GnRH agonist for triggering final oocyte maturation and prevention of OHSS

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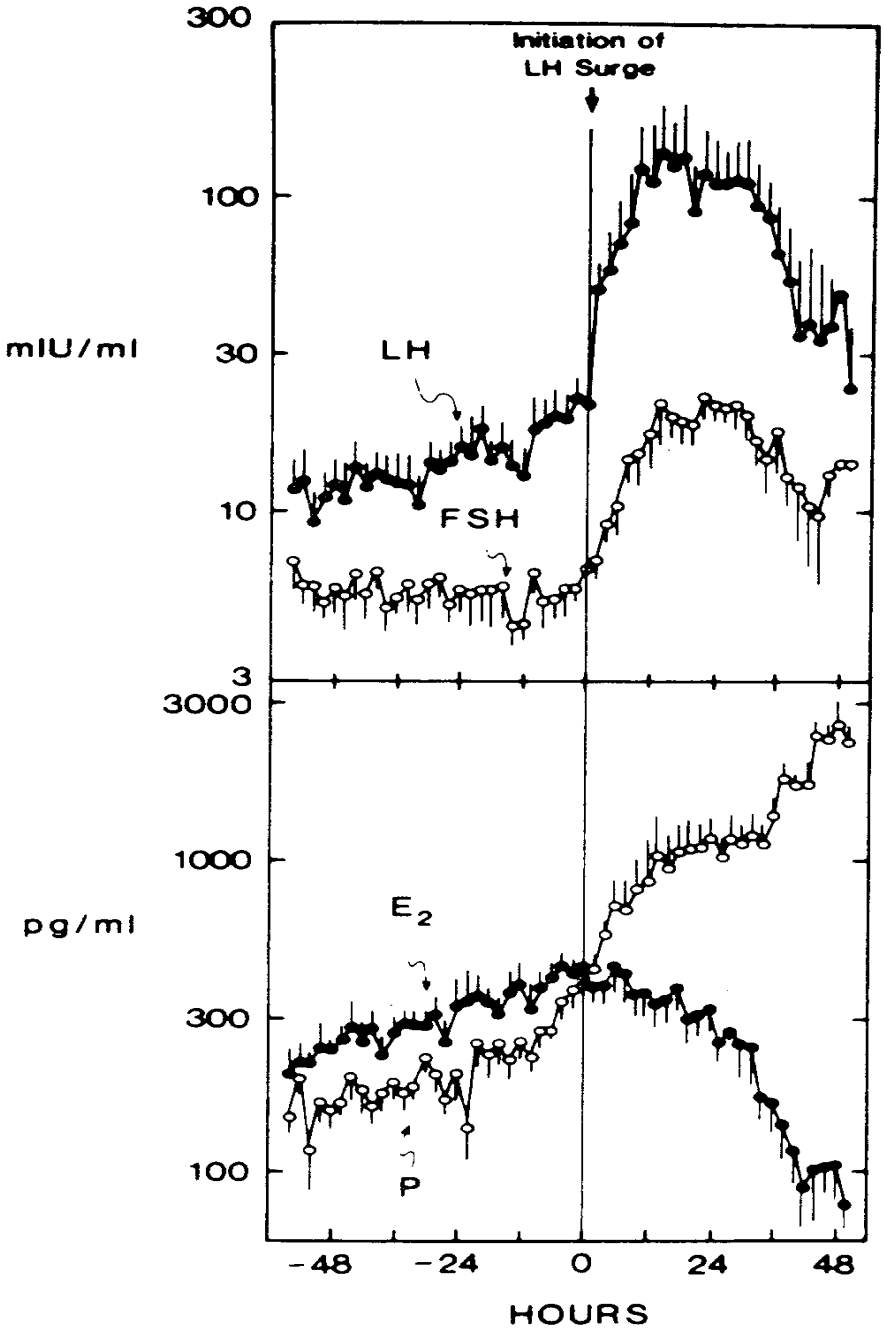
Normal LH surge



Hoff et al, 1983

The induction of LH surge and oocyte maturation by GnRH analog in women undergoing ovarian stimulation for IVF

Itskovitz et al, Gynecol Endocrinol 2(s): 165, 1988 *

"… GnRHa induces LH surge, oocyte maturation and fertilizable eggs. The early luteolysis that follows the injection of GnRH allows the control of progesterone and estrogen blood levels during the luteal phase by exogenously administered steroids. Furthermore, GnRHa offer a new means by which OHSS can be prevented..."

* International Symposium on GnRH Analogues in Cancer and Human Reproduction, Geneva, February 1988

Induction of LH surge by GnRH Analogs

Itskovitz et al	Gynecol Endocrinol	2(S2):165	1988
Lanzon et al	Gynecol Endocrinol	3:213	1989
Gonen et al	JCEM	71:918	1990
Emperaire et al	Hum Reprod	6:506	1991
Itskovitz et al	Fertil Steril	56:213	1991
Imoedemhe et al	Fertil Steril	55:328	1991
Segal et al	Fertil Steril	57:1254	1992
Van der Meer et al	Hum Reprod	8:1628	1993
Lanzon et al	Fertil Steril	62:35	1994
Shalev et al	Hum Reprod	9:417	1994

Induction of LH surge by GnRH Analogs Cont.

Scott et al	Fertil Steril	61:872	1994
Lewit et al	Gynec Endoc	9(S4):13	1995
Gerris et al	Hum Reprod	10:56	1995
Lewit et al	Hum Reprod	11:1399	1996
Olivennes et al	Fertil Steril	66:151	1996
Buckett et al	Hum Reprod	13:811	1998
Itskovitz et al	Hum Reprod	15:1965	2000
Fauser et al	JCEM	87:709	2002
Beckers et al	JCEM	88:4186	2003
Nevo et al	Fertil Steril	79:1123	2003

Induction of preovulatory luteinzing hormone surge and prevention of ovarian hyperstimulation syndrome by GnRH agonist

