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Standardization of Menstrual Cycle Data for the Analysis of Intensive Longitudinal Data

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Abstract

Daily diary methodology is becoming popular in human menstrual cycle (MC) research. However, variations in MC length makes it difficult to examine fluctuations in dependent variables (e.g., substance use levels), across the MC. Existing analytic approaches collapse data across MC phases, examining phase-related changes; however, a loss of potentially vital information can result when data is collapsed across phase. Additionally, current phase designation methods (phase designation and days within each phase) vary substantially across studies, making it difficult to interpret/compare results across studies. To address these problems, two methods were developed to standardize intensive longitudinal data collected via daily diary methodologies-phasic and continuous standardization. Phasic standardization accounts for individual variability in MC length by allowing luteal phase length differences while remaining phases are fixed, enabling the analysis of phasic variations. Alternatively, continuous standardization accounts for individual variability in MC length by standardizing the luteal phase to a seven-day phase, while remaining phases are fixed, allowing for the exploration of continuously reported variables across MC day. This chapter will discuss how to standardize daily diary data collected across the MC using phasic and continuous standardization methods and demonstrate the two standardization methods using two clinically-relevant hypothetical examples.

Keywords: addiction, substance use, behavioral addiction, mood, menstrual cycle

1. Introduction

Historically, females have been omitted from addictions research. One reason for this omission is that ovarian hormones fluctuate rhythmically across females' menstrual cycles and may impact their addictive behavior. As a result of this sex bias, theory and evidence pertaining to

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the nature, development, and maintenance of addiction are based primarily on research with male samples [1]. Given that females have been underrepresented in addictions research, many treatment and preventative intervention methods developed to date may not be suitable for females with addictions. This general failure to develop sex-specific treatment and prevention options is particularly problematic given the high occurrence of addictive behaviors in females. For example, the National Council on Alcoholism and Drug Dependence [2] has reported that 4.5 million American females abuse/are dependent on alcohol, 3.5 million misuse prescription drugs, and 3.1 million regularly use illicit drugs. Of further concern, the Substance Abuse and Mental Health Services Administration [3] has reported that 15.8 million American females, 18 years and older, have used illicit drugs within the past year. These statistics exemplify just how common addictive behaviors are in the female population.

Of further concern, the prevalence of addictive behaviors in females is increasing and closely approaching that of men. For example, increases in females' alcohol consumption and alcohol use disorders are evident, with prevalence rates converging upon those reported for males [4]. The documented convergence between female and male alcohol consumption and alcohol use disorders may be explained by a societal shift toward an increased acceptance for females to engage in potentially addictive behaviors, such as alcohol consumption and tobacco use [5]. Thus, investigating sex-specific factors influencing addictive behaviors is critical for the development of effective treatment and prevention options for females with addictions.

As a result of the current underrepresentation of females in addiction research and our substandard knowledge of sex-specific factors influencing addiction, many funding agencies (e.g., Canadian Institute of Health Research) have introduced a requirement that researchers consider sex when developing research questions and designs. With this sex-sensitive research focus, numerous researchers have begun exploring the potential influence of the menstrual cycle, a female-specific factor, on fluctuations in addictive behaviors (e.g., cigarettes smoked, gambling intensity) and mood (e.g., negative and positive affect).

To effectively examine fluctuations in addictive behavior across the menstrual cycle, researchers have begun employing daily diaries—a prospective methodology where participants are asked to complete surveys at various time points throughout the day. Using daily diary surveys provides researchers with the advantage of obtaining intensive longitudinal data. However, variation in female menstrual cycle length has made it particularly difficult to conduct such daily diary menstrual cycle researchers currently do not have a method to standardize variable menstrual cycle lengths, they are left with the sole option of breaking the menstrual cycle down into phases which vary not only in length across studies but also by the total number of menstrual cycle phases, which can be problematic.

