health* 2016;21:234–241

The Daily Routine[1,2]

1. Wake up and measure temperature sublingually

2. Record data

3. Check fertility status

1. E. Scherwitzl *et al*, *European Journal of Contraception and Reproductive Health* 2015;20:403–408;
2. E. Scherwitzl *et al*, *European Journal of Contraception and Reproductive Health* 2016;21:234–241

Natural Cycles is EU Certified as a Contraceptive

- **Natural Cycles** is backed by clinical research and had been CE certified in Europe as a class IIb medical device intended to be used for contraception
  - This places the app in the same category as the condom
  - **Natural Cycles** is the only contraceptive app to have this certification

CE 0123

Natural Cycles: Benefits and Limitations

- **Natural Cycles** offers a wide range of features that many women may find attractive, however, limitations do exist

Benefits

- Effective, non-invasive, contraception[1–3]
- EU certified form of contraception
- Non-hormonal, with no known side effects[1]
- Provides a more 'natural' approach to birth control and helps women to better understand their body and cycle
- Provides personalised information on fertility
- Compatible with planning for pregnancy or with other contraceptives
- No restrictions based on religious beliefs
- Easy to use

Limitations

- Couples must use protection (e.g. condoms) or abstain from sex on fertile days
- Requires a daily routine of measuring temperature, sublingually, every morning
- Does not protect against STIs
- Less effective than LARCs
- Does not provide hormone-related benefits (i.e. for endometriosis, heavy bleeding or cycle management)

1. E. Scherwitzl *et al*, *European Journal of Contraception and Reproductive Health* 2015;20:403–408;
2. E. Scherwitzl *et al*, *European Journal of Contraception and Reproductive Health* 2016;21:234–241;
3. E. Scherwitzl *et al*, *Contraception* 2017;96:420–425

LARCs, long-acting reversible contraception; STI, sexually transmitted infection

Natural Cycles: Example Users

The typical **Natural Cycles** user is:

- ~29 years of age
- Has a daily routine
- Is in a stable relationship

1 Women between the ages of 18 and 45 years, in a stable relationship

AND

2a Who are looking for a more 'natural' approach to birth control (either preference or cannot use IUD or OCP) and are comfortable with using protection (condoms) on fertile days

OR

2b Who want to track their fertility in order to plan a pregnancy, or who are pregnant and want to monitor their pregnancy

AND

3 Would like to better understand their body and their menstrual and reproductive cycle

AND

4 Who don't mind measuring their temperature sublingually every morning

IUD, intrauterine device; OCP, oral contraceptive pill

Natural Cycles

The Algorithm

How does Natural Cycles
differ from fertility trackers?

Natural Cycles Tracks the Menstrual Cycle
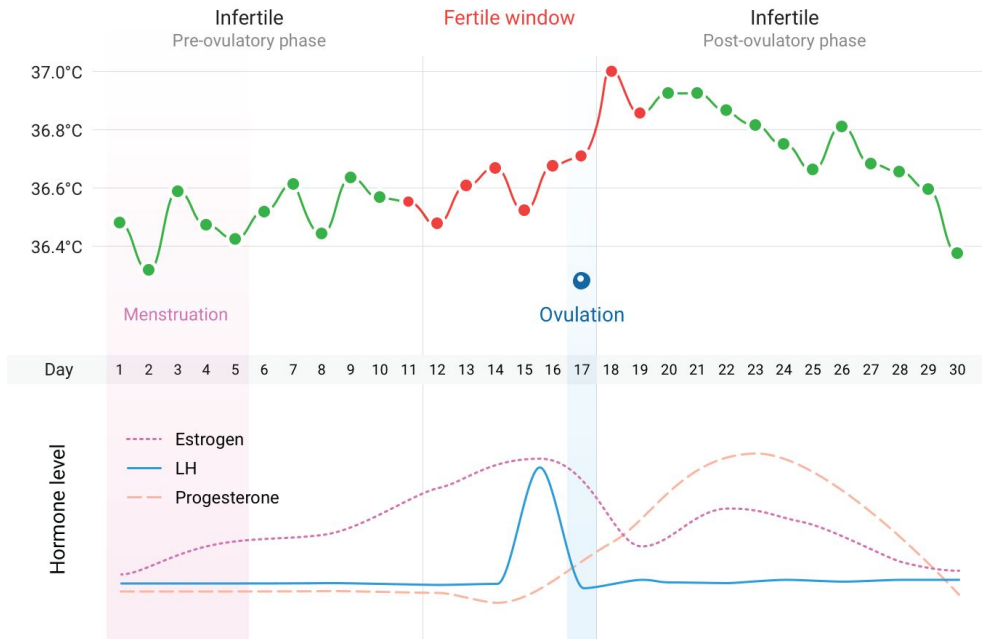
- Temperature acts as an indirect measure of progesterone level[1]