Itskovitz et al, Fertil Steril 56:213, 1991

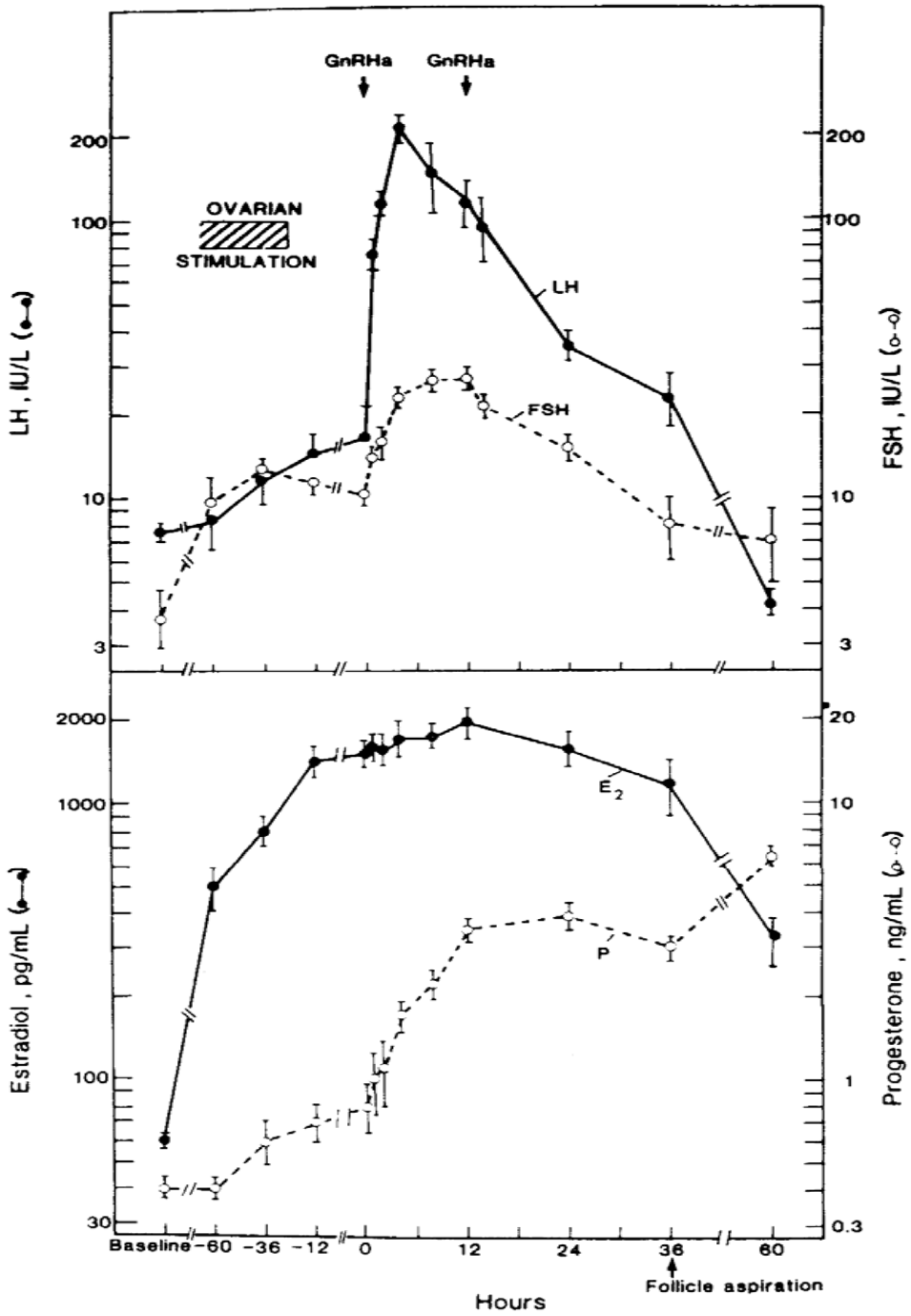
Induction of LH surge

	Estradiol (pg/ml)	Dosage of buserelin acetate (µg)	No. of MII oocytes mean ±SD
Group A (n=6)	1494 ±422	500x2	8.2 ±3.4
Group B (n=8)	7673 ±3028	250x2, 500x1,250x1	20.2 ±5.4