Currently, two predominant problems in menstrual cycle research are evident. First is the lack of comparability across studies with respect to the data which goes into each menstrual cycle phase. Although the division of data into menstrual cycle phases itself is not necessarily problematic, issues appear when inconsistencies arise within phase designation methods across studies. Researchers commonly divide the menstrual cycle into a different number of menstrual cycle phases, with each phase consisting of various days, which further confounds

the picture. Inconsistencies in menstrual cycle phase designations were demonstrated in a literature review where studies reporting addictive behaviors across the menstrual cycle were examined. In our literature review, two studies, both examining sexual behavior across menstrual cycle phase, divided the menstrual cycle into two and seven menstrual cycle phases, respectively [6, 7]. Two additional studies, examining cigarette use/nicotine intake across the menstrual cycle, designated the premenstrual phase as 3 and 5 days prior to menstruation, respectively [8, 9]. With these evident discrepancies in menstrual cycle phase designation between studies, our ability to effectively compare research findings is substantially limited. To effectively compare research findings in the menstrual cycle field, the development of standardization methods is warranted. Given these problems, we propose a method to standardize menstrual cycle phase given variable menstrual cycle lengths across different female participants. Throughout this book chapter we will refer to this form of standardization as 'phasic standardization' which can be analyzed using statistical methods such as repeated-measures analyses of variance (ANOVAs), for example.

Even though phasic standardization eliminates one problem, another problem arises. When data is collapsed across days within phases, a daily average per phase is produced. However, collapsing data across menstrual cycle phase to produce a phasic average still results in a loss of potentially important information. Instead, data can be examined continuously across menstrual cycle days using another form of standardization to eliminate the problem of collapsing data across days within each menstrual cycle phase. As a solution to this second problem, we propose a method to standardize menstrual cycle day given variable menstrual cycle lengths across females. Throughout, we refer to this as 'continuous standardization'¹, which can be analyzed using data analytic techniques like time varying effects models (TVEMs).

The current chapter aims to eliminate the standardization problem in menstrual cycle research by providing a method for researchers to standardize intensive longitudinal data collected using daily diary methodology across the female menstrual cycle. We will explain how researchers can standardize such intensive longitudinal data across the menstrual cycle using one of two methods (i.e., phasic or continuous standardization). We also provide two clinically-relevant hypothetical examples of the proposed standardization methods. We will also explore the statistical methods which can be used to analyze such standardized menstrual cycle data, including repeated measures ANOVAs and TVEMs. This book chapter may be of practical use to researchers working in the menstrual cycle field as it provides standardized methodology for examining fluctuations in dependent variables, such as substance use levels and mood, across the menstrual cycle. The purpose of this chapter is to provide standardization methods to examine menstrual cycle data as means to enhance our understanding of the menstrual cycle as a female-specific factor in the field of addiction and mental health.

¹Please note that continuous standardization does not refer to the continuous nature of the dependent variable or continuous outcomes but rather examining data at the daily level (continuously) rather than at the phasic level.

2. Menstrual cycle data standardization

On average, a female's menstrual cycle lasts between 23 and 35 days (average length = 28 days) [10], indicating a large range of individual variability in menstrual cycle length. Based on ovarian hormone fluctuations, the menstrual cycle has been divided into two overarching phases: the follicular (from menstrual bleeding until ovulation) and luteal phases (from ovulation until the day prior to menstrual bleeding) [11]. Furthermore, rhythmic fluctuations in progesterone, estrogen, follicle-stimulating hormone, and luteinizing hormone concentrations, allow for further subdivision of the menstrual cycle, resulting in the following five more specific phases: menstrual, follicular, ovulatory, luteal, and premenstrual [11–14] (see **Figure 1**).

Variability in female menstrual cycle length has been attributed to differing luteal phase lengths [15]. Although the literature is mixed in the sense that some literature points toward the follicular phase as the phase that contributes the most to menstrual cycle variability [16], the bulk of the literature suggests that the luteal phase is the main contributor to variance in menstrual cycle length [15]. That menstrual cycle length variability occurs specifically at the luteal phase is supported by two facts. Firstly, although the timing of the ovulatory phase may differ on an individual basis, research shows the ovulatory phase typically occurs between days 13–16 of the menstrual cycle [11] suggesting there is little variability prior to the ovulatory phase. The second is that the premenstrual phase has been defined as occurring 5 days prior to menstrual bleeding [17]. Thus, it is the luteal phase, which precedes the menstrual phase, that is subject to variable lengths. Based on the fact that variability in a female's menstrual cycle occurs during the luteal phase, we have developed two methods to standardize menstrual cycle data, consisting of phasic and continuous standardization, respectively (see Sections 2 and 3 for methodological procedures and clinically-relevant hypothetical

