Prof. Dr. Abha Majumdar

Director, Center of IVF and Human Reproduction
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President's Medal' for best medical graduate 1970-75
'Dr. B.C Roy's award' 1999 for outstanding contribution towards medicine
'Vikas Ratan Award' 2002 by Nations economic development & growth society
'**Chitsa Ratan Award**' 2007 by International Study Circle
'Life time Medical excellence award' Obs & Gyne by Hippocrates foundation 2014
'Abdul Kalam gold medal' by Global Economic Progress & Research Association 2015
Course director for post doctoral **Fellowship in Reproductive Medicine** by NBE since 2007 and by FOGSI for basic & advanced infertility training since 2008.

Member of Editorial board of '**IVF Worldwide', P**eer reviewer for '**Journal of Human Reproductive Sciences',** Member of advisory board for '**Journal of Fertility Science & Research**' and consultant advisor for queries to NDTV.com
More than 30 chapters in OB/GYN books & original articles in indexed journals

Field of interest: Infertility, ART, Reproductive endocrinology, Endoscopic surgery for pelvic resurrection. and ART.

The role of ovulation documentation and timed intercourse

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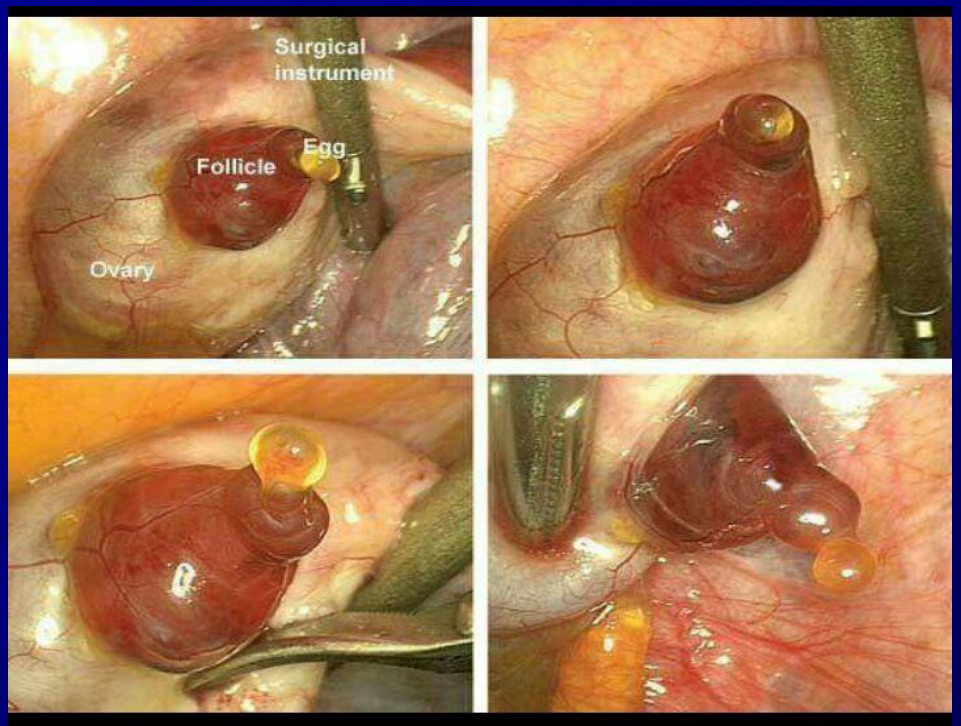
Novak's Gynaecology, 15th addition 2012

Disorders of ovulation account for approximately 30 - 40% of all cases of female infertility



Ovulation

- What is ovulation: the release of an oocyte from a mature follicle of >17 to 18 mm in size.
  - Ovulation follows a series of hormonal changes in the *follicular phase* of menstruation which lead to *selection and growth* of a goandotropin sensitive follicle containing the oocyte
  - Oocyte also matures with the growth of the follicle under the effect of FSH and then LH which releases the oocyte from follicle causing ovulation

Sequence of events in a natural ovulatory cycle

- FSH rise starts before initiation of menstruation
- Development of a cohort of gonadotropin (FSH) sensitive follicles in both ovaries in early follicular phase
- Estradiol production starts from cohort of growing follicles which reflects as rising serum E2 levels
- Rising serum E2 causes negative feedback of the pituitary, to plateau further FSH secretion by day 5 of follicular phase.

