



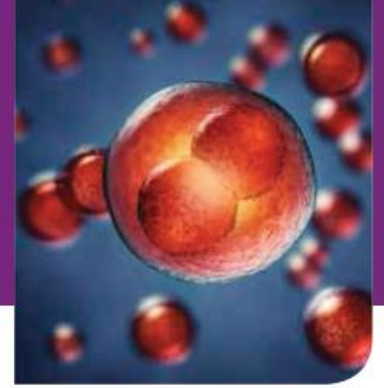
BUENOS AIRES
icos 2015
Individualized Controlled Ovarian Stimulation



Edson Borges Jr.
MD. PhD.

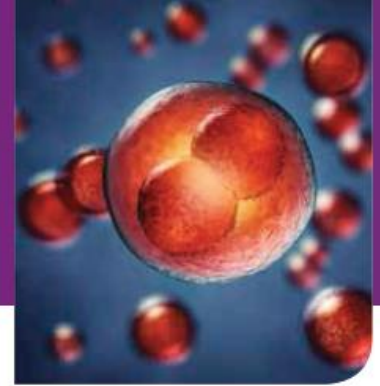
iCOS hiperresponderas: Definición, diagnóstico, incidencia y tratamiento y resultados esperados

Agenda

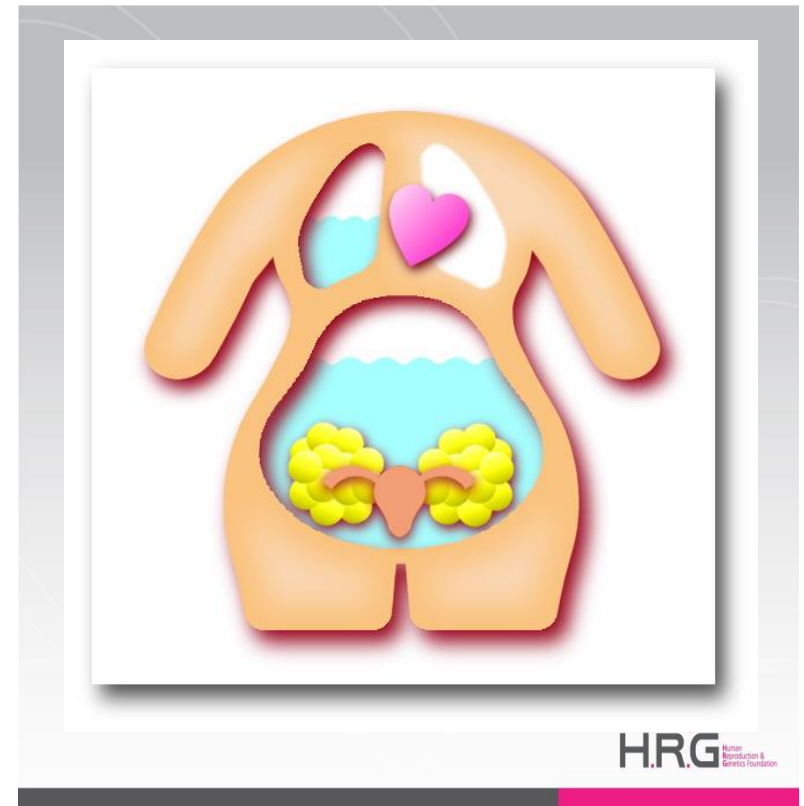


- Definition, Diagnosis, Prevalence
- Distinction among ovarian response and reserve; what is more appropriate?
- Diagnosing of a potentially high responder (AMH/AFC)
- Management of a high responder
- OHSS free clinic: time has come?

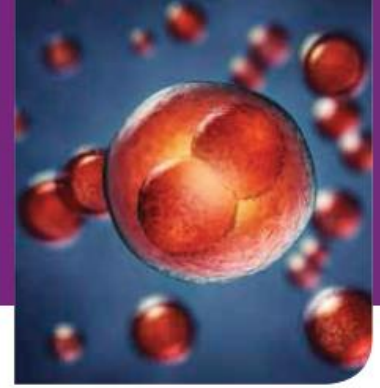
OHHS



- ✓ Ovarian Hyperstimulation syndrome (OHSS) is a iatrogenic complication of OI and ovarian stimulation for ART
- ✓ Is characterized by cystic enlargement of the ovaries and rapid fluid shifts from the intravascular compartment to the third space.
- ✓ Severe cases need hospitalization and in extreme scenario might turn into fatal
- ✓ Prevalence of 2-10%
- ✓ hCG (exogenous or endogenous) is the triggering factor



OHHS - Pathogenesis



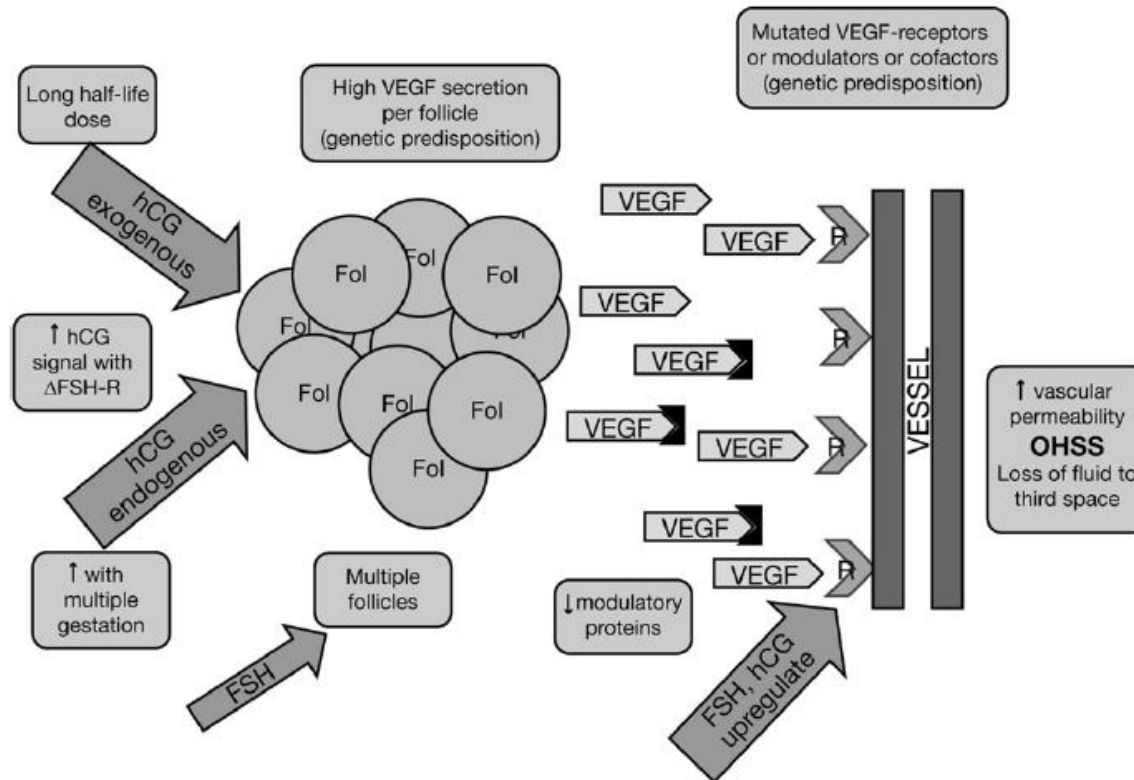
- Equilibrium between pro-angiogenic (*VEGF – vascular endothelial growth factor*) and anti-angiogenic factors in follicular fluid
- Neo-angiogenesis and increase capillary permeability of enlarge ovarian and endothelial surfaces. Fluid and proteins shift from intravascular space to extravascular (abdomen, pleura, pericard).
- mRNA expression of VEGF in luteinized granulosa cells is time- and dose dependent of hCG

OHSS - Pathogenesis



FIGURE 1

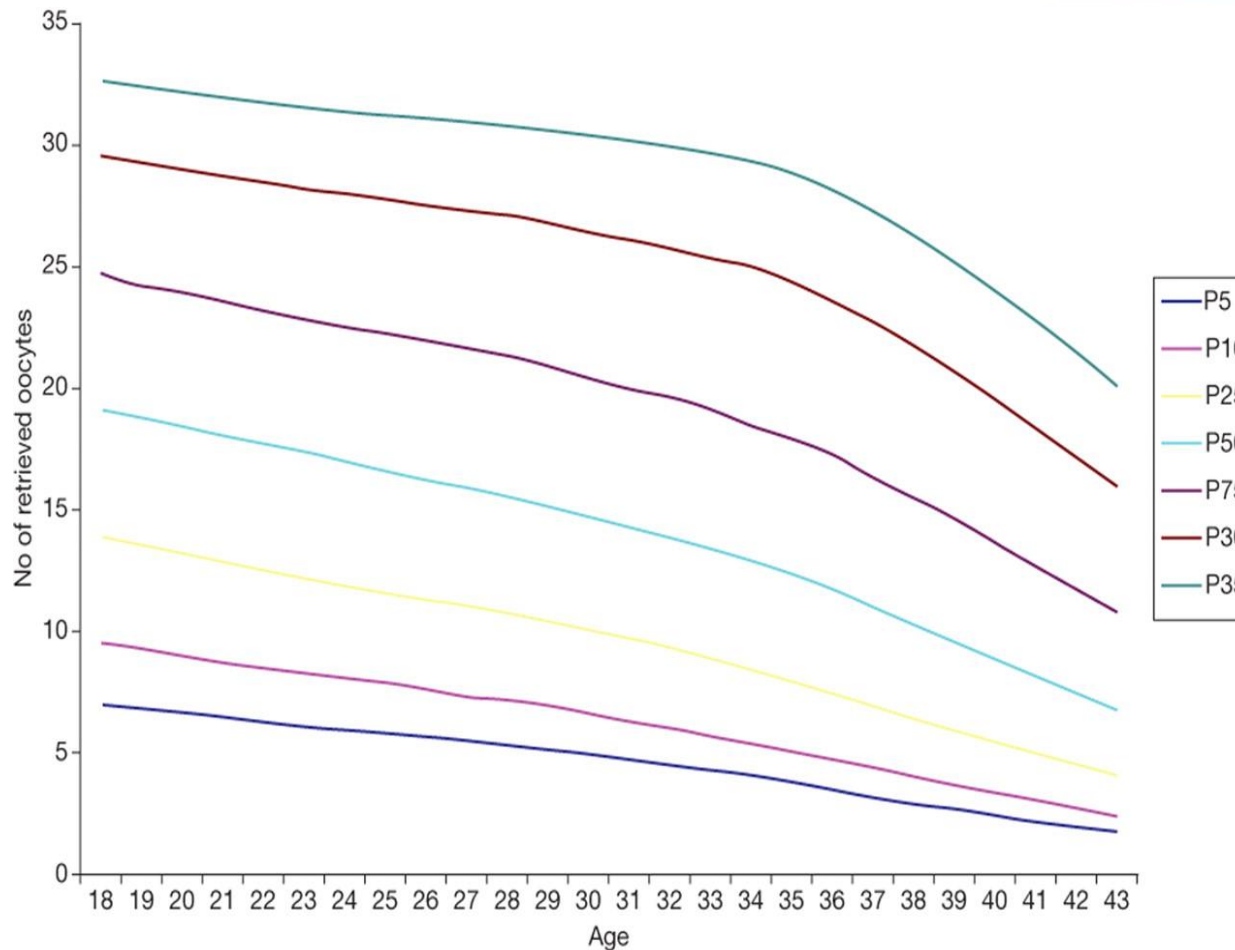
The pathogenesis of OHSS.



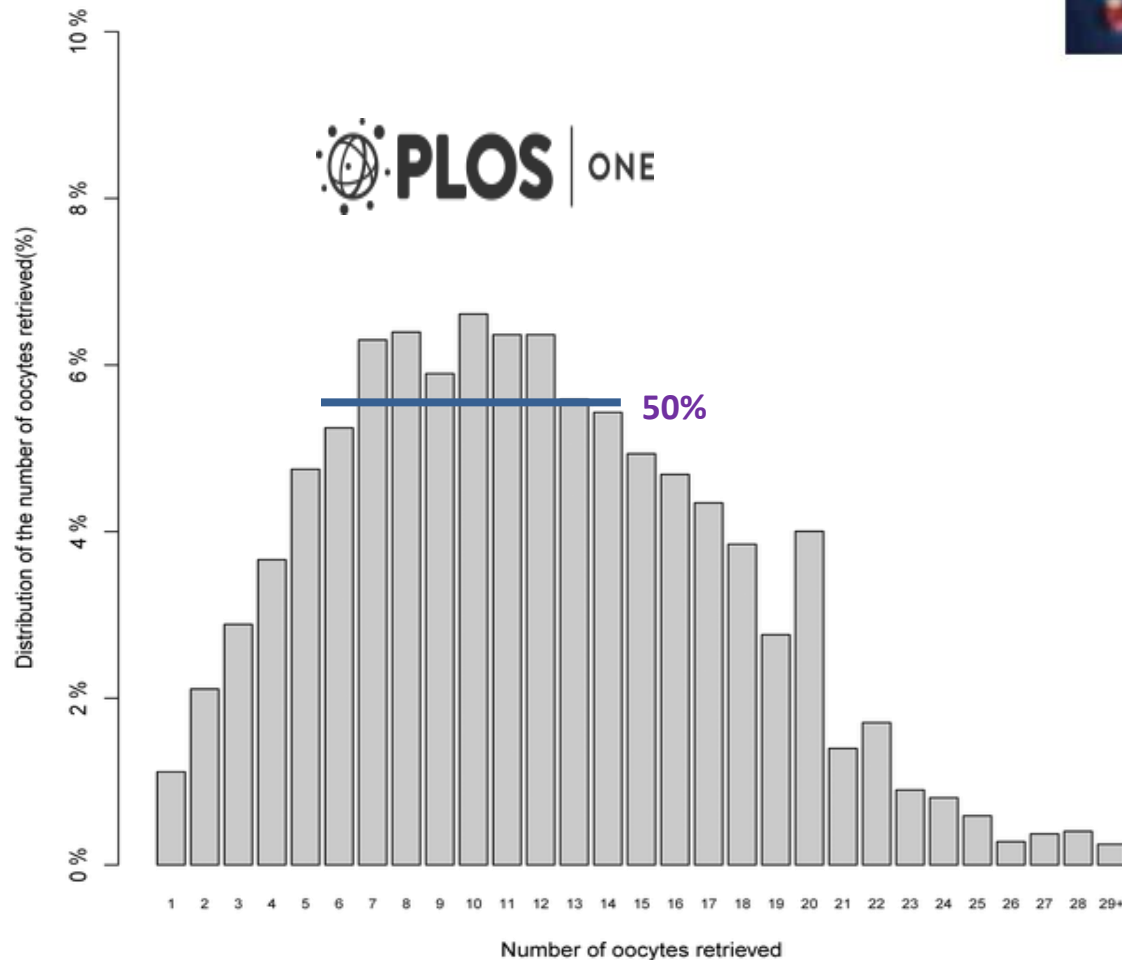
Normal responders Normal or Hyper-responders