Mean ±SD

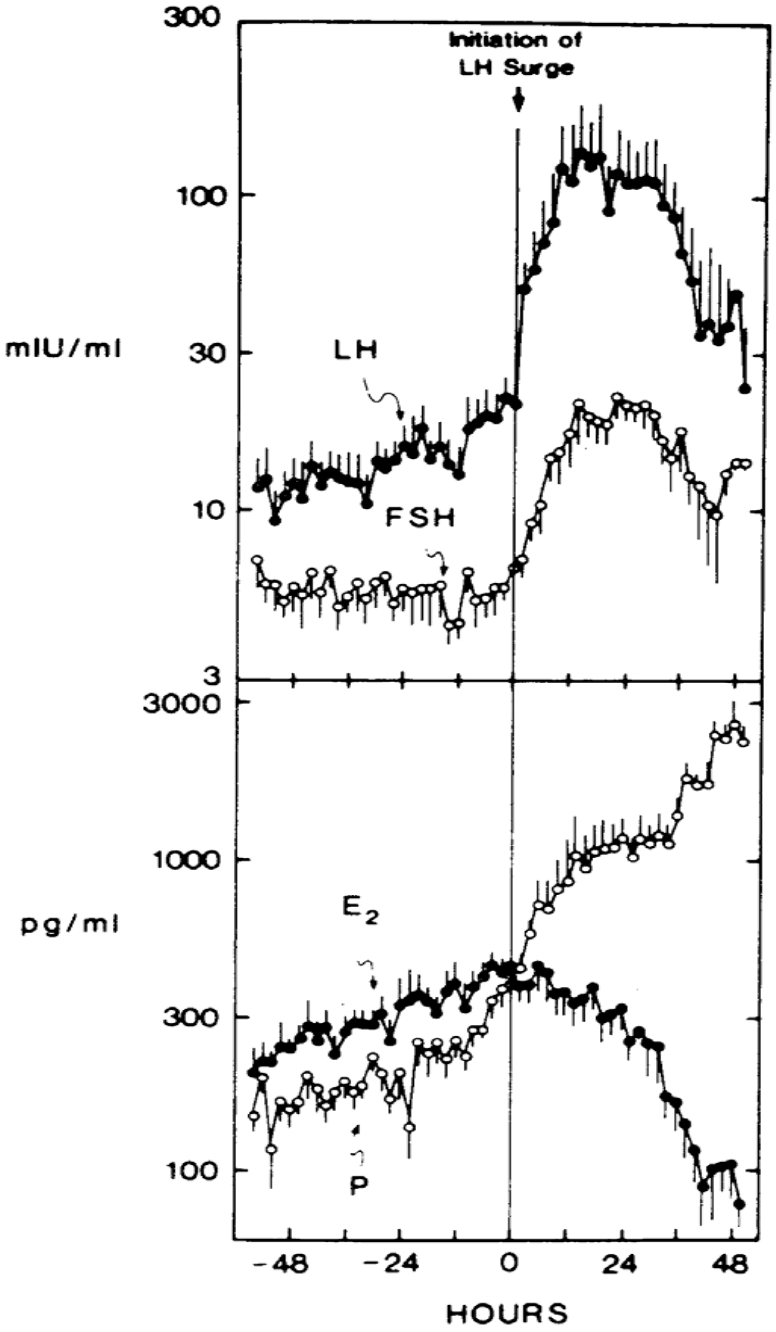
Itskovitz et al, 1991

Normal responders



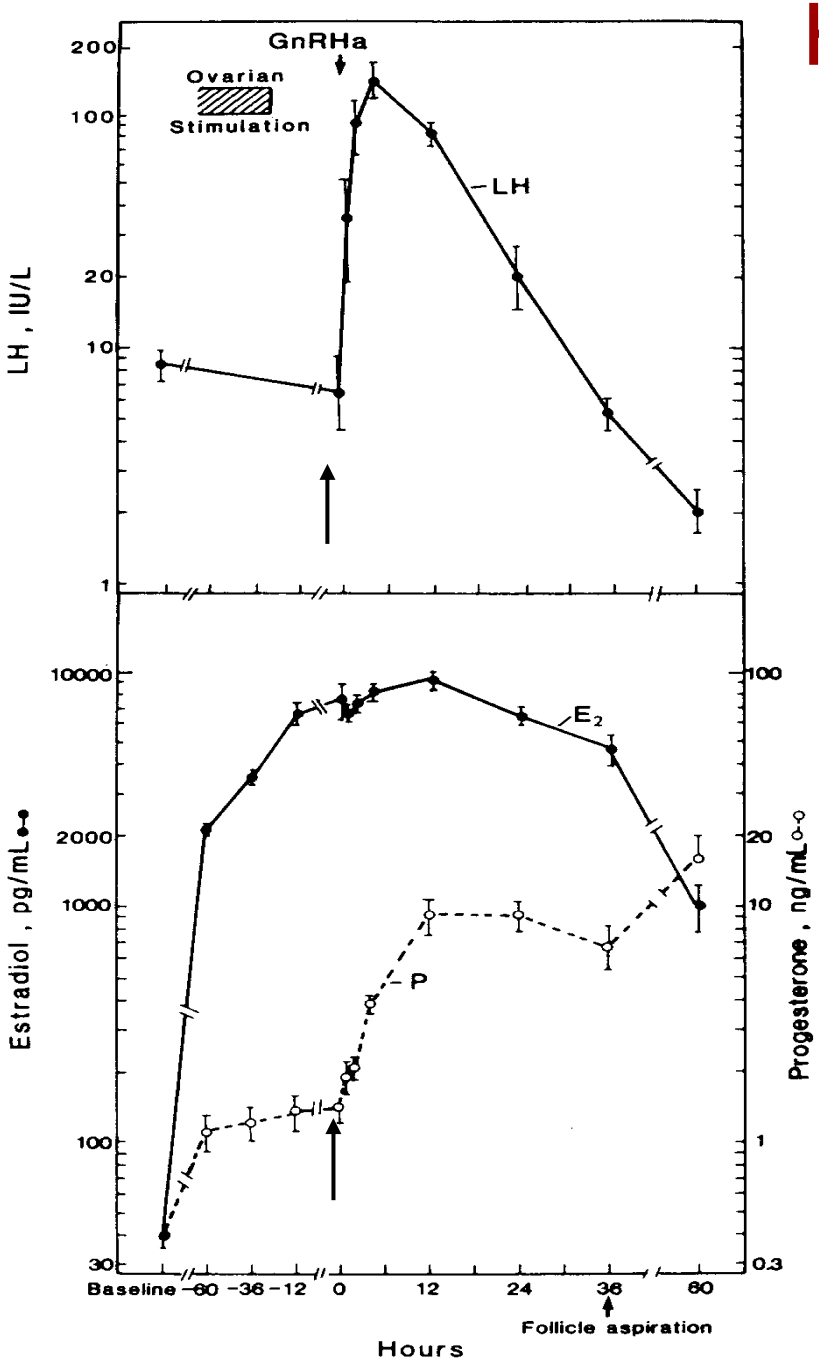
Itskovitz et al, 1991

Normal LH surge



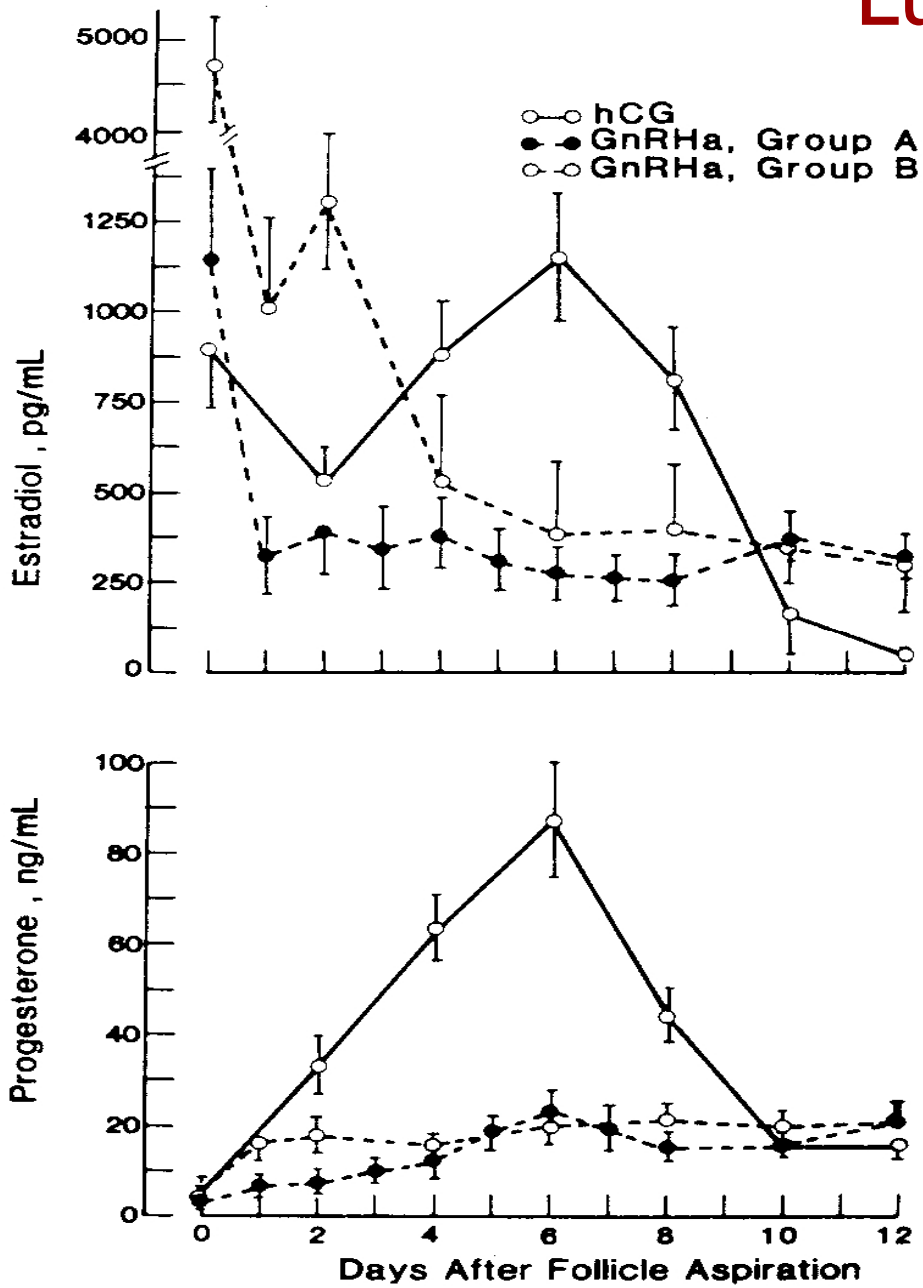
