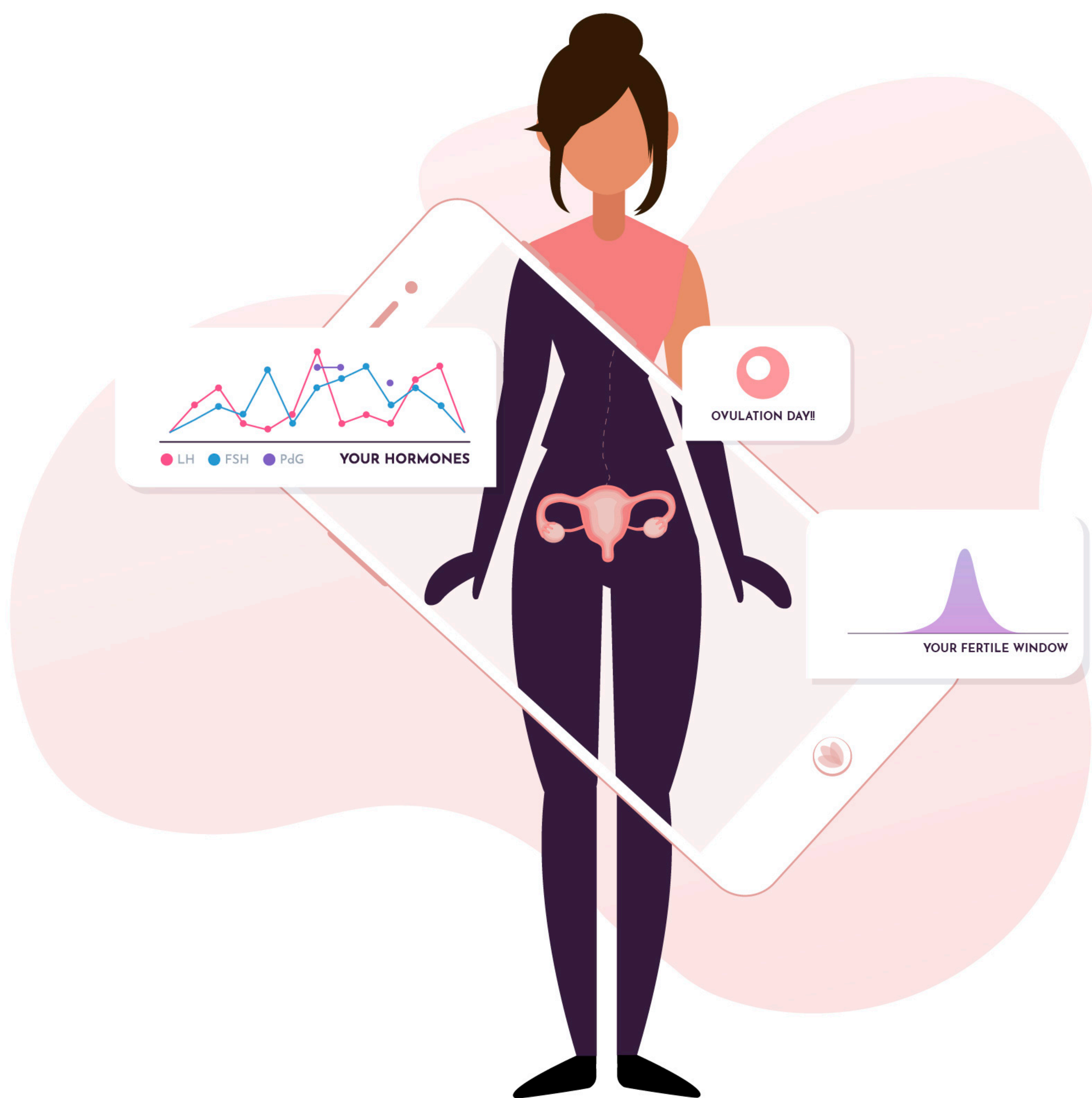


The Pearl Fertility System

Information for Healthcare Professionals



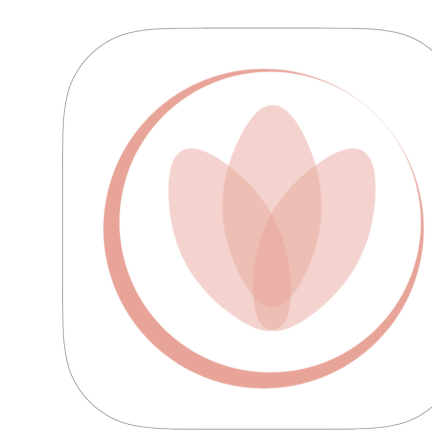
Pearl Fertility



...cycle Insights simplified.

The Pearl Fertility System

Investigator's Brochure



Pearl Fertility

Dec. 2019

The Pearl Fertility App is a mobile tool intended for the estimation of the most fertile days during a woman's menstrual cycle. The App works in combination with urine hormone test strips for a more accurate estimation of Ovulation and the Fertile Days. The hormone tests supported by the Pearl Fertility App are Follicle Stimulating Hormone (FSH), Luteinising Hormone (LH), and Progesterone (PdG). Pearl differs from other cycle tracking apps because it monitors and charts the daily hormone levels. It uses data analytics on recorded hormone profiles to calculate a personalized Fertile Window each cycle. The difference to other OPKs, or ovulation tests, is that Pearl digitizes the daily hormone values of the three hormones directly from the tests. Pearl relies on the Colorimetrix® core technology for smartphone colorimetric analysis.

Hormone Analysis: The ultimate observation of the menstrual cycle

Methods, such as calendar calculations, examination of cervical mucus and a change in basal body temperature, as well as ovarian morphology, have been historically used to monitor and predict ovulation [1]. However, all these methods rely on physiological signs which are in turn governed and triggered by hormonal changes. Therefore, a more direct and primary observation of the menstrual cycle and ovarian activity is the individual hormonal fluctuations [2]. LH, FSH, Estrogen (E), and PdG are four key urinary metabolites [3], largely studied as markers of the cycle because of their abundance, and ease of self-detection at the point-of-care [1]. The relationship between urinary and ovarian excretion rates of such metabolites is well known [5], with strong correlations between urinary and serum concentrations [4].

