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Potential Fertility – Defining the Window of Opportunity

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The ClearPlan Easy™ Fertility Monitor* predicts the times of high potential fertility, i.e. the times when sexual intercourse is most likely to result in conception. The test procedure identifies the times of specified changes in the concentration of urinary hormone metabolites during each ovarian cycle. The results are displayed in terms of prior knowledge about the time-specific probabilities of conception. This paper contains a summary of the scientific background that led to the development of the ClearPlan Easy™ Fertility Monitor.

KEY WORDS: ClearPlan Easy™ Fertility Monitor; Potential fertility; Ovulation; Conception rates; Urinary luteinizing hormone; Urinary estrone glucuronide

Introduction

For some time there has been a need to develop accurate, easy-to-use self-tests to predict the most potentially fertile times in women who want to plan a pregnancy. The aim of this paper is to highlight the biological concepts and principles that led to the production of the ClearPlan Easy™ Fertility Monitor (developed by Unipath Ltd, UK) for this purpose. The test procedure involves identifying the times of defined changes in the daily concentration of an estrogen metabolite and gonadotrophic luteinizing hormone (LH) in urine. Prior knowledge about the time-specific probability of conception relative to the estimated time of ovulation is used to interpret the test results in terms of potential fertility.

Women who want to become pregnant need to know in advance when the most fertile days will occur after their last menses. We have termed this period 'the window of opportunity'. Women who want to avoid a pregnancy need to know the start and end of each potentially fertile period and about 'the risk of pregnancy' from acts of intercourse either within or outside the derived limits. A personal contraceptive system (PERSONA™)† has been developed (by Unipath Ltd, UK) to identify the times of change in the levels of urinary hormone metabolites.[1] The system involves the use of immunochemical urine test sticks, and an electronic reader and microprocessor.

The ClearPlan Easy™ Fertility Monitor is based on the same technology for identifying potential fertility. There are, however, important differences between the two monitors in the frequency of sampling

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and in the decision-making algorithms that are used – depending on whether the aim is to avoid, or achieve, a pregnancy. The intention, for contraceptive purposes, is to minimize the risk of pregnancy and emphasis is placed on ensuring that the infertile days are accurately located over a long period of time, with little chance of false–positive signals. Conversely, the intention for achieving pregnancy is to maximize the chances of conceiving as soon as possible by predicting the most potentially fertile days for sexual intercourse.

Background

Physiological, biochemical and statistical evidence for cyclical periods of potential fertility in women has been reviewed.[2–4] The scientific principles that underlie the concept of a 'window of opportunity' can be summarized as follows. A 'window of opportunity' occurs only when ovulation leads to the presence of a viable oocyte in the female reproductive tract. Ovulation and the ability of the female and male gametes to meet and form a conceptus, and the ability of the latter to implant in the endometrium, are dependent upon the production of female hormones – primarily estradiol and LH.[2] Defined changes in the production of estradiol and LH (e.g. from the levels of the hormones in serum[5,6] or their metabolites in urine[3]) can be used to predict ovulation and, in relation to calculated conception rates on specific days,[4] the most potentially fertile time.

The 'window of opportunity' becomes the fertile period if pregnancy occurs and day 1 of menses is used as the reference point for serial testing. The dominant ovarian follicle starts to secrete increasing amounts of estradiol from around days 7 – 18 in women with regular menstrual cycles.[7] Increasing levels of estradiol in the peripheral circulation initiate immediate changes in the volume and consistency of cervicovaginal fluid and, around a week later, produce a surge (and distinct peak) in the excretion of pituitary LH.[8] The increased level of circulating LH initiates the resumption of oogenesis, the process of follicle rupture and, hence, presumed ovulation,[9] by initially increasing the supply of blood (and hence oxygen) to the follicle[10] and subsequently effecting its redistribution away from the apex,[11] where rupture usually occurs. LH also decreases the ovarian secretion of estradiol and increases the secretion of progesterone.[3] Higher levels of circulating progesterone are associated with a reduction in the volume[12] and consistency of cervicovaginal fluid,[8] which is associated with reduced passage of sperm into the uterus.[13]