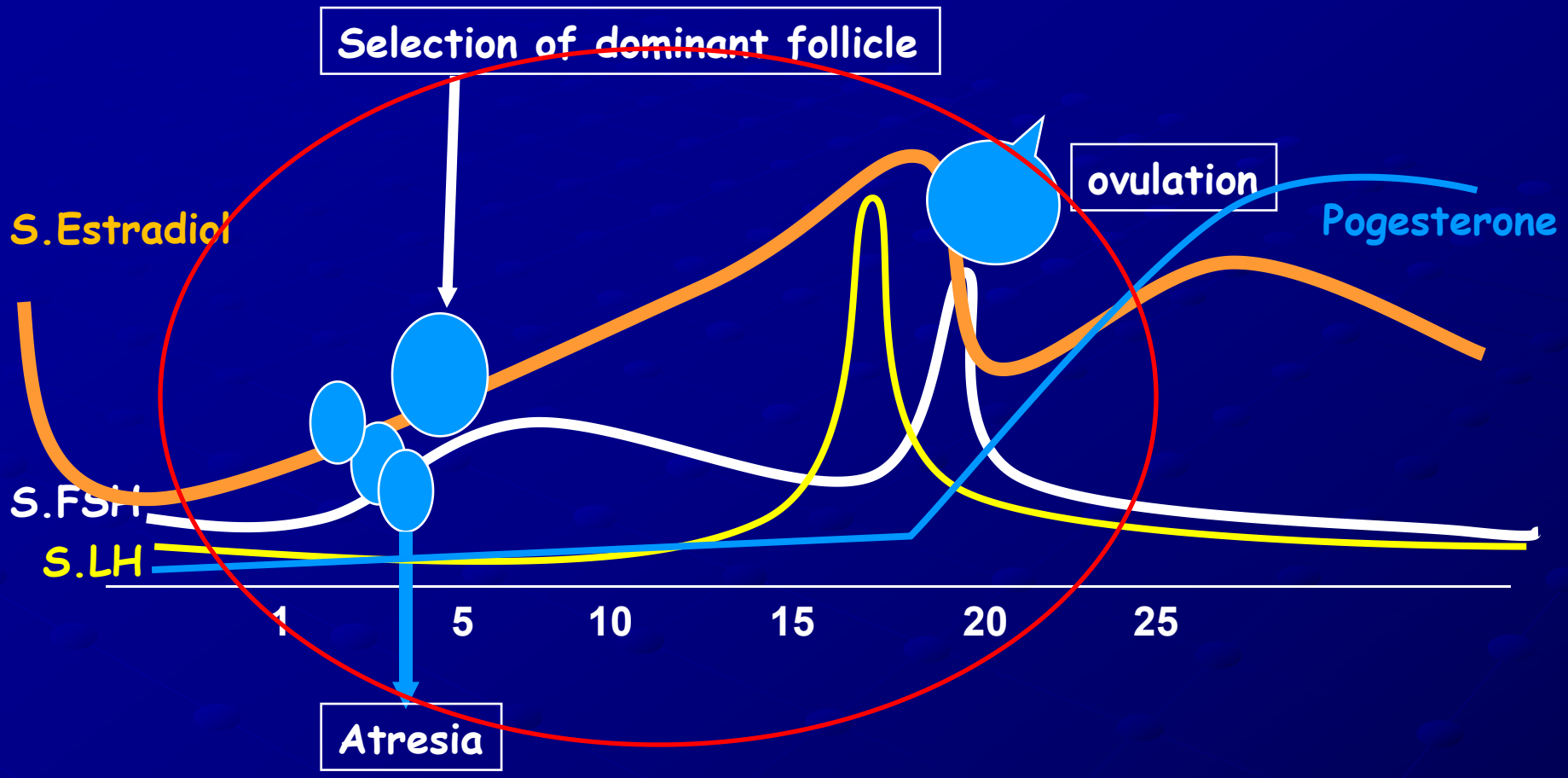
- Plateauing FSH levels lead to atresia of cohort except the follicle which has acquired highest number of FSH receptors
- LH receptors appear on the granulosa cells after selection of dominant follicle (around day 5 of FP)
- LH receptors increase in density under the effect of increasing E2 serum levels
- As the follicle crosses diameter of 17/18 mm rising E2 triggers LH surge from the pituitary to act on the follicle

What does LH surge do to the dominant follicle?