- Increased LH levels trigger ovulation[1–3]

- Conception can only occur within ~24 hours of ovulation[3]

  ○ Sexual intercourse up to 5 days prior to ovulation can result in pregnancy due to ability of sperm to survive[3]

  ○ Different days in the fertile window have different probabilities of conception[2,3]

1. https://www.naturalcycles.com/en/science/menstrual-cycle;
2. Wilcox AJ, et al. *BMJ* 2000;321:1259–62;
3. Wilcox AJ, et al. *NEJM* 1995;333:1517–21

LH, luteinizing hormones

Data Input

Data Input by the user

Daily temperature readings

Monthly menstruation data

LH/ovulation tests (optional)

Data gathered during onboarding

Includes

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

Refers to the main algorithm used to prevent, plan and monitor pregnancy
1. E. Scherwitzl *et al*, *European Journal of Contraception and Reproductive Health* 2015;20:403–408

LH, luteinizing hormones

The Algorithm*: An Overview

Default – Red Day

Data assessment

Ovulation has occurred or predicted far enough in the future

YES → **Green Day**

NO → **Red Day**
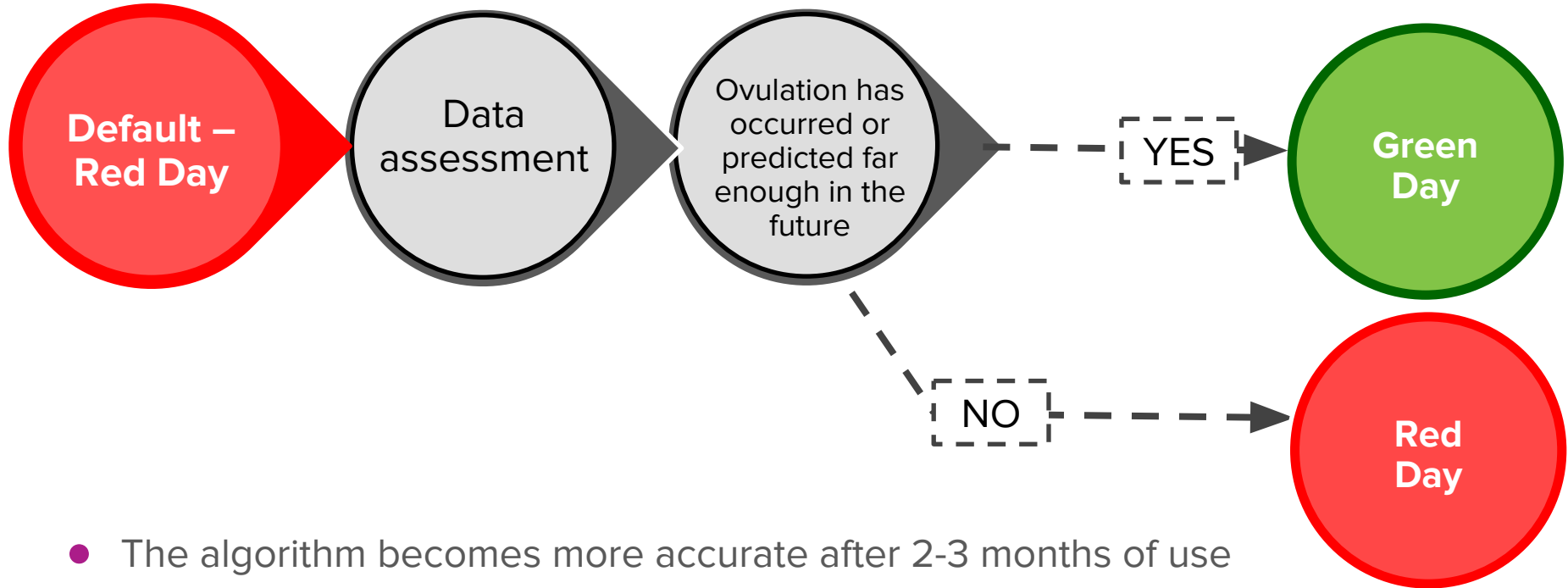
- The algorithm becomes more accurate after 2-3 months of use

