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ORIGINAL ARTICLE



Identification and prediction of the fertile window with a new web-based medical device using a vaginal biosensor for measuring the circadian and circamensual core body temperature

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ABSTRACT

Fertility awareness-based (FAB) methods represent a term that includes all family planning methods that are based on the identification of the fertile window. They are based on the woman's observation of physiological signs of the fertile and infertile phases of the menstrual cycle. The first approach consists basically in symptothermal methods accompanied by cervical mucus measurements and clinical menstrual cycling data recording. The second most often used methods are the urinary measurement of E3G and luteinizing hormone (LH) with a personalized computer system. Hence these systems lack the efficacy of the continuous circadian and circamensual measurement of the core body temperature. Only this approach enables the accurate detection of the ovulation during the fertile window. A new medical device called OvulaRing has been developed to fill this gap. In the present study, the system and its first clinical results are presented. OvulaRing is a medical device used just like a tampon. The device is a vaginal ring of evatane that contains an integrated biosensor. This sensor measures continuously every 5 min the core body temperature throughout the entire cycle. This device allows a circadian and circamensual intravaginal exact measurement. With this system, 288 measurements are created per day. The system can detect retrospectively and predict prospectively the fertile window of the users. One hundred and fifty eight women aged between 18 and 45 years used this medical device in an open non-randomized clinical study for 15 months. A total of 470 cycles could be recorded and were able for analysis. By the same time in a subgroup of patients, hormonal assessments of LH, follicle-stimulating hormone, estradiol and progesterone as well as vaginal ultrasound were performed in parallel between the 9th and the 36th day of the cycle. The validation error due to software errors was 0.89% for the retrospective analysis; that means that the accuracy for the detection of the ovulation was 99.11%. Accuracy of 88.8% for a window of 3 days before ovulation, the day of ovulation and the 3 days after ovulation was achieved for the prospective analysis. In the subgroup of woman with recorded pregnancies, it could be shown that after 3.79 months of use (median) pregnancies were observed. In 67.72% in up to 3 months, in 16.36% between 3 and 6 months of use, in 7.27% between 7 and 9 months, in 5.45% between 10 and 12 months and in 1.82% between 13 and 15 months of use of the system. With this new web-based system, a precise determination of the fertile window even in women with ultralong cycles (>35 days) could be detected independently of their personal live circumstances. Exact determination of the fertile window is herewith possible so that OvulaRing represents an evolution in the FAB method for the cycle diagnosis of women with regular, irregular or anovulatory menstrual cycles.

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Introduction

Fertility awareness-based (FAB) methods is a term that includes all family planning methods that are based on the identification of the fertile time. They are based on the woman's observation of physiological signs of the fertile and infertile phases of the menstrual cycle. This knowledge can be used to plan or avoid pregnancy. FAB methods depend on two key variables: first, the accurate identification of the fertile days of a woman's menstrual cycle (the fertile time) and second, the modification of sexual behavior either to plan a pregnancy or to use this knowledge to avoid pregnancy. When couples use FAB methods of family planning to avoid pregnancy, they practice different sexual behavior

during the fertile time. When FAB methods involve sexual abstinence during the fertile time, this method is called natural family planning (NFP). When FAB methods involve occasionally using a barrier method during the fertile time, the method is called FAB method with barriers. It must also be recognized that although many couples state they are practicing a FAB method, sometimes they do not adhere to the guidelines and unprotected intercourse or other kinds of genital contact occur during the fertile time. Since the first descriptions of FAB by Pryll [1], the efficacy of FAB methods to avoid pregnancy has been critically reviewed by several authors [2–9]. Several issues have been identified when attempting to compare the different FAB methods.

The first is that most FAB methods have evolved concurrently over the last 40 years in different countries; each has been led by pioneers who have developed guidelines for their respective groups. This has resulted in many cases in a lack of evidence-based guidelines being developed and subsequently modified to conform to best scientific evidence.

