Prediction of Fertile Window Using a Contact-Free Under-the-Mattress Sensor

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Abstract

The purpose of the presented study was to evaluate the performance of a novel contact-free under-the-mattress sensor in prediction of women's fertile window (FW), at home environment. Thirty eight normal-ovulatory women at the age of 22-40 years took part in the study. Heart rate, heart rate variability, and respiration rate values were measured during a period of 3-6 months. These measurements were recorded at home environment, during night time, using a contact free sensor positioned under the participant's mattress. Predictions of the FW were obtained using an algorithm based on the sensor measurements and menses dates, as reported by the participants. For each participant, and each cycle, the "Gold standard" reference ovulation day was established by daily blood tests to measure hormone levels (LH, estrogen, and progesterone), and transvaginal ultrasound scans to follow follicular growth and rupture. All of the blood hormone tests and the ultrasound test were conducted and reviewed by expert physicians to determine the actual ovulation day and the potential FW. The accuracy of the sensor FW prediction was calculated as the overlap between the "Gold standard" reference and predicted FW (based on sensor's measurements). Comparisons were also made to standard methods of FW prediction, which relies on the duration of a woman's previous menstrual cycles.

Overall, a total of 354 menstrual cycles were recorded. Predicted FW overlapped 61.3 % ± 5.0 % (Mean ± SE) of the "Gold standard" reference after the first menstrual cycle and 70.9 % ± 5.1 % after three menstrual cycles. In comparison, the "Simple calendar estimate" average overlap was 52.3 % and the "Multi month estimate" overlap after three cycles yielded results that were at least 10 % lower than the sensor's results.

The results suggest that the use of a contact free sensor enhances the ability to accurately predict the FW as defined by the expert reference. Alternative available methods for fertility prediction, require the user to follow a strict protocol, such as measuring basal body temperature or urine LH levels, on a daily basis at morning time. The new contact free sensor requires minimal compliance from the user and may increase the chances to conceive, compared to the standard prediction method based only on the duration of menstrual cycles.

1. Introduction

Correctly identifying the fertile window (FW) could play a crucial role for those who attempt to conceive. Nevertheless, as its timing and length may vary within and between individuals, it was proven hard to determine in any given instance when the FW occurs (or will occur) and how long is it [1]. For that, there are many methods aiming to detect FW. The most accurate and validated techniques require medical examination (i.e., transvaginal ultrasound and tracking reproductive hormones using blood tests). However, the rate of success and precision decreases rapidly and complexity increases as the woman leaves the clinic and attempts to identify her approaching FW independently. Popular methods range from prediction of ovulation day based on average cycle length and the assumption of constant luteal phase duration, to daily measurements that try to measure physiological changes such as body temperature at the early morning (Basal Body Temperature, BBT), observation of cervical mucus or tracking the luteinizing hormone (LH) level changes using a daily urinary test [2]. These methods require compliance, are frequently cumbersome, and their results are comparably low [3]. Moreover, detection of rise in BBT or LH indicate the end of the FW and might be too late to allow for successful conception.

Evidence suggest the involvement of different reproductive hormones in the cardiovascular system changes [4, 5], mainly the progesterone and estrogen. Heart rate (HR), respiratory rate (RR) as well as heart rate variability (HRV) tend to oscillate throughout the different menstrual phases [6, 7]. HR rises during the luteal phase, presumably due to the corresponding progesterone surge which affects basal body temperature. RR is relatively low during the end of the follicular phase and the ovulation phase and increases toward the menses. Similarly, the high frequency (HF) variability of the HR during sleep follows the same pattern, i.e. comparatively low during the ovulation phase and rises toward the menses.

Furthermore, relationship between the menstrual cycle and cardiovascular activity were also found during sleep. For example, it was shown that the HF component of the HRV is lower during the mid-luteal phase, compared to the late-luteal and follicular phases in both rapid eye movement (REM) and non-REM sleep stages [8]. In addition, HR was relatively higher in the mid-luteal phase, compared to the late-luteal and follicular phases during sleep.