Fertile and Non-Fertile Days

- **Non-fertile days (green)** are considered safe from the risk of conception

Green days are calculated when:

o Ovulation can be detected in the past[1]

o Ovulation is predicted far enough in the future to account for sperm survival[1]

o Ovulation is predicted far enough in the future to account for 0.1% (SD≥3) uncertainty of the predicted ovulation day

If these criteria cannot be fulfilled, a red day is calculated[1]

Abstention from intercourse or use of protection is required on red days

1. E. Scherwitzl *et al*, *European Journal of Contraception and Reproductive Health* 2015;20:403–408

SD, standard deviation
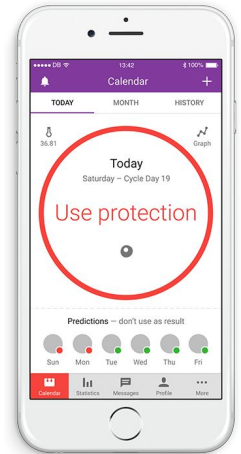
Non-Fertile Days

- Regular data input leads to better measurements; therefore, more **green days** can be calculated

  - For the typical user,* the average percentage of **green days** calculated per cycle is **55–61%** (includes all women and cycles)[1]

    - During the first and second cycles of app use the average is lower (~**40% green days** in the first cycle[1])

  - Method failure rate is 0.5 pregnancies per 100 woman years (Pearl Index: 0.5)[2]

Plan a Pregnancy

- **Planning a pregnancy** can also be supported through use of the **Natural Cycles** algorithm to identify the fertile window

  - A scale identifying the level of fertility for each **'red day'** is calculated

- The algorithm is able to **detect pregnancy** according to temperature changes that occur just after the fertilized egg implants in the uterus

  - The user is then asked to confirm with a pregnancy test

- May enable the timely identification of infertility issues
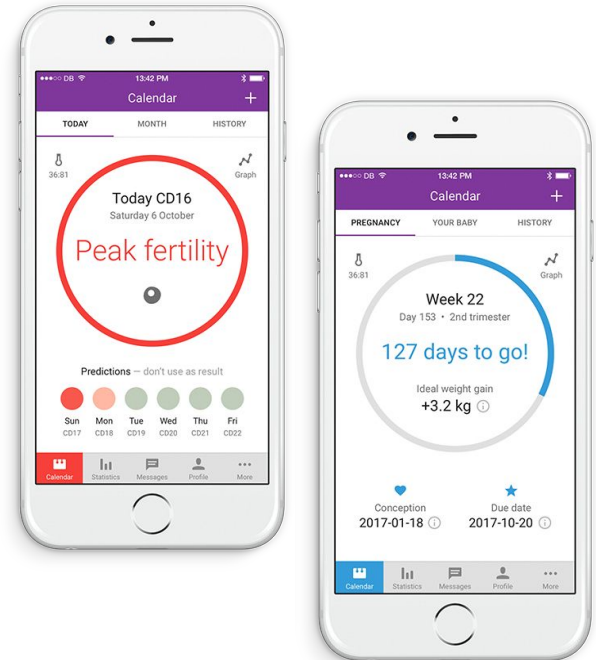
Clinical Studies