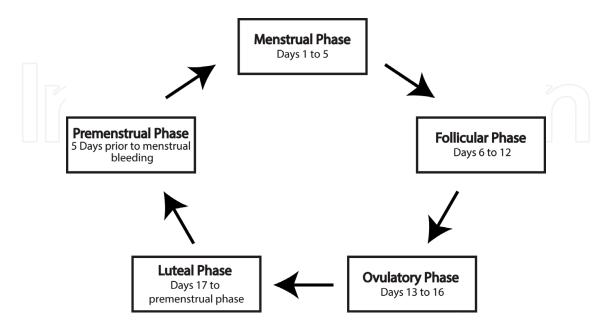


Figure 1. A depiction of the menstrual cycle divided into five specific phases.

examples of the two standardization methods). It is cautioned that the two standardization methods described herein solely be implemented for menstrual cycle lengths between 23 and 35 days. Females with menstrual cycle lengths outside of the average 23–35 days should not be included in the menstrual cycle standardization methods discussed in this chapter. The accuracy of standardizing data from females with menstrual cycle lengths outside of the average 23- to 35-day range is questionable. Abnormally short/long menstrual cycles have an unduly influential role in ovarian hormone fluctuations. Thus, such individuals are typically categorized as not normally-cycling and are not included in studies of the normal female menstrual cycle [10].

2.1. Phasic standardization

If a researcher is interested in variations in specific behaviors (e.g., substance use or other addictive behavior) occurring during certain phases of the menstrual cycle, we have developed a standardized method to examine phase-related changes in behavior. We refer to this standardization method as phasic standardization. In this method, data collected via daily diary across an entire menstrual cycle is standardized as a means for examining addictive behaviors by phase rather than as a function of days across the entire menstrual cycle (see continuous standardization in the next section of the chapter). When conducting phasic standardization, all menstrual cycle phases are held at fixed lengths, save the length of the luteal phase which will differ based on the participant's total menstrual cycle length. Each phase length is as follows: menstrual (days 1–5), follicular (days 6–12), ovulatory (days 13–16), luteal (days 17-premenstrual phase), and premenstrual (5 days prior to menstrual bleeding; see **Table 1**). Each variable of interest is examined as a mean per phase. Each mean per phase variable is calculated by summing each variable per phase and dividing that sum by the total number of days within that menstrual cycle phase.

Data obtained through phasic standardization can be analyzed through the implementation of statistical methods such as repeated-measures ANOVAs or dependent-sample planned contrasts. A repeated-measures ANOVA will identify whether there is a significant difference across menstrual cycle phases on a given dependent variable (e.g., bidding quantity). If the repeated-measures ANOVA reveals a significant effect of MC phase, post-hoc comparisons can be conducted to determine which menstrual cycle phase(s) are characterized by higher/ lower levels of the dependent variable relative to which other MC phase(s).

2.2. Continuous standardization

Since variability in menstrual cycle length occurs during the luteal phase [15], the luteal phase can be standardized to a seven-day phase, based on the average 28-day cycle, while the remaining phases are held fixed. We refer to this method as continuous standardization. Upon conducting continuous standardization, the length at which each phase is held constant is as follows: 5 days for the menstrual phase (menstrual cycle days 1–5), 7 days for the follicular phase (menstrual cycle days 6–12), 4 days for the ovulatory phase (menstrual cycle days 13–16), and 5 days for the premenstrual phase (5 days prior to menstrual bleeding), accumulating to a total of 21 days. Next, the 21 days are subtracted from the participant's total menstrual cycle

Menstrual cycle day	Menstrual cycle phase	Bidding occasions	Average number of bidding occasions per phase
1		8	
2		6	
3	Menstrual	0	4
4		2	
5		4	
6	Follicular	11	
7		2	
8		8	
9		10	6
10		6	
11		0	
12		5	
13		13	9
14	Ovulatory	8	
15		7	
16		8	
17	Luteal	8	7
18		6	1
19		2	
20	Premenstrual	1	
21		4	2
22		0	
23		3	

Table 1. Method to standardize intensive longitudinal data into the five menstrual cycle phases using phasic standardization.