The time of sleep, and even more specific, the end of the night, is considered to be a time in which the body is in 'baseline mode', thus, any effect of previous day's activity, e.g., eating, drinking, sport activity, stress of any kind, is thought to be reduced to minimum. This may be the reason that trying to predict the FW by measuring cardiovascular performance during daytime led to mixed results and that existing in-home methods and solutions target the measurements to the end of the night.

Ideally, a preferred solution for tracking the menstrual cycle at home entails easy-to-use solution that is as automated as possible, measures baseline at the night, and removes the compliance issue. Recently, a study that tried to meet these requirements tracked the woman's HR using a wearable device (a photoplethysmographic sensor, located on the wrist) and found a significant HR differences between different time periods within the menstrual cycle, specifically, the time of ovulation, the mid-luteal term and the menses [9]. While the above study utilized a wearable device that requires some compliance of actually wearing the device to bed every night, EarlySense has developed a contactless fertility cycle monitoring device that is placed under the mattress and continuously monitors HR, RR, HRV and other sleep parameters [10]. The system includes a piezoelectric sensor that is installed once under the bed mattress and in no way contacts the person in bed. A software package downloadable on a smartphone or tablet analyses the recorded physiological signals, tracks the woman's cardiovascular activity, and uses this information to calculate her fertility cycle.

The aim of the current study was to establish the accuracy of the predicted FW based on continuously tracking the menstrual cycle at the home of the woman. It is reasonable to assume that predicting the FW at home, with minimal disturbance to the woman's life as possible, will serve as a preferable solution for those who are interested in better identifying their FW not in the context of professional or medical settings with a highly automated system.

2. Methods

2.1. Study population

The study included 38 women at the average age of 32 (range: 22-41), weight 61 kg (48-90), BMI 22 (17-30). All participants were healthy, with normal menstrual cycle and no known ovulation or fertility issues. The study was approved by the local Institutional Review Board (IRB) committee of the Herzliya Medical Center. Written informed consent was obtained from each participants.

2.2. Protocol and data acquisition

Following the women's consent, the participants were provided with a piezoelectric sensor (EarlySense, LTD) to locate under their mattress, preferably under their sternum when lying on their bed, and an application to install on their private smartphone or tablet. If known, the participants were asked to fill-in their last menses' dates. After the installation was completed, the system automatically tracked and recorded respiration and cardiovascular activity during night time in which the woman was in bed. The participants were also asked to document in the application their coming menses dates, once attained.

2.3. "Gold standard" reference and testing

In order to assess the ability of the algorithm to accurately predict ovulation time window, each of the participants was requested to come for 4-12 in-clinic visits during each of her menstrual cycles and take a medical examination which included the following tests:

- Transvaginal ultrasound which measure the follicular growth and the thickness of the uterine lining.
- Blood tests that measure the estrogen and progesterone levels in the blood as additional indicator of the follicular growth and ovulation.
- Appropriate blood tests to confirm pregnancy (if applicable).

The results of the above tests allowed the medical experts to determine ovulation dates. These dates were documented and used as "Gold standard" reference for offline comparison analyses.

2.4. Data analysis

The data analysis was conducted offline. For each of the nights of all participants, the system used the piezoelectric sensor data to measure HR and RR throughout the night. In addition, the system ability to identify sleep stages allowed the extraction of HR and RR during the non-REM time intervals. Previously, a study that aimed to validate the system capability in measuring HR, RR, and sleep performance indicated for 96.1 % and 93.3 % accuracy rate for HR and RR, respectively, and in terms of sleep stages, an accuracy rate of 90.5 % [10]. In addition, a dedicated algorithm was developed to process and analyze, for each of the participants and for all of the menstrual cycles, the sensor data and the logged menses dates. The result of the algorithm was a prediction of in which dates the next FW should occur as well as the prediction of the next menses.

2.5. FW prediction algorithm

The Algorithm was divided into two parts: the learning phase and the FW prediction phase. The purpose of the first phase (learning) was to select the features that will be used to predict FW time window. The process compared, for each of the examined features, for each women and for all menstrual cycles, the feature's values in the three days before the ovulation window and the three days after the ovulation window and tested different threshold values that yielded a success rate which means how many days were correctly characterized as 'before' or 'after' ovulation window. The features that generated the best success rate were selected to be used in the FW prediction phase. Also, for each of the selected features the process computed a weight to be used in the prediction phase.

