Controlled Ovarian Hyperstimulation vs. personalized preparation of the ovaries for egg collection

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No conflict of interest

OVARIAN CLUB VIII
BUILDING A BRIDGE BETWEEN SCIENCE AND CLINICAL PRACTICE
4-6 NOVEMBER, 2016 · PARIS, FRANCE

Induction of ovulation for in-vitro fertilization using Buserelin and gonadotropins

RN Porter, W Smith, IL Craft, NA Abdulwahid, HS Jacobs

The Lancet (1984)

OVARIAN STIMULATION PROTOCOL AND OOCYTE QUALITY: THE ROLE OF GnRH ANALOGUES AND GONADOTROPINS

The use of GnRH agonists in IVF practice:

- Lower cancellation rates
- An increased number of oocytes retrieved
- Higher pregnancy and live birth rates

Hughes EG et al., Fertil Steril 1992

The introduction of GnRH antagonists:

- Allowed for less aggressive and more individualized protocols
- Increased safety
- Avoided the initial flare up and subsequent estrogen deprivation symptoms

Frydman R et al., Fertil Steril 1991
Diedrich K et al., Hum Reprod 1994

Key players in successful implantation

- The embryo
- The endometrium
- The maternal immune system

All affected by the way we stimulate the ovaries

Success of IVF is clearly dependent on the size and quality of the oocyte cohort

- Type of gonadotropins given
- Dose of gonadotropins given
- Regimen of pituitary suppression used
- Type of ovulatory trigger
- Administration of adjuvant agents

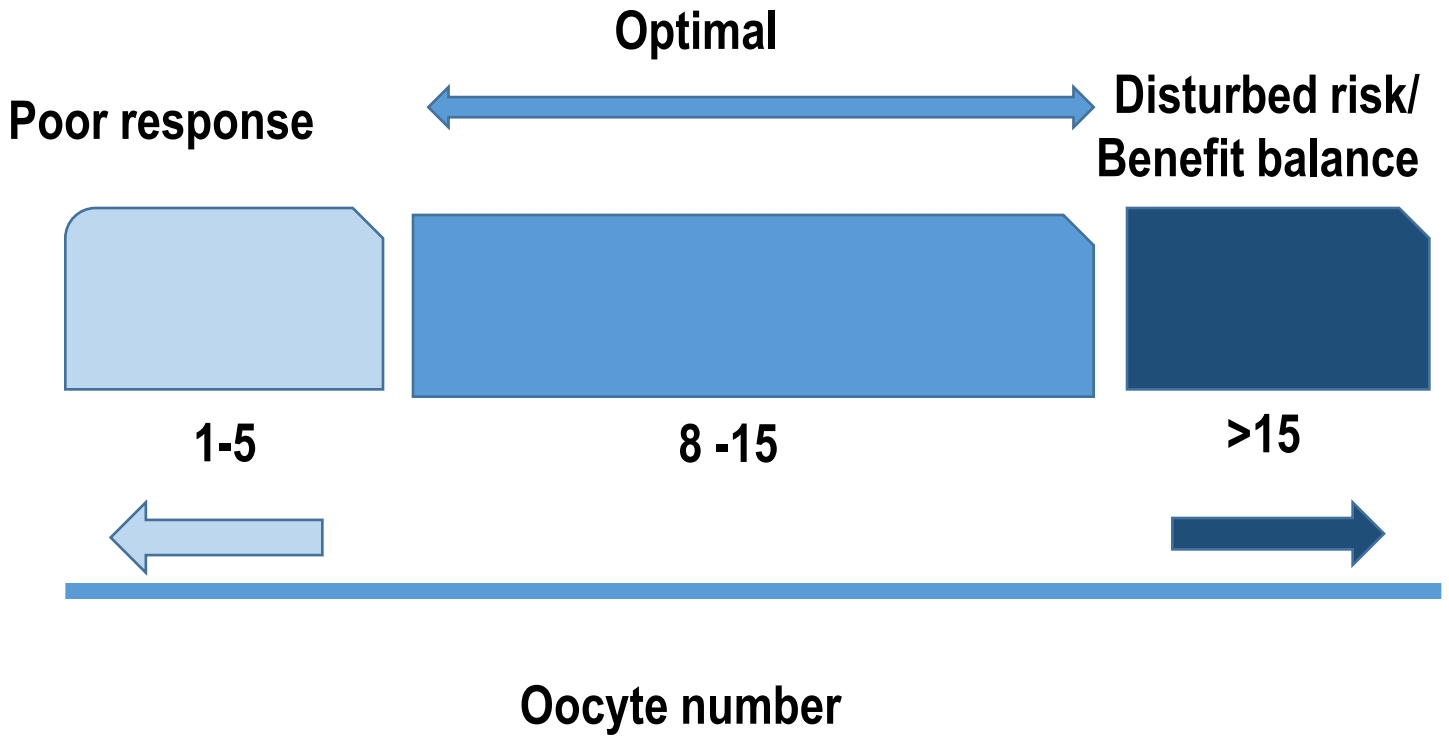
Types of stimulated cycles in IVF

- Fresh IVF cycle
- Segmented IVF cycle

Success of IVF is clearly dependent on the size and quality of the oocyte cohort

- Type of gonadotropins given
- Doses of gonadotropins given
- Regimen of pituitary suppression used
- Type of ovulatory trigger
- Administration of adjuvant agents

Ovarian stimulation for IVF: what is optimal?

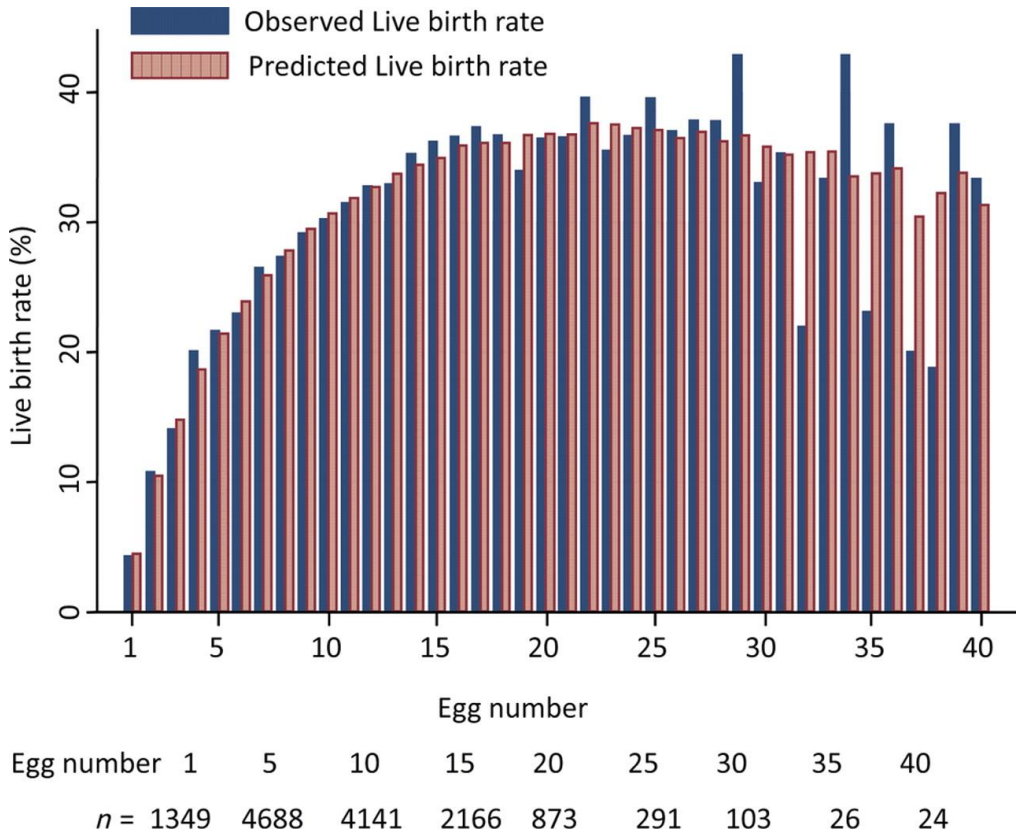


Human Reproduction, Vol.0, No.0 pp. 1–7, 2011
doi:10.1093/humrep/der106

human reproduction

ORIGINAL ARTICLE *Infertility*

Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles



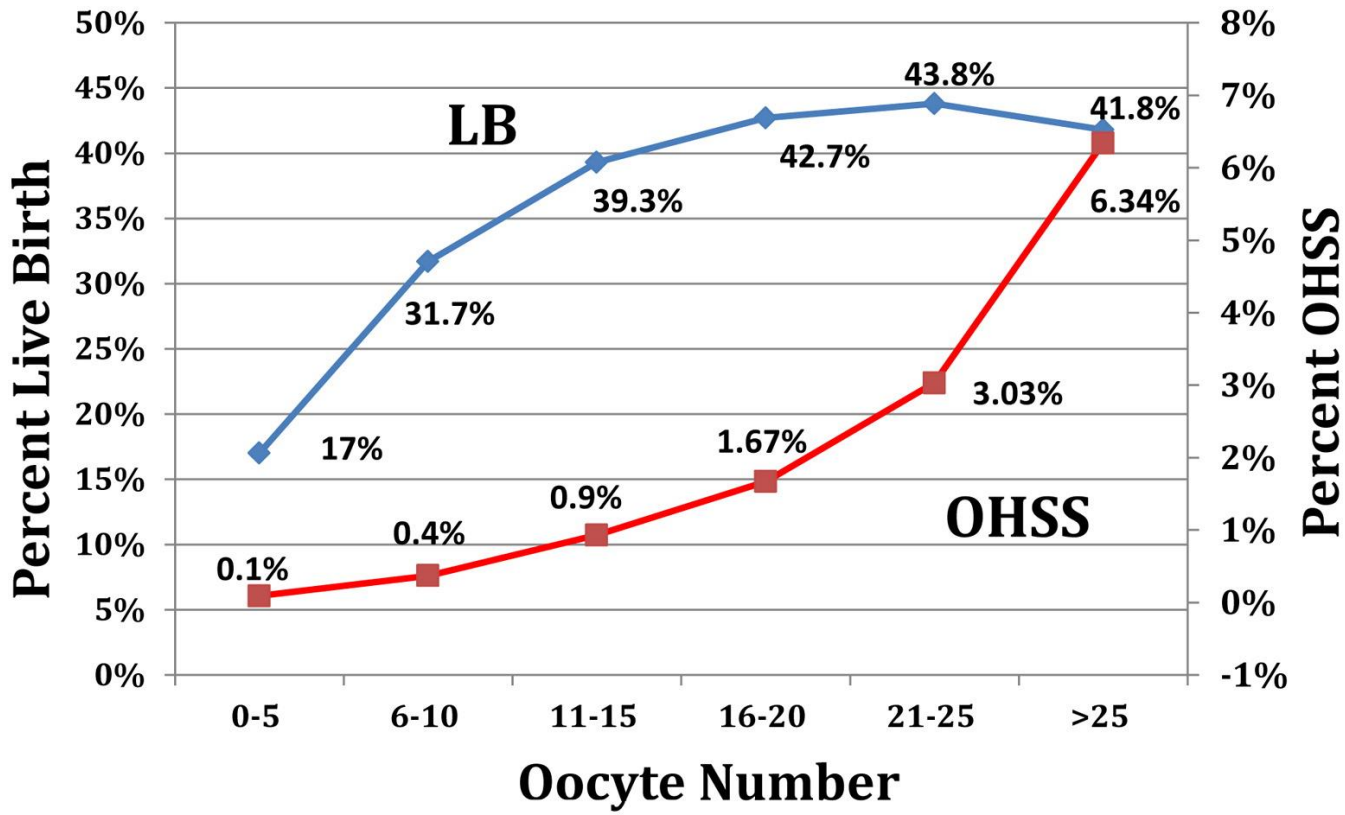
Egg number	1	5	10	15	20	25	30	35	40
n =	1349	4688	4141	2166	873	291	103	26	24

