

Individualization of COS is the right tool to optimize ART success

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Context

Historical

- Monumental growth of ART in 40 years
- iCOS protocols are at the helm
- Universality of clarity and acceptance for effective shift to iCOS

Needed

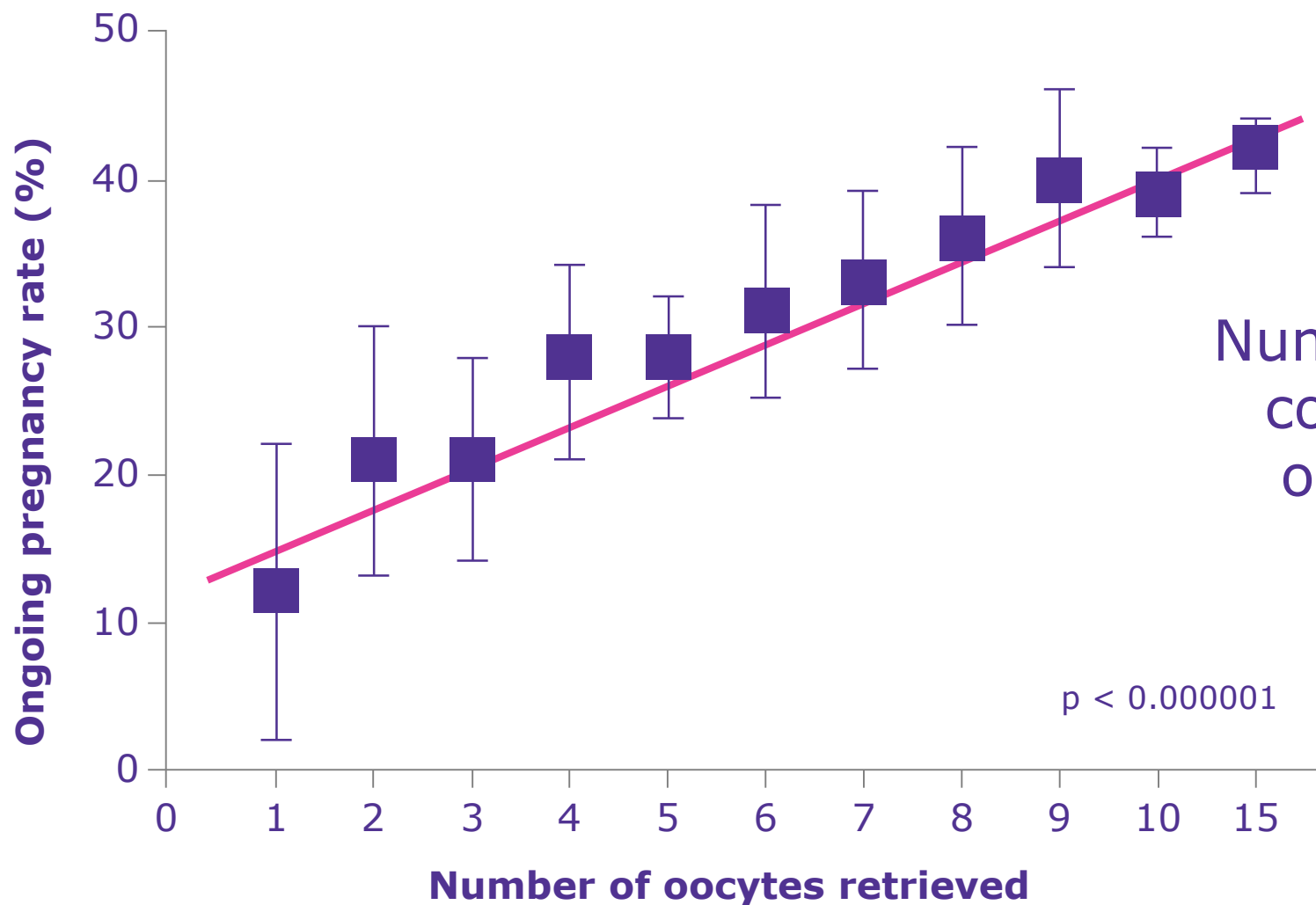
- Predictability of stimulation outcomes
- Objective individual consideration in application of stimulation protocols