Prediction: the FW prediction was calculated using a Linear Discriminant Analysis (LDA). At the time of documenting the menses date the algorithm computed a score for each of the previous nights. The score was computed by summing the z score of each of the selected features multiplied by their weights. This resulted in a vector with values that were positive or negative. The algorithm searched the score vector for 'transitions' which were defined as time location in which a sequence of negative scored nights were followed by a sequence of a positive scored nights. The transition that was closest to the estimated FW time location and produced the longest sequences before and after the date of the transition was selected as the date of ovulation. Once the ovulation date of all previous menstrual cycles were available, the following ovulation date was predicted by adding the mean of all previous follicular phases to the date of the current menses.

2.6. Accuracy testing

Analysis of accuracy was performed by measuring the overlap between the FW as detected by sensor technology to the FW as determined by the "Gold standard" reference method (i.e., expert physician decision based on results of the reference tests). FW was considered to be during the 5 days prior to the actual day of ovulation plus the day of ovulation for a total of 6 fertile days [1].

For example, when a FW as detected by the sensor has a 4 day overlap with the reference window, it was calculated that the sensor is accurate by 66% for this specific ovulation cycle.

This analysis (sensor vs. "Gold standard" reference) was also compared to the accuracy of two additional common methods to predict ovulation day and fertility window as following:

Method 1: "Simple calendar estimate" is a common method used by physicians and includes an assumption that the duration of the luteal phase is 14 days for every woman. Hence, by subtracting 14 days from the presumed upcoming day of menstruation (based on women's reporting on their previous menses days), an estimation regarding the day of ovulation and accordingly the fertile window is made.

Method 2: "Multi month estimate" is achieved using the same method as method 1, with the difference of calculating the average duration of at least three menstrual cycles, and not relying only on the duration of one.

3. Results

3.1. FW prediction

Figure 1 presents the timeline of a. HR and b. RR throughout the menstrual cycle for all participants as were measured during non-REM sleep. Significant changes were identified in the value of HR between the menses and the late follicular phases (t_{243}=1.80, p<0.01) and between the late follicular phase and the ovulation days (t_{243}=2.45, p=0.01), stemmed from a gradient increase in HR throughout the follicular and ovulation days. Also, the late follicular time period was characterized with a slow breathing rate (15.9 bpm) which was gradually increased throughout the luteal term and reached the value of 16.4 bpm (t_{243}=2.58, p=0.01).

Figure 2 presents the average detection accuracy (overlap %) between the contactless sensor predicted FW vs. "Gold standard" reference, for each month. The accuracy of the "Simple calendar" and the "Multi month" estimations methods relative to the "Gold standard" reference and in comparison, to sensor's detection capability is also presented. Comparisons between the three method results were done using a one-tailed paired ttest. All three methods' initial result was 52.3 % due to the fact that they all based on the same data at that time point- the women's latest menses. However, a relative advantage for the use of the sensor was notified after the first menstrual cycle (61.3 %, 52.3 %, and 56.3 % for the sensor, "Simple calendar", and "Multi month" estimations, respectively). After the second menstrual cycle (3^{rd} point in the graph), significant differences were found between the sensor's prediction rate (62.5%) and the "Simple calendar" (t_{31}=2.44, p=0.01) and the "Multi month" (t_{31}=1.78, p=0.04) estimates. Continuing with the same trend, after the third menstrual cycle (4^{th} point), the sensor was significantly more accurate (71 %) as compared to both the "Simple calendar" estimation (t_{25}=2.54, p<0.01) and the "Multi month" estimation (t_{25}=2.61, p<0.01).

Figure 3 shows an example of one parameter (nightly average respiratory rate) for one participant with 6 cycles. As can be seen in the figure the ovulation is better predicted with the sensor's measurement compared to the estimate based on past cycle length.

3.2. Menses prediction

Following the encouraging results of the FW prediction algorithm, an additional algorithm was developed, aiming to use the above collected sensor dataset and predict the dates of the coming menses.

