OV-Watch®: History of its Scientific Development

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Preamble

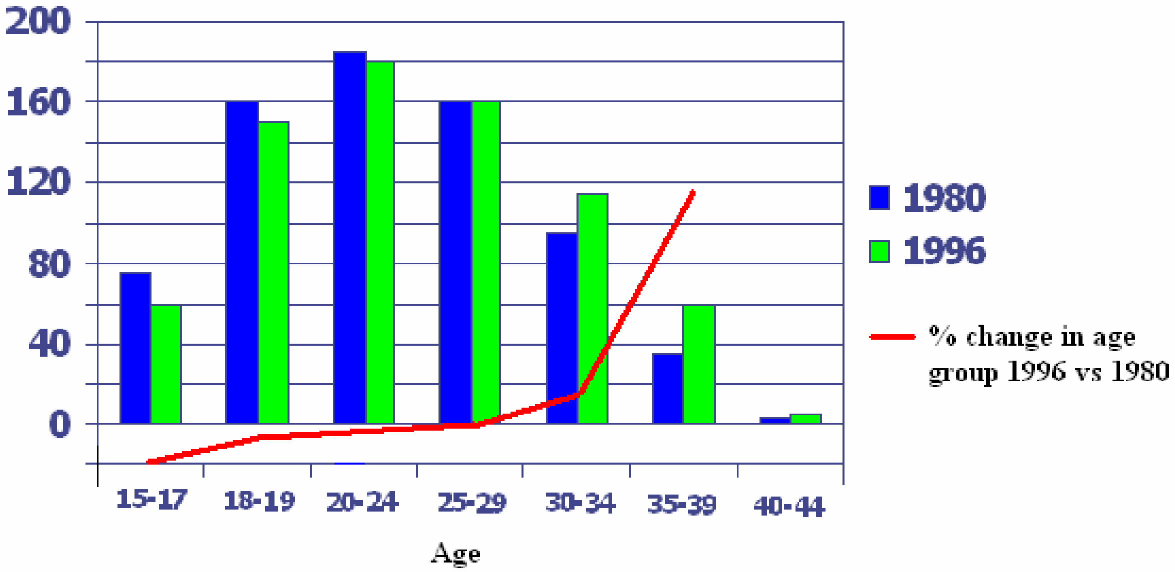
The fertility monitor described herein was originally developed by Pheromone Sciences Corp. (**PSC**) of Toronto Canada under the trade names **"PSC Fertility Monitor"** and **"Fertilite-Ov"**. In Sept., 2004, this technology was purchased by HealthWatchSystems, Inc., (**HWS**) of Sarasota, Florida. It is now marketed under the trade name **"OV-Watch®."** These names are used interchangeably throughout when describing the product along its development history.

Note: Graphs herein generally display a peak in concentration going "up", with the exception of graph 1 and 2 on pages 3 and 4, respectively, which show it going down (trough). In these two graphical exceptions, acid ion H+ increases with decreasing pH, explaining why the patterns in these graphs have an inverted shape compared to all others.

Increasing Infertility Trends

Over the last two decades, an increased emphasis on career and financial stability have led couples to postpone the age at which they first try to have children. One in five couples now seek to begin families at age 35 or later. Figure 1 shows that between 1980 and 1996 pregnancy rates declined for women aged below 25, whereas for women between 30 and 39, pregnancy rates rose significantly during the same time period, with the greatest percentage change in the 35 - 39 age group.

Figure 4: Pregnancy Rates in the US (number of pregnancies per 1000 women by age of mother, 1980 - 1996.)



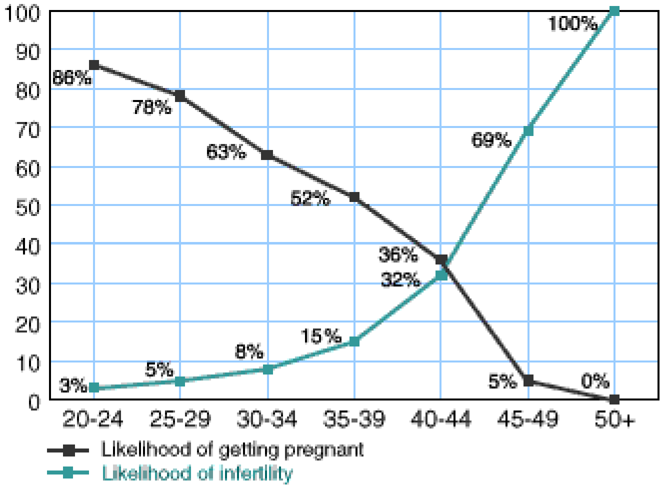
[1] Adapted from the Center for Disease Control and Prevention, National Center for Health Statistics, Serial 21, No. 56, Trends in Pregnancies and Pregnancies Rates by Outcome: Estimates for the United States 1976-96.

However, for biological reasons, the likelihood of conception is inversely related to a woman's age (Figure 2). Therefore, the trend to delay the start of a family has significantly increased the number of couples who experience problems with fertility. The postponement of pregnancy and resultant decline in fertility have thus created a large market need for products that enhance the probability of conception.

Figure 5: % Probability of Conception and of Infertility as a Function of Age:

Both of the line graphs are for women with normal reproductive function, after having unprotected intercourse for one year.

Source: Management of the Infertile Woman by Helen A. Carcio and The Fertility Sourcebook by M. Sara Rosenthal

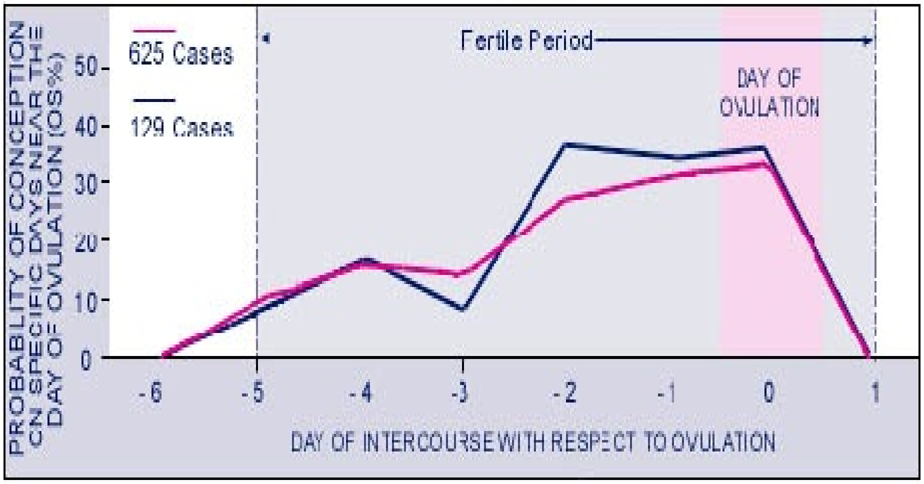


The Fertile Window

The Importance of Timing Ovulation – the Wilcox Study (1995)

The rationale for timing ovulation to optimize conception is based on the fact that a healthy woman has a limited number of days per month when intercourse can lead to conception. This time period can last up to six days per month. The reasons for the six-day length of this “fertile window” are the following: Sperm can survive up to 5 days in cervical mucus secreted under the influence of Estrogen. In a typical woman, there are four days of high fertility prior to the LH surge; ovulation then occurs within one day of the LH surge; and there is one day (or part day) after ovulation that the ovum is still available for fertilization. Thus, if a woman times her ovulations and has intercourse on the most fertile days, she will significantly increase the chance of getting pregnant. In this 1995 paper they found that the highest probabilities of conception with intercourse occur during the 4-5 days prior to ovulation and the day of ovulation itself. Figure 6A below highlights the chances or probability of conception based upon sexual intercourse on specific days within the fertile window.