Effectiveness Measurements

Pearl Index

The number of pregnancies per 100 woman-years of exposure[1]

Perfect use: used both consistently and correctly in accordance with the directions for use

Typical use: actual use, including correct, incorrect, or inconsistent use

Method Failure Rate

The number of pregnancies resulting from a falsely attributed green day[2]

1. Trussell J and Portman D. *Contraception* 2013;88:604–10;
2. E. Scherwitzl *et al*, *European Journal of Contraception and Reproductive Health* 2016;21:234–241

The Natural Cycles Studies

1
N=317

Aim: Validate the ability of the **Natural Cycles** app to detect ovulation and identify/predict the fertile window

Key finding: Natural Cycles was in good agreement with the use of ultrasonography to detect ovulation[1,2]

2
N=4054

Aims: investigate the **method failure rate**, and the **perfect and typical** use contraceptive effectiveness of **Natural Cycles**[3,4]

Key findings: Both studies were in good agreement

3
N=22,785

- Typical use Pearl Index = **7**
- Perfect use Pearl Index = **1.0**
- Method failure Pearl Index = **0.5**
- The **Natural Cycles** Pearl Index is comparable to that of the pill (typical use Pearl Index 9)[5]

1. Scherwitzl E, et al, *European Journal of Contraception and Reproductive Health* 2015;20:403–408; 2. Behre HM, et al. *Human Reproduction* 2000;15:2478–82; 3. E. Scherwitzl *et al*, *European Journal of Contraception and Reproductive Health* 2016;21:234–241; 4. E. Scherwitzl *et al*, *Contraception* 2017;96:420–425; 5. Trussell J. *Contraception* 2013;88(5):604–610.

Identification and Prediction of the Fertile Window

Identification and prediction of the fertile window using NaturalCycles

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A B S T R A C T   **Objectives**   The aim of the study was to evaluate the ability of a novel web and mobile application to identify a woman's ovulation day and fertile window, in order to use it as a method of natural birth control.
Methods   A retrospective study was performed on 1501 cycles of 317 women aged 18 to 39 years. Women entered their basal body temperatures, ovulation test results and date of menstruation into the application.
Results   The mean delay from the first positive ovulation test to the temperature-based estimation of the ovulation day was 1.9 days; the length of the luteal phase varied on average by 1.25 days per user. Only 0.05% of non-fertile days were falsely attributed and found within the fertile window.
Conclusions   The method is effective at identifying a user's ovulation day and fertile window and can therefore be used as a natural method of birth control.

Aim

Investigate the relationship between ovulation, temperature shift and LH surge

Size

N=317 women and 1501 menstrual cycles

Inclusion Criteria

Women 18–40 years (sexually active) using only Natural Cycles to prevent pregnancy