Improvement of menses prediction was demonstrated in cycles that had sufficient data recorded (occurred in 30% of cycles) and showed an average error of 1.38 days, of these cycles 27% had 0 error, and 57% had an error up to 1 day. This is compared to "Multi month estimate" (average over previous months' cycle length) which resulted in 1.87 days error with 17% 0 error, and 54% with an error up to 1 day.

4. Discussion

The aim of the current study was to examine whether a contact-less sensor that measures cardiovascular activity during the night can help to better predict the user's FW. Overall, the results indicate that the performance of the sensor and its dedicated algorithm outscored other accepted methods.

During the timeline of the menstrual cycle, different reproductive hormones are involved in synchronizing the fertilization process [11, 12, 6, 7]. The end of the follicular phase is characterized with a fast increase of LH (LH surge) to initiate ovulation. Progesterone and estrogen levels elevate after ovulation to support implantation and fall if implantation did not occur. It is apparent that on top of their role in the reproductive system, they influence other systems as well, including the respiration and the cardiovascular systems. The progesterone increase during the luteal phase has positive effect on central noradrenaline release which in turn contributes to an increase in HR. The estrogen surge at the end of the follicular phase reduces RR. These lead to a large difference between the end of the follicular phase and the beginning of the luteal phase. This study's results indicate a significant higher HR values during the ovulation and luteal phases, compared to the menses and the follicular phases [8]. Moreover, a relative low RR was found at the end of the follicular phase, which gradually increases up until the end of the luteal phase. Therefore, the results of the current study support the HR and RR oscillated trends. In addition, the results can be used as evidence for the ability of the contactless sensor to accurately measure HR, RR throughout the menstrual cycle.

For many of those who want to conceive, recognizing the FW is essential. However, this appears to be a challenging concern [1]. Previous works disagree on what is the number of fertile days within the menstrual cycle and it varies between 2 [13] up to 13 [14], highly depended on the specific population and the measurement methods used. Calculating FW based on the time of the previous menses is a straight forward method. Nevertheless, it is based on a guess of what is the length of the current menstrual cycle and of that the length of the luteal phase is relatively stable and lasts 14 days ("Simple calendar estimate"). If the individual's menstrual cycle length is not constant, the average of the last few cycles should improve accuracy ("Multi month estimate"). The results presented in figure 2 indicate that both the "Simple calendar estimate" and the "Multi month estimate" overlapped with the "Gold standard" reference in 52.3% to 65% of FW. The results of the current study's algorithm outscored both conservative methods with an accuracy that reached the level of 71 % after three menstrual cycles.

It is important to note that the potential of the three methods to improve their accuracy as time goes by is different. The "Simple calendar estimate" depends on the last and only month. It assumes strict rules- the lengths of the luteal phase and the menstrual cycle. Therefore, its accuracy, as appears in Figure 2, is rather limited (52.3 %). The "Multi month estimate" relies on several menstrual cycles and therefore is considered to be more precise throughout time due to the fact that the two "Simple calendar estimate"' assumptions are not stable and accurate for all women [15, 16]. This is in accordance to the current study results as the accuracy of the "Multi month estimate" is higher than the "Simple calendar" estimate (Figure 2), however, the difference was not found to be significant. In contrast to that, the current's study algorithm results did improve throughout the months. The advantage for the use of the sensor increases as months pass. Figure 3 demonstrated this notion. In the presented example, both the current study's algorithm and the "Multi month estimate" performed relatively the same at the first two months. However, unlike the current study' predictions, an error evolved in the "Multi month estimate" method as months continued to pass.

5. Study limitations

The population of the current study comprised of women with a BMI of 30 or lower, with no known health problems, with normal menstrual cycle and no known ovulation or fertility issues. However, as the sensor was previously used and tested with obese individuals (up to 400 lb; unpublished data), no reduction in accuracy of HR and RR was noted and therefore no change in the algorithm accuracy is expected. In addition, the respiratory and cardiovascular systems are affected by many daily activities that should be taken into account such as illness, habits of sport, smoking, food intake, and even alcohol consumption. In fact, this was the reason for focusing in non-REM sleep time intervals only in the analysis. It could be assumed that once these behaviours are documented and take into consideration, the algorithm performance and the system's accuracy should improve.