Only a proportion of apparently ovulatory cycles result in the development of a viable conceptus after appropriately timed intercourse. For example, Wilcox *et al.*[14] concluded that daily acts of intercourse during the potentially fertile period failed to produce a viable pregnancy in approximately 66% of presumed ovulatory cycles according to hormonal indices. Accordingly, 'the window of opportunity' can only be described in statistical terms due to uncertainty about the time or occurrence of ovulation, the variable life-spans of the ovum and sperm in the female reproductive tract,[4] and the contribution of other factors to the potential fertility of an individual couple.

Tests of potential fertility

Between the 1950s and the 1990s, significant progress was made in developing technologies to improve the ability of women to identify the probable time of ovulation[15] and to locate the outer limits

of the fertile period. In particular, the approaches moved from the very imprecise technique of calendar rhythm, and the limited use of basal body temperature (BBT) measurements, to monitoring changes in the quantity and quality of cervical mucus; from relatively unsophisticated bioassays and colorimetric methods to immunoassays for the measurement of reproductive hormones; from complicated laboratory procedures to simple do-it-yourself methods for the measurement of human chorionic gonadotrophin (hCG) and LH; and from the first use of transabdominal ultrasonography in the late 1970s and early 1980s to observe follicular development and rupture to transvaginal color Doppler imaging. The latter also permits the study of blood velocity changes in the follicle, corpus luteum, uterine arteries and endometrium.[16]

Research into the measurement of hormones in different body fluids resulted in the recognition that salivary progesterone could be used as a good marker of ovulation and luteal function and that measurement of the urinary metabolites of estradiol, LH and progesterone could be used as a proxy for plasma or serum hormone levels and patterns of secretion.[17] The development of home assay kits for urinary hCG to diagnose or confirm pregnancy, and the urinary LH tests to assist in identifying the days of maximum fertility, made the term 'kitchen chemistry' a reality.

Role of the World Health Organization (WHO)

In 1973, the WHO Special Program of Research, Development and Research Training in Human Reproduction convened a Task Force to monitor and encourage work in the area of ovulation detection. The Task Force started with the limited scope of understanding the hormonal control of ovulation and developing indirect methods to assess whether the event was likely to have occurred during a particular menstrual cycle.

By the end of the 1970s, the Task Force redefined its mandate to include methods for the prediction of ovulation and, subsequently, it expanded its brief to become the Task Force on Methods for the Determination of the Fertile Period. Author JM Spieler was the Manager of the Task Force from its inception to 1983, and author WP Collins was a member of the Steering Committee of the Task Force and the primary consultant for its work on ovulation prediction and detection.

In order to empower women to determine the times of potential fertility using hormonal measurements, the Task Force embarked on a worldwide program to seek and develop simple immunochemical tests that could be used in the home to predict or detect ovulation. Another early objective was to determine the temporal relationships between ovulation and defined changes in the level of circulating hormones.[5,6] The principal findings are summarized in Table 1.

A decision was then made that the measurement of estradiol or a primary metabolite would offer the best opportunity to predict ovulation early enough to account for the fertilizing life-span of sperm in the female reproductive tract. Since it was also decided that the measurement of plasma or serum hormones was impractical for home use, it was necessary to identify which of the urinary metabolites of 17β-estradiol could be used to form the basis of a home test.