Temperature data recorded for ≥30 days

LH, luteinizing hormones

Ovulation Detection

- Temperature-based ovulation detection by **Natural Cycles** was in good agreement with the use of ultrasonography to detect ovulation[1,2]
  - Strongly indicates identification of the correct ovulation day
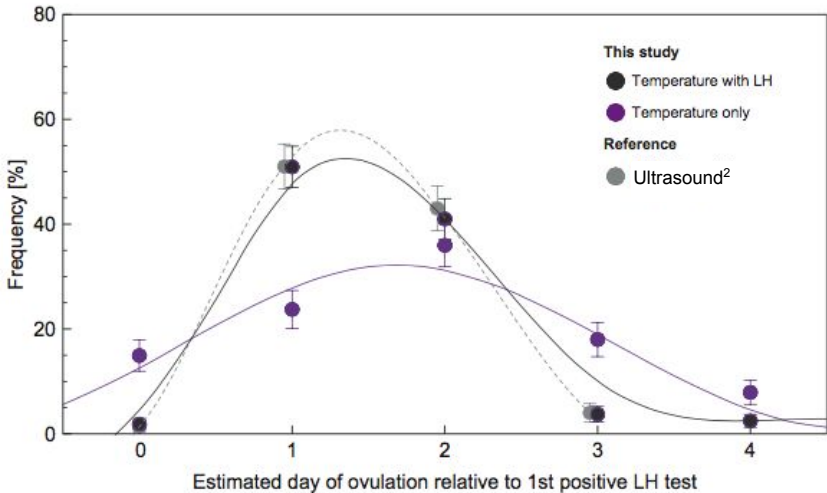
Mean ± SD delay from the first positive ovulation test to the **Natural Cycles** estimation was 1.9 ± 1.4 days[1]
  - Mean ± SD delay associated with ultrasound detection was 1.5 ± 0.6 days[1]

Green Days were falsely assigned within the fertile window in **0.05%** of cases[1]

The proportion of **green days** per cycle was, on average, 55–61% after 3 months[1]

1. Scherwitzl E, et al, *European Journal of Contraception and Reproductive Health* 2015;20:403–408;
2. Behre HM, et al. *Human Reproduction* 2000;15:2478–82

Effectiveness Study (N=22,785)

Contraception

ELSEVIER

Contraception xx (2017) xxx–xxx

Original research article

Perfect-use and typical-use Pearl Index of a contraceptive mobile app☆

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Abstract

Objectives: The Natural Cycles application is a fertility awareness-based contraceptive method that uses dates of menstruation and basal body temperature to inform couples whether protected intercourse is needed to prevent pregnancies. Our purpose with this study is to investigate the contraceptive efficacy of the mobile application by evaluating the perfect- and typical-use Pearl Index.
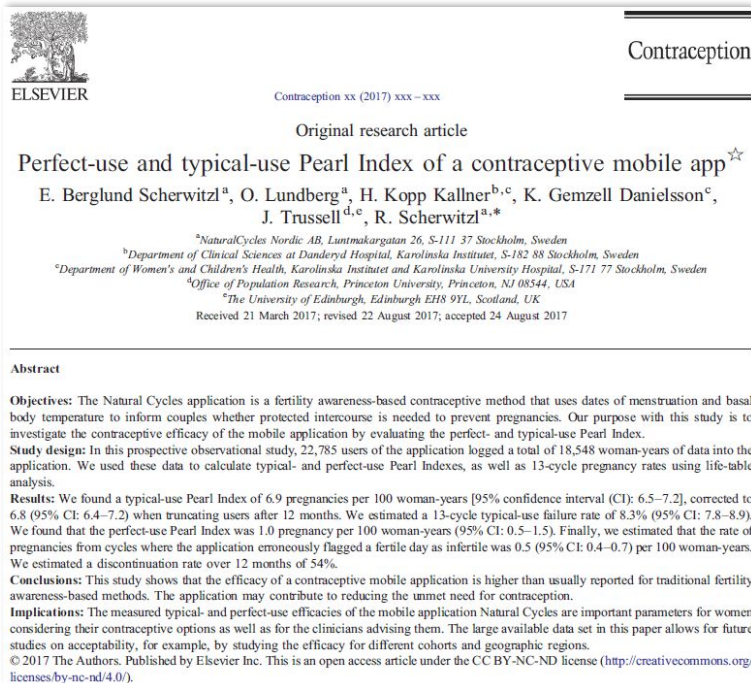**Study design:** In this prospective observational study, 22,785 users of the application logged a total of 18,548 woman-years of data into the application. We used these data to calculate typical- and perfect-use Pearl Indexes, as well as 13-cycle pregnancy rates using life-table analysis.
Results: We found a typical-use Pearl Index of 6.9 pregnancies per 100 woman-years [95% confidence interval (CI): 6.5–7.2], corrected to 6.8 (95% CI: 6.4–7.2) when truncating users after 12 months. We estimated a 13-cycle typical-use failure rate of 8.3% (95% CI: 7.8–8.9). We found that the perfect-use Pearl Index was 1.0 pregnancy per 100 woman-years (95% CI: 0.5–1.5). Finally, we estimated that the rate of pregnancies from cycles where the application erroneously flagged a fertile day as infertile was 0.5 (95% CI: 0.4–0.7) per 100 woman-years. We estimated a discontinuation rate over 12 months of 54%.
Conclusions: This study shows that the efficacy of a contraceptive mobile application is higher than usually reported for traditional fertility awareness-based methods. The application may contribute to reducing the unmet need for contraception.
Implications: The measured typical- and perfect-use efficacies of the mobile application Natural Cycles are important parameters for women considering their contraceptive options as well as for the clinicians advising them. The large available data set in this paper allows for future studies on acceptability, for example, by studying the efficacy for different cohorts and geographic regions.
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Aim

