

# The influence of ovarian manipulation on the endocrinology of PCOS

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# Question

- How has PCOS, a mainly familial condition causing anovulation, “survived”?

# Observation

- Following vaginal examination, many amenorrhoeic women with PCOS started to ovulate and even conceive spontaneously.
- Is this a reflex ovulation following ovarian manipulation?





# Reflex ovulators at intercourse

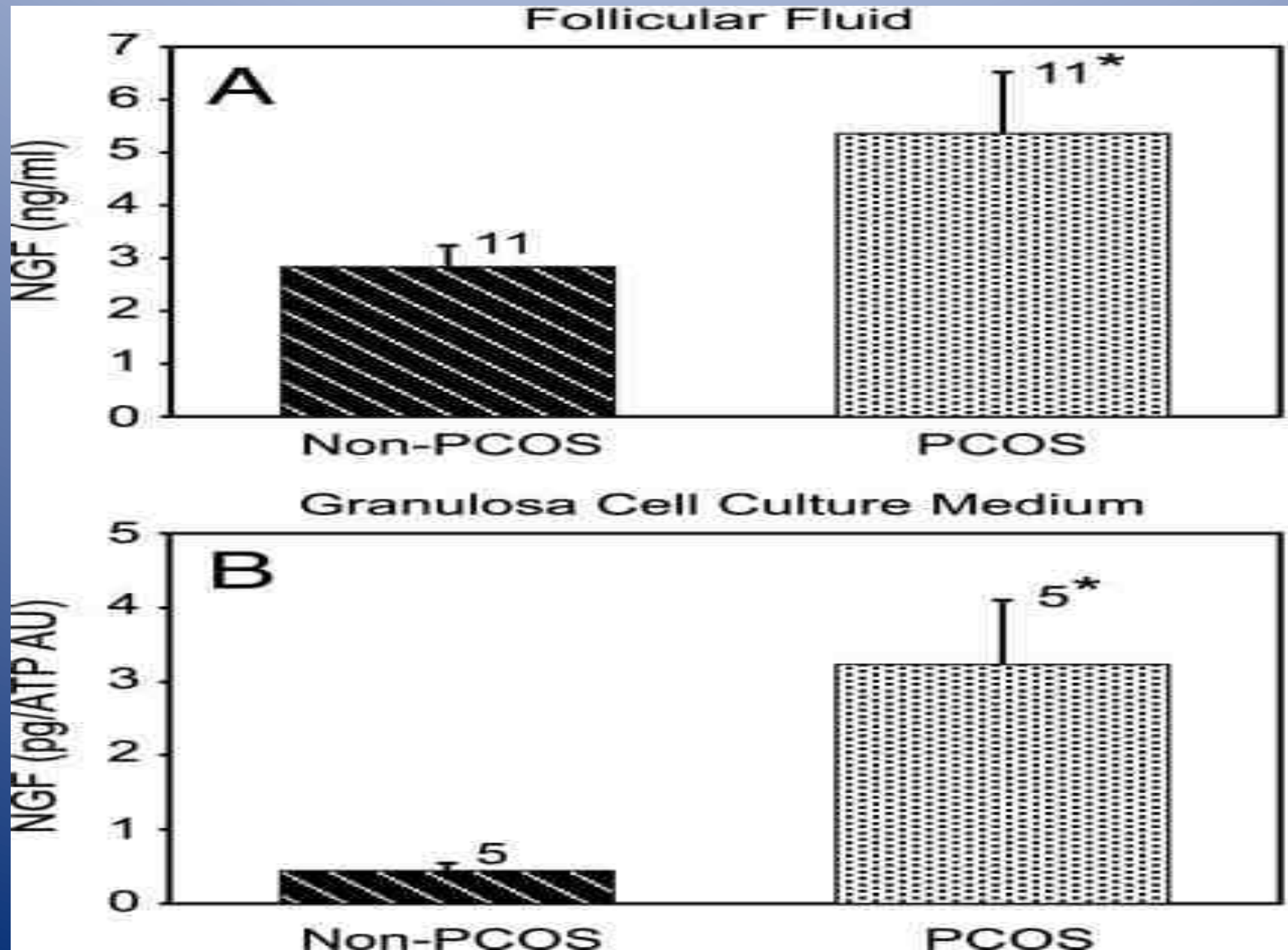
- Voles – massive release of GnRH/ LH  
(Versi et al, 1982; Sutherland et al, 1984)
- Rabbits – Norepinephrine as potent stimulator of GnRH/LH (Ramirez et al, 1986)
- Ferrets – not related to E2 (Bakker et al, 1999)
- Musk shrew – kisspeptin plays a role  
(Inoue et al, 2011)
- Alpacas – due to factor in seminal plasma  
(Ratto et al, 2005)

# Nerve growth factor (NGF)

- NGF is ovulation inducing factor in seminal plasma (Ratto et al, PNAS, 2012) and is a potent stimulator of LH secretion.
- Has a dose-dependent effect on ovulation via systemic, autonomic neurological pathways.
- New pathway for direct influence of the male on hypothalamo-pituitary-gonadal axis of the inseminated female!.....
- ...but man has no influence on woman!

- Ovarian manipulation rather than semen is key.
- In humans intercourse apparently has no influence on the hormonal environment, follicular development or ovulation.
- Human ovary, richly innervated.
- Have PCOS women used this mechanism in order to reproduce?

Dissen et al, Endocrinol;2009



- Sympathetic hyperactivity is a hallmark of overexpression of nerve growth factor in peripheral tissues including the ovary.

(Stener-Victorin et al, Biol Reprod, 2000)

