Short Introduction to bioZhena Technology

Breakthrough Technology

bioZhena is an early-stage medical device and informatics company dedicated to improving female healthcare. bioZhena's vaginal sensor technology is designed to help women more effectively manage their reproductive health throughout their lifetime. This includes helping women conceive, and to do so on their own timeline, providing a built-in detection of pregnancy and identifying early pregnancy loss (EPL), forecasting the time of delivery, helping to plan for the baby's gender, as well as helping to provide a new level of control for other challenges such as menstrual cramps, PMS, menopause management and cervical cancer detection.

In order to make dramatic improvements in reproductive health, it is essential that both diagnoses and treatments are administered during the right time of the menstrual cycle, which varies not only from woman to woman but also from month to month for any given woman. Technologies on the market today merely *estimate the approach of* a key part of the cycle – ovulation:

- The ovulation estimates are based on changes in body temperature or changes in circulating hormone levels, which can vary with time of day, stress, medication, medical issues, etc.
- They assume that each woman's cycle is consistent from one month to the next, which impacts accuracy.
- Some are difficult to use and must be administered at specific times of the day.
- No single hormone monitoring system can do what this technology does – detect the integrated end-organ effect of all the hormones, which is required for accuracy of fertility determination.

bioZhena's technology is truly transformational because it tracks the mechanism of the complex biological process that causes menstrual cycles, around which women's health and lifestyle revolves. This technology will change the way both women and their physicians manage reproductive and general health, not just conception.

How It Works

The bioZhena product portfolio includes the Ovulona™, an over-the-counter vaginal electronic monitoring device, and the companion Ovulograph™ data management system for healthcare providers. The Ovulona is designed to track the entire menstrual cycle (a.k.a. folliculogenesis) by electrochemically measuring the fertility status of the uterine cervix. The Ovulograph will then (optionally) receive the Ovulona data from any number of patients providing longitudinal patient histories for better diagnoses.

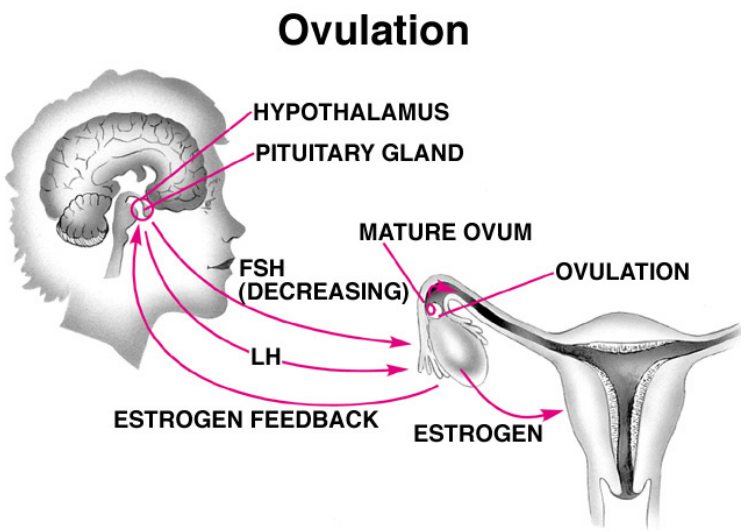


Fig 1 - Folliculogenesis is the complex interaction between a woman's brain and her ovaries – the foundation of her well-being.

The Ovulona detects and records, and our proprietary algorithm identifies, with unprecedented accuracy and ease-of-use (e.g. "fertile day 1"), the only 3 days of any menstrual cycle when the user can become pregnant.

