Evidence in support of using the day after the surge in levels of luteinising hormone (LH+1) as a marker for conception

Key Points

- The LH surge is a marker for ovulation[1-15,31-41]
- Conception occurs very shortly after ovulation[16-21,23,25,30]
- The LH surge can therefore be used as a marker for conception

Introduction

Luteinizing hormone (LH) is produced over a period of a few days around the time of ovulation. At the time of menstruation, follicle stimulating hormone (FSH) initiates follicular growth and with the rise in estrogens, the maturing follicle produces an increasing amount of estradiol. Eventually at the time of the maturation of the follicle, the estrogen rise leads to a release of LH. Over the course of several days, the levels of LH peak, ovulation occurs and levels of LH fall again. This is termed the LH surge and the day of LH surge is defined as the first day LH is elevated above baseline or the day of peak LH depending on the study. The time that ovulation occurs after the LH surge has been studied in order to determine whether the LH surge can be used as a suitable marker for ovulation.

Time of ovulation after the LH surge

Key Points

- Ovulation occurs 24-36 hours after the LH surge or rise in LH levels[5,31-41] and ovulation and LH levels have been shown to be significantly correlated[4,12]

The original evidence on timing from LH surge to ovulation came from a study on women undergoing sterilisation[2]. Volunteers provided daily blood samples prior to surgery and visual examination of ovaries, histology of the corpora lutea and recovery of ova was used to establish ovulation. The time from serum LH peak to ovulation was 9 hours. An early study comparing ultrasound with initial appearance of LH in urine found that in 19/23 (83%) of normal volunteers, ultrasound detection of ovulation and appearance of LH coincided within 24h[36]. It was proposed that ovulation should be considered to occur 12-36h post LH appearance in urine. A larger study of 177 women was conducted by the WHO examining serum hormonal levels and ovulation by laparotomy[1]. It was found that the median time interval from hormonal event to ovulation (95% CI) was: LH-rise 32h, (23.6-38.2) and LH-peak 16.5h (9.5-23). In 90% of cases, ovulation occurred between 16-48 hours of the initial increase in LH. The World Health Organisation (WHO) state in its publication that a defined rise in the concentration of circulating LH is the best parameter of impending ovulation. This is supported by the observation of 100% correlation between ultrasound detection of ovulation and urinary LH increases measured by Clearplan home ovulation tests[4]. The authors concluded that "measuring LH levels is an excellent method for determining ovulation".

Different methods of ovulation detection, including LH tests, ratios of levels of estrogen and progesterone, basal temperature and transvaginal ultrasound have been compared in normally cycling women aged 19-45, cycle length 24-34 days[3]. The average delay between the expected date of ovulation based on LH and ultrasound detection of ovulation was +0.46 days. When analysing

LH peak versus ultrasound, 67.6% occurred within -1 to +1 days of each other (184/272 cycles), but with a wide spread of -7 to +7 days (however some of these cycles were long with two LH peaks). When LH initial rise was used instead, 73.6% occurred within -1 to +1 days of ultrasound detection (range -7 to +7 days). Temperature measurement and ratio of estrogen and progesterone were less accurate than LH for predicting ovulation.

Comparison of the use of serum LH, and urine LH detected by a home ovulation test and sonographic criteria with confirmation by normal luteal-phase progesterone levels (3 ng/mL or greater) found that the time from the first positive urine LH test to ovulation was 20 +/- 3 hours (95% CI 14-26)[5]. This study also drew a comparison between results obtained by other studies, and showed that the predictive value of urinary LH for estimating time of ovulation (confirmed by ultrasound) ranged from 90-100% for sonographically identified ovulation within 2 days following the LH surge, with two exceptions (65%, n=17, and 80%, n=20).

A small (n = 7 women) but detailed study by Fritz[6] on serum hormone profile in relation to follicle rupture as measured by every 3 hour blood samples and every 12 hour ultrasound found that follicle rupture occurred 37.6±4.2h after peak LH was detected. Bischof [7] studied 35 cycles from normal women and found follicle rupture occurred 9-51 hour (full range) after the urine LH surge (automated assay). A similar estimate of 37.5 hours from LH initial rise to rupture was obtained by Collins [8], with 17.5h from LH peak to rupture, while in another study a mean time from LH rise to follicle rupture of 35 hours was reported [9]. Intriguing evidence[10] suggests that in conception cycles, ovulation always occurs within 24 hours of peak serum LH, but in non-conception cycles, this is pushed out to up to 48 hours later. Further early studies include Wetzels[11] where ultrasound detection of ovulation occurred 11-48 hours after LH initial rise and 11-24 hours after peak, and Vermesh[12], which found no significant difference between ultrasound and serum LH measurement to predict ovulation. Seibel[13] found the time lag between LH surge and ovulation to be 38 hours, whereas Taymor[14] determined it to be 36-38 hours (or 22-26 hours from peak LH). Follicle puncture for in-vitro fertilization ("IVF") at various times in relation to the LH surge found ovulation to occur at 36-38 hours post-surge[15].