Urinary hormone metabolites

The measurement of urinary, rather than plasma/serum, hormones was chosen because the procedure is safe and makes frequent

TABLE 1:
Temporal relationships between defined hormonal indices of ovulation

Variable	No. of observations	Evidence of ovulation	Time to ovulation (h)		
			Median	Min	Max
Plasma estradiol rise[5]	64	Histological	83	54	172
Urinary E3G rise[8]	58	Urinary LH peak	118	24	240
Plasma LH rise[5]	97	Histological	32	24	56
Urinary LH rise[16]					
6-hourly sampling	11	Follicle rupture	32	24	48
24-hourly sampling	11	Follicle rupture	24	8	48

E3G, estrone-3-glucuronide; LH, luteinizing hormone.

sampling easier; it is non-invasive and practical, and it is less stressful for the woman. The principal immediate metabolites of 17β-estradiol are estradiol-17β-glucuronide and estradiol-3-glucuronide (Fig. 1). Estradiol is also readily converted to estrone, which is metabolized to estrone-3-glucuronide (E3G). The metabolic process tends to favor the formation of E3G, therefore the reagents used to measure this and other urinary metabolites of estradiol[18] (and of progesterone) were incorporated into radioimmunoassays.

The WHO Task Force supported many international and multicenter studies to evaluate the excretion patterns of each metabolite and the relationship of defined concentration changes to the time of presumed ovulation (using the LH peak or follicle rupture as reference points). Studies also aimed to determine the most feasible approaches to developing simple methods of measurement.[19 – 21] The end result was the selection of E3G as the most appropriate metabolite for developing simple methods to

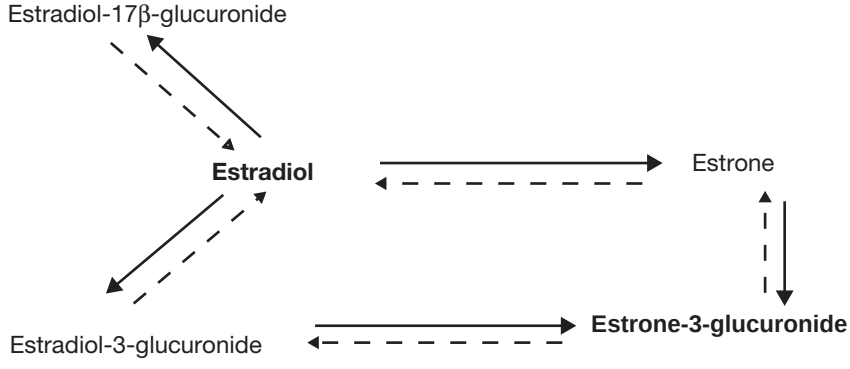

FIGURE 1: Principal interconversions of estradiol and related phenolic estrogens

predict ovulation and the start and end of potential fertility; the urinary concentration of E3G is relatively high compared with other estrogen metabolites and the molecular structure lends itself to the production of reagents for immunoassay. The measurement of urinary LH was selected as the best hormonal method for predicting imminent ovulation.[7,8]

The first one-step immunochemical test for detecting an increased level of urinary hCG was marketed by Unipath in 1988, and a related test for detecting changes in urinary LH (ClearPlan™ One Step)* was released in 1989. The ClearPlan Easy™ Fertility Monitor (and PERSONA™), as described in the paper by May,[22] this supplement, use urinary E3G and LH measurements in early-morning urine samples as the basis for defining the fertile and infertile days of the menstrual cycle. The choice of analytes was based on the close relationship between the serum and urine levels of the respective indices.

Figure 2 shows the levels and patterns of plasma estradiol and urinary E3G in relation to the day of the serum LH peak in 10 women who ovulated regularly.[21] The mean patterns of excretion are almost identical, with a correlation coefficient (*r*) of 0.92. The levels of both estradiol and E3G show a defined rise prior to the LH peak day. A similar relationship between the concentrations of plasma estradiol and