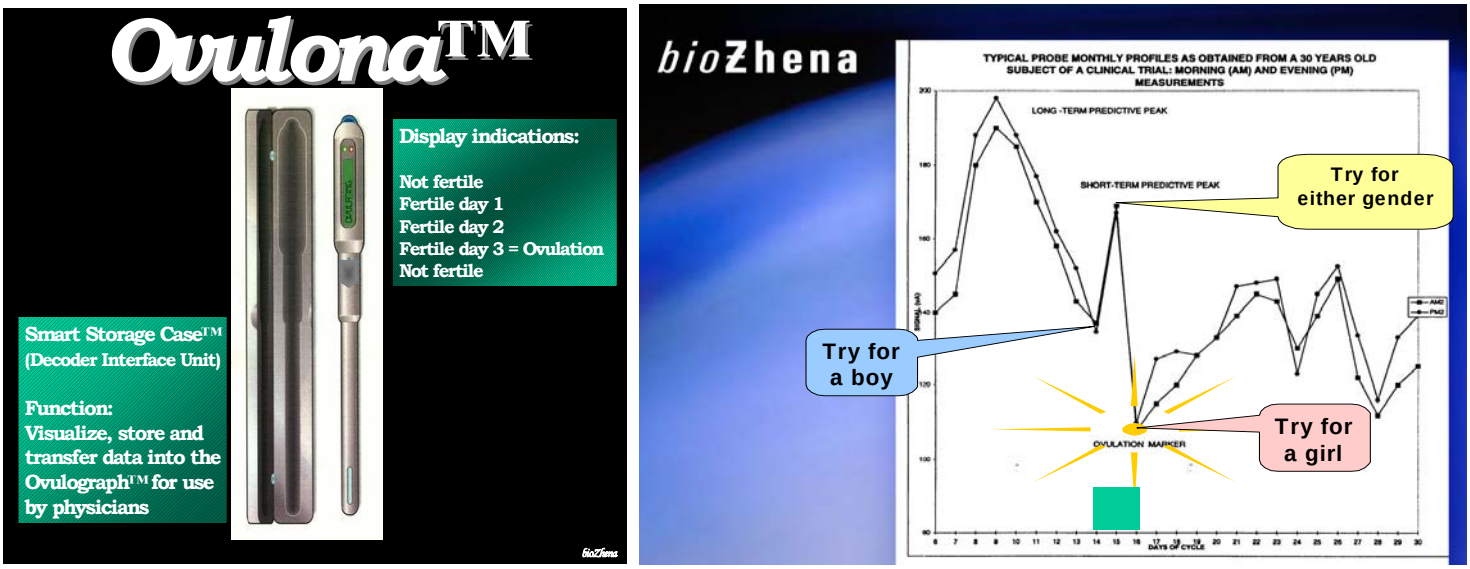


Fig. 2 -The personal home-use device determines the 3 days during which conception can occur

Because the Ovulona is designed to detect the rich information content in the folliculogenesis cyclic profile (unlike any other methods on the market today), it can distinguish the non-fertile days of the cycle from the 3 fertile days in which the probability of conception is high, regardless of whether the cycle is normal or affected more or less seriously by stress or other health or lifestyle conditions.

The underlying method of measurement is called admittance (a measure of movement of electric charges) – the inverse of impedance. The measurement can be described in electrochemical and physiological terms and can be simply put as the ease, with which the target allows an innocuous movement of charges. The Ovulona sensor detects the overall effect of all of the biological stimuli that the cervical tissue receives from the ovaries and from the brain (called the end-organ effect). The measurement process is innocuous because the minute electric charges are made to merely oscillate between the sensor and cervical and fornix tissues.

The multitude of repeatable features of Ovulona's proprietary cyclic profile throughout the menstrual cycle makes it possible to determine the boundaries of the personal fertile window for any individual in any month. A key distinction of this tissue-monitoring technique is that the dynamic range (the vertical span) is the same in all cycles and in all women. This is one of the reasons that Ovulona can be used for natural birth control whereas the other technologies cannot.

In the graph illustrated above (Fig. 2, right) are the morning and evening cyclic profiles from one of several baseline subjects of a study using this technology. The morning and evening curves were later superimposed, on the day of the ovulation marker. The data tracks the maturation of the dominant follicle culminating in ovulation.

The data in the graph above (Fig. 2) show remarkable similarity between the morning and evening cyclic profiles. The superimposition of the morning and evening profiles shows that the data reflect the folliculogenesis process in progress over the course of the hours between morning and evening measurements. We see subtle quantitative differences:

- Higher dominant-follicle-driven data (long-term predictive peak) in the evening;
- Properly developed first follicular wave (post-ovulatory part of the profile) in PM;
- All three waves are higher in the PM than in the AM record, which is consistent with folliculogenesis progressing during the day.