Fig. 6A: The Fertile Window



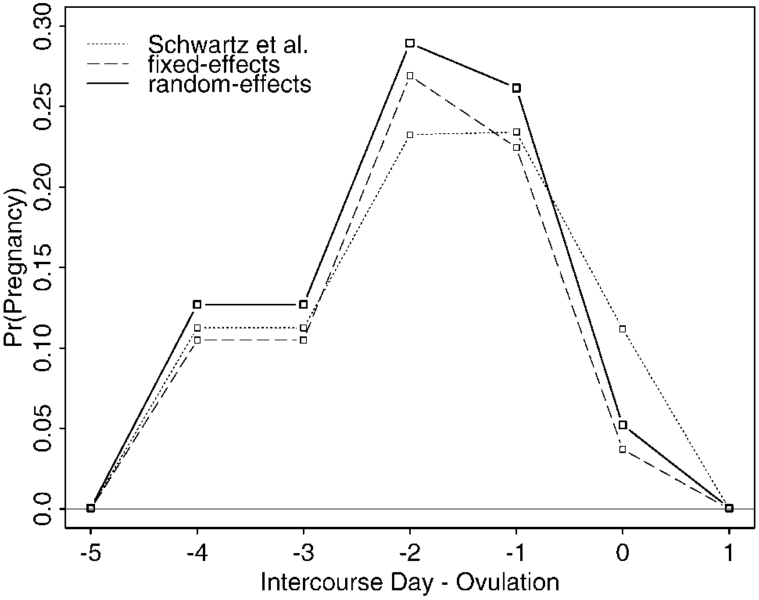
As can be seen from this graph, the fertile window begins about 5 days prior to actual ovulation, and extends to about 1 day after. The probability of conceiving is highest from day –2 to day 0. (Ref: Wilcox AJ, et al. Timing of sexual intercourse in relation to ovulation. The New England Journal of Medicine 1995; 23; 1517-1521.)

The dramatic increase in fertility-related problems caused by the deferral of pregnancy in older women has thus created a large marketing opportunity for products that can enhance the probability of successful conception. A useful fertility predictor that notifies the woman 4 days in advance of ovulation (and her entire 6 day fertile window) would also be valued by the millions of couples who might not be having fertility problems, but who, for scheduling and lifestyle reasons, have a need to precisely time intercourse.

The Dunson Re-Analysis of the Wilcox Data (2001) and its Implications for the Fertile Window

In 2001, D. B. Dunson co-authored a paper with Wilcox re-examining the data from Wilcox's 1995 paper using a number of statistical techniques to adjust for ovulation measurement errors in the prior method. This paper sought to refine the findings of the original paper and come up with a more accurate assessment of the probabilities of conception on different days throughout the Fertile Window. Results of this study are shown in Fig. 6B.

Fig. 6B: Estimated day-specific probabilities of clinical pregnancy
From: D.B. Dunson, et.al, Statistic in Medicine 2001;20:965-978.



Day of Intercourse Relative to Ovulation	**Probability of Conceiving** (From graph above, Random Effects Model)
4 days before	13%
3 days before	13%
2 days before	28%
1 day before	26%
Day of ovulation	5%
1 day after	0%

Quoting Dunson, “In particular, we estimate that the probability a pregnancy results from intercourse on only the day of ovulation is slightly less than 5 per cent, which is lower than previously estimated.”

The most remarkable result of this re-analysis of the Wilcox data was that it showed the probability of conception after intercourse was highest in the 4 days prior to ovulation, and dropped to much lower levels on the actual day of ovulation. This highlighted the paramount importance of advanced notice of ovulation in effective family planning, *and overturned the wisdom that the day of ovulation is the most fertile day.*

The Search for Advanced Notice of Ovulation

It became increasingly evident given the Wilcox data that a device which could give notice of impending ovulation several days ahead of time would be highly useful for women in achieving pregnancy. Devices on the market in the mid-1990’s focused primarily on the actual time of ovulation, giving either little prior warning or letting the user know after the fact. Researchers at Pheromone Sciences Corp. began investigating the effect of menstrual cycle hormones on sweat electrolyte metabolism in women in 1994, prior to the Wilcox study, looking for such advanced notice. This was based on the understanding of sperm lifetime after intercourse, which predicted a similar window of fertility prior to ovulation of around 4 days.

Early Third Party Research (1966 – 1969)

Research on the effect of menstrual cycle hormones on women’s rate of sweating and the kinds of salts released dates back to the mid-1960’s. Jack Lieberman began investigating the fluctuations in sweat electrolyte levels in women over their menstrual cycles in 1966.[1] He examined 57 women in his studies. He was the first to observe an apparent surge in chloride ion levels around the presumptive time of ovulation in many of the women. He also noted a peak in sweat chloride concentration in some women just prior to their period. The paper was groundbreaking, but the measurements had low resolution due to the readings only being taken about once every 4-5 days, and the actual time of ovulation being presumptive.

A second paper appeared in 1969 by J. Richard Taylor, who looked at the variation in the sweat gland function during the menstrual cycles of 20 young women.[2] He found that “when an alteration in eccrine ductal activity could be detected, it occurred after or in association with ovulation. These findings are in keeping with Lieberman who demonstrated essentially the same patterns of fluctuation in sweat electrolyte concentrations. “

His observations also confirmed an increase in sweat duct activity at the time of presumed ovulation, and at the end of the menstrual cycle. Again, the readings were taken on each patient about every 4-5 days, so a detailed look at how the sweat ions change over the menstrual cycle would have to wait for later, more sophisticated studies. (References – see page 10)

Initial Discovery at PSC – 1995-1997

Introduction:

PSC began working in the area of fertility detectors in 1994, when the company was developing a new fertility monitor for Imogen Inc. The management of this company had been involved for some time in the charting of women’s menstrual cycles using basal body temperature and vaginal mucus viscosity measurements for predicting ovulation. They received N.R.C. sponsorship for the development of a new vaginal mucus conductivity detector, which the company designed and built for them. It became common practice to discuss the details of women’s symptoms leading up to ovulation, and on one particular day an unusual symptom was brought to the attention of the CSO. In this case an associate believed that around the time of ovulation, she would get skin discoloration under her wedding ring. After some investigation, other women were found who had the same thing happen with their rings. This phenomenon was looked into, which became tentatively known as the “ring reaction “. A jeweler had suggested that this might be due to increased acidity of the skin, and it was decided to follow up this suggestion with an experiment. A protocol was created to monitor the skin sweat pH of male and female sexual partners, to look for changes in acidity which could cause the so called “ring reaction”.

Materials and Methods:

pH Measurement: A liquid membrane ionophoric pH electrode was manufactured in the lab specifically for this experiment. The H+ ionophore ETH1907 was obtained from Parish Chemical Co. Polyvinyl chloride, dioctyl sebecate, and potassium tetraphenyl borate were obtained from Aldrich Chemical Co. Alternatively, a flat membrane glass combination pH electrode was used (Omega Scientific model PHE-2171). All readings were performed using a Fisher Accumet 640 pH meter.
The ionophoric membrane was constructed as previously described, (Oesch et. al (1986) Anal. Chem 58, 2285-89). On testing in various pH buffered solutions , its pH response versus the calomel electrode was Nernstian in the acid range, at 51 mV/pH unit between pH 3 - 8. (Nernstian response - the exchange of one proton for one electron, with an ideal response of 59 mV/pH). This was appropriate, as the normal skin pH is in the 4-6 range. The glass combination electrode showed as similar response between pH 2-12.

Luteinizing Hormone (LH) Determination: Urinary LH was assayed using Clearplan LH test kits provided to each woman, and the LH surge was determined from the first morning urine between days 10-17 as suggested in the manufacturer’s instructions.

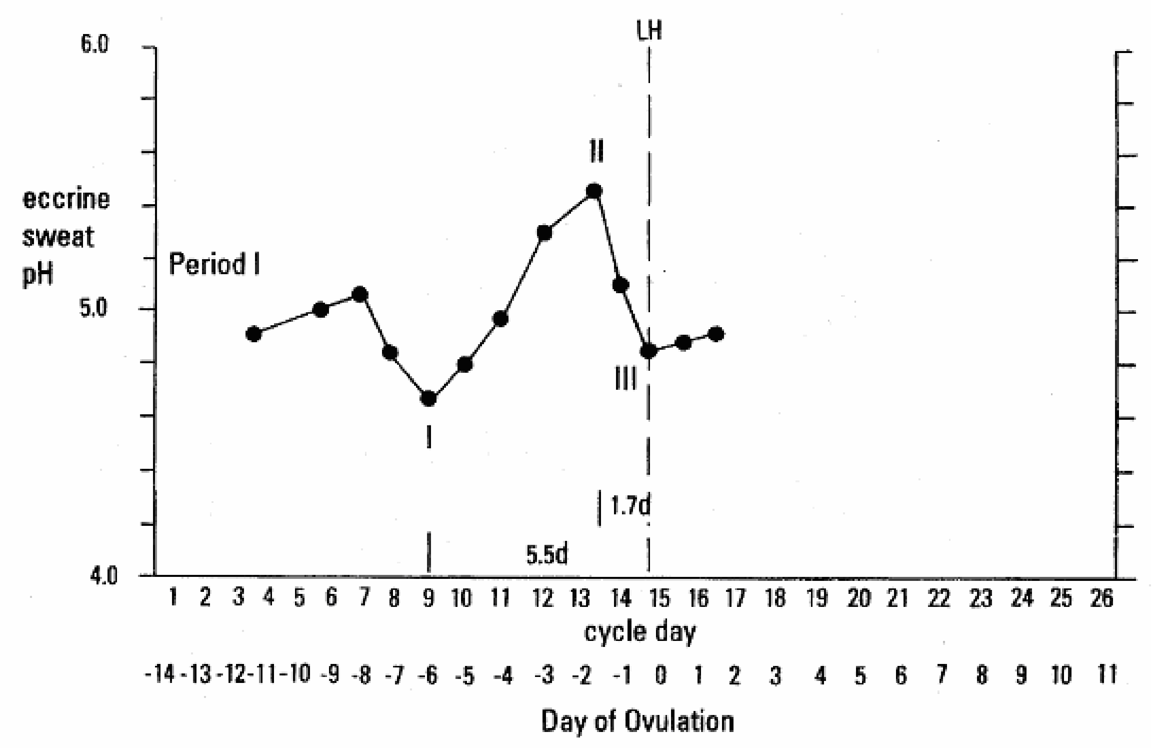
In this experiment the skin pH of four female subjects was tested each day during their pre-ovulatory menstrual cycle, and used their male partners concurrently, when available, as controls. A total of 10 menstrual cycles were examined. The electrode was calibrated with reference buffers immediately before each test. A total of six reading were taken on each person each day, and averaged. These readings were on the left and right palm, left and right lower wrist, and left and right upper wrist. These readings were then plotted onto computer charts and stored for later analysis.