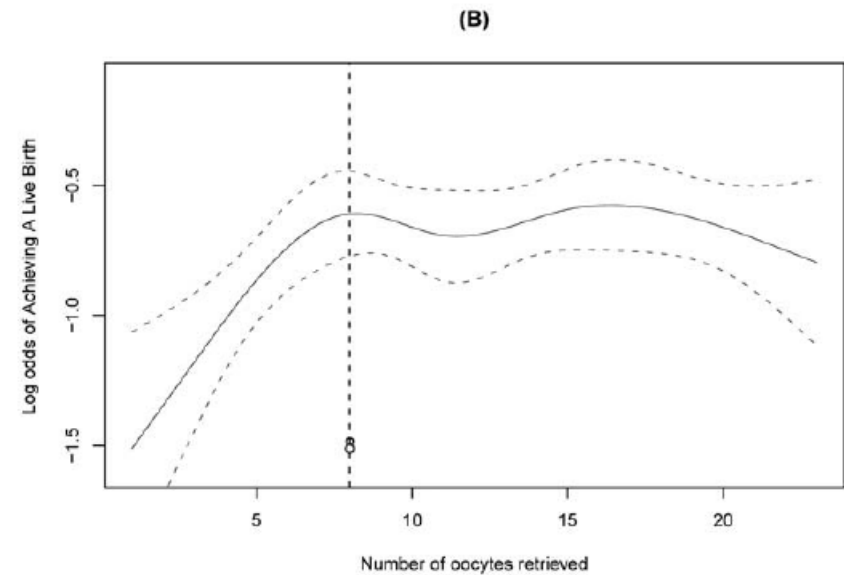
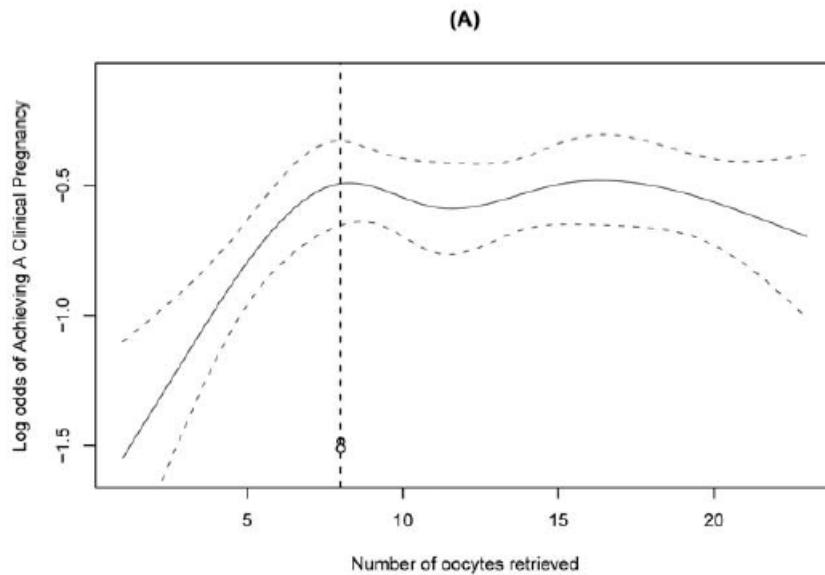
Ovarian response in IVF treatment



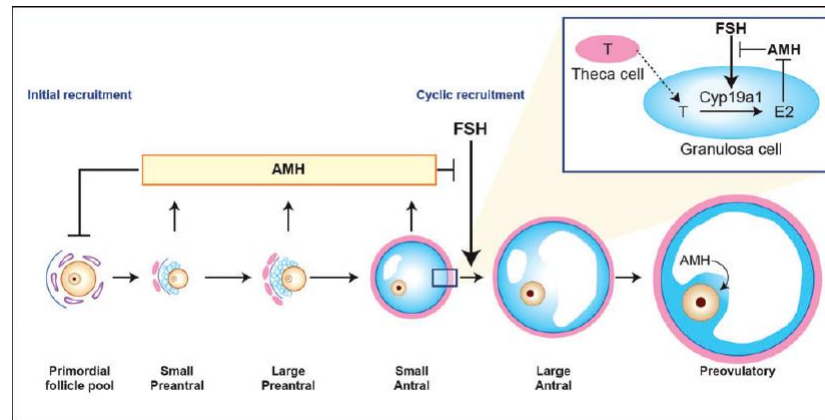
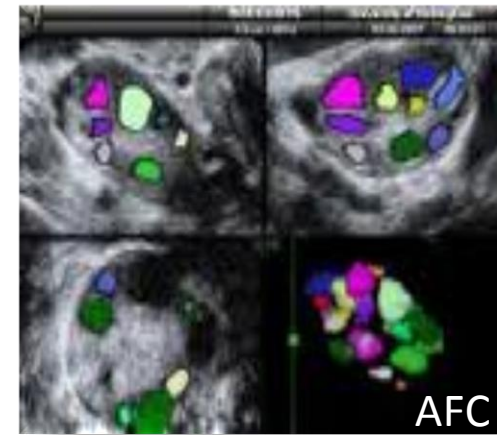
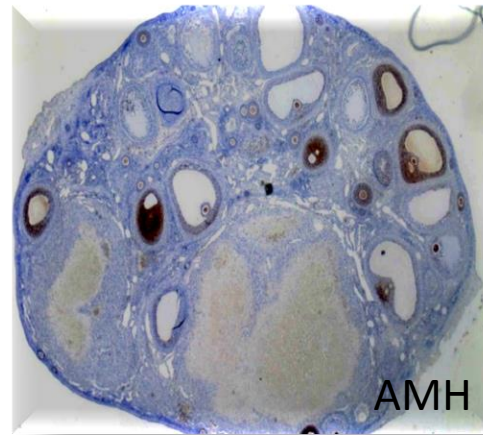
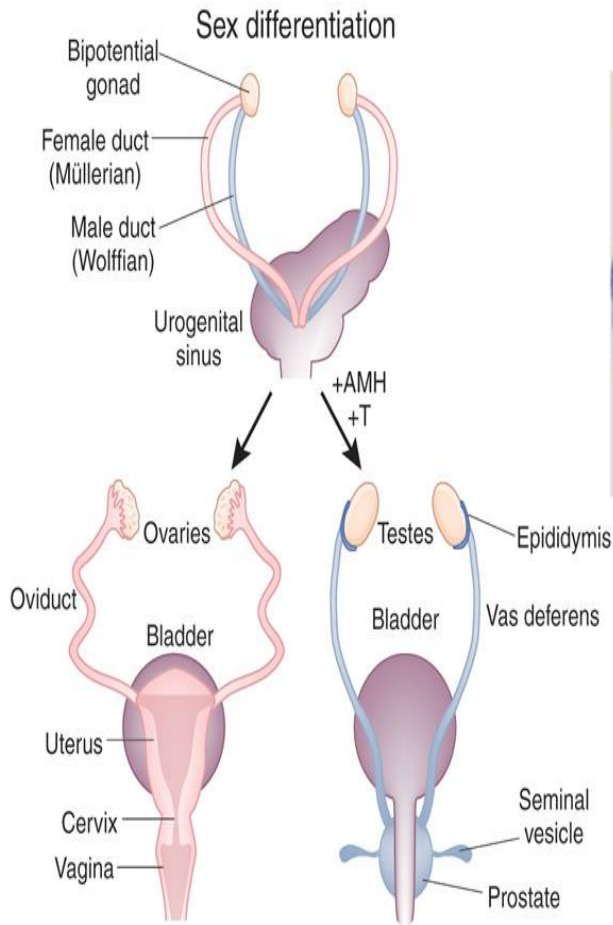
Distribution of number of oocytes retrieved



Association between the number of oocytes retrieved and the IVF outcomes after fresh ET



AMH and AFC: Best predictors of ovarian response

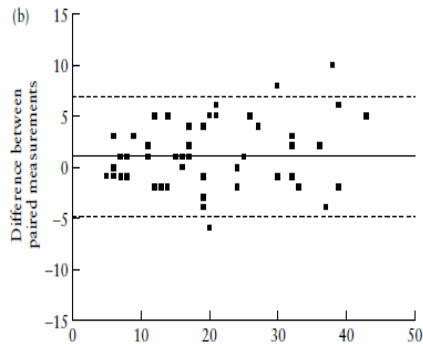


Katie Vicari

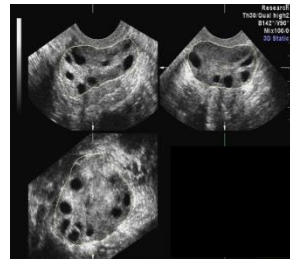
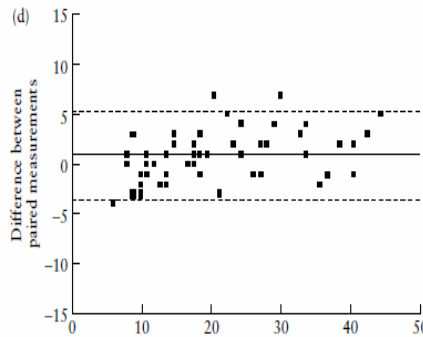
Both now have reduced technical variability



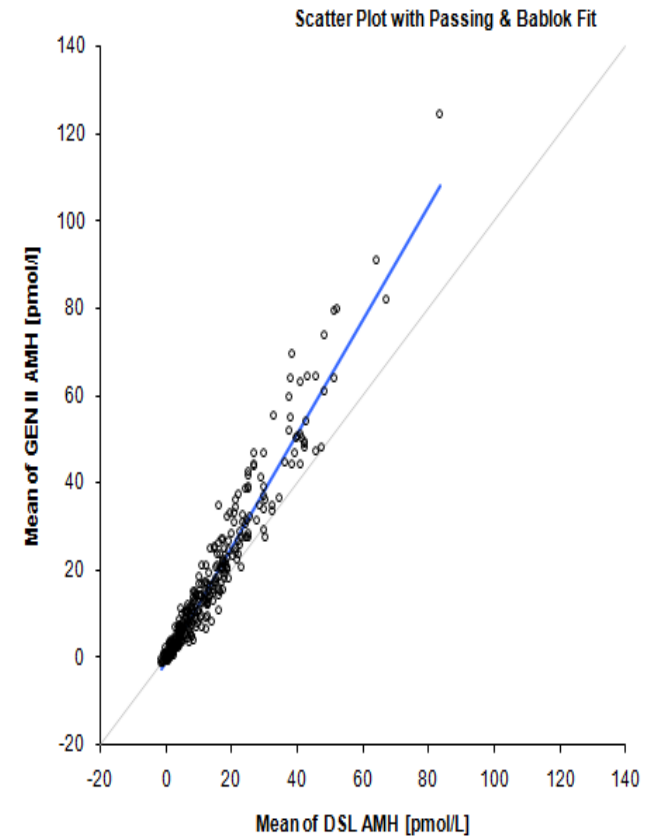
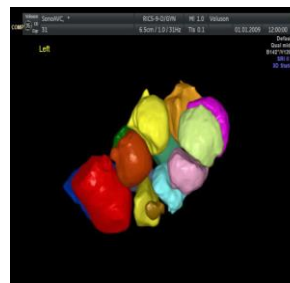
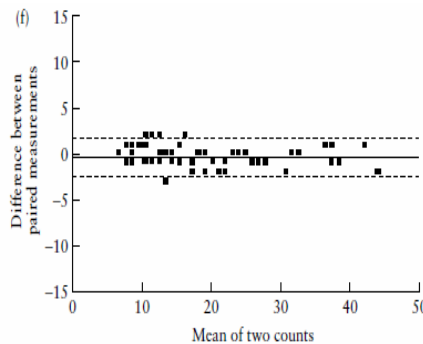
2D



3D



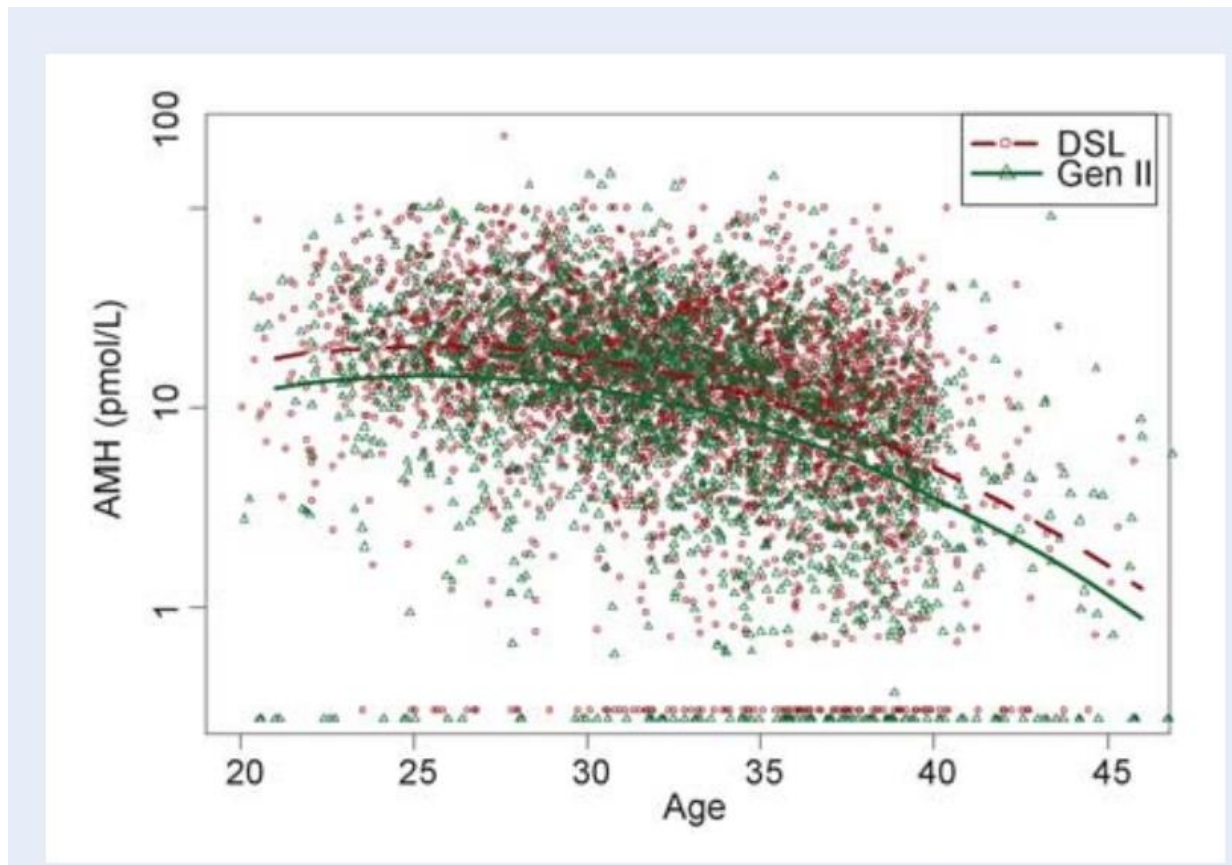
3D automated



Deb S et al *Ultrasound Obstet Gynecol* 2009
 Van Disseldorp et al *Hum Repro* 2009
 Wallace et al *Ann Clin Biochem* 2011