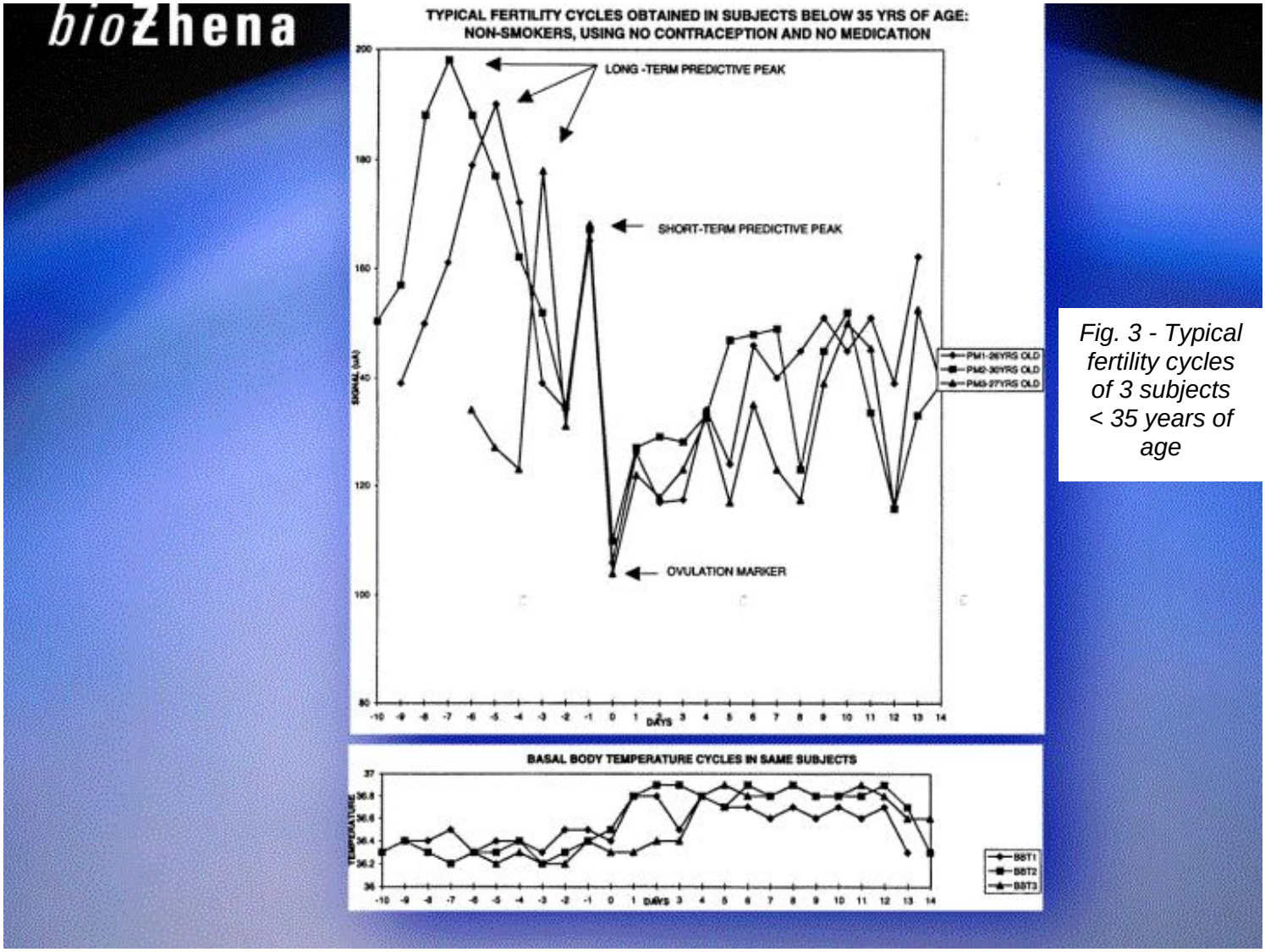


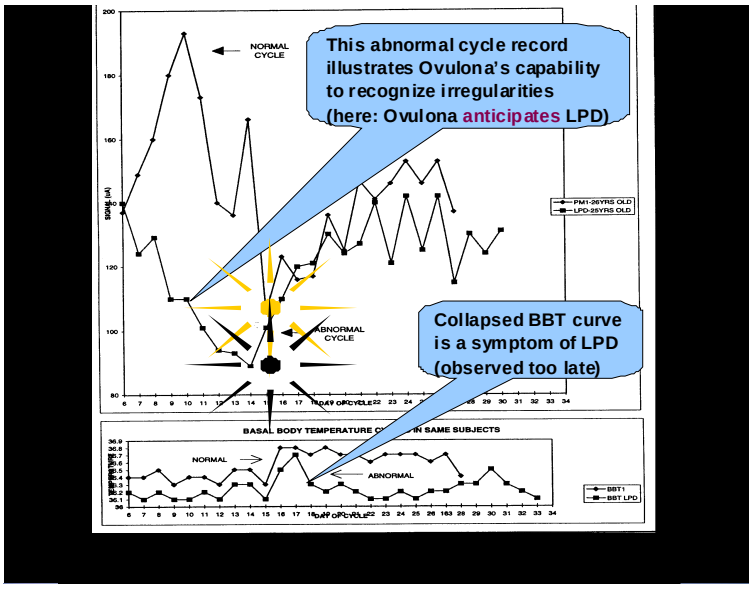
Fig. 3 - Typical fertility cycles of 3 subjects < 35 years of age