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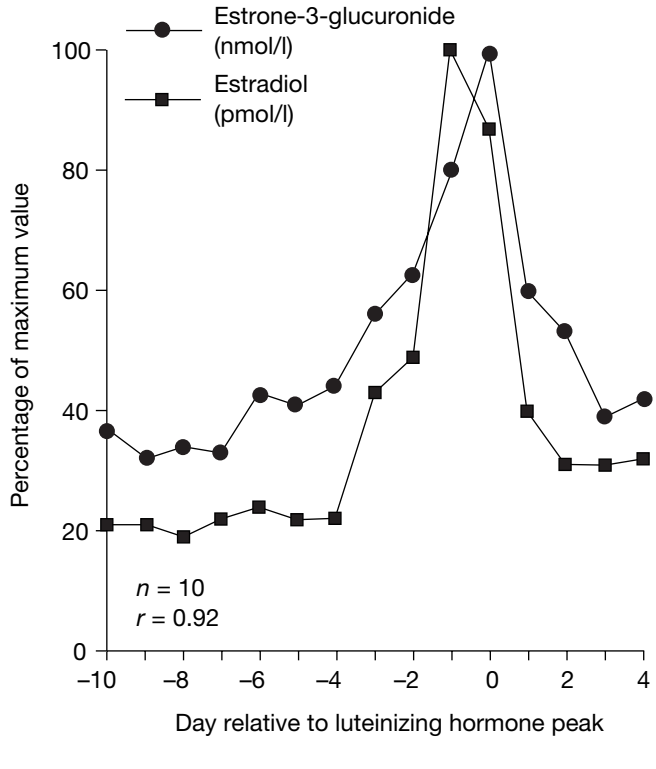

FIGURE 2: Relationship between the mean concentrations of estradiol in peripheral plasma and estrone-3-glucuronide in early-morning urine[21]

urinary E3G was reported throughout 10 control menstrual cycles in a study of infertile women.[23] Either index (serum hormone or urinary metabolite) could be used in an appropriate algorithm to predict the LH peak day and, hence, the presumed day of ovulation.

Depending on where the threshold level (e.g. the defined rise above a baseline value) is selected, it is possible to obtain more, or fewer, days of warning of the LH surge or rise. The results of a large study of 445 women with regular menstrual cycles showed that the median time for a defined rise in the concentration of urinary E3G occurred on day 9 of the menstrual cycle.[7] The time of the defined rise in urinary E3G occurred approximately 118 h before the urinary LH peak (Table 1).[8]

Urinary E3G and cervical mucus

The relationship between the concentration of urinary E3G and the presence and type of cervical mucus within the vagina has been studied over 58 cycles from 10 women.[8] The first day of mucus was defined as the day on which there was a sensation of dampness (i.e. no longer dry) or the first visual appearance of mucus. The first day of fertile-type mucus was the first day that a sensation of wetness or a slippery feeling was recorded (with or without the appearance of any kind of mucus) or the appearance of clear, stretchy mucus. The day of peak mucus was the last day of the fertile-type mucus, which could only be determined retrospectively.

The cumulative frequency (%) of days on which the signals for first mucus and first fertile-type mucus occurred relative to the day of the urinary LH peak is shown in Fig. 3. An algorithm, based on cumulative (CUSUM) analysis, was developed to give a cumulative frequency curve for the day of defined rise in the concentration of urinary E3G, which fell between the curves for first mucus and first fertile-type mucus.[8] The algorithm could be modified to produce a curve to the left or right to obtain more or fewer days warning of ovulation, respectively – depending on the clinical objective. The mean time for the day of peak mucus occurred on the same day as the peak of urinary LH.

Urinary LH and ovulation

Peak LH in daily urine samples was used as an index of ovulation to study the pattern of E3G excretion during regular menstrual cycles.[19] The use of these hormonal indices to validate the value of transabdominal ultrasonography for the detection of follicle rupture (presumed ovulation) was reported in 1980.[24] More recently, a positive ClearPlan™ One Step test result for urinary LH has been used as a reference point to study detailed changes in ovarian and uterine structure and blood flow using transvaginal ultrasonography with color Doppler imaging.[25,26] These studies added further data to support the hypothesis that a good blood supply and complementary structural changes in the follicle and endometrium are associated with high potential fertility.

