Online fertility monitoring: some of the issues

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***Abstract*—Many women choose to monitor their menstrual cycle and a variety of physiologically relevant measurements are employed. The demand is so great that many apps and devices are now available and online monitoring is imminent. However, many of the current apps are unreliable for at least two reasons. First, it is often the case that the data collected are not meaningful because they are not obtained reproducibly. Second, it is not sufficiently appreciated that reliable menstrual cycle data can be difficult to interpret because cycles are often physiologically complex. Errors in the monitoring or interpretation of the menstrual cycle can have serious and prolonged repercussions. The reliability of online menstrual cycle monitoring should be based on the best possible measurements and the most appropriate analysis informed by extensive experience in the interpretation of the data. The prospect of online monitoring raises issues of privacy, rights to data and the uses to which they might be put. Women have to be aware of these issues and providers bear the responsibility for ensuring that there is no ambiguity. The networking of menstrual cycle monitoring provides an opportunity to reverse the current tendency for the data to be in silos. The accumulating data could be used to assist in improving the measurements and the analytical tools, but this relies on the informed cooperation of women, the willingness of providers and open communication.**

***Keywords*—data analysis, fertility, measurement, menstrual cycle, privacy, reliability.**

I. Introduction

Point of care (POC) testing is based on the idea that clinical tests should be carried out near or in the presence of the patient rather than in a remote laboratory using a sample that might have been collected hours or days earlier. The person making the measurement need not be a scientist and is frequently the patient. Familiar examples in which the patient obtains the measurement are the glucose sensor, used to enable those living with diabetes to monitor their blood glucose concentration, and the urine-based pregnancy test. The intention is that the patient is directly involved in the process, obtains a rapid response to the data collected and thereby experiences a more efficient process. For these reasons, and others, POC testing is increasingly important and there is a considerable demand for new tests [1].

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Some, but not all POC tests employ specific devices, as is the case for the glucose sensor, and these are increasingly being connected to the internet. Data are uploaded from a device and, in some circumstances, measurement settings, calibration values and/or interpretative information may be downloaded to it. In some cases the data are used by clinicians to monitor their patients and to inform treatment and future analyses. It has been suggested that such data could be a vital resource in the effort to develop new clinical approaches [2]. It is argued that large quantities of data facilitate significantly more powerful analyses that enable the provision of more reliable information to users. While more data may be useful, it is more important that the data are physiologically relevant and reliable and that the analysis is informed by sound comprehension of the physiology.

The preoccupation of people with their own health, combined with the increasing reliance on data and 'intelligent' devices, has accelerated this development and, combined with the endlessly rising cost of healthcare, leads to concepts such as 'diagnosis on demand' and continuous monitoring [3]. In the former, for example, data collected using various devices are transmitted through a network to a clinician who provides a diagnosis without having seen the patient. Three classes of data are associated with such systems: (i) volunteered data created and explicitly shared by patients, (ii) observed data captured by recording the actions of individuals, and (iii) data inferred from the analysis of volunteered or observed information [4]. Of course, such ideas prompt concerns about data ownership and privacy, and the uses to which the data might be put.

Here we consider some of the issues surrounding the networking of fertility monitoring as an example that has great significance for many women. For convenience we provide an outline of the basics of fertility monitoring before considering the potential modes of operation and issues associated with intellectual property that arise.

II. Fundamentals of fertility monitoring

Almost 30 years ago, Carl Djerassi [5] suggested that a woman might conclude that "… the determination of when and whether she is ovulating should be a routine item of personal health information to which she is entitled as a matter of course". The proportion of women who share this view is increasing.

Women wish to monitor their fertility for a variety of reasons. Those who want to conceive, especially if they have had difficulty in doing so, may wish to use the data to maximise their chances; other women wish to avoid conception without having to use contraceptive drugs or devices[1]; and others simply want to be informed, perhaps because of some sort of menstrual cycle disturbance[2], to control the interval between children, to monitor the return to fertility after childbirth or after ceasing the use of contraceptives.