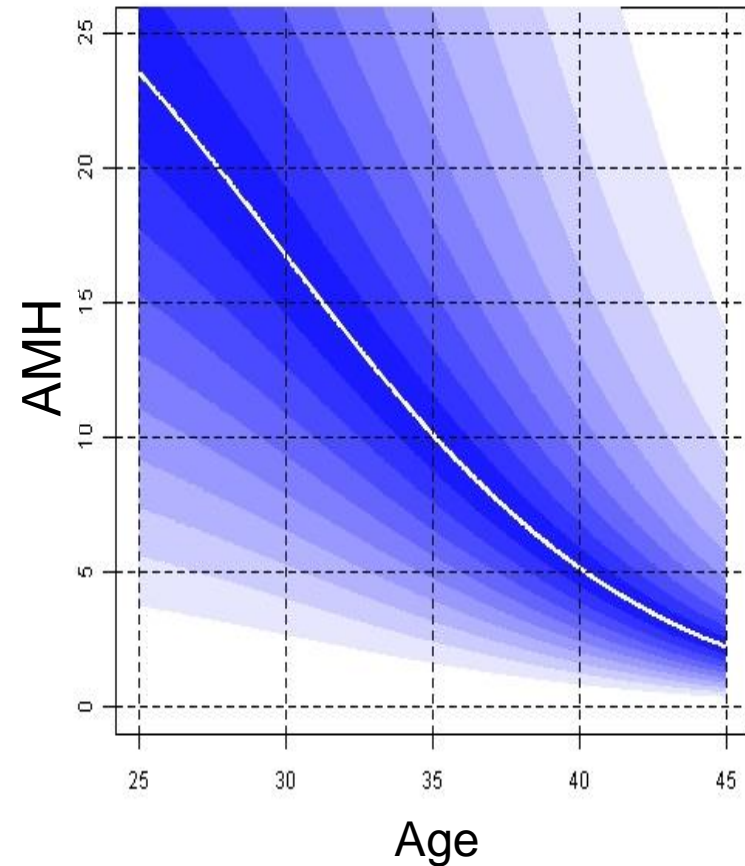
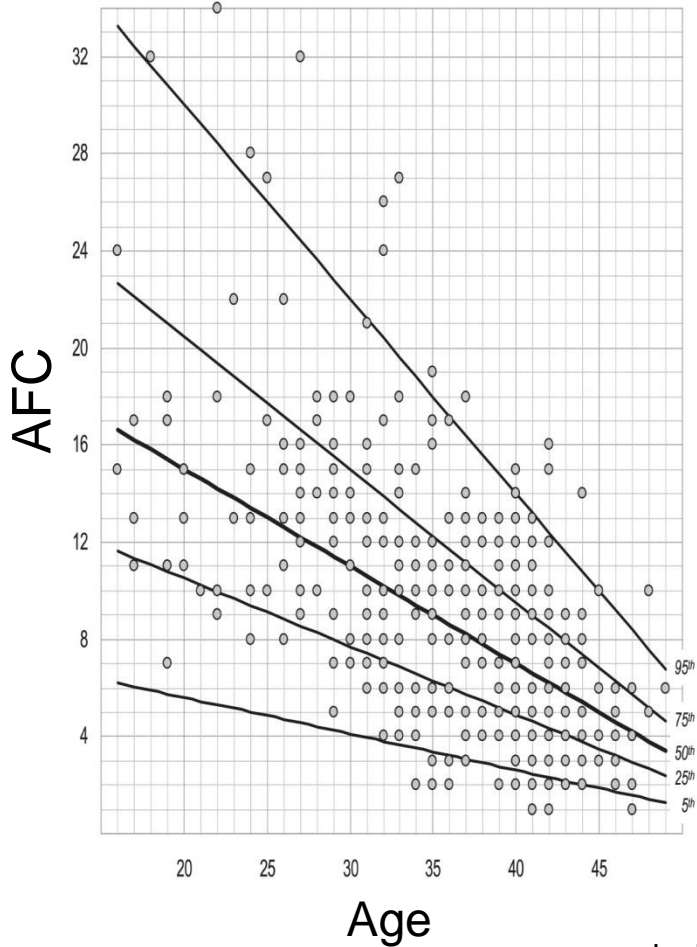


Both now have reduced technical variability

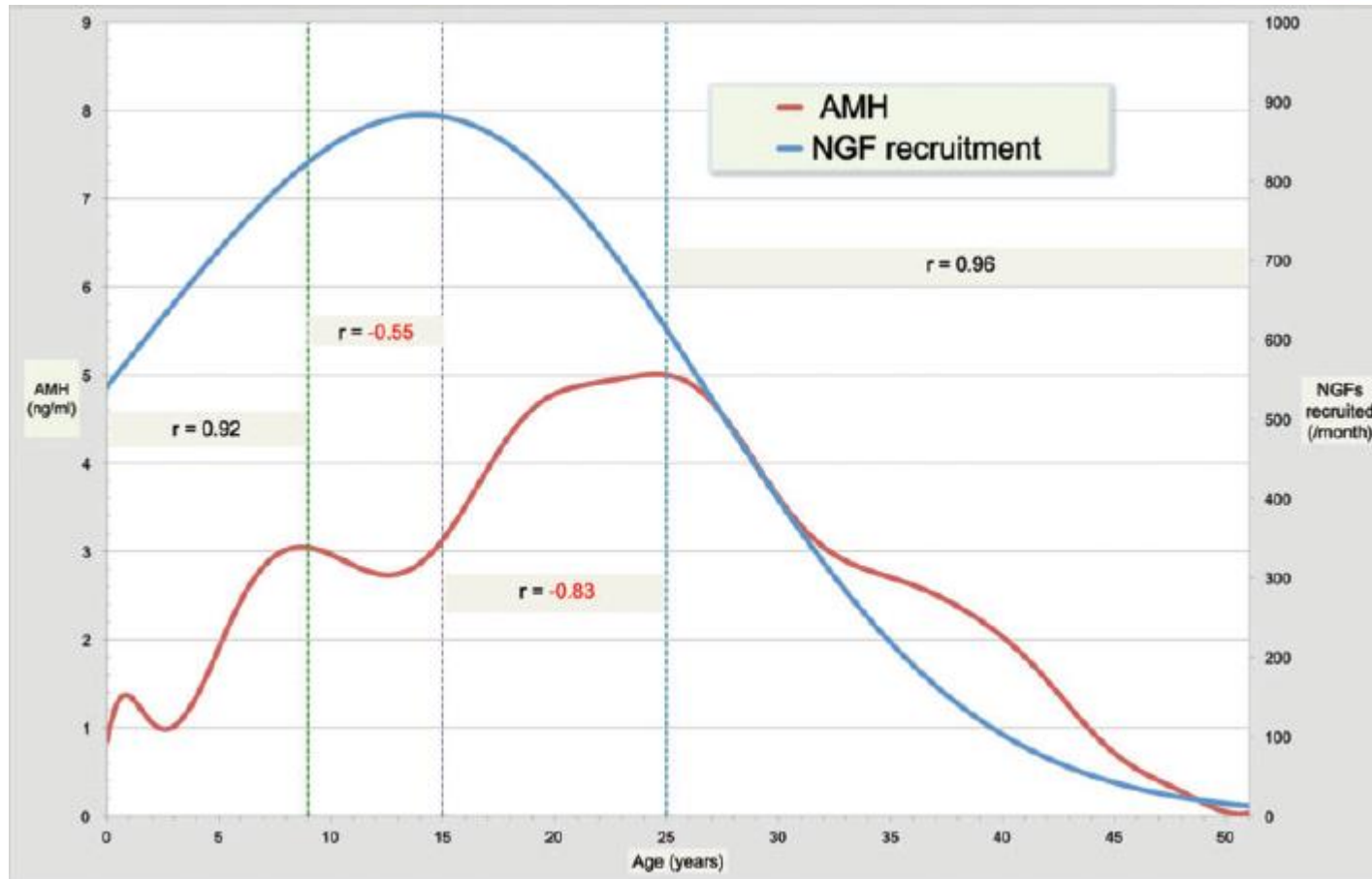


Rustamov O, et al. *Hum Reprod* 2014

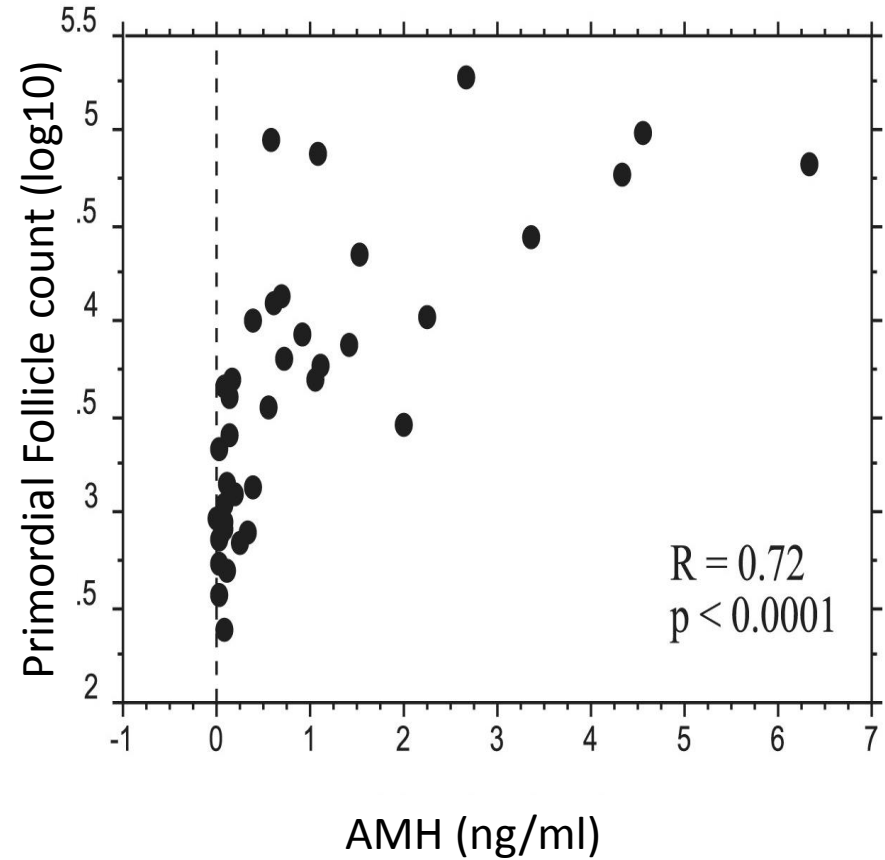
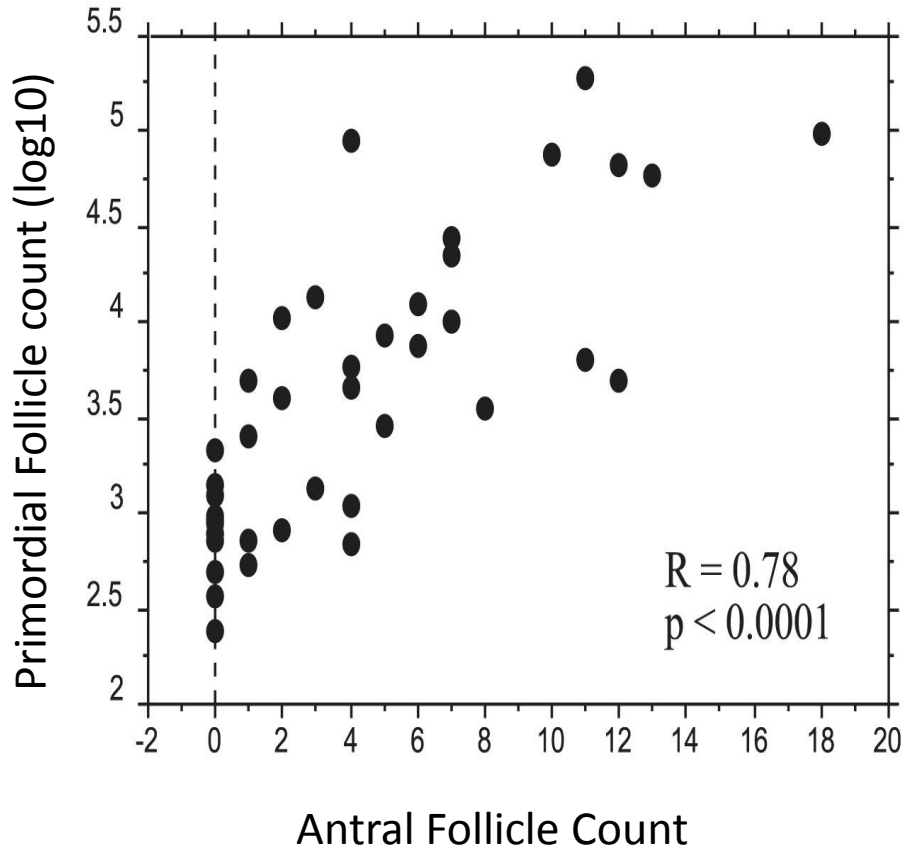
Both decline with age



AMH and Age



Both reflect the ovarian reserve

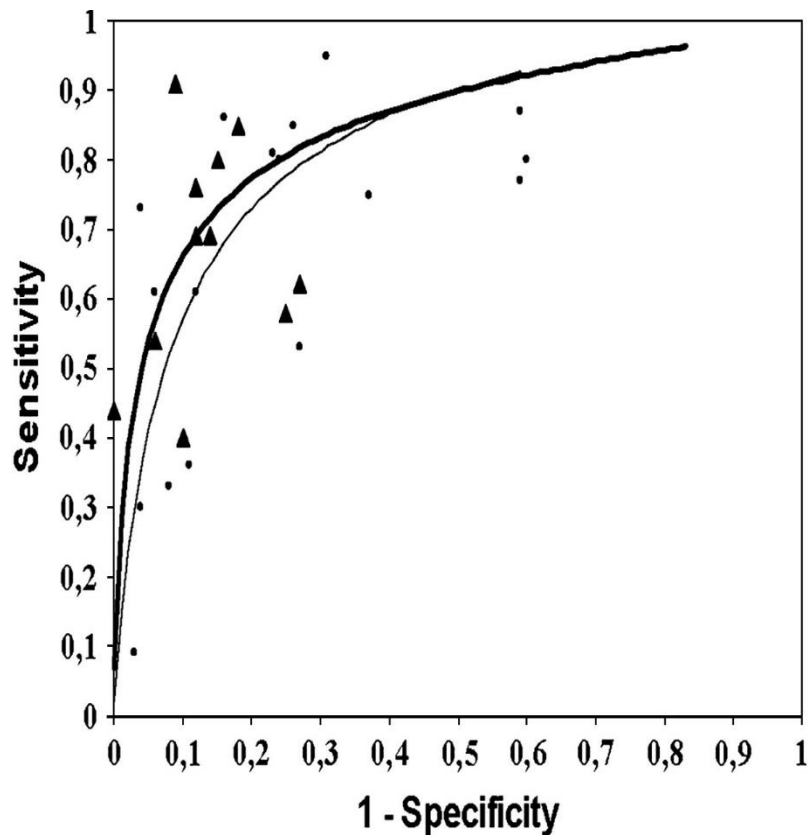


Hansen et al *Fertil Steril* 2010

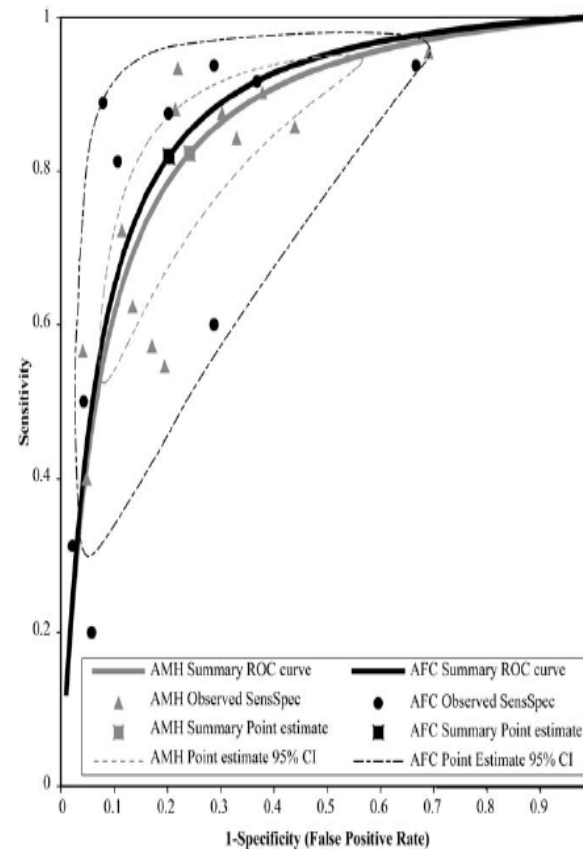
Both predict extremes of ovarian response