The temporal relationships between a positive ClearPlan™ One Step test result and follicle rupture, using data from 6-hourly or 24-hourly sampling, have also been reported,[16] and the results are shown in Table 1. It is reassuring that the median and range of values compare favorably with those obtained from the WHO study, which involved defined changes in the level of plasma LH and histological evidence of ovulation.[5] The range of values from the urinary LH rise to ovulation with 24 h sampling (8 – 24 h) suggests that the use of

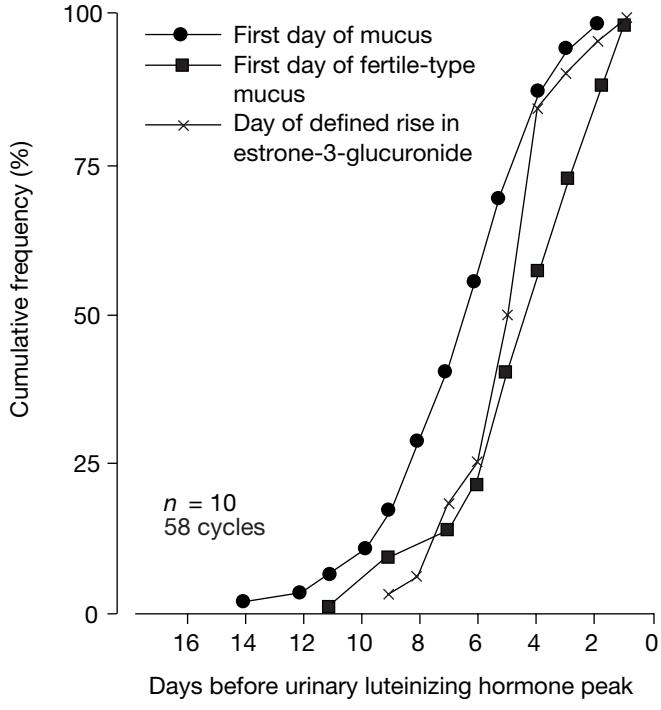

FIGURE 3: Cumulative frequency of days on which first mucus, first fertile-type mucus and a defined rise in estrone-3-glucuronide occurred relative to the urinary luteinizing hormone peak, as reported by women using the symptothermal method of natural family planning[8]

the LH index alone for high potential fertility may occur too late to be of practical value for some women.

Probability of conception

The definitive method for defining the time of potential fertility should determine the probability of conception on different days around the estimated time of ovulation. Several approaches have been used for the same cohort of women based on information about the days of intercourse, the daily BBT values, and the occurrence of viable pregnancies.[27 – 29] The results from a prospective cohort study, designed to investigate early pregnancy loss in healthy women, afforded investigators the opportunity to examine conception and hormonal data from a subgroup of 625 ovarian cycles from 217 women who were planning to become pregnant.[14] The time of ovulation was estimated from the ratio of urinary E3G to pregnanediol-3-glucuronide (PG) in daily early-morning urine samples. There were 129 live births. A single act of intercourse was recorded for 129 cycles (21% of total) during a 6-day potentially fertile period.

The probability of conception from single acts of intercourse on specific days, and from a statistical model, relative to the estimated day of ovulation is summarized in Fig. 4. The probability of pregnancy from single acts of intercourse ranged from 0.08 (5 days before ovulation) to 0.36 (on day of ovulation). The corresponding probabilities from the statistical model and data from all 625 cycles

