

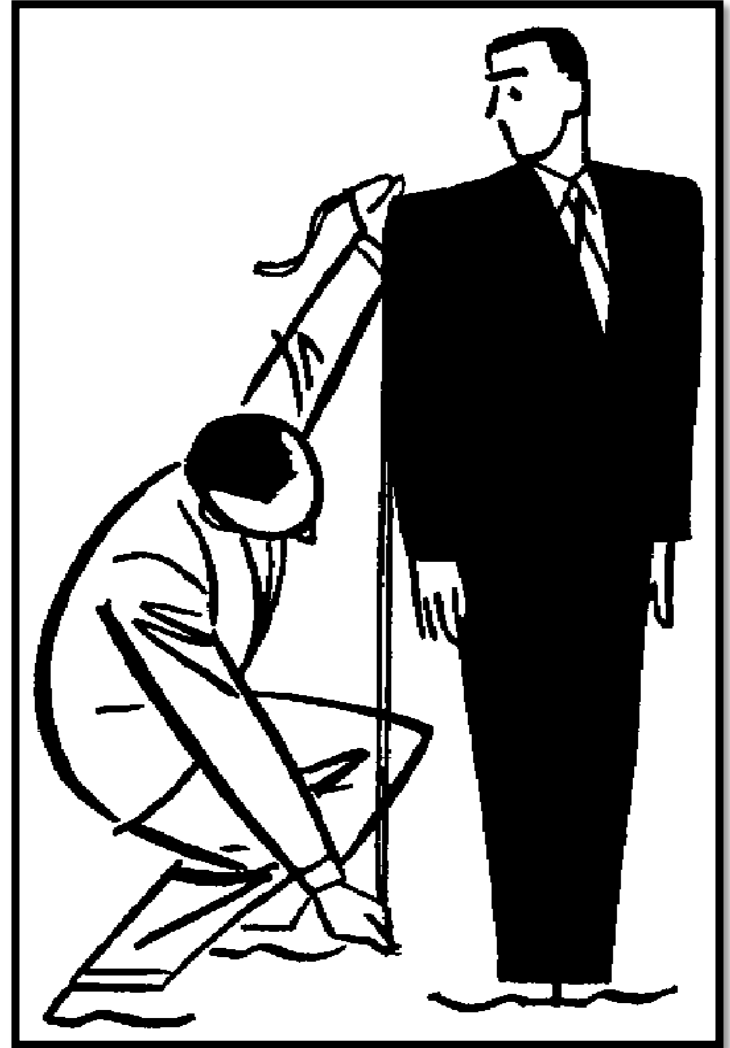


Individualized controlled ovarian stimulation (iCOS)

Gurkan BOZDAG, M.D.

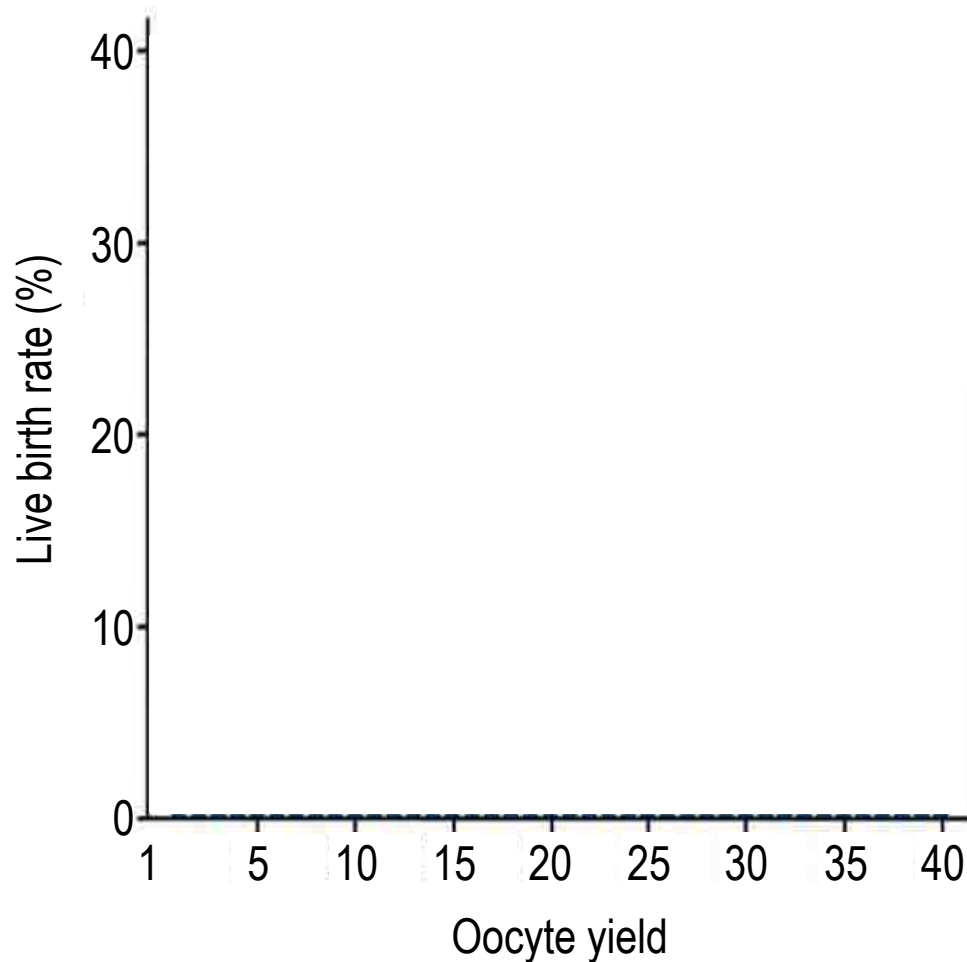
Dept. of OBGYN, School of Medicine Hacettepe
University, Ankara, TURKIYE

Tailoring the COS (iCOS)



- EFFICACY
 - Achieve max LBR by attaining optimum number of oocytes
- SAFETY
 - Avoid excessive response and minimize risk of OHSS
- BURDEN
 - Physical and psychological

We want an optimal oocyte yield



Sunkara SK et al Hum Reprod. 2011 Jul;26(7):1768-74

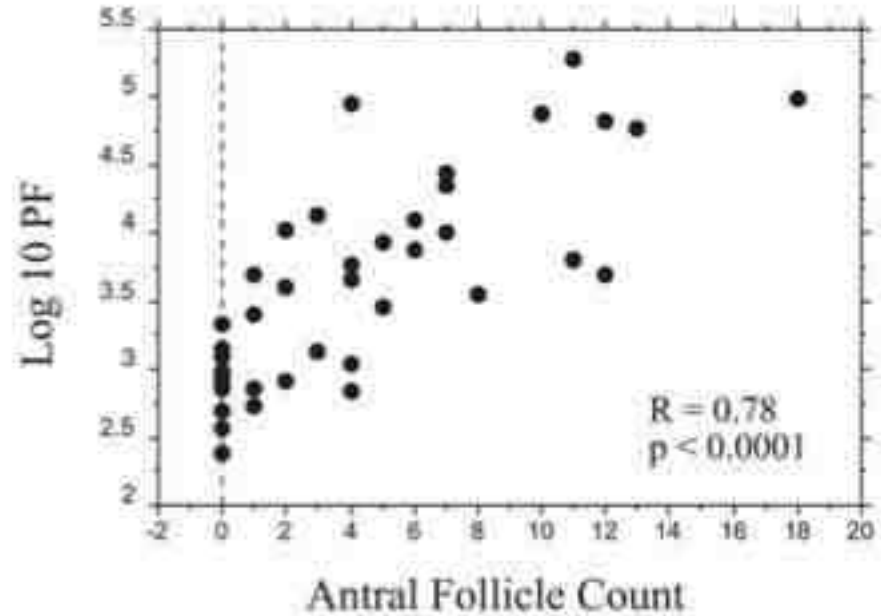
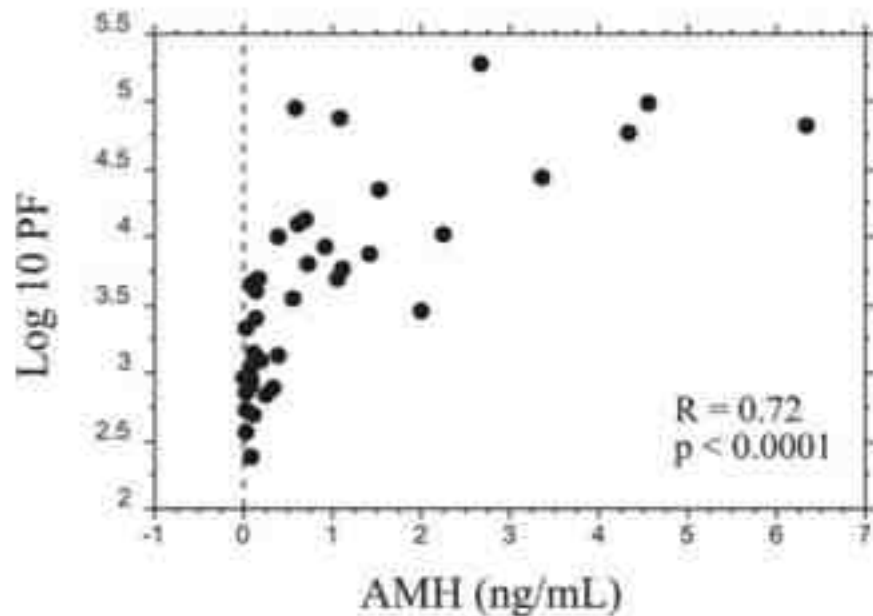
We want an optimal oocyte yield...