The second issue is that efficacy rates may vary because they are derived from studies done with volunteers and researchers from different cultural backgrounds where motivation to avoid pregnancy and rigor of research methods may vary [10–12]. To be able to make an informed choice when selecting a family planning method, couples need to know the efficacy of a method when used consistently and imperfectly. Trussell and Grummer-Strawn [13,14] are critical about how efficacy has been calculated in previous studies. They argue that previously published rates of method and user failure for all contraceptive methods suffer from methodological errors and are biased downwards. Trussell and Grummer-Strawn [13,14] recommend a new model of calculating perfect and imperfect use pregnancy rates which up to now has rarely been applied. This is likely to be due to the fact that this approach requires documentation of all sexual behavior during each cycle. Frank Herrmann et al. [15] described a cohort of couples who used a method that consisted of recording the cervical secretion pattern, changes of basal body temperature and the application of a calculation rule. It is called the symptothermal method (STM) of NFP. The beginning and the end of the fertile time are identified by two parameters in order to have double-check system.

The following two guidelines are given to each couple to identify the first fertile day—both guidelines are applied and the first fertile day is the earliest day identified:

Change of cervical secretion: first appearance of cervical secretion.

Calculation guideline: the first fertile day is the sixth day of the cycle (In NFP methodology, this is called the ‘5 days rule’ which states that the first 5 days of the cycle are infertile days.) or after a woman has completed 12 cycles of use this guideline is replaced by a calculation that takes the earliest temperature rise in the last 12 cycles and subtracts 7 days to identify the first fertile day (In NFP methodology, this is called the ‘minus eight rule’: earliest temperature rise in the last 12 cycles minus 8 days to identify the last infertile day.)

But independent of these existing methods, it is known that during the average woman’s menstrual cycle, there are 6 days when intercourse can result in pregnancy; this ‘fertile window’ comprises the 5 days before ovulation and the day of ovulation itself [16–18]. Just as the day of ovulation varies from cycle to cycle so does the timing of the six fertile days. Reliable methods to predict ovulation are lacking, therefore predicting the fertile window is also unreliable. Clinical guidelines suggest the cycle days during which the fertile window is most likely to occur, but these guidelines are outdated. Wilcox et al. [19] provided in a cohort of more than 200 women new estimates based on a prospective study. In only ~30% of women is the fertile window entirely within the days of the menstrual cycle identified by clinical guidelines—that is, between Days 10 and 17. Most women reach their fertile window earlier and others much later. Women should be advised that the timing of their fertile window can be highly unpredictable, even if their cycles are usually regular.

Another approach for determining the exact window of fertility is the hormonal one. Researchers have used a variety of approaches in an attempt to measure hormone levels in a meaningful way given the inherent variability of these markers.

Nevertheless, many studies rely on a single serum sample drawn on an arbitrary day of each woman’s menstrual cycle, which seems inadequate, even with adjustment for cycle day or for cycle phase status (determined by the sample’s progesterone level) [20–22]. Other studies have attempted to time specimen collection to key hormonal events based on self-reported cycle length or cycle day or the assumption that the luteal phase is 14 days [23–25], but these methods assume that women can reliably report their cycle length or that the timing of hormonal fluctuations is the same across women, both of which are unlikely to be true [26–30]. The ‘gold standard’ is daily collection of first-morning urine specimens, which ensures that critical hormone windows are captured if compliance is adequate, but the protocol is burdensome, which affects recruitment and compliance. Ideally, it would be possible to characterize hormone levels across the menstrual cycle by collecting fewer, well-timed measurements, but it is unclear what algorithm should be applied to prospectively assess when the samples should be collected. So, luteinizing hormone (LH) measuring systems have been developed to close this gap [31]. But these participants that were provided with home fertility monitors that measured urinary estrone-3-glucuronide and LH had monitor recording data that showed a surge during 76% of the first cycles and 78% of the second cycles [31].

Therefore, new and more accurate systems have to be developed. In this article, we present a new concept for improving the accuracy in the detection of the fertile window of women.

A medical device called OvulaRing has been developed and first clinical data have been obtained that demonstrate the evolution in this segment of fertility monitoring.