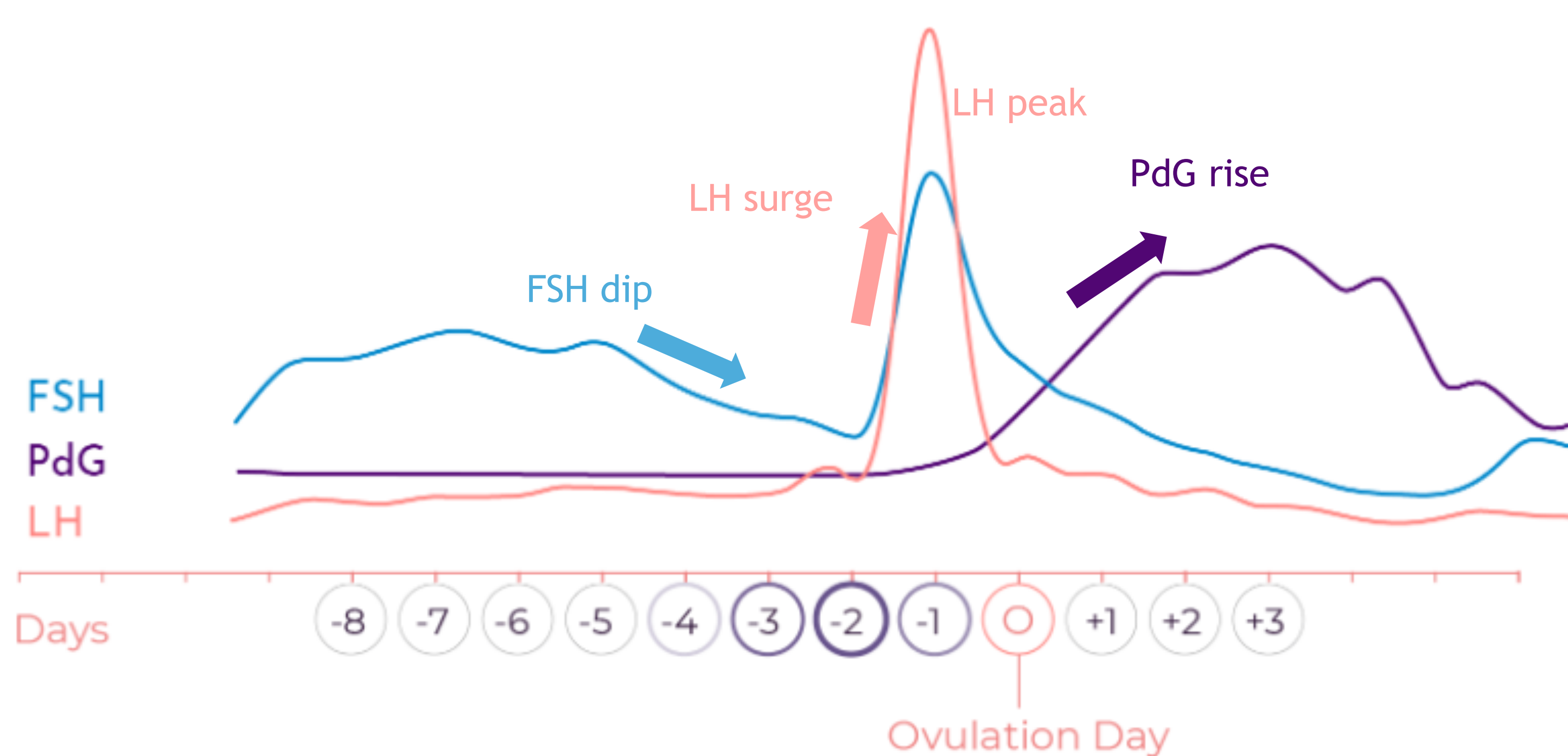


Figure 1. Urinary concentrations of three key menstrual cycle hormones representatives of the three phases of the cycle: Follicular, Transition (ovulation), and Luteal. Averages from Abbot ARCHITECT analyzer study [6].

The variability of the menstrual cycle, and the continuum of ovarian function throughout the reproductive life [7], makes fertility prediction, based solely on information from previous cycles, overly inaccurate [8,9]. Today, point-of-care urinary hormone assays are non-invasive, provide timely results without the need for expensive equipment, and are easier than serum tests [5]. Also, self-testing promotes awareness and responsibility in patients at home [10].

The Fertile Window

The timing of ovulation following the hormonal variations along the cycle: a rise or surge, a peak, or decrease; has been widely studied and predicted with high accuracy based on this evidence [11]. LH has a sharp rise about 24 to 48 hours (av. ~33h) before the ovulation date, this is also referred to as an LH surge or rise [12]. The LH peak occurs around 6 to 28 hours (av. ~17h) before ovulation [12]. Similarly, the FSH level rises 2 to 19 hours (av. ~12h) before ovulation and shortly after LH [13]. FSH has another particular characteristic: it experiences a dip approximately 6 days before ovulation during the variable phase of the cycle.

The Fertile Window usually identifies 3 to 6 days when fertility is highest each cycle, although it can span up to 10 days [14]. After ovulation, the egg survives for up to 24 hours [15], during this time it can be fertilized by sperm, however, sperm can survive from 2 up to 6 days after intercourse [16], depending on sperm quality and interaction with cervical fluid. This gives the characteristic distribution of the chances of getting pregnant from the ovulation date, this is the most important characteristic of the Fertile Window, its correlation to the ovulation day.