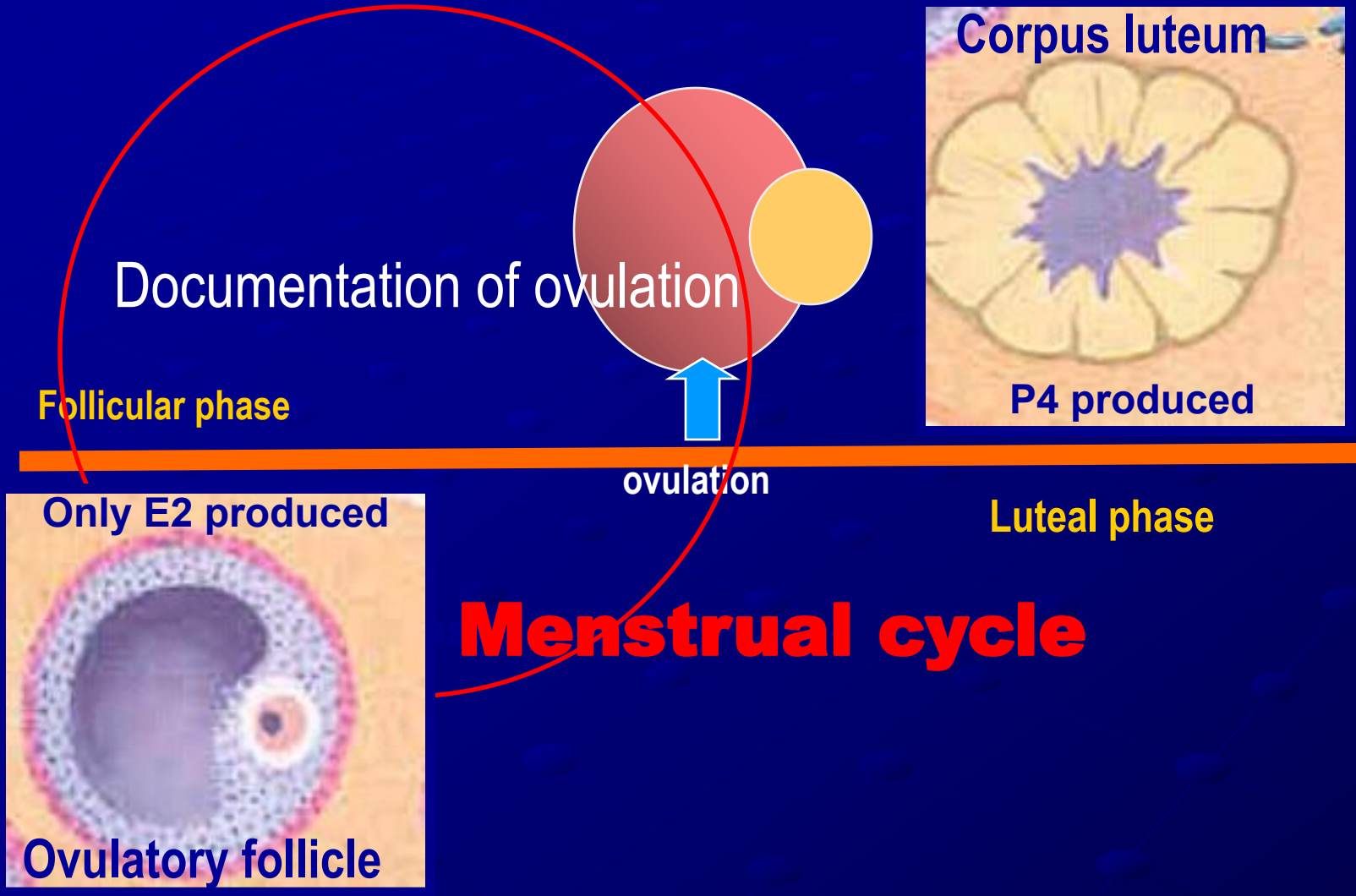
- Leutinization of granulosa cells which lead to production of progesterone (P4)
- Release of second meiotic division of oocyte
- Release of gap junctions within cumulus to loosen oocyte in follicle
- Increase in follicular pressure with ostia formation followed by release of oocyte from follicle …..OVULATION!!!!!