- Van der Gaast et al-2006 - **13 oocytes**; below and above PRs are compromised (n=7,422)
- Verberg et al-2009 - 5 for mild stimulation and **10 oocytes** for conventional stimulation (meta-analysis ; mild-313 cycles ; conventional-279 cycles)
- McAvey et al-2011 - Yielding **>6 MZ** does not further improve live birth rates (n=737)
- Bosch et al-2011 - LBR + **15 oocytes** maximize the chances of pregnancy (n=7954)
- Ji et al-2013 - Optimal - **6-15 oocytes** for LBR below and above PRs are compromised; however, cumulative LBR increase with increasing oocyte number (n=2,455)
- Fatemi et al-2013 - A high ovarian response **18 oocytes** does not jeopardize LBR in fresh ET's and even is associated with increased cumulative PR (Engage; n=1,506)

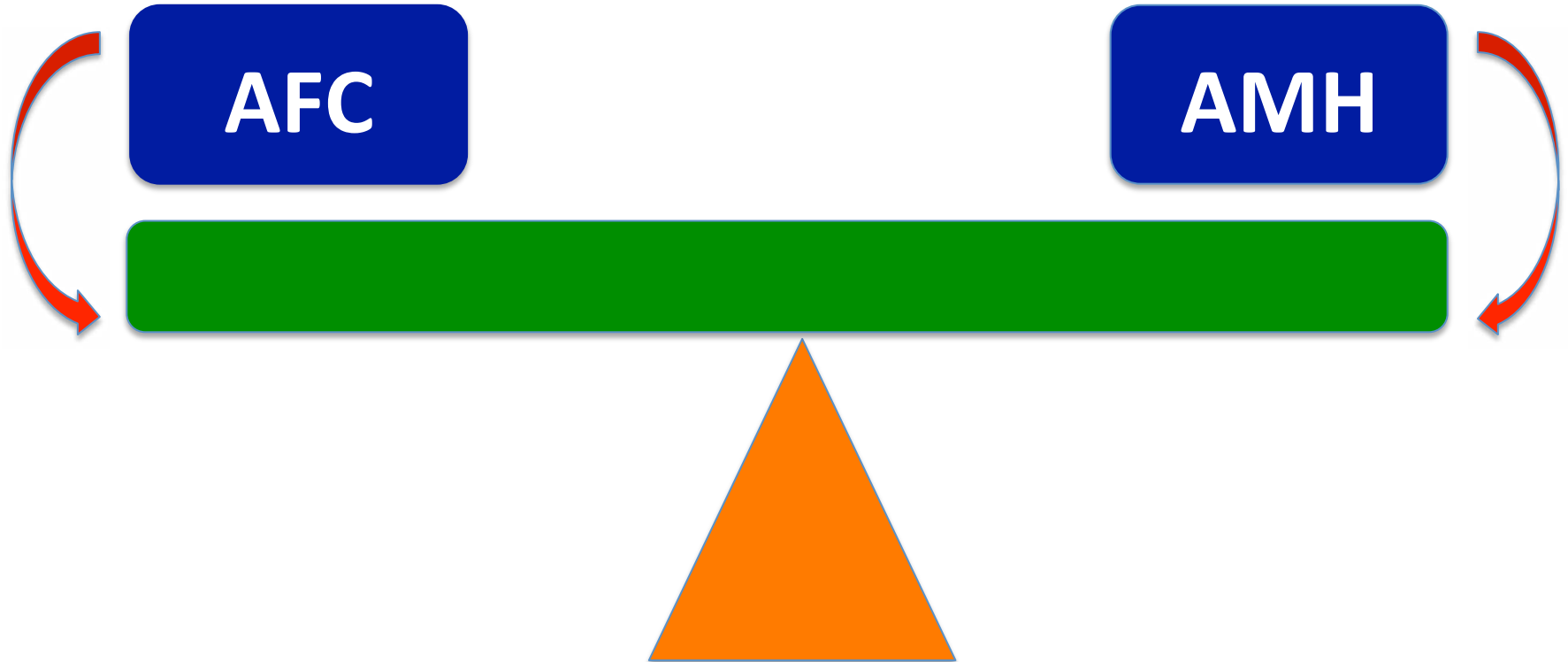
8 - 15 Oocytes Retrieved

How to predict “optimal response” ?

**Both AFC and AMH correlate well with
primordial follicle number**

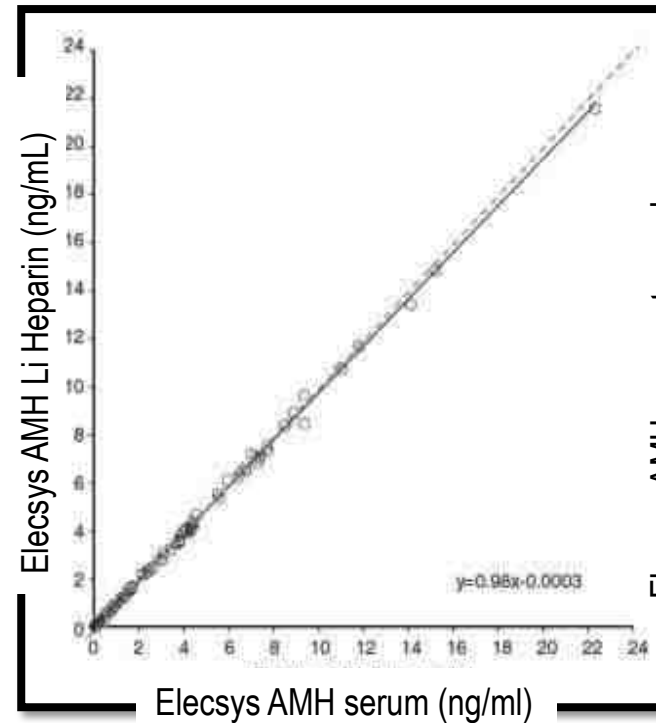


Which one ?

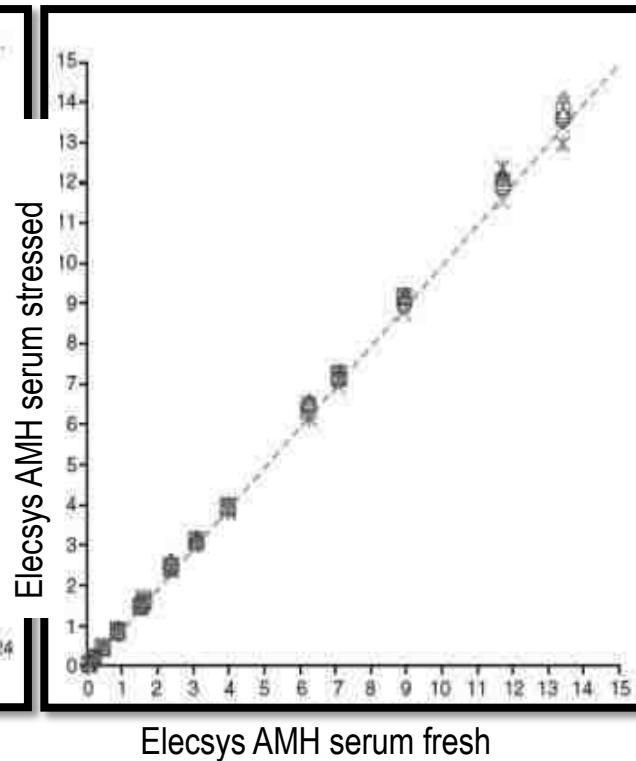


AUTOMATED ASSAYS

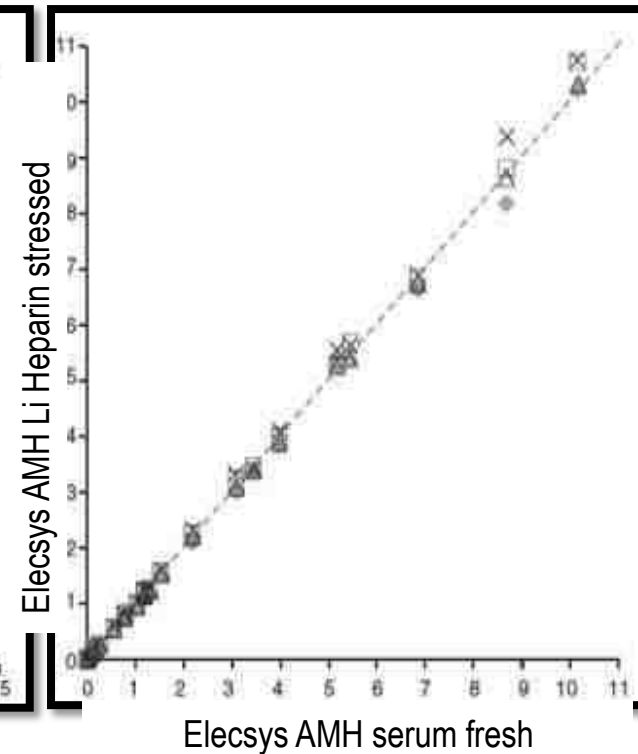
(Elecys-Roche; Access-Beckman Coulter)