Overall, reports indicate that ovulation occurs between 24 and 36 hours after the LH surge. Data from various studies on the time of ovulation following LH surge are compiled in the summary table on next page.

Conception and the Fertile Window

Key Points

- The ovum is very short-lived[19,20,21]
- No cases of intercourse leading to conception have been documented after the day of ovulation[16,17,18]
- The fertile window significantly declines on the day after ovulation [23, 25, 30]

Evidence suggests that conception must occur very shortly after ovulation. Intercourse leading to conception occurs during the window that spans 5 days prior to ovulation and the estimated day of ovulation (EDO) itself, with no documented cases occurring after the EDO[16,17,18]. This is because the mature ovum has a limited lifespan. IVF typically is conducted 2-6h post oocyte retrieval, with little success in insemination of oocytes 16h post-collection[19]. Studies on intra-cytoplasmic sperm injection (ICSI) show oocyte's viability is limited to hours rather than days[20]. The mean length of time of survival of ova has been demonstrated to be 0.7 days[21].

Ovulation in relation to LH surge – Summary Table

Publication	Methods	Time of ovulation (% of women ovulating within given time of LH surge)
Pauerstein (1978)[2]	Women undergoing hysterectomy have Blood sampling and dating of corpus luteum	9h from LH peak to ovulation
Queenan (1980)[36]	23 normal women, with ultrasound and urine LH	83% by Day LH +1
WHO (1980)[1]	Laparotomy, serum LH rise and peak, and other hormones	32h after LH rise,16.5h after LH peak
Behre (2000)[37]	53 normal women, cycle length 21-43 days, 150 cycles, urine LH rise (Clearplan)	51.1% (serum) 14.8% on day of surge and 76.3% following day (urine)
Fritz (1992)[6]	9 normal women, 3h blood samples and 12h ultrasound	Time from LH to ovulation 37.6h ±4.2h
Pearlstone (1994)[35]	Infertility centre, 296 cycles (some with 2 or more ovulations) – unstimulated and clomiphene citrate cycles	35% on day LH+1 and 61% on day LH+2. Ovulation significantly later in multi-ovulatory cycles
Luciano AA (1990)[31]	Infertile but normally ovulating women - 50 cycles (10 induced with chomiphene citrate)	6% on day LH+1, 70.8% on LH+2 and 21% on LH+3
Ecochard (2001)[3]	Normal cycling women (19-45), ovulation study	67.7% from LH peak 73.6% from LH rise within LH+1
O'Connor (2006)[38]	Normally cycling women, LH surge considered gold standard	LH surge occurred day 13-14 (from LMP); ultrasound ovulation mean day 14.3
Bischof (1991)[7]	35 cycles from normal women, urine LH and ultrasound	Follicle rupture 9-51h later than LH surge
Nulsen (1987)[39]	LH surge and ultrasound	Ovulation occurred 0-24h from LH surge
Brockelbank (1984)[40]	Normal women, size of maximal follicle size and urine peak LH	11% less than 1 day, 50% following day
Singh (1984)[41]	24 normal women, ultrasound and serum LH surge	100% in 12-24h
Wetzels (1982)[11]	28 normal cycles, LH compared to ultrasound	Initial rise to rupture 11-48h, peak to rupture 11-24h
Zegers-Hochschild (1984)[10]	Ultrasound detection of follicle rupture and serum LH in normal women wanting to conceive	In conception cycles LH peak to ovulation was less than 24h In non-conception cycles this increased to up to 48h
Wetzels (1982)[11]	Ultrasound and LH	Initial rise to ovulation 11-48h, peak to ovulation 11-24h
Seibel (1982)[13]	LH surge to ovulation	38h
Taymor (1983)[14]	LH surge to ovulation	36-38h (22-26h from peak LH)
Testart (1981)[15]	Follicular puncture to observe ovulation in relation to serial LH measurements	36-38h post LH surge
Collins (1991)[8]	Ultrasound and LH	LH initial rise to rupture 37.5h LH peak to rupture 17.5 h

Length and Timing of the Fertile Window

There has been much research on the timing and, more specifically, the length of the fertile window in the menstrual cycle. Much of this work has centred around the probability of becoming pregnant on any given day in the menstrual cycle in relation to the time of ovulation. Many of these studies are difficult to interpret as the likelihood of conceiving is known to depend on a number of factors including frequency of intercourse, age of couple, lifestyle choices such as smoking, fertility of the couple and the timing of ovulation, which is often measured using different methods, each with their own margin of error.