Hoff et al, 1983

High responders



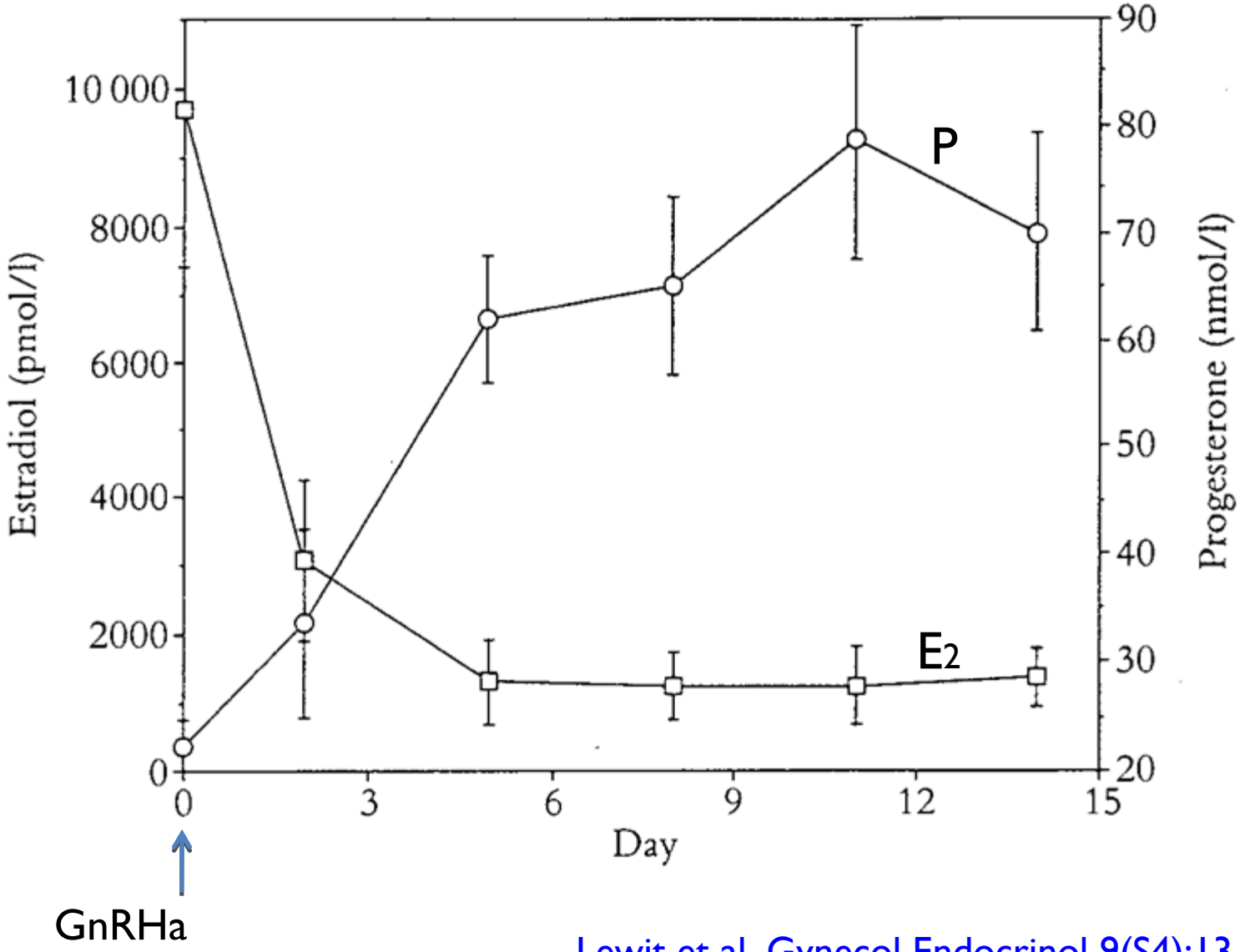
Itskovitz et al, 1991

Luteal phase



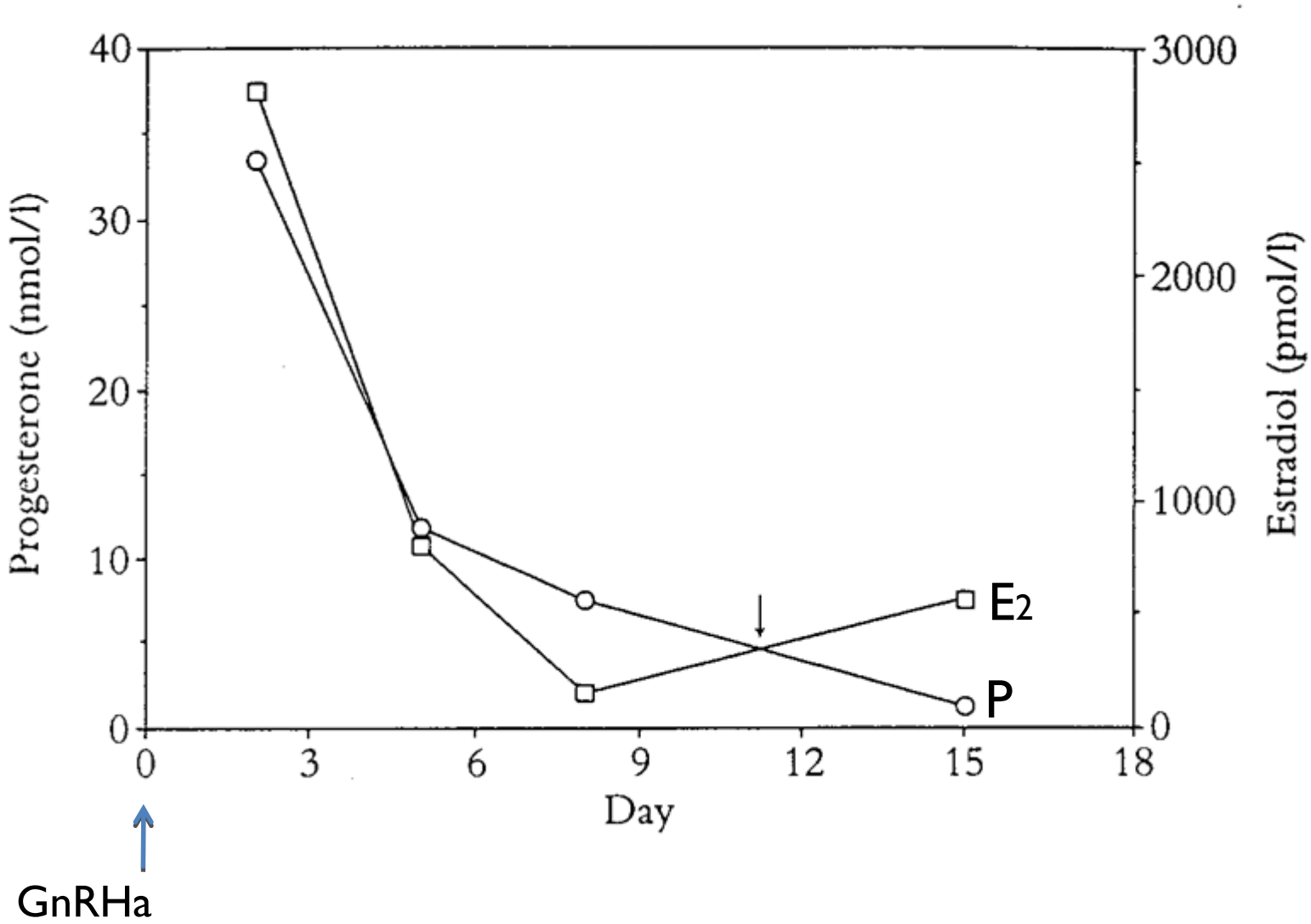
Itskovitz et al, 1991

Luteal phase – with support (44 women, 73 cycles)