Most commonly, fertility has been monitored by recording daily observations[3] of basal body temperature (BBT), properties of cervical fluid or mucus, vulval sensation, or reproductive hormone levels (especially luteinising hormone (LH) and the various derivatives[4] of oestrogen (E) and progesterone (P)). However, these tend to be used in a variety of combinations, some of which are illustrated in Figure 1. For example, the Billings, Creighton and other 'ovulation' methods are based purely on observations of mucus and vulval sensation [10], whereas symptothermal methods (STMs) and symptohormonal methods (SHMs) combine such observations with measurements of BBT [11] and hormones [12], respectively. A small number of systems rely only on urinary measurements of derivatives of E and P [13].

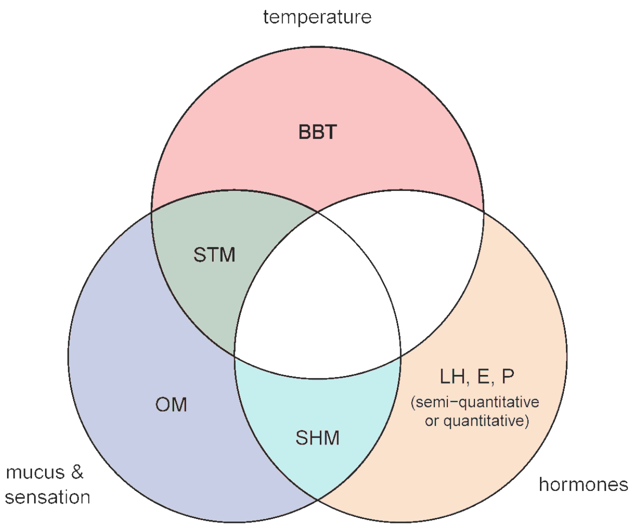

Figure 1. Venn diagram illustrating the main combinations of measures used in fertility monitoring. Symptothermal methods (STM) and symptohormonal methods (SHM) combine observations of vulval sensation and mucus with measurements of BBT and selected hormones, respectively, whereas the 'ovulation' methods (OM) rely only on observations of vulval sensation and mucus. The 'electrical resistance' technique [14] is not shown.

[1] The rate of unplanned pregnancy associated with the current conventional birth control methods is surprisingly high and so some couples use more than one method. The rate at which women (or their partners) choose sterilisation as a form of contraception is also significant [6].

[2] Disturbed cycles are common in at least some reports [7, 8], but are probably under-represented in published studies because researchers usually exclude women with disturbed cycles.

[3] This list does not include other techniques, such as electrical resistance or differential skin temperature measures [9] which are less commonly employed.

[4] For simplicity we have avoided being explicit about the many derivatives of E and P, but in urine the most commonly measured forms are oestrone glucuronide and pregnanediol glucuronide, respectively.

These apparently disparate measures are physiologically connected (see Vigil *et al.* [15] and Blackwell *et al.* [16] for more details than are provided here). Briefly, a cycle usually lasts about a month towards the middle of which a woman may be fertile for a few days and there are corresponding changes in the levels of hormones, in BBT, of mucus and sensation (Figure 2). The rise towards the peak of LH or E levels mark the beginning of the fertile period [17] and an increase in P beyond a specific level marks the end of the fertile period [18]. As P tends to increase temperature [19-21] and E modulates the temperature downwards [22-24], during the first half of the cycle, throughout which P is low, BBT is also low and as P rises from about the day of ovulation, BBT also rises (Figure 2, A and C). Oestrogen also affects the properties of the cervical mucus, making it easier for sperm to pass though the mucus around the day of ovulation and extending sperm survival time. The changes in sensation are less clearly understood.

