Self-Monitoring of Fertility Hormones: A New Era for Natural Family Planning?

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Abstract

Natural family planning (NFP) methods have served many generations well, and in particular, the symptothermal or symptohormonal methods. The comparison of daily mucus and temperature records for individual cycles with daily hormone measurements, which is now possible, shows that some of the assumptions underlying NFP may not be completely accurate. The various methods are inadvertently depending on an element of chance, which, of course, cannot be known by the NFP user. However, it is statistically inevitable that such errors will result eventually in an unexpected pregnancy, and these discrepancies are the likely reason for the method failures. Further research and integration of home hormone measurements with NFP symptoms are needed.

Summary: Traditional NFP methods, based on the observations of temperature, mucus, and luteinizing hormone, can work well. However, these data are sometimes difficult to interpret, and significant changes in the variables are sometimes “missing” from some cycles. Changes in these variables are elicited by the estrogen and progesterone released from the ovaries. It follows that the direct measures of events in the ovaries are the levels of estrogen and progesterone or their derivatives in blood or urine. Measurements of urinary derivatives of estrogen and progesterone can be used to monitor the ovaries directly and are clearer indicators than traditional NFP methods.

Keywords

urinary hormones, self-monitoring, natural family planning

The possibility of fertility requires (i) ovulation, which is the release of a ripe ovum, or egg, from a follicle, (ii) a previous deposit of spermatozoa into the female genital tract within five to six days of ovulation, and (iii) no confounding factors. After ovulation, the egg remains viable for only eight to twelve hours (Stanford, White, and Hatasaka 2001), but sperm can survive in the genital tract for up to six days, if the conditions are favorable (Pal-lone and Bergus 2009). Thus, conception can occur at any time in this six- to seven-day “fertile window”

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(Xiao et al. 2010; Bigelow et al. 2004). Outside this window, the probability of conception is extremely low. For this reason, it has been stated that for 80 percent of a woman's reproductive life, she could not get pregnant even if she wanted to.

A couple's fertility is determined by the combination of male and female factors, and a couple's knowledge of their combined fertility is necessary if they are to optimize their chances of pregnancy and also if intercourse is desired but pregnancy is not (Thijssen et al. 2014). Successful self-management of fertility requires access to accurate markers of the beginning of the fertile window, the day of ovulation, the most fertile day of the cycle, and the end of the fertile window. It is also useful to be able to determine whether a pregnancy has been achieved or might have been possible based on markers of the quality of the corpus luteum that develops and then regresses in the time after the fertile window closes.

The physiology of the menstrual cycle is complex (Beshay and Carr 2013) and not completely, or widely, understood. The textbook model involves important roles for follicle-stimulating hormone (FSH) and luteinizing hormone (LH), but, whatever be the fine details of their modes of action, neither is a definitive marker of ovarian events. Both suggest, or predict, that a specific result could follow (World Health Organization 1980), but the expected result may not occur at all or only occur in part (Kesner et al. 1998). Hence, markers that relate directly (or positively) to the actual physiological events of follicle growth, ovulation, and corpus luteum formation are necessary. When a follicle starts to grow in the ovary, there are two possible outcomes: it may change from excreting mainly male hormones (androgens) to start excreting female hormones (estrogens) as well, or it may fail to achieve this transition and die. Only the first path can, although not necessarily, lead to ovulation. The key to this successful transition is that the follicle starts to produce an enzyme (aromatase) that converts male steroid hormones into female steroids. This happens when the follicle is about four to ten millimeters in diameter, and from then on, the follicle is the dominant source of estrogens in the female body (over 80 percent of the total and increasing with time until ovulation occurs). This means that a rise in serum estradiol (the main bioactive estrogen) indicates definitively that a follicle is well established and the possibility of fertility must be assumed. Fortunately, this occurs on average about six days prior to ovulation, which gives sufficient warning to account for the longest sperm survival times (Blackwell and Brown 1992; Blackwell et al. 2013).

Which Are the Best Biological Markers of Fertility?

Ovulation is the key event in the menstrual cycle, and knowing the day it occurs is central to the practice of natural family planning (NFP). When ovulation occurs, the high estrogen production ceases for a period, and this results in a sharp mid-cycle peak in estrogen production. This peak is recognized easily and is therefore a good marker of ovulation that occurs usually in the following twenty-four to thirty-six hours (Martinez et al. 1995). The follicle from which the ovum has been released produces a second hormone (progesterone) around the time of ovulation, and luteinization, a process in which the remnants of the follicle convert to a corpus luteum, can be observed as a massive increase in serum progesterone (Hoff, Quigley, and Yen 1983). These increases in progesterone differentiate between the preovulatory follicle that defines the end of the fertile window and any earlier, nonovulatory peaks in serum estradiol that may occur (Alliende 2002; Baerwald, Adams, and Pierson 2003; Blackwell et al. 2013). Ovulation must occur between the day of the estrogen peak, which is usually accompanied by a small rise in progesterone (Hoff, Quigley, and Yen 1983), and the following rapid increase in progesterone associated with luteinization.