Sunkara et al. Hum. Reprod. 2011

Oocyte number as a predictor for ovarian hyperstimulation syndrome and live birth: an analysis of 256,381 in vitro fertilization cycles

Fertility and Sterility® Vol. 101, No. 4, April 2014

Ryan G. Steward, M.D.,[a] Lan Lan, Ph.D.,[b] Anish A. Shah, M.D., M.H.S.,[a] Jason S. Yeh, M.D.,[a] Thomas M. Price, M.D.,[a] James M. Goldfarb, M.D.,[c] and Suheil J. Muasher, M.D.[a]



Success of IVF is clearly dependent on the size and quality of the oocyte cohort

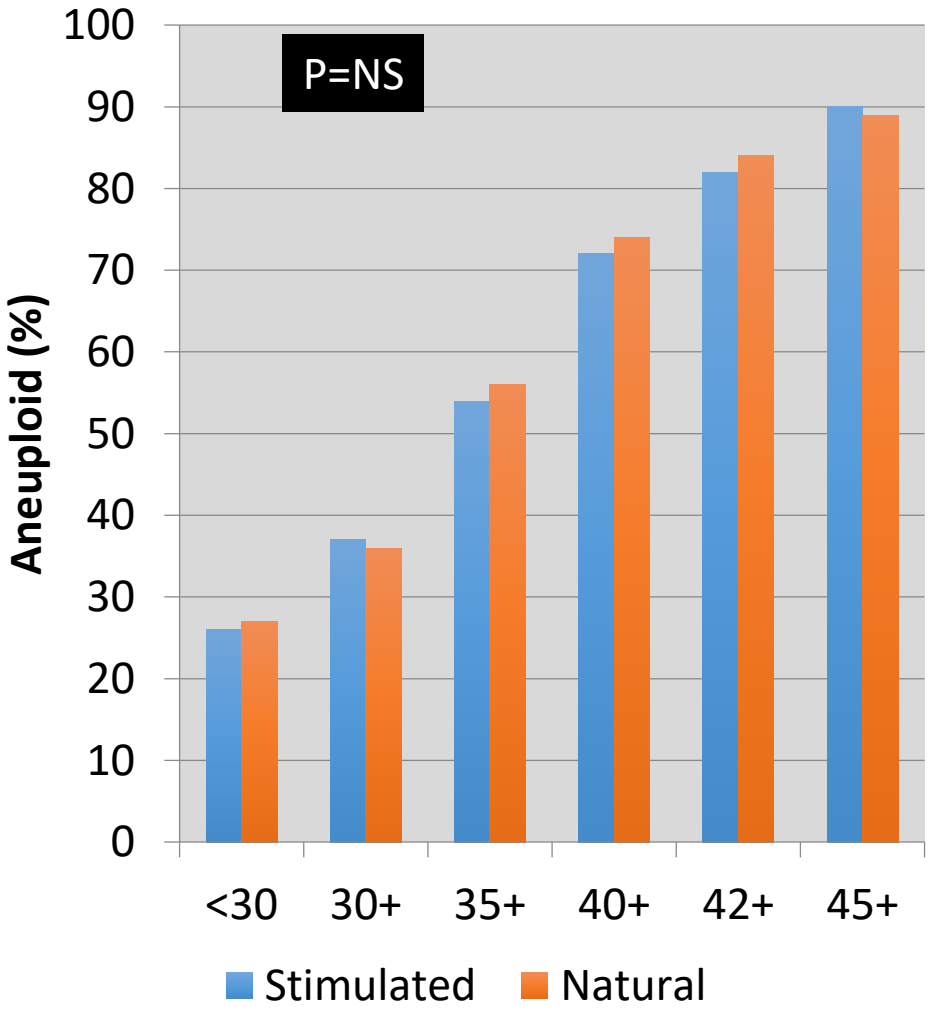
Does the size of the cohort affect oocyte quality?

Success of IVF is clearly dependent on the size and quality of the oocyte cohort

- Oocyte – largest cell in the female body
- Cytoplasmic maturation and quality
- Sufficient to support normal chromosome segregation
- Not necessarily successful implantation
- Limited access to study oocyte quality

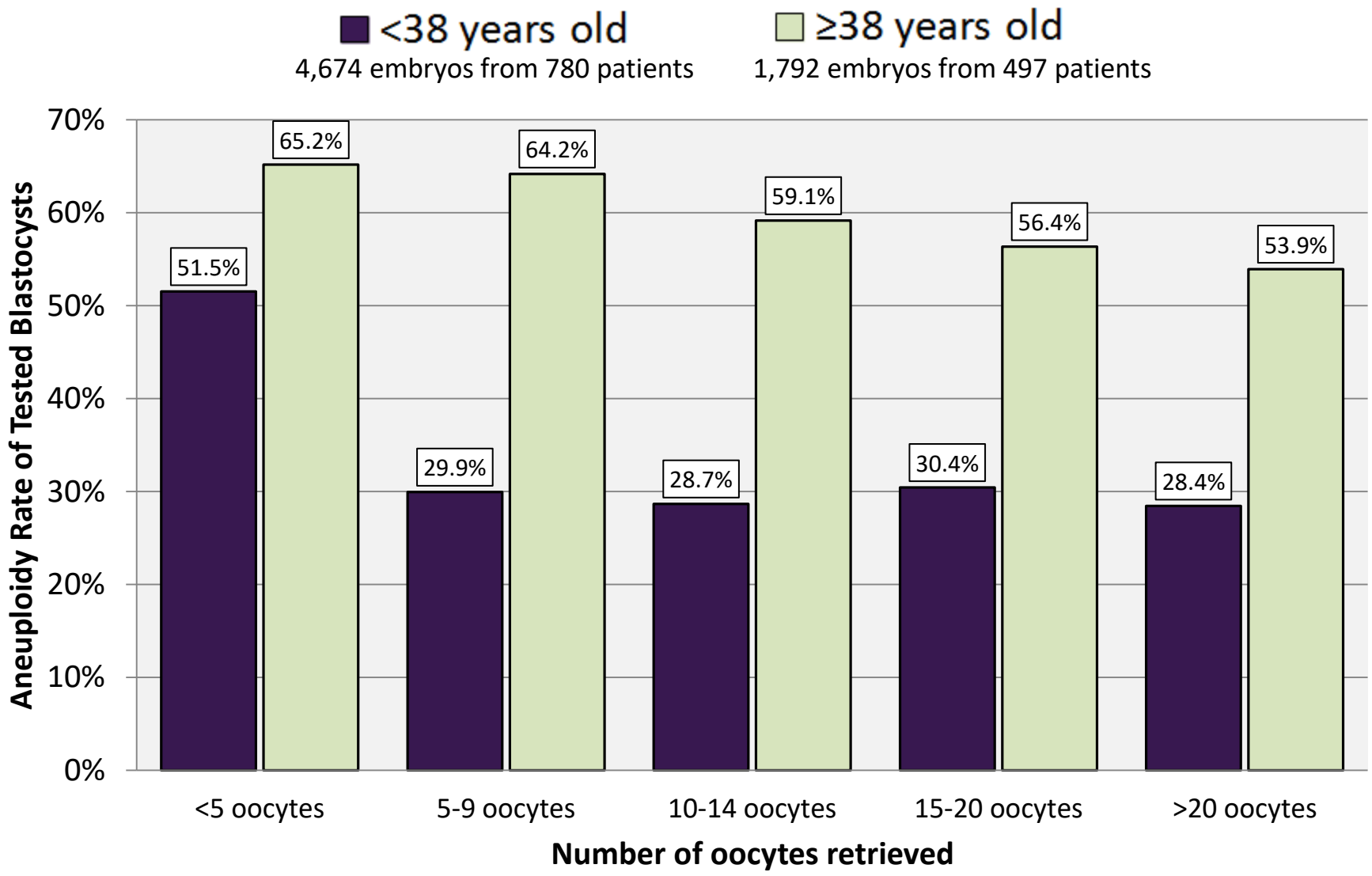
Natural versus Stimulated Folliculogenesis and Embryonic Aneuploidy

- Prospective observational
- Historic Control
- Ages 21-49 years
- Follicular diameter at retrieval ~ 21 mm
- hCG induced follicular maturation



Hong ASRM 2014

Aneuploidy vs. No. Oocytes Retrieved



Source: RMANJ, 1st CCS cycle per patient 2010-2012

Embryonic aneuploidy in natural and stimulated cycles

Embryonic aneuploidy rates do not differ:

- In natural cycles
- Following mild stimulation
- Following intense stimulation

These data do not support a causative role for gonadotropin stimulation in embryonic aneuploidy

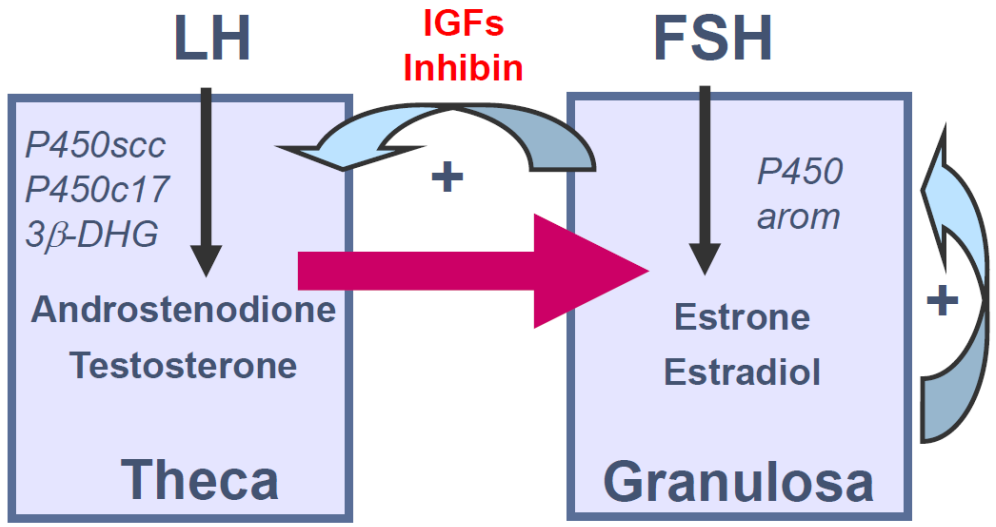
~50% of euploid blastocysts do not implant…