## Sympathetic Nerve activity In PCOS

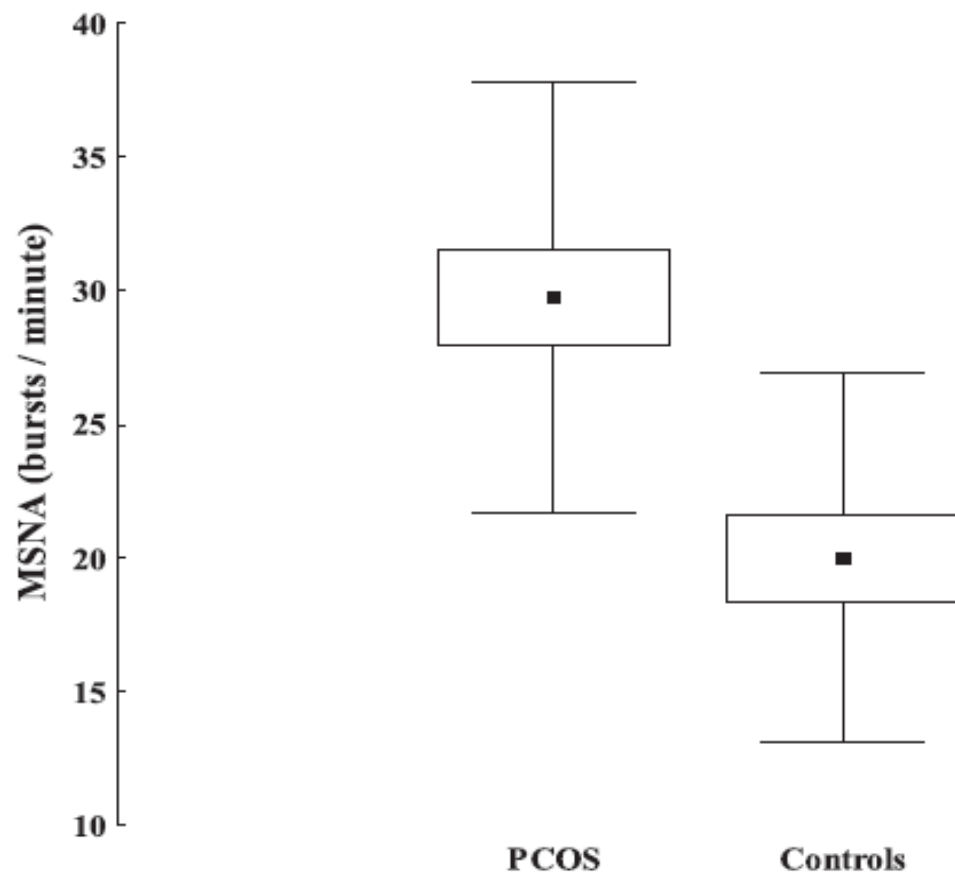
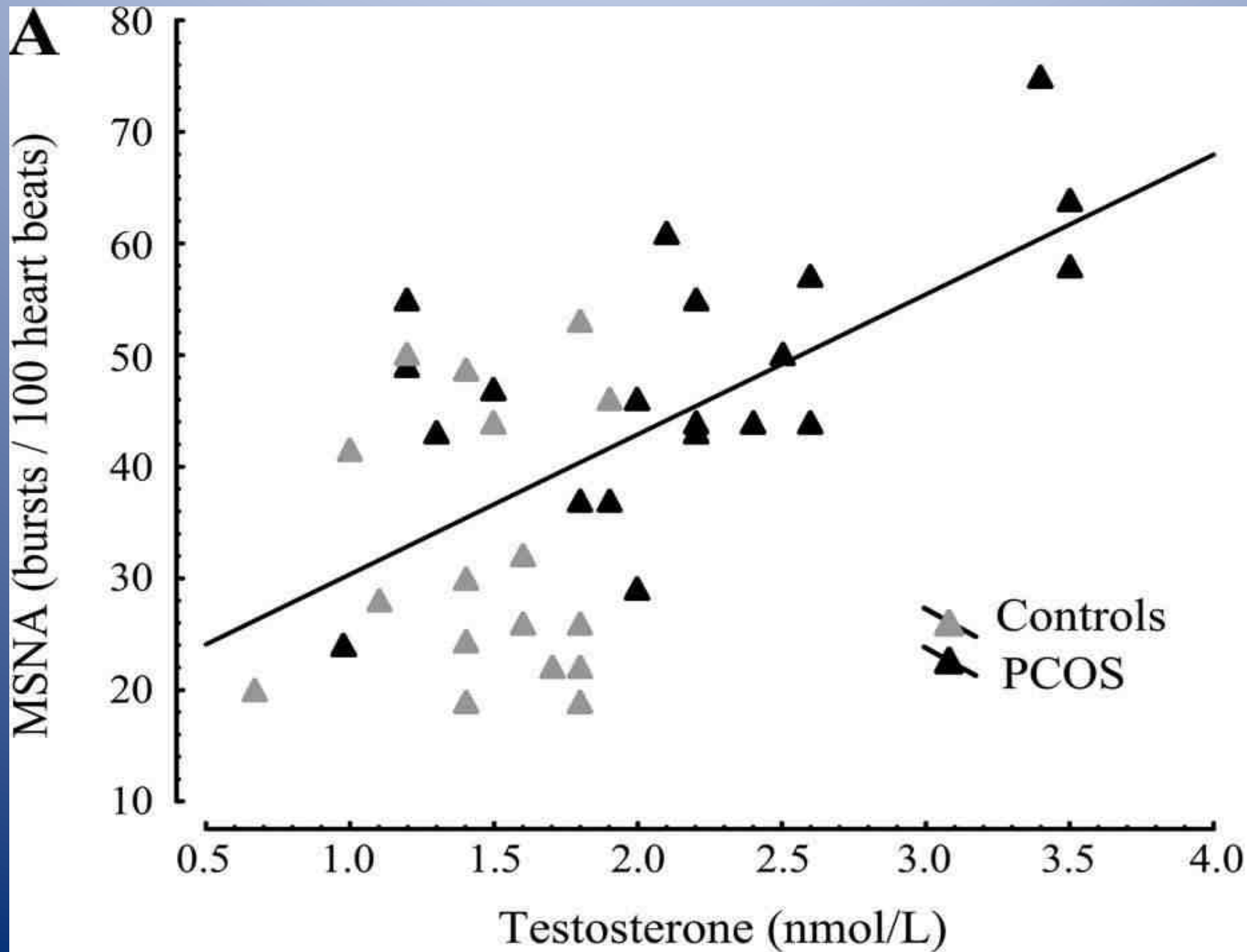
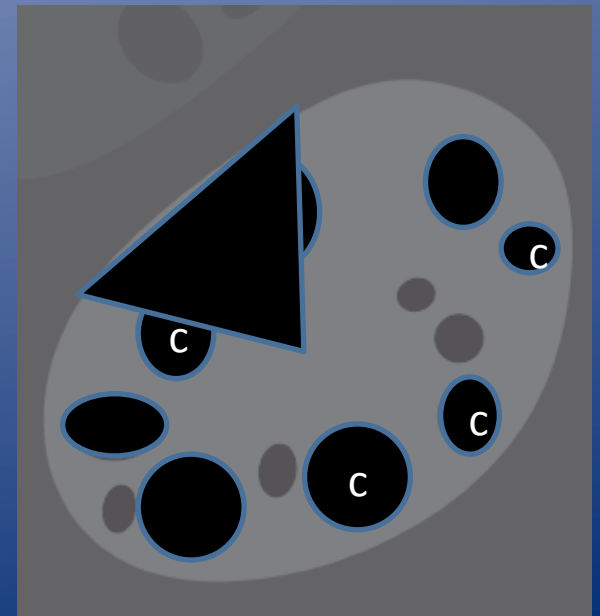


Fig. 1. Muscle sympathetic nerve activity (MSNA) expressed as burst frequency (bursts/min) in women with polycystic ovary syndrome (PCOS) and in healthy matched controls ( $P = 0.0003$ ).