Robust to
type of collection

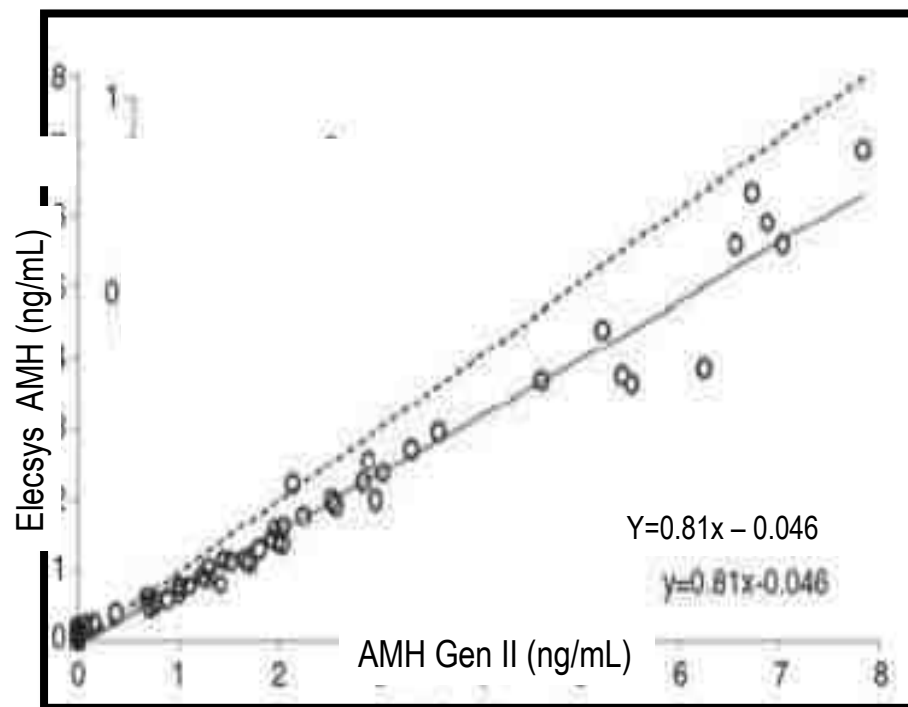


Robust to sample
storage temperature



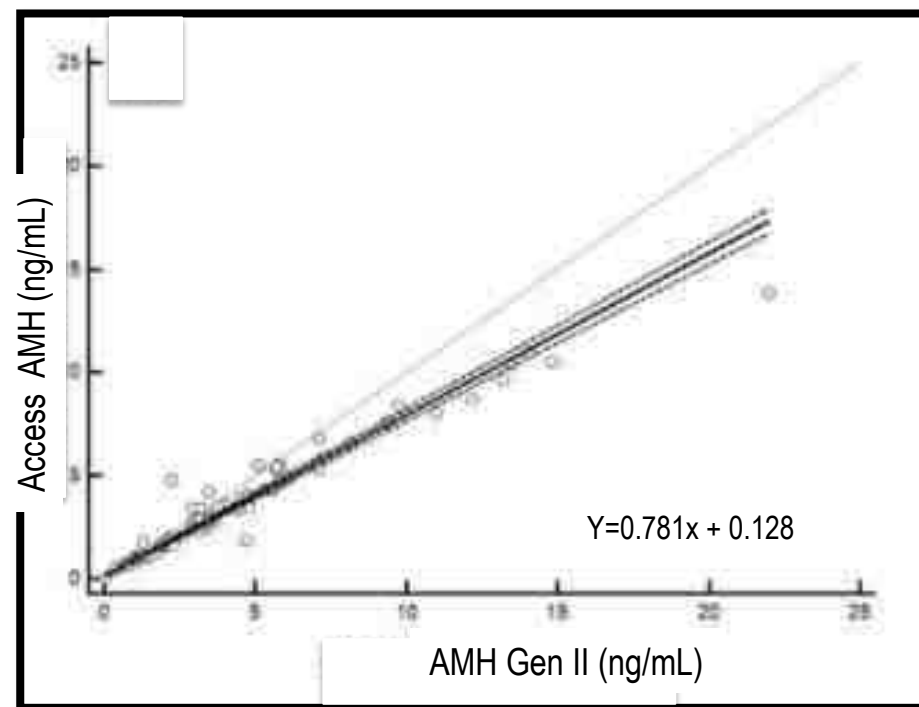
Robust to short
and long-term storage

New reference ranges again...



20% lower than AMH Gen II

Gassner and Jung Clin Chem Lab Med 2014



10-15% lower than AMH Gen II

Nelson et al. Fertil Steril 2015

INTERNATIONAL STANDARDIZATION OF MEASUREMENT IS URGENTLY REQUIRED

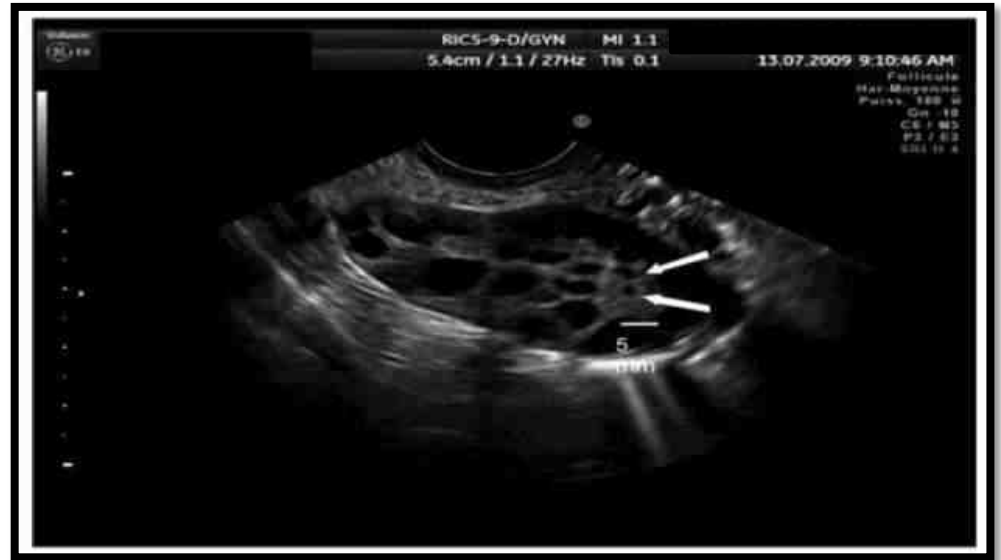
What about AFC?

The AFC assay has also changed..