Lewit et al, Gynecol Endocrinol 9(S4):13-17, 1995

Luteal phase – no support



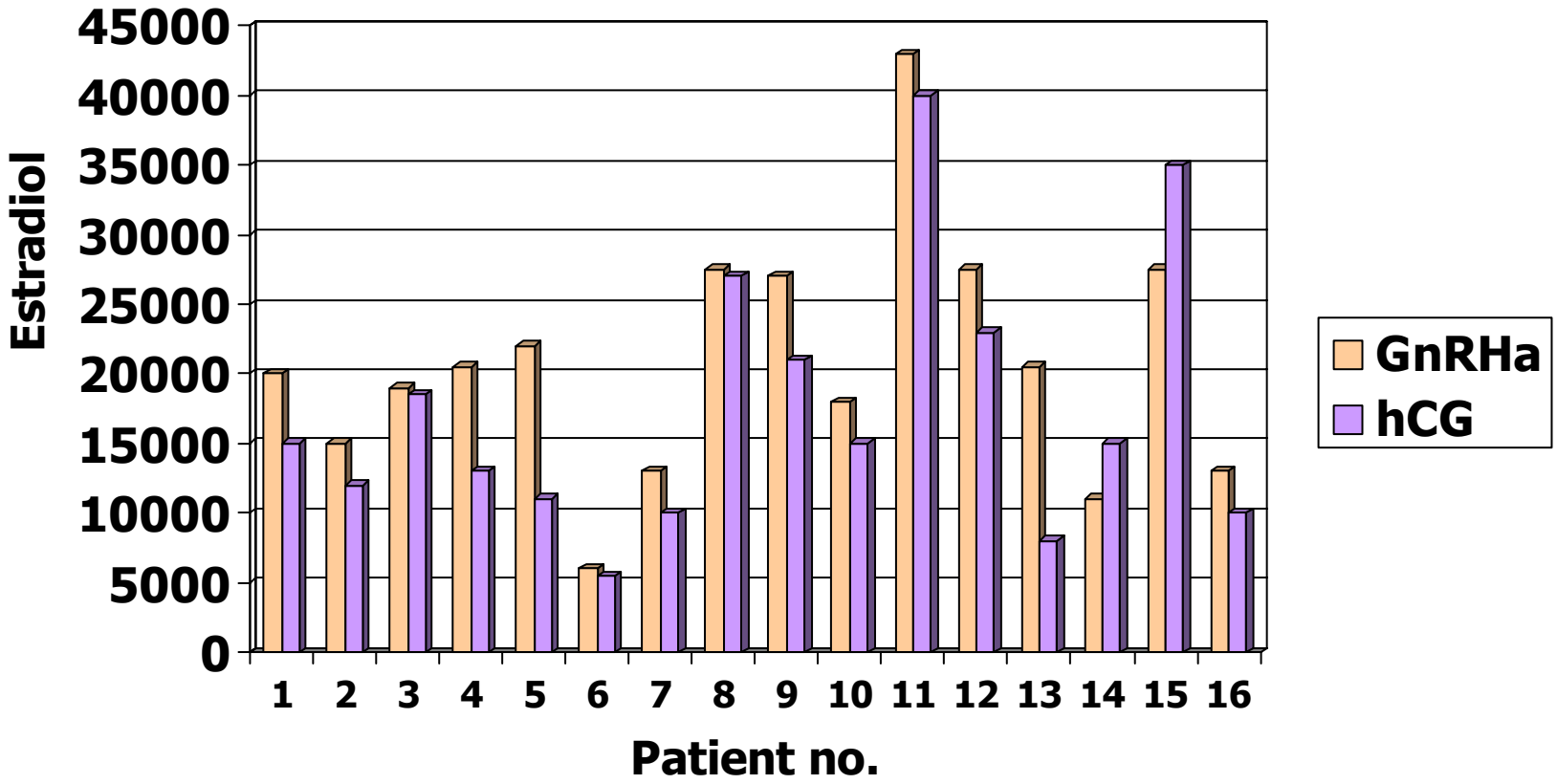
Lewit et al, Gynecol Endocrinol 9(S4):13-17, 1995

Comparison of GnRH analogues and hCG for the induction of ovulation and prevention of OHSS: **a case-self control study**

Lewit et al, Hum Reprod 11:1399, 1996

Study group: 16 IVF patients who had severe OHSS in previous cycles in which hCG was administered to trigger ovulation, were studied in subsequent cycles in which GnRH-agonist was used.

Serum E2 levels (pmol/l) on day of ovulation induction with hCG or GnRHa



Comparison of stimulation variables (x±SD)

Group	E2 on day of ovulation induction (pmol/l)	No. of oocytes	MII oocytes	No. of hMG ampules used	Severe OHSS
hCG	16969 ±8948	28 ±11	83%	24 ±6	16/16
GnRHa	20816 ±9568*	36 ±14	80%	21 ±4	0/16*

* P<0.01

Lewit, 1996

CAUTION: When used to prevent spontaneous LH surge ("long protocols"), GnRHa will fail to trigger ovulation.

Use of a single bolus of GnRH agonist triptorelin to trigger ovulation after GnRH antagonist ganirelix treatment in women undergoing ovarian stimulation for assisted reproduction with special reference to the prevention of OHSS: preliminary report

Itskovitz-Eldor et al, Hum Reprod 15:1965, 2000

Materials and methods

- 8 Women considered at risk of developing OHSS: >20 follicles >11mm and/or E2 levels>3000ng/ml on the last day of stimulation.
- Induction of LH surge with a single injection of triptorelin 0.2mg SC ~30hr after the last injection of ganirelix.
- Ovarian stimulation with rFSH (150IU or 225 IU daily) and ganirelix 0.25mg daily from day 6.

Results

- Mean no. of follicles>11mm=25.1±4.5
- Median E2 (pg/ml)=3675 (range 2980–7670)
- Mean number of occytes=23.4 (±15.4), 83% MII
- Mean number of embryos=15.4±6.6
- 7 ETs from fresh embryos: 1 pregnancy
- 17 ETs from frozen-thawed embryos: 4 pregnancies

Median values of serum LH and E2 after injection of triptorelin 0.2mg

Time after injection (n=8)	*Serum LH (IU/l)*	*Serum estradiol (pg/ml)*
Pre-dose	2.4	4775
0.5 h	12.7	4630
1 h	14.3	4505
2 h	73.7	5080
4 h	219	5540
10-12 h	71.0	6000
Day of OPU	7.9	2375
Day of ET	0.8	963
First week post-ET	1.0	145

Itskovitz et al, 2000

Summary

- The ability of a single bolus of triptorelin 0.2mg to trigger an adequate LH surge in stimulation cycles using a GnRH antagonist protocol was demonstrated.

- The results suggest that this regimen may prove highly effective in terms of OHSS prevention, though further studies are needed to establish this potential advantage

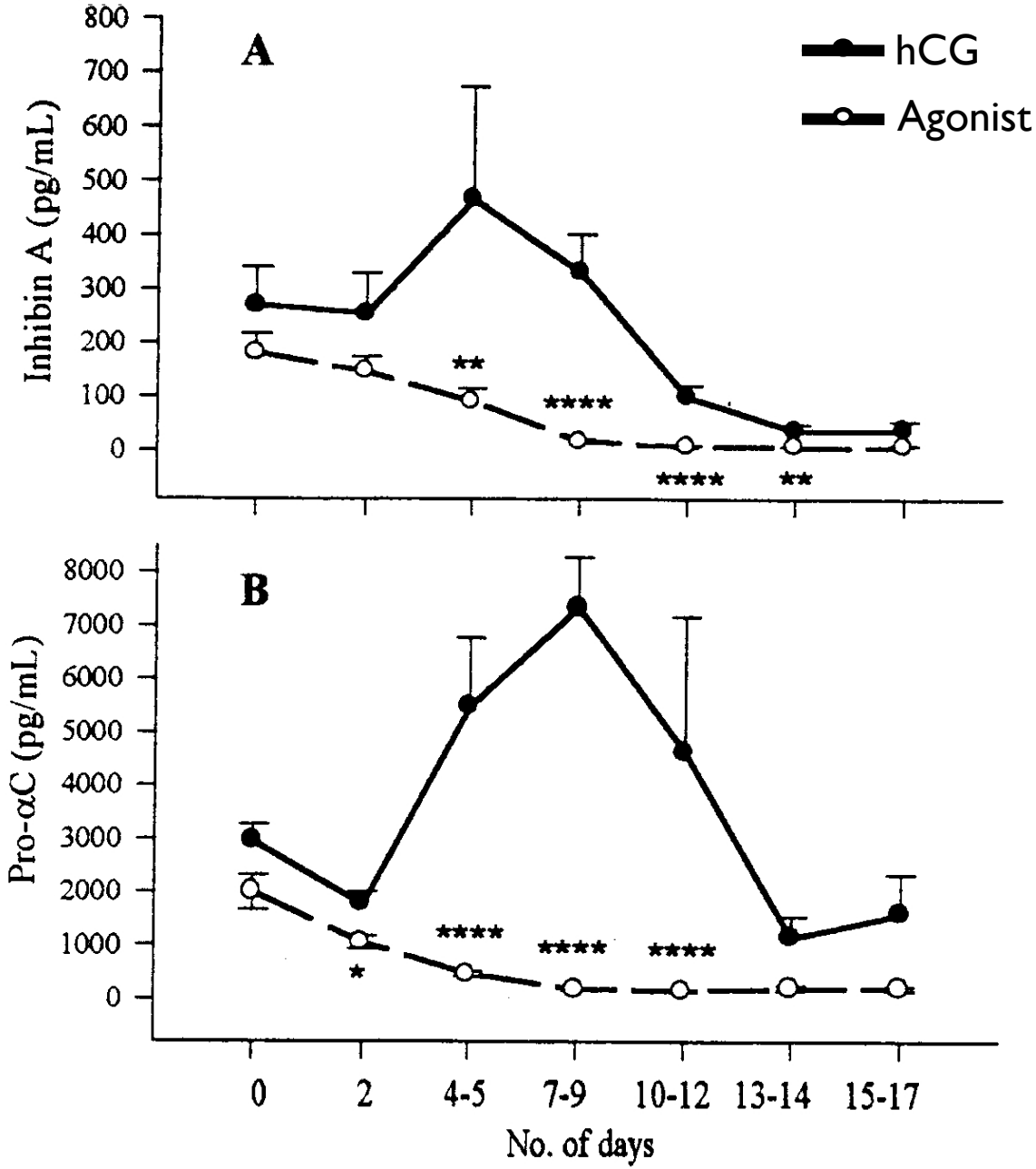
Lower levels of inhibin A and pro-alpha C during the luteal phase after triggering oocyte maturation with GnRH agonist versus hCG