# Operative management

- The first suggested treatment option for PCOS
- Goal: to induce ovulation
- Result: spontaneous regular ovulatory cycles



# Ovarian drilling in PCOS

- Mode of action not fully understood
- Multiple endocrine changes

Hendriks et al. Hum Rep Update 2007

- Which changes are related to ovarian drilling?

# Short-term changes in hormonal profiles after laparoscopic ovarian laser evaporation compared with diagnostic laparoscopy for PCOS

Hum Reprod 29, 2544, 2014

Hendriks ML, König T, Korsen T, Melgers I, Dekker J, Mijatovic V, Schats R, Hompes P, Homburg R, Kaaijk EM, Twisk JW & Lambalk CB.

VU University Medical Center  
Amsterdam, The Netherlands

# Study Aim

- Differentiate between endocrine changes after
  - Ovarian drilling
  - Manipulation reproductive organs / anaesthesia
- First time all known relevant hormones measured in one study
- Optimal controls: PCOS undergoing diagnostic laparoscopy

# Materials & Methods

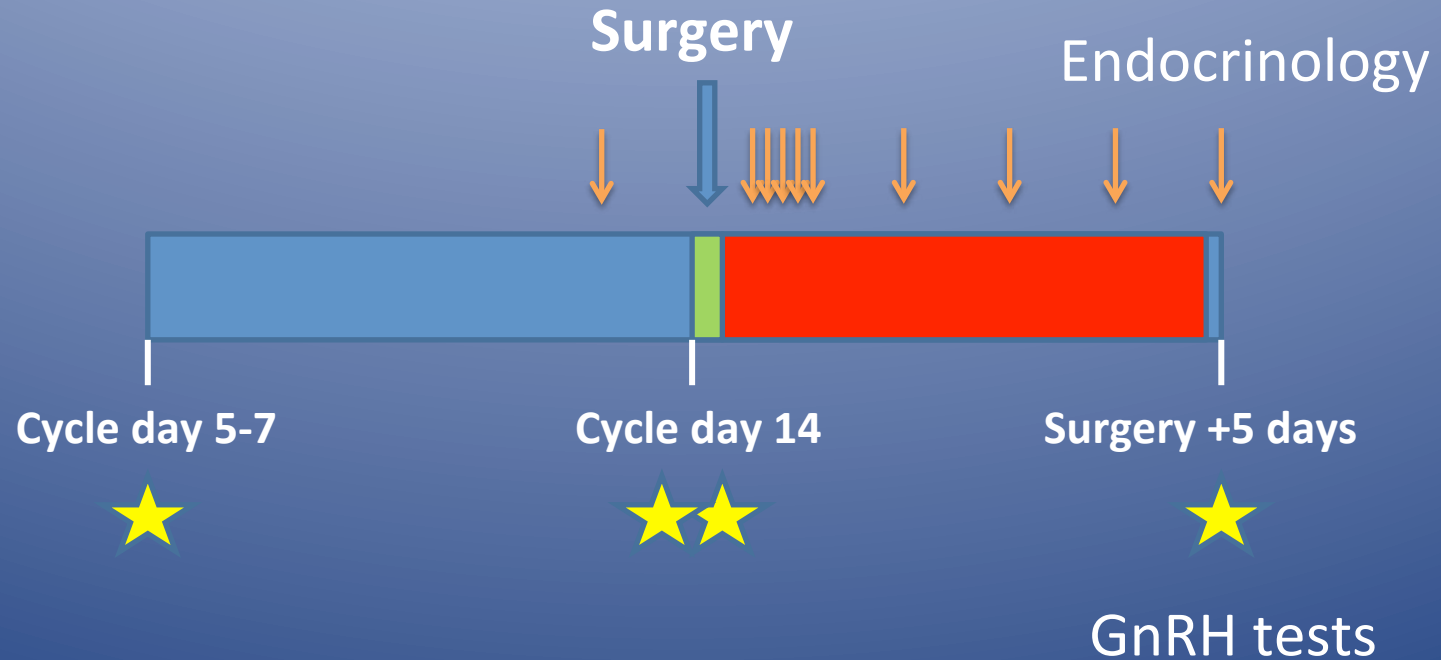
## Inclusion criteria

- PCOS patients with *all* Rotterdam criteria
  - Oligo- or amenorrhea
  - Hyperandrogenism
  - Polycystic ovaries
- LH >6.5 U/L
- Indication for surgery
  - Clomiphene resistance up to 150mg/day
  - After 6 x ovulation induction with FSH

# Materials & Methods

- Choose between
  - Laparoscopic laser evaporation of the ovaries
  - diagnostic laparoscopy
- 21 PCOS patients
  - 12            Laser evaporation
  - 9             Diagnostic laparoscopy controls