Material and methods

OvulaRing is a medical device used just like a tampon. The device is a vaginal ring of evatane that contains an integrated biosensor. This sensor measures continuously every 5 min the core body temperature throughout the entire cycle. This device allows a circadian and circumensual intravaginal exact measurement. With this system, 288 measurements are created per day. With a reading device and a mobile software, the data are transferred to a central database and evaluated. With the use of mathematical algorithmic, these data are evaluated and a prediction model is assessed. The system is able to predict retrospectively and prospectively the fertile window of the users. Three recorded cycles from which two have to be ovulatory are needed to obtain the accurate data of this new technology in the prospective data evaluation.

One hundred and fifty eight women aged between 18 and 45 years used this medical device in an open non-randomized clinical study for 15 months. The body mass index (BMI) of these women ranged between 18.2 and 36.9 with a median of 22.2. A total of 470 cycles could be recorded and were able for analysis. By the same time in a subgroup of patients hormonal assessments of LH, follicle-stimulating hormone, estradiol and progesterone were performed in parallel between the 9th and the 36th day of the cycle using commercially available ELISA assays.

All the data were expressed in form of a cyclofertilogram (CFG). This is the graphical representation of the obtained circadian and circumensual data or the continuous 5-min measurement.

A subgroup of women was specifically evaluated in regard to the rate of intended pregnancies with the use of this tracking system. Sixty-two women were retrospectively randomized for the