progesterone induces secretory changes in endometrium to prepare it for implantation

Events in a natural cycle



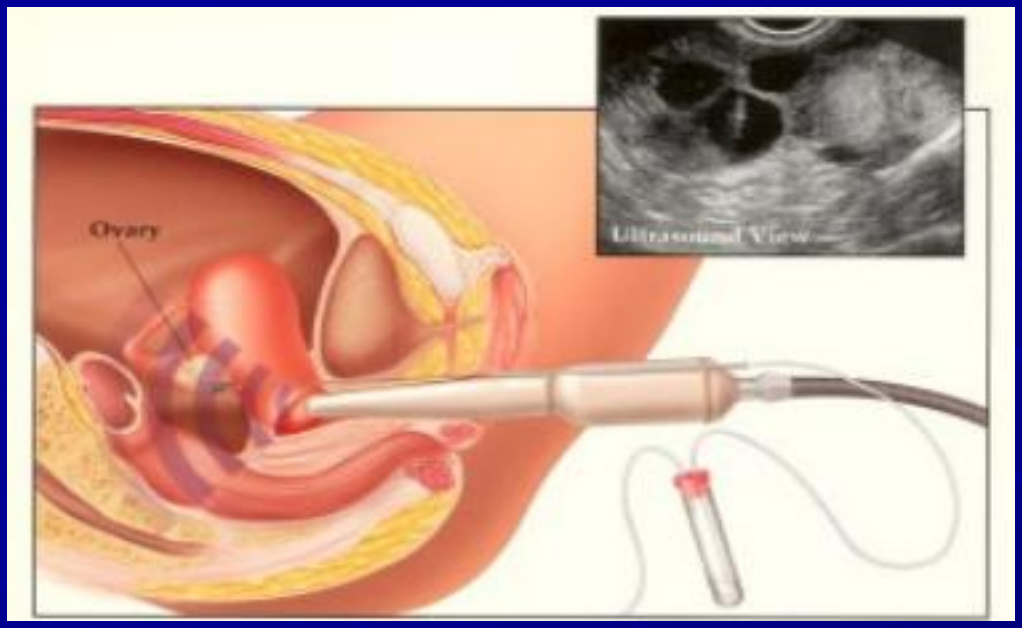
The follicular & the luteal phase

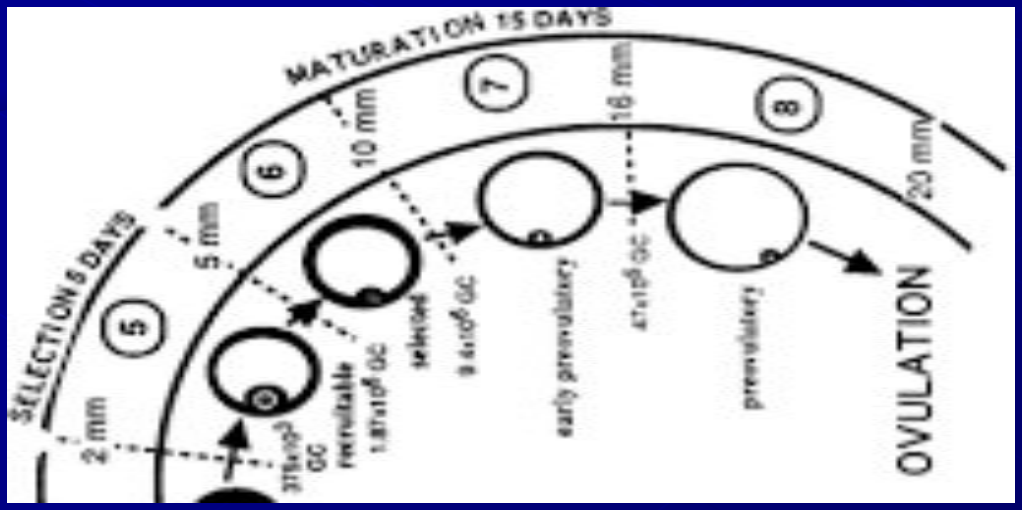


2 methods of ovulation documentation

Prospective	Retrospective
Follicle monitoring by ultra-sono-graphy LH surge detection by urinary kits	Mid luteal serum progesterone >5.6ng/ml Luteal or pre-menstrual endometrial biopsy to detect secretory changes

