

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

Authors: Sonya Godbert¹, Chris Shreeves¹, Sarah Johnson¹

¹SPD Development Company Ltd., Bedford, UK

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

Publication	Sample size (total number of women AND total number of cycles)	Definitions	Numeric LH surge definition
Baird et al. (1991) ¹	221 women 707 cycles	LH peak initially, then the ratio of estrogen-3-glucuronide and pregnanediol-3-glucuronide	Look at five day sequence in which the ratio value for the first day is the highest of the five, and the ratio values for the last two days are $\leq 40\%$ of the first-day value. The second day in this sequence is designated as the day of luteal transition
Brown et al. (1993) ²	11 women normal cycles	Analysis of eumenorrheic womens' 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	Rises in LH which exceeded two standard deviations above both the immediately preceding and following 5 days' means
Direito et al. (2013) ³	107 women 283 cycles	LH surge was designated as the series of high LH values close to the ultrasound-determined day of ovulation	30% of the amplitude of the LH peak
Hoff et al. (1983) ⁴	5 women	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	First LH value exceeding the mean plus two standard deviations of the six preceding values served as an initial estimate
Johansson et al. (1971) ⁵	22 women 42 cycles	First significant rise above the follicular phase urinary LH level in the individual cycles was designated day 0	Four fold increase from that of baseline
Keye & Jaffe (1975) ⁶	10 women	Investigating the effect of synthetic gonadotrophin-releasing hormone on the maximal LH increase and mean area subtended	Not given
Moghissi (1983) ⁷	30 women	Peak used as day 0 on graphs with the LH surge, discussed in results without definition	Not given
Park et al. (2007) ⁸	46 women 46 cycles	Designated day of LH surge onset – first LH value with a visually marked increase, as compared with that of prior LH values. Baseline LH – mean of five LH values immediately preceding the designated day of onset of the LH surge	2.5-fold from baseline
Seibel (1986) ⁹	N/A	First point rising above the baseline which is followed by a sustained increase	Using CUSUM (cumulative sum control chart) to determine the appearance of a sustained increase from baseline
Testart et al. (1981) ¹⁰	20 women	Deduced ovulation occurs 36–38 hours after the onset of the LH surge	$\geq 180\%$ of the mean of the preceding four values
Young & Jaffe (1976) ¹¹	16 women 19 cycles	Investigating the effect of synthetic gonadotrophin-releasing hormone on the maximal LH increase and mean area subtended	Observed serum estradiol levels generally increased 72 hours prior to any LH rise
Zeeman et al. (2003) ¹²	N/A	Modelling coupled oscillators with frequency modulation, through which the LH surge could arise as transient resonance	Computed by convolving with exponential decay

N/A, not available

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 varying number 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 AutoDELFIA 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
- Provisional 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 (106 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.