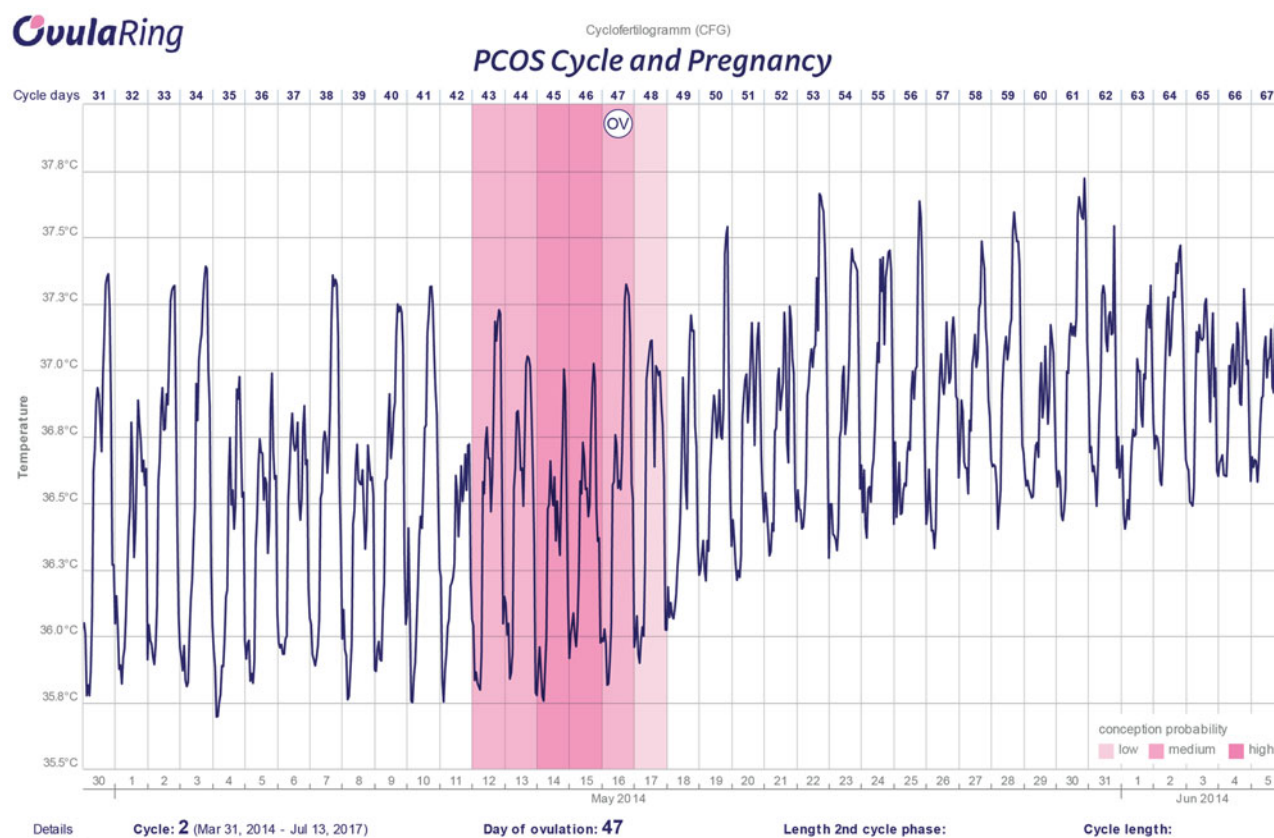


Figure 1. CFG of a patient with a PCOS. Ovulation occurred at Day 47. This CFG shows a pregnancy as the core body temperature remains high.

analyses. Of these women, data were obtained from 55 and the time use of the system till achieving a pregnancy was evaluated.

The present clinical trials were approved by the ethical committees of the University of Dresden, Germany (EK270072013) and the University of Leipzig, Germany (EK-MPK-MO-1/12-1).

Results

From the recorded 470 cycles, 83.4% were biphasic cycles. The shortest biphasic cycle had a length of 20 days and the longest of 58 days (Figure 1 depicts a CFG of an ultralong ovulatory biphasic cycle). Of the cycles, 8.8% showed a reduced corpus luteum phase (<12 days) and 16.6% of the cycles were monophasic or even anovulatory (Figure 2). The shortest monophasic cycle had a length of 20 days and the longest of 77 days. Of the anovulatory cycles, 10.1% had a length of >50 days.

It could be shown that 69.5% of the women had an ovulation after the 15th day (54.9%) of the menstrual cycle or before the 13th day (14.6%). In 17.3% of the cycles, ovulation was detected at Day 20 or later of the menstrual cycle

In fifteen percent of the women with cycles ≥ 35 days, a PCOS syndrome was diagnosed with ovulations even after the 36th day of the cycle. Of these women, 4.5% showed ovulations after Day 26 of the cycle.

The median body core temperature was in all monophasic cycles 36.6 °C and 36.7 °C in the biphasic cycles.

The interindividual changes of ovulation showed a median average of 3 days.

Using this fertility awareness system, the validation error for the retrospective analysis was 3.69%; that means that the accuracy of the detection of the ovulation was 96.31%. Only 0.89% of the validation errors were due to software errors and the

remaining 2.8% were due to compliance errors of the users. Excluding users errors the exact determination of ovulation was 99.11%.

In regard to the efficacy to predict the window of opportunity after three measured ovulatory cycles this was the following: accuracy of 88.8% for a window of 3 days before ovulation, the day of ovulation and the 3 days after ovulation.

In the subgroup of woman with recorded pregnancies, it could be shown that after 3.79 months of use (median) pregnancies were observed. In 67.72% in up to 3 months, in 16.36% between 3 and 6 months of use, in 7.27% between 7 and 9 months, in 5.45% between 10 and 12 months and in 1.82% between 13 and 15 months of use of the system (Figure 3 depicts a CFG with ovulation).

Discussion

In one of the first reviews ever published to specify the fertile window by Pryll (1916) [1], a high amount of pregnancies occurred during the Days 6–11 of the menstrual cycles that were recorded. Even if his analyses were not intended to define a fertile window, it shows retrospectively the high variation in the accuracy of this item especially taking into consideration that he described the follicular ovulation days of Schröder (Days 14, 15 and 16) and the follicular ovulation day after Fränkel (Day 20). These data suggest that the follicular phase of those recorded women must have been shorter than expected [1]. Many effects have been taken since then to define with more accuracy the fertile window of the menstrual cycle.