length. The remainder provides the total number of days in the participant's luteal phase (see Table 2). All participant's menstrual cycles can then be standardized to a 28-day cycle by allotting 7 standardized days to the participant's luteal phase length (i.e., 28-day cycle – 21 days (sum of non-luteal phase days) = 7-day luteal phase). Thus, we can express the variance as a ratio of 7/x where x is the participant's actual luteal phase length (see Table 2). With this luteal phase ratio, we can determine the standardized luteal phase day for each actual luteal phase day. This is calculated by treating the ratio as a factor to be added to day 16 (the last day of the ovulatory phase) to obtain the standardized luteal phase day (see Table 2). Each number obtained is then rounded up (\geq 0.5) or down (<0.5) to the nearest whole number, representing the new standardized luteal phase day. This method can be used for menstrual cycle lengths shorter and longer than the average 28-day cycle. For cycle lengths shorter than 28 days, data from the luteal phase will be "elongated", and data will be missing for certain menstrual cycle days during the luteal phase. Conversely, for cycle lengths longer than 28 days, data from the luteal phase will be "condensed", and the same standardized day may be obtained for two data points (i.e., two data points may be identified as standardized luteal phase day 18). In the latter circumstance, any variables of interest with the same standardized luteal phase day must be averaged and that datapoint will be linked to the given standardized luteal phase day.

Menstrual cycle data standardized using continuous standardization can be analyzed using more intricate statistical analyses, such as TVEMs [18]. TVEMs allow for the identification

Total menstrual cycle length	Luteal phase lengthª	Luteal phase ratio ^b	Standardized menstrual cycle day ^c
23 days	2	7/2	3.5
24 days	3	7/3	2.33
25 days	4	7/4	1.75
26 days	5	7/5	1.4
27 days	6	7/6	$1.1\overline{6}$
28 days	7	7/7	1
29 days	8	7/8	.875
30 days	9	7/9	.77
31 days	10	7/10	.70
32 days	11	7/11	.636
33 days	12	7/12	.583
34 days	13	7/13	.538
35 days	14	7/14	.50

Table 2. Method to standardize continuous intensive longitudinal data to a 28-day menstrual cycle.

of cyclical changes in addictive behaviors, mood, and their inter-relations as a function of menstrual cycle day by providing an estimate of the relationship between predictor and outcome variables. TVEMs can function similarly to a mediational analysis over time as they identify menstrual cycle days on which elevations (or reductions) in an outcome variable are due to elevations (or reductions) in another variable. For example, in our prior research we used TVEMs to demonstrate that elevations in alcohol consumption during days corresponding to the menstrual phase were explained by elevations in coping drinking motives during these same menstrual cycle days. The implementation of such statistical analyses allows for a more comprehensive understanding of the relationship between addictive behaviors and other factors.

In our prior research [19], we have biologically validated standardizing menstrual cycle length via continuous standardization through the collection of saliva samples. In our research, we collected saliva samples during times of theoretically low (days 1–7) and high (days 18–24) progesterone concentrations [19]. Enzyme-linked immunosorbent assays (ELISA) were then carried out to determine progesterone concentrations for each participant and a paired-sample t-test followed to validate participant's menstrual cycle day using the identified progesterone concentrations. Results suggested that menstrual cycle days 18–24 (theoretical high) had significantly higher progesterone concentrations than menstrual cycle days 1–7 (theoretical low). Findings provided biological validation for standardizing menstrual cycle data via continuous standardization based on an average 28-day menstrual cycle.

3. Clinically-relevant examples

To provide a more comprehensive understanding of the methods employed to standardize data, we have developed two clinically-relevant hypothetical examples. These hypothetical examples were designed to illustrate the types of effects that have been established in the literature on addictive behaviors across the menstrual cycle.

3.1. Phasic example: gambling involvement

In this hypothetical example, the researchers wanted to examine bidding quantity per menstrual cycle phase to determine if bidding quantity increases or decreases during specific phases of the menstrual cycle relative to other phases of the menstrual cycle (e.g., does bidding frequency increase during the ovulatory phase relative to other menstrual cycle phases?). Let us imagine that this hypothetical data was collected using daily diary methodology. Each day for an entire menstrual cycle, female gambler participants were asked to report their menstrual cycle day and the number of times they bid throughout the day. Here, the researchers collapsed the data by phase, using phasic standardization, to assess whether differences in bidding frequency occurred as a function of menstrual cycle phase.

Using the phasic standardization method, we can produce standardized data that allows for the comparison of data at specific menstrual cycle phases between participants, even though such phases may not be identical in length (see **Figure 2** for a hypothetical example). Phasic standardization is conducted in the same manner, regardless of the participant's menstrual cycle length. Collectively, using phasic standardization allows for the identification of phase-specific differences in addictive behaviors (or mood states, for example) across the menstrual cycle.

