Critique of design flaws of the Unipath Persona – Inverness Clearblue fertility monitor

One competitor device that performs a simple (semaphore-like) electronic interpretation of certain kind of fertility status data is the Persona electronic colorimeter for urine analysis. It is originally from Unipath Ltd. of Britain, acquired by the US firm Inverness Medical (now a joint venture SPD GmbH), and sold in America under the name of Clearblue - only as a tool for assisting conception. It relies on detecting, in a woman's urine, both the luteinizing hormone (LH) surge that typically marks the ovulation day, and also a metabolite of estrogen, i.e., another hormone, which anticipates the luteinizing hormone surge by about one day. Since, unlike our technology, their method depends on biochemical reagents and since the supply of the reagents is limited, the user needs to estimate on which day of her menstrual cycle she should start using the device. She does that based on her history of menstrual cycles as though the length and the timing of the present menstrual cycle were the same as in her previous cycle(s). Because of variable lengths of successive cycles in most women, this is a weak feature in the design of the Unipath system. It is a significant weakness of their ovulation-assessing method, which depends on data pooled from other women and on the user's estrogen and LH data history, if available, stored in the memory of the device.

The Persona Contraceptive System of Unipath Ltd. was an improvement upon the commercially available luteinizing hormone (LH) kits that only aim to detect the LH surge in the woman's urine. Two beneficial features were introduced by Unipath: 1. the addition of an estrogen metabolite to the diagnostic measurement so as to anticipate the LH surge, and 2. the measurement is performed instrumentally rather than as a subjective judgment by the woman-user of a color change. However, ovulation as such is not detected by the Persona/Clearblue device. It is merely assumed to occur some hours after the LH surge. This is a fundamental flaw because ovulation is, in fact, known to fail to occur in approximately 20% of the follicles that, triggered by the LH, undergo the cyclic event of follicle rupture. Ovulation also fails to occur with another type of follicles, the so-called luteinized unruptured follicles. Yet, the LH surge can be seen in either case and is therefore a false indicator. Furthermore, when stress causes a delay or absence of ovulation, this cannot be detected by the hormone-based approach.

Author's contact data: vaclavkirsner@yahoo.com 970-484-1272

A key practical problem of the Persona is that the monitored urinary concentration of the estrogen metabolite E3G peaks only about 24 hours prior to the LH surge. This is not early enough to serve as a marker of the beginning of the fertile phase. The Unipath literature states that "a sustained rise in E3G can be used to identify the start of the fertile phase", referring to a slow gradual increase that eventually becomes the peak of E3G concentration. While the Unipath Persona Personal Contraceptive System was introduced to the market in Britain, the clinical testing of its reliability was still in progress. The attempt by Unipath to use an ill-defined rise - rather than the peak in the cyclic profile of the estrogen metabolite - is not a viable solution to the fertile window problem. Even if the ill-defined E3G rise in the urine were correlated with a clearly defined stage of the egg development towards ovulation, a serious flaw of the Unipath method is their reliance on pooled data in defining the start of the fertile period in a given cycle. The rate of the E3G rise differs from cycle to cycle, as do the blood concentrations of E3G. The initially slow increase of the E3G concentration in the urine proceeds at different rates in different cycles, not only at different rates in different women. The rise cannot be predictably associated with the beginning of the fertile period. The reasons are:

1. Estrogen is known to have both stimulatory and inhibitory effects on LH secretion and, to be effective as a stimulant, it must rise to its peak levels (> 150 to 200 pg/ml) and must remain elevated for at least 36 hours [J. Hotchkiss and E. Knobil in E.Y. Adashi, J.A. Rock and Z. Rosenwaks, editors: Reproductive Endocrinology, Surgery and Technology, Lippincott-Raven Publishers, 1996]. And, the monitored E3G rise indicates something else, namely:

2. The E3G profile does not reflect the local interplay of estrogen with progesterone because it only reflects clearance of one of at least 10 metabolites of estrogen from *peripheral* blood circulation into the urine, after oxidative conversion in the liver. Whatever the rate of this clearance process, there are "local mechanisms due to which the quantification of ovarian steroids in peripheral blood or in urine is rendered interesting but of little value in predicting the genital end-organ effect" [C.J. Verco, in A.M. Siegler, editor: The Fallopian Tube. Basic Studies and Clinical Contributions, Futura Publishing Company, 1986]. This makes for the same basic flaw as that suffered by the Zetek Cue/OvaCue.

Author's contact data: vaclavkirsner@yahoo.com 970-484-1272

Thus, the 2-hormone approach is in the end as inaccurate as the other old techniques. Therefore, it cannot be approved for pregnancy avoidance since the failure rate would be unacceptably high. In fact, a law suit ensued in England when Unipath did sell it as a "contraceptive system", and a number of unintended pregnancies resulted to the users.

Ovarian vein-to-artery exchange of steroids, prostaglandins and other bioactive substances is a local transfer mechanism. As such, it enables local regulation of ovarian, tubal and uterine functions, with genital organs therefore exposed at any given time to hormonal concentrations that are higher than the peripheral concentrations. This kind of acute exposure is of particular relevance to the regulation of the physiology of the genital organs. The local, as opposed to peripheral, blood concentrations of the steroid hormones are also believed to work with the innervation of the female genital tract. The cervix, like the isthmus region of the fallopian tube, has a particularly dense innervation by, for example, the vasoactive intestinal polypeptide nerve [C. Owman et al., idem.]. The effects of these local and acute regulatory mechanisms remain undetected by these prior art techniques that focus on peripheral biomarker variables. The peripheral or systemic techniques then resort to pooled averaged data as though synchronization of menstrual cycles were present. Systemic (in this case, body fluid) monitoring for pregnancy avoidance cannot work. They call for long abstinence period for this reason.

The same flawed assumption of similar timing of menstrual cyclic events from one cycle to another has been a problem for the microprocessor-controlled thermometers. Since the late sixties, the microprocessor technology has been applied by a number of people to the well-tried basal body temperature approach to family planning. This approach is no longer recognized as medically valid even if it may be acceptable to some of the older physicians. This is because the so-called basal body temperature (BBT) is a systemic variable that reflects, among other things, progesterone rise in peripheral blood after ovulation, usually one or two days later. Even though in some women in some cycles a little-understood dip in the temperature graph may be observed one day before the post-ovulatory temperature rise, it is clear that the BBT method is of little value due to its lack of predictive capability and due to its fundamental unreliability. The BBT-rise data is known to have a large error bar since the rise can occur from 3 days before to 3 days after ovulation. Tracking systemic effects (circulating hormones) is not good enough for fertility status determination if the purpose is pregnancy avoidance.

Author's contact data: vaclavkirsner@yahoo.com 970-484-1272