Success of IVF is clearly dependent on the size and quality of the oocyte cohort

- Type of gonadotropins given
- Doses of gonadotropins given
- Regimen of pituitary suppression used
- Type of ovulatory trigger
- Administration of adjuvant agents

Type of gonadotropin used

A synergic and synchronized action of FSH and LH at the follicular level
Crucial to achieve an adequate steroidogenesis for proper oocyte maturation and endometrial development



In the ovarian stimulation for IVF context:

- FSH is related to ovarian response in terms of oocyte yield
- LH modulates follicular steroidogenesis

LH action induces androgen synthesis for their aromatization into estrogens

Type of gonadotropin used

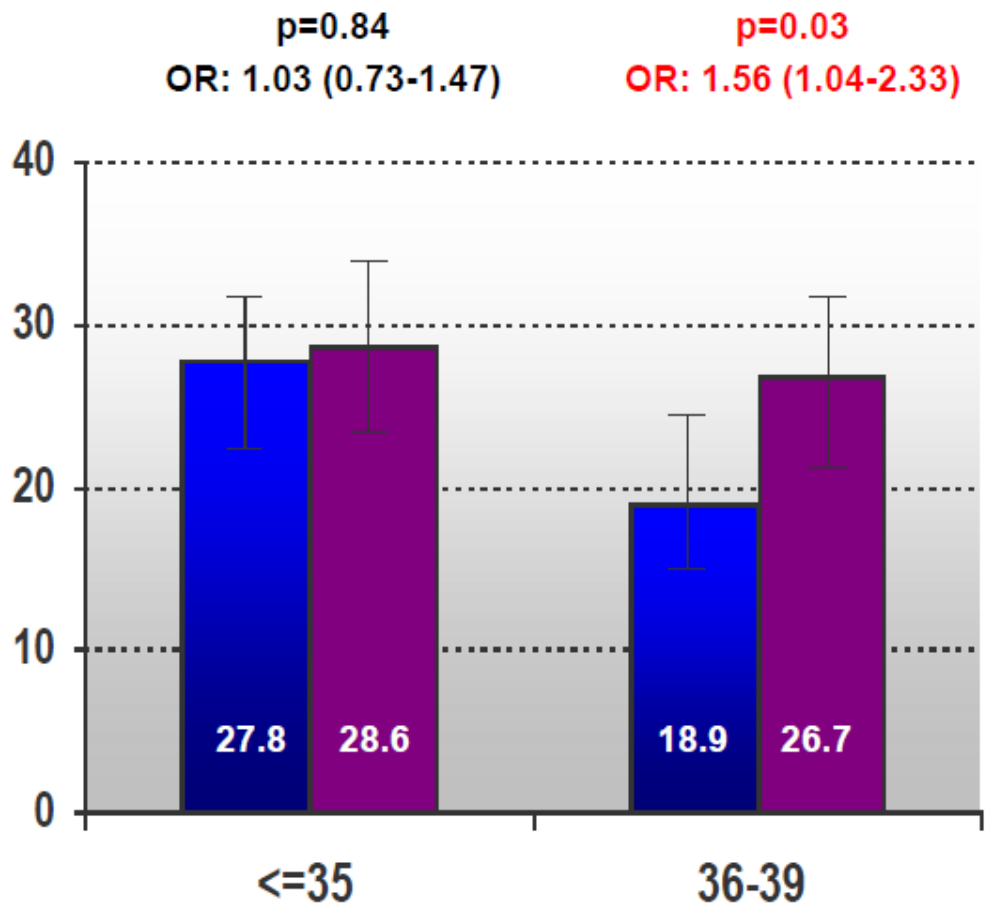
- The physiologic role of LH during the follicular phase of a natural cycle is unquestionable

- Its impact during a COS cycle remains controversial

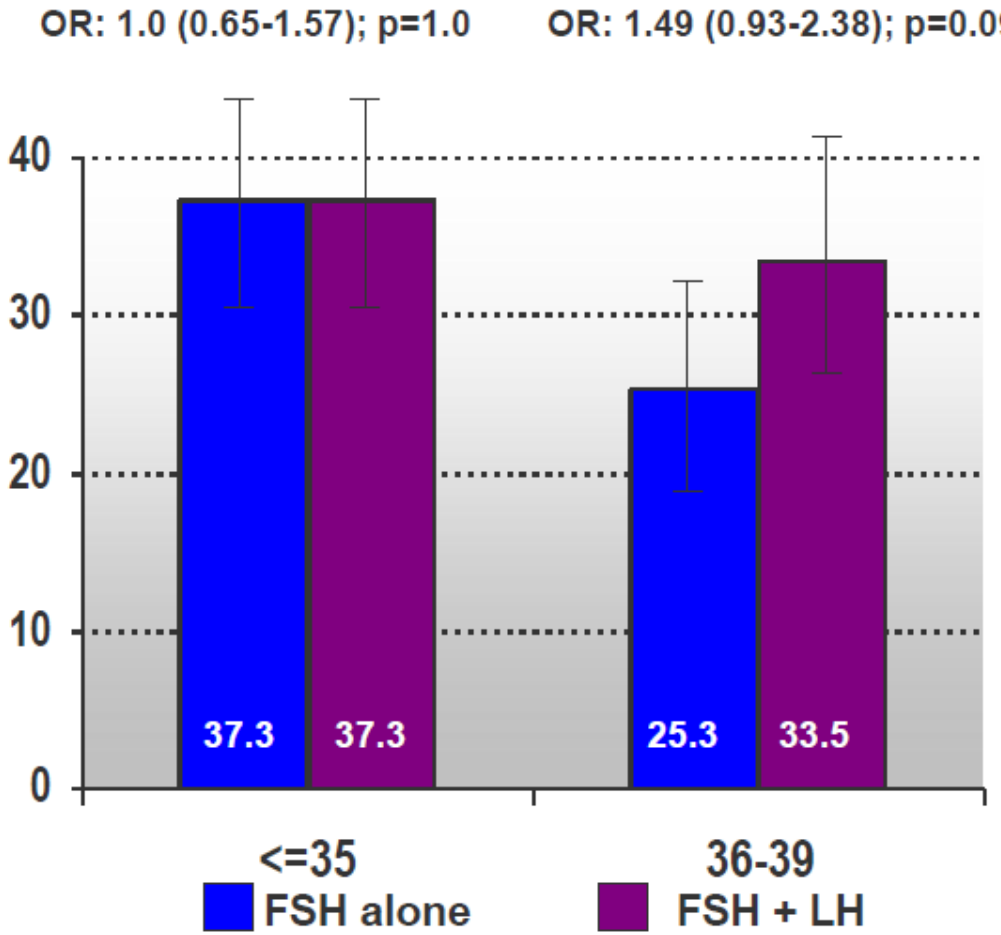
- To date there seems to be no clear benefit obtained by combining LH and FSH in unselected normogonadotrophic patients

Kolibianakis et al., Hum Repord Update 2006
Mochtar et al., Cochrane Database Syst Rev 2007

Implantation rate



Ongoing Pregnancy rate per Randomized patient (ITT analysis)

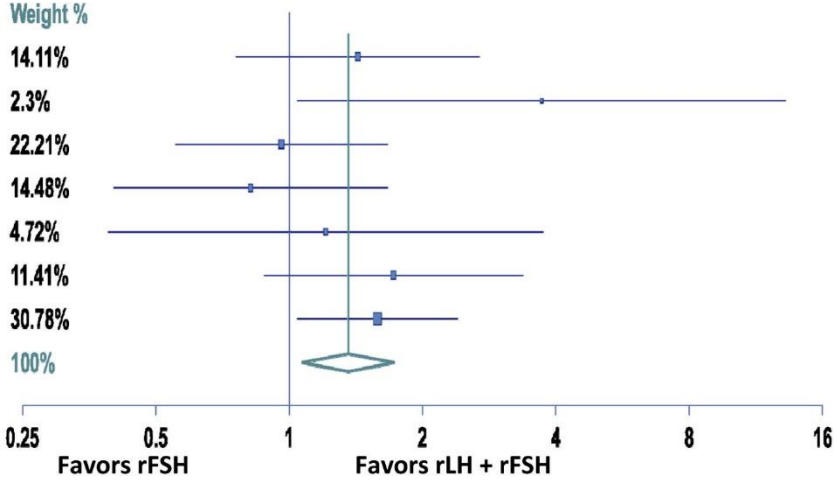


Bosch et al (2011) Fertil Steril 95; 1031-6
ASRM 2008 General Program Price Paper Award

Rec h-LH in patients with advanced reproductive age: a meta-analysis

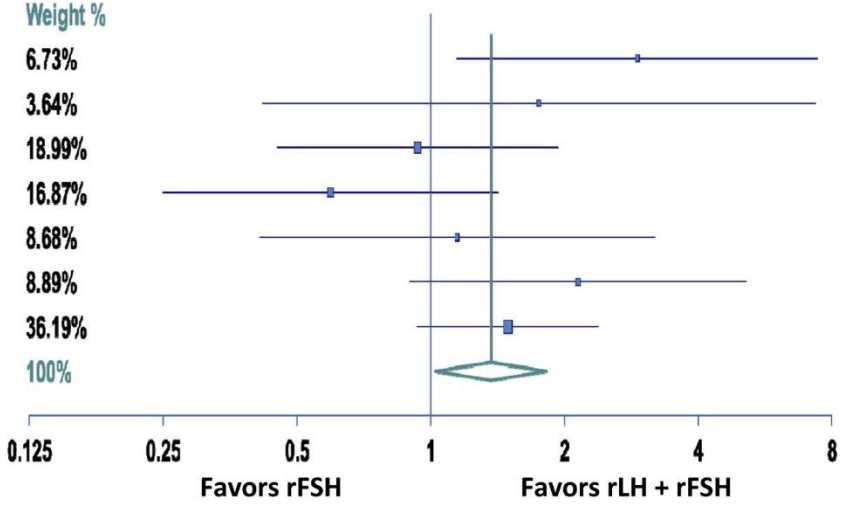
Forest plot of embryo implantation

Study	Sample size (embryos)	Measure (CI)	Weight %
Marrs 2004	262	1.43 (0.76; 2.69)	14.11%
Humaidan 2004	63	3.71 (1.04; 13.22)	2.3%
Fabregues 2005	320	0.96 (0.55; 1.67)	22.21%
NyboeAndersen 2008	170	0.82 (0.4; 1.67)	14.48%
Barrenetxea 2008	184	1.21 (0.39; 3.74)	4.72%
Mattoras 2009	285	1.72 (0.88; 3.37)	11.41%
Bosch 2011	526	1.58 (1.04; 2.4)	30.78%
Synthesis	1810	1.36 (1.05; 1.78)	100%



Forest plot of clinical pregnancy

Study	Sample size (patients)	Measure (CI)	Weight %
Marrs 2004	88	2.91 (1.14; 7.42)	6.73%
Humaidan 2004	39	1.75 (0.42; 7.35)	3.64%
Fabregues 2005	120	0.93 (0.45; 1.93)	18.99%
NyboeAndersen 2008	100	0.59 (0.25; 1.42)	16.87%
Barrenetxea 2008	84	1.15 (0.41; 3.19)	8.68%
Mattoras 2009	131	2.14 (0.9; 5.12)	8.89%
Bosch 2011	340	1.49 (0.93; 2.38)	36.19%
Synthesis	902	1.37 (1.03; 1.83)	100%



Hill. Recombinant LH in patients of advanced reproductive age. Fertil Steril 2012.