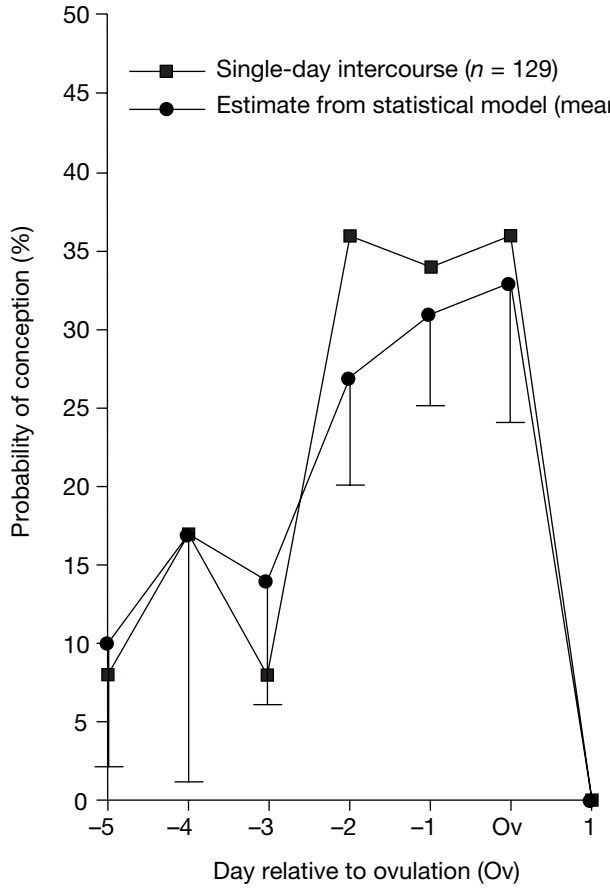

FIGURE 4: Probability of conception from intercourse on specific days relative to the day of ovulation[14]

were 0.10 – 0.33, respectively. The same data and analysis suggest that daily intercourse during the 6-day potentially fertile period would produce the highest probability of conception per cycle (0.37; 95% confidence interval 0.31 – 0.48). The value would be reduced to 0.33 following acts of intercourse that occurred on average every other day, and to 0.15 for untimed intercourse averaging once per week. The probability of conception on different days of the cycle with respect to ovulation using different indices, models and cohorts of women has been reviewed.[30]

Time of most potential fertility

A systematic attempt to investigate the effect of changing variables in a statistical model, to identify the time of maximum conception probability from the concentration of E3G in daily early-morning urine samples, has been reported.[31] Data from 118 prospective cycles (12 conceptional) were analysed. The aim was to obtain a prospective signal of the most potentially fertile days near the time of urinary E3G peak. The best algorithm gave a successful signal in 75% of cycles, and the

mean time interval to the urinary LH peak was –0.87 days. The corresponding values using the time of maximum follicular diameter as the reference point for ovulation in 38 cycles were 82% and –0.42 days. The success rate for the 12 conception cycles was 92%.

These data, together with the studies with ClearPlan™ One Step[25,26] and the life-span of the ovum,[29] suggest that a test based upon the measurement of urinary E3G and LH could be devised to locate the overall time of most potential fertility during an ovarian cycle. Signals from the measurement of both hormone metabolites should enable intercourse to be timed so that sperm have access to the ovum whether their passage is rapid or follows storage in the cervical crypts or in the distal (uterine intra-mural) isthmus of the fallopian tube.[32] Furthermore, an interim report from a European multicenter study of conception probabilities suggests that the number of days with the most fertile-type mucus has a major impact on potential fertility,[33] and we believe this finding should be reflected by the changing levels of urinary E3G and LH and the time interval from the LH signal to the demise of the ovum.

Conclusions

Data accumulated over the past 50 years show there is a good statistical correlation between a number of home, laboratory-based and clinical tests of potential fertility during each ovarian cycle and actual fertility. Moreover, defined changes in BBT or urinary hormone ratios have been related to day-specific conception rates. This information and technical developments in assay format and microprocessing have stimulated the development of the new ClearPlan Easy™ Fertility Monitor, which involves the concurrent measurement of E3G and LH in daily samples of early-morning urine. There is still a need, however, to study the potential effect of many factors such as diet, drugs and strenuous exercise on the efficacy of the test (and even the ability to conceive).

The ClearPlan Easy™ Fertility Monitor is, nevertheless, likely to be a valuable aid to many couples who wish to locate the 'window of opportunity' and conceive as quickly as possible. The test is easy to perform and the results may indicate the need to change lifestyles. It is interesting that preliminary data show that subfertile women significantly improve their chances of conception when a method of stress reduction, or the use of a support group, is included in their treatment.[34] We anticipate that the use of the ClearPlan Easy™ Fertility Monitor by subfertile women should improve pregnancy rates and facilitate research into factors affecting potential fertility and conception.

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