# Materials & Methods



# Results

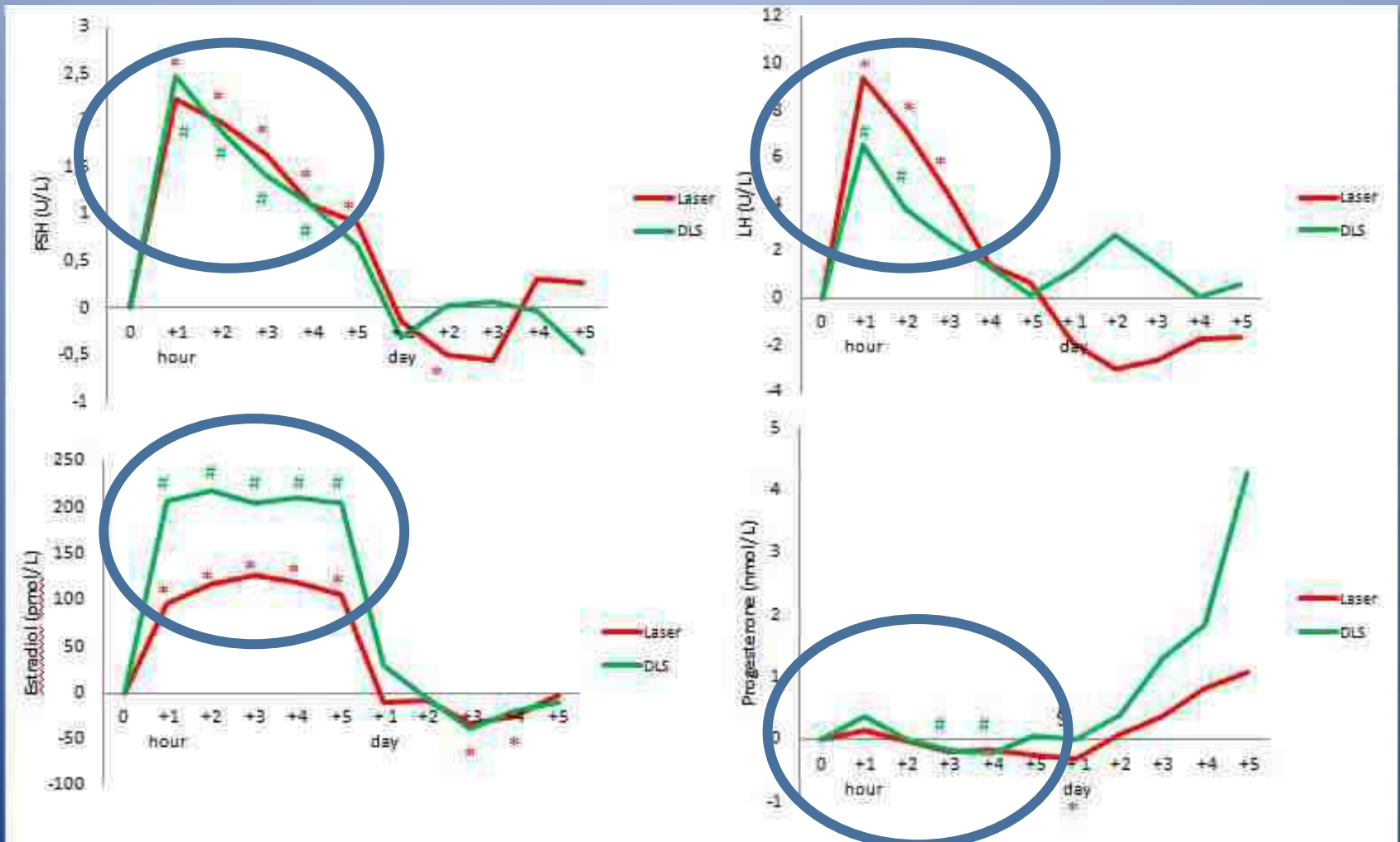
- January 2007 until December 2010
- 21 PCOS patients
  - 12 Laser evaporation
  - 9 Diagnostic laparoscopy controls

# Baseline

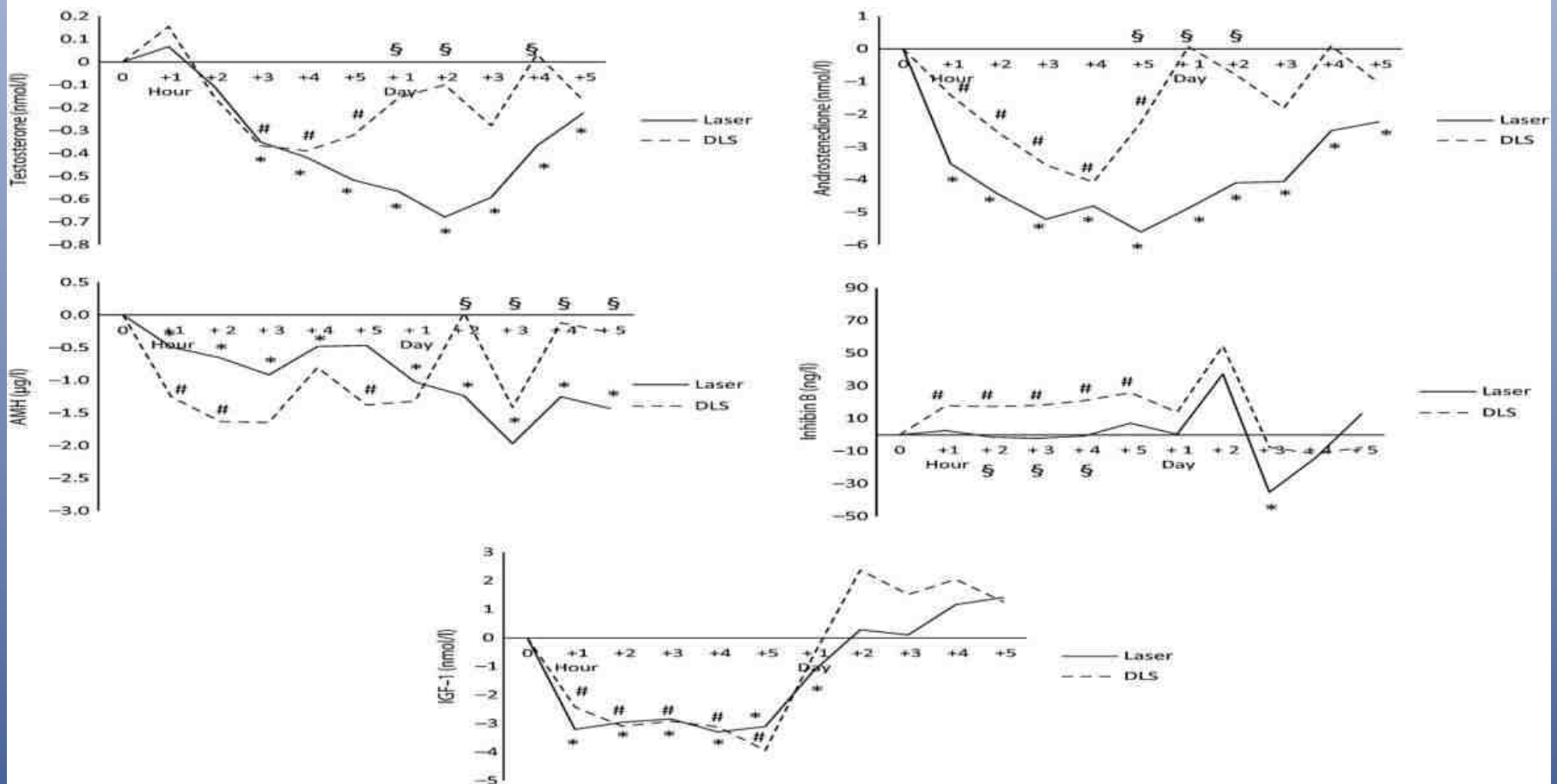
	<b>Laser (n=12)</b>	<b>Laparoscopy (n=9)</b>	<b>P-value</b>
FSH (U/L)	5.4	5.4	0.95
LH (U/L)	10.7	7.36	0.42
Estradiol (pmol/L)	196.5	250.6	0.35
Progesterone (nmol/L)	0.84	0.78	0.74
Testosterone (nmol/L)	2.1	1.9	0.32
FAI (%)	8.0	5.0	0.11
Androstenedione (nmol/L)	11.9	10.4	0.38
AMH (µg/L)	9.2	10.2	0.76
IGF-1 (nmol/L)	21.0	23.6	0.29
Inhibin A (ng/L)	20.0	22.2	0.24
Inhibin B (ng/L)	99.2	104.6	0.68