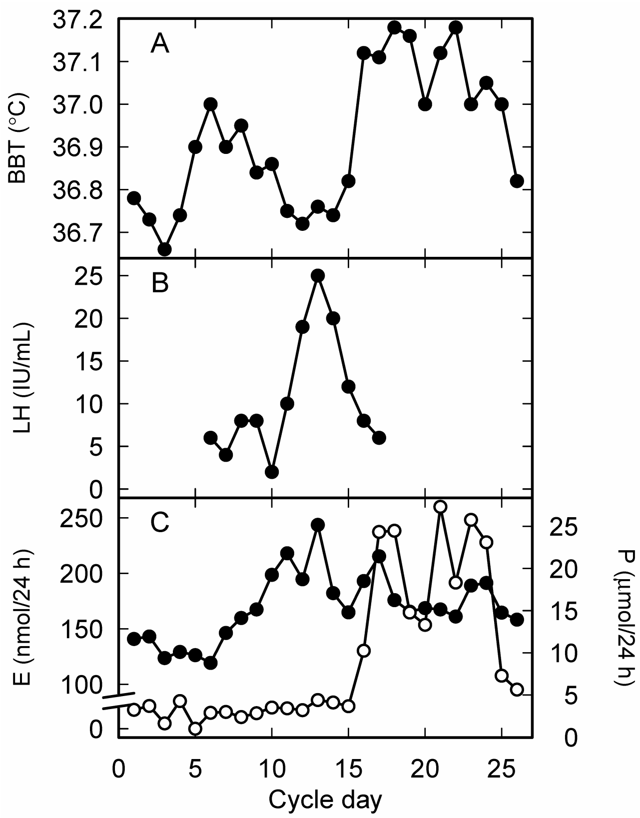

Figure 2. Example of measurements of (A) BBT, (B) LH, (C) E (●) and P (○) during a single menstrual cycle. In (C) note the break in the E axis. More extensive versions of this can be found elsewhere [25, 26].

Despite these and other physiological connections [9, 15], the patterns in the data are complex and can vary considerably between women and from cycle to cycle for individuals [16, 27]. Consequently, the interpretation of the data is not simple, which might partly explain the poor performance of much of the current software tested in recent trials [28, 29]. Such poor performance means that a single unfortunately timed error can have serious long-term consequences. Historically, and for the STM, STH and Billings methods today [11, 12, 30], this has meant that the data collected by each woman are often interpreted by an experienced advisor. At least two current applications for monitoring fertility (Billings' mentor [30] and Fondation Symptotherm [31]) offer users the help of an advisor to supplement the output of the software, others claim to rely on the data alone. A variety of devices are available to obtain these measurements and these have been reviewed recently [32-37].

III. Modes of fertility monitoring

Irrespective of which approach is employed, analysis of the menstrual cycle is usually focused on the identification or prediction of the 'fertile window' during which conception is possible. In each case, the patterns are complex and depend on the physiological state of the woman. Consequently, considerable experience is needed to interpret the cycles of hormone excretion rates [27], changes in basal body temperature [38] or the other observations that are used.

Most women who choose to monitor their cycles still rely on measurements of BBT, with or without other observations [39]. The main advantage of the 'ovulation' methods is that they are essentially cost free, whereas the temperature-based methods (BBT and STM) require a thermometer, but are free of cost thereafter, while the hormonal (and SHM) measurements require ongoing expenditure. The question is whether the increased reliability of the temperature-based and hormonal methods justifies the expense to the user.