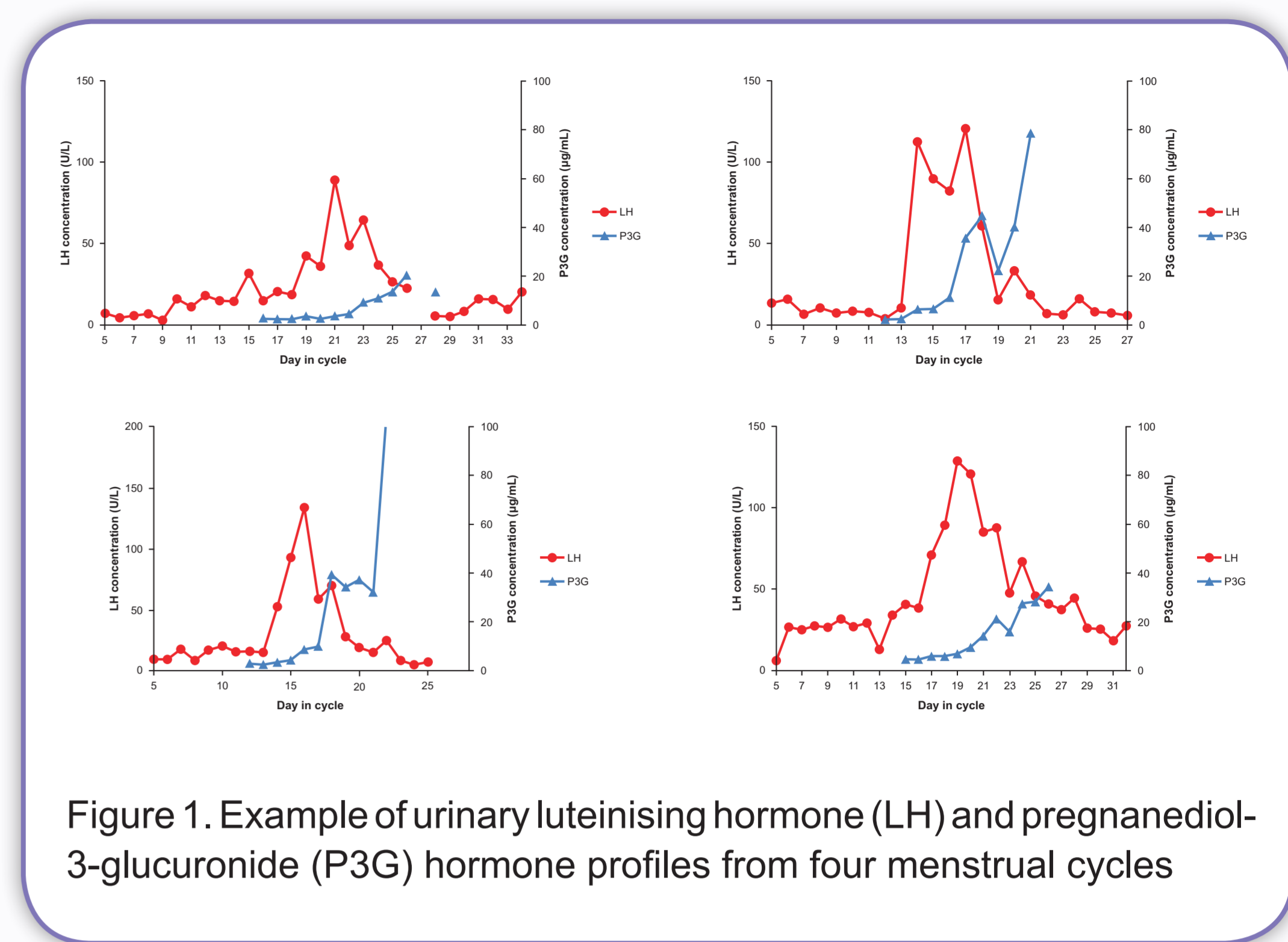
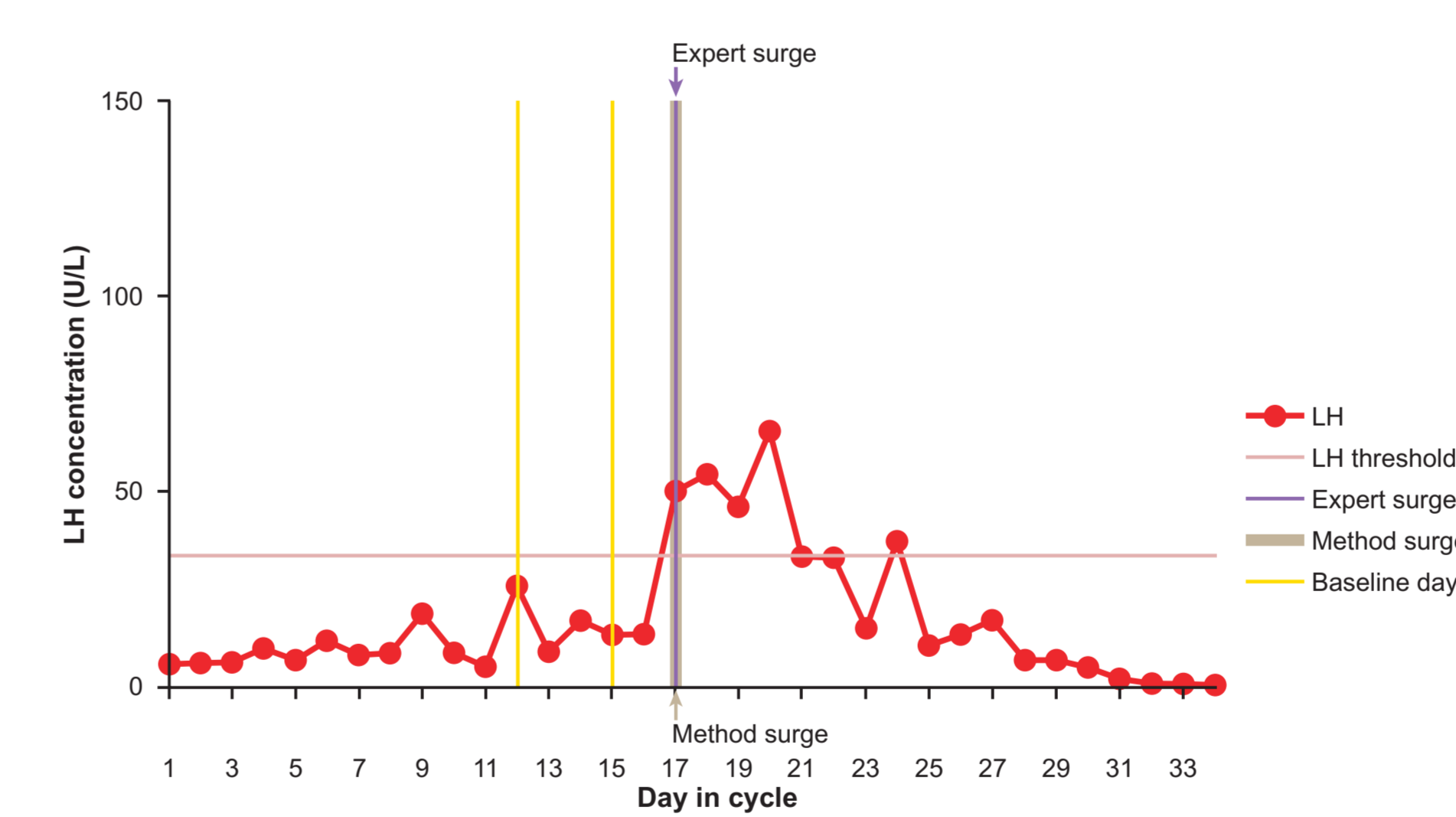