Conclusion: type of gonadotropin used

The addition of LH activity to FSH induces variations in follicular steroidogenesis that may benefit older patients (>35 years) through a higher synthesis of androgens, which are diminished in older women

Apart from the arbitrary criteria of age, there is a lack of an appropriate biomarker to determine the need of LH in a COS cycle in a given patient

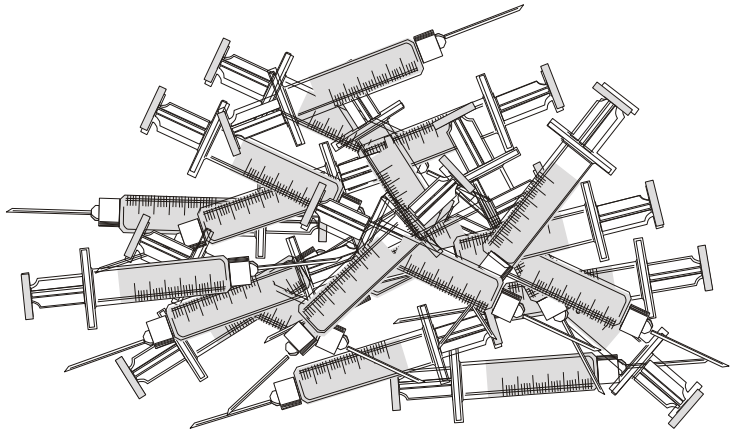
Success of IVF is clearly dependent on the size and quality of the oocyte cohort

- Type of gonadotropins given
- Doses of gonadotropins given
- Regimen of pituitary suppression used
- Type of ovulatory trigger
- Administration of adjuvant agents

Long Agonists vs. GnRH Antagonists: meta-analysis of RCTs:

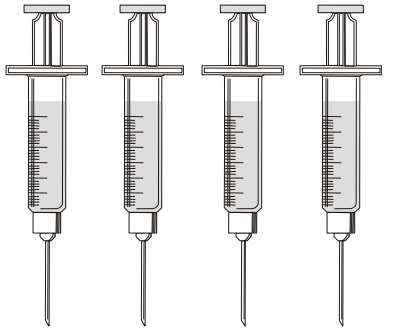
	No. of RCTs	Ongoing pregnancy/Live birth rate	Severe OHSS
Al-Inany et al. Cochrane Colab. 2011	45	OR= 0.86 95% CI 0.69-1.08	OR= 0.43 95% CI 0.33-0.57

Agonist

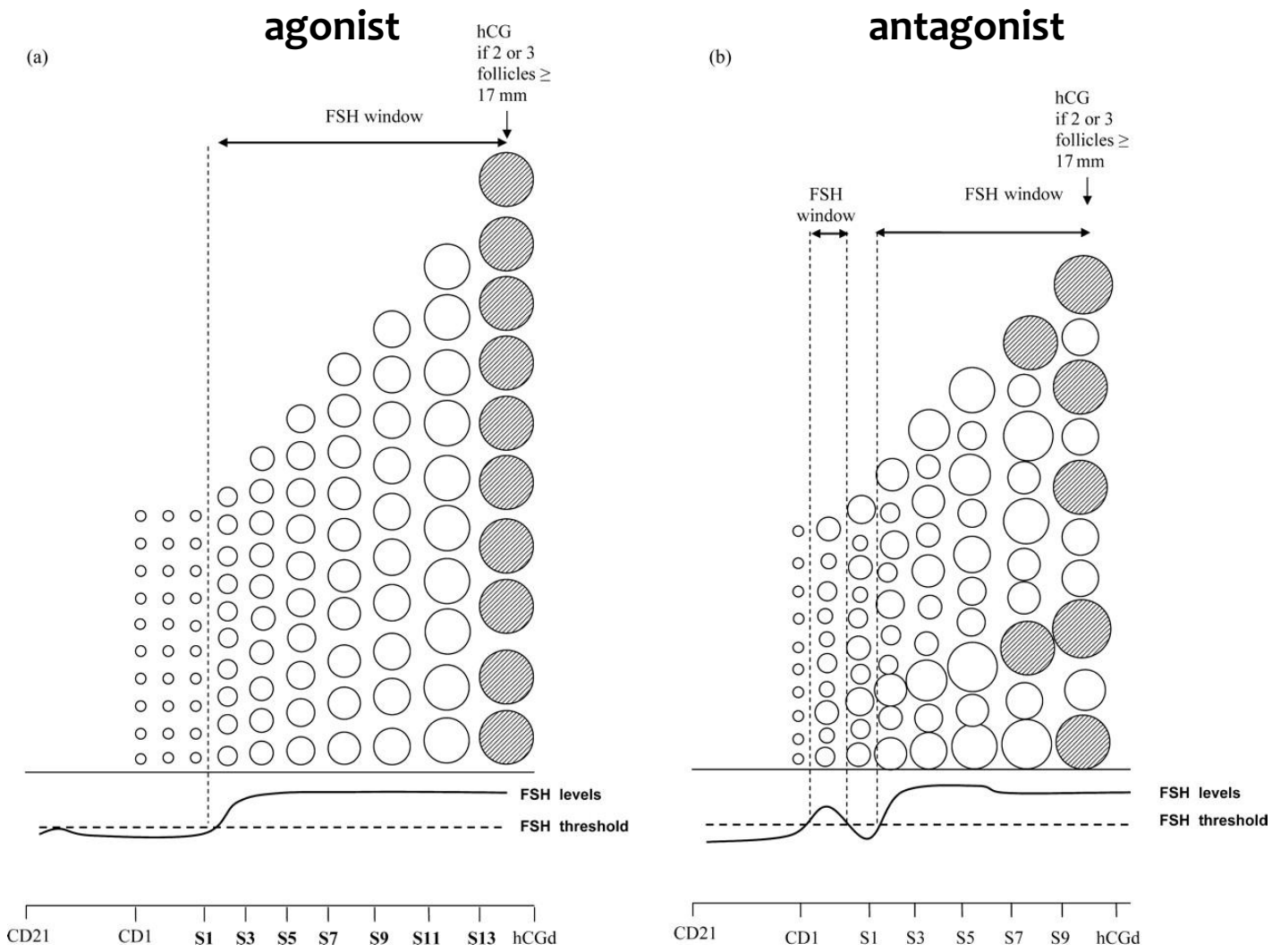


VS.

Antagonist



(a) Synchronized follicular development after FSH administration in a long GnRH agonist regimen and (b) Follicular development in a fixed day 6 GnRH antagonist regimen without OC pre-treatment



J.A. Huirne et al. Hum. Reprod. 2007;22:2805-2813

Conclusion: regimen of pituitary suppression used

GnRH antagonist cycles offer similar live birth rates
with improved safety compared with the GnRH-a long protocol

Nevertheless, patients with endometriosis,
or those with accelerated folliculogenesis,
could benefit from a GnRH-a long protocol,
owing to the better control of endogenous gonadotropins
and follicular growth

There is a lack of an appropriate biomarker to determine
a-priori which patients would benefit from a GnRH-a protocol

Success of IVF is clearly dependent on the size and quality of the oocyte cohort

- Type of gonadotropins given
- Doses of gonadotropins given
- Regimen of pituitary suppression used
- Type of ovulatory trigger
- Administration of adjuvant agents

Types of ovulatory triggers currently in use

- hCG
- GnRH agonist trigger
- Dual trigger

→ Individualized luteal support regimen

GnRH agonist trigger

→ Individualized luteal support regimen

- Intensive luteal support
- Adjuvant low dose hCG
  - Dual trigger with hCG (range 1,000 - 2500IU)
  - Adjuvant hCG at time of oocyte retrieval
  - Very low hCG dose
- Recombinant LH
- Freeze all

Combination gonadotropin-releasing hormone agonist, a novel approach to avoid ovarian hyperstimulation syndrome and enable fresh-embryo transfer in high responders

Itai Bar-Hava, M.D.,[a,b] Yossi Mizrachi, M.D.,[c] Daphne Karfunkel-Doron, M.Sc.,[a] Yeela Omer, B.A.,[a] Liron Sheena, M.D.,[a] Nurit Carmon, Bs.C.D.R.,[a] and Gila Ben-David, M.D.[a,b]

- 46 patients at risk for OHSS
- GnRH-a trigger
- Nafarein (Synarel) 200 μg*2 daily from the evening of OPU
- No other form of luteal support

Oocytes retrieved	23 (8–67)
Single-embryo transfer	38 (82.6)
Midluteal P level (nmol/L)	190 (2.3–600)[a]
Midluteal E_2 level (pmol/L)	5,381 (224–18,155)
P level at first positive pregnancy test (nmol/L)	190 (1.9–1,750)
E_2 level at first positive pregnancy test (pmol/L)	5,407 (89–16,089)
Clinical ongoing pregnancies	24 (52.1)

Fertil Steril, 2016

ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Gonadotropin-releasing hormone analogue as sole luteal support in antagonist-based assisted reproductive technology cycles

Itai Bar Hava, M.D.,[a] Moran Blueshtein, Ph.D.,[b] Hadas Ganer Herman, M.D.,[a] Yeela Omer, M.D.,[a] and Gila Ben David, M.D.[a]

TABLE 1

Baseline characteristics and primary results for the GnRH agonist (GnRH-a) and the P supplementation groups.