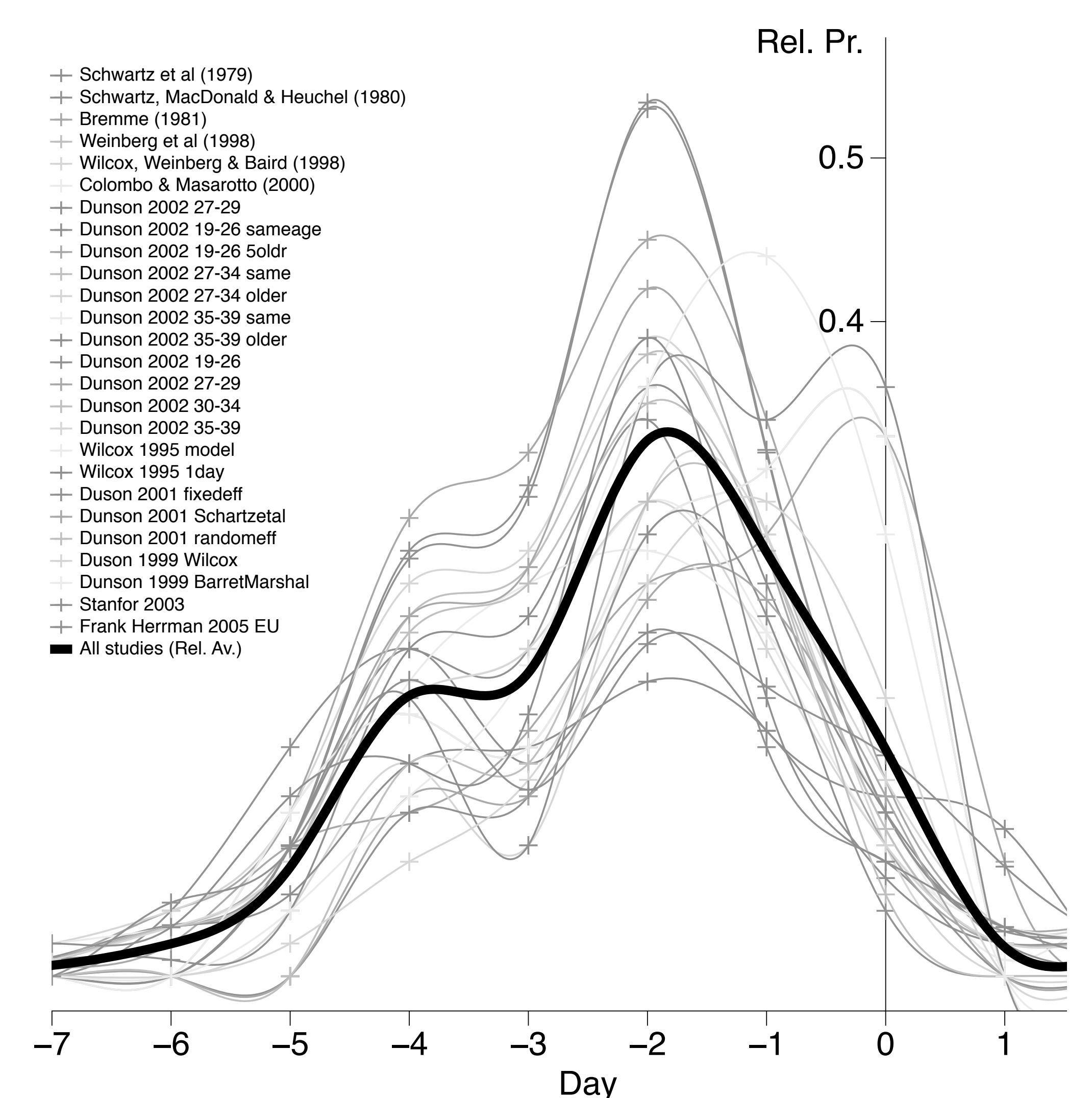


Figure 2. Collection of clinical studies of the Fertile Window characteristics. It opens around day 6 and the highest probability of pregnancy is encountered from days -4 to -1 from the ovulation date [17].

How Pearl reads hormone tests

Pearl relies on the Colorimetrix® core technology for the analysis of lateral flow immunoassays (LFIAs). LFIAs contain a control line, a blank space, and a test line. The test line is the reporter of the concentration. The Pearl test strips all have sensitivities of 25 mIU/mL, which is sufficient to cover the physiological range. The phone camera feed analyzes the color information of each pixel and deconvolutes the color channels into a coordinate system. This coordinate system is then calibrated in the laboratory to a concentration calibration curve, as a result a concentration can be read directly from the tests via the camera module [18]. The algorithms are the same across all the operating system and phone models.

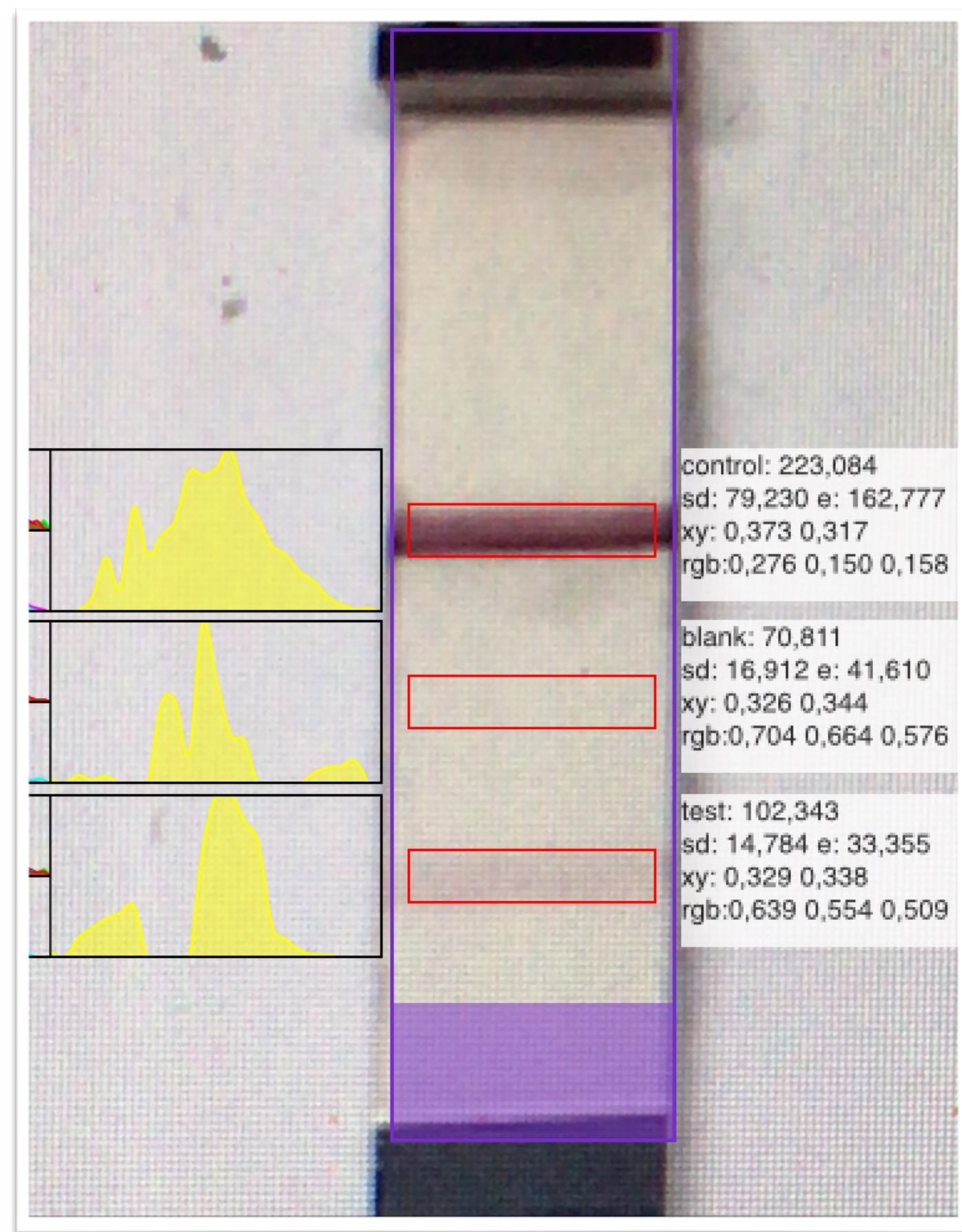


Figure 3. Color analysis by the Colorimetrix® core engine with reading accuracy is 80% [19].