	Agonist (n = 8)	hCG[a] (n = 8)
Age (years)	28.7 ± 5.4	30.6 ± 4.4
Duration of infertility (years)	4.3 ± 1.9	5.9 ± 4.2
No. of patients with primary infertility	7	6
Cause of infertility (no.):		
Male factor	6	6
Unexplained	1	2
Mechanical	1	
Treatment cycle no.	1.62 ± 0.9	1.75 ± 0.8
Duration of FSH treatment (days)	9 ± 1.2	9.5 ± 1.6
No. of follicles ≥11 mm at day 0	11.75 ± 3.3	15 ± 4.8
No. of oocytes retrieved	9.25 ± 3.8	11 ± 5.5
No. of clinical pregnancies	4	4

[a] P = NS for all characteristics.

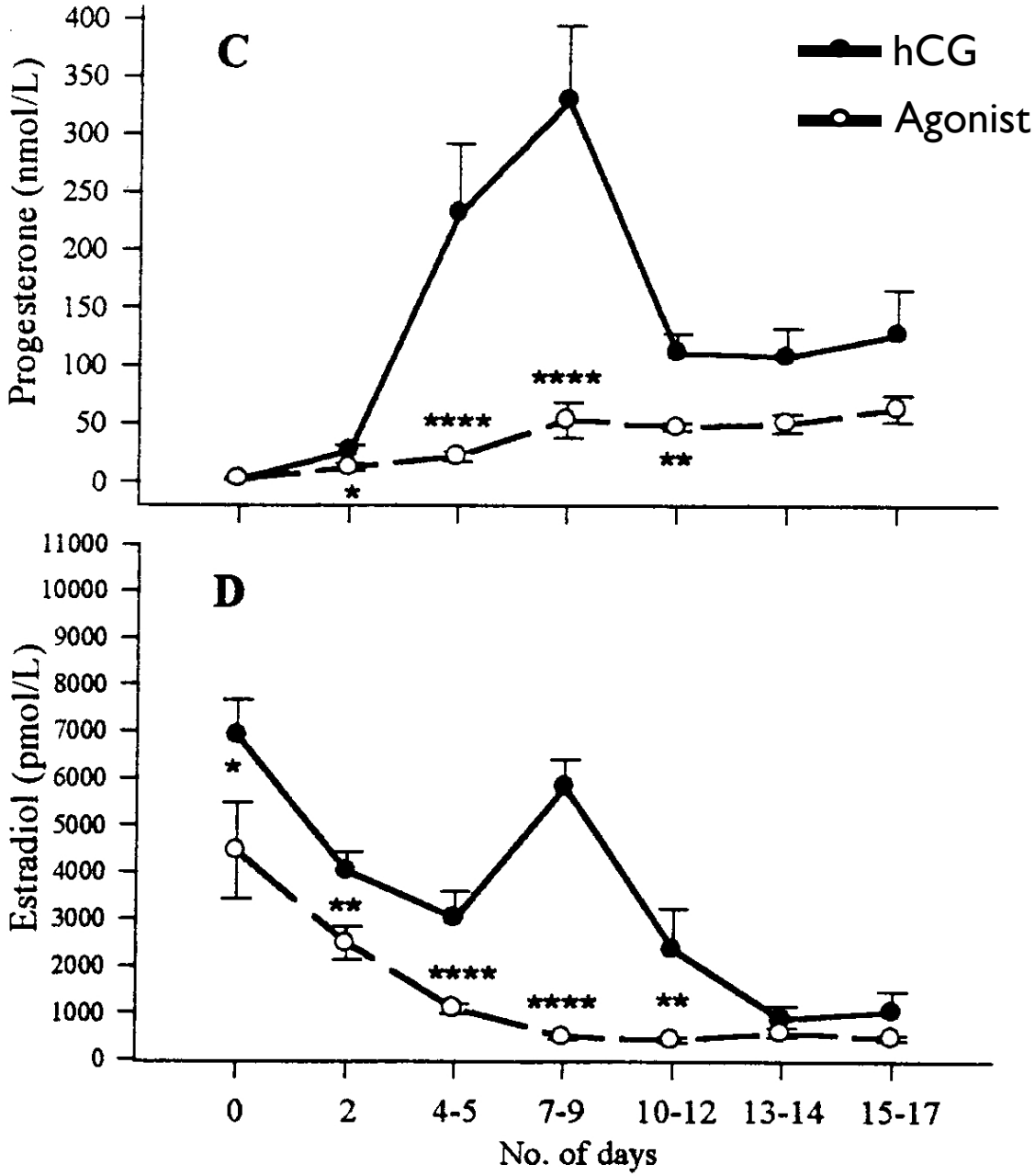
Nevo et al, Fertil Steril 79:1123, 2003

Luteal phase



Nevo et al, 2003

Luteal phase



Nevo et al, 2003

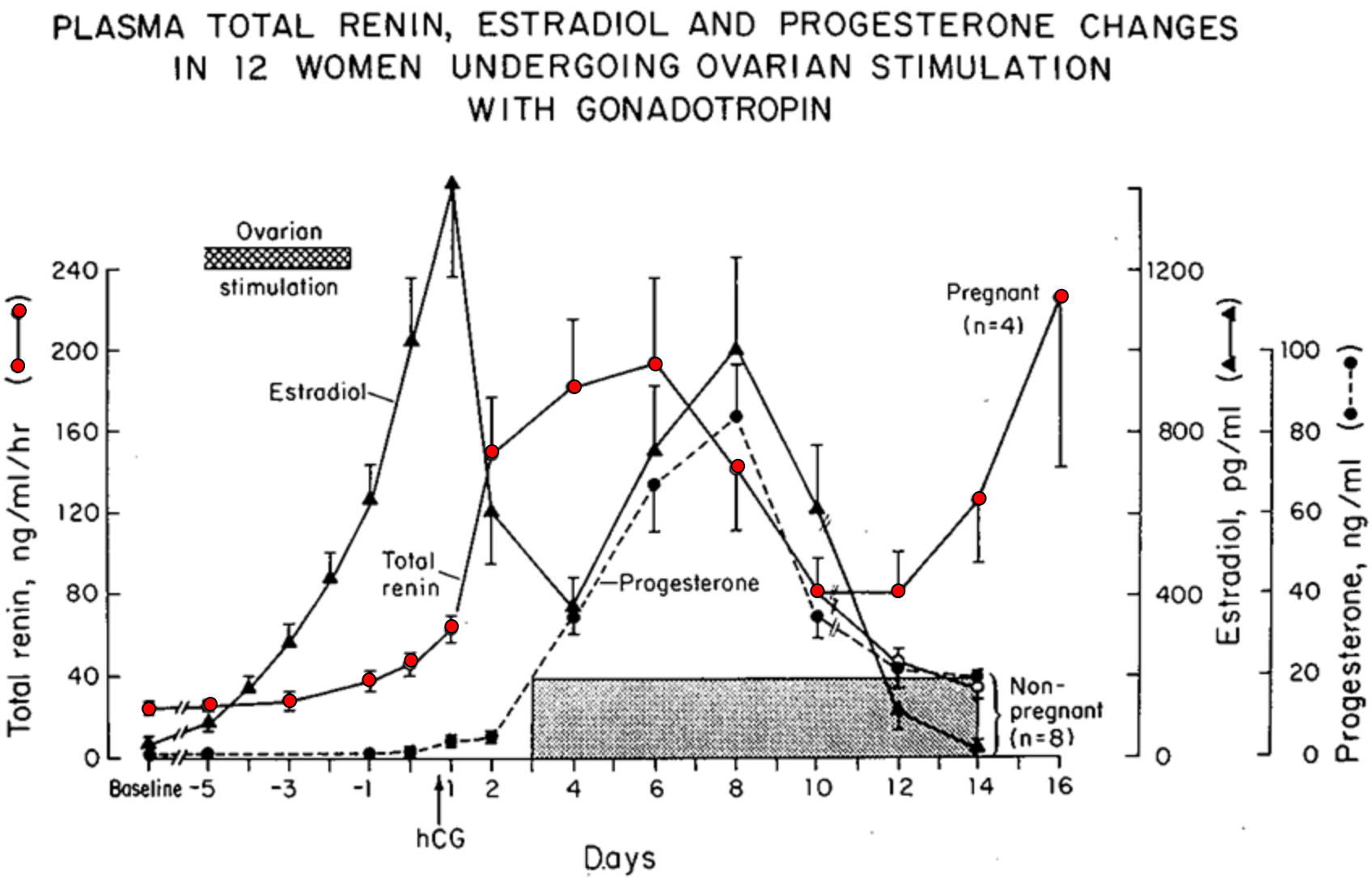
Summary

- The GnRH antagonist-based protocol for ovulation induction and IVF enables the use of GnRH-a in the final stage of oocyte maturation

- The lower levels of steroidal and nonsteroidal hormones, which are secreted by corpora lutea, mimic to a greater extent the physiological range in patients treated with GnRH agonist and may explain, at least in part, the role GnRH-a plays in the prevention of OHSS