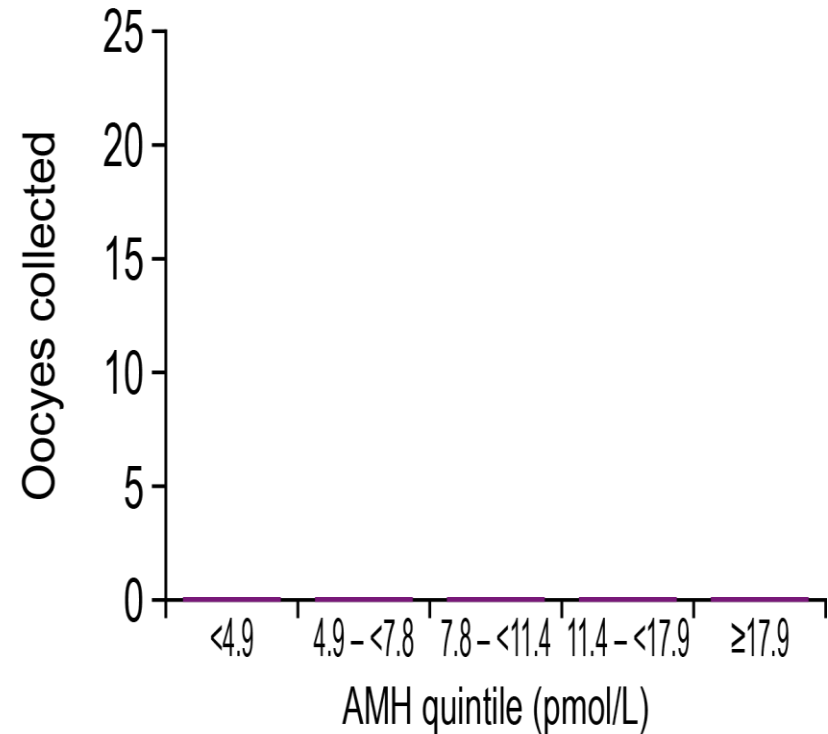
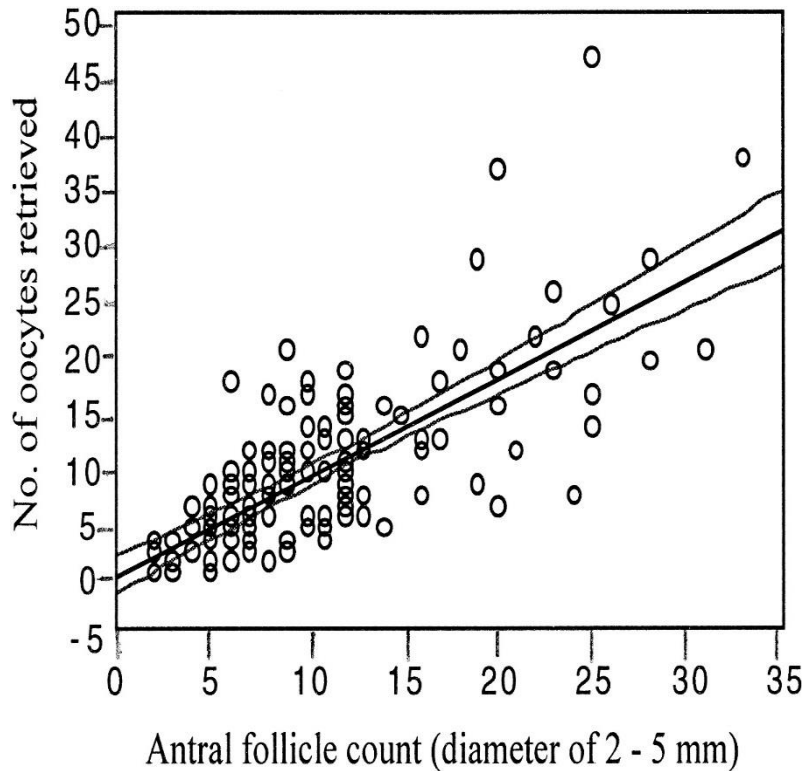
Poor



Excessive

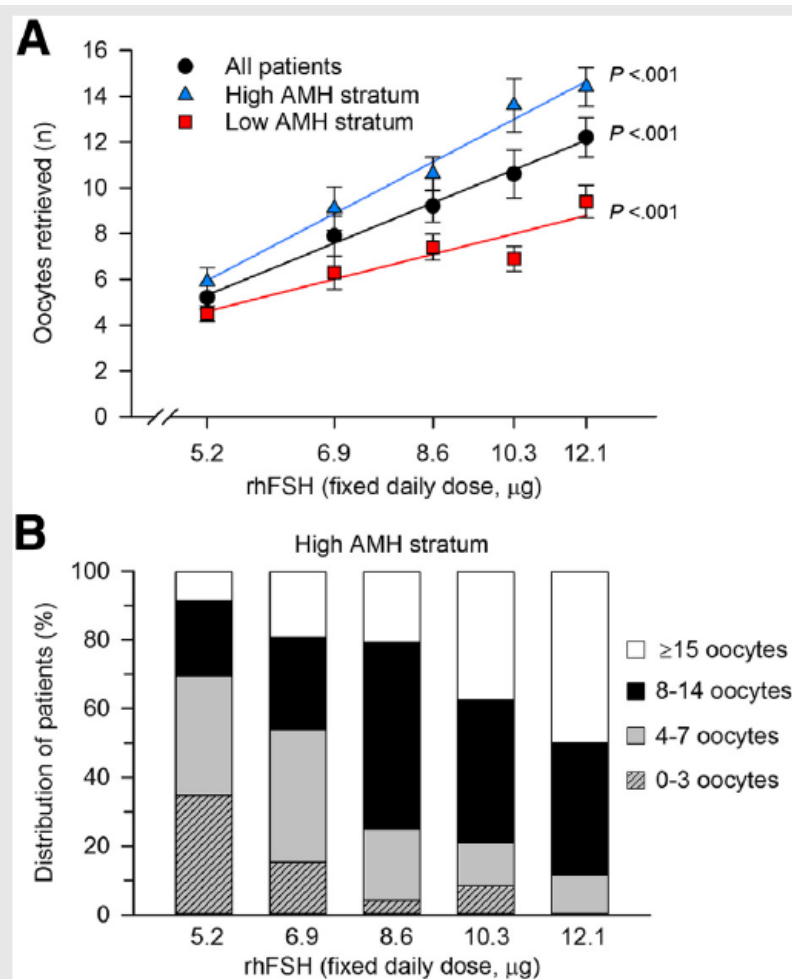


Both predict oocyte yield



Chang et al *Fertil Steril* 1998
Nelson et al *Hum Reprod* 2007

AMH predict oocyte yield according rFSH dose



Ovarian Reserve Markers

(La Marca & Sunkara, H.R. Update, 2014)

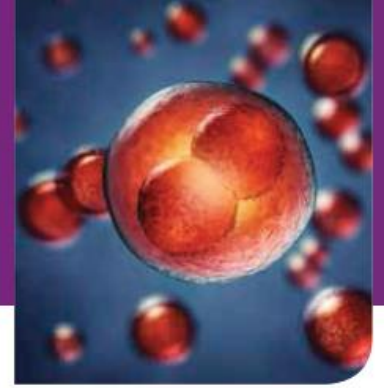


Table III Comparison of characteristics of the most widely used markers of ovarian reserve (modified with permission from **La Marca et al. (2010)**).

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.

But what do we need to conclude about these two markers?



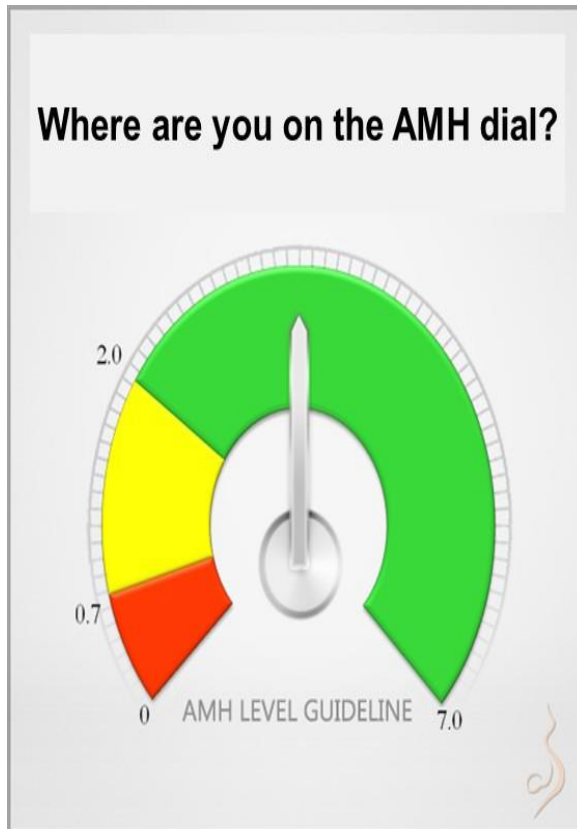
- Indexes of follicular quantity!!!!
- Not indexes of follicular capacity
- Not indexes of oocyte quality



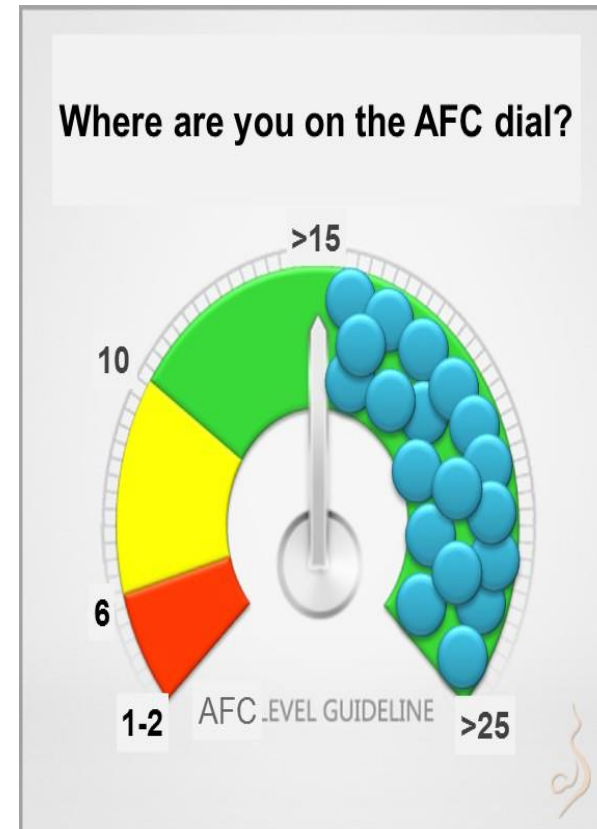
To avoid an hyper-responses we MUST define...



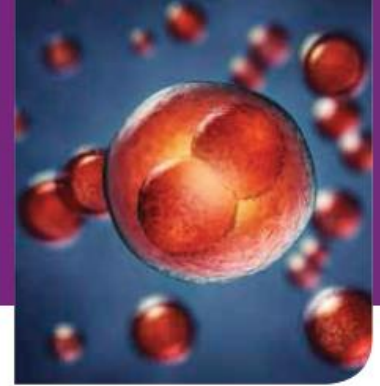
Where are you on the AMH dial?



Where are you on the AFC dial?

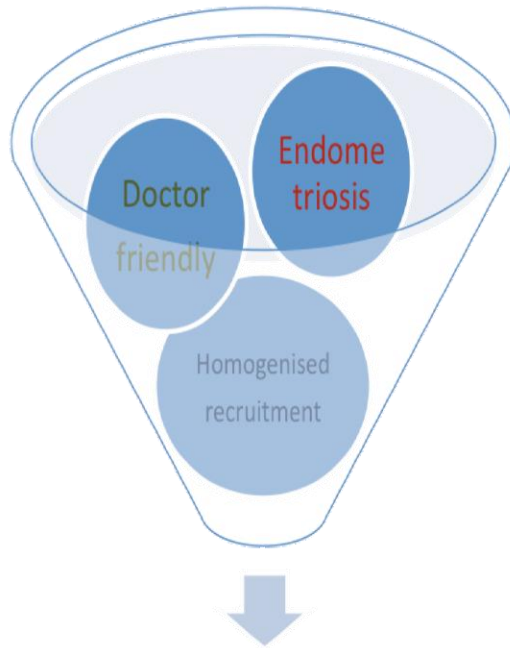
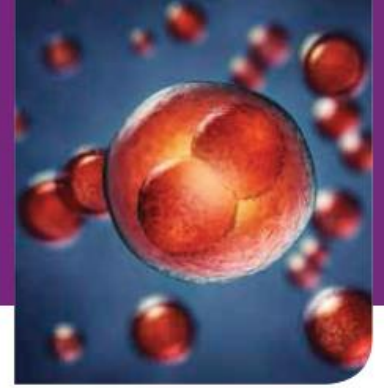


We also MUST secure...

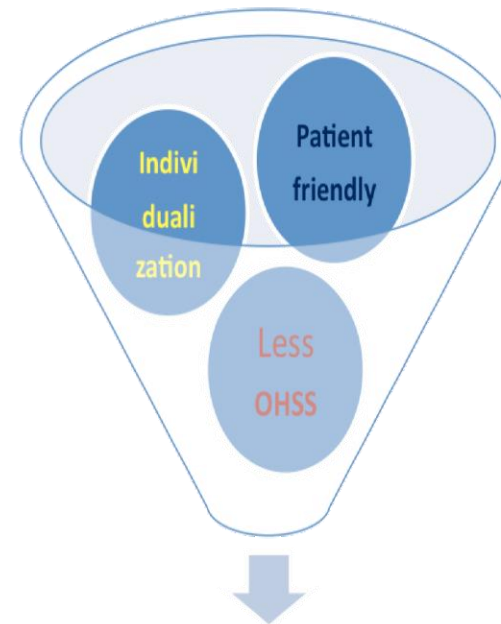


- ✓ Aiming 10-15 follicles
- ✓ Choosing the appropriate Gonadotropin
- ✓ Use potential algorithms to define safest dose or be pragmatic...
- ✓ Use the right protocol to minimize OHSS

Now what about the protocol



Agonist



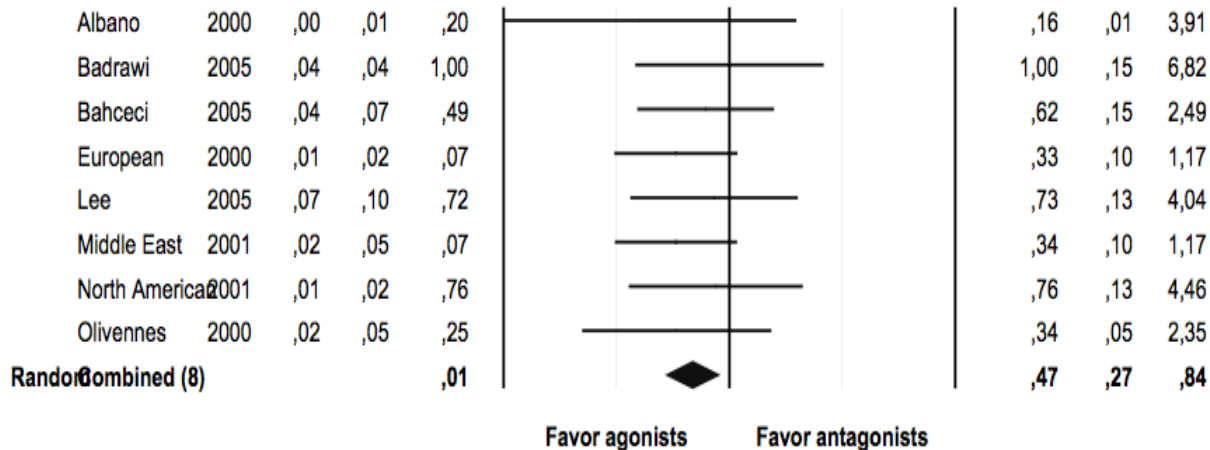
Antagonist

So what are the treatment options?

Antagonist is safer...



Antagonist protocol - Hospital admission due to OHSS



RR : 0.47 ~ 2 times less risk for hospital admission due to OHSS with GnRH antagonists

Antagonist trigger is safer...



- Current protocol
 - rFSH / Antag/ GnRHa

Complications	0.41% (17)
Intraabdominal bleeding	0.34% (14)
Severe pain	0.05% (2)
Ovarian torsion	0.02% (1)

Bodri et al. 2008


- Practically no OHSS risk
 - as no hCG is used
 - and no embryo transfer performed

...and even more efficient!



ARTICLE IN PRESS

Reproductive BioMedicine Online (2015) ■■, ■■-■■

ELSEVIER

COMMENTARY

The updated Cochrane review 2014 on GnRH agonist trigger: repeating the same errors

S. Kol ^{a,*}, P. Humaidan ^b, B. Alsbjerg ^b, L. Engmann ^c, C. Benadiva ^c,
J.A. García-Velasco ^d, H. Fatemi ^e, C. Yding Andersen ^f

- ✓ Cochrane 2010 and 2014: GnRH agonist trigger prevents OHSS to the detriment of live birth rates
- ✓ ***NOT comparable lutel fase support!!!!***

What type of gonadotropins to choose?