Estradiol and progesterone are thus definite or positive markers of the mid-cycle events and should be the physiological indicators of choice for accurate monitoring of a menstrual cycle. The markers indicate definitively the presence of a growing follicle and show when ovulation has actually occurred, or is occurring, within a day (Brown and Gronow 1985).

Follicle stimulating hormone (FSH), as the name suggests, stimulates the growth of a cohort of follicles. However, a rise in FSH indicates only that a number of follicles may be growing, but not that one is on a trajectory ending in ovulation. Most of the cohort become atretic and do not excrete estrogens (Gore et al. 1995). Simply knowing that FSH has increased does not ensure that the events anticipated will follow. In marked contrast, rising estrogen excretion rates are almost certainly due to a dominant follicle. Hence, if the estradiol secretion rate rises, then it is clear that FSH has carried out its function correctly.

Similarly, although rising LH levels are related to ovulation and luteinization of the follicle remnants, the increase cannot provide certainty that ovulation has occurred. However, if the progesterone secretion rate increases, it is certain that luteinization has

occurred to some extent. The release of an ovum from a follicle at ovulation may lead to a fully functioning corpus luteum, but there are many other possibilities that only estradiol and progesterone hormonal markers can identify. Therefore, estradiol and progesterone are the best and most reliable markers of the ovarian events: these two direct markers emanate directly from the ovary, but all others, for example, FSH, LH, mucus, and basal body temperature (BBT), are indirect. It is also understood that calendar-type calculations are not needed, as real-time monitoring of both estradiol and progesterone means that any cycle can be monitored accurately as it unfolds, irrespective of whether it is short, long, normal, or abnormal. In effect, it is possible to infer ovarian function accurately by monitoring the chemical messages from the ovary.

Unfortunately, no serum estradiol or progesterone home assay exists, and even if it were, daily blood sampling is not a practical option. Fortunately, metabolites of estradiol and progesterone (estrone glucuronide [E1G] and pregnanediol glucuronide [PdG], respectively) are excreted in urine, and it is well established that the rates at which these metabolites are excreted give the same information as serum estradiol and progesterone (Munro et al. 1991). When the urinary E1G excretion rate increases significantly, a follicle must be growing, and in the absence of any other information, potential fertility must be assumed. Once started, the follicle will grow for another four to five days on average, and each day, the E1G excretion rate will increase by 30–40 percent until the sharp drop occurs, which defines the mid-cycle peak (Brown 2011). In association with this drop, rising urinary PdG excretion rates will confirm ovulation. Ovulation occurs between the E1G peak day and the rise in PdG excretion rate. A series of universal thresholds in the PdG excretion rates serve to define reliably the end of the fertile window for all women and identify any cycle variants (Blackwell et al. 2013; Brown 2011). Hence, a woman can monitor her cycles simply, but accurately, at home based on these changes in E1G and PdG excretion rates (Blackwell et al. 2003, 2012, 2013, 2016).

An underappreciated aspect of this is that reliable measurement of the excretion rates requires that the daily fluctuations in the rate of urine volume production, which can exceed 10 fold and hence mask the daily rises (Blackwell, Brown, and Cooke 1998), are taken into consideration. Johnson et al. (2015) claimed that urine volume correction is unnecessary but did not substantiate this assertion with any measurements of excretion rate.

Ordered and Disordered Cycles: Classification on the Basis of Urinary Steroid Profiles—The Continuum

Before considering the various indirect markers of fertility, it is essential to have an appreciation of the possible variants of the menstrual cycle. A cycle can be fertile, subfertile, or infertile, and it is important to know which of the variants can be followed by a normal ovulatory cycle without an intervening bleed. It is clearly important to know whether a marker gives an unexpected result that the cycle was normal, before deciding that the marker is deficient.