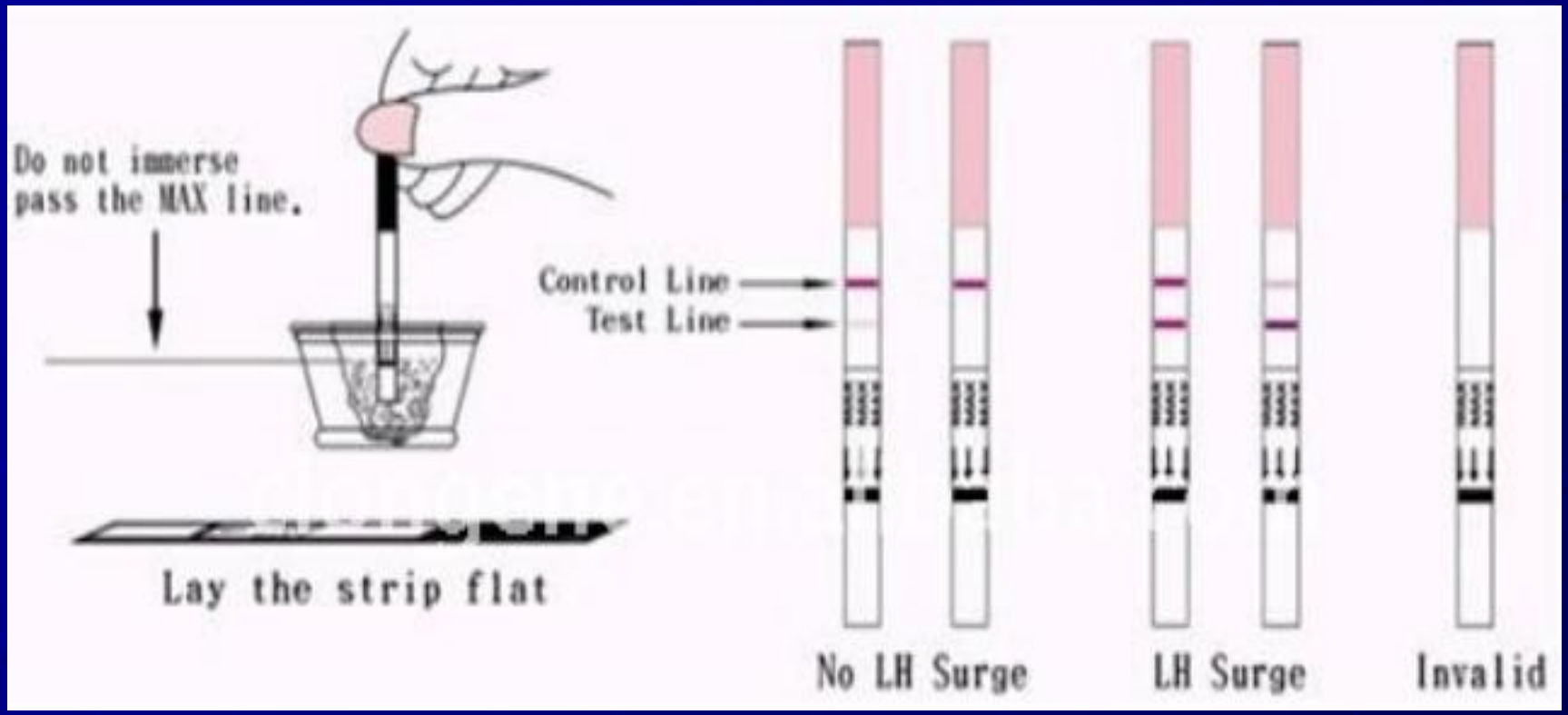
Follicle monitoring by TVS





- Ultrasound is invaluable in measuring the follicular diameter .
- Serial USG measurements are required during cycles where ovulation inducing agents are administered.
- 1st USG on Day 2 or 3 of starting OI
- Trans vaginal USG most accurate in identifying follicular growth
- At follicular diameter of >17mm ovulation impending

