2022

breathe ilo

CLINICAL EVIDENCE PAPER

breathe ilo

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breathe ilo: Clinical Evidence Paper

1. LITERATURE REVIEW

Respiration varies considerably during the female menstrual cycle, with the current literature detailing significant rhythmic variations at different time points.[1] The peer-reviewed research literature suggests that these changes result from progesterone and oestradiol and its role in stimulating a persons' respiratory drive. Although the exact mechanism remains unknown, studies suggest that this influencing occurs either centrally or via the peripheral chemoreceptors.[2] A literature review was therefore conducted to shed some light on these respiratory variations and also identify how these changes reflect on carbon dioxide partial pressure (pCO_2). A systematic search of PubMed and Scopus was conducted to identify all relevant research. Furthermore, a leading researcher in this field was consulted to expand on the existing literature concerning the biphasic pattern of pCO_2 throughout the menstrual cycle.

Fluctuations in End-Tidal Carbon Dioxide Pressure

Fluctuations in the pCO_2 during the menstrual cycle are a physiological phenomenon that is well known and described since the 40s of the last century.[4] The target value of CO_2 significantly increase between the follicular and luteal phase and significantly decrease between the luteal and menstrual phase.[3] This leads to a decrease in end-tidal carbon dioxide pressure ($P_{ET}CO_2$) between the follicular and luteal phase and an increase before and during the menstrual phase. The biphasic phenomenon itself was investigated in greater detail by Doering et al. in 1948, which observed a substantial change in pCO_2 two days prior to ovulation.[4]

A research described by Jacob et al. in 1997 confirmed a 4-8mmHg change in $P_{ET}CO_2$ around ovulation,[6] with the decrease occurring 1-8 days (median of 4.5 days) prior to the LH peak.[5,7] Identifying the fertile phase of the menstrual cycle through biphasic changes in $P_{ET}CO_2$ was investigated in a 2008 trial conducted by Hadžiomerović et al which is underpinned by the research by Jacob et al. Here, the $P_{ET}CO_2$ was measured across 195 menstrual cycles in 160 women who had a history of regular menstrual cycles. Blood samples were collected from 145 participants and LH, E_2, and P were determined from cycle day ten to the day of the LH peak, while urine test samples were used to determine LH in 15 additional participants. The results demonstrated that $P_{ET}CO_2$ followed a biphasic pattern with the luteal phase pressure values being lower than during the follicular phase by an average of 6.5mmHg. These observations were consistent across all participants included in the study and suggest a characteristic pattern of carbon dioxide pressure throughout the menstrual cycle.[5]

The body of research from empirical studies consolidates that $P_{ET}CO_2$ decreases around ovulation and is significantly lower during the luteal phase compared to the follicular phase.

This observation suggests that CO_2 concentration is superior to basal body temperature as a parameter for predicting a woman's fertile days, as fluctuations in $P_{ET}CO_2$ occur before and during ovulation, providing users with advance warnings that ovulation is about to occur. Basal body temperature measurement, on the other hand, can only indicate when ovulation has already occurred. Until recently, measuring CO_2 levels in a convenient way and at home has not been possible due to the lack of clinical capnometers available to the general population.

2. breathe ilo DEVICE

The breathe ilo device presents a solution to this challenge, with its technology making home testing of $P_{ET}CO_2$ easy and affordable by offering a similar precision level to clinically used capnometers. As the breathe ilo device is an easy-to-use tool for women who want to learn more about their bodies and the individual patterns of their menstrual cycle or want to get pregnant.

Changes in a person's CO_2 partial pressure can be accurately detected by the breathe ilo device. This device has been developed to support the monitoring of the menstrual cycle for women between the age from 18 to 45. The two primary focuses of breathe ilo are for women to learn more about their bodies through analysis of their cycle patterns and also to assist women trying to get pregnant by identifying the time of ovulation and proving ovulatory cycles. In this section, we will discuss the device in more detail, providing information on how it works, how samples are taken, and the mode of operation.