Variable	GnRH-a (n = 1,436)	P (n = 1,093)	*P* value
Positive β-hCG, n (%)	401 (27.9)	217 (19.8)	<.001
Chemical pregnancy	51/401 (12.7)	32/217 (14.7)	.48
Miscarriage	74/401 (18.4)	65/217 (29.9)	.001
Live birth	254/401 (63.3)	108/217 (49.7)	.001
Midluteal P (mmol/L)	194.3 ± 146.0	134.0 ± 113.4	<.001
Midluteal E_2 (mmol/L)	3,453.7 ± 2,826.8	1,810.1 ± 2,314.2	<.001
Pregnancy with P (mmol/L)	222.1 ± 155.0	144.9 ± 82.6	<.001
Pregnancy with E_2 (mmol/L)	6,921.3 ± 4,476.7	3,407.5 ± 2,970.0	<.001

Note: Data presented as mean ± SD, unless stated otherwise. BMI = body mass index.

Dual trigger

Potential biological role for the FSH surge at the time of final oocyte maturation:

- FSH stimulates plasminogen activator activity
  within granulosa cell cultures
- Involved in dissociating the oocyte from the follicular wall
  and weakening the wall to facilitate rupture
- Improved oocyte recovery with higher follicular fluid FSH levels
- FSH promotes formation of LH receptors in luteinizing granulosa cells
- Keep gap junctions open between the oocyte and cumulus cells
- Promote nuclear maturation and cumulus expansion

Strickland et al., J Biol Chem 1976
Morioka et al., Prog Clin Biol Res 1989
Rosen et al., Reprod Biol Endocrinol 2009

Atef et al., Mol Reprod Dev 2005
Zelinski-Wooten et al., Hum Reprod 1998
Yding Andersen et al., Mol Hum Repord 1999

Dual trigger
GnRH-agonist and a standard dosage of hCG

Significantly higher proportion of mature oocytes in patients with a previous history of >25% immature oocytes

Griffin et al., Fertil Steril 2014

In normal responders GnRH-antagonist IVF cycles:

- More oocytes MII oocytes
- Significantly improved implantation, CPR and LBR
- Improved endometrial receptivity?

Comparison of the standard and dual-trigger methods: outcomes of in vitro fertilization/intracytoplasmic sperm injection cycles.

Variable	Control group (hCG)	Study group (hCG + triptorelin)	*P* value
Implantation rate (%)	18.43 (106/575)	29.68 (160/539)	<.001
Clinical pregnancy rate per ET (%)	40.11 (75/187)	50.79 (97/191)	.047
Abortion rate (%)	18.67 (14/75)	16.49 (16/97)	NS
Live-birth rate per ET (%)	30.49 (57/187)	41.36 (79/191)	.042
	N=187	**n=191**	

Lin et al., Fertil Steril 2013

Key players in the successful implantation

- The embryo
- The endometrium
- The maternal immune system

Impact of high serum progesterone during the late follicular phase on IVF outcome

Charlotte Sonigo*, Géraldine Dray, Clémence Roche,
Isabelle Cédrin-Durnerin, Jean-Noel Hugues

- Serum P may increase during the last few days of ovarian stimulation
- P increase does not reflect ‘premature luteinization’
- The risk of endogenous LH surge is controlled by simultaneous administration of GnRH analogues
- Primarily related to the intensity of the ovarian response to FSH [No. of follicles; No. of oocytes; Serum E2 levels]
- Also dependent on the studied population

Reproductive BioMedicine Online (2014) 29, 177–186

ORs for pregnancy achievement in women with PE when compared with those without PE

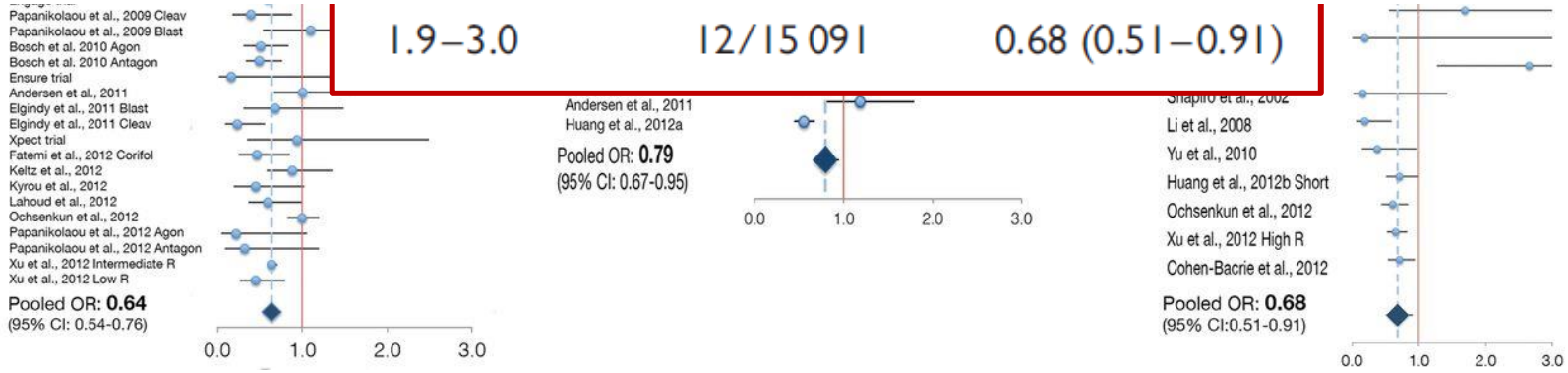
a) 0.4-0.6 ng/mL b) 0.8-1.1 ng/mL c) 1.2-1.4 ng/mL

Human Reproduction Update, Vol.19, No.5 pp. 433–457, 2013
Advanced Access publication on July 4, 2013 doi:10.1093/humupd/dmt014

human reproduction update

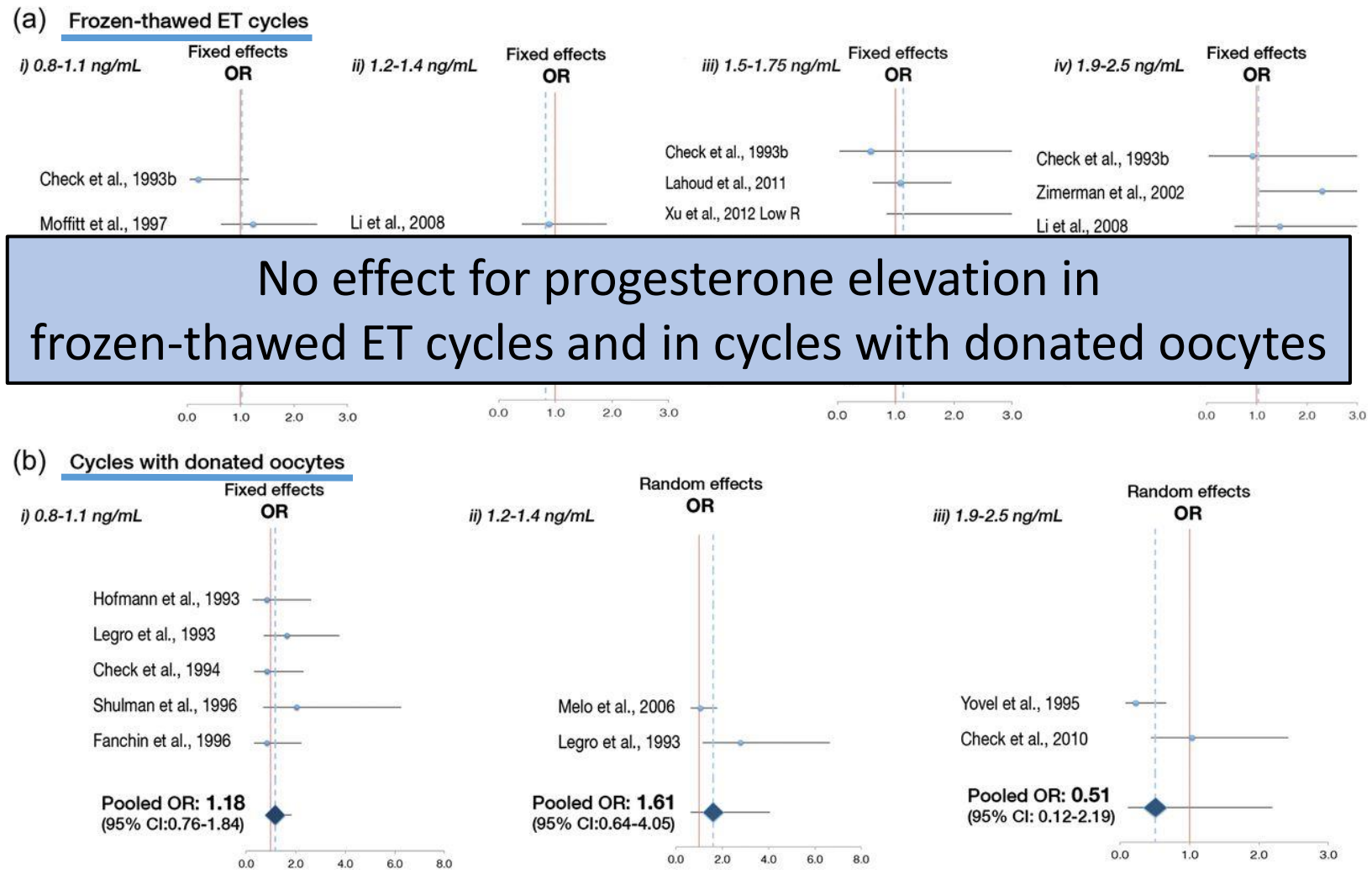
Progesterone elevation and probability of pregnancy after IVF: a systematic review and meta-analysis of over 60 000 cycles

C.A. Venetis*, E.M. Kolibianakis, J.K. Bosdou, and B.C. Tarlatzis



Venetis et al. Hum. Reprod. Update 2013;19:433-457

Odds ratios for achievement of pregnancy in women undergoing (a) FET and (b) oocyte donation after a fresh cycle with or without progesterone elevation

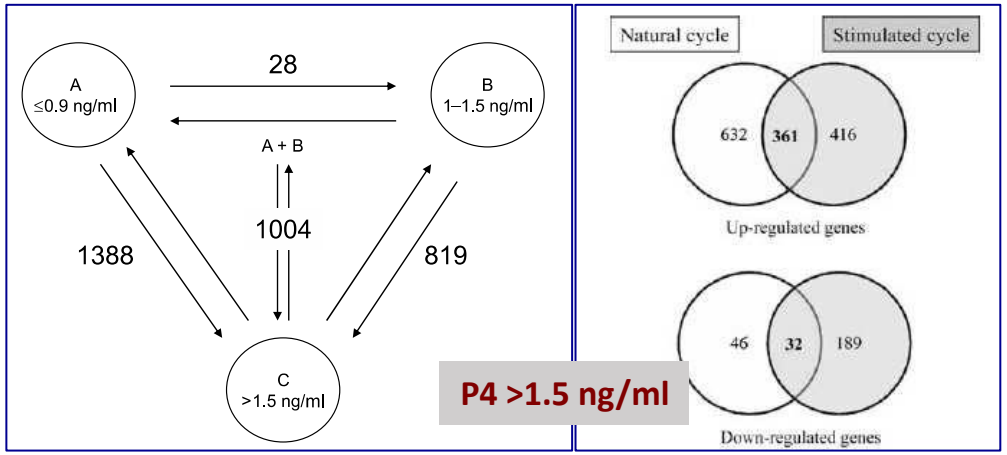


Venetis et al. Hum. Reprod. Update 2013;19:433-457

A distinct difference in endometrial gene expression profile between patients with P concentration above and below1.5 ng/ml on the day of HCG administration