The graph in Figure 3 is an illustration of the evening measurement records from 3 different baseline subjects. It shows how the cycle length depends on the rate of maturation of the dominant follicle (the long-term predictive peak). The basal body temperatures (BBTs) generated by the same subjects were included for comparison.

The cyclic pattern, captured by the Ovulona to be displayed by the Ovulograph, exhibits a number of well-defined peaks and troughs. The first repeatable feature is the first post-menstruation minimum occurring typically on day 6, 7 or 8. This is driven by the *selection* of the dominant follicle. The signal then rises to a maximum (the long-term predictive peak), which indicates the *maturation* of the dominant follicle. This is followed by the narrow short-term predictive peak, which falls off directly into a trough (the lowest reading in the cycle) marking *ovulation*. This marker is viewed as the effect of the switch in hormone levels upon ovulation (estrogen to progesterone dominance). Note that the corresponding BBT curves rise to the post-ovulatory high level after the ovulation marker. This indicates, to the extent to which the BBT data can be relied on, that ovulation did in fact occur. We have found the ovulation marker to correlate with the LH and FSH urinary hormone peaks that are known to precede ovulation by about 12 hours, therefore marking the day of ovulation.

The post-ovulation (luteal phase) peaks and valleys have only recently been recognized as associated with the *follicular waves*. This means that this part of the cyclic profile can now be used as a diagnostic tool to help identify the rate of the depletion of the ova or eggs – how fast a woman is approaching menopause. It can also provide a very early detection of pregnancy (waves do not appear after conception) and an early indication of pregnancy loss (waves will reappear) – unique capabilities that no other ovulation-predicting device can replicate. Both are important for women trying to get pregnant.

The Ovulona sensor stores the data, which can be downloaded into the Ovulograph system for healthcare professionals. This will enable the correlation of symptometric and other auxiliary data with folliculogenesis, enabling both better diagnosis and treatment capabilities. With this added functionality, the technology can reach way beyond fertility monitoring, providing a feedback for treatment and for behavioral changes, such as in hormone therapy or, say, in smoking cessation or in treatment of PMS. By virtue of being an end-organ effect monitor, it can help in the management of the highly prevalent menstrual cramps, PMS/PMDD, peri-menopause, and - as a tool for management of PCOS (Poly Cystic Ovary Syndrome) - it can be explored to help prevent major killer diseases of women: diabetes, cardiovascular disease, ovarian cancer, and strokes.



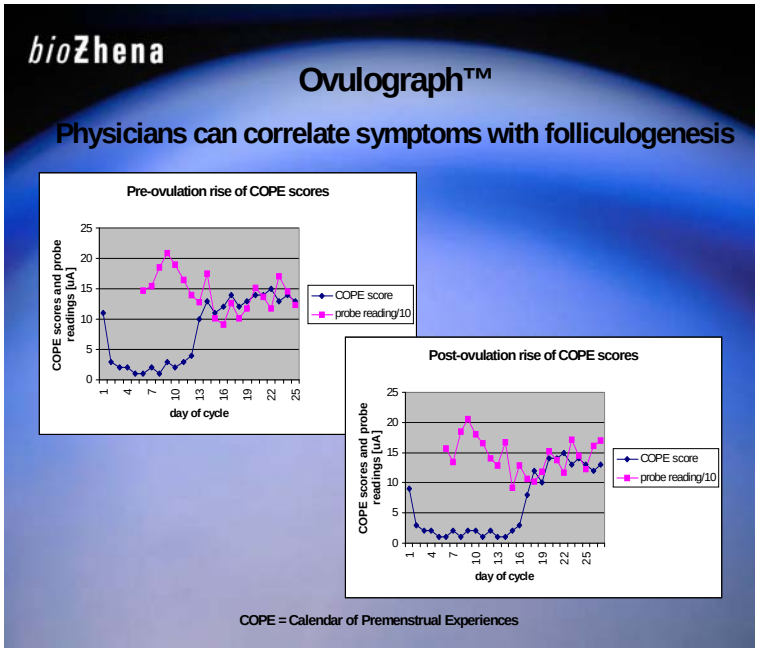


Fig. 4 - Illustrations of how the Ovulograph can be used by healthcare providers. Upper: Anticipate failure to conceive (absence of dominant follicle maturation). Lower: Enable differential diagnosis (here, clinical depression vs. PMS/PMDD – symptom score rise before vs. after ovulation).