2.1. How it Works

The technology used within the device is similar to a capnometer, with the measurements being taken via infrared spectroscopy. A capnometer is the most prevalently utilised method of measuring CO_2 levels in the exhaled gas and is widely adopted to monitor the respiratory status of patients in the clinical setting. The difference is that breathe ilo is small, easy to use and brings capnometer technology to the patient's home.[8] The breathe ilo system consists of four main components: the handheld device, also known as the breath gas analyser, a smartphone app available for both Android and iOS users, a mouthpiece, and a nose clip. To use the device, the user will breathe through the mouthpiece, which has been designed for long-term, sustainable usage.

The two key components of the analytic software are as follows:

1. The raw signal provided in the breath sample is pre-processed by the handheld device, whereby the data are filtered to ensure only the required data are transferred to the smartphone app. This transfer of data is carried out via Bluetooth, with the app continuously syncing with the cloud to ensure the data are backed-up and can be accessed from various devices.

2. The smartphone app then conducts the second portion of the data analysis. Here, the pre-processed data are used to calculate the fraction of CO_2 which is exhaled during breathing. This creates a calibration curve specific to the user's device, which is continually updated through a self-learning algorithm that processes new data alongside the historical data of each user. Daily collection of these values gives an accurate timeline of the user's fertile phase during their cycle.

Beyond the highly precise measurement, we have implemented an advanced data algorithm to process the raw data and several quality checks in our device to consider the impact of environmental factors. For example, the device will recognise an uncommon breathing rate and recommend that the user repeat the sample and differences in air pressures are considered and corrected to comparable levels in the algorithm.

2.2. Sampling with the Device

The breathe ilo device requires a 60 second breath sample that can be taken at any point during the day, as $P_{ET}CO_2$ levels do not have a circadian rhythm and so do not fluctuate throughout the day. pCO_2 does not follow a circadian clock, studies demonstrates a significant two-hour and 24-hour stability of pCO_2 in women.[9] Therefore, breath samples for measuring $P_{ET}CO_2$ can be taken at any point during the day. The sampling time for 60 seconds guarantees that the algorithm will observe several $P_{ET}CO_2$ peaks from the user that will provide a solid set of data from which to obtain a stable median value for the $P_{ET}CO_2$ value.

breathe ilo is not calibrated for absolute CO_2 measurement as the focus of our technology is to detect the change in patterns. As a result, we exclusively compare the relative CO_2 changes with gold-standard devices. When compared to a clinical-grade stationary reference device, changes in CO_2 levels detected with the breathe ilo device achieved a less than 1% measurement error, in line with our precision goal.

3. METHODOLOGY

The field study was conducted with the company's clinical partner Fertility Clinic Potsdam over a one-year period. The four days prior to ovulation, the day of ovulation and the day after ovulation (as the oocyte can be fertilised up to 24h after actual ovulation) were recorded as a possible six-day fertile window. Although the number of fertile days in the female menstrual cycle are difficult to specify. According to a study by Wilcox, their data suggest that the fertile period lasts about six days and ends on the day of ovulation. This is consistent with indirect observations regarding sperm survival. This is because sperm retain the ability to fertilize an egg for up to five days in the female reproductive tract.[10] The primary endpoint was how many of these days were accurately detected by the breathe ilo device.

3.1 Participant Selection

The total sample comprised 36 participants, spanning 92 menstrual cycles, with data being included from 33 participants and 77 cycles. Data were included in the final sample if the participant had a menstrual cycle between 21 and 45 days, and five or fewer measuring errors, inclusive of missed measurements, during the study period. This final sample subdivided into two reference groups; one group handed hormonal test strips for home testing and one group regularly visiting the Fertility Clinic Potsdam. Before the study, participants were assessed for eligibility via a self-questionnaire and were included if they were: a) aged between 20 and 38 years, b) were not taking hormonal contraception, c) had two previously normal cycles, averaging between 21 and 36 days.

3.2 Measurement Protocol

As discussed in Section Two, the breathe ilo device requires a 60-second idle breath sample that can be taken at any point during the day. If the device detects uneven breathing, the user is instructed via the app to repeat the measurement to ensure breathing is idle and that the validity of the data is not compromised.