Results:

All women were found to have regular menstrual cycles whose length varied between 26 and 33 days. In all cases the women had normal LH peaks occurring between day 13 and 16 (median 14.4 days). In some cases women reported other subjective sensations such as ovulatory pain which was timely with the measured LH peak.

It was found that with all of the women tested, the pH of their eccrine sweat was found to vary between pH 4.0 and pH 6.0. A graph of the individual menstrual cycle is shown in **Figure 1.** A graph of the average variation of 10 menstrual cycles (pre-ovulatory phase) is shown in **Fig 2**. For **Fig. 2**, the cycles were averaged based on day 0 being the LH peak determined for each women using the Clearplan LH urine test. The ordinate displays the average pH for each day (uncorrected). As can be seen from the **figure 2**, a consistent pattern of pH change through the pre-ovulatory part of the cycle was observed. During menstruation and shortly after, the pH of the women’s sweat averaged around pH 5.2. However, approximately 7-4 days prior to the LH peak, each woman experienced an acidification of her sweat which varied between 0.3 - 0.8 pH units. This reached a peak acidity around 5.5 days prior to the LH peak. This was generally the most acidic period measured in the pre-ovulatory phase. Following this acidification, , the pH would rise to an alkaline peak about 1.5 -2 days prior to the LH peak. The pH would then drop back to more intermediate levels (around pH 5) towards the time of ovulation. In a few cycles there was a second acidification at the time of ovulation. This pattern was somewhat consistent and reproducible from woman to woman. However, in the 6 cycles examined where the women were wearing gold rings, there was no correlation seen between the appearance of the “ring reaction” and the acid or alkaline peaks.

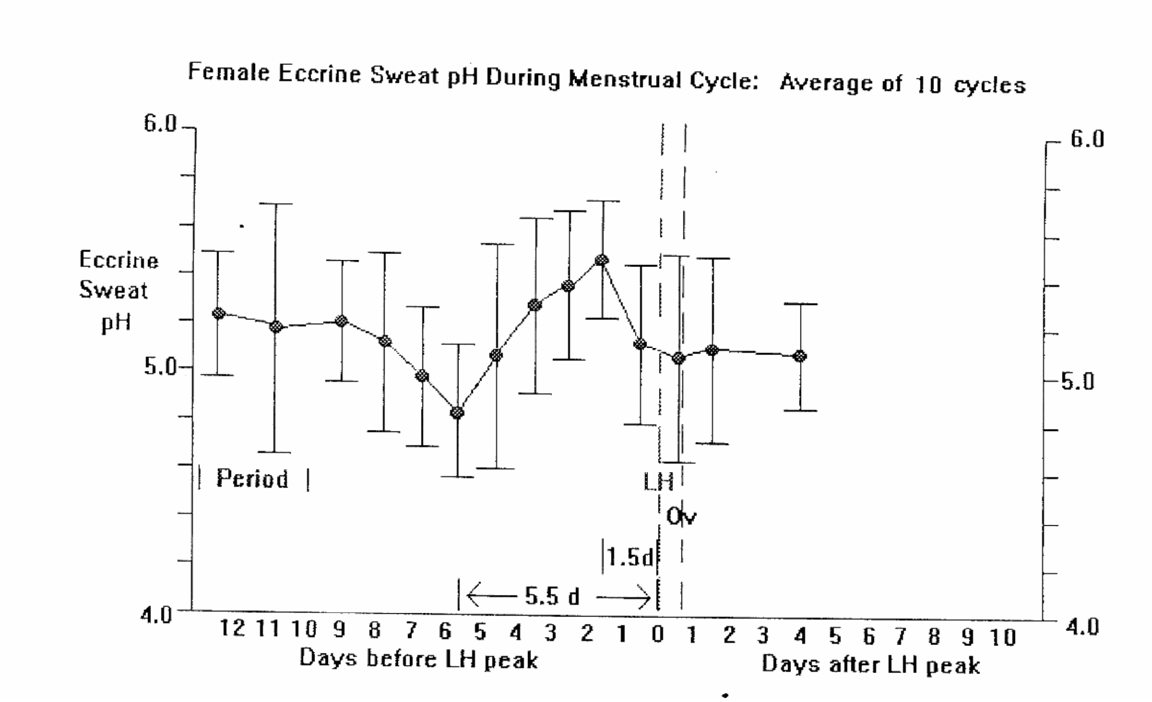
Fig. 1:



Discussion and Conclusions:

Previous studies have found that the eccrine sweat of women is generally between pH 4 -6, which is consistent with our observations (Dikstein et. al. Acta Derm. Venereol (Stockh) 1994: Suppl. 185: 18-20.). Previous studies have suggested that the pH of eccrine sweat is buffered by either the lactic acid/lactate system , free amino acid secretion, or CO2/bicarbonate. (Dikstein ibid.) However, they admit that there is no satisfactory mechanism to explain skin acidity. We have observed what appears to be a previously unknown relationship between a woman's menstrual cycle and her eccrine sweat pH. An alkalinization of the women's sweat reached a peak on average 1.5 -2 days prior to the urinary LH surge in 9 of the ten cycles. This occurred at around the same time as the expected peak in total blood estrogen levels. Serum estrogen E2 levels reach a peak usually around 1 day prior to the serum LH peak, and 37 hours prior to ovulation. This would make the serum estrogen E2 peak approximately 1.5 days prior to the urinary LH peak, which lags behind the serum LH peak by 6-12 hours (Moghissi, K., (1992) Reprod. Endocrinol. 21 (1), p. 39-55). The LH surge is known to have a diurnal dependence and most often occurs in the middle of the night. Thus in some cases, if the urine test is performed first thing in the morning, the serum LH levels may not yet have exited to the urine. For the most meticulous timing of ovulation therefore, it is recommended that the LH test be performed again at around 5 PM. For practical reasons we could not do this, so it is possible that in some cases the LH peak was not registered until the following first morning urine. Thus it is expected that the most common error is to have a longer period between the presumptive estrogen peak and the urinary LH peak. This was also corroborated by the fact that in two cycles the women were found to have ovulation pains indicative of egg release on the day *before* the registered urinary LH peak.

Fig.2:



In this study it was thus possible to predict the time of ovulation by adding 2.1 days to the time of the sweat alkaline pH peak. The average accuracy was +/- 14 hours, and the maximum deviation was 1.4 days.

An acid peak was also found to occur around 5-6 days prior to the urinary LH peak. Its occurrence is correlated to the urinary LH peak with a mean gap of 5.5 days +/- 19 hours, and a maximum deviation of 24 hours. This acid peak occurred in every cycle examined. It was not found to correlate in time with any of the known menstrual cycle hormones. There was no correlation between the occurrence of any pH changes and the so called “ring reaction”. Further studies (data not shown) have implicated the copper found in copper-alloyed gold as the main reactive species. Copper is dissolved in sweat at a slow rate, and is readily reduced by substances such as glucose and cysteine. Glucose is less likely to be responsible since it reduces copper under alkaline conditions to a green precipitate. The black precipitate observed on the women could be reproduced using cysteine reduction of the rings under mild acid conditions. It is most likely that the reduction is caused by the binding of copper by the cysteine residues of albumin found in sweat, or excess sweat glucose (Suzuki, et.al. (1989) Archives of Biochem.and Biophys. (1989) 273 (2), p. 572-77). This phenomenon does not appear to have anything to do with ovulation.