Phasic standardization can be illustrated with a hypothetical example (see **Table 3**). Here the fictional participant's 23-day menstrual cycle can be divided into five menstrual cycle phases as outlined in Section 2.1 above. In **Table 3**, the luteal phase is comprised of all days that are not non-luteal phase days (i.e., days that are not accounted for by another menstrual cycle phase where the other phases are of fixed length). In this hypothetical example, days 17–18 represent the luteal phase. Once the data is divided based on menstrual cycle phase, the bidding quantity variable was averaged for all days within each specific phase. Using phasic

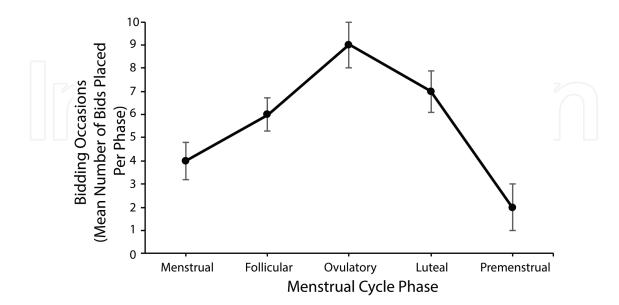


Figure 2. Example of the mean number of bidding occasions across the five menstrual cycle phases. Error bars represent standard error.

standardization, we obtain one datapoint for each variable of interest per phase per participant. Based on the hypothetical case discussed (see **Table 3**), it appears as though the average number of bidding occasions is lowest during the menstrual phase, peaks during the ovulatory phase, and progressively declines thereafter, consistent with the researcher's hypothesis. Once collapsed across participants in the sample, these phasic means can be compared using statistics like repeated-measures ANOVA to answer the researcher's question of whether bidding increases during the ovulatory phase relative to the other menstrual cycle phases.

3.2. Continuous example: cigarettes smoked

In this second hypothetical example, imagine that a group of researchers wanted to examine cigarette use across the entire menstrual cycle (i.e., across days) to elucidate if, and where, cigarette use increases or decreases across the menstrual cycle. Imagine that these researchers collected information using daily diary surveys to determine participant menstrual cycle day and the number of cigarettes smoked each day across each participant's entire menstrual cycle. Let us imagine that the researchers in this example were primarily interested in examining cigarette use across the entirety of the menstrual cycle to determine where the level of cigarettes smoked rise and fall (i.e., which menstrual cycle days). This more specific level of

Menstrual cycle day	Menstrual cycle phase	Bidding occasions	Average number of bidding occasions per phase
1		8	
2		6	
3	Menstrual	0	4
4		2	
5		4	
6		11	
7	Follicular	2	
8		8	
9		10	6
10		6	
11		0	
12		5	
13		13	9
14	Ovulatory	8	
15		7	
16		8	
17	Luteal	8	7
18		6	
19		2	
20		1	
21	Premenstrual	4	2
22		0	
23		3	

Table 3. A worked hypothetical example of the phasic method for standardizing a 23-day menstrual cycle across the five phases.

detail might not be captured using a phasic evaluation; thus, these researchers would choose to employ continuous standardization rather than phasic standardization.

As mentioned previously, in a normally-cycling sample, we would expect inclusion of individuals who have menstrual cycle lengths that are below and others who have menstrual cycle lengths that are above the average menstrual cycle length of 28 days. Given this, we will provide two examples of continuous standardization using each of these types of cases (i.e., longer than average cycle lengths, shorter than average cycle lengths, respectively) from a hypothetical dataset.

Using this method, we can produce standardized data with all participants having exactly a 28-day standard menstrual cycle (see **Figure 3** for an example). This enables us to compare data between participants with variable cycle lengths to determine if specific standardized days are associated with greater (or reduced) addictive behaviors as, following standardization, each day would represent the same time point across participants. Additionally, this process enables us to not only examine specific days, but also identify specific menstrual cycle phases where changes are occurring as all participants have a standardized 28-day cycle with each phase length being consistent across participants. Collectively, we can identify phase-specific and day-specific differences in addictive behaviors across the entirety of the menstrual cycle, using this method of standardization.