Objective in ovarian stimulation

- Multifollicular development in order to enhance chances of transferring embryos with the highest implantation potential
- Avoidance of high cycle cancellation rates (up to 35%) due to poor- and hyper-responders

Unpredictability of response have made the need for search of individualized stimulation strategy discernible

Relationship between number of oocytes retrieved and ongoing pregnancy rate



Number of oocytes retrieved correlates positively with ongoing pregnancy rate

Key milestones in evolution towards iCOS

- Pituitary down-regulation:
 - Enabled ovarian control and reduced frequency of cycle cancellation
- Biomarkers with high predictive value:
 - AMH: a marker of magnitude of ovarian response in ART, a good predictor of OHSS
 - AFC (functional biomarker): indicator of primordial follicles pool, correlates well with AMH
- Recognition of impact of age as a factor in OS

Important considerations in iCOS

Patient characteristics:

- Age
- Ovarian reserve
- Endometriosis
- PCOS
- BMI

Treatment should be:

- Efficacious
- Patient-friendly
- Safe

Aspects of individualization:

- Starting dose
- Choice of protocol (agonist/antagonist)
- Adjuvants
- Trigger

Issues yet to be resolved

- Higher precision in prediction of outcomes
- Identification of abnormal variants of FSH receptor
- Abnormalities of gene coding for LH and its receptors

Characteristics of potential markers for response to COS

Characteristics of an effective 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	+++	+++	+	+
Low cost of applying test	+++	-	-	-

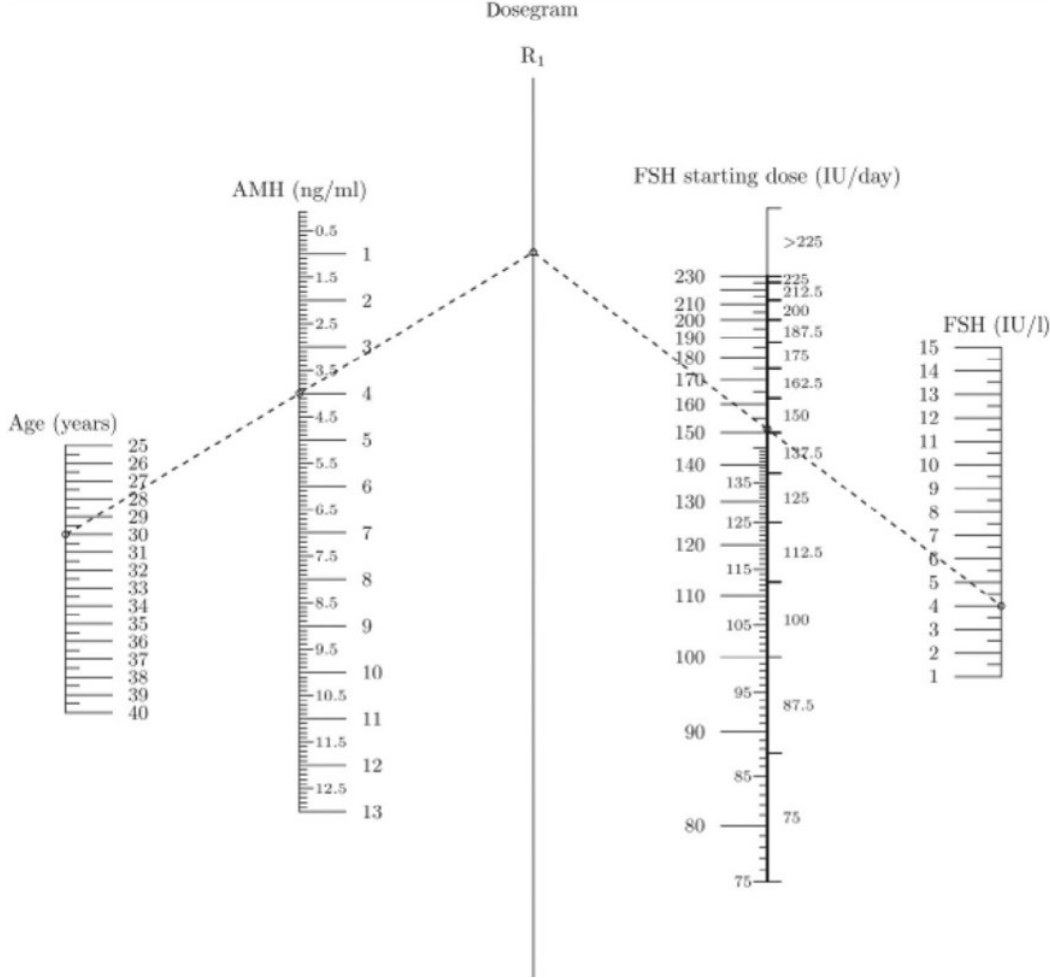
+++ indicates degree to which characteristic is present.
AFC, antral follicle count; COS, controlled ovarian stimulation.