The possible menstrual cycle variants are described by professor Brown (2011) as the “continuum” and are also defined by the changes of follicular and corpus luteum hormone secretion as measured each day by E1G and PdG excretion rates in urine (or estradiol and progesterone in blood). These variants range from those in which there is no follicular activity to those with fully fertile ovulatory cycles in which there is follicular activity but no ovulation and those with increasing maturation of the ovulatory mechanism (Brown 2011). Brown envisaged a continuous gradation of these variants which he called the continuum based on the hormonal profiles and considered that all the variants he had observed were normal responses to the physiological environment.

The cycle variants do not necessarily repeat themselves from cycle to cycle. For example, a woman may experience periods of amenorrhea, irregular anovular bleeding, luteinized unruptured follicles, or deficient or short luteal phases interspersed with fully fertile cycles. When familiar patterns of fertility are replaced by unfamiliar variants, a knowledge of the continuum is necessary to reassure women. These variants can only be identified unambiguously by hormone measurements.

Three widely held beliefs about women’s reproduction are not true, and medical practice would benefit considerably from their correction.

- (1) *All types of ovarian activity that are not potentially fertile (i.e., cannot cause a pregnancy) are abnormal.* The menstrual cycle is a complex system that is exquisitely susceptible to a wide range of influences and so a fully fertile ovulatory cycle is no more “normal” compared to any other nonpathological variant.

- (2) *All ovulatory cycles are fertile.* Certain types of ovulatory cycles (deficient luteal phase) are infertile, and these can be recognized from the hormone output during the luteal phase. These explain apparently erratic fertility.
- (3) *A history of regular menstrual cycles is evidence of regular ovulation.* The hormone results show that this is only partially true (Blackwell et al. 2013) and that anovulatory activity can be associated with regular bleeding patterns.

The possible sequels to the variants of the continuum need to be understood by women, that is, whether they intend to achieve or avoid pregnancy, because continuation of established patterns of fertility can never be assumed. Vigilance is always required to detect the onset of fertility.

There are many reasons for a disordered cycle. In home monitoring of fertility, it is usual to simply divide them into those that are considered normal versus those that are anovulatory or exhibit some sort of luteal deficiency. Essentially, a normal cycle exhibits an LH peak, cyclic changes in E1G in the follicular and luteal phases, mid-cycle and luteal phase increases in PdG and usually lasts between twenty-four and thirty-six days. Disordered cycles lack one or the other features or fail to meet specific thresholds. Usually, disordered cycles are considered to be relatively rare, but the literature concentrates on normal cycles, ovulation, and instances of pregnancy, so the data appear to be relatively dispersed. Based on the available data (e.g., Blackwell et al. 2016), it is not unusual for 10–20 percent of a population with supposedly normal cycles to be disordered (usually either anovulatory or with a deficient luteal phase).

The Indirect Indicators (FSH, LH, Cervical Mucus, and BBT)

Direct observation of the ovaries using ultrasound is considered the “gold standard” measure of the cycle’s progress, which is obviously not a viable home method. On ovulation, the follicle ruptures rapidly and fills with blood, forming the corpus hemorrhagicum, within an hour (de Crespigny, O’Herlihy, and Robinson 1981). Subsequently, the corpus luteum appears as a hypoechoic center enclosed by thick hyperechogenic walls (Bakos et al. 1994), which is observed sometimes but not always. Although ultrasound is said to be the best means of determining the day of ovulation, it has some

difficulties and is not always unambiguous. In some cycles (11 percent), one of the two or three apparently dominant follicles collapses during the preovulatory phase, prior to the actual ovulation (Ecochard et al. 2000).

The common measures used to monitor the menstrual cycle are LH, estradiol, progesterone, BBT, mucus, and vulval sensation. Of these, we distinguish direct measures (estradiol and progesterone or E1G and PdG), emanating directly from the follicle or corpus luteum, from indirect measures (LH, BBT, mucus, and sensation) that are usually elicited by changing estrogen (observed as serum estradiol or urinary E1G) and progesterone (observed as serum progesterone or urinary PdG). Indirect measures are used in most methods of natural family planning. In an ideal situation, all of these would be available, but in general only a subset is used. This prompts one to ask how reliable and how consistent these indirect measures might be.

Since the late eighties the E1G and PdG excretion rates were measured reliably and accurately at home (Blackwell et al. 2003, 2012, 2013, 2016), but the method is not readily available. So most women have had to rely entirely on the indirect indicators if they wish to avoid invasive or chemical methods of family planning. Over many years, in a variety of NFP methodologies, comprehensive sets of rules have been established to cover most eventualities in a woman’s reproductive life. It has been shown in many studies that the symptoms are closely, but not exactly, related to serum estradiol or progesterone or their urinary metabolites. For example, it has been shown that the mucus peak day occurs within ± 3 days of ovulation in close to 100 percent of cycles (Brown, Holmes, and Barker 1991; Fehring 2002; Guida et al. 1999; Hilgers, Abraham, and Cavanagh 1978; Ecochard et al. 2015) and within ± 1 day of ovulation in 78 percent of cycles (Brown et al. 1987). An important but unresolved question is what is the relationship of the 22 percent (with a mucus peak ≥ 2 days before or after ovulation) to the underlying daily urinary PdG excretion rate profiles for the NFP practice, and little research has been published on this issue.