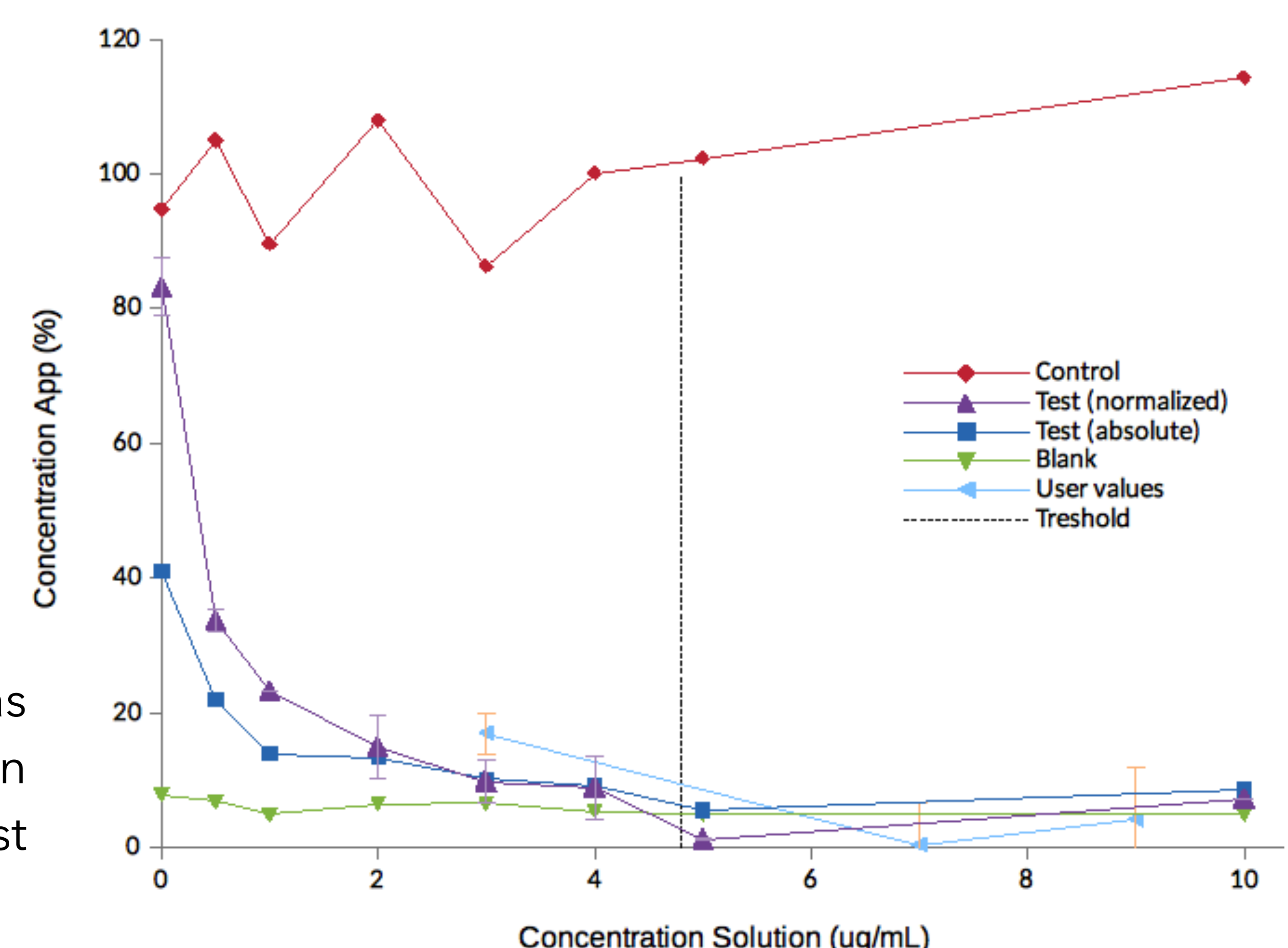
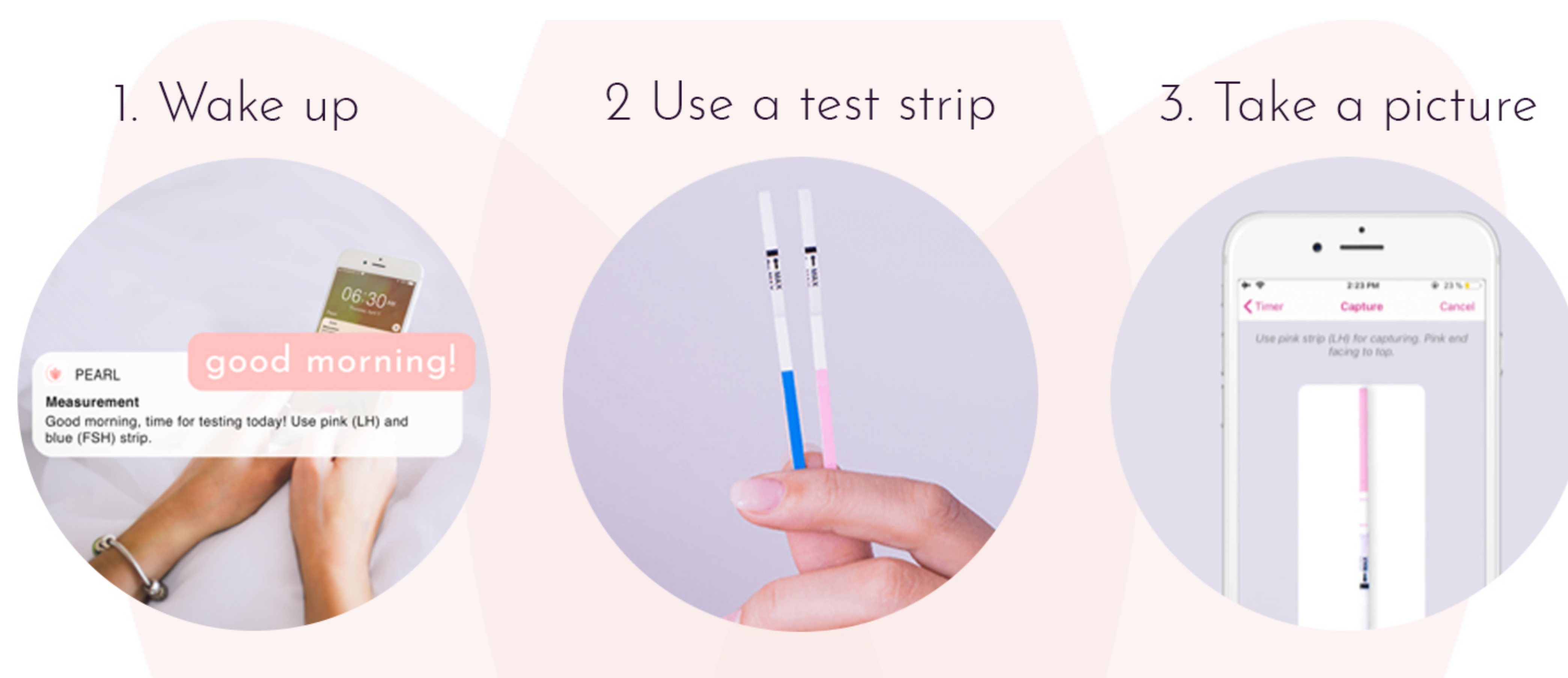


Figure 4. Concentration correlation as measured by the mobile application from standard solutions for blank, test and control lines. [19].