Figure 1. Example of urinary luteinising hormone (LH) and pregnanediol-3-glucuronide (P3G) hormone profiles from four menstrual cycles

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 provisional surge day as an initial estimate, four days for baseline, with the last day of the baseline being the provisional surge day minus two days



The best method was deemed to be: using the provisional surge day as an initial estimate, four days for the baseline, with the last day of the baseline being the provisional surge day minus two days. For a routine algorithm, it is proposed that two methodologies should be used, and when they agree, use this as the day of the LH surge, and if they do not, then highlight for expert panel review.

Verification of the final methodology was performed on a separate dataset of 39 cycles from individual women; using the method of an initial estimate of the LH surge correctly identified the LH surge to the same day as, and within one day of, the expert panel in 71% and 100% of the cycles, respectively.

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 provisional surge day as an initial estimate, four days for the baseline with the last day of baseline being the provisional 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

- Baird DD *et al.* Stat Med 1991;10:255–266
- Brown JR *et al.* Endocr J 1993;1:467–474
- Direito A *et al.* Fertil Steril 2013;99:279–285
- Hoff JD *et al.* J Clin Endocrinol Metab 1983;57:792–796
- Johansson EDB *et al.* Acta Endocrinol 1971;68:502–512
- Keye WR & Jaffe RB. J Clin Endocrinol Metab 1975;41:1003–1008
- Moghissi KS *et al.* Fertil Steril 2007;88:684–690
- Seibel MM *et al.* J Reproductive Medicine 1986;31:754–759
- Testart J *et al.* Fertil Steril 1981;36:50–54
- Young JR & Jaffe RB. J Clin Endocrinol Metab 1976;42:432–442
- Zeeman ML *et al.* Reprod Biomed Online 2003;7:295–300

Declaration

Sonya Godbert, Chris Shreeves and Sarah Johnson are employees of SPD Development Company Ltd., a fully owned subsidiary of SPD Swiss Precision Diagnostics GmbH, the manufacturers of Clearblue Pregnancy and Fertility tests. This study was funded by SPD Development Company Ltd.