The Billings' method is said to have a very low rate of unplanned pregnancies, but it is hard to contemplate it being used as a predictor of the fertile window. Similarly, BBT alone is complicated by the effects of environmental temperature, illness and exertion on temperature, as well as the measurement-related issues [40]. However, the symptothermal method (STM) that combines measurements of BBT with observations of mucus and sensation can be an amazingly reliable technique for women with the necessary self-discipline. Unfortunately, mucus is not always observed by every woman [41]. Of the hormonal methods, those based on the measurement of urinary LH concentration are theoretically capable of identifying the start of the fertile window, but not its end. Moreover, the LH peak can be missed, for example, Baird *et al.* [42] reported that the LH peak could be identified in only 49% (210 of 430) of cycles. The rise to the E1G peak seems a more reliable marker of the start of the fertile phase [17], although careful analysis can be required to interpret the data [43]. Only those methods involving the measurement of P can identify the end of the fertile phase on the day it occurs [18], rather than some days later as is the case with BBT or STM [16, 44, 45].

One of the issues associated with the hormone-based techniques is that several of the assays measure the concentration of hormone derivatives which is just

$$\text{concentration (mol L}^{-1}) = \frac{\text{quantity in urine (mol)}}{\text{volume of urine (L)}} .$$

As we all know, the volume of urine is highly variable, if only because the volume we drink and the time between voids fluctuate, and so the hormone concentration will vary even if its quantity does not. The idea underlying the use of reproductive hormones in fertility monitoring is that the changing rates of hormone production reflect the physiological events. As it is impractical to measure the rates of production directly in a POC test, the most convenient accurate estimate of hormone production is actually the rate at which it is excreted

$$\text{rate of excretion (mol h}^{-1}) = \frac{\text{quantity in urine (mol)}}{\text{time between voids (h)}} .$$

This is related to the concentration by what is usually called the 'urine volume', but is actually the rate of urine accumulation

$$\text{'urine volume' (L h}^{-1}) = \frac{\text{volume of urine (L)}}{\text{time between voids (h)}}$$

and, of the current hormonal methods, only the Ovarian Monitor [13] takes this into account. It has been argued, without any direct substantiation, that 'urine volume correction' is unnecessary [46], but this is correct only if semi-quantitative measures are considered satisfactory. Where significant events in the menstrual cycle are marked by specific hormone thresholds [18, 47], such semi-quantitative approaches are unreliable at best. Given the implications of making a mistake about a woman's fertility, it is extraordinary that anyone could contemplate making approximations of this sort.

Irrespective of which method is used, a common issue is a failure to satisfy the method requirements [48] and the most problematic of these can arise when users have to abstain from intercourse. For example, to avoid pregnancy without the use of contraception, a woman (and her partner) must abstain from intercourse during her fertile period. The longer the period of abstinence, the greater the likelihood of non-compliance. For this reason, it is important to women (and their partners) that the identified fertile period is no longer than is strictly necessary, which requires that (a) the measurement(s) are reliable and (b) the analysis of the cycle is informed by a thorough understanding of the physiology.

One of the main prospects arising from online fertility monitoring is the possibility of sharing data, subject to the consent of users and the necessary protections. For many decades the monitoring streams ('ovulation', STM, SHM and hormonal) have largely operated independently. Specific research programmes have obtained all or most of the standard measures (one example is [49]), but this has rarely been possible for ordinary users. Moreover, even in those cases where comprehensive sets of measurement have been obtained, they tend not to be readily available. With some consideration of the data format and specification of the measurements, it could be possible to accumulate very large quantities of data which might enhance the analytical tools to the ultimate benefit of women.

IV. How big might the demand be?

A significant fraction of women have cycles that differ from the textbook model (although they do form a natural part of the Continuum view of the cycle [27]). They differ because the cycles are anovulatory, 'deficient' or disordered in some other way [7, 8]. This means that (i) ongoing data collection is necessary if the current cycle is to be interpreted correctly and (ii) each woman's cycle would have to be analysed every day. According to the United Nations, about 1.6 billion women, representing about 31% of all women, were of childbearing age (ages 15-45) in 2015 [50]. If only 1% of those women monitored their cycle, then more than 10^7 cycles would have to be analysed each day. Presently, cycles are analysed using many different apps, only some of which rely on access to any database. Nevertheless, it is clear that this is by no means unmanageable, but it does require reliable software to ensure that women have confidence in the information they obtain. While it might seem attractive simply to acquire more measurements, the inevitable correlation between the available measures (such as between P and BBT or E and mucus) means that it is inevitable that this is not necessarily helpful, except, perhaps, as an aid in identifying possible measurement errors. Instead, it is necessary to select the best measures and then interpret the data carefully based on the science. This is not just another statistical problem.

