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The LH surge and ovulation re-visited: a systematic review and meta-analysis and implications for true natural cycle frozen thawed embryo transfer

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Abstract

Background: Efficient and safe embryo vitrification techniques have contributed to a marked worldwide increase in the use of elective frozen embryo transfer (FET). Pinpointing the day of ovulation, more commonly by documentation of the LH surge and less commonly by ultrasonography, is crucial for timing of FET in a true natural cycle (t-NC) to maximize the reproductive outcome.

Objective and rationale: The definition of the onset of the LH surge should be standardized in t-NC FET cycles; however, a clear definition is lacking in the available literature. The first search question concerns the definition of the onset of the LH surge in a natural cycle. The second search question relates to the duration between the onset of the LH surge and ovulation.

Search methods: We searched PubMed, Web of Science and Cochrane Library databases for two search questions from inception until 31 August 2021. 'Luteinizing hormone'[MeSH] OR 'LH' AND 'surge' terms were used to identify eligible articles to answer the first question, whereas 'Luteinizing hormone'[MeSH] OR 'LH' AND 'surge' OR 'rise' AND 'ovulation'[MeSH] OR 'follicular rupture' OR 'follicular collapse' were the terms used regarding the second question. The included publications were all written in the English language, conducted in women of reproductive age with regular ovulatory cycles and in whom serial serum or urine LH measurement was performed. For the quality and risk of bias assessment of the included studies, the Strengthening the Reporting of Observational Studies in Epidemiology and modified Newcastle Ottawa Scale were used.

Outcomes: A total of 10 and 8 studies were included for search Questions 1 and 2, respectively. Over the years, through different studies and set-ups, testing in either serum or urine, different definitions for the onset of the LH surge have been developed without a consensus. An increase in LH level varying from 1.8- to 6-fold above the baseline LH level was used in seven studies and an increase of at least two or three standard deviations above the mean of the preceding LH measurements was used in two studies. An LH level exceeding the 30% of the amplitude (peak-baseline LH level) of the LH surge was defined as the onset day by one study. A marked inter-personal variation in the time interval between the onset of the LH surge and ovulation was seen, ranging from 22 to 56 h. When meta-analysis was performed, the mean duration in hours between the onset of the LH surge and ovulation was 33.91 (95% CI = 30.79-37.03: six studies, 187 cycles).

Wider implications: The definition of the onset of the LH surge should be precisely defined in future well-designed studies employing state-of-art laboratory and ultrasonographic equipment. The window of implantation in a natural cycle is still a black box, and future research is warranted to delineate the optimal interval to time the embryo transfer in t-NC FET cycles. Randomized controlled trials employing different precise endocrine and/or ultrasonographic criteria for timing of FET in a t-NC are urgently required.

Keywords: LH surge; frozen embryo transfer; natural cycle; ovulation; true natural cycle; ultrasound; window of implantation.

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