Modern methods available on the market are based on symptothermal systems using the clinical data of menstruation, the single-morning wake-up measuring of the body temperature and

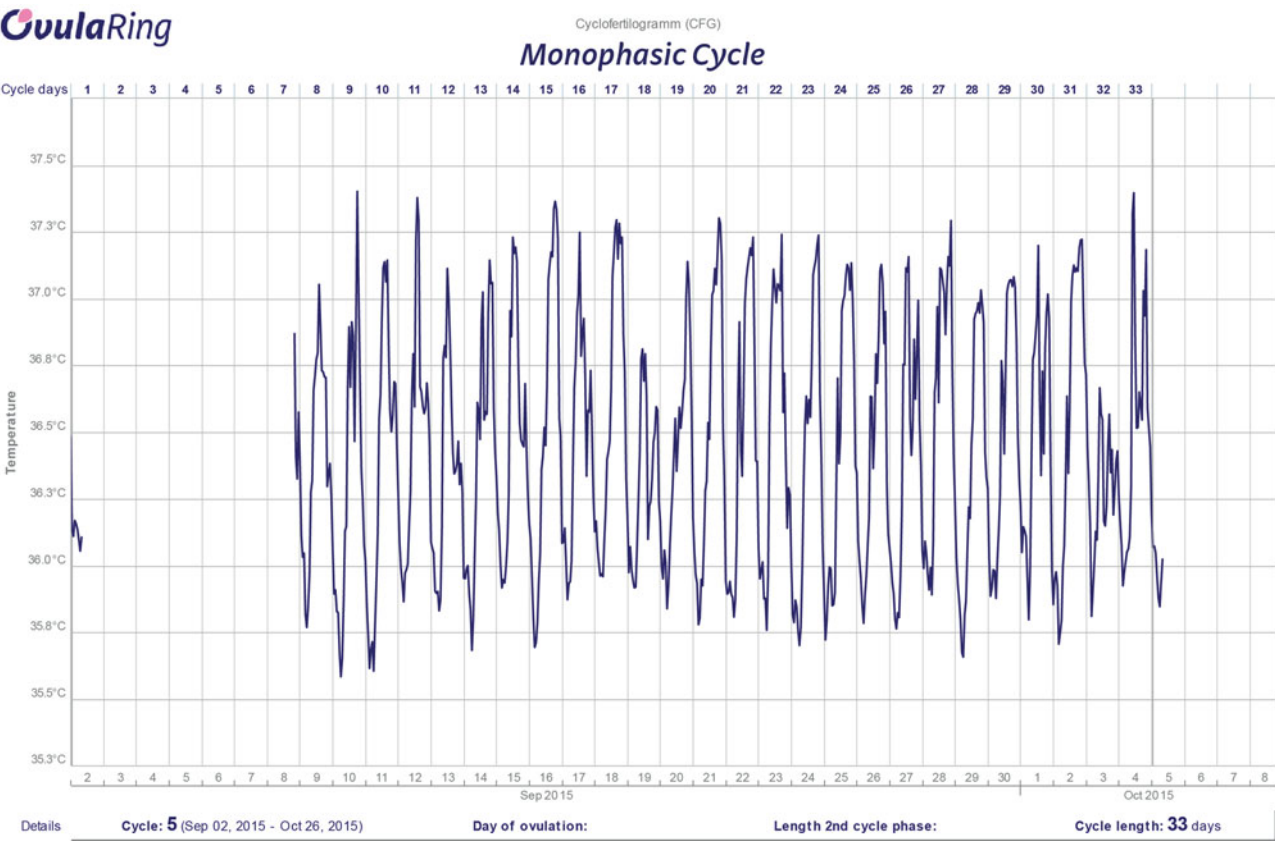


Figure 2. Monophasic anovulatory cycle. No increase in core body temperature can be observed.