How Pearl interprets hormone profiles

Pearl charts the hormone levels overtime for each hormone independently. The app offers a comprehensive guide on how to test with videos and illustrations, and notifications for the testing schedule.



As a result, the app logs all values for each hormone every day which then are used by the prediction algorithms (see Figure 1). These, algorithms interpret the changes and trends (dips, rises, and peaks) and anticipate the ovulation date.

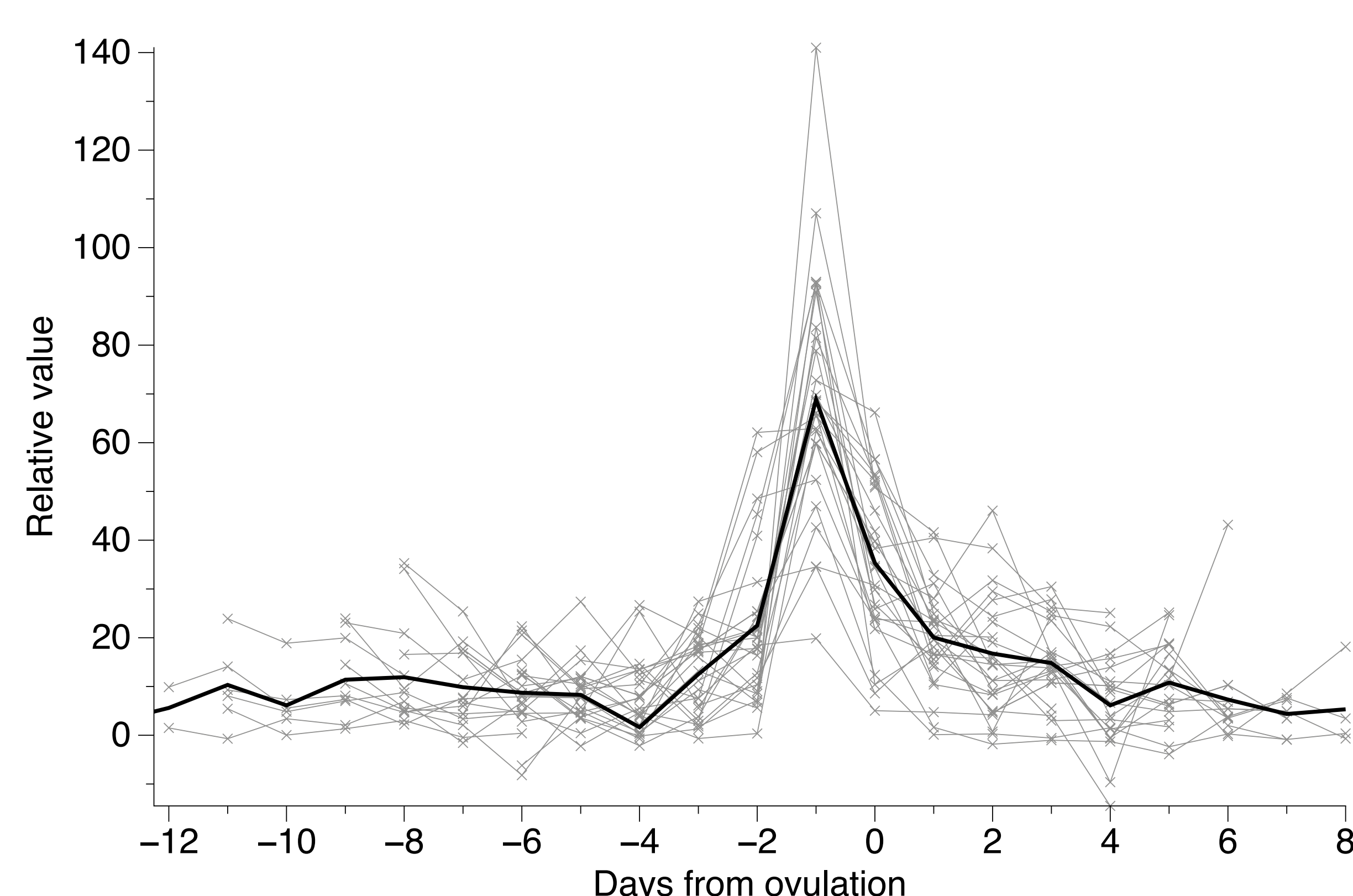


Figure 5. Collection of LH profiles from US clinical study as captured by the Pearl App [19]. Algorithms run over the profile over time to identify trends. Ovulation date is treated a 0 and hormone levels are relative values from the test control, test and blank lines.

The first prediction in the app is made by the FSH downward trend, this prediction is set to be triggered around 6 days before the ovulation date. Then an LH rise algorithm identifies LH rising up to 2 days before the ovulation date. Finally the LH peak algorithm confirms the ovulation date and a PdG threshold algorithm confirms the cycle was ovulatory [21].

Hormonal predictions of ovulation by the Pearl algorithms

The earliest prediction of ovulation is performed up to 6 days in advance with the patented Pearl FSH pattern detection algorithms [22]. At first the app does not know anything about the user, except their age, with this information the Pearl app is able to display an average menstrual cycle duration from an age-cycle length database, and with this information and the known statistical averages, then an estimated ovulation date and fertile days are displayed. Many apps give a fake sense of certainty by not showing statistical variability when estimating ovulation by cycle length. Pearl remains objective showing the statistical variability of the ovulation predictions based solely on cycle length.

Figure 6. Evolution fo the Pearl Fertility app ovulation and fertile window predictions overtime. **a)** statistics only, based on age and cycle length, **b)** earliest prediction of ovulation based on FSH downward trend, **c)** prediction of ovulation based on LH rise, **d)** confirmation of ovulation date having detected a complete LH peak.



What are the statistical parameters and how accurate they are?

The first Pilot Clinical Study (IRB 2017/11/7) carried out with an earlier version of the Pearl Fertility App showed that ovulation can be predicted in advance at: 1.2 days (s.d. 0.87), 1.5 days (s.d. 0.82), 6.2 (s.d. 2.9) for the LH rise, LH peak, and FSH downward trend respectively. A second clinical study in Europe (BfArM 011226) showed that the FSH downward trend may be influenced by average cycle length and age, for which future versions of Pearl should account for.