Independent samples t-test

# Measured hormones before and after surgery, in relation to baseline levels before surgery



M.L. Hendriks et al. Hum. Reprod. 2014;29:2544-2552



Measured hormones before and after surgery,  
in relation to baseline levels before surgery

M.L. Hendriks et al. Hum. Reprod. 2014;29:2544-2552

# Conclusions

- Ovarian laser evaporation resulted in a significant sustained decrease
  - Testosterone
  - Androstenedione
  - AMH
  - (Inhibin B)
- Pituitary sensitivity did not change after laser evaporation
- All other immediate endocrine shifts are surgery related

# Influence of ovarian manipulation on reproductive endocrinology in PCOS and normally cycling women

Hendriks, Konig, Soleman, Korsen, Schats, Hompes, Homburg, Lambalk.

Eur J Endocrinol 2013;169,503

# Ovarian manipulation

- PCOS (n=10)  
and non-PCOS (n=10)
- Manipulation of the ovaries  
in late follicular phase of  
ovulation induction with FSH.
- Blood drawn every 10 mins  
for 3 hours before and after  
manipulation.



Vaginal probe



	PCOS ( $n=10$ ; $\pm$ s.d.)	Controls ( $n=8$ ; $\pm$ s.d.)	<i>P</i> value
Age (years)	30.2 (4.2)	33.6 (5.0)	0.15
BMI (kg/m <sup>2</sup> )	29.2 (5.5)	23.2 (3.1)	0.06
Average cycle length (days)	70 (44)	27 (1)	<b>0.01</b>
Size of largest follicle (mm)	17.4 (1.8)	17.4 (1.4)	0.96
Endometrial thickness (mm)	8.8 (1.6)	8.4 (2.3)	0.66
Cycle day (test day)	19.0 (4.0)	11.1 (1.4)	<b>&lt;0.01</b>
Mean coital frequency/week	1.8 (1.1)	1.5 (0.6)	0.44