Impact of age on live birth rates in OS

Age (years)	LBR (%)
< 35	80
35–39	61
≥ 40	26

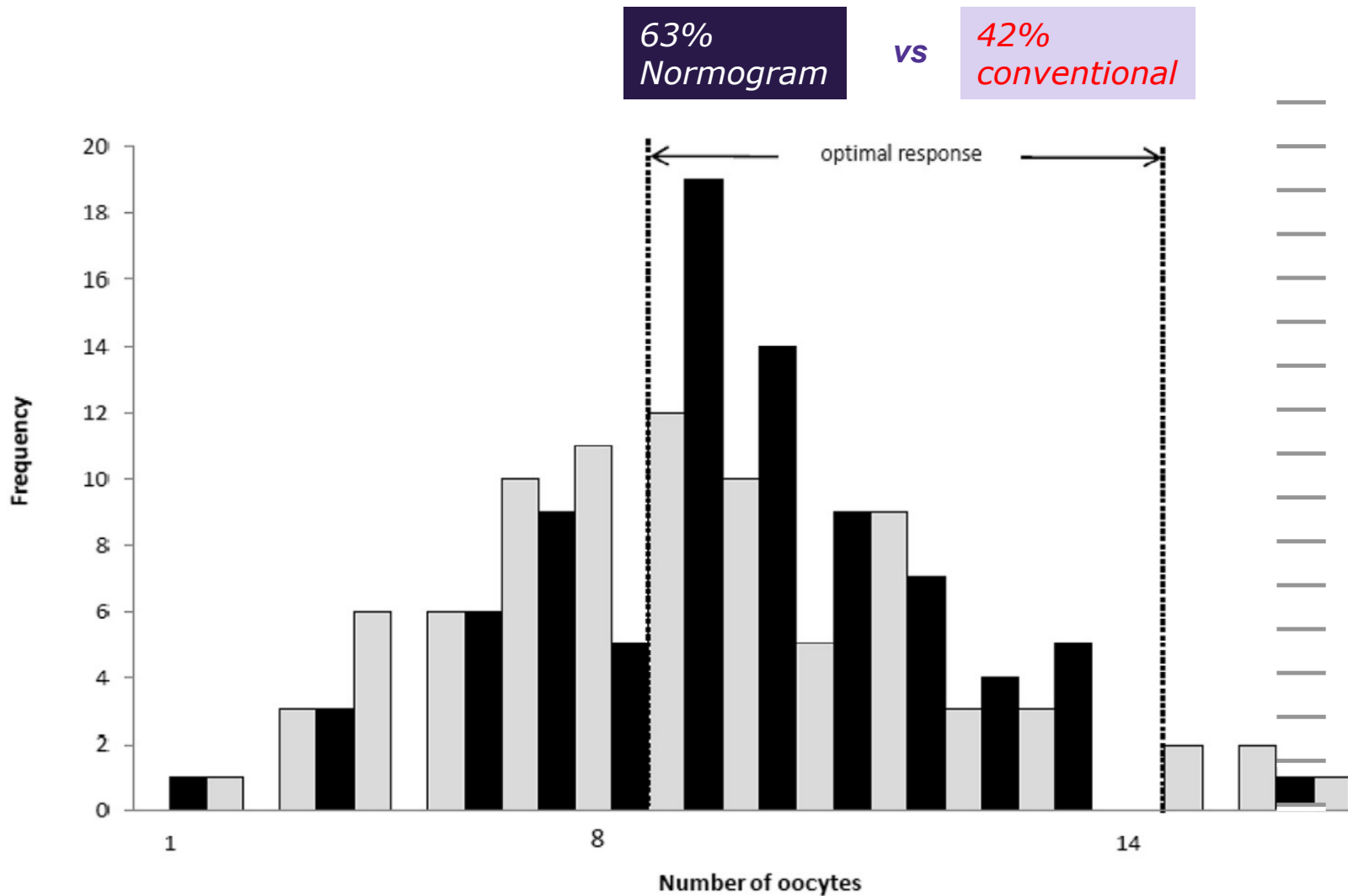
Indicative of a need for age-based iCOS

Predictive normogram for starting FSH dose



Use of predictive normogram to determine the initial dose of FSH helps to individualize stimulation protocols

Allegra A, Marino A et al. Reprod Biomed Online 2017;34(4):429-438



Use of predictive normogram to determine the initial dose of FSH resulted in significantly larger proportion of patients with optimal response than in the arm with fixed FSH dosage – this supports the benefit of iCOS

Allegra A, Marino A et al. Reprod Biomed Online 2017;34(4):429-438

AMH tailored protocols vs conventional COS: changes attributable to iCOS

Aspect	Change
Embryo transfer rate	79% to 87%
Pregnancy rate per cycle	17.9% to 27.7%
Live births per cycle started	15.9% to 23.9% p = 0.007
Fall in OHSS	96.9% to 2.3%
Fall in fertilization rate	2.8% to 4.5% p = 0.066

Hyperstimulation

- The joy of achieving multifollicular stimulation with urinary gonadotropins was counteracted by the disappointment of OHSS as a by-product
- hCG-triggered excessive release of VEGF from increased mass of granulosa cells causes increased vascular permeability, with resultant increased fluid shift to the third compartment
- Worst situations: multi-organ thrombotic phenomenon and cardiorespiratory embarrassment

Individualized care in OHSS

Prediction: biomarkers

- AFC > 14 (sensitivity 82%, specificity 89%); AMH: similar predictive values
- Activating FSH receptor mutations confers higher response, but this has not yet been exploited

Prevention

- Choice of stimulation protocol: antagonist/agonist protocol
- Trigger strategy: low hCG dosage; antagonist

OHSS: secondary preventive measures

- In vitro maturation: still experimental
- Coasting: FSH withdrawal until estrogen levels are $< 3,000$ pg/ml due to granulosa-cell apoptosis in small susceptible follicles
- Pre-iCOS metformin (2 months)
- Cycle cancellation
- Dopamine agonist (cabergoline): prevents phosphorylation of VEGF
- Progesterone, and not hGC, for LPS
- Albumin i.v.

Treatment targets the correction of specific pathophysiological events

Duostimulation (DuoStim)