Urine LH surge testing

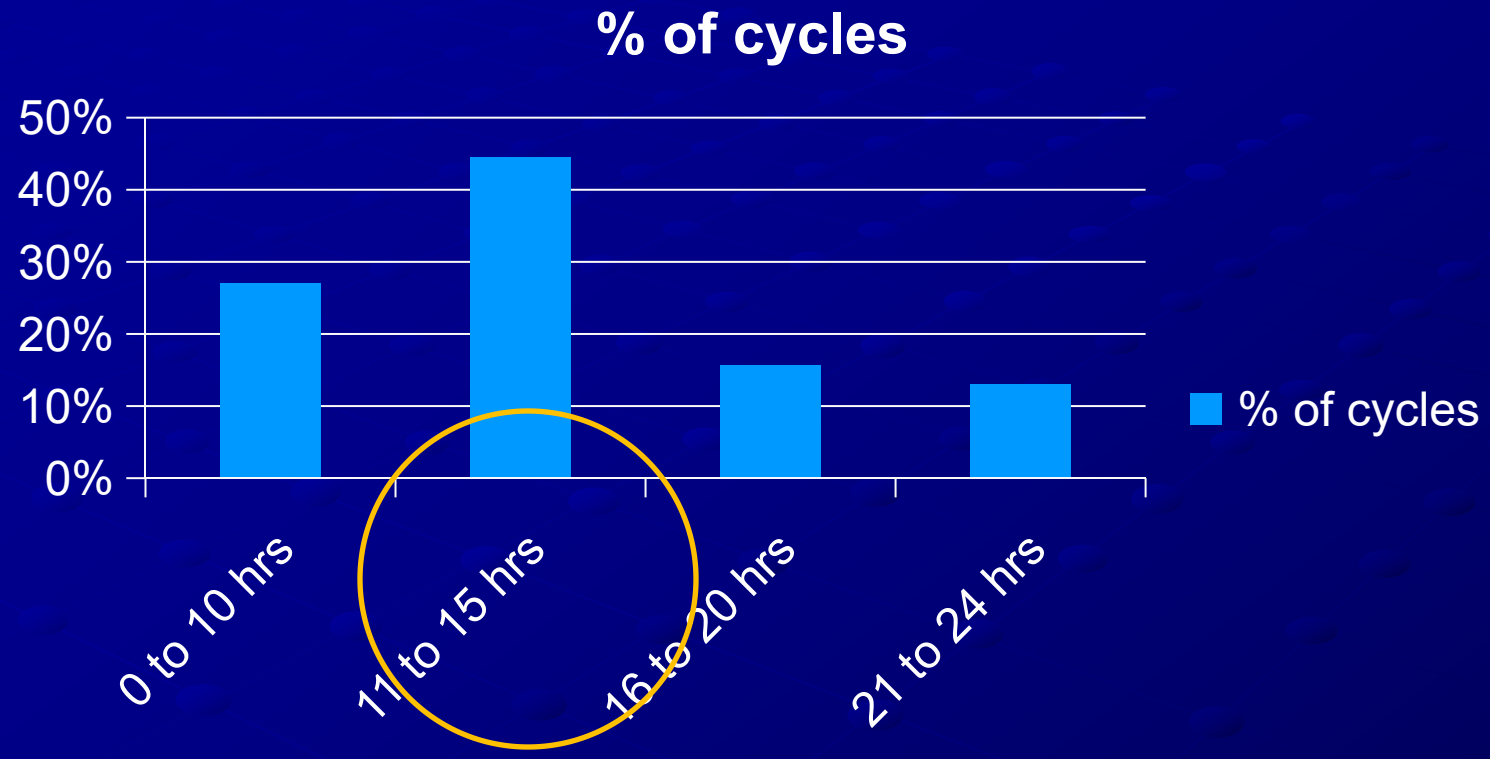


Defining onset of LH surge within few hours.

- Testing 2–3 days before the first likely date of onset of the LH surge. (28 day cycle - start collecting from day 11).
- 4 samples of urine collected daily after holding urine for 4 hrs
  - early morning(04:00–10:00)
  - lunch-time (11:00–15:00)
  - tea-time (16:00–20:00)
  - bed-time (21:00–00:00)
- Only lunch-time urine sample tested daily
- Other samples stored in refrigerator and only tested in retrospect if lunch-time sample positive
- Refrigerated sample test after warming to room temperature otherwise discard.