## LH levels before and after ovarian manipulation

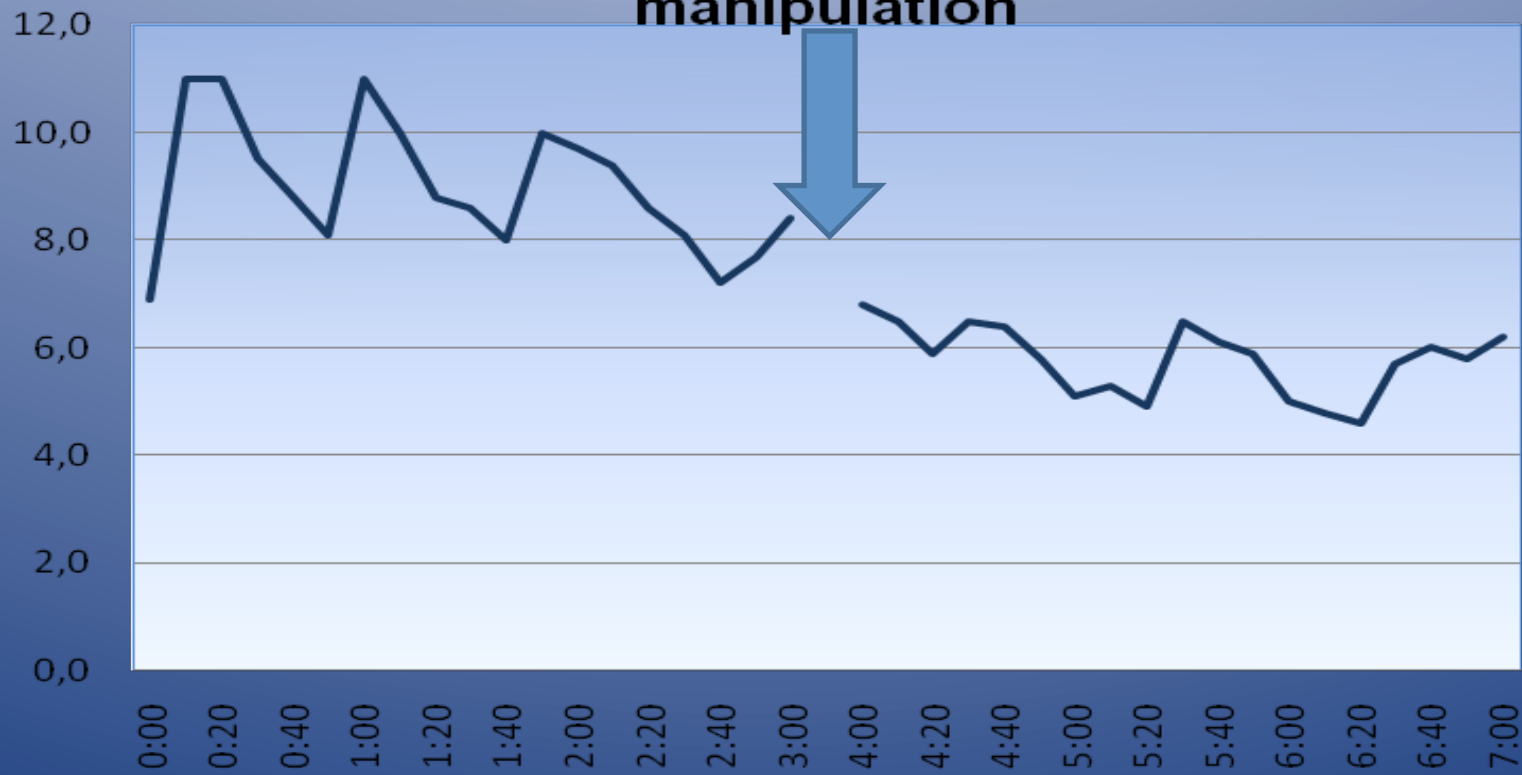
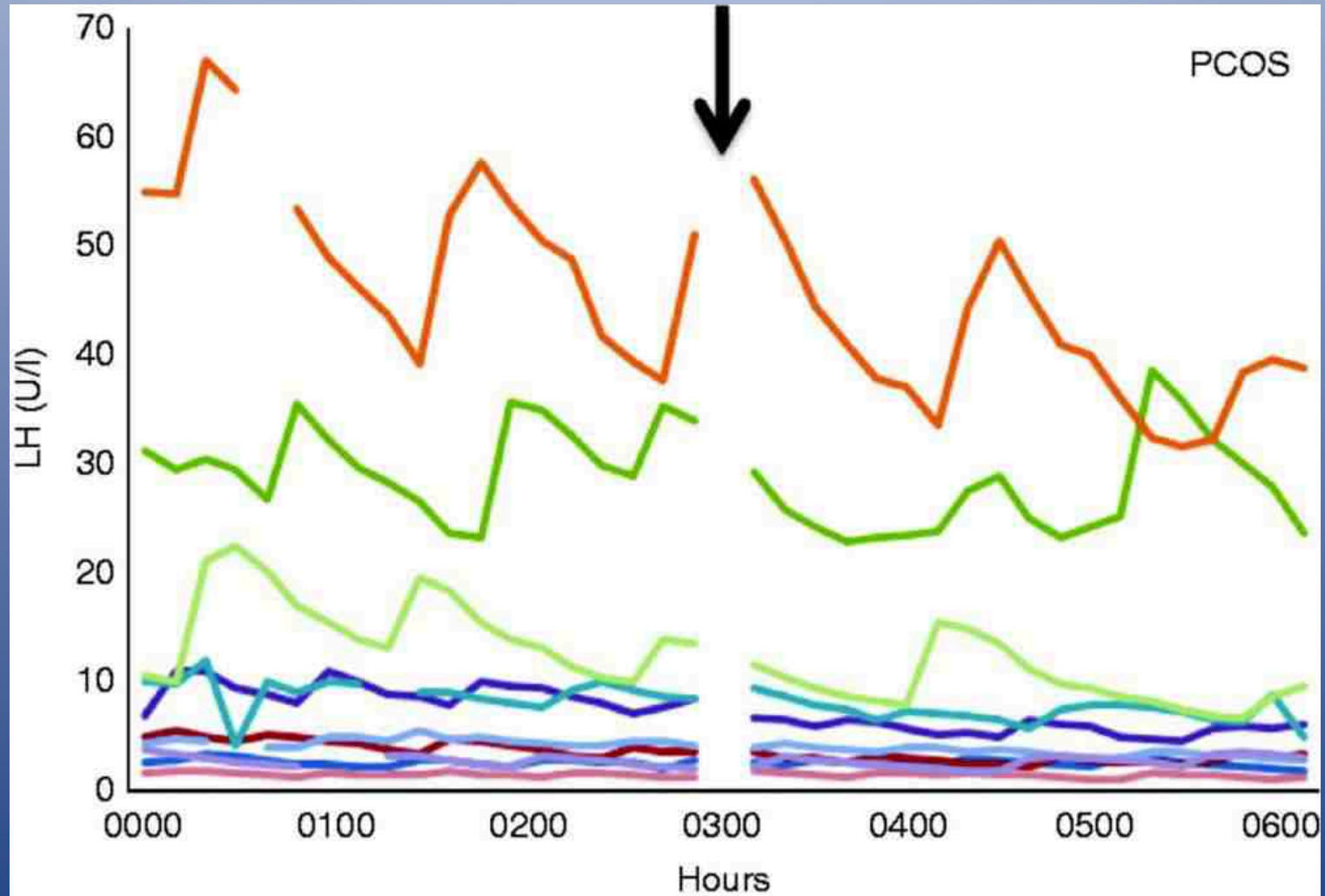


Figure 1 LH levels before and after the ovarian manipulation of all PCOS patients.



M L Hendriks et al. Eur J Endocrinol 2013;169:503-510

## PCOS ( $n=10$ ; $\pm$ s.d.)

	Before	After	P
LH (U/l)	13.0 (15.7)	10.4 (13.1)	<b>0.005</b>
LH pulse interval (min)	58 (13)	68 (26)	0.31
LH pulse amplitude (U)	4.1 (5.0)	3.8 (4.6)	0.61
Mean no. of LH pulses/3 h	3.1 (0.7)	2.7 (0.8)	0.21
LH pulses times LH amplitude	12.8 (15.0)	8.2 (8.9)	0.07