For example, as illustrated in Figure 4, the Ovulona can be used by healthcare providers to recognize irregularities in a patient's cycle that would indicate it is not a good time to administer fertility treatments, saving time, costs and increasing the probability of future success. In another example, the charts in the lower part of Figure 4 examine the correlation of COPE (Calendar Of Premenstrual Experiences) scores with Ovulona cyclic data. This is essential for effective differential diagnosis of PMS/PMDD vs. clinical depression.

The Ovulona is a diagnostic device that women and their physicians will embrace from adolescence (menstrual cramp management) to menopause (hormone therapy management). Once in mass use, the Ovulona will provide an affordable cervical cancer screen for women everywhere without the drawbacks of the important, but not perfect, Pap smear test. In due course, we shall also introduce a hardware add-on in the form of a medication delivery means for the better way of administering medications.

What Makes bioZhena Technology Unique

The bioZhena technology is unique because it utilizes the natural feature of design of the female reproductive organs, namely that the cervix monitors the interactions between the brain and the ovaries with great accuracy, in order to perform its function. The Ovulona monitors all the inputs into the reproductive system, which the cervix integrates and the sensor detects as end-organ effects.

The detection of ovulation separately from its multiple quantitative anticipation is unique. So is the ensuing determination of the fertile window. Because the device is a tissue biosensor, it is expected to detect tissue aberrations such as early signs of cervical cancer.

Technologies on the market today merely estimate the approach of ovulation, or its passing, and do so only for those trying to conceive. These estimates are based on changes in basal body temperature [BBT] or changes in circulating hormone levels

detected after clearance into the woman's urine, which are remote indicators of single hormones. First of all, the measurement of one hormone is not enough. Even if it was, remote or indirect measurements are much less effective because when the circulating hormone passes through different organs, the measurement is less accurate.

The old BBT measure of circulating progesterone is retrospective, indicating that ovulation has most likely occurred (+/- up to 3 days) but not providing a signal that the woman's body is getting ready to ovulate, whereas the other methods that monitor estrogen or its body-fluid effects (such as crystalline appearance or conductivity) merely estimate the likely approach of ovulation but do not detect it.

Since no single hormone indicates the beginning or the end of the fertile window, the focus on single hormones or their effects on body fluids makes the old methods ineffective for natural family planning [NFP] method of birth control. In so far as helping women trying to conceive [TTC], the old methods often help a woman by focusing her to seek the likely occurrence of the brief fertile window of opportunity - but many TTC records show that conception was assisted by the self-examination of one's cervical appearance, feel and secretions (taught by NFP teachers) – rather than by the old-generation technological tools.

Fertility results from a complex interplay of numerous physiological stimuli. The old approach of measuring one or in one case two hormones in a body fluid is fundamentally flawed. bioZhena's technique is the only device to monitor end-organ effects at optimal settings of pertinent parameters, determined empirically and implemented in a simple, hand-held, user-friendly device. In the development process, we eventually discovered that our focus on the particular anatomy resulted in the unprecedented monitoring in vivo of folliculogenesis.

Technology Development Status

The first Ovulona product application has FDA 510k certification as a fertility-monitoring device and can be launched within the first year of funding.

Milestones achieved to-date include the following:

- Kirsner's Ovulon monitor: FDA 510k clearance number K973860
- Proof-of-concept monitoring data has been correlated with conventional indices of ovulation in published and unpublished studies
- 15 patents are in various stages of completion: 6 patents granted, 6 patent applications published, and 3 are ready for filing after the company is funded
- Contract manufacturing has been secured with a manufacturing contractor firm in Colorado, which could be acquired by bioZhena, if deemed advantageous

Fig. 5 - Photograph of rapid prototyping model of the Ovulona™ Personal Fertility Smart Sensor™

bioZhena Corporation
2908 Killarney Drive, Laporte, Colorado 80535, USA
Vaclav Kirsner, PhD, Chairman and Founding CEO
vaclavkirsner@yahoo.com
970-484-1272