Investigate the contraceptive effectiveness of **Natural Cycles** via the perfect and typical use Pearl Index

Size

N=22,785 users and 18,548 woman years

Inclusion Criteria

Women 18+ years, who had registered to use **Natural Cycles** between Aug 2014 and Aug 2016

Recorded data for ≥20 days

1. E. Scherwitzl et al, Contraception 2017;96:420–425

Perfect and Typical use Pearl Index

- Perfect use Pearl Index was calculated to be 1.0 pregnancies per 100 woman-years
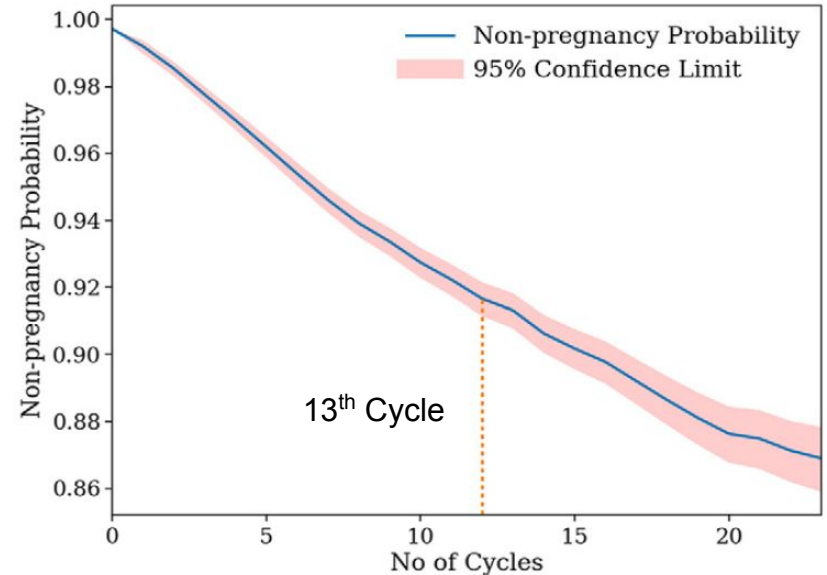
- Typical use Pearl Index = 6.9

	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
Method Failure	**0.5**	102	18,548	224,563

Results were consistent with the 2016 Natural Cycles study (Study 2)

*Pearl Index values represent data for all cycles
1. E. Scherwitzl *et al*, *Contraception* 2017;96:420–425

13-cycle Typical-use Pregnancy Rate

- Following the method of Trussel and Grummer-Strawn the 13-cycle probability of contraceptive failure was calculated[1,2]

  - Perfect use cycles and pregnancies were included[2]

  - Each woman contributed a maximum of 13-cycles[2]

  - Kaplan-Meier cumulated probability of non-pregnancy was calculated

The 13-cycle typical use failure rate was **8.3%** (95% CI:7.8%, 8.9%)[2]