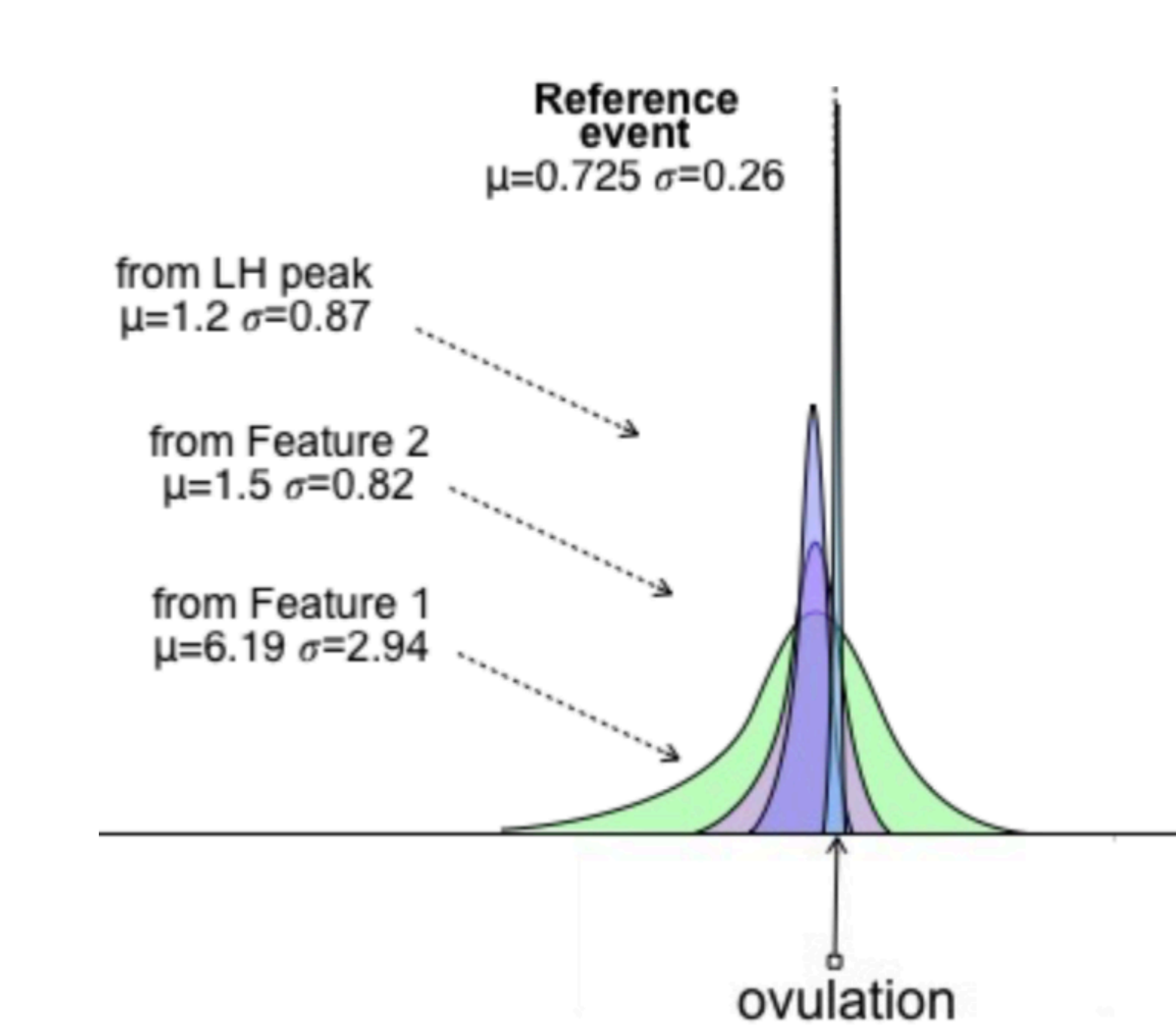


Figure 7. Statistical parameters used in the Pearl Fertility App. The variability of the prediction increases with time (s.d. = sigma). The reference event is ovulation from an observed LH peak and confirmed by direct observation.

Table 1. Confusion Matrix of statistical parameters for the predictive methods used in the app.

Parameter	LH peak	LH rise (Feature 1)	FSH (Feature 2)	PdG
False positive	1	3	3	7
False negative	5	1	6	5
True negative	4	4	4	21
True positive	19	21	16	47
Total	29	29	29	80
Sensitivity	0.79	0.95	0.73	0.90
Specificity	0.80	0.57	0.57	0.75
Accuracy	0.79	0.86	0.69	0.85

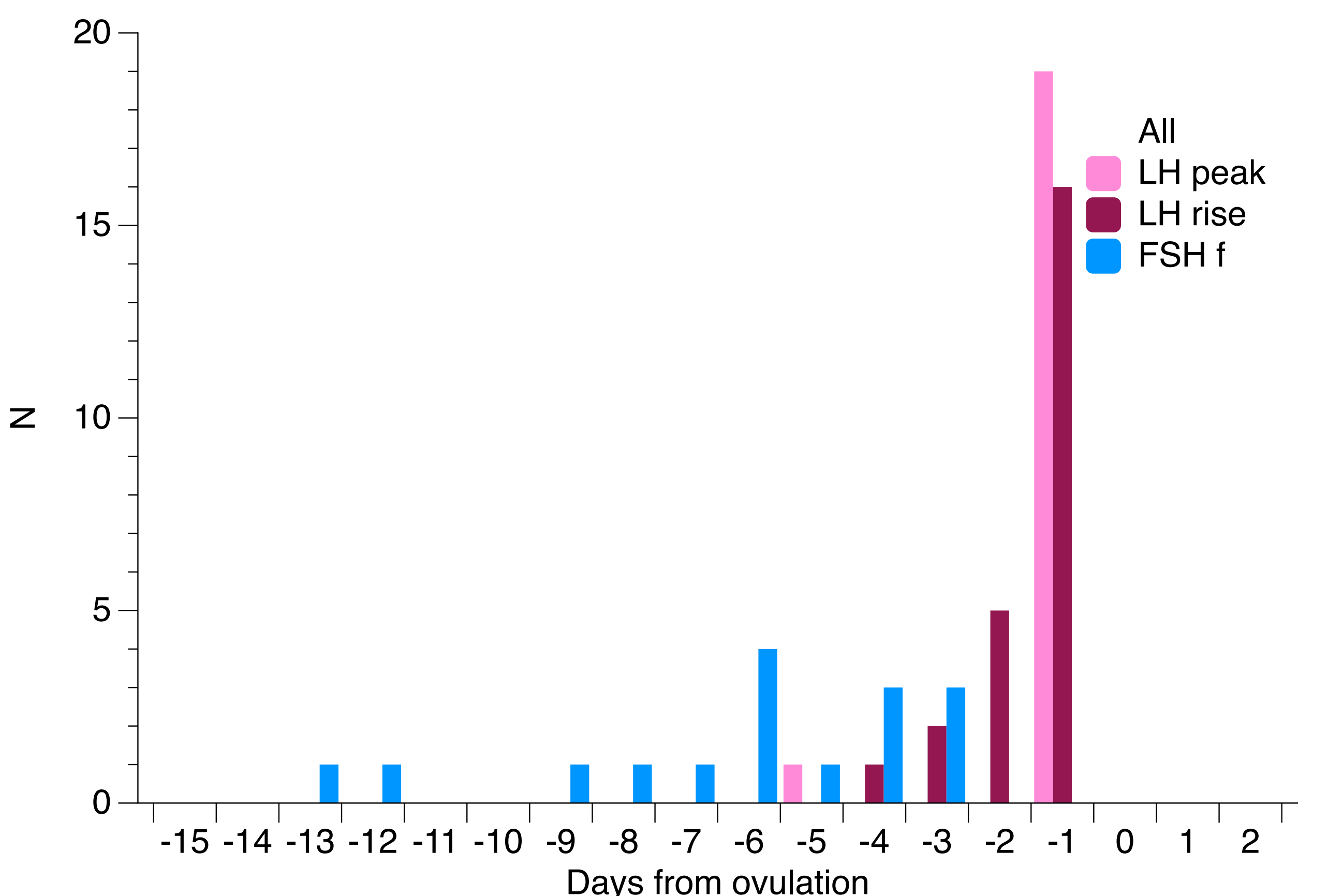


Figure 8. Pilot US clinical study results, n=30. An LH rise prediction 1.5 days earlier is more accurate than an FSH prediction 6 days earlier.