As has been argued previously [16], of the measures of events in the ovary available in a woman's home, the most direct are E and P. As will be apparent from the outline of the physiological connections between the measurements provided above, all other measures are indirect. While it might be useful to supplement measures of E and P with observations of LH, BBT or mucus, it should be clear that these are, to differing extents, correlated. For this reason, we use E- and P-based monitoring as the basis for considering the practical implications of online fertility monitoring.

V. How might devices for E- and P-based monitoring operate?

Quantitative hormone-based measurements require that the device convert the measurement obtained into an excretion rate [51] using a standard curve. Given the batch variation of lateral flow and other assays [13, 52], it is necessary that the device has calibration values that describe the standard curve for the batch in use. This requires either that the device can download the values or that they are incorporated into the data read by the device from the strip or tube. At least three distinct options might be contemplated.

1. The device could be completely reliant on network access, which means that all analysis and virtually all of the software can be kept in a small number of locations, allowing easy maintenance and limiting the need for security to be built into the device, although the security of women's data would have to be assured. Such network reliance could exclude some women from using the device.
2. The device could be completely independent of the network, which means that each device must have all the measurement information and analytical capabilities that might be required. This distributed approach eliminates any real likelihood that any one device would be corrupted, but it also eliminates any real possibility of updating the device during its lifetime. This raises no barriers to the user, but it does raise the possibility that new versions of the device would be made available.
3. A more realistic intermediate is the hybrid model which is a combination of these. In this model the device can operate independently of the network, subject to having the right calibration data, but will access the network when necessary or when the user wishes.

Inevitably there are issues associated with the collection of data in this way, particularly when the user is inexperienced. For example, the circumstances of measurement are necessarily undefined and there is no way to determine how this might have affected the data, although it has been demonstrated that the results of POC tests carried out by women at home and scientists in a laboratory can be of similar quality at least in some cases [53]. Nevertheless, there are clear distinctions between data and relevant data or between a measurement that might yield a number and a quantitative measurement that yields values on which one might be able to rely and it is unrealistic to rely on the users to know the difference. Even apparently simple measurements [54, 55] or well established devices [56, 57] can be unreliable, and simply introducing technology need not mean that the intended outcome is attained [58]. Consequently, the data have to be considered carefully if they are to be interpreted reliably.

VI. Online fertility monitoring: TOWS analysis

The advantages of online cycle monitoring depends on the model selected. We will not consider commercial issues, but to identify some of the practical issues, we consider the hybrid model in which the device can operate independently of a network at the discretion of the user. A standard approach to this is the SWOT analysis in which internal strengths (S) and weaknesses (W) and external opportunities (O) and threats (T) are considered. We use an extension of this, the TOWS matrix [59], in which possible responses to the factors identified in a SWOT analysis are systematically considered (Table I).

The internal strengths of this model include two general capacities. First, to update remotely analyses and device settings so that critical software components can be secured in just a small number of locations if they can only be accessed online. Second, to store data which not only permits personalised feedback to the user without necessarily having to involve an advisor, but, subject to consent, also allows data aggregation (and sharing, although this seems unlikely at present) that might enhance analytical capabilities. The weaknesses of the hybrid model are related to the strengths. First, the reliance on network access for some functions and the associated costs may tend to exclude some women. Second, whenever data are stored, there is a risk that personal data might be compromised. Third, data quality relies on correct or at least consistent usage, but this is true of all methods of monitoring fertility. Finally, depending on what information is transmitted regulatory issues may arise [60], but without further details it is impossible to asses the potential impact.