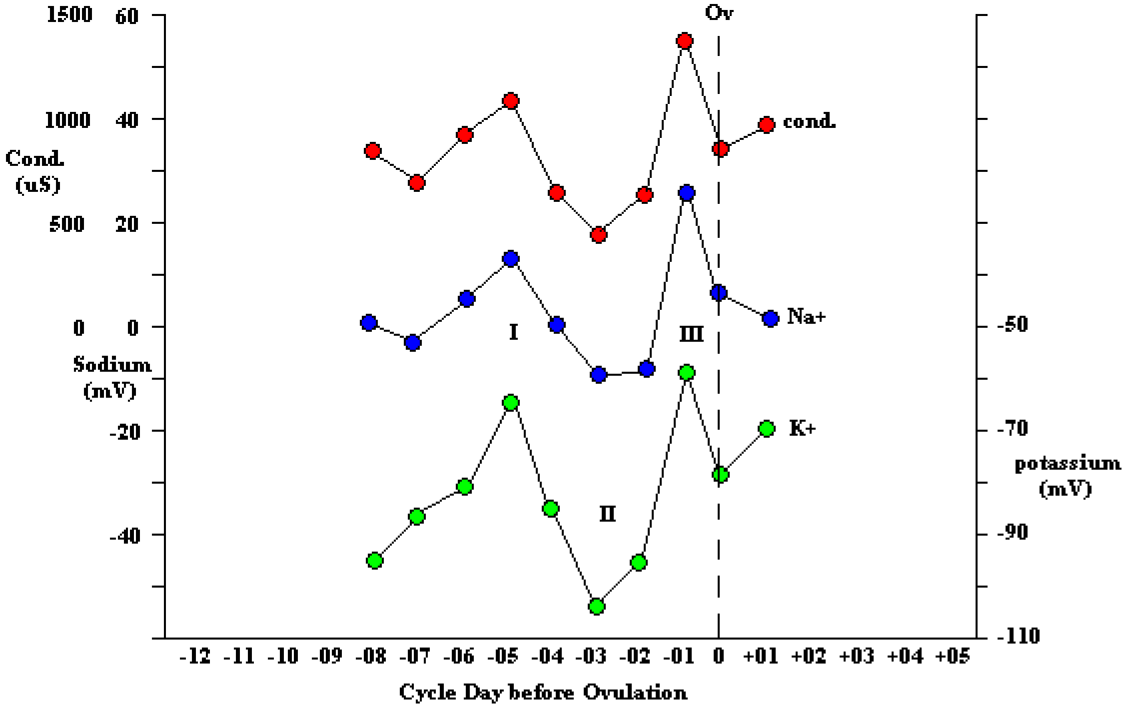
It can be concluded that there are consistent pH changes in eccrine sweat during a woman’s menstrual cycle which can be used to predict the time of ovulation. Since ovulation occurs generally on the day that the LH peak is detected in the first morning urine, other physiological phenomenon which occurs in a defined time relationship earlier in the cycle can be used as timing markers for such predictions. We have demonstrated that such markers exist in the sweat pH changes seen in the pre-ovulatory part of the menstrual cycle.

General Observations on other Sweat Ions - 1998-2000

PSC established by 1998 that pH changes in the eccrine sweat were occurring over the menstrual cycle, and these changes were largely due to the H+ ion. Our original ionophoric sensor also included potassium tetrakis tetraphenyl borate, a known potassium ion selective agent, and it was suspected that our probe might also be slightly sensitive to some sweat potassium changes. In order to further elucidate what was going on with other sweat ions over the menstrual cycle, a series of studies were initiated with subjects to quantitate the sweat the levels of sodium, chloride, potassium, as well as the bulk changes in conductivity.

In order to collect sweat from each subject during their menstrual cycle, female subjects were instructed to wash themselves thoroughly with 1L of distilled water each morning before showering throughout the follicular phase of their menstrual cycle. These samples were then collected and concentrated to a volume of 20mL for each day. Analysis of the sodium and potassium levels was performed using ion-selective electrodes, and conductivity was assessed using an Orion Conductivity Meter. Examples of samples obtained from a subject are shown in Fig.3. The menstrual cycle day is shown on the X-axis, and the inverse sweat ion level (in mV) is shown on the Y axis. *The curve appears to be the inverse pattern to the pH curve; however, this is because an increase in acidity is a decrease in pH. The pattern change is characteristic, but is presented upside down or right side up depending on the polarity of the ion and whether the curve is presented as a mV change or a concentration change.* As can be seen from the curves, the sodium, potassium, and conductivity readings all paralleled one another. A drop in all the curves was consistently seen 5-7 days prior to ovulation indicating a surge in the ions measured. Similarly, a second drop (surge) was observed on the day before the measured LH surge (ovulation). These observations were highly consistent with the previously observed pH changes during the menstrual cycle, and suggest that these phenomenon likely occur at the same time.

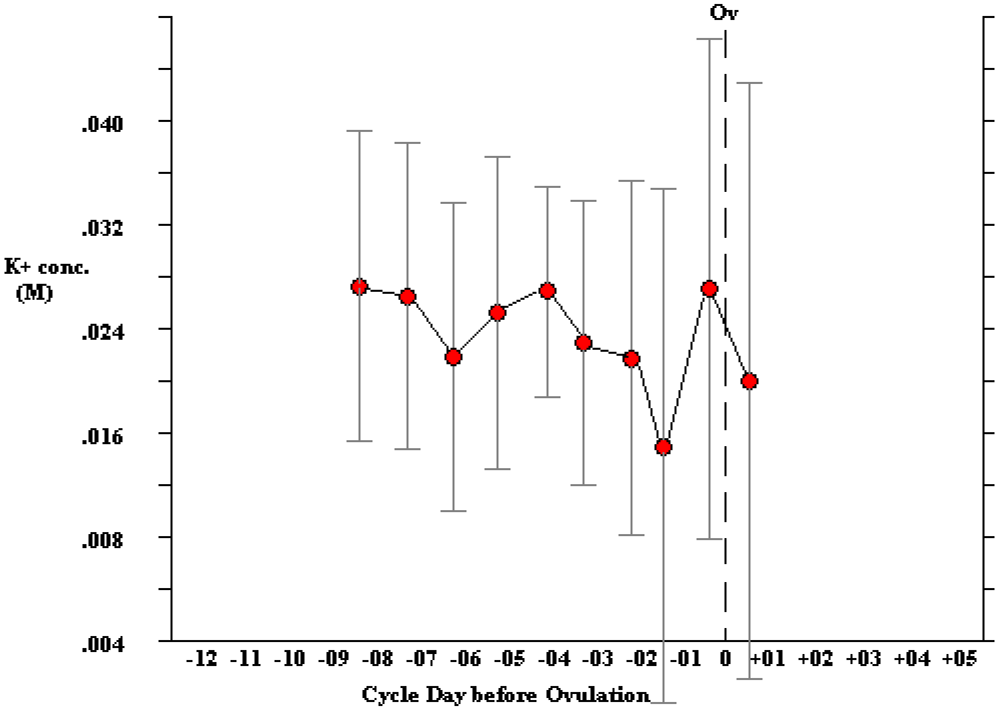
Fig. 3:



Correspondence between Sweat Potassium and Sweat Chloride Measured on the Wrist during the Menstrual Cycle:

It appeared obvious from the above data that if sweat sodium or potassium followed the anticipated pattern, than its primary counter ion, chloride, should do the same. In order to determine if this was true, a series of tests were run using ion-selective electrodes, monitoring the levels of either sweat potassium or sweat chloride directly on the wrist of each subject, every day during the follicular phase of their menstrual cycle. For potassium measurements, an Orion ionophoric membrane electrode was used, calibrated immediately prior to use. A calomel reference electrode was used for the reference half cell. A digital ion-selective electrode meter was used for all measurements. Six readings were taken each day on the subjects and averaged daily for plotting on the graph. **Fig. 4A** shows the data for the potassium readings on the wrists of 6 subjects. These values were averaged and the standard deviation in shown with the error bars. Again, the potassium value is shown inversely on the Y axis, with a drop corresponding to a rise in the actual potassium value. The X-axis shows the menstrual cycle day. The potassium determination again confirmed that a surge (shown as a drop) of potassium occurred approximately 5 days on average prior to the women's LH surge in the urine, and a second K+ surge occurred approximately 1 day prior to the LH surge.