- ✓ Use a highly bioactive rFSH...
- ✓ ...in low doses that can be slightly incremented and...
- ✓ ...precisely delivered in small increments of 12.5 IU
- ✓ Use pen devices to avoid patients mistakes in dosing!!
- ✓ Avoid using long acting drugs in patients at risk of OHSS (PCOS, high ovarian reserves and hypersensitive to FSH)

What type of gonadotropins to choose?



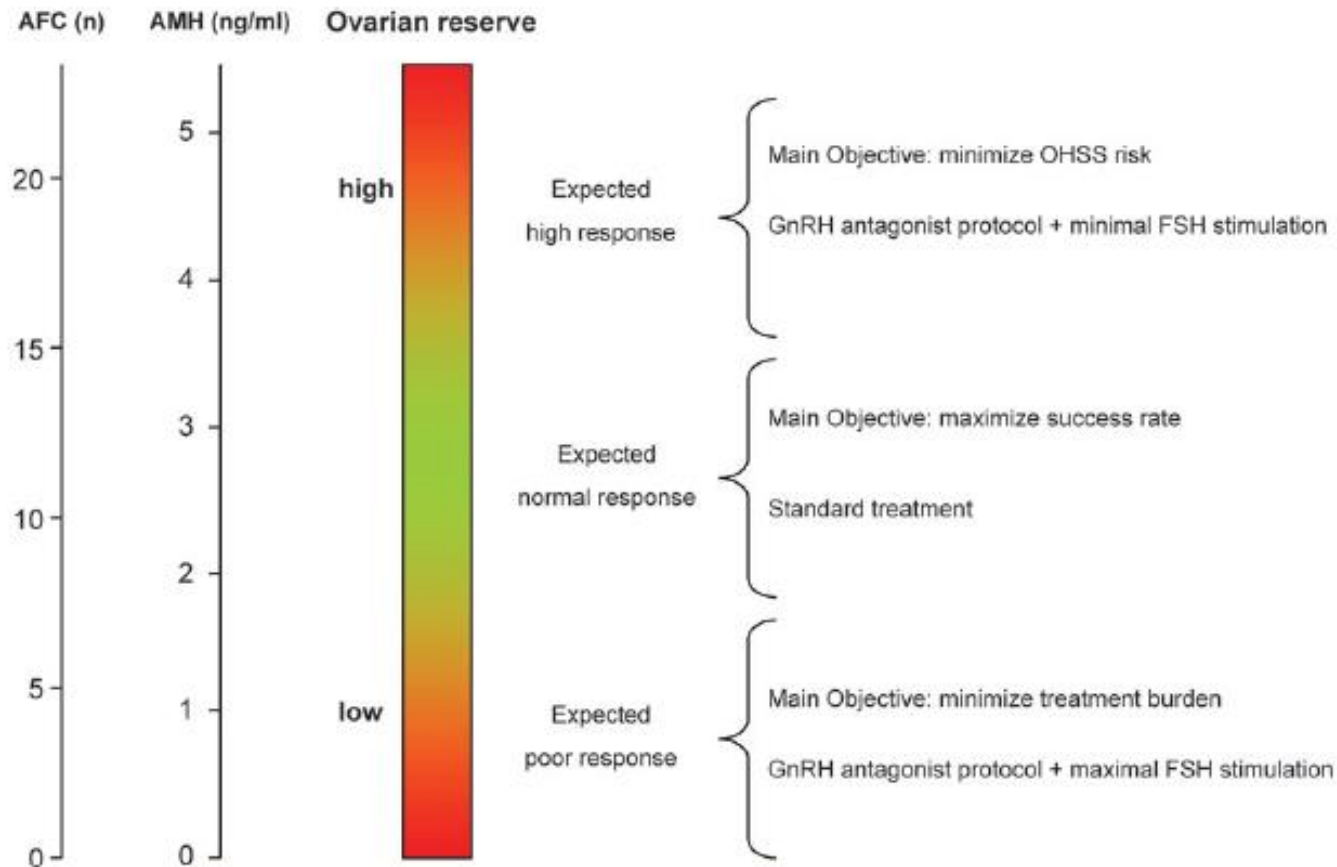
	<i>British Isles (763 patients)</i>	<i>The Netherlands (562 patients)</i>	<i>Nordic (1871 patients)</i>	<i>All (3196 patients)</i>
HCG given	735 (96.3)	529 (94.1)	1840 (98.3)	3104 (97.2)
Embryo transfer performed	651 (85.3)	432 (76.9)	1683 (90.0)	2766 (86.5)
1 embryo	55 (8.4)	119 (27.5)	760 (45.2)	934 (33.8)
2 embryos	549 (84.3)	275 (63.7)	862 (51.2)	1686 (61.0)
3 embryos	25 (3.8)	7 (1.6)	52 (3.1)	84 (3.0)
Not specified	22 (3.4)	31 (7.2)	9 (0.5)	62 (2.2)
Positive HCG test	244 (32.0)	153 (27.2)	600 (32.1)	997 (31.2)
Clinical pregnancy	182 (23.9)	112 (19.9)	444 (23.7)	738 (23.1)
Biochemical pregnancy	32 (4.2)	19 (3.4)	71 (3.8)	122 (3.8)
Extrauterine pregnancy	5 (0.7)	3 (0.5)	12 (0.6)	20 (0.6)
Miscarriage	21 (2.8)	16 (2.8)	58 (3.1)	95 (3.0)
No information	4 (0.5)	3 (0.5)	15 (0.8)	22 (0.7)
Multiple pregnancy				
2 sacs	41 (100.0)	30 (93.8)	67 (98.5)	138 (97.9)
3 sacs	0 (0.0)	2 (6.3)	1 (1.5)	3 (2.1)
All	41/738 (5.6)	32/738 (4.3)	68/738 (9.2)	141/738 (19.1)
Ongoing at 7 weeks	–	–	433	–
1 fetus	–	–	375 (87.4)	–
2 fetuses	–	–	53 (12.4)	–
3 fetuses	–	–	1 (0.2)	–
OHSS	40 (5.2)	21 (3.7)	77 (4.1)	138 (4.3)
Mild	23 (57.5)	13 (61.9)	–	–
Moderate	9 (22.5)	6 (28.6)	–	–
Severe	7 (17.5)	2 (9.5)	–	–

HCG = human chorionic gonadotrophin; OHSS = ovarian hyperstimulation syndrome.

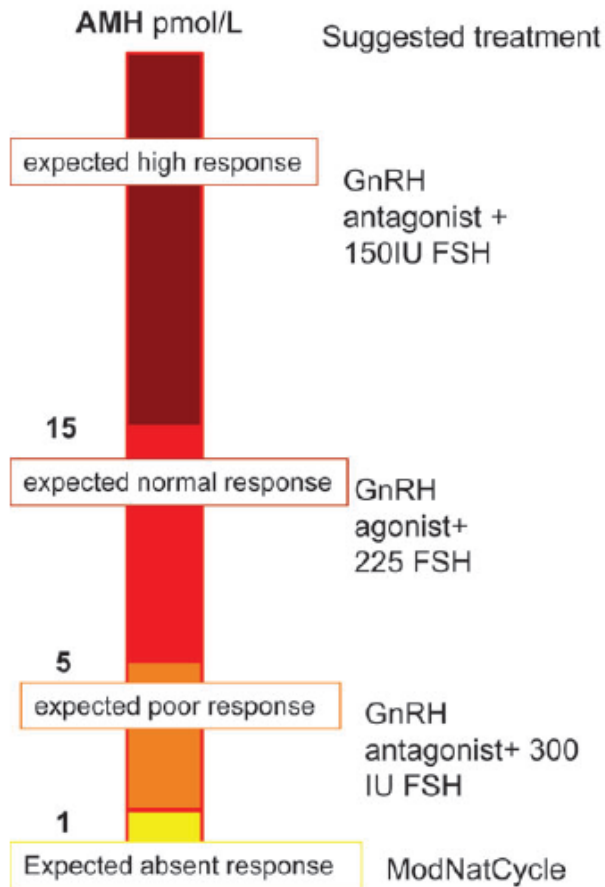
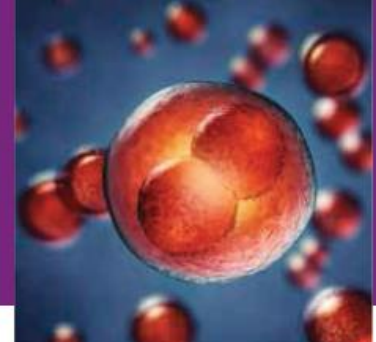
9/1282: 0,7%

Hovatta O. RBM Online Vol 18. No. 4, 2009

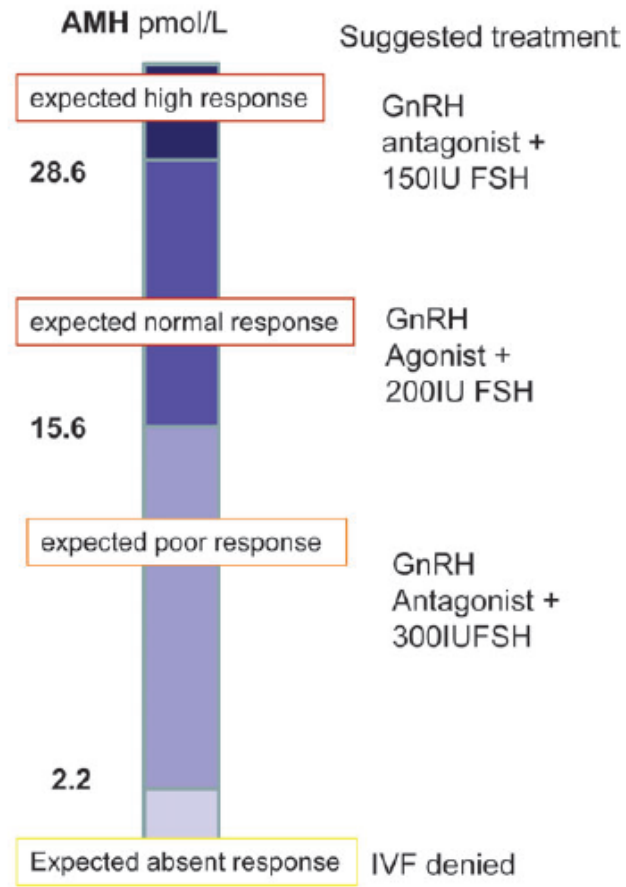
Individualizing the treatment



Individualizing the treatment



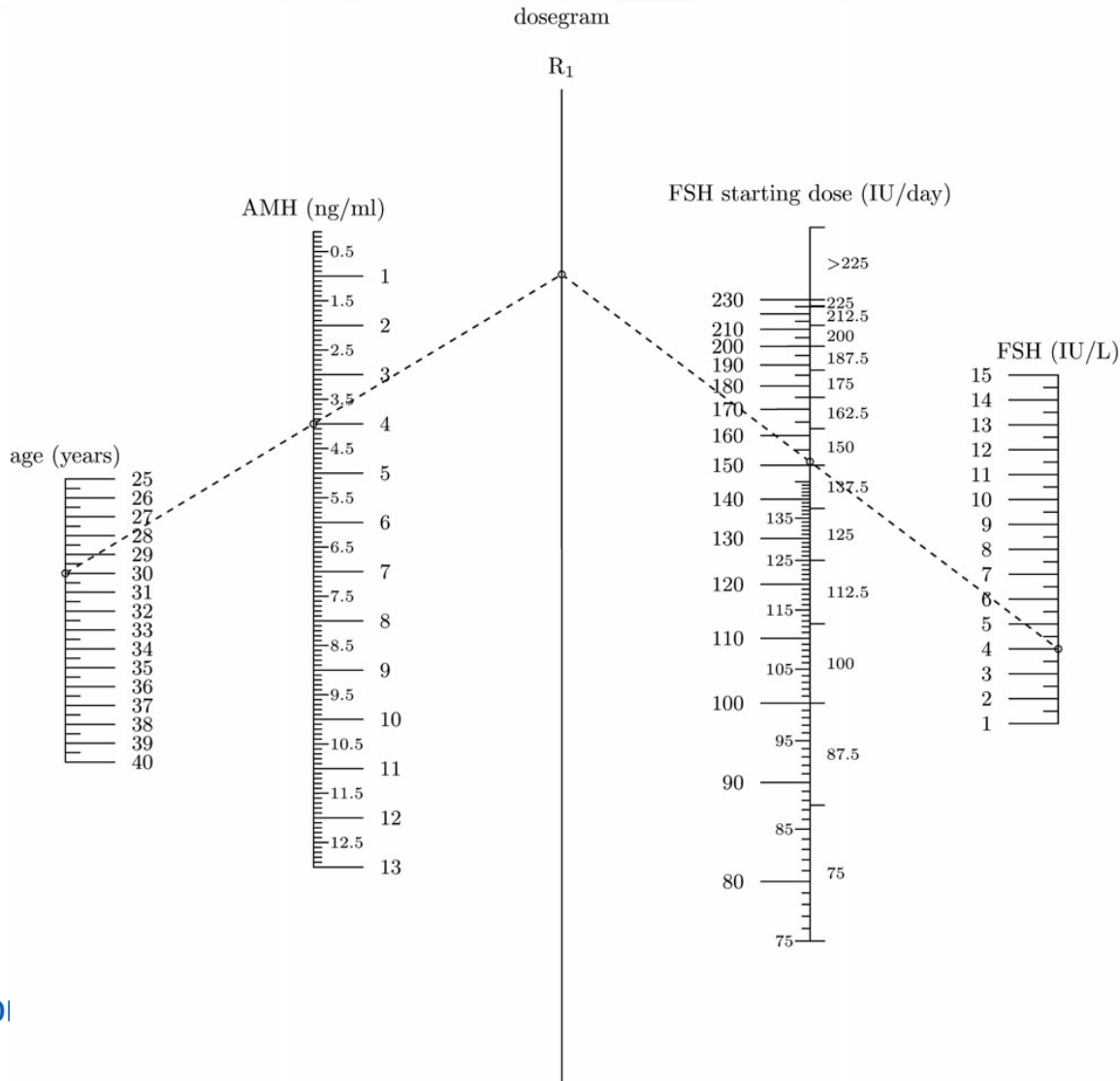
Nelson, Human Reprod, 2009



Yates, Human Reprod, 2011

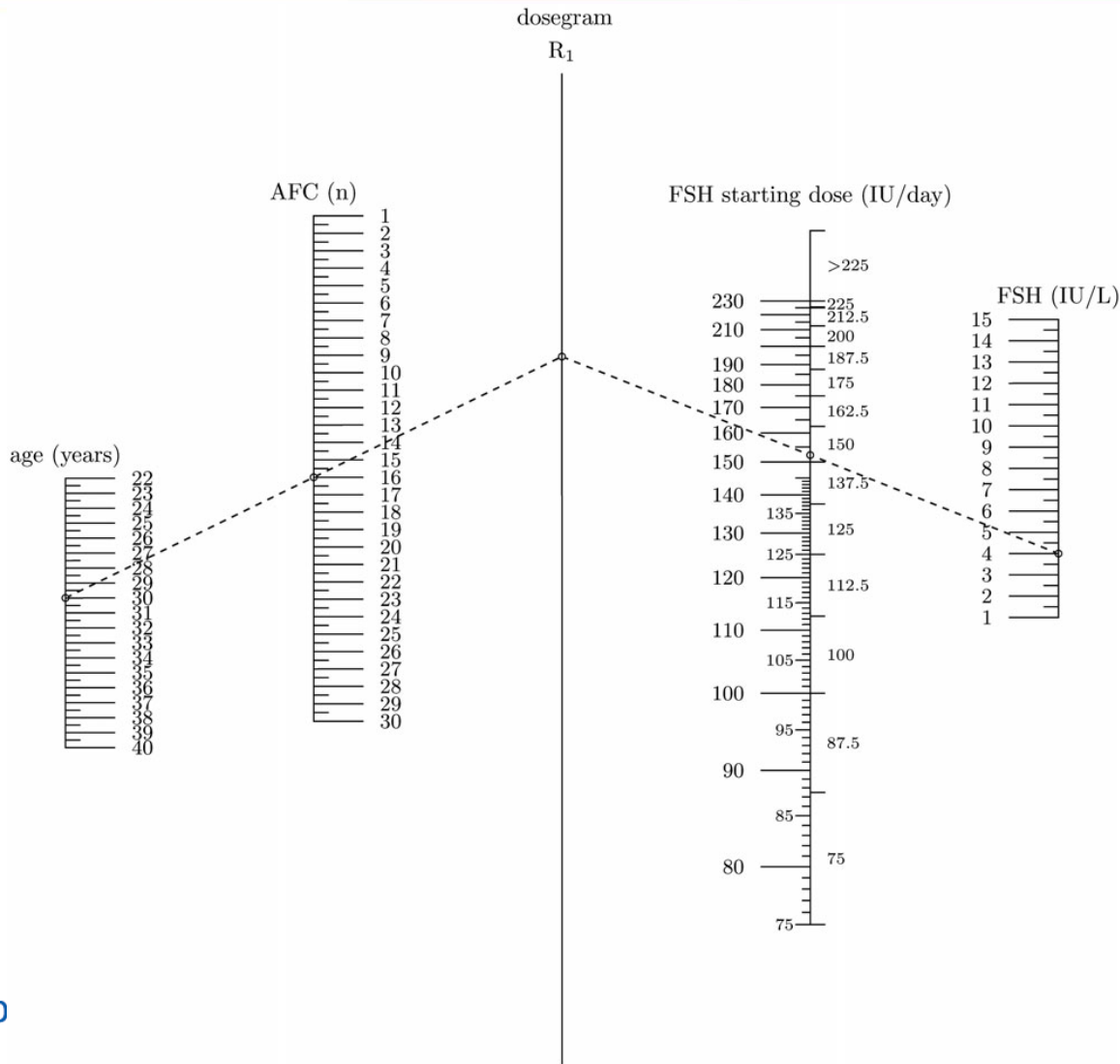
Normograms for the selection of the rFSH starting dose in IVF cycles and **AMH**