2001



2009



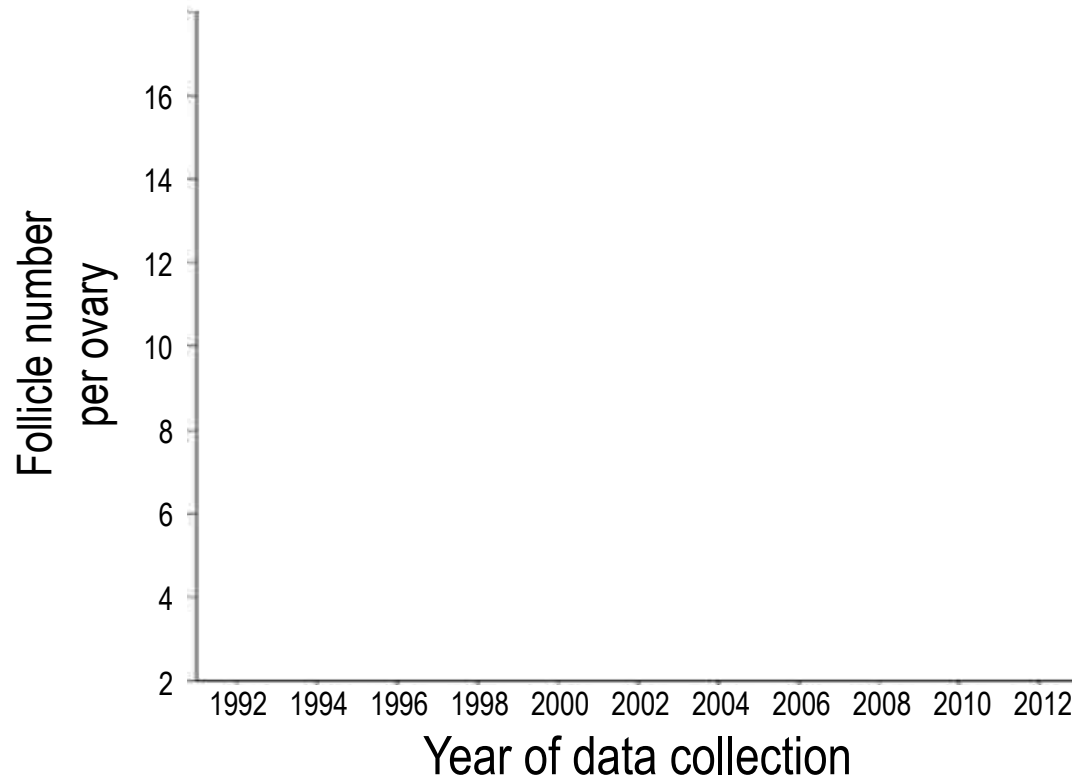
Dewailly, et al Hum Reprod Update 2011

Normal is now <25 follicles per ovary

Healthy
control
women

Max
Transducer
Freq (MHz)

6
7
7.5
8
8.5
9
12



Dewailly, et al Hum Reprod Update 2011

***What about
nomogram?***

Nomogram ?

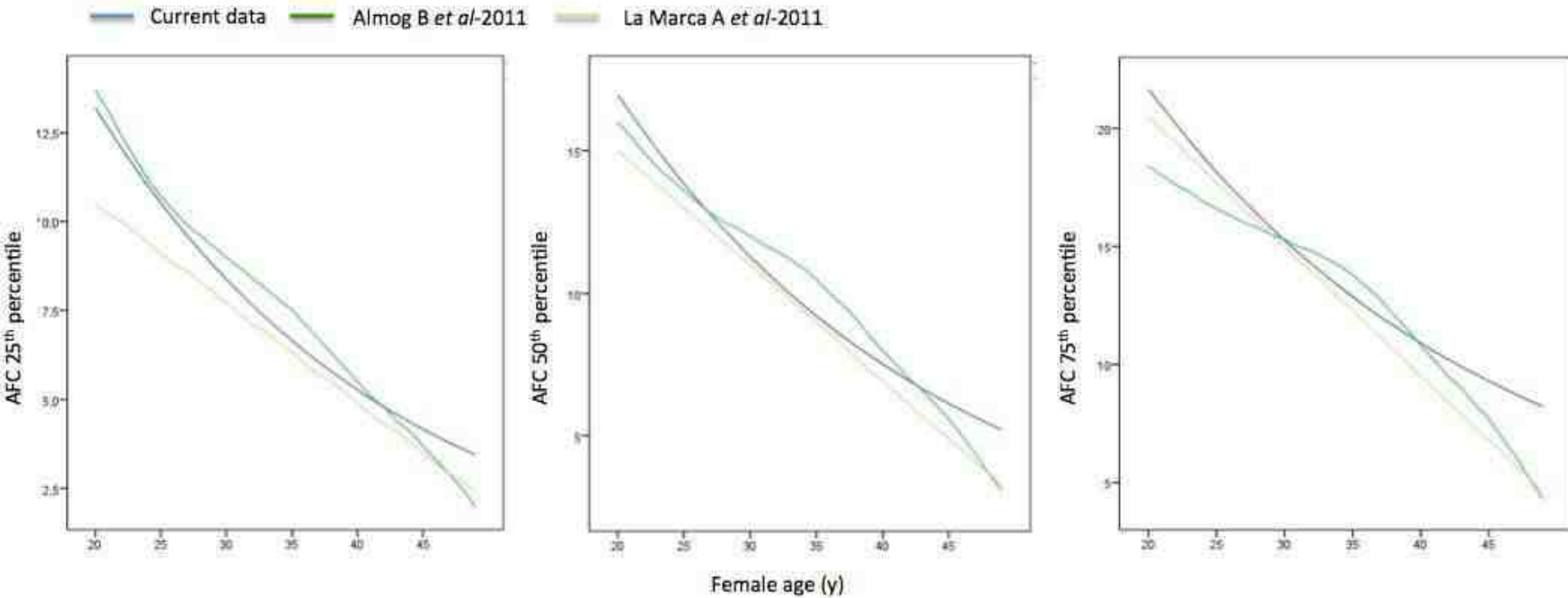


- Prospective, cross-sectional.
- Inclusion criteria:
 - (1) female age 20 – 50,
 - (2) regular menstrual bleeding between 21 to 35 days,
 - (3) being during the menstrual period of D1 to D12 and
 - (4) optimal visualization of both ovaries.
- The exclusion criteria were
 - (1) any hormonal drug or oral contraceptive pill use within the last 6 months,
 - (2) history of endometrioma cystectomy or detection of current endometrioma at the time of ultrasonography,
 - (3) impropriety for transvaginal probe application due to virginity and
 - (4) pregnancy.
- The status of fertility was not a criterion while deciding to include or exclude.



Female age (y)	5	100	250	500	750	900
20	4	10.5	13.2	17.0	21.7	26.8
21	9	10.0	12.6	16.7	20.9	26.0
22	13	9.5	12.1	15.6	20.2	25.3
23	18	9.0	11.6	15.0	19.5	24.5
24	22	8.5	11.0	14.4	18.8	23.8
25	19	8.2	10.5	13.8	18.1	23.1
26	17	7.8	10.1	13.3	17.5	22.4
27	20	7.4	9.6	12.8	16.9	21.8
28	18	7.1	9.2	12.3	16.3	21.2
29	16	6.7	8.8	11.8	15.8	20.6
30	17	6.4	8.4	11.3	15.3	20.0
31	19	6.1	8.0	10.8	14.7	19.5
32	21	5.8	7.6	10.4	14.2	19.0
33	18	5.5	7.2	10.0	13.8	18.5
34	12	5.2	7.0	9.8	13.3	18.0
35	14	5.0	6.7	9.2	12.8	17.5
36	15	4.7	6.4	8.8	12.3	17.1
37	12	4.5	6.1	8.5	12.0	16.7
38	16	4.3	5.8	8.2	11.7	16.3
39	18	4.1	5.5	7.8	11.2	15.9
40	17	3.9	5.3	7.5	10.8	15.5
41	11	3.7	5.0	7.2	10.6	15.2
42	20	3.5	4.8	6.9	10.2	14.8
43	16	3.3	4.6	6.7	9.8	14.5
44	7	3.2	4.4	6.4	9.6	14.2
45	12	3.0	4.2	6.1	9.3	13.8
46	4	2.9	4.0	5.9	9.0	13.7
47	9	2.7	3.8	5.7	8.7	13.3
48	11	2.6	3.6	5.4	8.5	13.2
49	6	2.5	3.5	5.2	8.2	13.0
50	2	2.3	3.3	5.0	8.0	12.8

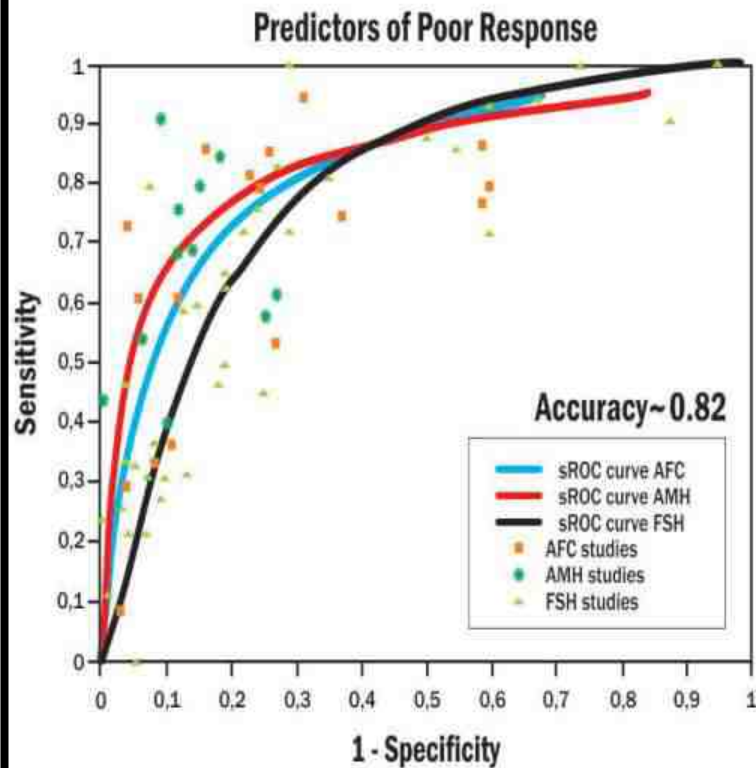
Nomogram ?