3.3 Reference Methods

The reference ovulation day was determined by Blood E2, LH, and progesterone testing for the test group that regularly visited the fertility clinic. These tests were carried out by fertility expert Moeller at the Fertility Clinic in Potsdam prior to and post-ovulation for 16 cycles and were used as the gold standard clinical reference. For the self-testing group, the ovulation day was determined by combined (Estradiol and LH) hormonal ovulation urine test strips, specifically Clearblue strips, for 61 cycles. The maximum fertile day according to the test plus a possible deviation of one day was taken as the ovulation day. These references were conducted in parallel with the breathe ilo device. The doctors selected the reference group for participants, with the Clearblue test being carried out at home whilst the blood testing was conducted at the clinic.

3.4 The breathe ilo Algorithm

The algorithm employed by the company is a self-learning algorithm that continually incorporates individual user patterns from previous cycles. Besides tracking the measured pCO_2 levels of each user, the breathe ilo device also compares the patterns observed to a large cycle database, taking into account user entries. This enables robust results to be displayed to the user, based on a comprehensive, holistic analysis of the ongoing cycle.

3.5 Statistical Analysis

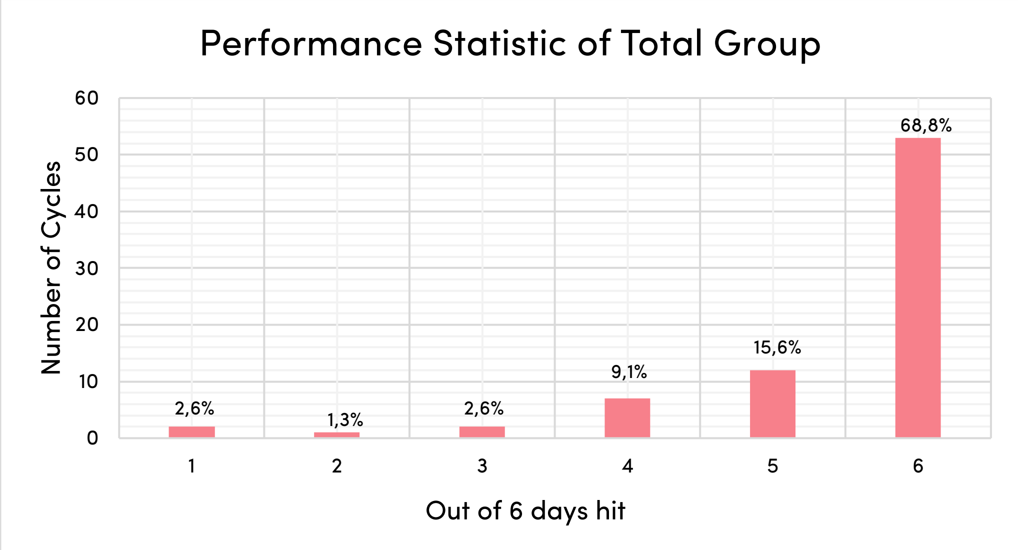
The four days prior to ovulation, the day of ovulation and the day after ovulation were recorded for the breathe ilo device users and the clinical and the urine test reference groups. Performance statistics were then computed to compare the breathe ilo algorithm's accuracy with the reference groups' results.