(La Marca & Sunkara, 2014)

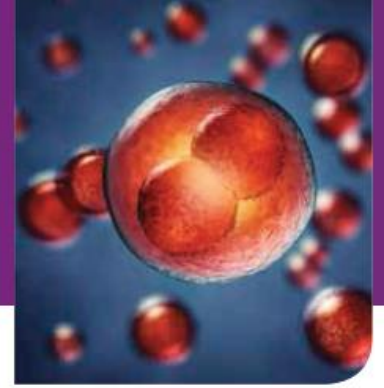


Normograms for the selection of the rFSH starting dose in IVF cycles and **AFC**

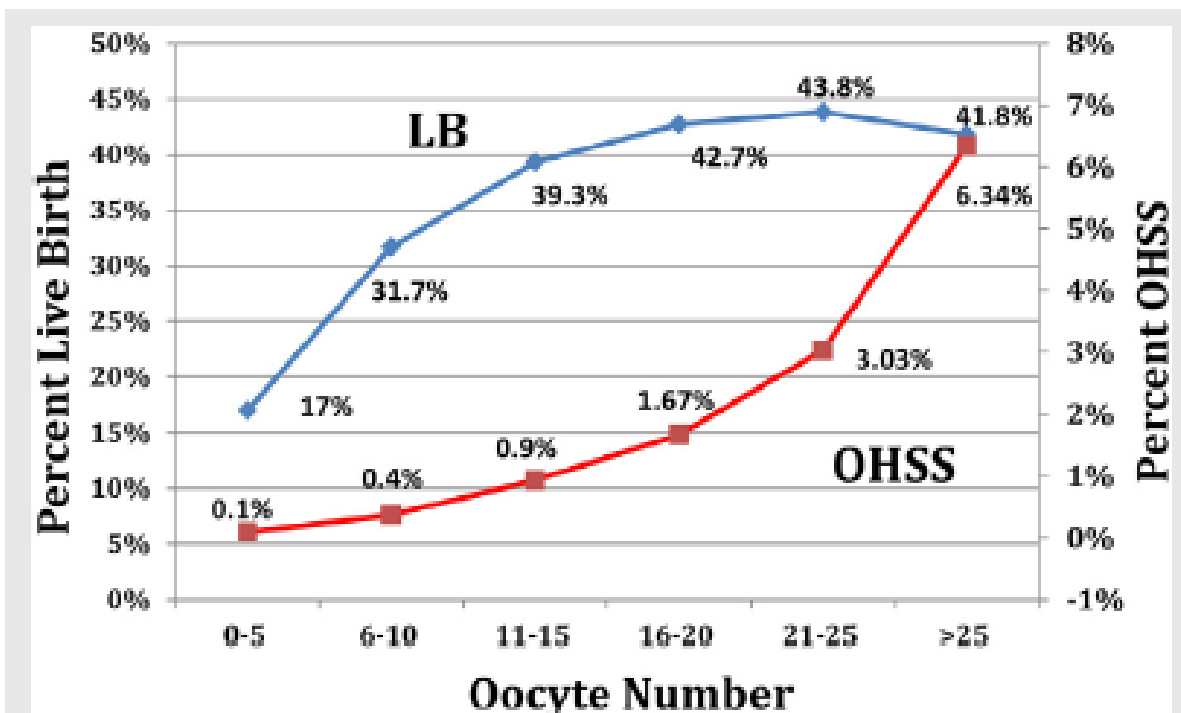
(La Marca & Sunkara, 2014)



Now what about a pragmatic decision on dosing



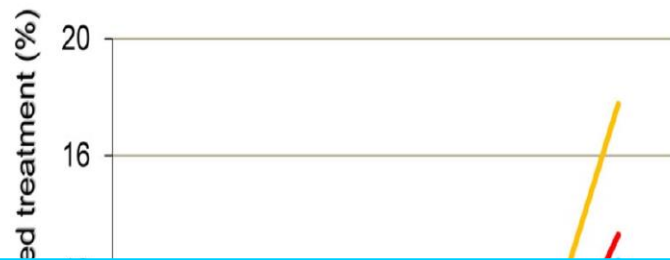
Oocyte number as predictor for OHSS and live birth (256,381 cycles)



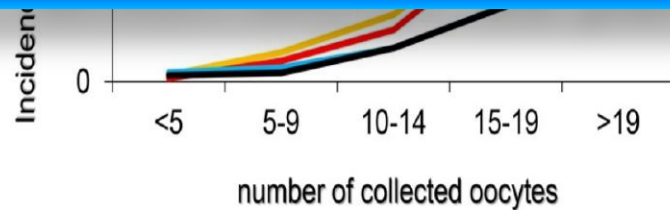
Percentages of ovarian hyperstimulation syndrome (OHSS) and live birth (LB) per retrieved oocyte numbers per IVF cycle among SART members from 2008 to 2010. Other abbreviations as in Figure 1.

Steward. Retrieved oocyte number, OHSS, and LB. Fertil Steril 2014.

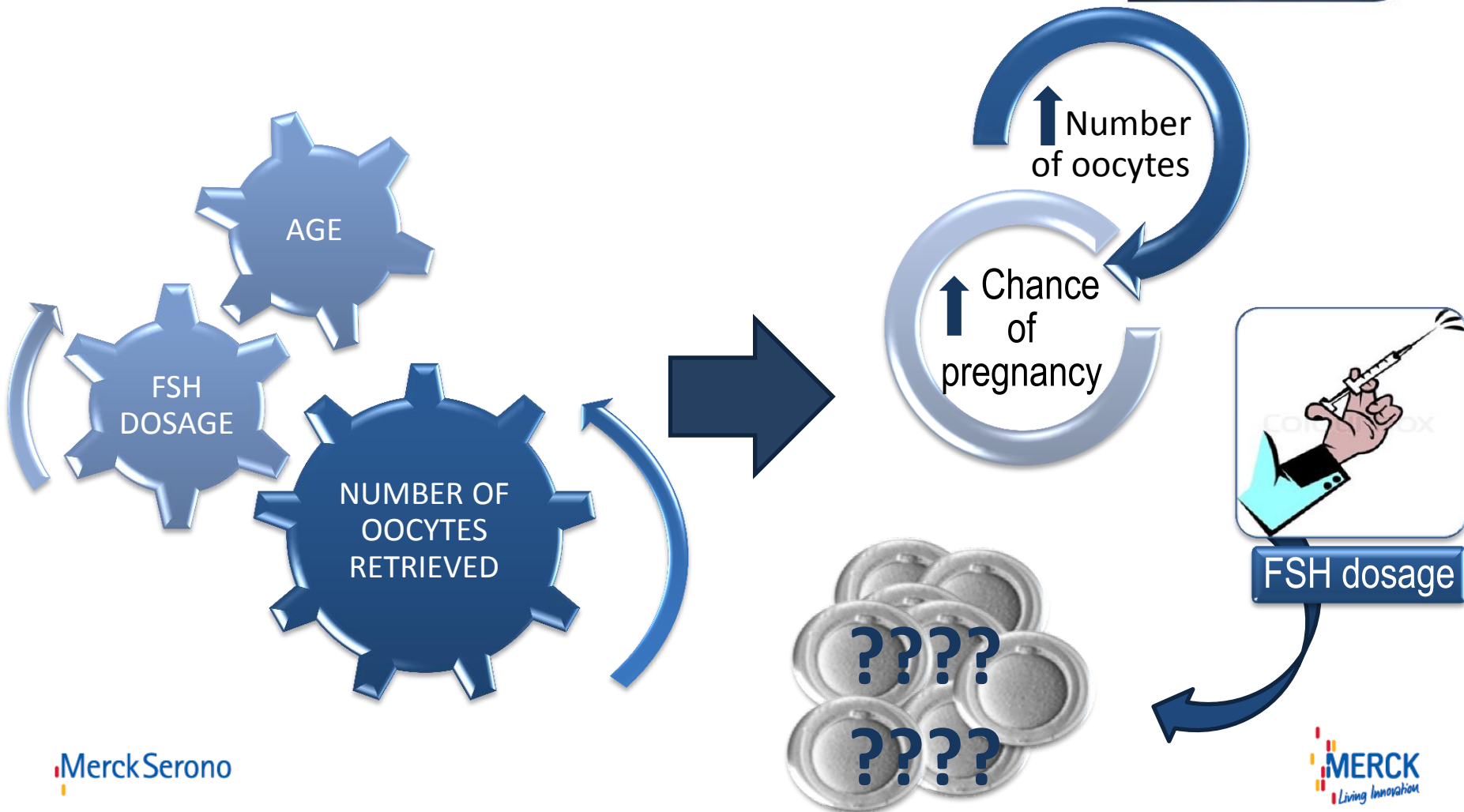
We MUST find the right balance!



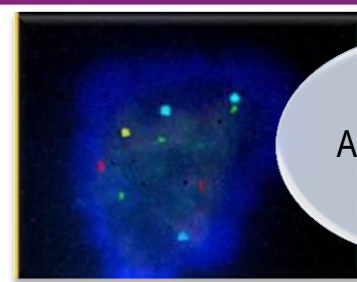
Maximize Efficacy by collecting what we have in the ovaries without compromising patient Safety which MUST be paramount!



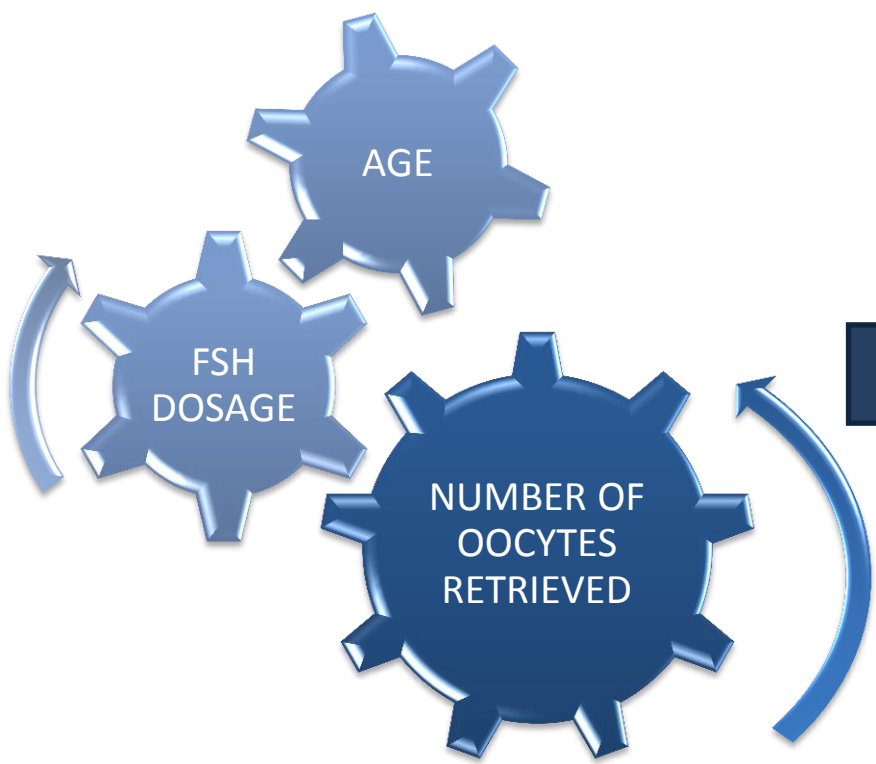
FSH dosage: Number x Quality



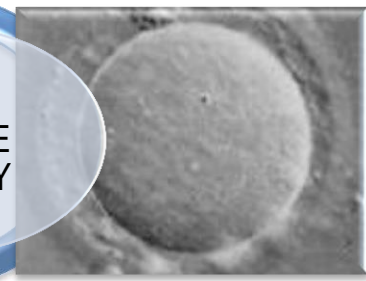
FSH dosase: Number x Quality



ANEUPLOIDY



POOR OOCYTE QUALITY



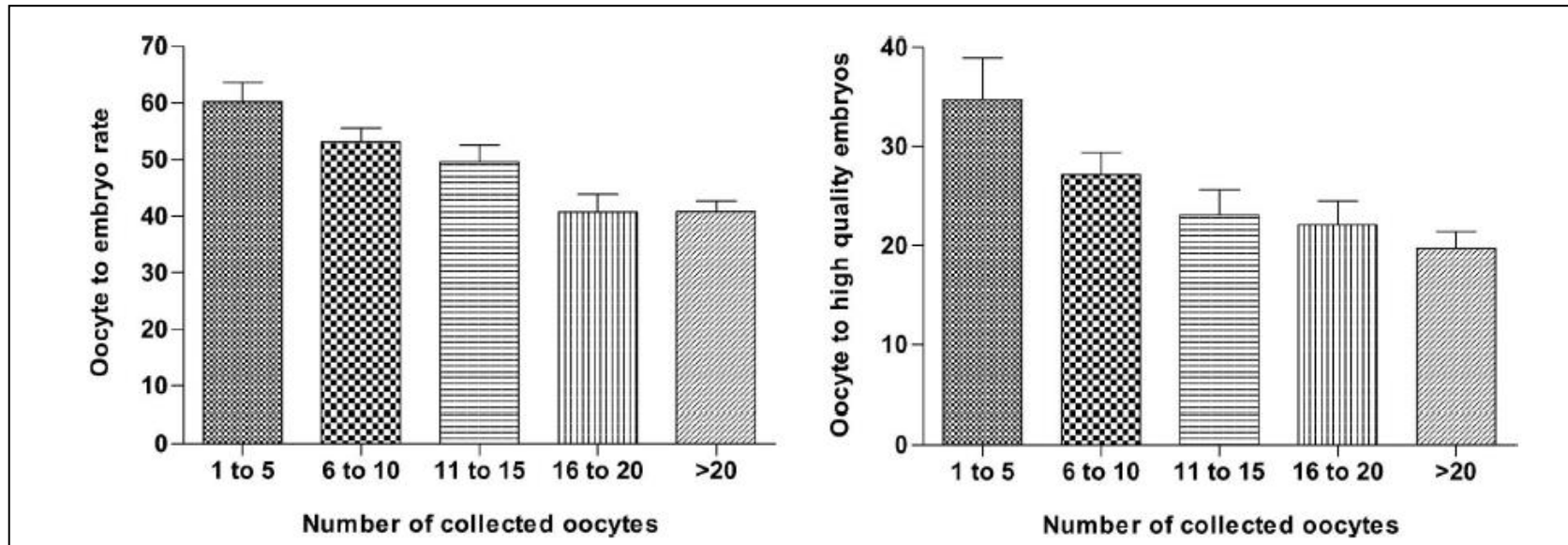
POOR EMBRYO QUALITY

Oocyte yield and dysmorphisms as indicators of biological efficiency in intracytoplasmic sperm injection cycles