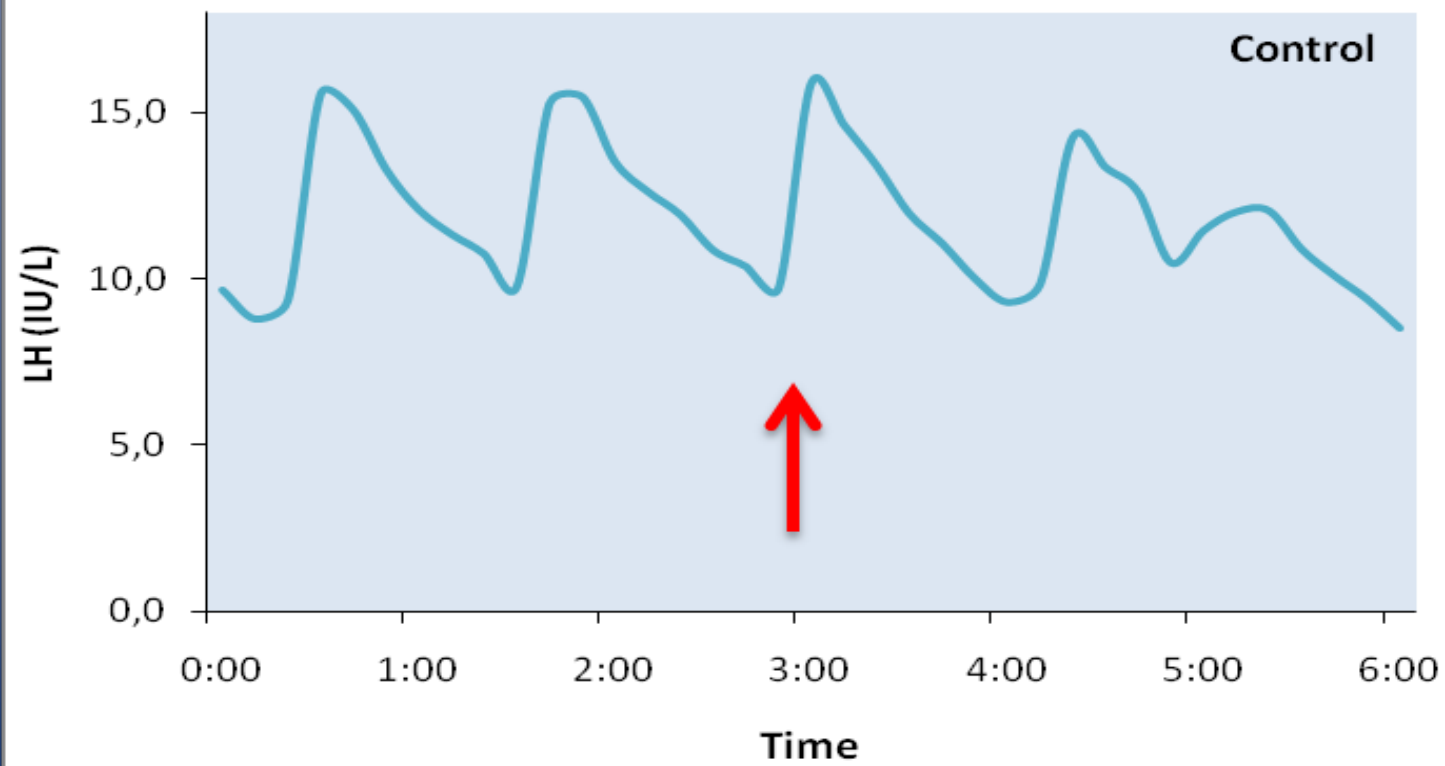
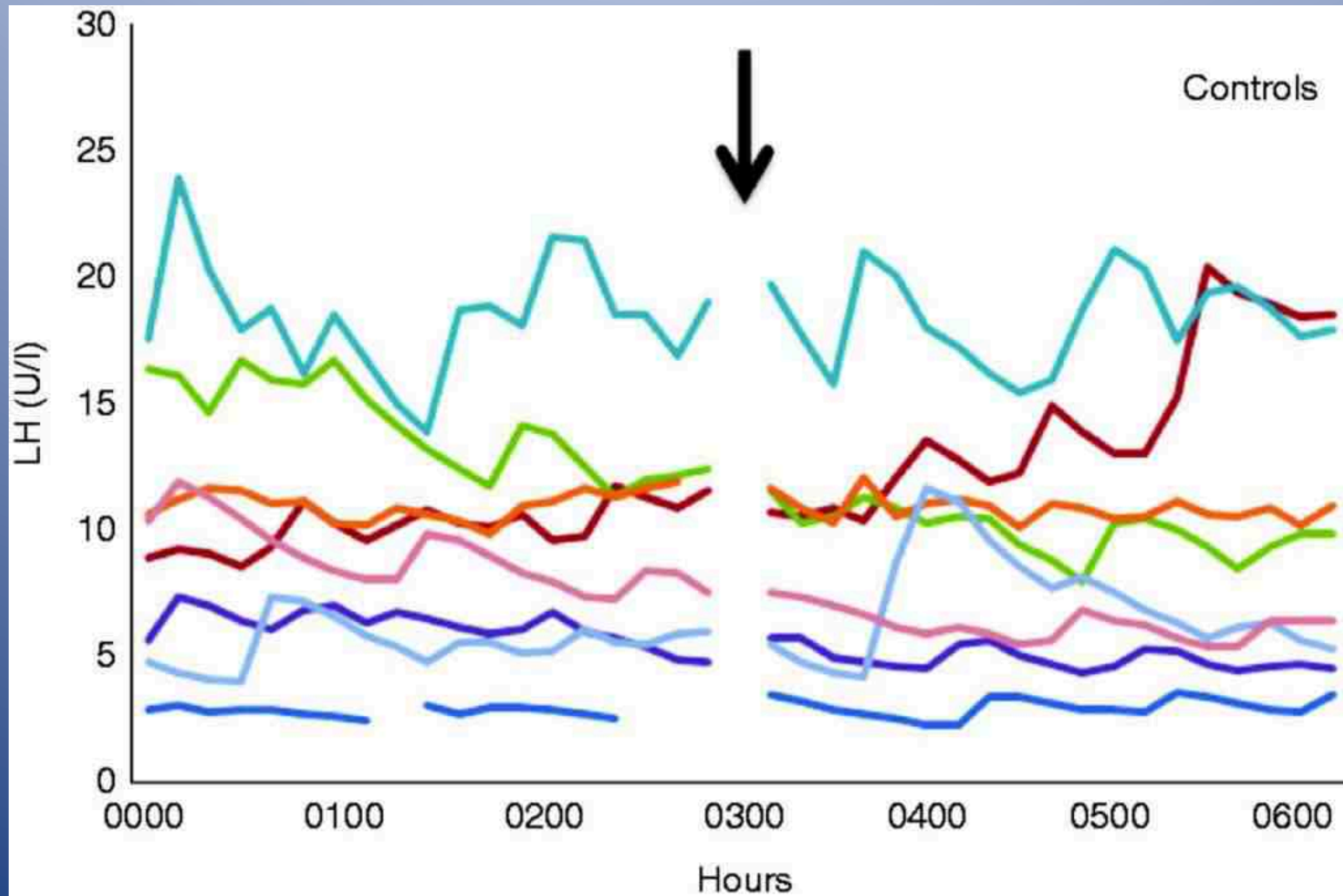


Figure 2 LH levels before and after the ovarian manipulation of all regularly ovulating controls.