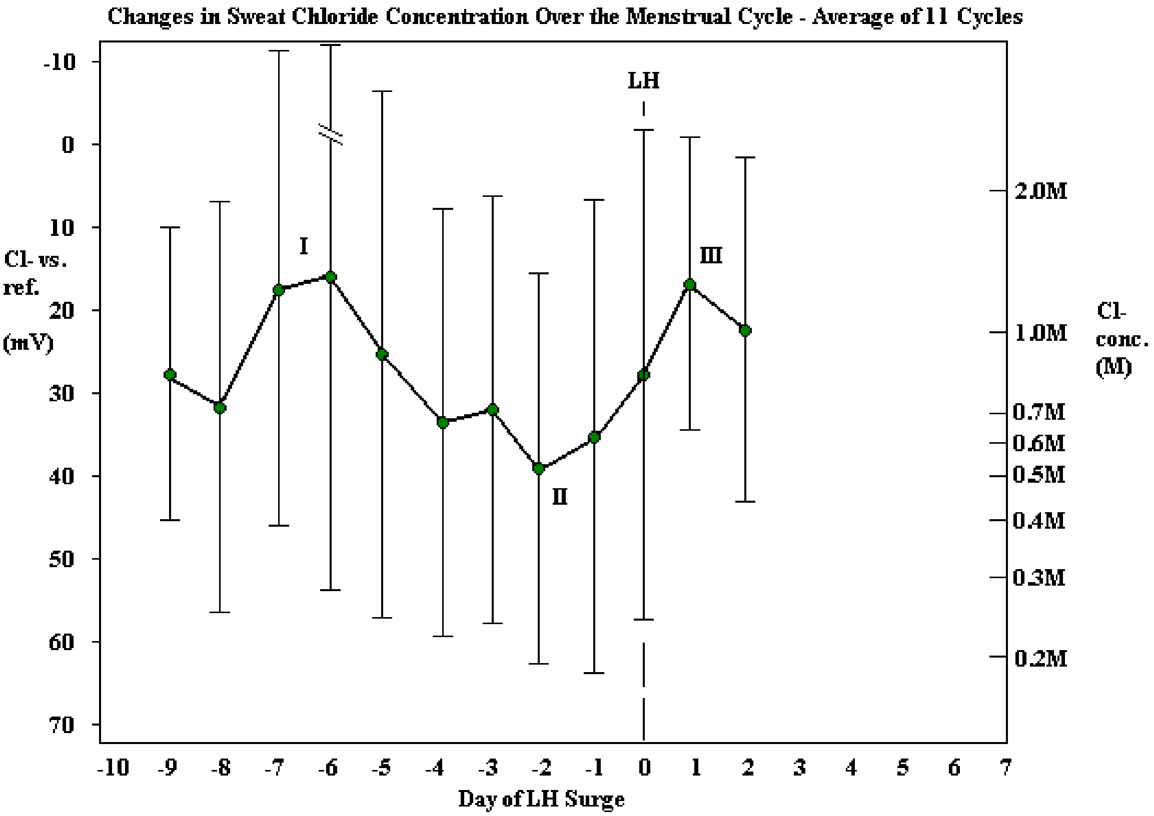
Fig. 4A:



For the chloride measurements, the readings were taken using the PSC fertility monitor fitted with a chloride sensitive ion selective electrode, and a silver/silver chloride reference element. Subjects were instructed to take manual readings with the watch every hour, 8-12 times per day, throughout their follicular phase. The readings were written into special logs given to the subjects, and analyzed at the end of the trial. The average data, with error bars, is shown in figure 5A (n=11). This chloride data showed a rise in chloride secretion 5-7 days prior to the urinary LH surge, a drop around 2 days before the LH surge, and a rise again just after the time of the LH surge.

These results appear to confirm our contention that a generalized increase in sweat ions (H+, Na+, K+, Cl-) occurs 5-7 days prior to ovulation, in most but not all subjects, and again around or just after the urinary LH surge, as measured with Clearplan LH sticks. In between these surges, there is often a significant drop in ion secretion, which corresponds in time with the rising estrogen levels in the body of the female subjects.

Fig. 5A:



Discussion:
Human Sweat Gland Function and Hormones

Changes in human sweat gland function over the menstrual cycle have been examined previously on a number of occasions. Lieberman performed a study with 57 women looking at sweat chloride, sodium and potassium. He noted that in approximately half the women tested, an ovulatory peak in sweat ions could be observed, as well as a second peak a few days prior to menses. This was observed with sodium or chloride ion measurements, but not with potassium. Readings on the women were only twice weekly, limiting the resolution. (JAMA, Feb. 21, Vol. 195, No. 8, P. 117-123. 1966). In another paper, Taylor et. al. Observed a similar pattern in sweat duct free water clearance (J. Invest. Derm. Vol. 53, No. 3, P. 234-237, 1969). These effects can largely be explained by the effect of estrogen and progesterone on body electrolyte balance. Eisenbeiss et. al. noted that estradiol up regulates the renin-angiotensin system followed by electrolyte and water retention (Brit. J. Dermatol. Vol. 139, 462-467, 1998) Further, estradiol and progestererone affect the levels of aldosterone and vasopressin which reduce fluid secretion. All of these factors work together to affect the salt concentration of sweat in the days prior to ovulation.

In PSC's investigation of sweat ion changes with female subjects during the menstrual cycle, there was observed a similar peak in sweat sodium, potassium, and chloride ion at the time of ovulation. However, further patterns of sweat ion change in the pre-ovulatory phase were observed which has been previously unreported. This involves a peak in sweat ions (based on Na+, K+, or Cl-) approximately 5 days (4-7days) prior to ovulatory luteinizing hormone (LH) peak, followed by nadir in sweat ion concentration around 2-3 days before the luteinizing hormone peak. Finally, a second peak in sweat ion concentration occurs at around the time of the LH peak. This first peak in sweat ions has not been previously observed and is largely unexplained, but correlates with other physiological phenomenon reported in women at a similar time in the pre-ovulatory phase. Jacobs et. al reported a peak in salivary impedance approximately 5-7 day prior to the LH peak in a group of test subjects (Obstetrics and Gynecology Vol. 73, No. 5, part 1, P. 817-822, 1989). Fehring et. al.

reported changes in vaginal mucus electrical admittance 5-7 days prior to ovulation in a group of test subjects (J. of Nurse-Midwifery Vol. 43, No. 2, March/April 1998). Hartmann and Prosser reported an acute change in breast milk Na+, K+ and Cl- 5-6 days prior to ovulation in lactating, ovulatory women. Finally, in our own prior U.S. patent 5,685,319 it was reported that a significant pH nadir in female eccrine sweat was found to occur around 5-6 days prior to ovulation. This effect appears to be real, but the hormonal basis for it is still to be resolved.

Conclusions:

This paper has attempted to provide evidence to show that menstrual cycle events appear to have a dramatic effect on the level of sweat ion release onto the skin from day to day. The primary effect is an increase in the concentration of sweat ions on the skin , peaking at around 5-7 days prior to ovulation, followed by what is possibly an estrogenic suppression of sweating in the period between 1-3 days prior to the LH surge. At about the time of the blood LH surge (up to one day prior to the measured urinary LH surge) the level of sweat ions increases again. This effect may be the direct result of LH, or may be due to some other hormonal factor related to ovulation. We have seen these patterns, or variations thereof in many, but not all women. Reasons for not seeing these events in some women may be due to sensor errors, other insidious factors influencing the rate of sweating, or differences in hormonal secretion patterns amongst different women. However, there does appear to be a relatively reproducible pattern of ion secretion in most women that can be made the basis of an ovulation prediction method. We currently favor the solid state chloride ion sensor (with an appropriate reference electrode) due to its simplicity of manufacture, its robustness, and its superior stability as compared to ionophoric membrane ion sensors, which are readily contaminated and have greater stability problems.

Canadian Pilot Clinical Trial of Fertilite (OV-Watch®):

This trial, performed by Dr. RF Casper, Dr. TG Hannam, and L. Gotlieb, was the first independent trial of the original Fertilite-Ov product in women. The trial was completed Oct. 31st, 2000. The results of this trial were presented at the Society of Obstetricians & Gynecologists of Canada (SOGC) Annual Meeting, St. John's, Newfoundland, 18 June 2001. The summary of this trial is presented below.

PREDICTION OF OVULATION WITH A NOVEL FERTILITY MONITOR IN REGULARLY CYCLING WOMEN

TG Hannam, L Gotlieb, RF Casper
Reproductive Biology Unit, Department of Obstetrics and Gynecology
Mount Sinai Hospital, 600 University Avenue, Toronto Ontario M5G 1X5

Objective:

Anticipatory fertility monitoring can provide valuable information for the infertile couple. The sensitivity and specificity of physiologic markers of ovulation such as changes in basal body temperature or spinnbarkeit have been well characterized; in addition, several commercial test kits are available for detection of urinary luteinizing hormone. The purpose of this clinical pilot study was to evaluate the Pheromone Sciences Corporation (PSC) Fertility Monitor, the first commercial device designed to correlate variances in conductivity due to transcutaneous secretions of ions, with ovulation. It has been constructed to resemble a wristwatch.