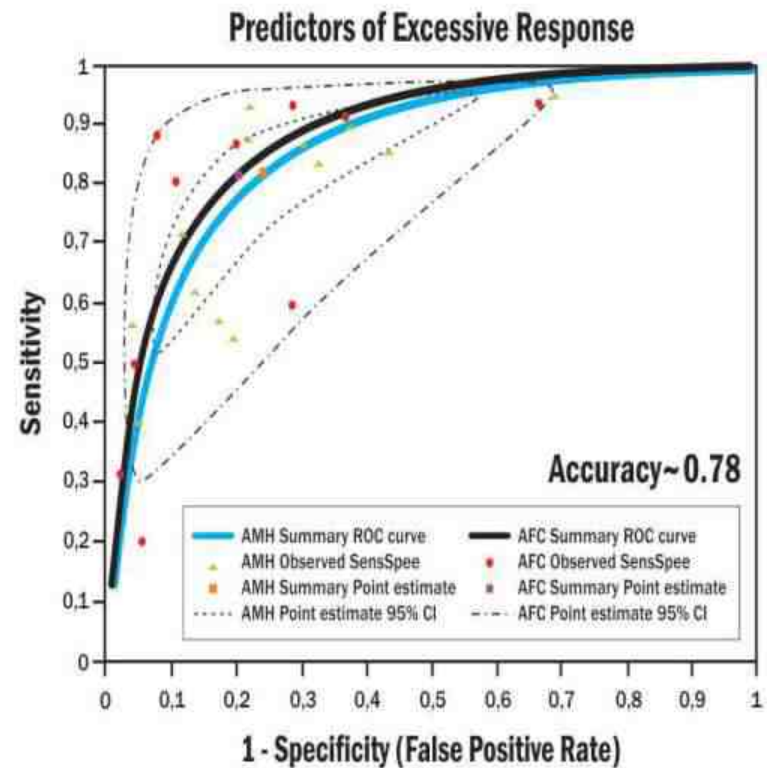
Annual decrease in AFC was 0.41 (0.40 and 0.35 in previous studies)

Who is who before iCOS?

AMH ~ AFC > FSH > Age

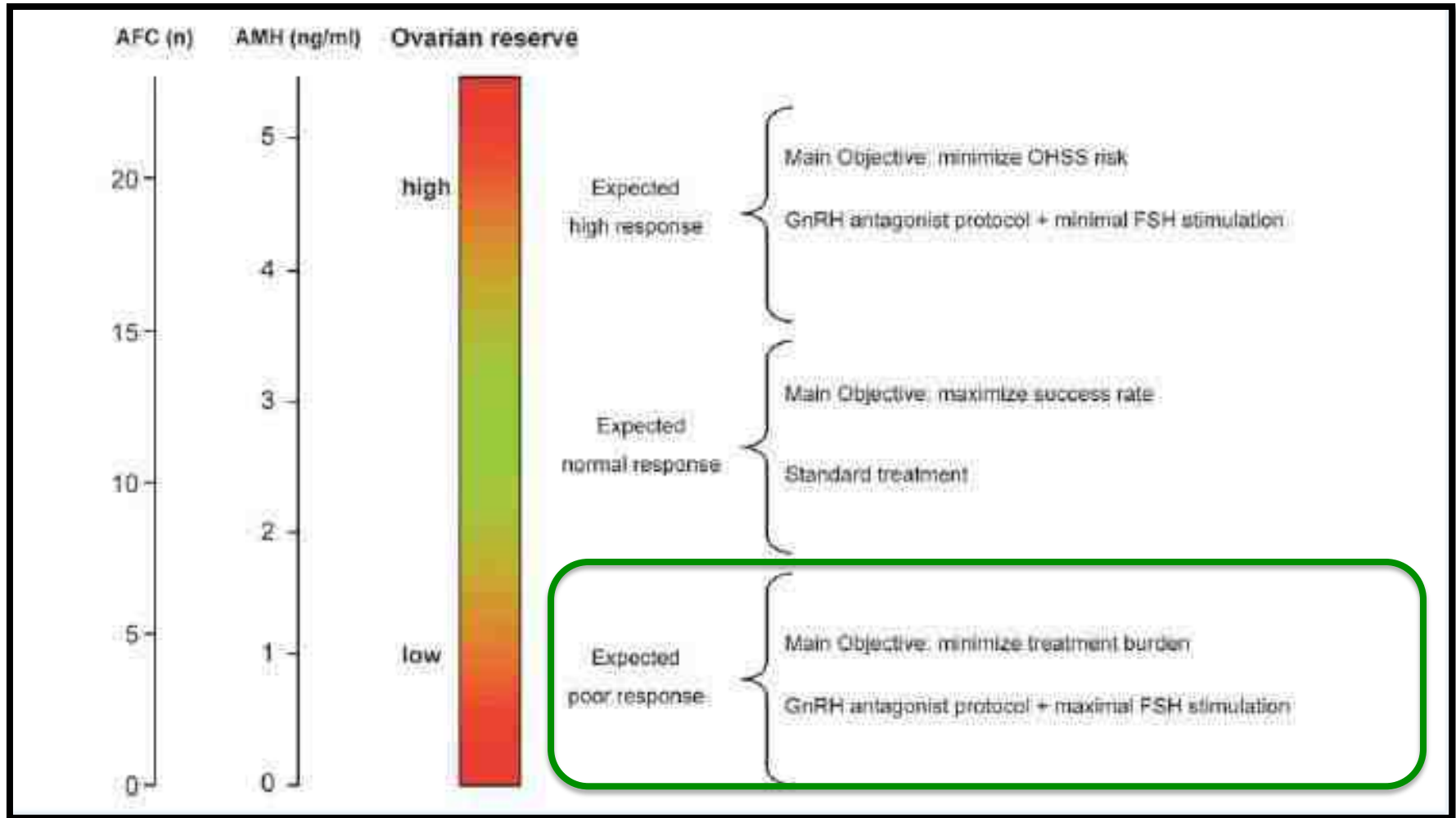


Broer et al. Fertil Steril 91:705; 2009



Broer et al. Hum Reprod Update 17:46; 2011

Main objectives for iCOS...



iCOS-Decision Making (Normal-responder)

- GnRH Agonist or Antagonist ?
- FSH dosing ?
- Sub-optimal response ?

PROFILE

AMH: 2 - 4 ng/mL

AFC: 10 – 20

Mostly 30 – 40 yr old

History of normal response in previous therapy

GnRH-a vs GnRH-ant (Meta-analysis)

- 23 RCT's (3,961 cases)
- Normal responders
 - OPR
 - OR: -0.87 (0.74 to 1.03)
 - LBR
 - OR: 0.89 (0.64 to 1.24)
 - OHSS
 - OR: **0.59** (0.42 – 0.82)

GnRH-a vs GnRH-ant (Meta-analysis)

- Length of stimulation (d)

- MD: **-0.66** (-1.04 to -0.27)

- Gonadotropin dose

- MD: **-2.92** (-5.10 to -0.75)

- E₂ on the day of hCG

- MD: **-330** (-510 to -150)

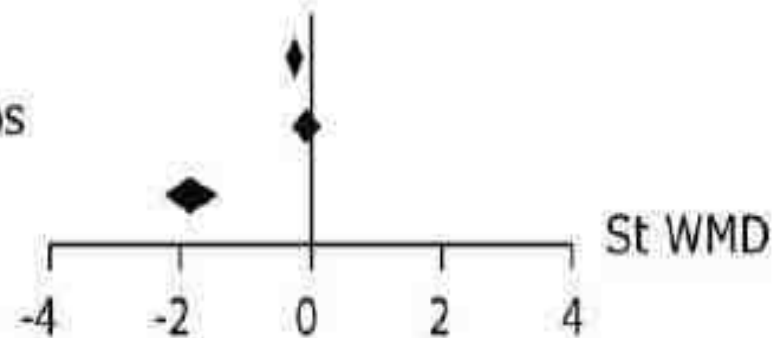
LESS TREATMENT BURDEN...