Impairment of endometrial receptivity, which is reflected as lower PRs

Differential gene expression between groups of P4 concentration



140 genes <u>significantly dysregulated</u> (64 up- and 76 down-regulated) regardless of GnRH analogue used. These genes are required for cell adhesion, developmental processes & immune system functioning

<u>Results in moderately altered receptivity in 86%</u>

<u>Strongly altered receptivity in 14%</u>

Haouz et al HR 2009
Labarta et al HR 2011
Van Vaerenbergh et al RBM Online 2011

Serum progesterone threshold and type of GnRH analogue

Serum progesterone at the time of HCG triggering is significantly higher in women treated with GnRH agonist as compared with GnRH antagonist

Stronger ovarian response to FSH as attested by the average difference of about two oocytes in favor of GnRH agonist

Bosch et al., 2010;
Hugues et al., 2011;
Papanikolaou et al., 2012

Higher endogenous LH concentration is observed during the last few days of stimulation in women treated with GnRH agonist as compared with those who received GnRH antagonist

Hugues et al., 2011

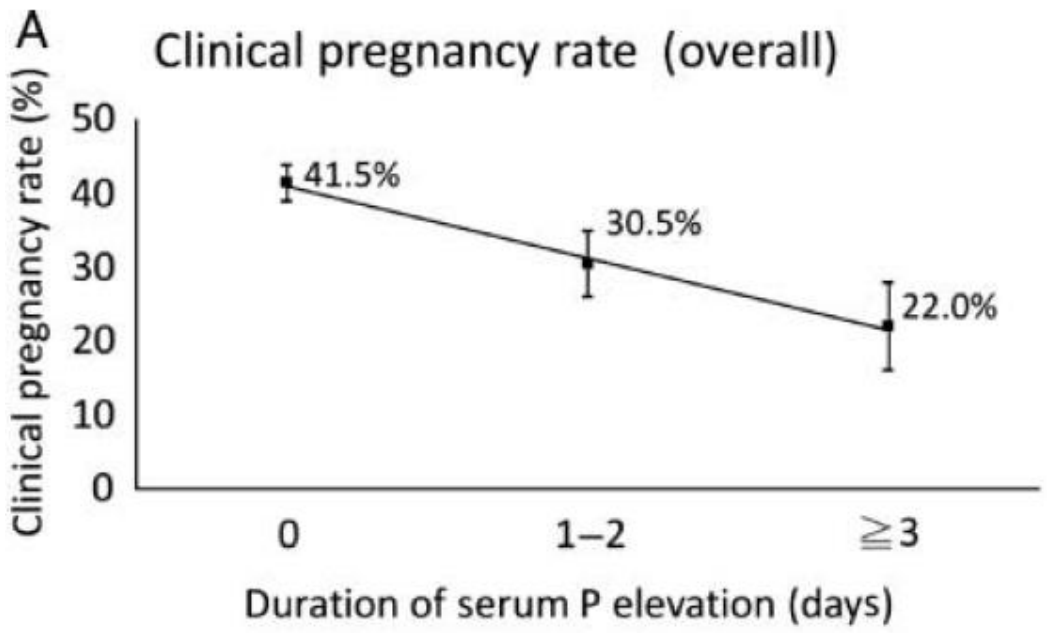
Human Reproduction, Vol.27, No.7 pp. 2036–2045, 2012
Advanced Access publication on May 4, 2012 doi:10.1093/humrep/des141

human reproduction ORIGINAL ARTICLE *Infertility*

The duration of pre-ovulatory serum progesterone elevation before hCG administration affects the outcome of IVF/ICSI cycles

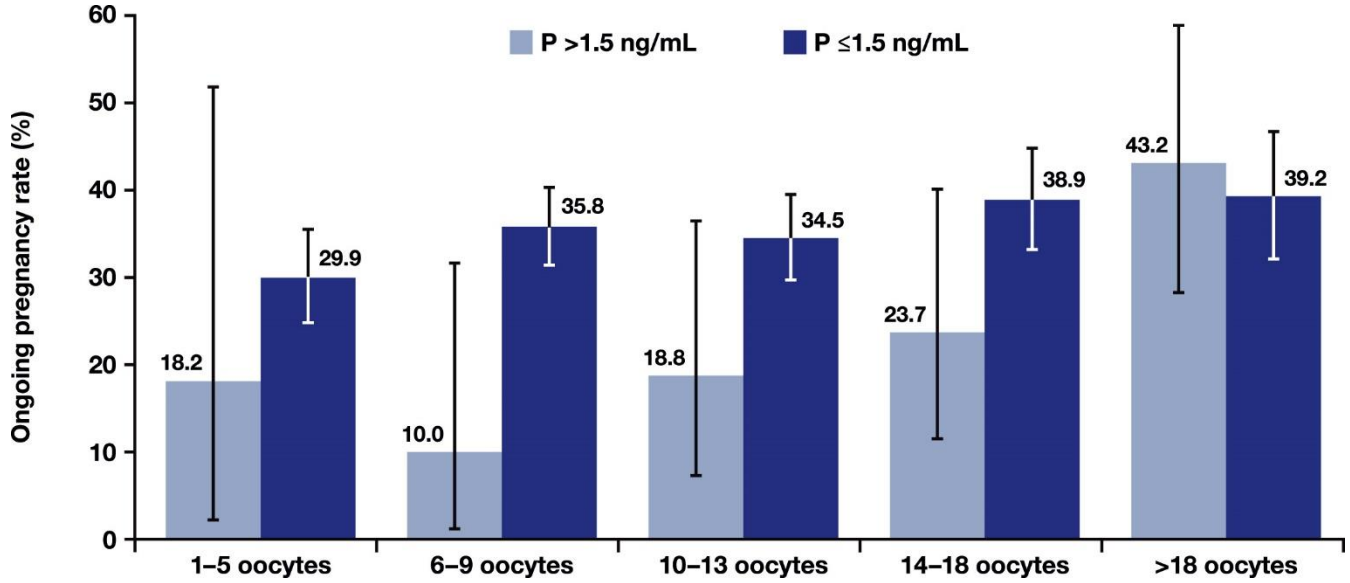
Huang et al.

- Retrospective, single-centre cohort study
- 1784 IVF and/or ICSI-ET cycles



Progesterone elevation does not compromise pregnancy rates in high responders

- Retrospective analysis from 6 clinical trials
- rFSH/GnRH antagonist protocol



Ongoing pregnancy rate per embryo transfer and associated 95% confidence interval by number of oocytes retrieved and serum P level on the day of hCG.

Griesinger et al. Fertil Steril 2013

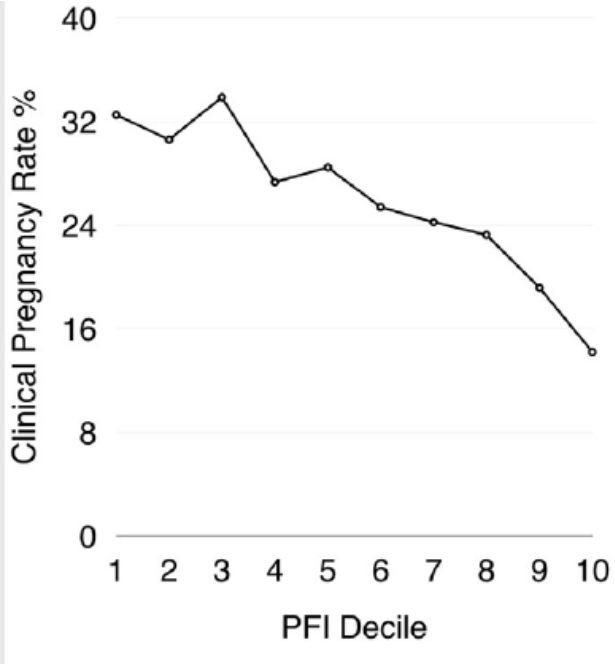
Progesterone-to-follicle index [PFI] is better correlated with in vitro fertilization cycle outcome than blood progesterone level

- Retrospective study
- 8,649 IVF cycles in normal responders

- PFI= Progesterone (nmol)
- #follicles ≥ 14 mm

Late elevations in follicular blood P:
[1] Increased P production per follicle - High PFI - detrimental
[2] the recruitment of additional follicles, with no change in the P secreted from each one of them - Low PFI – benign

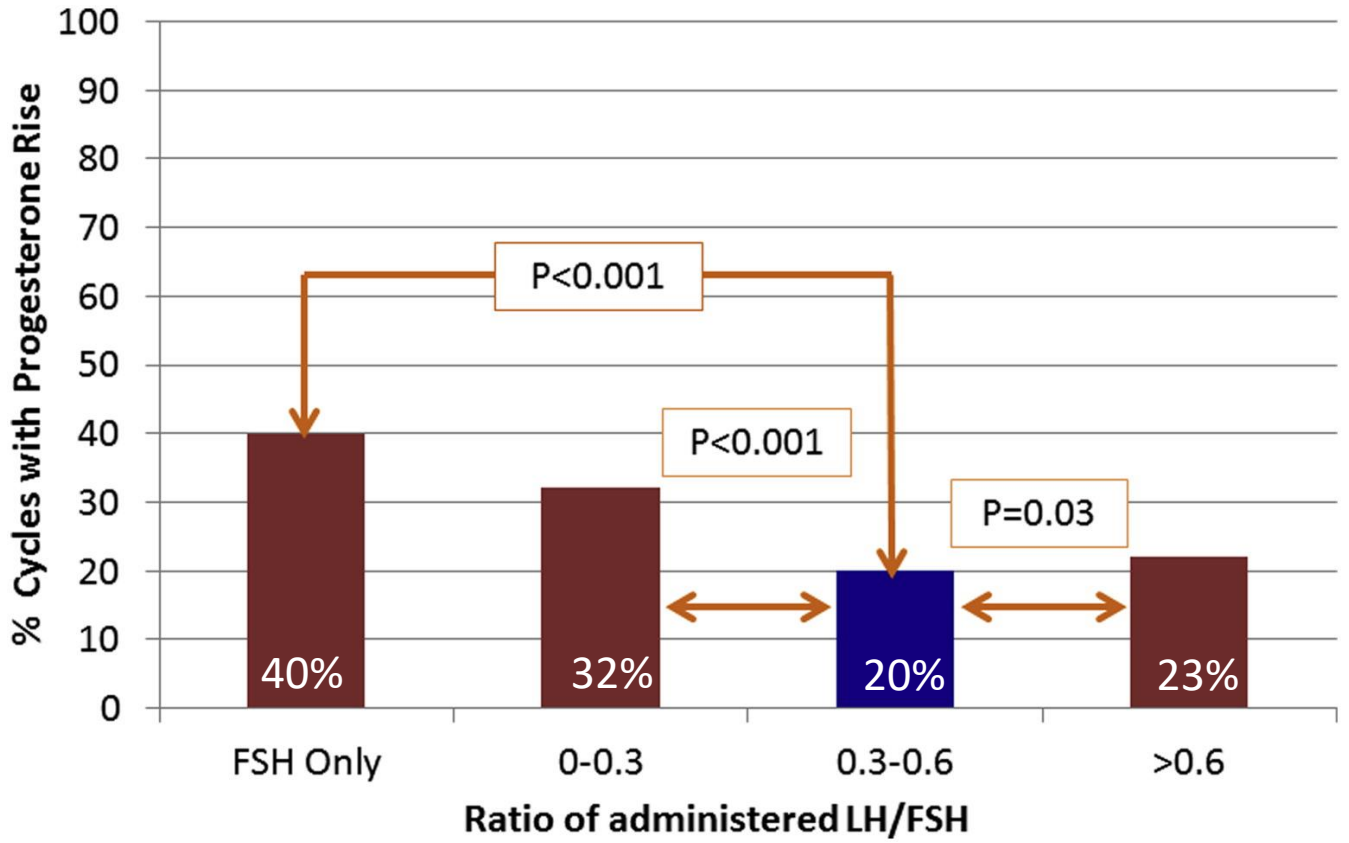
The PFI enables clinicians to differentiate these conditions