The assumptions underlying the use of the indirect indicators in natural fertility regulation methods are as follows:

1. The cervical mucus characteristics depend on the circulating levels of estrogens in a predictable way and indicate the start of the fertile window (Thijssen et al. 2014).

2. When the serum progesterone concentration rises, it
 - a. changes the mucus characteristics in a recognizable way (Thijssen et al. 2014), culminating in the “peak mucus” symptom, however defined, which is used to estimate the end of the fertile window by adding four days
 - b. causes a shift in BBT (Thijssen et al. 2014), which is recognized retrospectively and can be used to estimate the end of the fertile window by adding three days.

Reliability of the Indirect Indicators (LH, BBT, and Mucus)

These self-observed symptoms have been used for many years by women to manage their own fertility noninvasively and without drugs with varying degrees of success. The fact that these natural methods of fertility regulation are still not widely used indicates the requirement of something more. It is now possible to compare the daily mucus and/or BBT records of trained NFP users with the underlying direct indicators, that is, using urinary E1G and PdG excretion rates as done in a World Health Organization–sponsored study (Blackwell et al. 2003, 2012, 2013, 2016). Only in this way can the questions be asked as to how reliably the indirect measures of daily self-observed symptoms reflect the underlying daily hormonal changes (the direct measures), which are directly related to the physiological events in the ovary.

The main questions to be answered are as follows:

1. How accurate are these natural indicators?
2. How reliable are the underlying assumptions?
3. Does it matter?

As far as the indirect indicators and the symptoms are concerned, the following behavior should be expected (Brown 2011):

- (i) an LH peak should be expected in all cycles, except those in which estradiol and progesterone are consistently low, because estradiol is supposed to trigger LH release and estradiol increases in all the other variants;
- (ii) mucus symptoms should be expected in all cycles, except those in which estradiol and

progesterone are consistently low, because estradiol is supposed to cause mucus secretion from the crypts of the cervix (Menárguez, Pastor, and Odeblad 2003) and estradiol increases in all the other variants; and

- (iii) a biphasic BBT record should be expected in all cycles, except the variants where only estradiol increases because progesterone is supposed to cause the BBT shift and progesterone increases to some extent in all other variants except during the anovular cycles.

Experience has shown that the above expectations are not always met. When used individually or in combination, BBT, LH, and mucus symptoms are capable of identifying only a proportion of the common cycle variants defined by estradiol and progesterone or their urinary metabolite excretion rates. However, the addition of quantitative measures of E1G and PdG, urinary surrogates for serum estradiol and progesterone, represents a more powerful tool compared to a combination of LH, BBT, and mucus symptoms or of E1G and LH.

LH Peaks

Evidence shows that the LH peak is “missed” in a significant proportion of cycles. An LH peak is said to be missing rather than absent because it is assumed that LH is essential for initiating ovulation. A meta-analysis shows that the proportion of missing LH peaks varies considerably, but on average, the LH peak is missed in about 13 percent of cycles (reports range from 0 percent to 57 percent; Baird et al. 1991; Bischof, Bianchi, and Campana 1991). For example, in a study of 113 normal cycles, only 101 had a discernible LH peak (Blackwell et al. 2013). The LH peak can also be split, complex, prolonged, and small (Alliende 2002; Blackwell et al. 2013; Ecochard et al. 2015), and there may be peaks in the cycle at “unexpected” times, including the luteal phase (Blackwell et al. 2013; Ecochard et al. 2015). It is possible to (a) ovulate without seeing an LH peak, (b) not ovulate despite seeing an LH peak, and (c) see an LH peak and ovulate. Such patterns might be difficult for many women (and most software) to interpret, which prompts one to doubt the absolute reliability and status of LH as the gold standard indicators of ovulation. An LH peak is not an absolute indication for ovulation (Zalanyi 2001), and so an LH peak, or the lack of such a peak, is always potentially ambiguous.