FSH Dosing (Meta-analysis, 10 studies)

Presumed Normal responders (< 39 yr, FSH: N, regular menses)

B 150 IU/d versus 200-250 IU/d

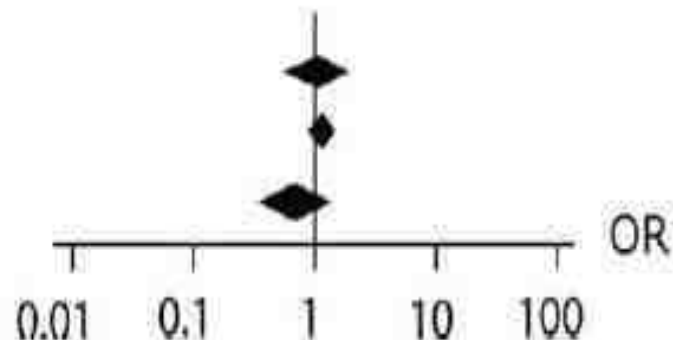
→ Number of oocytes per OPU
Number of cryopreserved embryos
Total amount of recFSH (IU)



Chance of OPU

→ Chance of pregnancy

→ Chance of OHSS



FSH Dosing (Multivariate models)

■ Popovic-Todorovic et al-2003

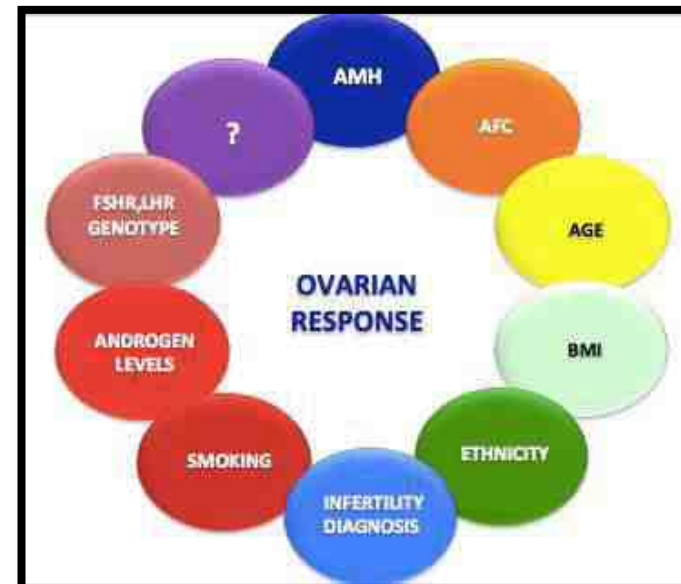
- RCT; Standard patients (n=262)
- 150 IU vs calculated Dose; Agonist
- AFC, Ovarian volume; Doppler score; Female Age; Smoking habit

■ Olivennes et al-2009

- CONSORT; Prospective uncontrolled
- Calculated dose; Agonist
- Basal FSH, BMI, Female age and AFC

■ La Marca et al-2012, 2013

- Female age, AMH/AFC, FSH



Can any intervention in normo-responders benefit ?

- ✓ **rFSH vs hMG in long protocol: No difference** Andersen et al, 2006 (MERIT)
- ✓ **rFSH vs hMG in antagonist protocol: No difference** Bosch et al, 2008; Devroey et al, 2012 (Megaset)
- ✓ **rLH supplementation in long protocol: No difference** Kolibianakis et al, 2006
- ✓ **rLH supplementation in antagonist protocol: No difference** Griesinger et al, 2005; Bosch et al, 2010
- ✓ **Mild vs conventional stimulation: No difference** Hohmann et al, 2003
- ✓ **Long acting vs daily FSH: No difference** Devroey et al, 2009

iCOS for “Normal responders”

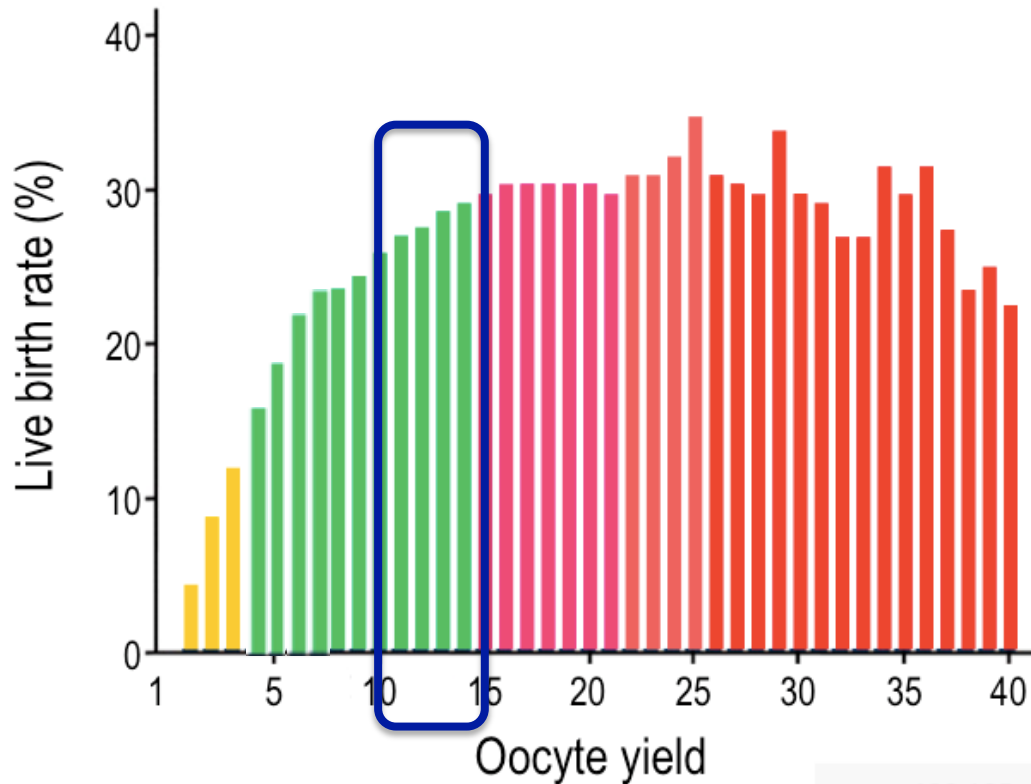
Interval Conclusion

- Similar live birth rates with Agonist and Antagonist
- Significantly less moderate/severe OHSS with hCG administration in Antagonist cycles
- Optimal dose of FSH is around 150 IU / Day.



De Placido et al, 2004; 2005 and Ferraretti, 2004

Sub-optimal responders? (4-9 oocytes)



Sunkara, et al *Hum Reprod* 2011

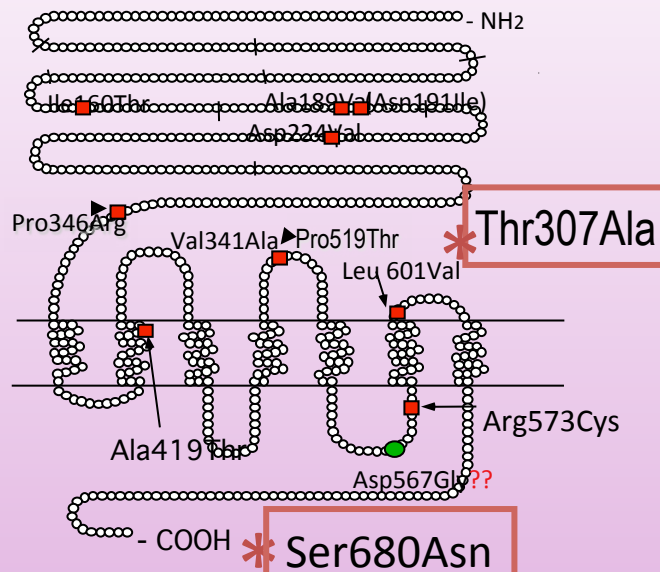
n = 400,135
fresh ICSI-cycles

- **20-30 % lower LBR** compared to normo-responders (10-15 oocytes)

Why patients may demonstrate a sub-optimal response to ovarian stimulation ?