RITA DE CÁSSIA SAVIO FIGUEIRA¹, DANIELA PAES ALMEIDA FERREIRA BRAGA^{1,2},
LUCIANA SEMIÃO-FRANCISCO¹, ASSUMPTO IACONELLI Jr.^{1,2}, &
EDSON BORGES Jr.^{1,2}
Human Fertility, March 2011; 14(1): 41–47

¹Fertility – Assisted Fertilization Center, São Paulo, SP, Brazil and ²Sapientiae Institute, Educational and Research Center in Assisted Reproduction, São Paulo, SP, Brazil

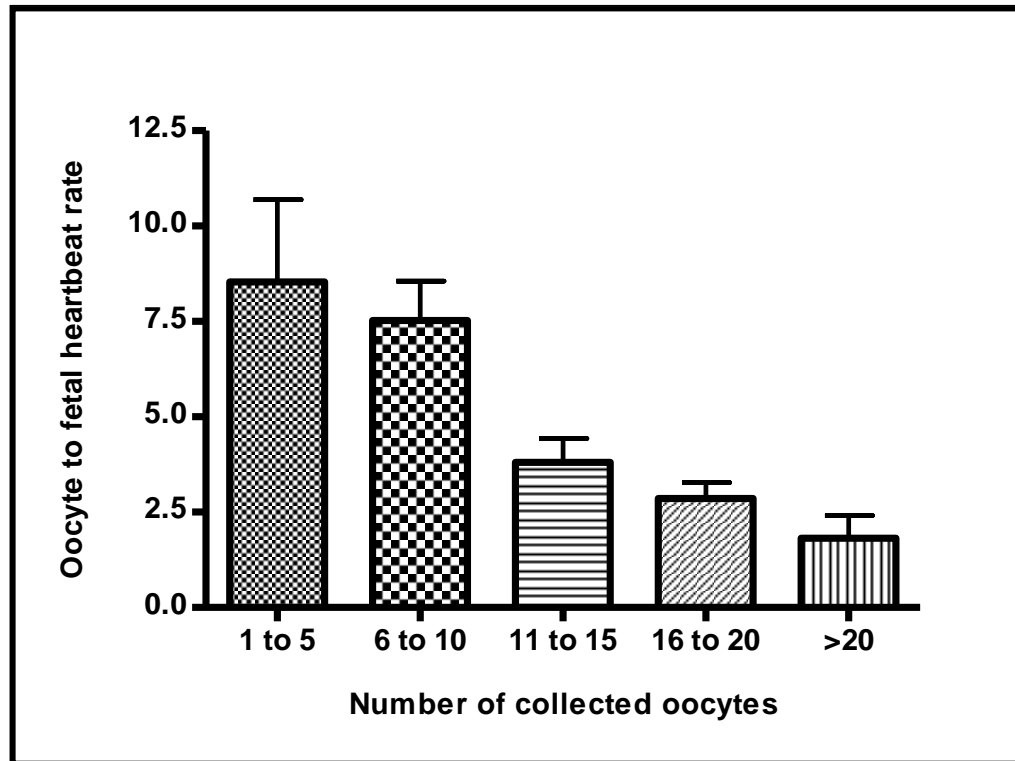


Oocyte yield and dysmorphisms as indicators of biological efficiency in intracytoplasmic sperm injection cycles



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¹Fertility – Assisted Fertilization Center, São Paulo, SP, Brazil and ²Sapientiae Institute, Educational and Research Center in Assisted Reproduction, São Paulo, SP, Brazil



Response to Ovarian Stimulation and Miscarriage

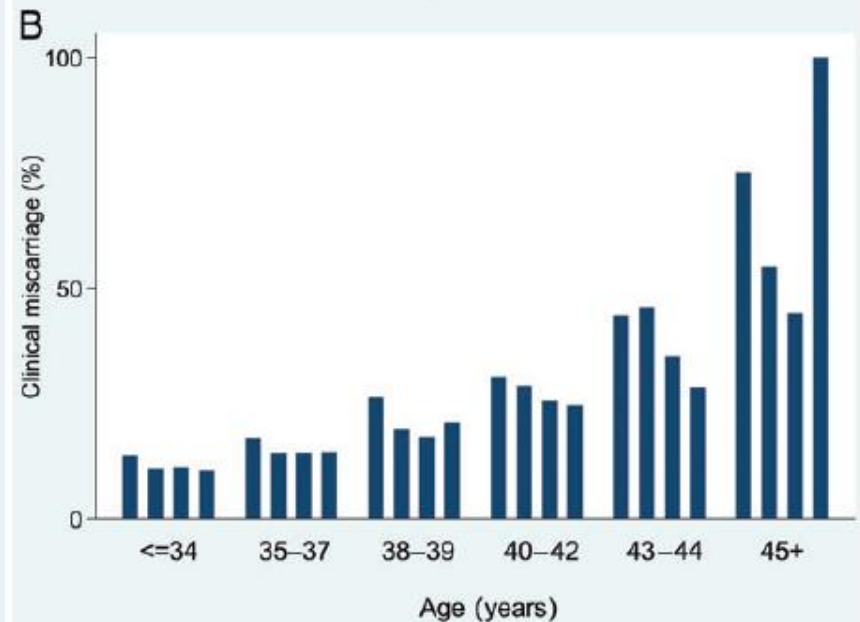
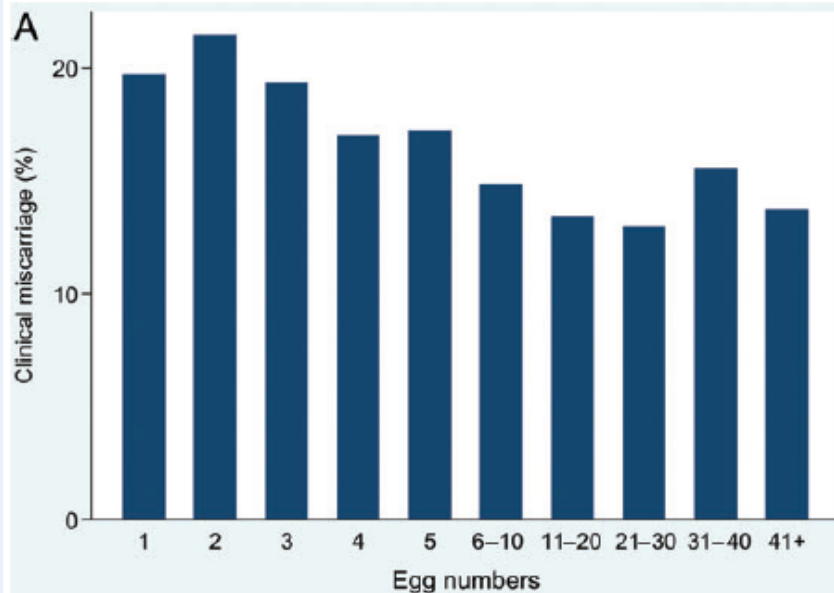
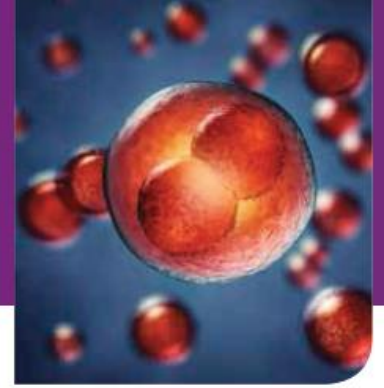


Figure 3 Relationship between oocyte number and clinical miscarriage rate. **(A)** Overall association. **(B)** Stratified by age group. Each age group was divided according to oocyte number; from left to right: 1–3 oocytes, 4–9 oocytes, 10–14 oocytes, ≥ 15 oocytes.

1. Agonist triggering in Antagonist cycles



➤ *GnRHa trigger: luteal LH-like/LH rescue protocol
– more physiologic*

1. Leuprolide acetate 1,0 – 2,0 mg
2. Triptorelin 0,2 mg
3. Buserelin 0,5 mg

1. Agonist triggering in Antagonist cycles

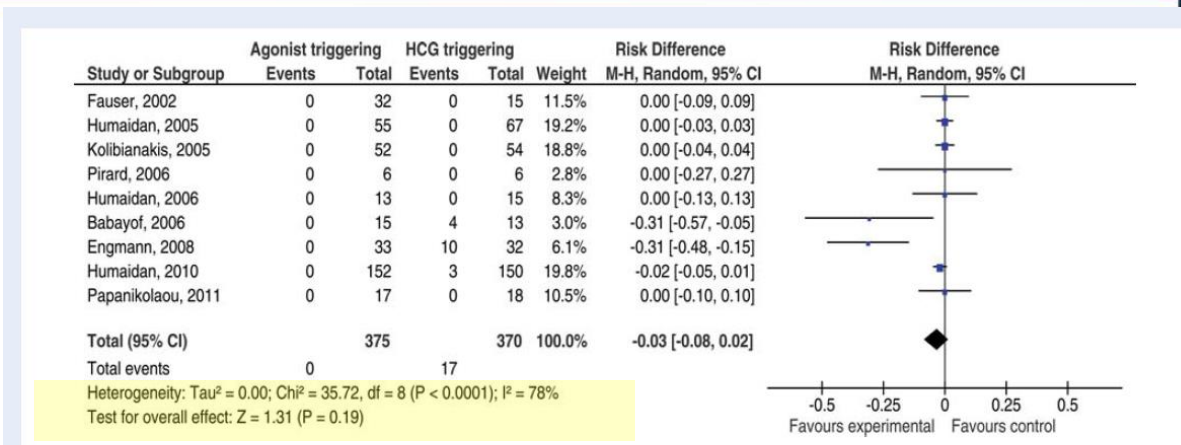


Figure 3 OHSS rate in fresh IVF cycles with embryo transfer.

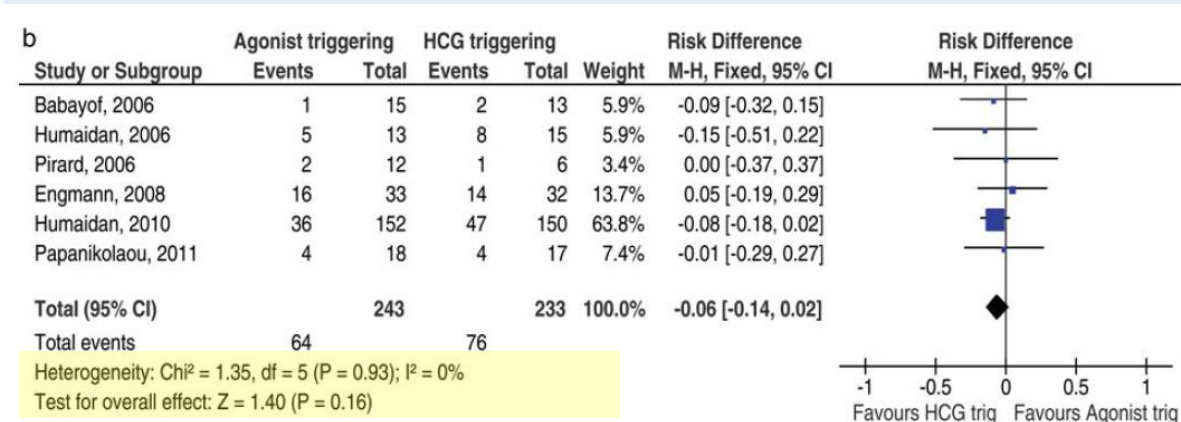
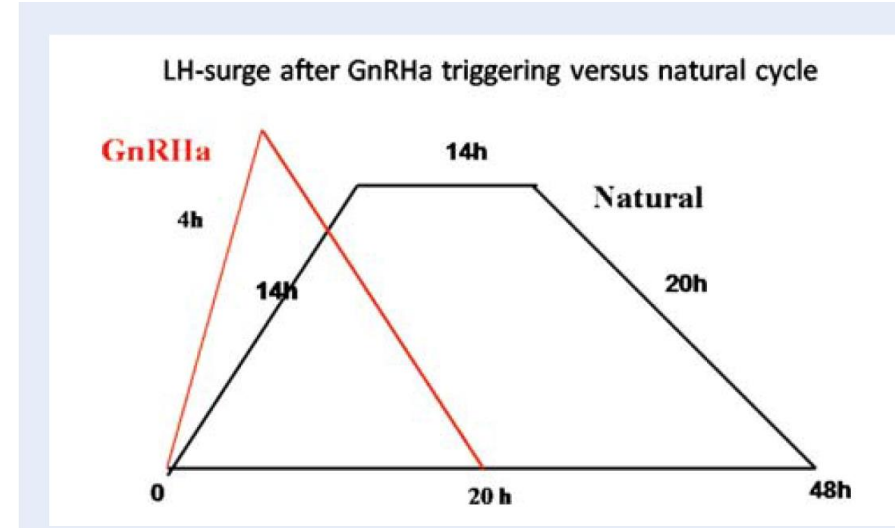
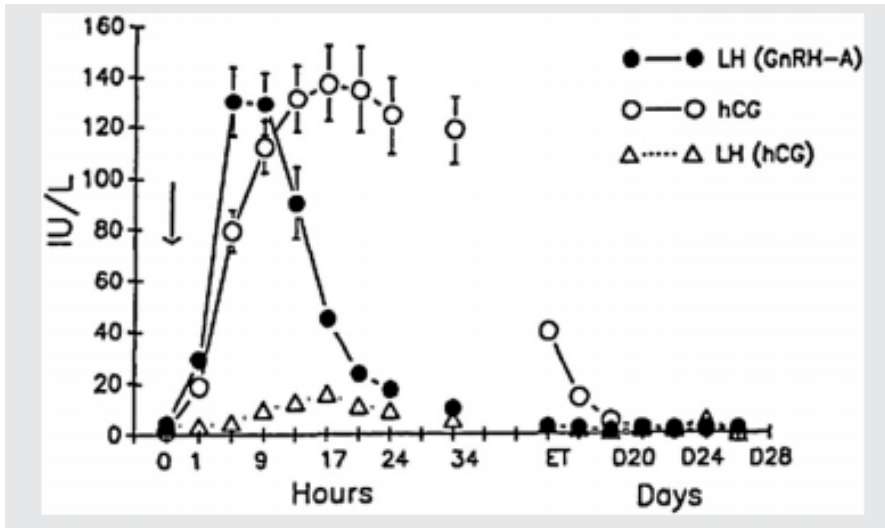


Figure 2

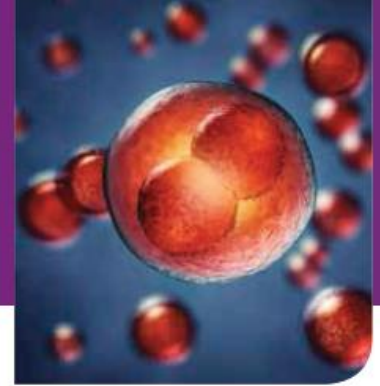
(b) Delivery rate after modified luteal support.