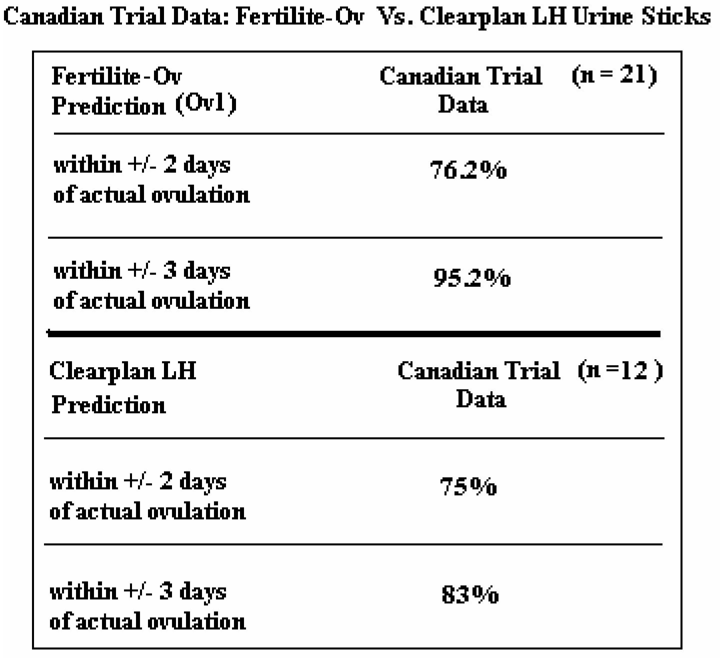
Study Methods:

After informed consent, eighteen regularly menstruating women were followed for a total of 21 ovulatory cycles. Subjects recorded upcoming, or imminent, ovulation as detected by the Fertility Monitor. In the same cycle, subjects also received cycle monitoring at a fertility clinic, receiving transvaginal ultrasound to follow ovarian follicles, blood sampling for serum luteinizing hormone, or both. Clinic staff was blinded to the Fertility Monitor results.

Results:

The PSC Fertility Monitor confirmed ovulation within 2 days of actual ovulation in 16 of the 21 cycles (76.2%), and within 3 days in 20 of 21 cycles, compared to the clinic standard.

Fig. 7



Canadian Trial Data: Fertilite-Ov Vs. Clearplan LH Urine Sticks

Fertilite-Ov Prediction (Ovl)	Canadian Trial Data (n = 21)
within +/- 2 days of actual ovulation	76.2%
within +/- 3 days of actual ovulation	95.2%

Clearplan LH Prediction	Canadian Trial Data (n =12)
within +/- 2 days of actual ovulation	75%
within +/- 3 days of actual ovulation	83%

Conclusion:

From this pilot study, the PSC Fertility Monitor may be comparable to other home methods of ovulation detection in normally cycling women. Further large-scale studies would be necessary to accurately determine sensitivity, specificity, and positive and negative predictive values of this device in a broader population of reproductive aged women.

US Pivotal Clinical Trial of Fertilite (OV-Watch®):

Comparison Devices:	**Fertilite-Ov Fertility Monitor** **Clearplan Urine LH test strips** **Basal Body Temperature**

Summary:

A non-randomized, prospective multi-center clinical trial was conducted at Duke University and Woman's Institute in Philadelphia to assess the clinical usefulness of OV-Watch as a non-invasive method of predicting impending ovulation in women. Dr. Arthur Haney (formerly of Duke) was the Principle Investigator.

A total of 105 female participants were selected for the comparison of two commercially available ovulation predictor products and OV-Watch. Importantly, each device that was involved in the trial measured changes of different parameters. While OV-Watch predicts a woman's 6-day fertile window by monitoring changes in Cl -ion concentration on the skin, Clear Plan Easy measures the luteinizing hormone surge (LH surge) in the urine and the BB Thermometers measure basal body temperature changes, (BBT).

The prevailing standard method for determining ovulation in this trial was the rise in blood LH in each subject. Ovulation was confirmed after 7 days by measuring blood progesterone levels. All patients were accounted for at the end of the study period.

The trial compared the effectiveness of each device at predicting the primary or secondary endpoint, namely making a correct prediction of ovulation with +/- 2 days, or +/-3 days of the actual day of ovulation based on the serum LH determinations for each patient.

The general conclusions from the trial were that Fertilite-Ov was substantially equivalent to other ovulation prediction products on the market, such as Clearplan LH. Based on the results of this trial, a US 510K application was submitted by PSC in March, 2002 for approval of Fertilite-OV as a medical device under FDA guidelines. This approval was granted by the FDA in September of 2002. Thus Fertilite-Ov (OV-Watch®) is currently available for sale in the US as an FDA approved ovulation prediction device.

In a secondary analysis of the data from the trial it was determined that OV-Watch identifies more fertile days of the “fertile window” (as identified by Dr. Allan Wilcox in NEJM , December, 1995) than urinary LH kits. 73% of women using OV-Watch in the trial versus 13% of those using LH kits detected 4 or more of their fertile days and 56% of these women actually detected 5 to 6, while 0% of the urinary LH kits users could make this claim. Additionally, nearly 66% more pregnancies are estimated to occur by month 6 with OV-Watch versus LH kits.

Sweat Chloride Changes and the Menstrual Cycle – U.S. Pivotal Clinical Trial.

Abstract:

This study was undertaken to examine how the eccrine sweat chloride concentration on the skin changed in women over their menstrual cycles during the US pivotal clinical trial. Sweat chloride concentration was followed over the cycles of 40 spontaneously-ovulating women, as part of a multi-centered trial on a novel fertility predictor (PSC Fertilite-OV/OV-Watch®). Data was collected automatically 12 times per day using watches with a specially constructed ion selective electrode and a computer-controlled data logger. The time of ovulation was confirmed using blood luteinizing hormone (LH) levels. Estradiol E2 was also monitored, which allowed a comparison of the levels of these two hormones with respect to the changing chloride ion pattern on the skin. The average chloride ion level increased to a broad peak around 1.25M, 5-7 days prior to ovulation. This was followed by a rapid decline to about 0.75M at 2 days prior to the blood LH surge. A second peak at 1.3 M occurred at the day of ovulation or the day after (blood LH +2). The chloride ion level then decreased somewhat again over the luteal phase, with a final peak (1.38M) a few days prior to menstruation, at 9 days after ovulation. These observations suggest that changing menstrual cycle hormones have an effect on the eccrine sweat duct chloride release, forming a pattern that can be used to predict the time of occurrence of the various phases of the menstrual cycle.

Introduction:

Menstrual cycle hormones such as estrogen have long been known to have an effect on sweat chloride release via its effect on aldosterone, an electrolyte homeostatis-regulating hormone. Liebermann[1] was the first to observe a peak in sweat electrolyte levels around the time of ovulation, and also noted a second peak before menses. Taylor et.al.[2] also observed a peak in sweat resorption near the time of ovulation. Both of these studies used readings spaced several days apart and thus gave only a crude measure of the pattern of chloride ion secretion in sweat over the menstrual cycle. In this paper we report a more detailed study of the sweat chloride ion concentration over the menstrual cycle in 40 spontaneously-ovulating female subjects, using measurements collected multiple times per day using a wearable data logger (OV-watch®).

Materials and Methods:

Healthy women, ages 21-40, which were not actively using contraception or fertility-promoting drugs, comprised the study group. By history, they had regularly occurring menses at 25-34 day intervals. They wore the fertility monitor device overnight, for at least 6 hours. During these six hours, the device would attempt to collect a reading from the chloride ion selective electrode in contact with the wrist, and store this data to memory. It would collect up to 12 readings overnight, which were averaged every calendar day to generate the daily reading. The daily reading information contained within the memory of the device was then downloaded at the end of the luteal phase of the cycle as part of a scheduled office visit with the trial nurse. Serum sampling of estrogen and LH were performed on each subject starting around 4 days prior to the expected LH surge, and continued until a LH surge was detected. The LH testing was performed at each trial site, but estrogen samples were frozen, stored, and measured at a central laboratory. A serum progesterone level of over 4 ng/mL one week after the LH surge was used as proof positive of ovulation. The day of ovulation was defined as the day of the blood LH surge +1. The blood LH surge day was defined as the day of LH value greater than 15 I.U., where the previous day was less than 15 I.U., and at least one day previous had an LH value less than 10 I.U.

Of the 70 spontaneously-ovulating women who completed the trial, 40 had complete chloride ion data, and this group's data was used in this analysis.