FSH-R: Ser⁶⁸⁰ genotype

- Three genotypes:
 - Asn/Asn (45%)
 - Ser/Ser (26%)
 - Asn/Ser (29%)

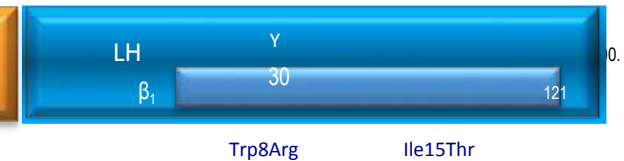


Locus FSHR (680)
polymorphic variability

LH-variant

To the native molecule

The common Trp8Arg/Ile15Thr

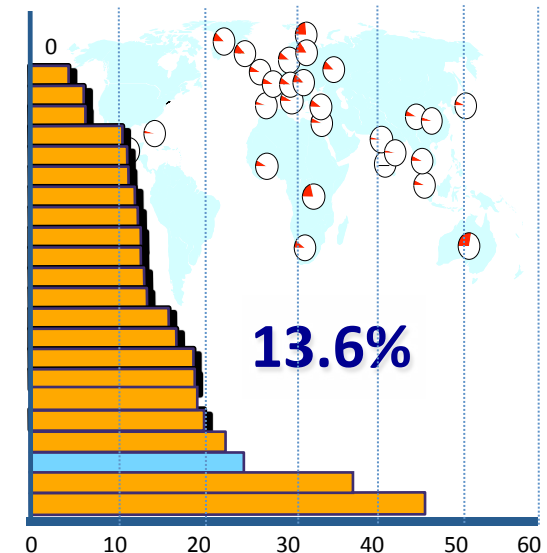


Additional sulphated
sugar at asn-13

Worldwide occurrence
Percent V/V + V/WT

Western India (Kota)
Mexico (Mayan)
Spain (Vasco)
United States (Hispanic)
Jordan

Thailand
Italy
Sweden (Göteborg)
China
The Netherlands
United States (black)
United Kingdom
South Africa (black)
Sweden (Stockholm)
Poland
Estonia
Greenland
Iceland
Faroe Islands
Finland
Finland (Lapp)
Australia/Aboriginals



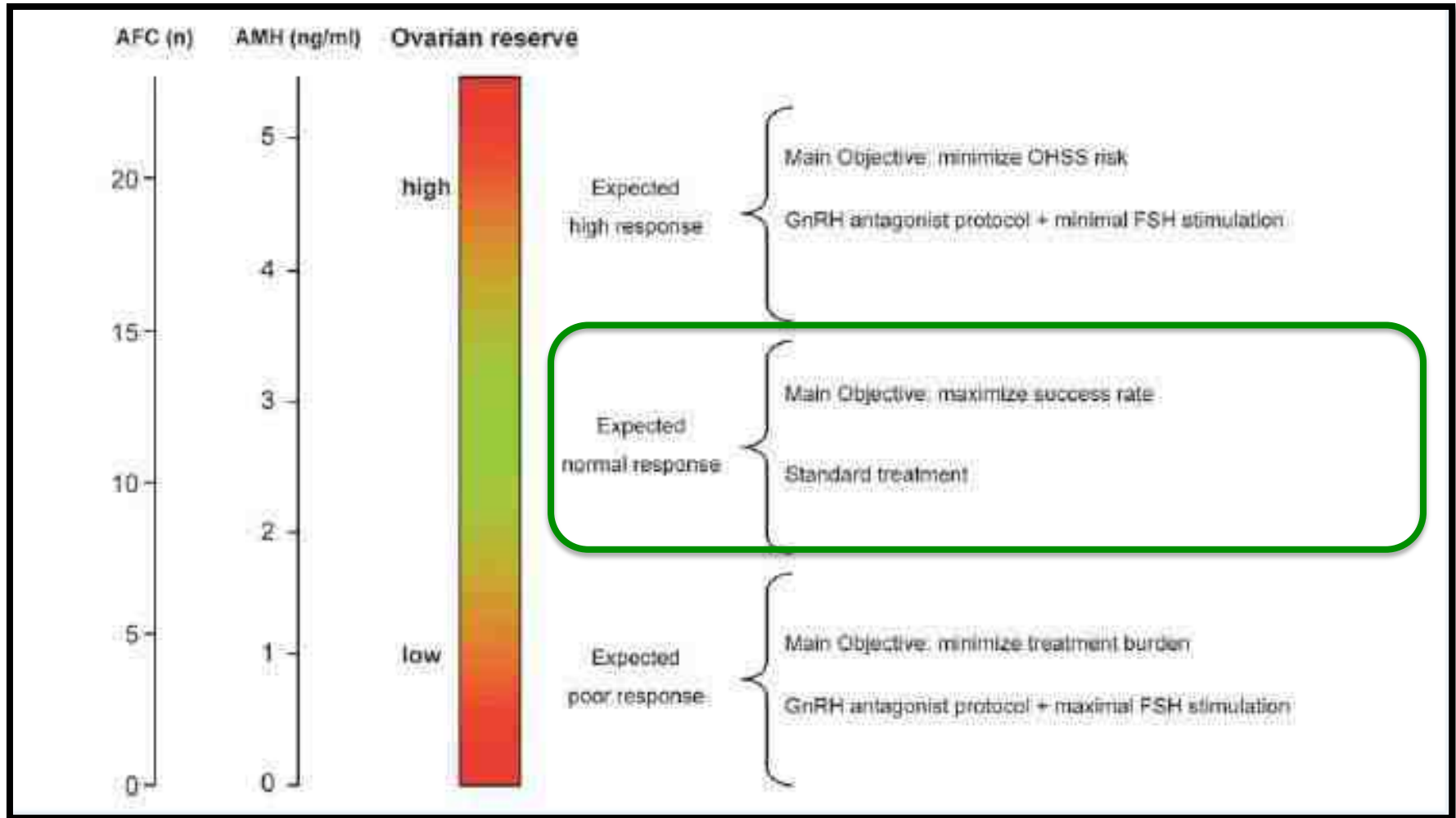
iCOS for 'Sub-optimal responders'

Interval Conclusion

- Further studies are warranted to delineate the best protocol for “sub-optimal responders” (4-9 oocytes)
 - Increase dose of FSH (FSH-R polymorphism)
 - Increase dose of FSH and add LH (v-LH)

De Placido et al, 2004; 2005 and Ferraretti, 2004

Main objectives for iCOS...



Mortality - OHSS



- The Netherlands National Registry
- Total ~ **100,000** IVF treatment cycles
- 6 deaths directly related to IVF
 - 3 OHSS,
 - 3 thrombosis and sepsis after egg retrieval
- Possibility of underreporting IVF related complications

iCOS-Decision Making (High responder)

- Which is the best COS protocol?
- How to individualize trigger and LPS?

PROFILE

AMH > 4 ng/mL

AFC > 20

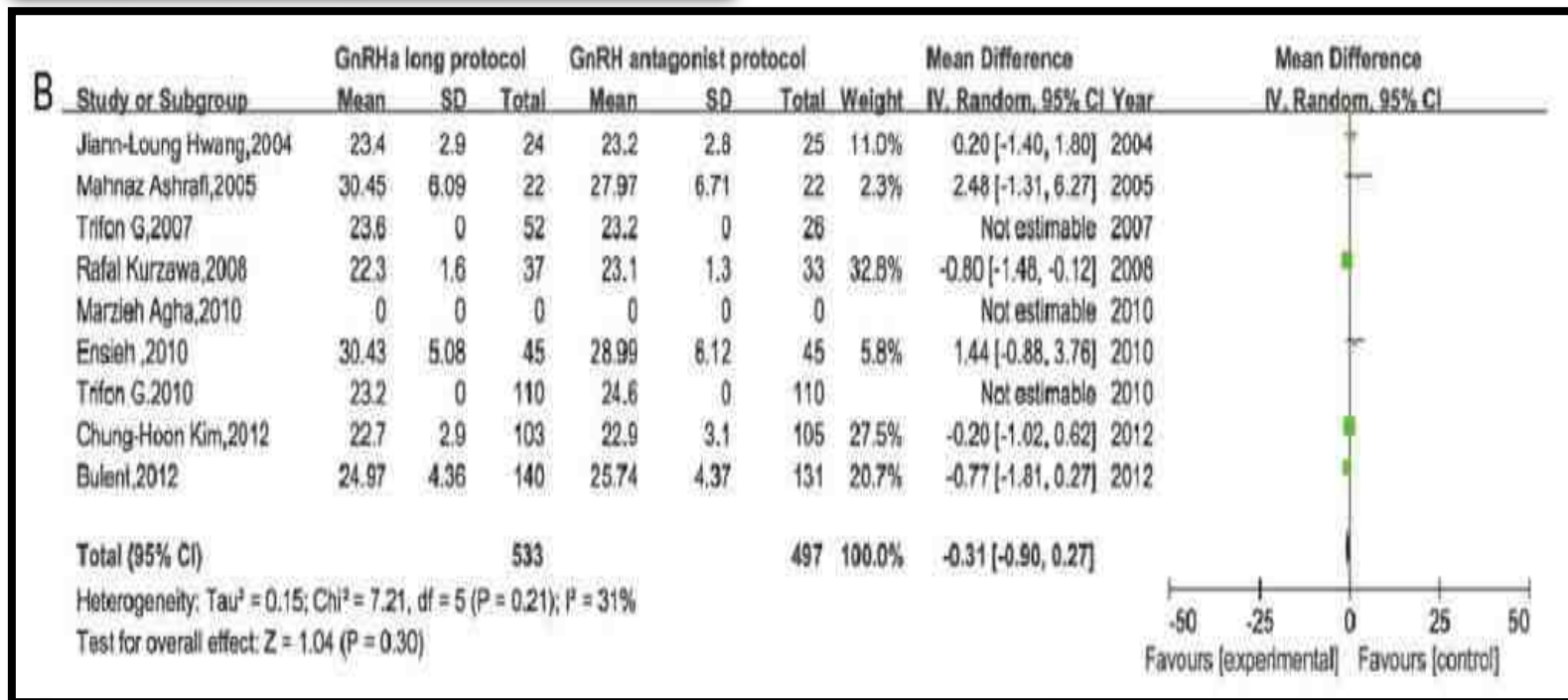
PCOS type; mostly younger

History of OHSS/multiple oocytes harvested in previous therapy

GnRH-a vs GnRH-ant (Meta-analysis)