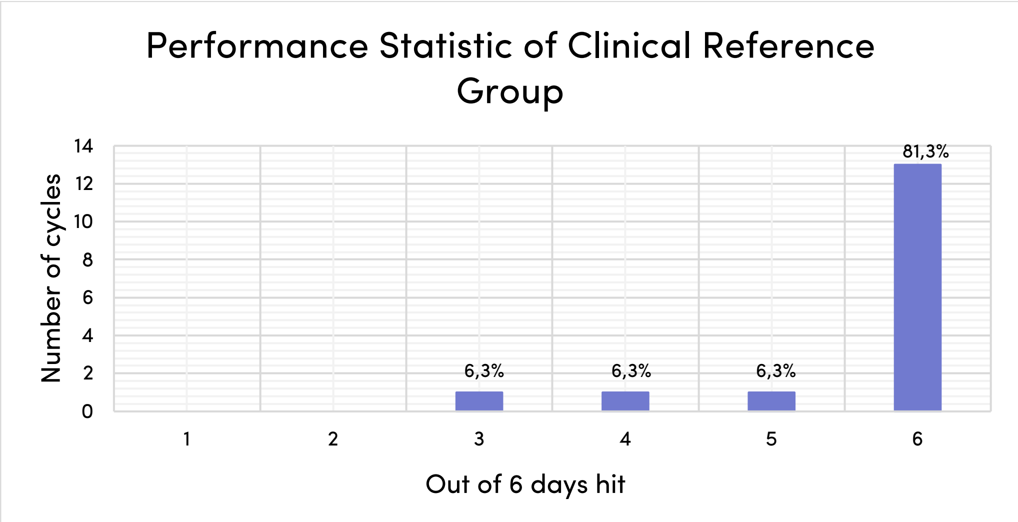
4. RESULTS

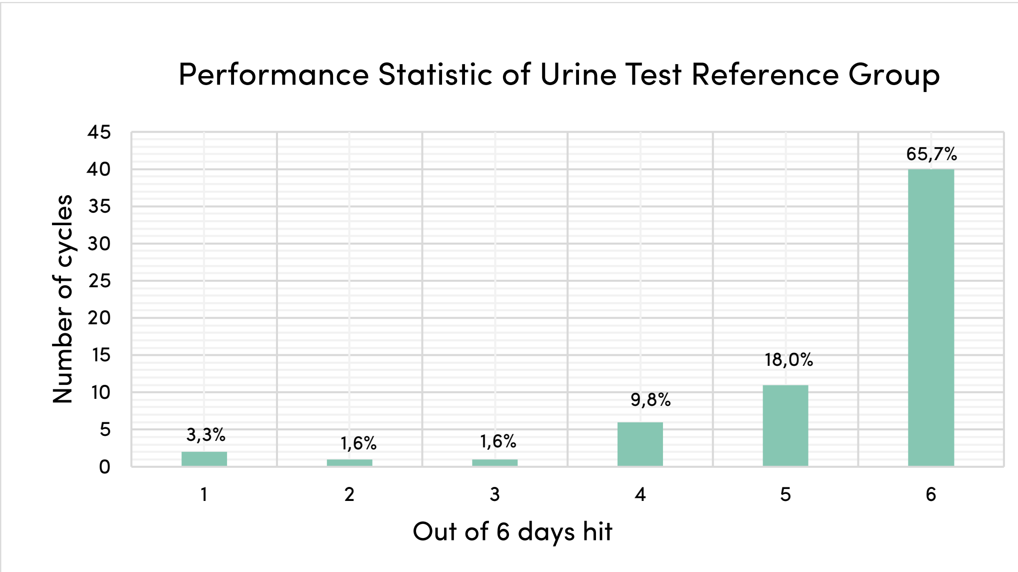
4.1 Performance Statistics

It is evident from the three graphs presented that there is consistency between the participant samples and the number of ovulation days accurately predicted by the breathe ilo device and reference measures. A 100% accuracy results if on average the participants of all groups hit all 6 out of 6 possible fertile days. The clinical reference group achieved the highest accuracy, at 94%, followed by the total group at 90%. The urine test strips attained an accuracy of 89%.

The following graphs illustrate the number of cycles recorded and how many of the 6 possible fertile days were hit per reference group.







The clinical reference group predicted the greatest number of ovulation days out of the three samples, achieving six out of six days in 81.25% of cycles. Overall, the breathe ilo device predicted six out of six days in 68.83% of cycles.

Although not significantly proven, the results of the breathe ilo device strongly correlated with the clinical reference test, indicating that the device may be superior to hormonal test strips (Table 2).

Table 2 – Group performance.

	Number of Cycles (%)		
Out of Six Days	Total Group	Clinical Reference Group	Urine Test Group
1	2 (2.60)	0 (0.00)	2 (3.28)
2	1 (1.30)	0 (0.00)	1 (1.64)
3	2 (2.60)	1 (6.25)	1 (1.64)
4	7 (9.09)	1 (6.25)	6 (9.84)
5	12 (15.58)	1 (6.25)	11 (18.03)
6	53 (68.83)	13 (81.25)	40 (65.67)