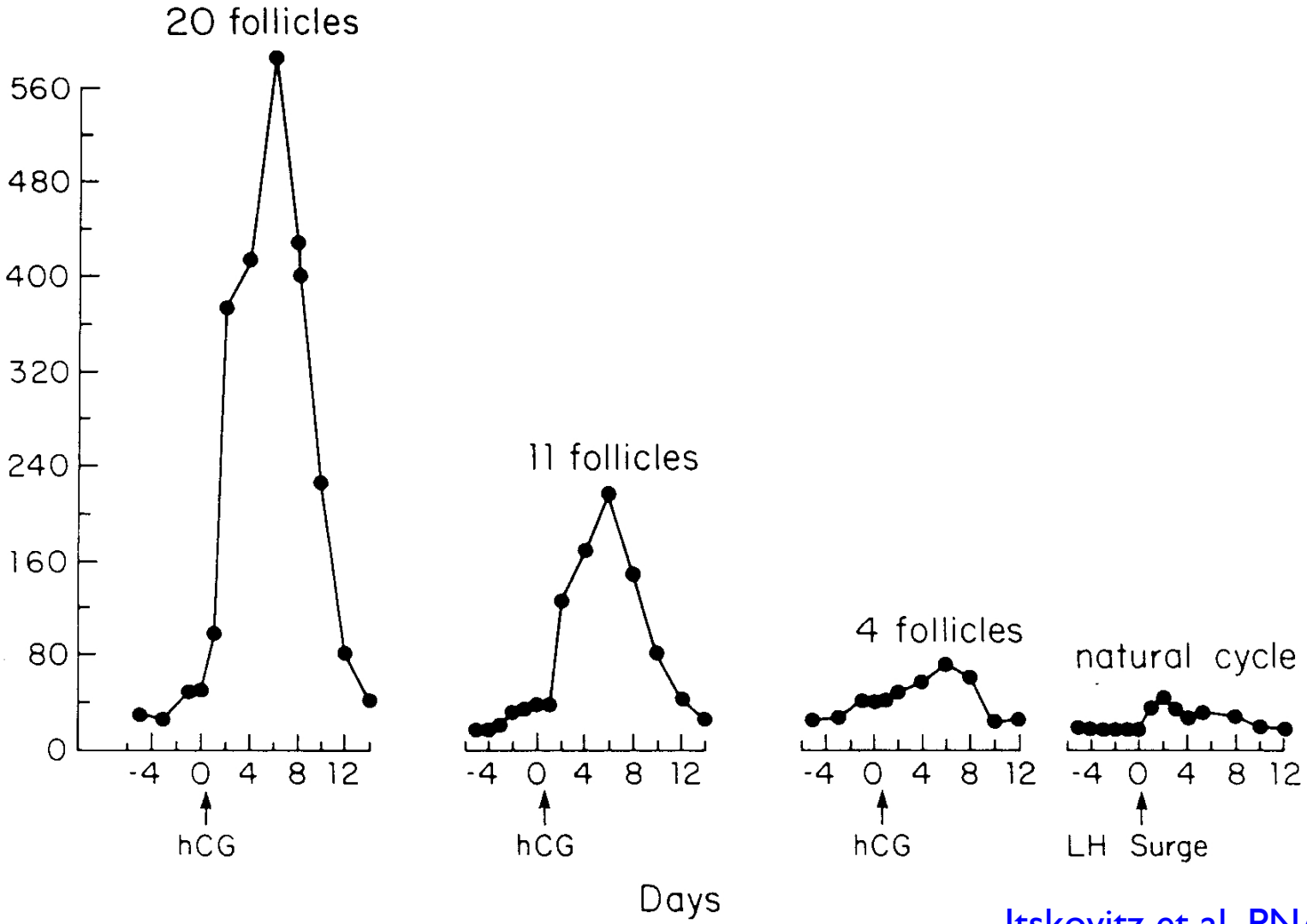
Nevo et al, 2003

Ovarian Renin-Angiotensin System



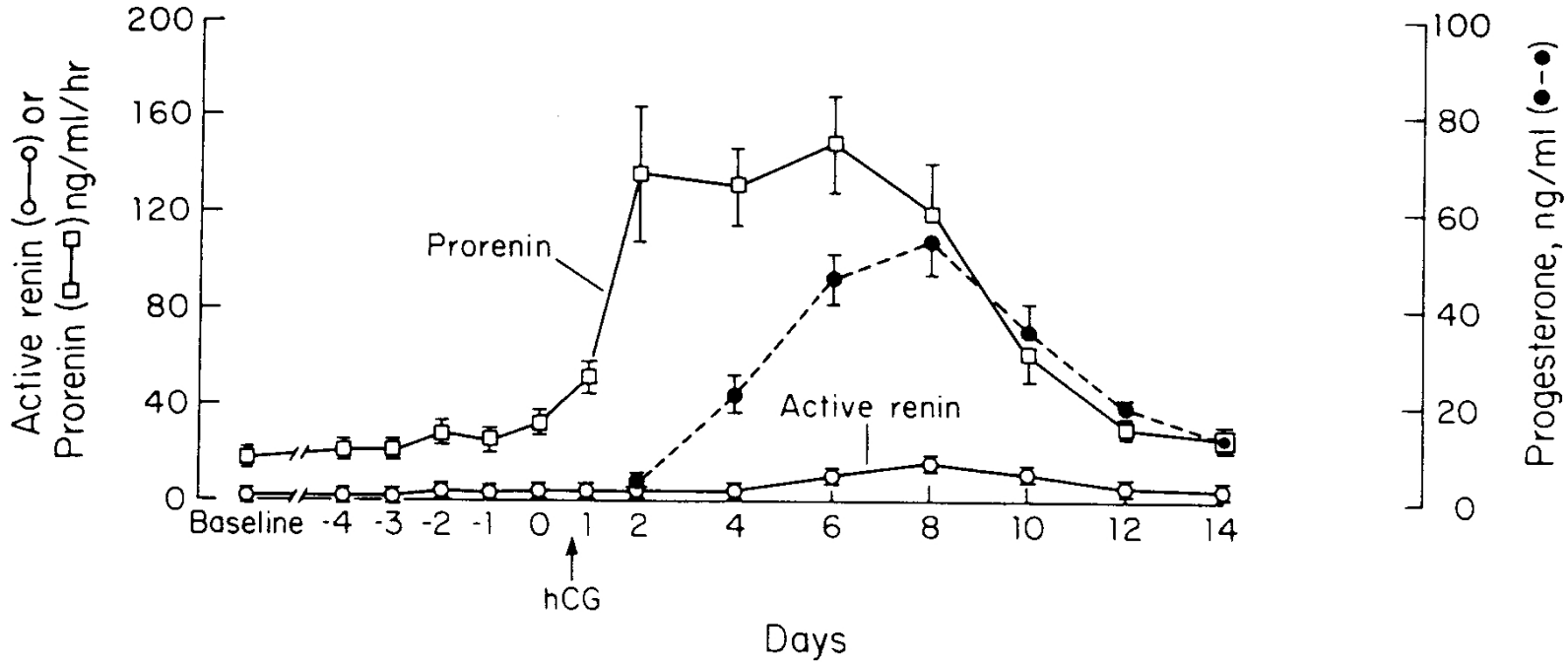
Itskovitz et al, PNAS 1987

Plasma prorenin vs. number of follicles (ng/ml/hr)



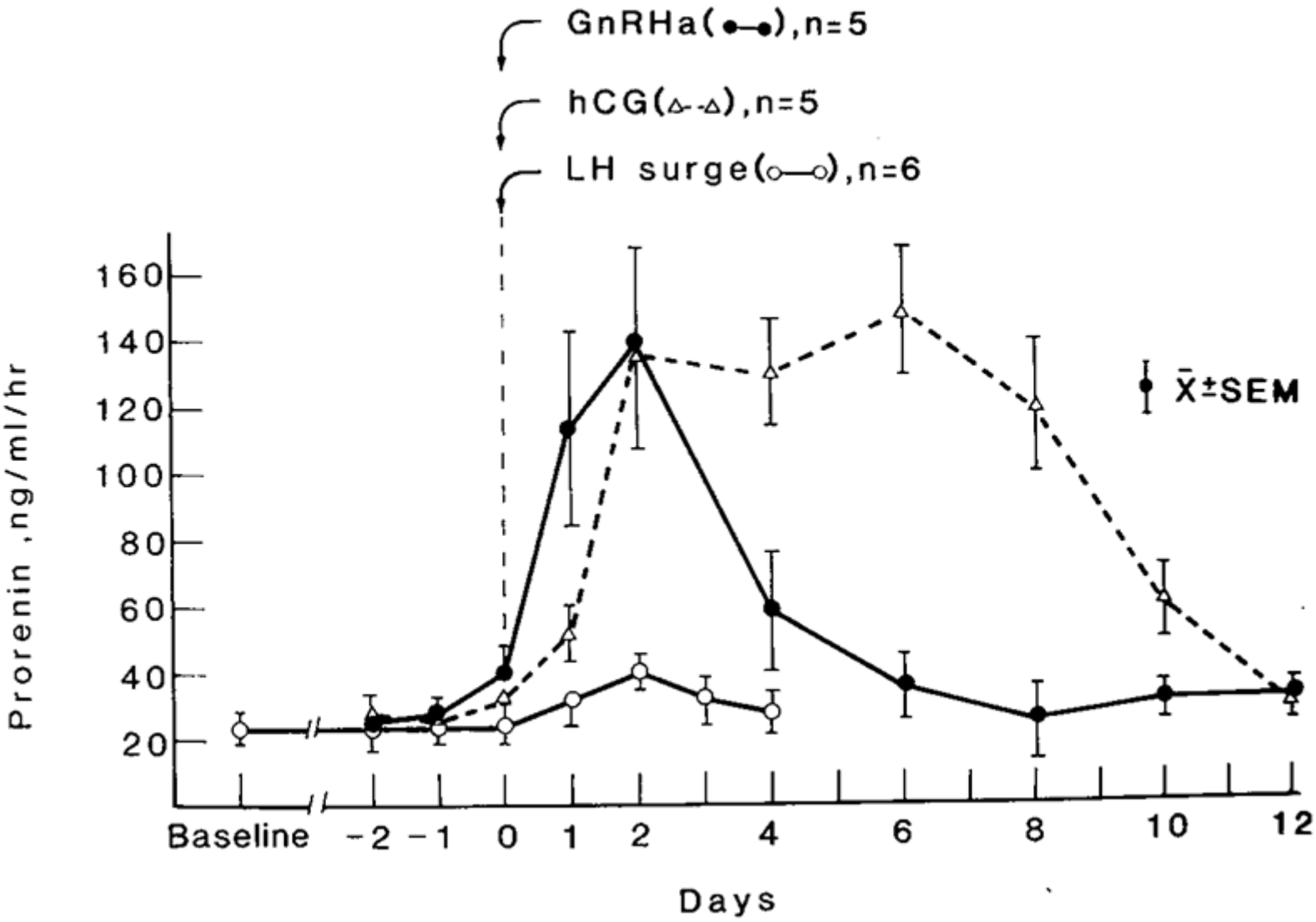
Itskovitz et al, PNAS 1987

Plasma prorenin, active renin and progesterone



Itskovitz et al, PNAS 1987

Plasma prorenin after ovulation induction



Reduced luteal steroidogenesis?

- Direct inhibitory effect on the follicle affecting the normal follicular-luteal shift in steroidogenesis
- Prolonged downregulation of pituitary GnRH receptors and reduced LH support of corpus luteum

Thank you