3.2.1. For cycle lengths fewer than 28 days

In Section 2.2., we described that the first step in continuous standardization is to calculate the number of luteal phase days by holding all other menstrual cycle phases constant in length. In **Figure 4**, the number of menstrual cycle days is listed for the average 28-day cycle. This information is then utilized to calculate the number of luteal phase days by subtracting the

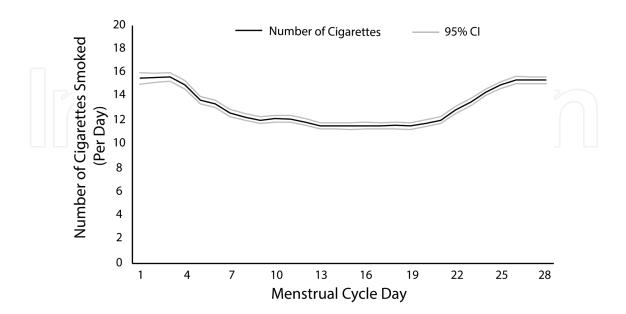


Figure 3. Hypothetical example of the mean number of cigarettes smoked across days of the menstrual cycle. Black lines indicate means and gray lines indicate 95% confidence intervals.

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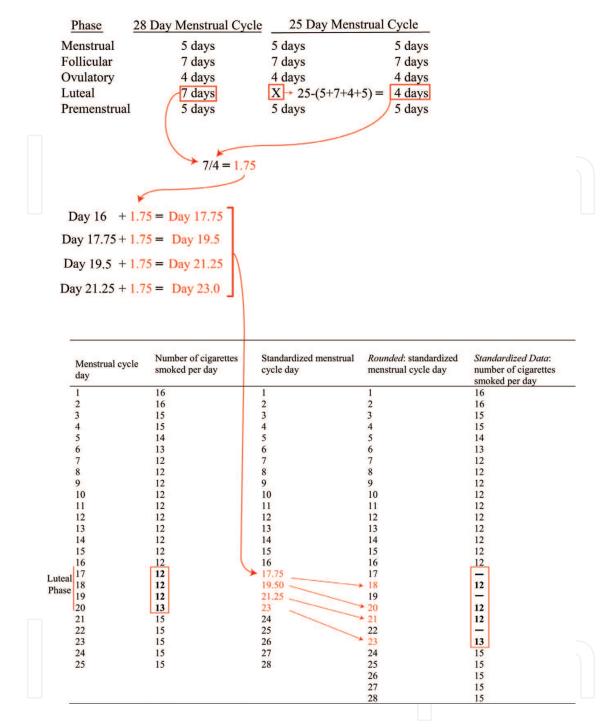


Figure 4. A worked hypothetical example of continuous standardization for a menstrual cycle less than 28-days (i.e., 25-day cycle). Note: A dash (–) signifies a missing data point.

total number of non-luteal phase days from the participant's entire menstrual cycle length. For instance, **Figure 4** illustrates this by subtracting 21 days (non-luteal phase days) from this hypothetical participant's entire 25-day menstrual cycle. The remainder (4 days) then becomes the divisor for the number of luteal phase days within the average 28-day cycle (i.e., seven) to identify the factor that must be successively added to day 16. This adding to day 16 occurs four times in this case (the same value as the number of days within the participant's

non-standardized luteal phase) to determine the participant's new standardized luteal phase days. Following the arrows in **Figure 4**, we derive four new standardized luteal phase days, which are then rounded to the nearest whole number and incorporated into our dataset.

The table in **Figure 4** highlights days 17–20 (column one)—the four non-standardized luteal phase days for this hypothetical participant—and the number of cigarettes she smoked on each of these days (column two). Each of the four standardized luteal phase days are then rounded to the nearest whole number (column three). It should be noted that standardizing a cycle with fewer than 28 days to a 28-day cycle will yield a standardized luteal phase with missing data (see resultant standardized dataset in column five of **Figure 4**). By comparing the red boxes between columns two and five, we can see that the data from the 25-day cycle is carried forward into the 'standardized data' column. The resulting data set includes data for this hypothetical participant's standardized 28-day menstrual cycle. The hypothetical participant's data (see **Figure 4**) suggests that cigarette smoking peaks during standardized days 1–5 (i.e., during the menstrual phase) and standardized days 24–28 (i.e., during the premenstrual phase) with a dip mid-cycle (i.e., during the follicular, ovulatory, and luteal phases). To determine where cigarette smoking increases and decreases, the standardized 28-day menstrual cycle susing a statistical analysis such as TVEMs.