13th Cycle

1. Trussell J, Grummer-Strawn L. *Fam Plan Perspect* 1990;22:65–75;
2. E. Scherwitzl *et al*, *Contraception* 2017;96:420–425

CI, confidence interval

Natural Cycles

Summary

Perfect Use versus Typical Use[1]

- Clinical studies have been conducted to evaluate the effectiveness of the **Natural Cycles** app for contraception

Typical-use effectiveness = 93%

- Peal index = 6.8
- This means that, on average, 7/100 women will conceive over the course of one year (includes all possible reasons)[*]

Perfect-use effectiveness = 99%

- Pearl Index = 1.0
- This means that, on average, 1/100 women will conceive over the course of one year due to the failure of alternative contraception on red days

*Unprotected intercourse on red days, or failure of the contraceptive method used on red days.

1. E. Scherwitzl *et al*, *Contraception* 2017;96:420–425

Comparison of Natural Cycles app with Other Commonly Used Short-acting Contraceptive Methods[1,4]

Contraceptive method	Percentage of women experiencing an unintended pregnancy within the first year of use		Percentage of women continuing use at one year
	Typical use	Perfect use	
Natural Cycles	7	1	46
Traditional* fertility awareness-based methods	24	0.4–5	47
Male Condom	18	2	43
Combined pill and progestin-only pill	9	0.3	67

*Non-digital, manual analysis methods

1. Berglund Scherwitzl E, et al. *Contraception* 2017;96:420–425; 2. Berglund Scherwitzl E, et al. *Eur J Contracept Reprod Health Care* 2016;21:234–241; 3. Berglund Scherwitzl E, et al. *Eur J Contracept Reprod Health Care 2017;*20:403–408; 4. Trussell J. *Contraception*. 2011;83(5):397–404.

Key Clinical Data

- The **Natural Cycles** application detects ovulation with an accuracy comparable to ultrasound[1]

- The 13-cycle typical use failure rate according to Kaplan-Meier life tables analysis was **8.3%** (95% CI:7.8%, 8.9%)[2]

- When used as a contraceptive, the **Natural Cycles** Pearl Index for typical use was calculated to be 6.9 pregnancies per 100 woman–years[2]
  - This is equivalent to 7 pregnancies among 100 women using the application for 1 year

- The Pearl index for typical use of the oral contraceptive pill is 9 pregnancies per 100 woman–years[3]

1. E. Scherwitzl *et al*, *European Journal of Contraception and Reproductive Health* 2015;20:403–408; 2. E. Scherwitzl *et al*, *Contraception* 2017;96:420–425; 3. Cooper DB and Adigun R. *NCBI Bookshelf* 2017:Oral Contraceptive Pills.

Summary of Features and Data

Database of over 300,000 cycles from more than 100,000 women

Period tracker
- Cycle length and variation
- Menstruation length

Pregnancy detector
- 'Take a pregnancy test'
- Conception and due date

Statistics

Ovulation detector
- Fertile/non-fertile days
- Length and variation of follicular and luteal phase
- Anovulatory cycles

Pregnancy monitor
- Miscarriage detector
- Content relevant to pregnancy

Additional data collected
- Intercourse frequency (protected/unprotected)
- Previously used contraception
- Age, BMI and smoking habits

BMI, body mass index

Natural Cycles can Provide HCPs with Valuable Information About Their Patients

Basal body temperature
- Baseline temperature
- Temperature fluctuations

Cycle characteristics
- Cycle length and regularity
- Average ovulation day
- Number of anovulatory cycles
- Number of fertile/non-fertile days per cycle
- Duration and variation of luteal and follicular phases
- Duration of menstruation
- Days with spotting

Result of LH test (if performed)

Timing of sexual intercourse

Daily user notes
- Includes factors such as PMS symptoms, pain and mood swings
- May help to identify possibility of conditions such as endometriosis[1]

1. Hsu LA, et al. *Clin Obstet Gynecol* 2010;53:413–19

LH, luteinizing hormones; PMS, premenstrual syndrome

Research @ **Natural Cycles**

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