Human Reproduction Vol.20, No.9 pp. 2542–2545, 2005

Best timing for urine LH surge testing



The percentage of cycles with first positive urine LH test by time. A x2-test was performed to investigate whether the number of positive tests was uniformly distributed across the four time categories and this hypothesis was rejected at the level of P , 0.001

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Ovulation documentation and timed intercourse

Prospective ovulation detection & documentation with timed inter-course is the key to successful conception

- 2 instances when ovulation documentation is required to attain fertility
  - Regular spontaneous cycle ovulation
  - Stimulated or ovulation induced cycle

Natural regular spontaneous cycle ovulation (28 day cycle)

Home monitoring

Urinary LH surge kit

- Start urine LH surge detection by afternoon urine daily from day 11 onwards
- 24 hours post LH surge 70% ovulation, 30% may take up to 56 hours
- LH surge positive – timed intercourse

Clinic monitoring

USG monitoring

- Base line USG to rule out cyst and ensure complete endometrial shedding
- Scan day 12 to see presence of dominant follicle
- Combine serum LH>20 or urine LH surge positive – timed intercourse

Stimulated or ovulation induced cycle

Clomiphene,Letrozole

i. Urine LH surge from day 11 daily afternoon

ii. USG-FM –base line d3 & then from d11, if no DF repeat every 2 to 3 days up to 21 days DF

iii. If progesterone <1ng/mg on day 21 induce withdrawal bleeding

Gonadotropins

- Base line USG r/o cyst and thick endometrium
- USG-FM after 5 days of stimulation and there onwards every 3 to 5 days as per response till dominant follicle
- Sexual intercourse with hCG trigger or LH surge

Facts associated with semen processing for IUI vs natural intercourse

Natural intercourse	Intra uterine insemination
• Post intercourse cervical reservoir of sperms for 48 hrs & may persist up to 96 hrs.	• Processed sperms fertilize oocyte only within 2 to 3 hours from preparation time.
• Sperm capacitation stops on entry in cervical mucous to restart when they release and reach the cumulus of oocyte	• Removal of seminal plasma initiates sperm capacitation by changes in the ions in the acrosome
• Sperm reservoir forms in cervical mucous	• No sperm reservoir in cervical mucous

Editorial :J Obstet Gynecol India Vol. 59, No. 5 : September/October 2009 pg 407-409
Relationship between the time interval from semen collection to sperm wash and IUI outcome Fertil Steril Vol 92, Issue 3, Supplement Page S145, Sept 2009

Facts associated with timing of ovulation

WHO probit analysis of natural cycles:

- Ovulation 24 to 56 hours after onset of LH surge
- After hCG injection ovulation after 36 hours & is sequential over several hours up to 48 hours

Oocytes fertilizable within 12 -16 hrs of release

Most favorable window of conception

- Window of fertilization for oocyte is 12 to 16 hours post release
- After hCG ovulation is sequential over several hours from 36 hrs to 48 hrs and after LH surge in 24 hrs (70%)
- Sperms live for 48 to 72 hours in cervical mucous after intercourse.
- Best time of intercourse appears *before ovulation or within 12 hours of ovulation* (with Urine LH surge or with hCG trigger).
- 16 to 24 hours post ovulation oocyte starts degenerating therefore intercourse 1 day after ovulation – very low probability of conception

Timed or uninfluenced intercourse? A systematic review and meta-analysis of indirect evidence.

No trials to compare timed intercourse (TI) with expectant management (EM) directly

IUI studies looking at PR comparing IUI with TI or IUI with EM were used to extrapolate evidence to compare timed inter-course with expectant management

of control groups was 2.8%. The difference between trials with TI and OI controls was not significant, neither in the 11 most relevant trials ($P = 0.82$) nor in a broader group of 19 trials and 2512 patients ($P = 0.20$). The additional benefit accruing to IUI from using TI as the control is not significant, but it is consistent with the possibility that pregnancy may be less likely in TI controls than expectant manage-ment controls (Snick *et al.*, 2008).

Snick HK, Collins JA, Evers JLH ;Hum Reprod 2008;23:2239–2245

Take home message

- Documentation of ovulation prospectively can be done by USG follicle monitoring or detection of urine LH surge or a combination of both.
- Intercourse before ovulation allows a larger window for achieving fertility rather than later
- Cervical reservoir forms on sexual intercourse not by IUI.
- TI after detection of ovulation may not lead to better PR vs expectant intercourse possibly due stress associated the anxiety for ovulation documentation

OVULATION INDUCTION IS NOT ONLY A SCIENCE BUT ALSO AN ART