Introduction

- Identifying the day of ovulation is important for natural family planning (for both conception and contraception purposes) and when timing procedures to coincide with a phase of the menstrual cycle.
- Direct observation of ovulation via transvaginal ultrasound is costly and invasive, therefore a simple alternative reference for ovulation is valuable.
- Onset of the luteinising hormone (LH) surge provides a reliable guide to ovulation.

However, many different methodologies have been described for determining the day of the urinary LH surge in pre-menopausal women.

- This can make it difficult to compare findings between studies.
- It is unclear which methodology is most appropriate.

Therefore, this research aims to determine the best objective method for defining the LH surge by:
- Conducting a literature review of published methodologies proposed for the allocation of LH surge day
- Applying the methodologies identified to a cycle dataset for the retrospective evaluation of their effectiveness.

Methods

A literature review was conducted and 12 important publications identified, describing the methods used to determine the LH surge.1-12 A summary of these is given in Table 1.

Table 1: Summary of publications reviewed

<table>
<thead>
<tr>
<th>Publication</th>
<th>(total number of women AND total number of cycles)</th>
<th>Definition</th>
<th>Numerical LH surge definition</th>
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</thead>
<tbody>
<tr>
<td>Baird et al. (1981)</td>
<td>221 women 707 cycles</td>
<td>LH peak initially, then the ratio of estrogen-3-glucuronide and pregnanediol-3 glucuronide</td>
<td>Look at five day sequence in which the ratio values for the first day are the highest of the five, and the ratio values for the last two days are ≤40% of the first day value. The second day in this sequence is designated as the day of ovulation transition.</td>
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<td>Brown et al. (1993)</td>
<td>11 women normal cycles</td>
<td>Analysis of eumenorrhoeic women's cycles to determine the increments of hormones which would be consistent with normally cyclic gonadal function – mid-cycle surges constrained to last for no more than two consecutive days.</td>
<td>LH surge was designated as the series of high LH values close to the ultrasound-determined day of ovulation. Precise determination of the onset of the LH surge to provide a reliable guide to the time of ovulation – deduced ovulation may occur 34-35 hours after the onset of the LH surge.</td>
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<tr>
<td>Direito et al. (2013)</td>
<td>107 women 239 cycles</td>
<td>LH surge was designated as the series of high LH values close to the ultrasound-determined day of ovulation. Precise determination of the onset of the LH surge to provide a reliable guide to the time of ovulation – deduced ovulation may occur 34-35 hours after the onset of the LH surge.</td>
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<td>Hoff et al. (1983)</td>
<td>5 women</td>
<td>First significant rise above the follicular phase urinary LH level in the individual cycles was designated day 5.</td>
<td>Four-fold increase from that of baseline.</td>
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<tr>
<td>Johanssen et al. (1979)</td>
<td>22 women 42 cycles</td>
<td>First significant rise above the follicular phase urinary LH level in the individual cycles was designated day 5.</td>
<td>Four-fold increase from that of baseline.</td>
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<tr>
<td>Kaye &amp; Jaffe (1975)</td>
<td>10 women</td>
<td>Peak as defined day 0 on graphs with the LH surge, discussed in results without definition.</td>
<td>Not given.</td>
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<tr>
<td>Moghissi (1983)</td>
<td>30 women</td>
<td>LH peak initially, then the ratio of estrogen-3-glucuronide and pregnanediol-3 glucuronide</td>
<td>Look at five day sequence in which the ratio values for the first day are the highest of the five, and the ratio values for the last two days are ≤40% of the first day value. The second day in this sequence is designated as the day of ovulation transition.</td>
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<tr>
<td>Park et al. (2007)</td>
<td>46 women 46 cycles</td>
<td>Designated day of LH surge onset – first LH value with a visually marked increase, as compared with that of prior LH values.</td>
<td>Using CUSUM (cumulative sum control chart) to determine the appearance of a sustained increase from baseline ≥180% of the mean of the preceding four values.</td>
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<tr>
<td>Sibbel (1988)</td>
<td>20 women</td>
<td>Baseline LH – mean of five LH values immediately preceding the designated day of onset of the LH surge</td>
<td>Using CUSUM (cumulative sum control chart) to determine the appearance of a sustained increase from baseline ≥180% of the mean of the preceding four values.</td>
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<tr>
<td>Skest et al. (1981)</td>
<td>16 women 19 cycles</td>
<td>Baseline LH – mean of five LH values immediately preceding the designated day of onset of the LH surge</td>
<td>Using CUSUM (cumulative sum control chart) to determine the appearance of a sustained increase from baseline ≥180% of the mean of the preceding four values.</td>
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<tr>
<td>Young &amp; Jaffe (1976)</td>
<td>12 women 25 cycles</td>
<td>Baseline LH – mean of five LH values immediately preceding the designated day of onset of the LH surge</td>
<td>Using CUSUM (cumulative sum control chart) to determine the appearance of a sustained increase from baseline ≥180% of the mean of the preceding four values.</td>
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<tr>
<td>Zeevan et al. (2003)</td>
<td>4 women 4 cycles</td>
<td>Baseline LH – mean of five LH values immediately preceding the designated day of onset of the LH surge</td>
<td>Using CUSUM (cumulative sum control chart) to determine the appearance of a sustained increase from baseline ≥180% of the mean of the preceding four values.</td>
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</table>