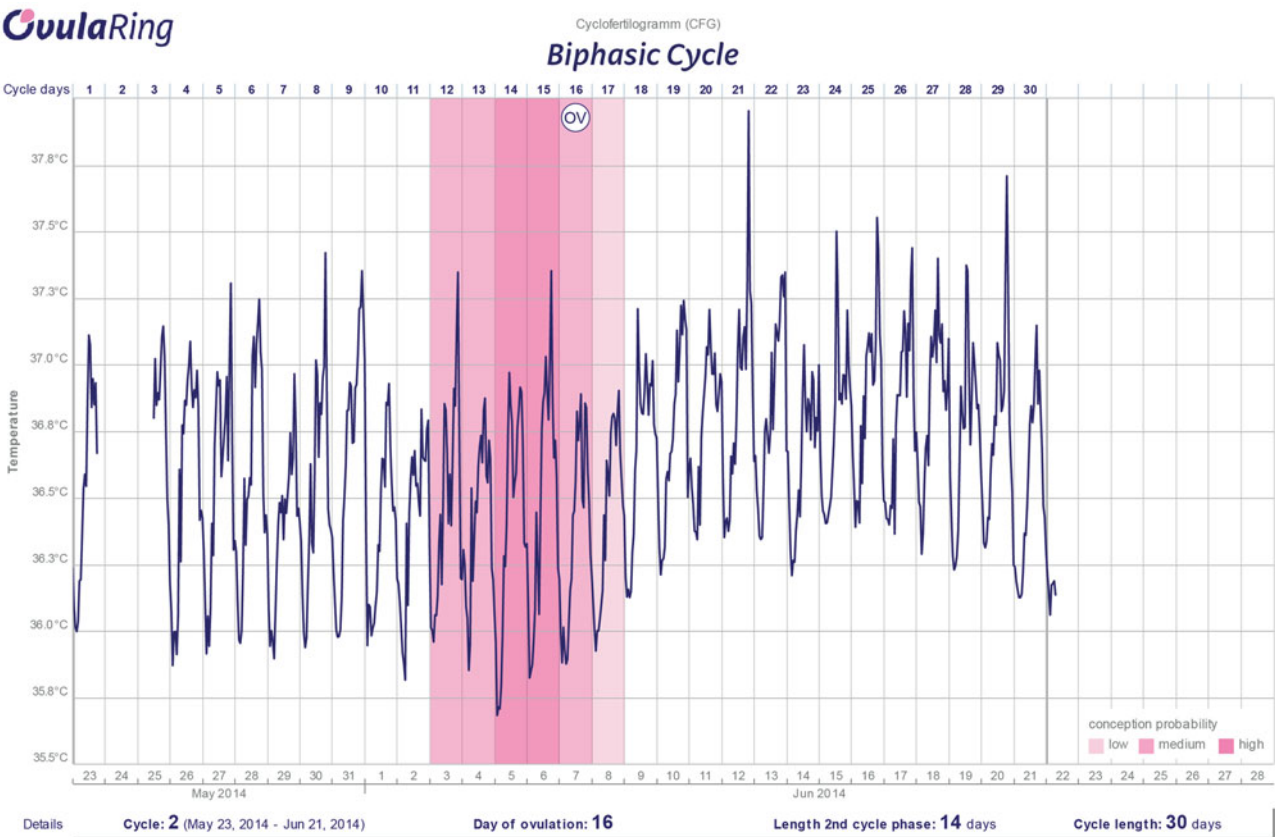


Figure 3. Normal biphasic cycle with ovulation at Day 16.

the observation of the consistency of the cervical mucus [15] or on the determination of hormones in the urine of women. Here, the combination of LH and E3G and also the clinical data of menstruation are used to define the window of fertility [32]. But as shown by Direito et al. [32], the interindividual variability of ovulation detected by ultrasound and LH surge ranged from -6 to $+5$ days demonstrating that also these measuring systems are not able to define precisely the individual characteristics of the female cycles.

The development of a device that measures constantly every 5 min the body core temperature represents therefore an evolution in the accuracy of the determination of the cycle characteristics and the window of fertility. As a continuous circadian and circamensual measurement is performed, a fast and exact awareness of temperature can be achieved. The fact that the rise in the body core temperature occurs not during the supposed time of the morning wake up but in the early night time, so that the accuracy of the main parameter in symptothermal systems is enhanced.

As the rise of the temperature occurs not only after the surge of progesterone [33] and the lowest core temperature is associated with the peak of E3G [32] and as E3G, LH surge and progesterone are not always associated with an exact prediction of the ovulation day [32], the fertile window detection remains complicated.

We could show with our new development that, using a consumer-friendly system that doesn't require urinary sample collection and allows a free daily behavior of the users and is applicable for women with continuous changing working and sleeping times, a precise ovulation day determination of 96.5% in retrospective cycles and in 88.5% in prospective cycles with a window of 7 days could be described.

This will help women in their realization of conception as they will improve their own knowledge of the fertile window.

Disclosure statement

Prof. Dr. P.-A. is Medical Director of Exeltis West Europe & Germany.

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