Results:

Fig. 8 shows the average chloride ion level on the skin for the 40 female subjects over their menstrual cycle. Day 0 is the blood LH+1 day, the day of presumptive ovulation. At 5-7 days prior to ovulation, there was a distinct rise in the chloride ion concentration, peaking around 1.25M (shown with numeral I). This was followed by a rapid decline to a minima at 3 days prior to ovulation (II). A second peak occurred just after the LH surge, the day after presumptive ovulation (III). Finally, a fourth peak (IV) occurred at 9 days after ovulation, 4 days prior to menses, which on average started on day 13 after Ov (range day 8-16). The average cycle was 27.5 days long. Fig. 9 shows the average estradiol E2 levels and luteinizing hormone levels measured concurrently in the same group of female subjects. The chloride ion pattern is superimposed onto this graph for comparison purposes.

Fig. 8:

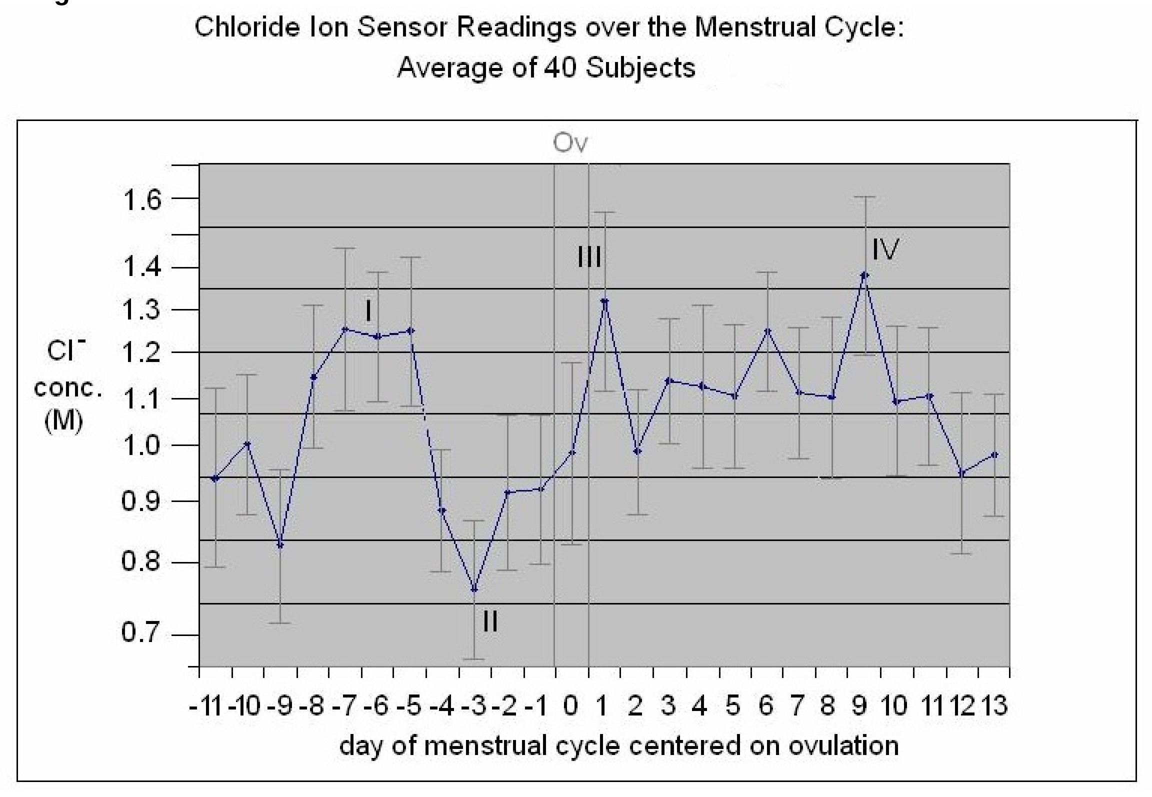
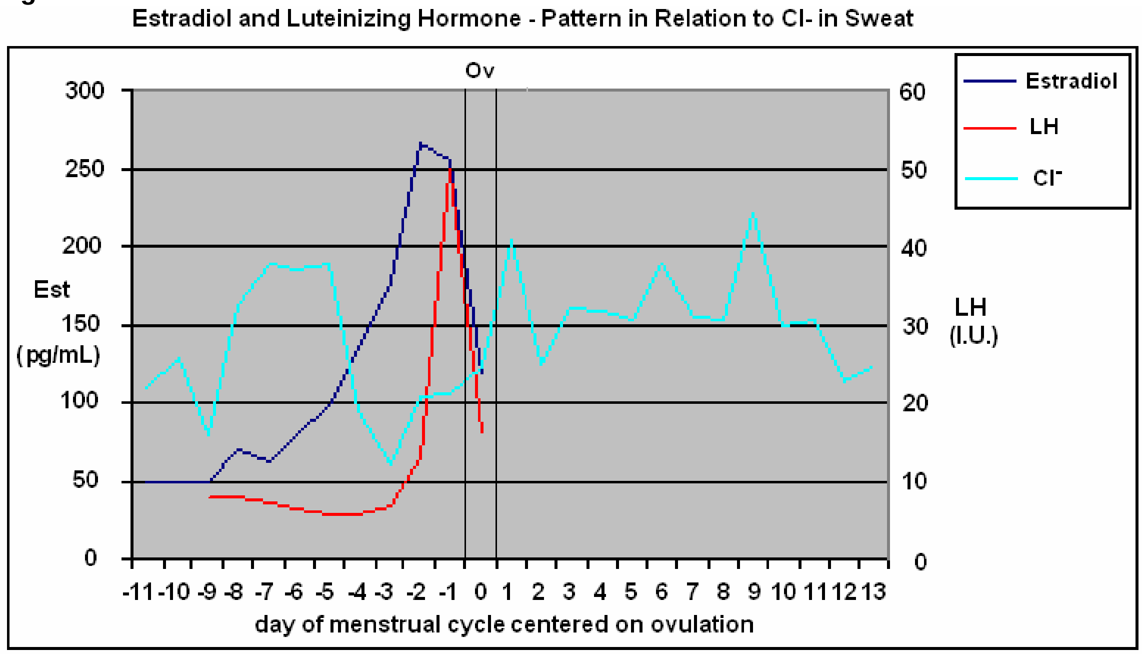


Fig. 9



Estradiol and Luteinizing Hormone - Pattern in Relation to Cl- in Sweat

Discussion and Conclusions:

The data obtained in this study shows a distinct pattern of chloride ion change over the menstrual cycle. This pattern of ductal chloride secretion is consistent with that previously reported.[3,4] However, this latest study combines the results of the largest group of female subjects to date, and includes the luteal phase for the first time.

Sweat chloride levels are governed by the body's electrolyte-regulating hormones. The rennin-angiotensin system, including aldosterone is responsible for sweat resorption. Atrial natriuretic peptide (ANP) is largely responsible for increased excretion. The menstrual cycle hormone estrogen is known to cause sodium retention, likely through its influence on aldosterone. Progesterone has an opposite natriuretic effect due to aldosterone antagonism.[6] Thus the sweat chloride excretion pattern is likely a complex interaction of these competing factors. The rise in chloride excretion 5-7 days prior to ovulation can not be explained by any one factor, but corresponds in time to the first rise in follicle stimulating hormone (FSH) and the selection of the dominant follicle. The 5-6 days leading up to and including ovulation are dominated by the resorption pressure of rising estrogen – the chloride level reaches its lowest level near the peak in estradiol E2, and then increases again to a second peak at the mid-cycle minima of estrogen. The luteal phase pattern is more variable due to the counteracting effects of both estrogen and progesterone. A final chloride ion peak was observed at 9 days after ovulation (about 4 days prior to menses). This corresponds roughly to the latter part of the expected peak in progesterone and 17-hydroxyprogesterone.[5] Clark also noted a peak in ANP at this time.[6]

What this latest study suggests is that menstrual cycle hormones influence the pattern of chloride ion released in sweat, and this pattern can be potentially used to give prospective notice of oncoming ovulation. The HWS OV-watch® is the first product on the market to use this methodology to predict the fertile period for women.