3.2.2. For cycle lengths above 28 days

The process of standardizing a cycle length above 28-days is similar to that employed for cycle lengths less than 28-days (see Figure 5). Using the same hypothetical dataset as an example, we have depicted the standardization method for a second hypothetical participant, this time with a menstrual cycle length of 30 days. When standardizing menstrual cycle data for individuals with cycle lengths greater than 28 days, note that a calculated standardized day may round to the same standardized day as an adjacent day, yielding two data points with identical standardized luteal phase days. In this situation, the data from the identical standardized luteal phase days must be averaged and linked to that standardized luteal phase day. In **Figure 5**, we see that in column three, two red arrows converge upon standardized luteal phase day 18, for example. Thus, on standardized day 18, the number of cigarettes smoked is averaged from the data for the original days 18 and 19 (i.e., 12 + 14/2 = 13). Then, the new datapoint of 13 is placed into column five to represent standardized data for standardized day 18 for the participant's standardized 28-day menstrual cycle. A similar process is used for obtaining the cigarettes smoked value for standardized day 21 (see Figure 5). Consistent with the findings for the hypothetical participant in Section 3.2.1., data from this hypothetical participant (see Figure 5) also suggests that cigarette smoking peaks during standardized days 1-5 (i.e., corresponding to the menstrual phase) and standardized days 24-28 (i.e., corresponding to the premenstrual phase) with a dip mid-cycle (i.e., corresponding to the follicular, ovulatory, and luteal phases). Using a larger sample of participants with 28-day standardized cycles, the researchers could employ TVEMs to statistically determine which menstrual cycle days and corresponding phases are associated with increases and decreases in cigarette smoking across a female's menstrual cycle.

One might similarly standardize data on mood across the menstrual cycle, for example, for these same participants. One could then determine whether elevations in negative mood menstrually and premenstrually, for example, account for rises in cigarette smoking on days corresponding to these same phases, again using TVEMs (e.g., see [19]).

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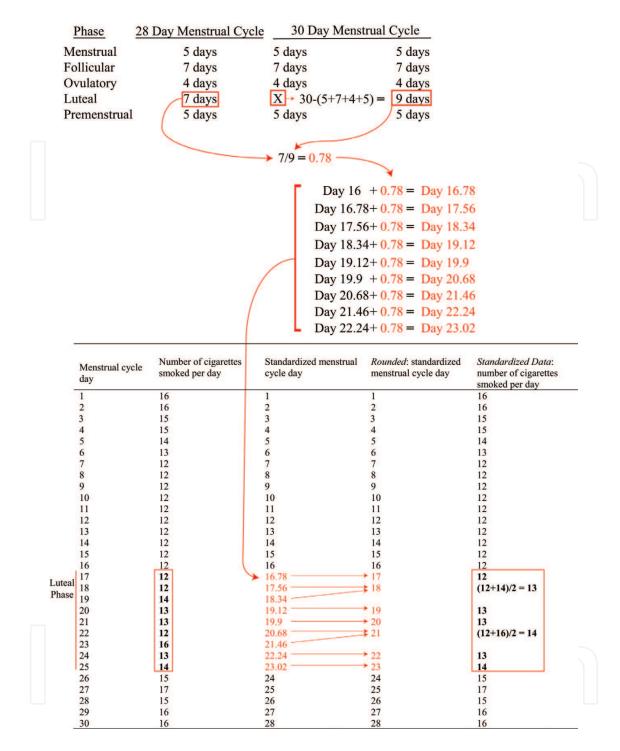


Figure 5. A worked hypothetical example of continuous standardization for a menstrual cycle greater than 28-days (i.e., 30-day cycle).

4. Conclusions

To conclude, this chapter describes two methods to standardize menstrual cycle data, including phasic and continuous standardization. By employing these methods, researchers will be able to more effectively examine fluctuations in addictive behaviors across the menstrual cycle, by allowing data from females with variable cycle lengths to be directly compared or combined across participants. Furthermore, this chapter provides standardization methods which can be

used to enhance our understanding of the menstrual cycle as a female-specific factor that may influence important outcome variables in the field of addiction and mental health. Standardized data using continuous standardization also allows for the use of more intricate statistical methods such as TVEM [19] which will significantly benefit behavioral research on the menstrual cycle.

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Conflict of interest

The authors have no conflicts of interest to declare.

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