4.2 Sample Characteristics

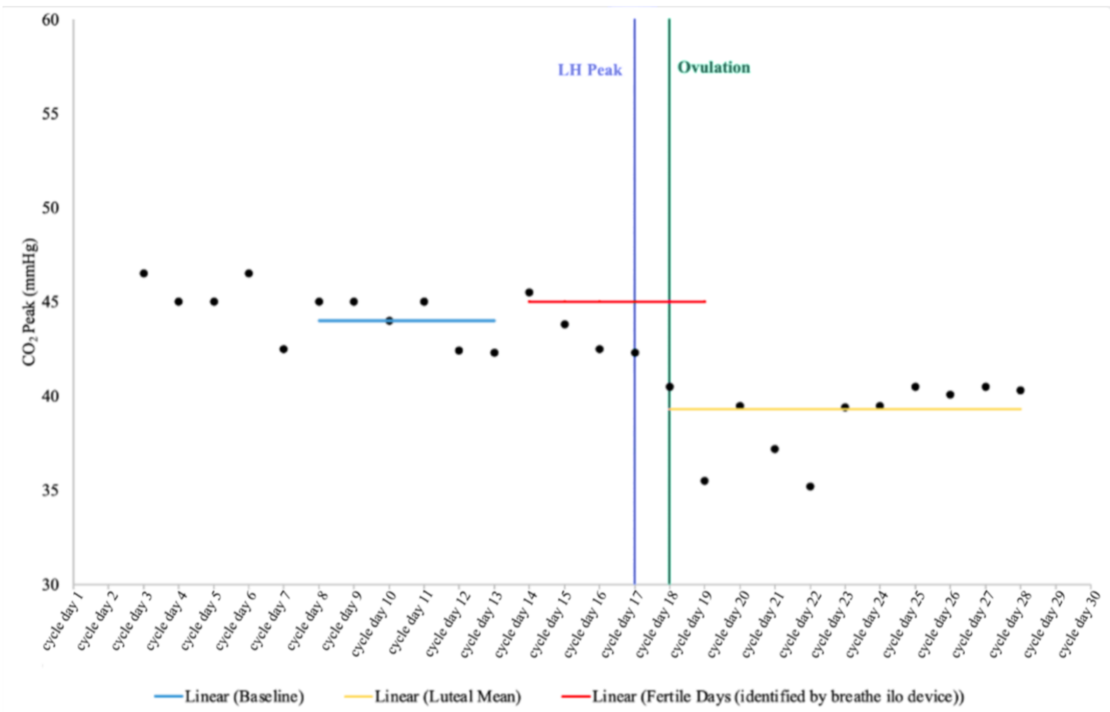
A total of 33 participants were included in the sample, with a mean age of 29.82 years (Table 1). The average age of participants was consistent in both the clinical reference and urine test group and was representative of the general population. Moreover, the range for the clinical reference and urine test groups was 25 to 35 years and 24 to 34 years, respectively.

Table 1 – Sample characteristics.

	Mean Age (years)	Number of Users	Number of Cycles
Total Group	29.82	33	77
Clinical Reference Group	29.88	8	16
Urine Test Group	29.80	25	61

4.3 Fluctuations in End-Tidal Carbon Dioxide Pressure

As evidenced in the graph below, a biphasic CO_2 pattern was observed throughout the menstrual cycle. An elevated plateau occurs prior to the LH surge and ovulation, whilst a decreased plateau is observed post-ovulation. The breathe ilo device identified the window of fertile days between day 12 and day 17, with ovulation on day 16. These data points represent the four days prior to ovulation, the day of ovulation and the day after ovulation.



5. CONCLUSION

The breathe ilo device is an effective method to accurately determine the cycle phases in women aged 20 to 38 years. This includes a prediction of the ovulation day plus four days before ovulation, the day of ovulation and one day after ovulation. The device obtained an overall accuracy of 90% while at the same time predicting six out of six fertile days (100%) in 53 out of 77 cycles. Although these findings should be continuously investigated in larger participant samples, it is evident that a relationship exists between CO_2 levels and the phases of the menstrual cycle. Moreover, the accuracy of the breathe ilo device is well comparable to the reference measures. These data plus the tremendous user convenience (breathing vs. urine testing) suggest a forthright advantage to other methods of natural family planning and menstrual cycle tracking.

6. REFERENCES

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