How the Pearl Fertility App displays the Fertile Window results.

The Pearl Fertility app runs calculations directly on the data captured in the phone without the need of an internet connection. This calculations of the statistical distribution of the predicted ovulation result in an ovule displayed as a circle on the date with the highest probability of ovulation. From this calculation, a Fertile Window is calculated from an proprietary statistical model built with results of over 20 clinical studies. The ovulation calculation and fertile days estimation with the less variability is the one shown to the user.

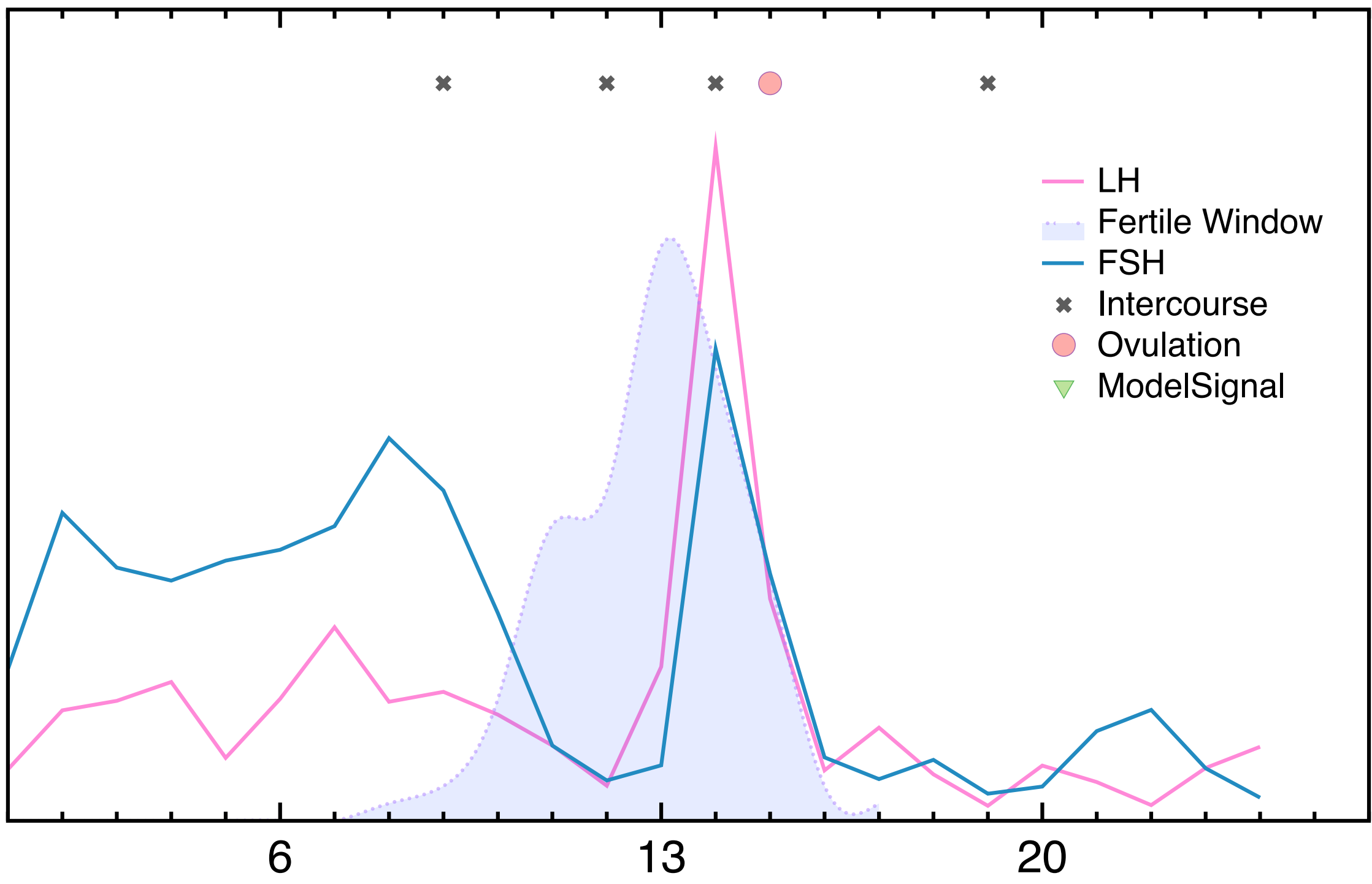


Figure 9. Hormone profiles (LH and FSH) for one individual, ovulation prediction (circle), and Fertile Window (shadowed area) from the predicted ovulation [20], as seen by the Pearl App.

In summary:

- 1) Pearl builds a hormone profile overtime and predicts ovulation with every measurement.
- 2) The best prediction (less variability) is chosen to display the Fertile Window
- 3) The Fertile Window is calculated and shown as a Flower Graph © which opening and closing is a function of the probability of getting pregnant if intercourse happens on the given date.