This review concluded:
- The LH surge was defined as a substantive rise above the baseline, which was assigned using a variety of methods.
- Most methods required an initial estimate of the LH surge prior to characterisation; this was usually the day of the peak LH concentration, or an initial estimate of the LH surge.
- Baseline LH was calculated using a variety of preceding days from the initial estimate: however, some authors alternatively used fixed days within the cycle as the baseline.
- The substantive rise (i.e. surge) was also defined in different ways, for example, multiples of the baseline level, or a number of standard deviations above the baseline level.
- Examples of the hormone profiles are given in Figure 1 to illustrate the divergent nature of the LH surge between volunteers. LH was measured using the Perkin Elmer AutoDELFI assay. Pregnanediol-3-glucuronide (P3G), a urinary metabolite of progesterone, was also measured using the Perkin Elmer AutoDELFI assay. Pregnanediol-3-glucuronide (P3G), a urinary metabolite of progesterone, was

The literature provided three main methodologies for determination of the baseline LH levels:
- Fixed days in cycle, starting at day five or six, and including four or five days in the baseline.
- Peak day as initial estimate, using the last day in the baseline as this estimate, minus three, four, five or six days and including four or five days in the baseline.
- Proportional surge day as initial estimate, using the last day in the baseline as this estimate, minus one or two days, and including four or five days in the baseline.

The LH surge is then the day at which the LH levels exceed:
- Mean of baseline + 2.5 x standard deviation of baseline.

The methodologies were assessed on 254 cycles of daily urine samples (109 non-pregnant and 148 conception cycles) from 227 women who were trying to conceive. Results of the methodologies were compared to the reference LH surge, as determined by an expert panel review of LH and P3G profiles.

Results

- Using fixed days within the cycle to assign the baseline was a poor method, as it was only able to correctly identify the LH surge within +/- 1 day of the reference day in 58% of the cycles.
- The method using the day of the peak LH concentration as the initial estimate performed much better, correctly identifying the LH surge within +/- 1 day in 90% of the cycles.
- The method using an initial estimate of the LH surge correctly identified the LH surge in 97% of the cycles. A worked example of this method is shown in Figure 2.

Figure 2. Example cycle illustrating methodology using the proportional surge day as an initial estimate, four days for baseline, with the last day of the baseline being the proportional surge day minus two days

Conclusion

Determining the day of the LH surge as a surrogate of ovulation is important in many large clinical studies. Therefore an objective, effective method for defining the surge is important. Although visual inspection of hormonal profiles can provide a very accurate assessment, it is not always practical and is dependent on clinical expertise.

We have found that not all methods described in the literature provide an accurate assessment, but the method of using the proportional surge day as an initial estimate, four days for the baseline with the last day of baseline being the proportional surge day minus two days, is a reliable method for the routine determination of the LH surge in ovulatory menstrual cycles, and has been verified on an independent dataset.

We recommend that the two methodologies used are based on different initial reference estimates, i.e. one using peak LH as an initial estimate, and one using an initial estimate of the LH surge. In cases where there is disagreement between the methods, review by an expert panel should be conducted.

As these parameters can be simply programmed, this should allow efficient, objective determination of the LH surge, which is especially welcome when examining large datasets of menstrual cycles.

References


Declaration

The authors have disclosed that they have no relevant financial or other interests, affiliations, or involvement in any organization that has or may have a direct or indirect financial interest in the subject matter discussed in this manuscript.

Review of methodology for determining the day of urinary luteinising hormone surge

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