9 RCT's; Agonist (n=588) vs Antagonist (n=554)

Ongoing pregnancy rate



OR: 1.05 (0.01-1.37)

GnRH-a vs GnRH-ant (OHSS)

- Al-Inani et al-2011
 - RD: **-0.10** (95%CI: -0.07 to -0.14)
- Pundir et al-2012 ^a
 - RR: **0.60** (95% CI: 0.48-0.76)
- Lin et al-2014 ^b
 - OR: 1.56 (95% CI: 0.29-8.51)

a: Moderate or severe

b: Severe

Individualization of triggering and LPS

No of follicles (≥ 12 mm)	Strategy
< 10	1500 hCG at OPU and OPU+5 + Standard LPS
10 – 14	1500 hCG at OPU + 500 IU hCG OPU+5 + Standard LPS
15 – 25	1500 hCG at OPU + Standard LPS
> 25	GnRHa and cryo-all

Individualization of triggering and LPS

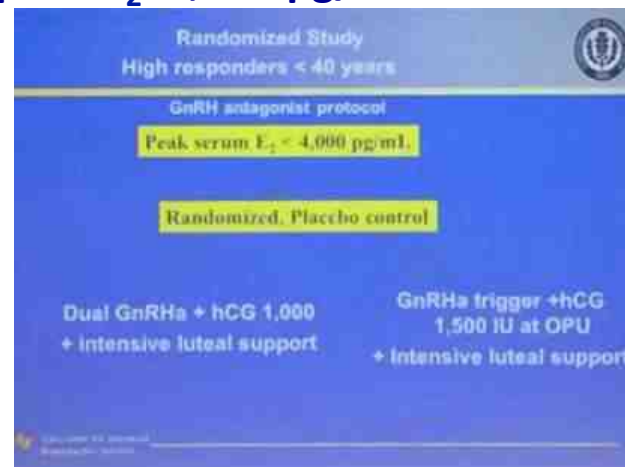
- **“European” Approach**

- 1500 IU hCG rescue
- Small bolus of hCG

- **“American” Approach**

- $E_2 > 4,000$ pg/ml-----Intensive Luteal Phase Support (ILPS)
- $E_2 < 4,000$ pg/ml-----Dual Trigger + ILPS

Currently, a RCT comparing hCG rescue at the time of OPU vs Dual trigger for high-risk patients with peak $E_2 < 4,000$ pg/ml is underway.. (NCT01815138)

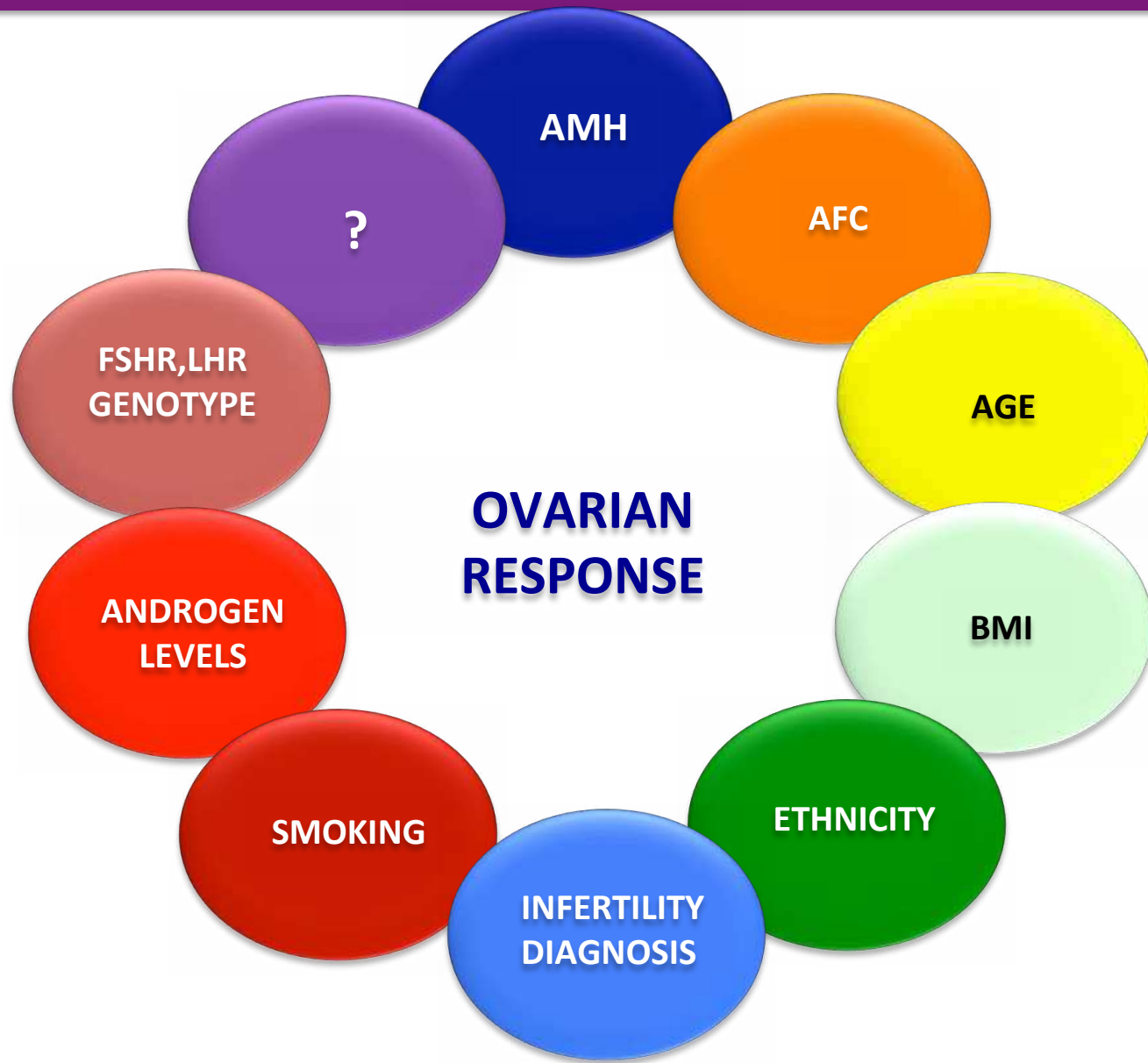


iCOS for 'High responders'

Interval Conclusion

- Antagonist is the protocol of choice with low dose of FSH (< 150 IU / day)
 - Similar LBR with agonist and antagonist
 - Significantly less moderate/severe OHSS even with hCG administration
 - Permits the use of agonist to trigger final oocyte maturation
 - LPS ?

To better individualize COS, we need better predictors



Excellence in ART: Clinical and Laboratory Perspectives

April 29-30, 2016 Double Tree by Hilton Cappadocia



www.excellenceart2016.org



TOPICS

- Individualized controlled ovarian stimulation
- Novel treatments to trigger final oocyte maturation and luteal phase support
- Endometrium as a biosensor of embryo quality
- Novel concepts in male-factor infertility-Clinical and Laboratory Perspectives
- Single versus sequential culture media
- Difficult patients for the embryologist: How to handle?
- Fresh, deferred or personalized blastocyst transfer-That is the question
- How to manage recurrent implantation failure?
- Controversies in clinical ART (Progesterone elevation, Blastocyst transfer for all, thrombophilia in ART, adjuvant treatment)
- Oocyte and embryo vitrification-Current status
- Female fertility preservation-State of the art
- Should all women deferring fertility beyond 36 consider egg freezing?
- Time-lapse: Any additional benefit beyond morphology?
- Complete chromosome screening-To whom, level of evidence and genetic technologies
- ART Lab: Conventional indicators and benchmarks
- Protocols for witnessing samples and patients