A study conducted by Barrett and Marshall in the 1960's[22] reported that the fertile window extends from four days before the EDO to the day after the EDO. In this study, ovulation was based on the basal body temperature measurement and was considered to have occurred on the last day of hypothermia (before the basal body temperature begins to rise) and encompassed 241 couples of known fertility who were not seeking pregnancy. The model used to analyse the original dataset by Barrett and Marshall based the determination of the fertile window on the timing and frequency of intercourse alone. Although this model is statistically straight-forward, it was biologically over-simplified. In reality conception does not only depend on the timing of intercourse but on several interacting factors, such as the penetrability of mucus and the capacity of the ovum to be fertilised. Schwartz therefore extended this model in 1980 to include the survival of the ovum and survival of pregnancy (at least 6 weeks or greater). This represented all of the hormonal, uterine and ovum-related factors that are favourable to conception and resulted in a widening of the fertile window to include the fifth day prior to the EDO, for a total of 7 fertile days in any given cycle including the day after the EDO[23]. Several years later in 1982, Royston put forward a further argument that accounted for the viability of both the ovum and sperm. The mean survival of sperm to be 1.4 days and the mean survival of the ovum was estimated to be 0.7 days, and with these factors added into the model, a fertile window that was 9 days in length starting on the seventh day prior to the EDO and ending on the day after the EDO was calculated. The probabilities of conception from intercourse on the sixth and seventh days prior to the EDO were, however very low - 4% and 2% respectively[21, 24].

In more recent years, Wilcox and colleagues have studied the timing of the fertile window in the menstrual cycle using a different method on 221 women. In this study (North Carolina Early Pregnancy Study), day of ovulation was estimated from the change in ratio of estrone-3-glucuronide (E3G) and pregnanediol-3alpha-glucuronide (P3G) concentrations measured in daily urine samples using radioimmunoassay. Using the Schwartz model, Wilcox and colleagues found that the fertile window was 6 days long, ranging from 5 days prior to the EDO to the EDO itself. Results showed that in every cycle in which conception occurred, there was intercourse at least once in this 6-day period and none of the cycles in which no intercourse occurred in this period resulted in pregnancy. The rapid drop in the probability of conception after ovulation suggests a short survival time for ova or a change in the cervical mucus after ovulation, which obstructs the entry of new sperm[16]. A further paper by Wilcox *et al*[25] confirmed the previous findings that the fertile window does not extend beyond the EDO. It was also found that the fertile window in any woman's cycle can vary considerably, particularly in women with irregular cycle length. The EDO was as early as the 8th day and as late as the 60th day of the menstrual cycle. Clinical guidelines assume that ovulation occurs 14 days before the next period and that women are fertile for several days before and after ovulation and that, therefore, in a 28 day cycle, fertile days fall between days 10 and 17[25].

Dunson and Weinberg later proposed an extension to the Schwartz model that included accounting for measurement error in identifying the day of ovulation. This model was applied to both the Barrett and Marshall and North Carolina Early Pregnancy Study data. They confirmed that the fertile window in both studies, after controlling for error, remains at 6 days, 5 days prior to the EDO to the day of EDO itself. In both studies the highest probability of conception when intercourse took place resulting in clinical pregnancy was found to occur on the day prior to the EDO and fell close to zero after. The maximum probability of pregnancy occurs one day prior to the estimated day of EDO. This comparison also showed that the hormone-based method used by Wilcox *et al* is less error prone than the basal body temperature-based method with 60% of the hormone-estimated days of ovulation being correct compared with 43% of the basal body temperature estimated days[17].

In 2001, Dunson developed a Bayesian model that incorporates observed and unobserved couple - and cycle-specific factors and allowed for multiple markers of ovulation. Applying this generalized model to the North Carolina Early Pregnancy Study data, they found that the length of the fertile window was unchanged, but that day-specific probabilities of conception resulting in clinical pregnancy were slightly lower than those calculated under the Schwartz model[18].

Two studies have found conception occurring after the EDO, however both relied on cervical mucus symptoms to determine ovulation, The cervical mucus peak day is variable in its timing relative to ovulation, and sometimes occurs after actual ovulation. Stanford[27] reported that the fertile window extended from 6 days prior to 4 days after the EDO and France[28] found conception based on one act of intercourse during the fertile phase to occur 6 days before to three days after the EDO. Results from these studies have been summarized by Lynch[42].

Frank-Herrmann[29] looked at European cycle databases on ovulation detection and determination of the fertile window performed by women themselves. The women recorded cycle parameters such as mucus changes and temperature rise to determine the fertile window. This study showed that the fertile window lasts from 6 days prior to 1 day after the EDO[29].

In summary, the studies using hormonal methods to define ovulation predict a 6 day fertile window, ending on the day of ovulation. The studies based on other biomarkers of basal body temperature and cervical mucus, while showing more variability of the fertile window in relation to the estimated day of ovulation, are fully consistent with the more precise hormonally based studies. It is now generally accepted that the fertile window closes on the day of ovulation[30].

Summary

Many detailed studies show that ovulation occurs between 24 and 36 hours after the LH surge. In addition, evidence that the fertile window closes on the day of ovulation, and that the ovum has a short viable life-span of less than a day, points to the time of conception being very close to the time of ovulation, and probably within hours. These data support the use of the day after the LH surge (LH+1) as a marker for conception, as has been used in the studies to develop and validate Clearblue Digital Pregnancy Test with Conception Indicator.

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