Cervical Mucus

Changes in cervical mucus are not always detected even if women are specifically trained to recognize them (Fehring 1990; Ecochard et al. 2015), and considerable training may be required before a woman becomes competent and confident in interpreting her symptoms. One important use of the ovarian monitor was to give a woman confidence in her mucus symptoms. A meta-analysis of the literature suggests that the overall mucus symptoms are not reported in about 10 percent of cycles of apparently normal cycling women (reports of missing mucus symptoms ranging from 0 percent to 24 percent; Depares et al. 1986; Ecochard et al. 2001). Most studies involving NFP do not include these women as only an experienced user can be included in the study, and thus, these study subjects are a self-selected group. Moreover, the mucus symptom does not prove the occurrence of ovulation, for example, in breastfeeding women, mucus symptoms are reported even in the absence of increasing estrogen levels (Kennedy et al. 1995). Furthermore, a small percentage of women show an increase in urinary PdG levels, when the change in cervical mucus characteristics that define the mucus peak day occurs later, or they report a mucus peak symptom when there is no rise in urinary PdG (Blackwell et al. 2016), and thus, the mucus peak is recorded early. This casts doubt on the simple dependence of a mucus peak symptom on an increase in serum progesterone. More research is needed regarding early mucus peaks and their relationship to the underlying serum estradiol and progesterone values as measured by the E1G and PdG excretion rate profiles.

Not everyone can detect mucus, and even those who can do not always do so. How certain can a woman be with the interpretation of her mucus symptoms? There may always be some doubt in some women leading to the associated tension.

The BBT Shift

The history of menstrual cycle monitoring using BBT is extensive (Fricke 1838; Palmer 1949; Viville 1912). However, the BBT shift does not always occur, and a monophasic BBT is recorded to indicate that progesterone failed to reach a level sufficient to increase the temperature (Kesner et al. 1992). A meta-analysis of the literature shows that a BBT shift is not detected in about 2 percent of apparently normal cycling women (reports range from 0 percent to 69 percent; Depares et al. 1986; Kesner et al. 1992). We found (Blackwell et al. 2016) that for a small

percentage of women, a rise in urinary PdG levels is possible, with no associated BBT shift, and a BBT shift is possible when there is no rise in urinary PdG. This casts doubt on the complete reliability of the BBT shift as an indicator of a rise in serum progesterone (as measured by the urinary PdG excretion rates). If there is a normal ovulatory cycle with no BBT rise, can the BBT shift always tell a woman when her fertile window closes?

Conclusion

An NFP works well for many women (Frank-Herrman et al. 2007; Gnoth et al. 1996) despite the sometimes opaque view of the underlying ovarian physiology provided by the symptoms compared with those revealed by the clearer E1G and PdG excretion rates. We do not intend in any way to disparage the success of NFP and the valuable role that NFP symptomology has played and is playing. We wish to promote its use. However, we are convinced that the ability to monitor E1G and PdG excretion rates in home tests (Blackwell et al. 2003, 2012, 2013, 2016) materially increases the efficacy and acceptability of NFP and will spread its use among women who currently find it difficult or consider it as unreliable. This particularly applies to women with difficult mucus symptoms, which were dealt with successfully in Melbourne, Australia (Brown, Holmes, and Barker, 1991), by the easy access to analysis of their hormones by home testing. Such apparently “incorrect” mucus and BBT symptoms need to be investigated as a function of the underlying progesterone (or PdG) increases and constitute an important area of research for improving NFP methodology. The goal must be to integrate into NFP a home analytical device, such as the ovarian monitor, to measure E1G and PdG excretion rates (which has been done in part in the Marquette method; Fehring and Schneider 2008). New methods, now in production, will provide even better tools. As the use of home monitoring of hormones spreads throughout the NFP world, some challenges are to be expected since the NFP methods are like seeing through a dark glass the underlying hormonal landscape. While the hormonal changes may not be always accurately reflected in the current NFP methods, it is important to note that the hormones are very unlikely to be wrong.

Additional Benefits of Combining Home Testing with Fertility Devices

A number of benefits can be envisaged in the availability of a new home fertility device:

1. As a teaching aid used in conjunction with the various NFP methods to help a woman recognize her mucus symptoms.
2. As an adjunct for an independent NFP user to reassure that she is making correct observation and interpretation. As an aid to accurately understand the timing of ovulation and define the fertile window.
3. As a demarcation for the day of maximum fertility and its relationship to the indirect indicators.
4. Allowing objective analysis of unexpected pregnancies, leading to further improvements in reliability.
5. Functioning as a pregnancy test.
6. All the methods that were used for laboratory estimation of ovarian hormone levels will now be available as a simple, rapid, accurate, and inexpensive investigation.

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