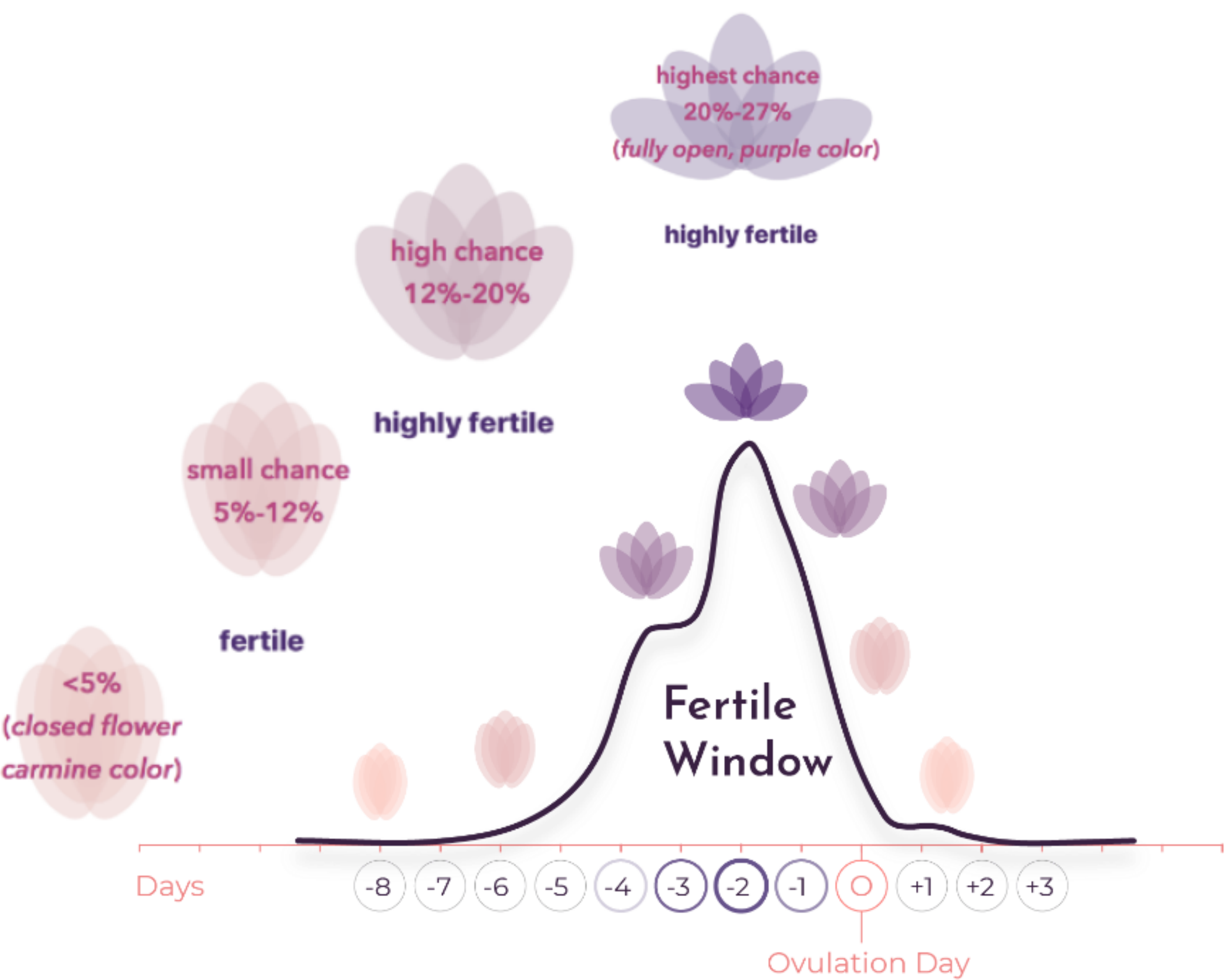
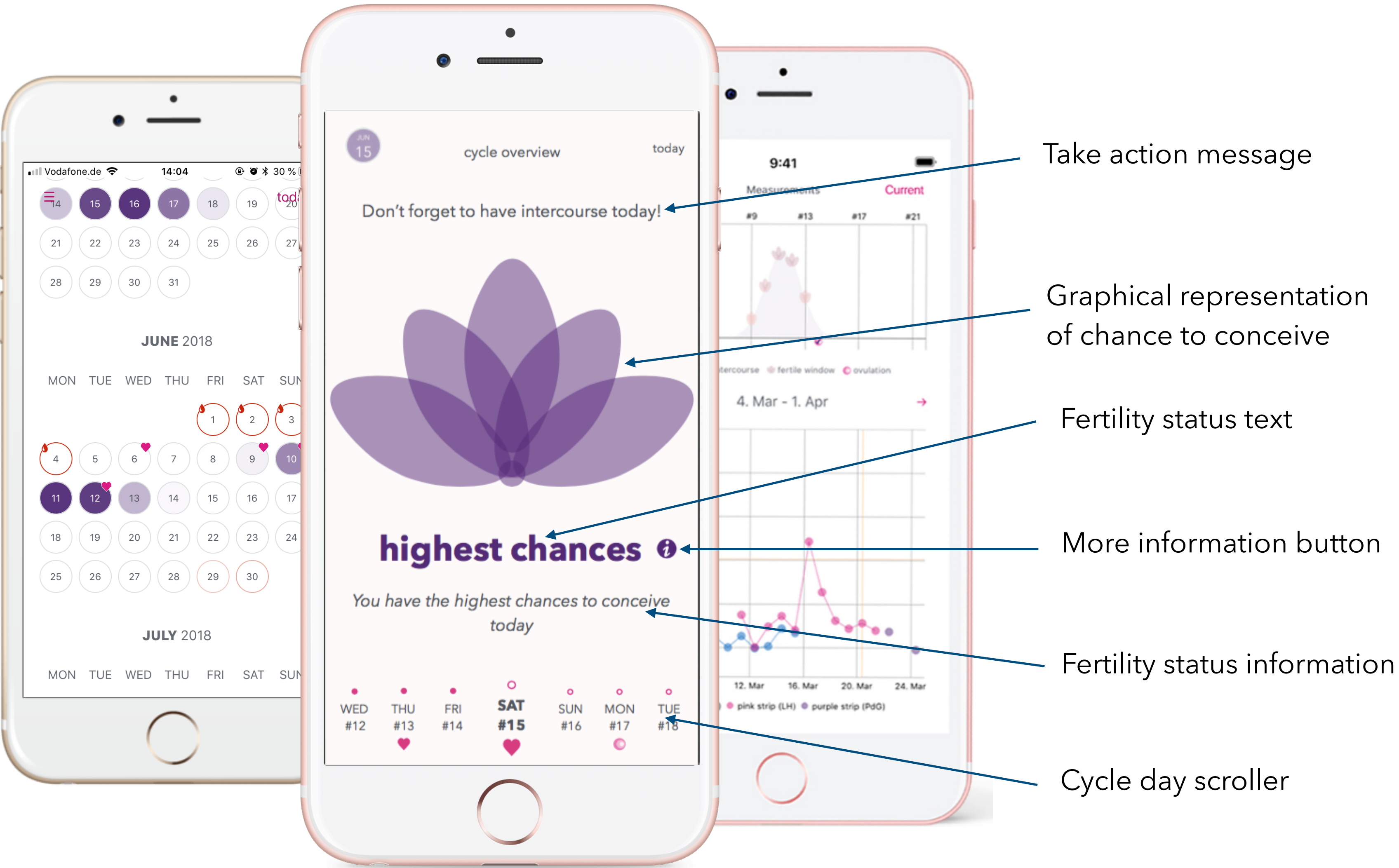


Figure 10. Graphical representation of the Fertile Window: the days of intercourse with the highest probability of getting pregnant in a given month [17]. The Pearl app draws a flower graph for which the opening of the petals are function of the actual probability of getting pregnant that day.

The Cycle Screen and User Interface and Certifications



Point your camera here for direct download



CE 0123
EC No.: V9 005315
Class: IVDD A
FDA
O.N.: 10059432
Class: LHD

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