6. Conclusions

The results of the current study suggest that the use of the piezoelectric sensor, enhances the ability to accurately predict the fertile window, compared to the "Gold standard" reference. The sensor's predictive capability was found to be superior to the two most common methods of estimation used based on historical menstruation cycles "Simple calendar" and "Multi month" estimations that are based on women's reporting on their previous menses days.

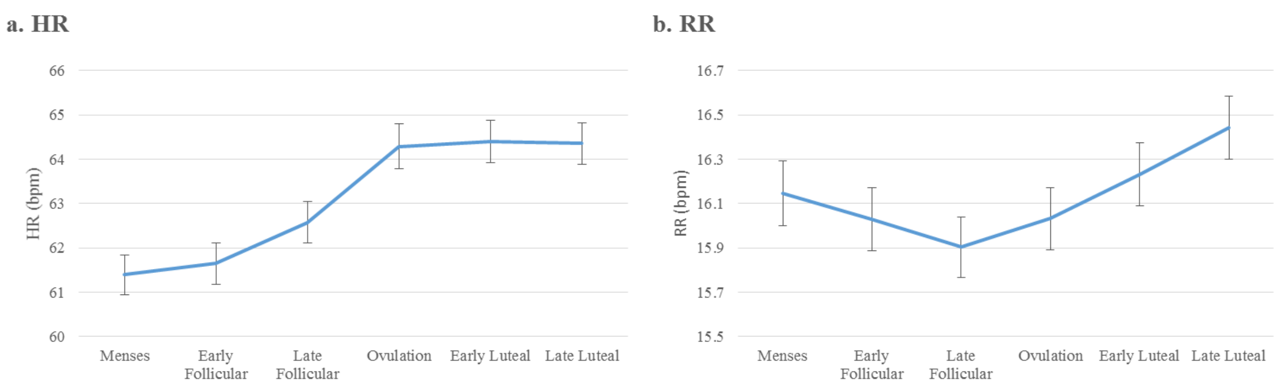

Figure 1. Group mean median (blue line) and standard error (error bars) for a. HR and b. RR during non REM sleep, throughout the menstrual cycle for all participants.