Shufaro et al. Fertil Steril 2015

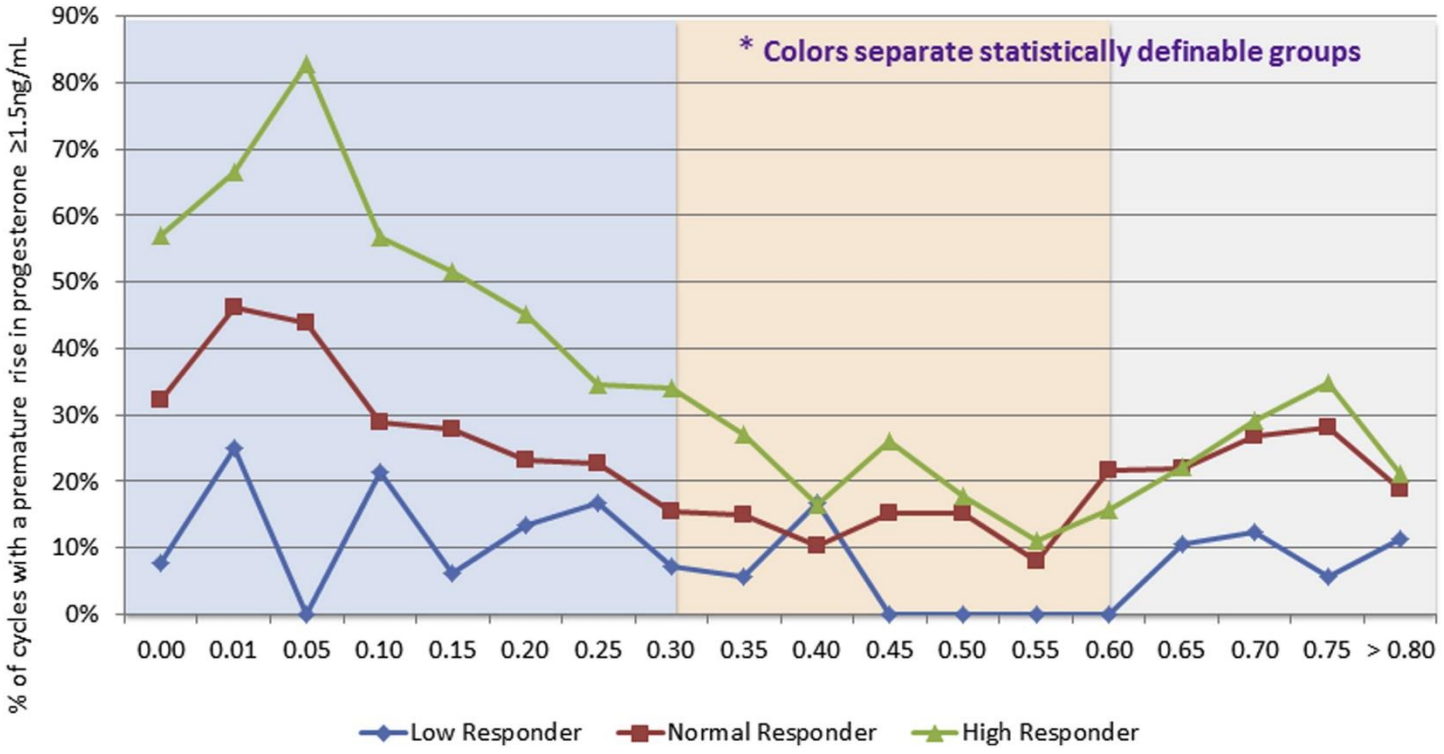
Progesterone elevation > 1.5 ng/mL and the ratio of total exogenous LH to-FSH dosing in stimulation

- 10280 first long agonist and antagonist cycles



Werner et al., Fertility and Sterility 2014 102, 1312-1317

The optimal ratio of exogenous LH-to-FSH to prevent a premature increase in P according to response group



- High response group - 37%
- Normal response group - 22%
- Low response group - 11%

P<0.001

Werner et al., Fertility and Sterility 2014 102, 1312-1317

Clinical practice: Preventing premature progesterone rise

- Progesterone elevation is strongly correlated to the intensity of stimulation
- Measurement of serum P is required before ovulation triggering
- P threshold should be individually defined in each center
- The starting FSH dose should be individually adjusted so as to not surpass the objective of getting 8–12 oocytes
- GnRH antagonist protocol should be preferred
- FSH should not be increased during ovarian stimulation because granulosa cells become highly sensitive to FSH
- Use of LH activity products - controversial

Sonigo et al, RBM Online 2014

Clinical practice: Which strategy in case of P elevation?

- In the case of gradual increase in serum P during ovarian stimulation,
  consider triggering ovulation earlier

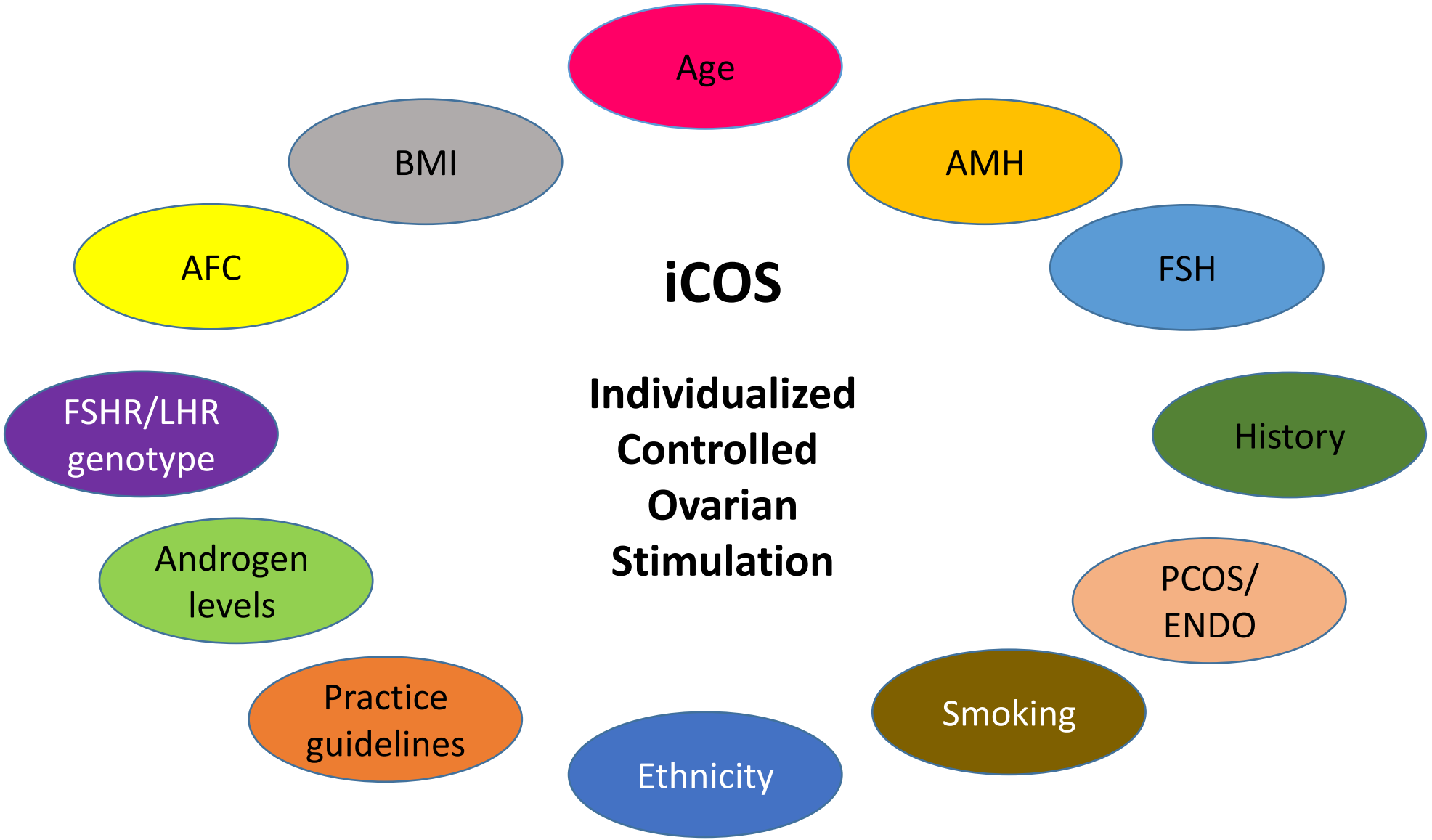
Kyrou et al., Fertil Steril 2011

- Administration of dexamethasone during ovarian stimulation
  may reduce the adrenal contribution to P secretion

Fanchin et al., Fertil Steril 1997

- Cancellation of oocyte retrieval is not recommended
- P elevation does not have any impact on oocyte quality
- Embryo transfer should be deferred
- Freezing the whole cohort of oocytes or embryos

Sonigo et al., RBM Online 2014


Age
BMI
AMH
AFC
FSH
iCOS
Individualized
Controlled
Ovarian
Stimulation
FSHR/LHR
genotype
History
Androgen
levels
PCOS/
ENDO
Practice
guidelines
Smoking
Ethnicity

Why iCOS?