M L Hendriks et al. Eur J Endocrinol 2013;169:503-510

## Controls ( $n=8$ ; $\pm$ s.d.)

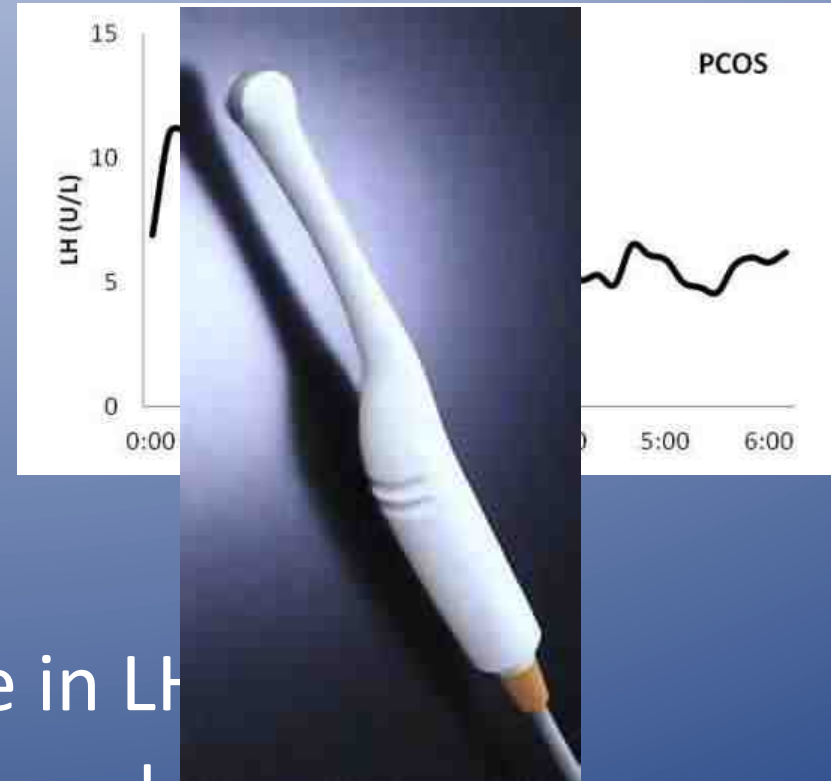
	Before	After	P
LH (U/l)	9.6 (5.0)	9.3 (5.1)	0.67
LH pulse interval (min)	53 (25)	65 (21)	0.18
LH pulse amplitude (U)	1.6 (1.0)	2.4 (1.6)	0.12
Mean no. of LH pulses/3 h	3.3 (1.3)	2.6 (0.5)	0.24
LH pulses times LH amplitude	5.5 (4.5)	6.4 (4.6)	0.40

	PCOS			Controls		
	Before	After	P	Before	After	P
FSH (U/l)	5.6 (2.6)	5.1 (1.9)	<b>0.005</b>	4.8 (1.6)	4.6 (1.8)	0.33
Estradiol (pmol/l)	865 (805)	842 (713)	0.96	736 (289)	758 (267)	0.48
Progesterone (nmol/l)	2.1 (0.1)	2.1 (0.1)	0.66	2.0 (0.0)	2.0 (0.0)	1.0
AMH (µg/l)	11.0 (6.4)*	10.8 (6.2)	0.10	3.6 (2.0)*	3.5 (1.9)	0.52
Inhibin B (ng/l)	275.1 (373.3)	287.8 (384.4)	0.17	77.1 (13.1)	66.1 (14.8)	0.09
Androstenedione (nmol/l)	12.3 (6.8)*	12.8 (5.4)	0.39	6.0 (1.7)*	6.5 (1.7)	0.14
Testosterone (nmol/l)	1.59 (0.88)*	1.57 (0.69)	0.51	0.86 (0.21)*	0.69 (0.34)	0.62
FAI (%)	5.12 (2.46)*	5.09 (2.34)	0.96	1.50 (1.06)*	1.51 (1.23)	0.67
Cortisol (nmol/l)	233.2 (87.7)	185.2 (81.8)	<b>0.009</b>	269.6 (75.5)	188.2 (75.1)	<b>0.012</b>
Prolactin (U/l)	0.20 (0.04)	0.20 (0.04)	0.34	0.18 (0.06)	0.17 (0.06)	0.34

# Ovarian manipulation

- PCOS and non-PCOS
- Manipulation of the ovaries

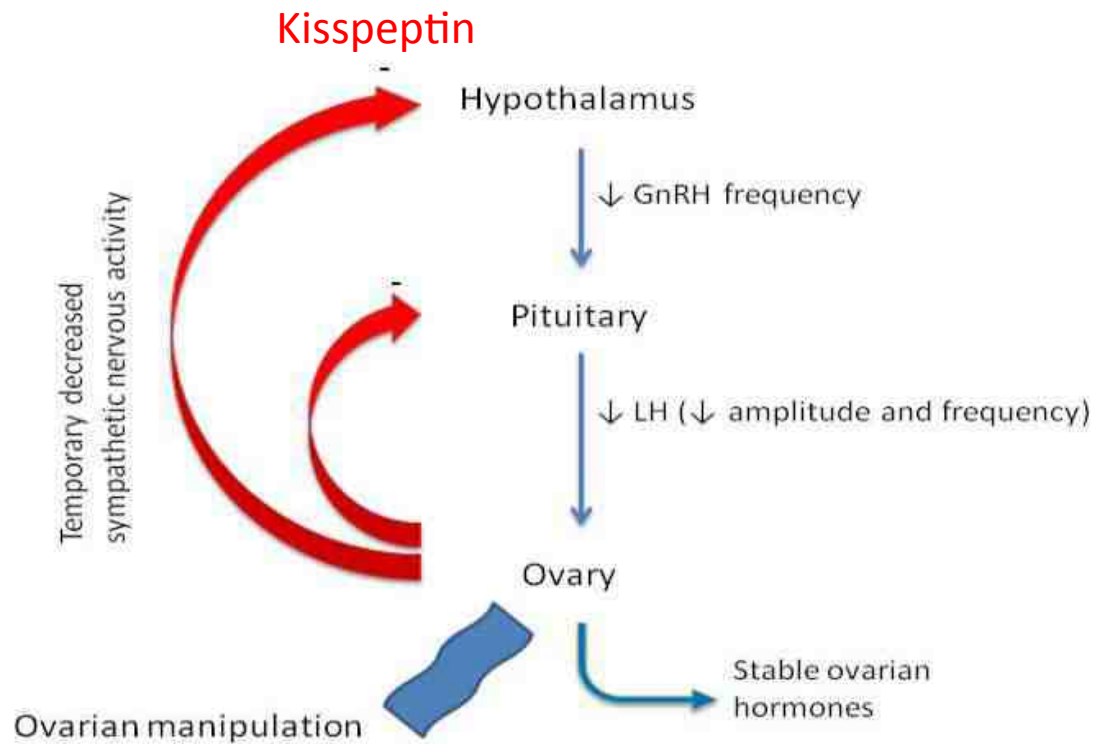
- PCOS: significant decrease in LH  
With no other ovarian hormonal changes → neuronal pathway?



Vaginal probe



# Potential mechanism of LH decrease after ovarian manipulation



# Conclusions

- Neuronal pathways are present in many species.
- First indication that a non-hormonal (? neuronal) communication from the ovaries to the pituitary exists in humans.
- Does temporary normalization of the high sympathetic tone innervating PCOS ovaries act as a salvage mechanism for restoration of ovulation?