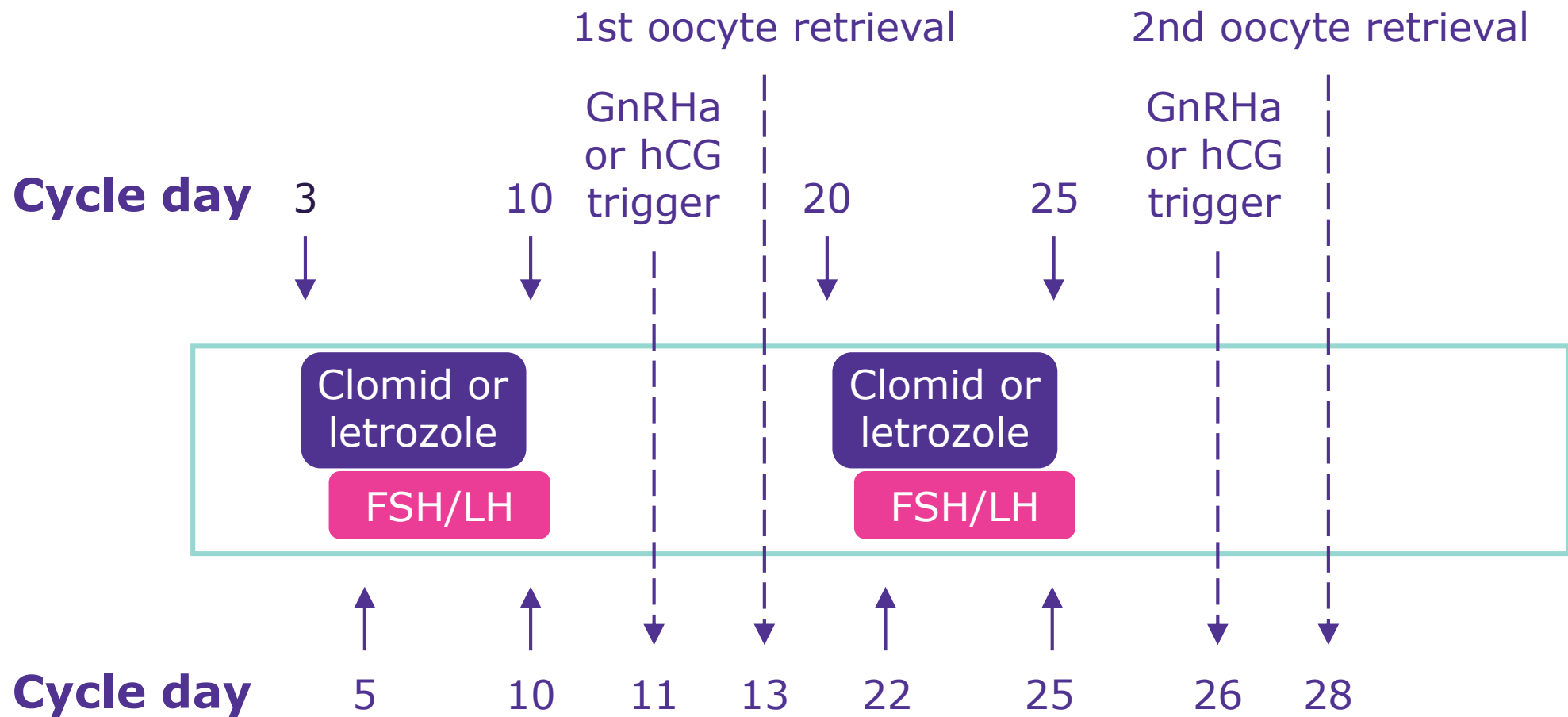
- Double stimulation in the same IVF cycle – a follicular and luteal phase stimulation
- Based on a new theory that other than the follicular cohorts, there exist waves of recruitable groups of oocytes
- Individualization is through:
 - Optimizing number of euploid oocytes in poor responder, especially the older one
 - Optimizing a freeze all strategy for pre-treatment cancer patient where time is of essence

Comparison of laboratory results for conventional protocol with DuoStim

	Conventional	DuoStim	P-value	Odds ratio (CI)
Collected oocytes, n	6.7 (2–13) ^a	11.7 (1–28)	0.007	
Mature oocytes, n	5.3 (2–11) ^a	9.23 (1–25)	0.010	
Fertilized, %	73.6 (51/69)	75.8 (91/120)	0.769	0.90 (0.46–1.78)
Blastocysts, %	51.16 (22/43)	46.2 (43/93)	0.593	0.82 (0.40–1.69)

^a Median (range).

DuoStim protocol



Conclusion

iCOS optimizes OS outcomes
and enhances safety in OS

THANK YOU