- Huge diversity in the population of infertile patients
- Individualization of a therapeutic strategy
- Prediction of extremes of ovarian response
- Correct selection of GnRH analogue
- Fine tuning of the gonadotropin dose
- Reduced risks and dropouts
- Reduced treatment burden

Table III Comparison of characteristics of the most widely used markers of ovarian reserve (modified with permission from La Marca *et al.* (2010)).

Characteristics for a Good Marker	Age	AMH	FSH	AFC
Prediction of poor response	+	+++	++	+++
Prediction of hyper response	+	+++	+	+++
Low inter-cycle variability	+++	++	−	++
Low intra-cycle variability	+++	++	−	++
Applicable to all patients	+++	++	+	+
Economic	+++	−	−	−

−, not appropriate; +, not very appropriate; +++, very appropriate. AFC, antral follicle count; AMH, anti-Mullerian Hormone.

Human Reproduction Update, Vol. 20, No.I pp 124 -140, 2014

796 units
593,200 cycles

RESEARCH & EDUCATION

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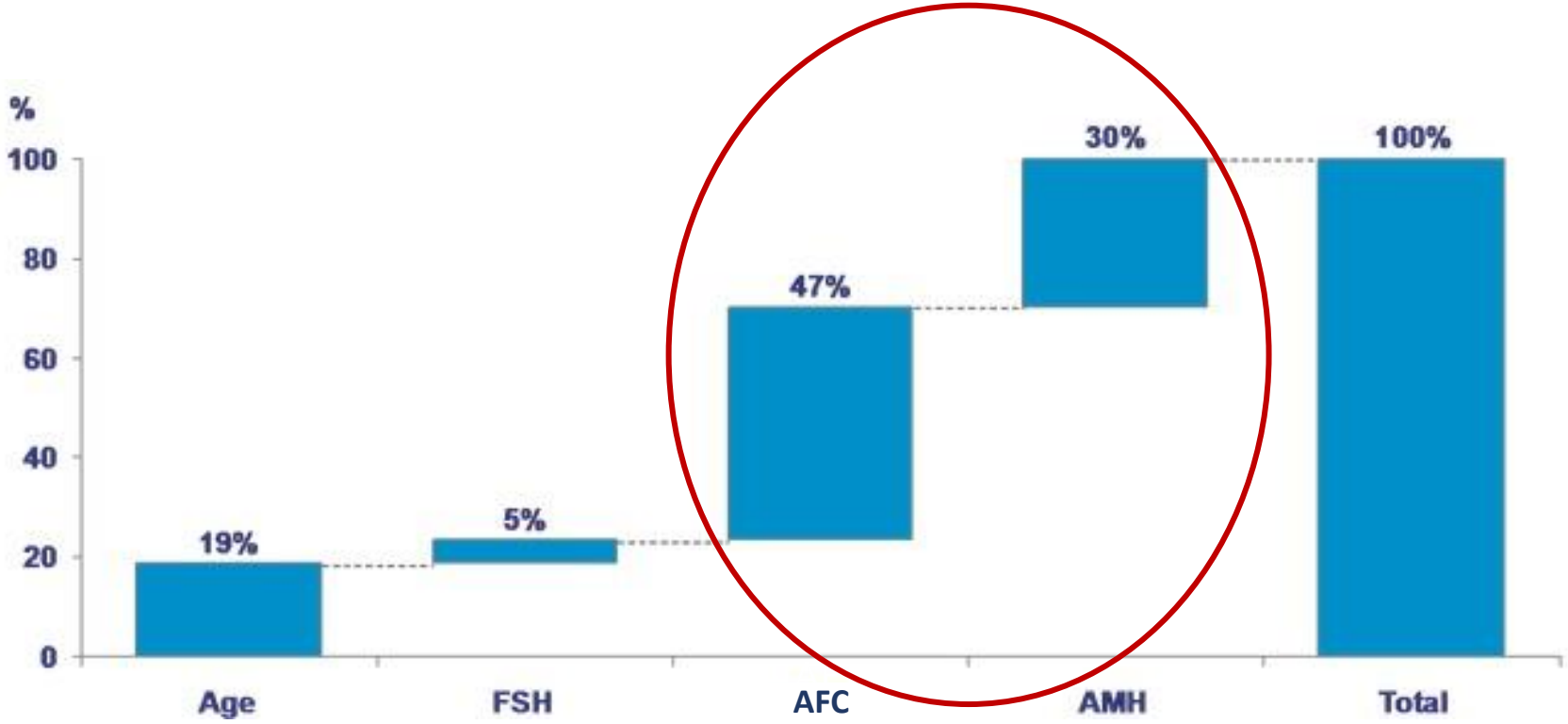
BACK

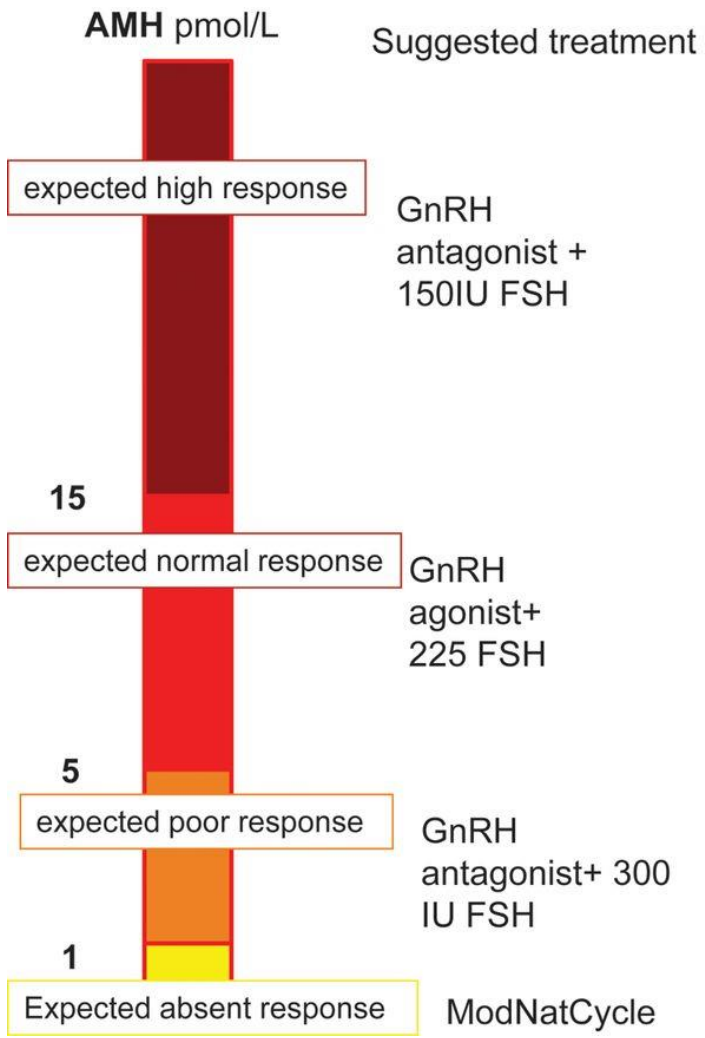
Anti-Mullerian hormone (AMH) and antral follicular count (AFC)

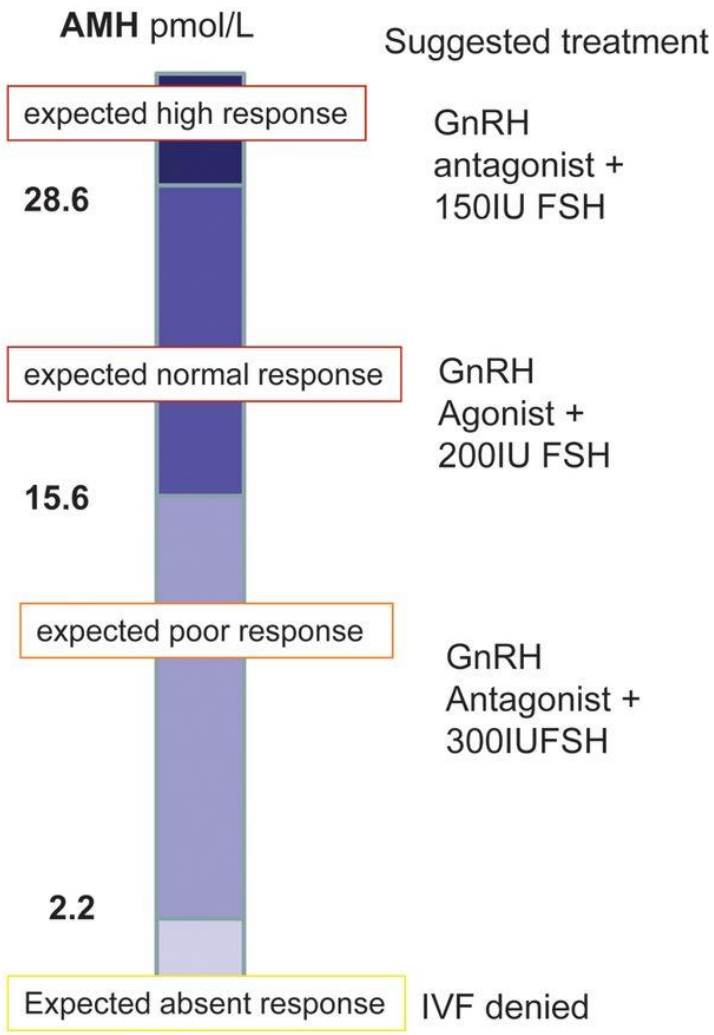


Question:

If you had to choose one of the factors listed below,
which would serve you best in assigning the starting gonadotropin dose ?

Strategic modelling of controlled ovarian stimulation on the basis of ovarian reserve markers





La Marca and Sunkara Hum. Reprod. Update 2014;20:124-140

The future: increased IVF success through the development and implementation of iCOS

AMH and AFC are currently the best biomarkers to predict ovarian response to iCOS

iCOS guided by such biomarkers is aimed to maximize the beneficial effects of treatment while minimizing complications and risks

iCOS should result in a better cycle final outcome and a more cost-effective approach

iCOS is still at its infancy…..

Needs to be validated in independent and prospective studies…

iCOS – Current recommendations

- Flexible GnRH antagonist protocol
- OCP or luteal estradiol with accelerated folliculogenesis
- 75-450 IU starting dose
- Use history, age, AMH, AFC, FSH, BMI for dosing
- Aim at 8-12 oocytes
- FSH:LH 2:1
- hCG/GnRH-trigger/dual trigger
- Segment the cycle if:
- Progesterone elevation/OHSS risk/no plan for fresh ET
- Good luck!


TEL AVIV
Thank You