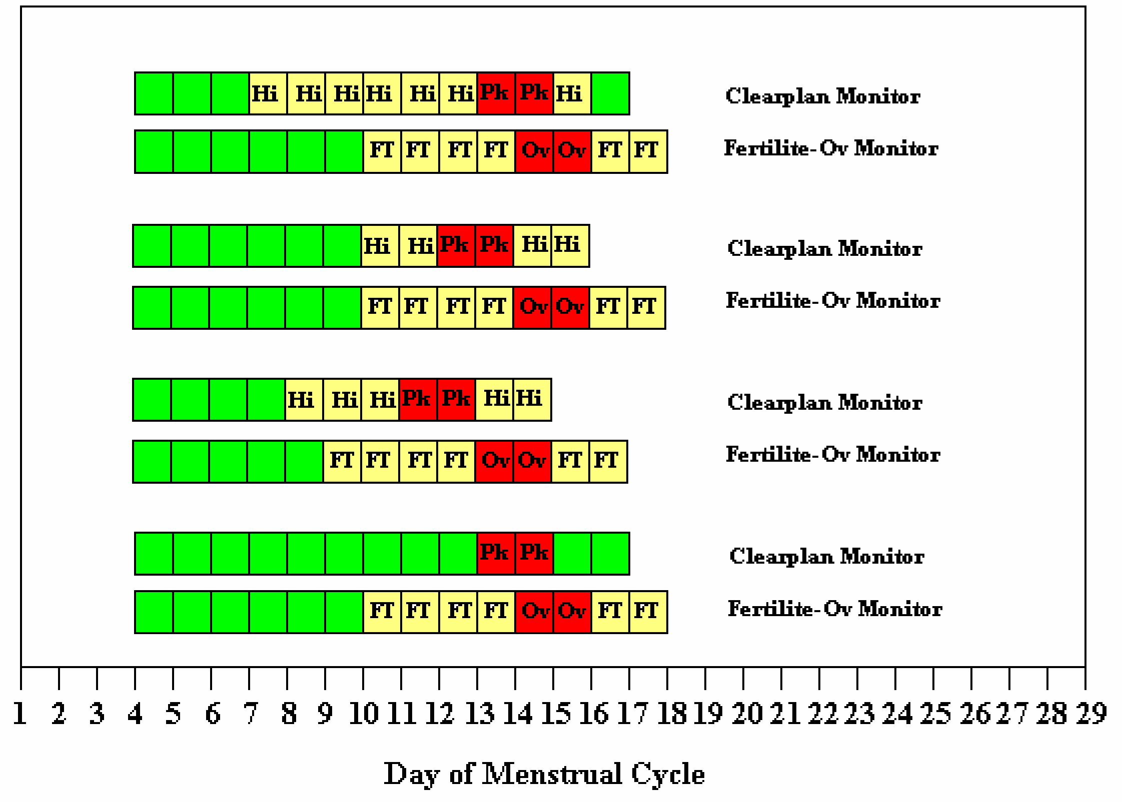
References:

1. Lieberman, Jack (1966), JAMA, Vol.195, No.8, p.117-123.
2. Taylor, Richard J., et.al.(1969) J. of Invest. Derm. Vol. 53, No.3, p.234-237.
3. US patent No. 5,685,319.
4. US patent No. 6,592,529.
5. Usuki, Satoshi, et.al., (2000) J. of Cardiovascular Physiology 36 (suppl.1):S421-S427.
6. Clark, Barbara, et.al., (1990) J. of Clinical Endocrinology and Metabolism., Vol. 70, No.2 , p. 349 – 352.

The Fertile Window:
Comparison of OV-Watch® to the Clearplan Fertility Monitor.

Both of these devices present a fertile window to the user prior to ovulation to allow the women to use as many fertile days as possible. However, the two devices vary considerably on how they present the fertile window. The OV-Watch® presents a consistent 4 day window prior to its prediction of ovulation, based on the symptomatic changes in sweat ions on the skin. The Clearplan monitor, on the other hand, creates a window of elevated fertility based on the urinary estrogen level of the woman crossing a specific threshold. It then indicates peak fertility (i.e. ovulation) after detecting the urinary LH surge. Due to the wildly different baseline urinary levels of estrogen in women, however, this results in a fertile window prior to ovulation which can be anywhere from 0-7 days long, based on data from their own Physicians Brochure (Clearplan Easy Fertility Monitor – Professional Information Brochure, Unipath, Inc., P. 9) Figure 10 below presents an actual comparison of the two products tested side by side over 4 menstrual cycles by study subjects.

Fig. 10:



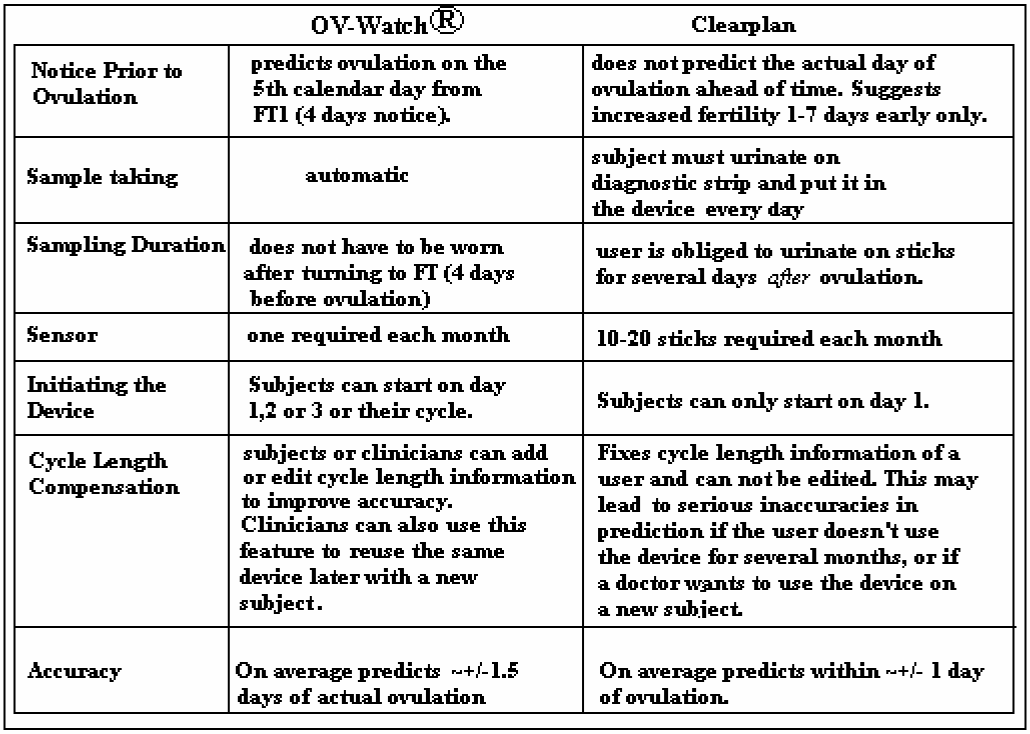
Comparison of Clearplan LH Monitor to Fertilite-Ov in Four Menstrual Cycles.

As can be seen from the figure, the predictions of ovulation by the two devices were close or overlapping. However, whereas the fertile window provided by Fertile-Ov (OV-Watch®) was a consistent 4 days prior to the ovulatory window, in the case of Clearplan, the “high fertility” window varied wildly from 0 days in length to six days in length. *The fundamental difference is obvious – a women using the OV-Watch®, once alerted of the start of the fertile window, will know she will ovulate about 4 days later (average uncertainty is about +/-1.5 days). With the Clearplan Fertility Monitor, on the other hand, the start of high fertility window provides no information about when to expect ovulation – it could be 7 days away, or it could be the next day.*

Consequently, the OV-Watch® provides a real advantage to its closest competitors when providing advance warning of ovulation.

Table 3 below highlights some of the additional advantages of the OV-Watch® over the Clearplan Fertility Monitor.

Table 3:



	OV-Watch®	Clearplan
Notice Prior to Ovulation	predicts ovulation on the 5th calendar day from FT1 (4 days notice).	does not predict the actual day of ovulation ahead of time. Suggests increased fertility 1-7 days early only.
Sample taking	automatic	subject must urinate on diagnostic strip and put it in the device every day
Sampling Duration	does not have to be worn after turning to FT (4 days before ovulation)	user is obliged to urinate on sticks for several days *after* ovulation.
Sensor	one required each month	10-20 sticks required each month
Initiating the Device	Subjects can start on day 1,2 or 3 or their cycle.	Subjects can only start on day 1.
Cycle Length Compensation	subjects or clinicians can add or edit cycle length information to improve accuracy. Clinicians can also use this feature to reuse the same device later with a new subject.	Fixes cycle length information of a user and can not be edited. This may lead to serious inaccuracies in prediction if the user doesn't use the device for several months, or if a doctor wants to use the device on a new subject.
Accuracy	On average predicts ~+/-1.5 days of actual ovulation	On average predicts within ~+/- 1 day of ovulation.

The OV-Watch® thus provides real advantages over its nearest competitors by providing a consistent fertile window prior to the prediction of ovulation for its users to utilize as many potential fertile days as possible.