The main opportunities associated with the hybrid model relate to the possibility of data sharing and the combination of different measurement methods. Together, these could provide even more insight into the menstrual cycle than has hitherto been possible. An analogous suggestion has been made for dementia [61] which, while recognizing that these are devastating conditions, fortunately does not affect 50% of the world population. The threats to this model include issues associated with data ownership, usage and access, data and software security, privacy and the security of users. One particular threat is that the data could be exploited to the disadvantage of women by third parties. For example, stored data might be used by insurance companies to deny women health cover [3], although this is just a specific instance of a much larger potential problem that is well known. Such undesirable uses of the data remain to be resolved, but the primary role of the provider in this context is to secure users' data and ensure their privacy.

Trivially, one way of avoiding all the problems is to decide not to implement online fertility monitoring (Table I), but we discount this option because it is already available. However, by encryption of the data and remotely updating the software most of the security concerns should be allayed. The real power of the hybrid model is that stored data and, perhaps, multiple measurement modes can be used to improve understanding of the menstrual cycle and develop better analytical tools and, therefore, provide better information to users.

VII. Conclusion

While many issues arise from fertility monitoring, two are of particular concern whether or not it is web-based. First, the data obtained by a women should be of the best possible quality, whatever measure is used. This is not synonymous with the collection of more data or with the collection of data more frequently, it merely means that those data that are collected should be reliable and obtainable without significant practical or financial barriers. Second, the analysis of the data is crucial to the success of any monitoring. This is frequently under-appreciated, not least by those who claim that the collection of more data will inevitably lead to success. Appreciation of the physiology of the menstrual cycle, and of the associated difficulties that are all too often encountered by women, is the only rational basis for cycle analysis no matter how sophisticated the mathematics that might be employed. Women deserve systems that are fit for this purpose, rather than those made available in the market because they yield the greatest profit for the least effort.

Table I. The TOWS matrix [59] of the practical issues associated with the hybrid model of online fertility monitoring.

	INTERNAL STRENGTHS (S) 1. data storage 2. remote updating of analyses and device settings 3. critical software components need not be on the device or the app 4. no or minimal data entry 5. personalised feedback without an advisor	INTERNAL WEAKNESSES (W) 1. reliance on (reliable) network access 2. no control over data entry unless measurement device is linked directly to the software 3. data quality relies on correct usage 4. cost of device, network access and consumables 5. no interoperability at present
EXTERNAL OPPORTUNITIES (O) 1. data aggregation (and sharing?) to improve analysis 2. combinations of measurement methods 3. physiological insight into menstrual cycle 4. several modes of operation	SO 1. improve analysis using stored data $(S_1 O_1)$ 2. improve understanding of the menstrual cycle using stored data $(S_1 O_2 O_3)$ 3. use and test improved analysis $(S_2 S_3 O_1 O_2 O_3)$	WO 1. reduce reliance on network access using hybrid model of operation $(W_1 W_4 O_4)$ 2. minimise usage issues by combinations of measurement methods $(W_2 W_3 O_2)$ 3. improve interoperability $(W_5 O_1)$
EXTERNAL THREATS (T) 1. issues of data ownership, usage and access 2. privacy issues 3. data and software security 4. issues around the sense of security of users 5. undesirable uses of the data	ST 1. reduce risk to software by remote updating $(S_2 S_3 T_3)$ 2. reduce risk of data compromise by encryption $(S_1 T_1 T_2 T_4 T_5)$ 3. enhance user privacy $(S_5 T_2 T_4 T_5)$	WT 1. improve user training $(W_3 T_4)$ 2. use most cost-effective and secure means of networking $(W_1 W_4 T_2 T_3 T_4 T_5)$ 3. do not network device $(W_1 W_4 W_5 T_1 T_2 T_3 T_4 T_5)$ (DISCOUNTED)

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