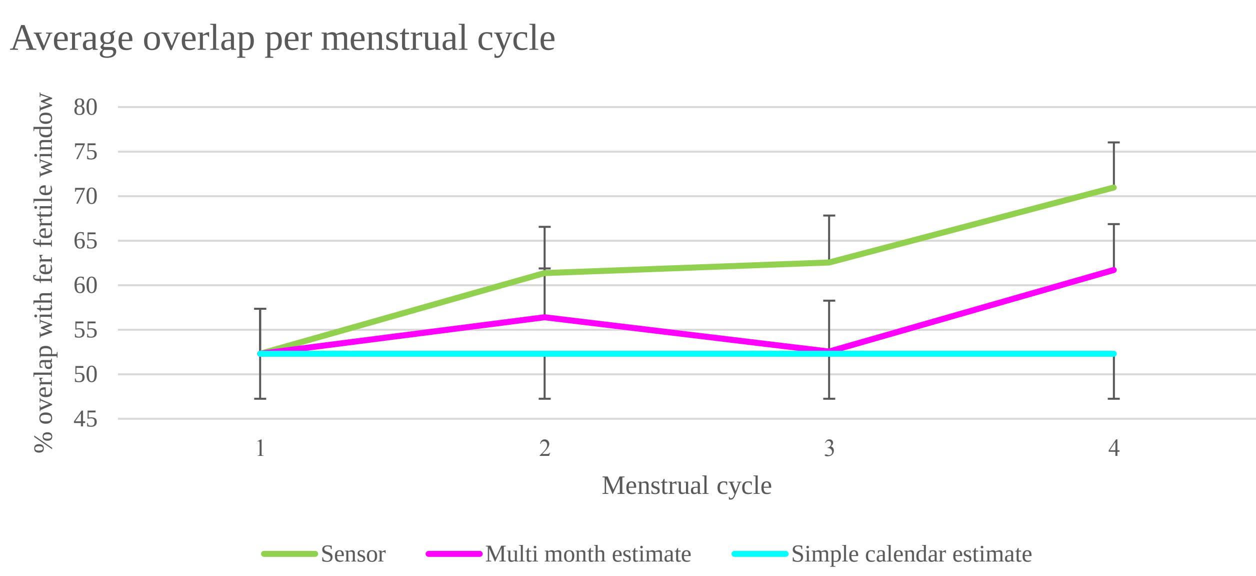

Figure 2: average detection accuracy (overlap %) between the contactless sensor predicted fertility windows vs. "Gold standard" reference, for each month. The accuracy of the "Simple calendar" and the "Multi month" estimation methods relative to the "Gold standard" reference and in comparison, to sensor's detection capability is also presented.

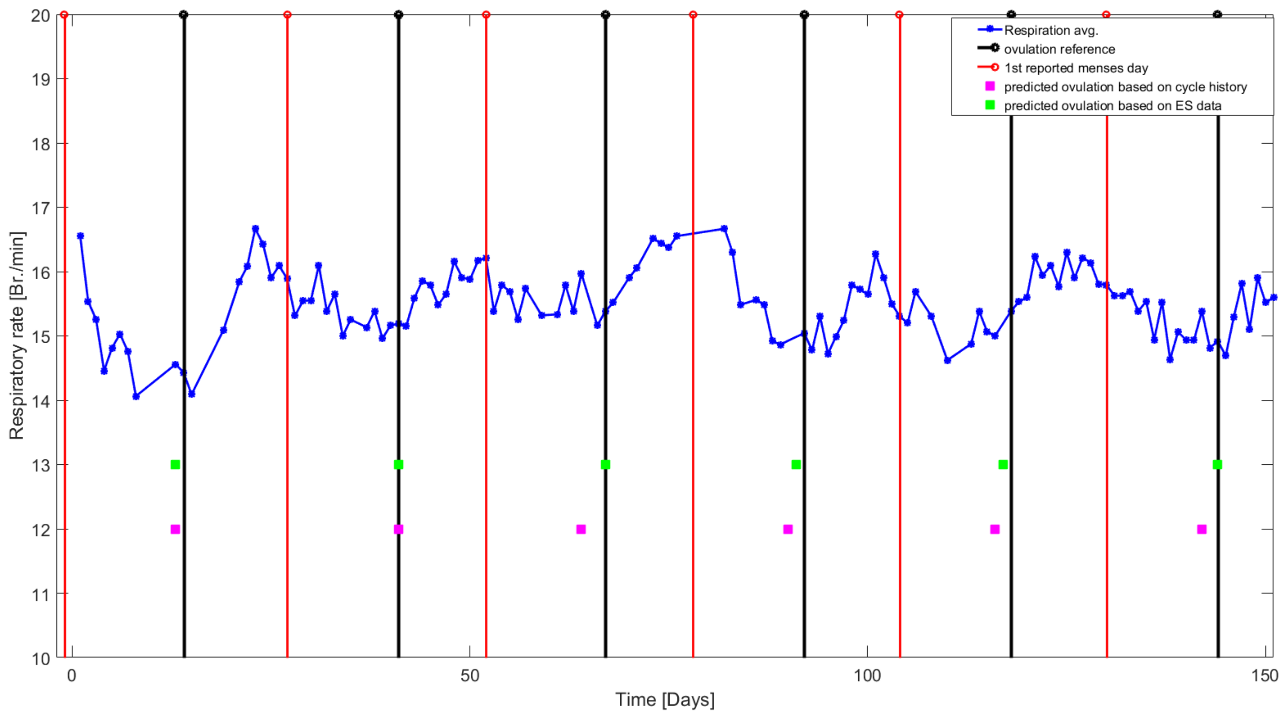

Figure 3: An example of one parameter (average respiratory rate – blue line) during 6 cycles (vertical red lines represents first day of the menses, vertical black lines represents ovulations). The squares indicate the predicted ovulation using "Multi month estimate" (purple) and the sensor's data (green).

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Conflict of interest

This research was supported by EarlySense LTD.

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