2. Modified Luteal Fase Support LH vs. hCG vs. GnRH



Casper R.F., Fertil Steril vol 103, No. 4, April 2015

Agonist triggering in Antagonist cycles need especial luteal support to avoid reduced pregnancy

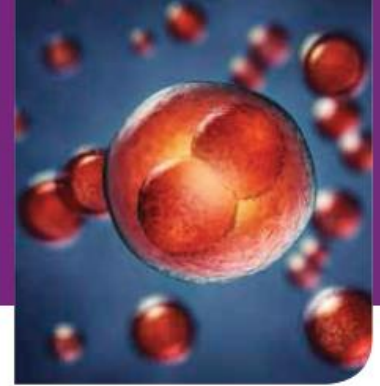


Bolus HCG OPU-day

Intense
Progesterone-
Estradiol
Luteal support

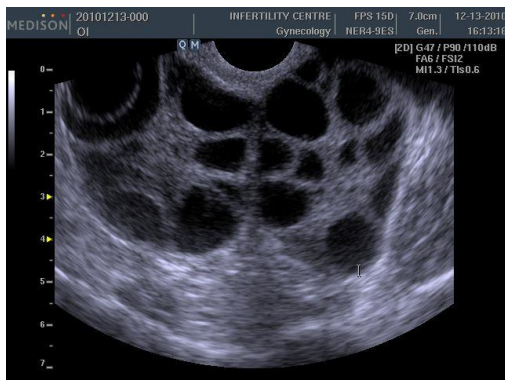
2. Modified Luteal Fase Support

Bolus hCG + E₂ – PROG support

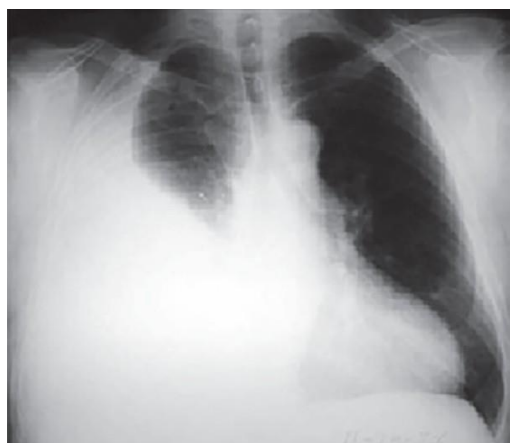
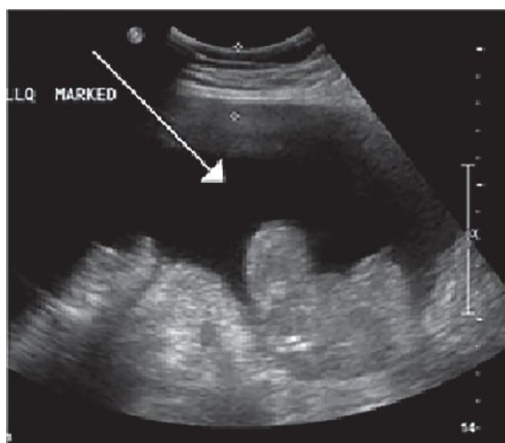


- *GnRHa trigger causes severe luteolysis, modifications of the standard luteal phase support are mandatory to maintain a good reproductive outcome after fresh embryo transfer*
- ✓ hCG rescue: one bolus of 1.500 IU hCG on the day of oocyte retrieval
- ✓ Oral or transdermal E₂ + vaginal PROG initiated directly after oocyte retrieval

2. Modified Luteal Fase Support: is it totally safe??



➤ ***Modified luteal phase support does not eliminate the risk of OHSS***

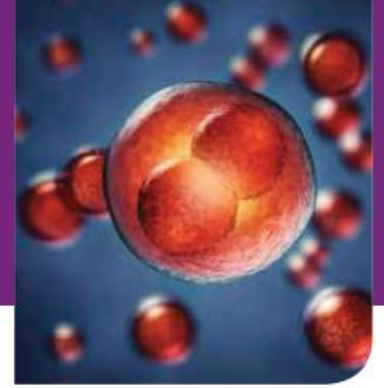


➤ ***If the patient became pregnant: LATE OHSS - multiple pregnancy***

➤ ***Limit: women with more than 25 follicles***

So what are the treatment options?

3. “Freeze all” strategy



➤ *Avoid endometrial and embryo exposure to extremely elevated steroid concentrations:*

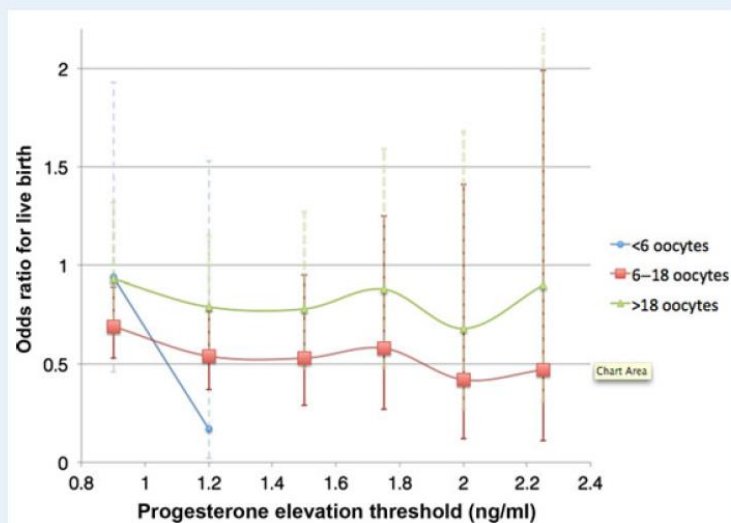
1. Histologic changes that are detrimental for endometrial receptivity and in the placenta formation
2. Embryotoxicity

Progesterone elevation: number of oocytes and live birth rates

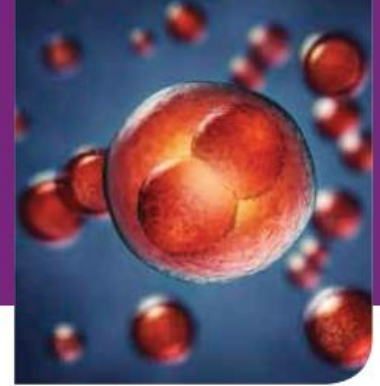


Table IV Distribution of cycles with or without PE according to the threshold used.

Threshold used (ng/ml)	<6 oocytes (n = 796) With PE, n (%)	6–18 oocytes (n = 1770) With PE, n (%)	>18 oocytes (n = 730) With PE, n (%)	Total (n = 3296) With PE, n (%)
0.9	158 (19.9)	849 (48.0)	470 (64.4)	1477 (44.8)
1.2	39 (4.9)	337 (19.0)	254 (34.8)	630 (19.1)
1.5	11 (1.4)	112 (6.3)	120 (16.4)	243 (7.4)
1.75	7 (0.9)	63 (3.6)	73 (10.0)	143 (4.3)
2.0	3 (0.4)	30 (1.7)	29 (4.0)	62 (1.9)
2.25	2 (0.3)	20 (1.1)	19 (2.6)	41 (1.2)



3. “Freeze all” strategy



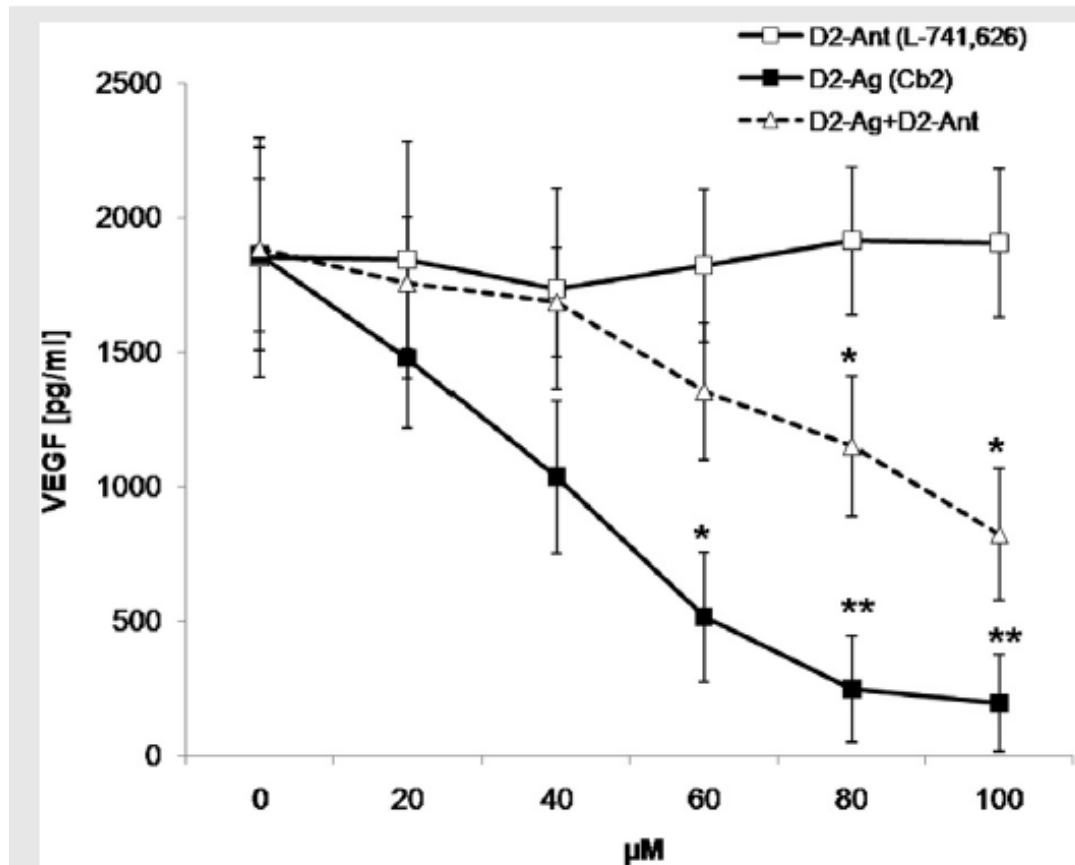
- *Pregnancies arising from frozen thawed IVF embryos had better obstetric and perinatal outcomes compared with pregnancies arising from fresh transfer IVF cycles*
- *Requires an optimal cryopreservation programme*

But...

Higher pregnancies loss?? Higher risk of epigenetic changes?? Higher malformation rates??

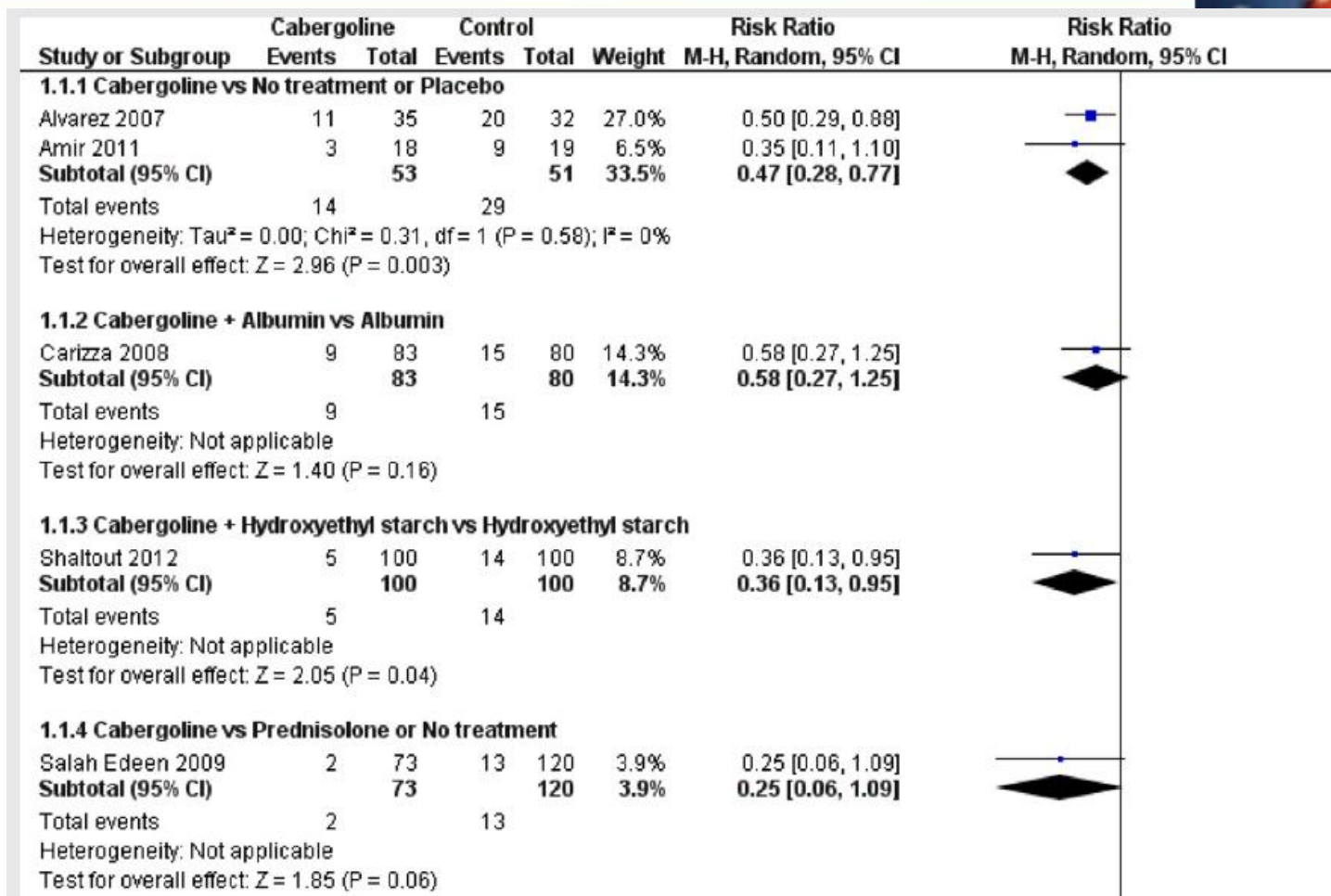
Minimize complications

Cabergolin: dopamine receptor 2 agonist



The effects of dopamine receptor 2 agonists (D2-Ag) and antagonists (D2-Ant) on vascular endothelial growth factor (VEGF) secretion by luteinized granulosa cells (GCs). Graph shows a dose-response

Cabergolin: OHSS prevention



Forest plot for moderate or severe ovarian hyperstimulation syndrome per allocated woman. CI = confidence interval; M-H = Mantel-Haenszel.

Cabergolin: OHSS prevention



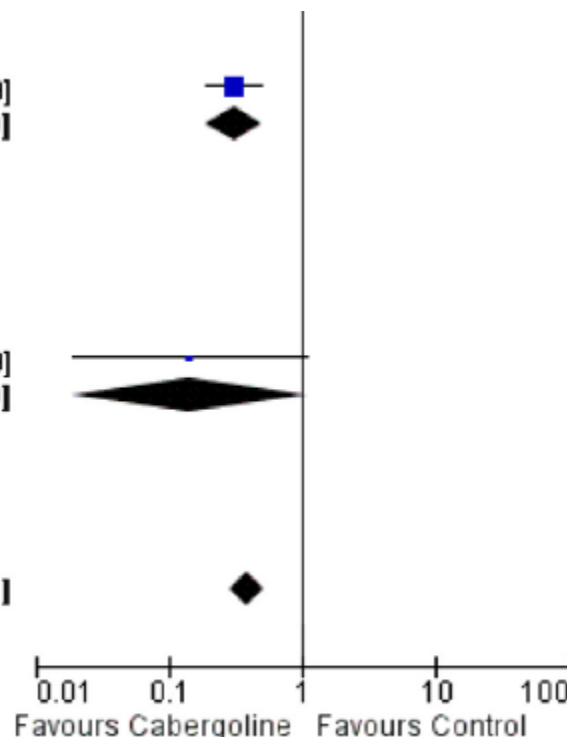
1.1.5 Cabergoline vs Albumin

Tehraninejad 2012	15	69	49	69	37.6%	0.31 [0.19, 0.49]
Subtotal (95% CI)		69		69	37.6%	0.31 [0.19, 0.49]
Total events	15		49			
Heterogeneity: Not applicable						
Test for overall effect: $Z = 4.91$ ($P < 0.00001$)						

1.1.6 Cabergoline vs Coasting

Sohrabvand 2009	1	30	7	30	2.0%	0.14 [0.02, 1.09]
Subtotal (95% CI)		30		30	2.0%	0.14 [0.02, 1.09]
Total events	1		7			
Heterogeneity: Not applicable						
Test for overall effect: $Z = 1.88$ ($P = 0.06$)						

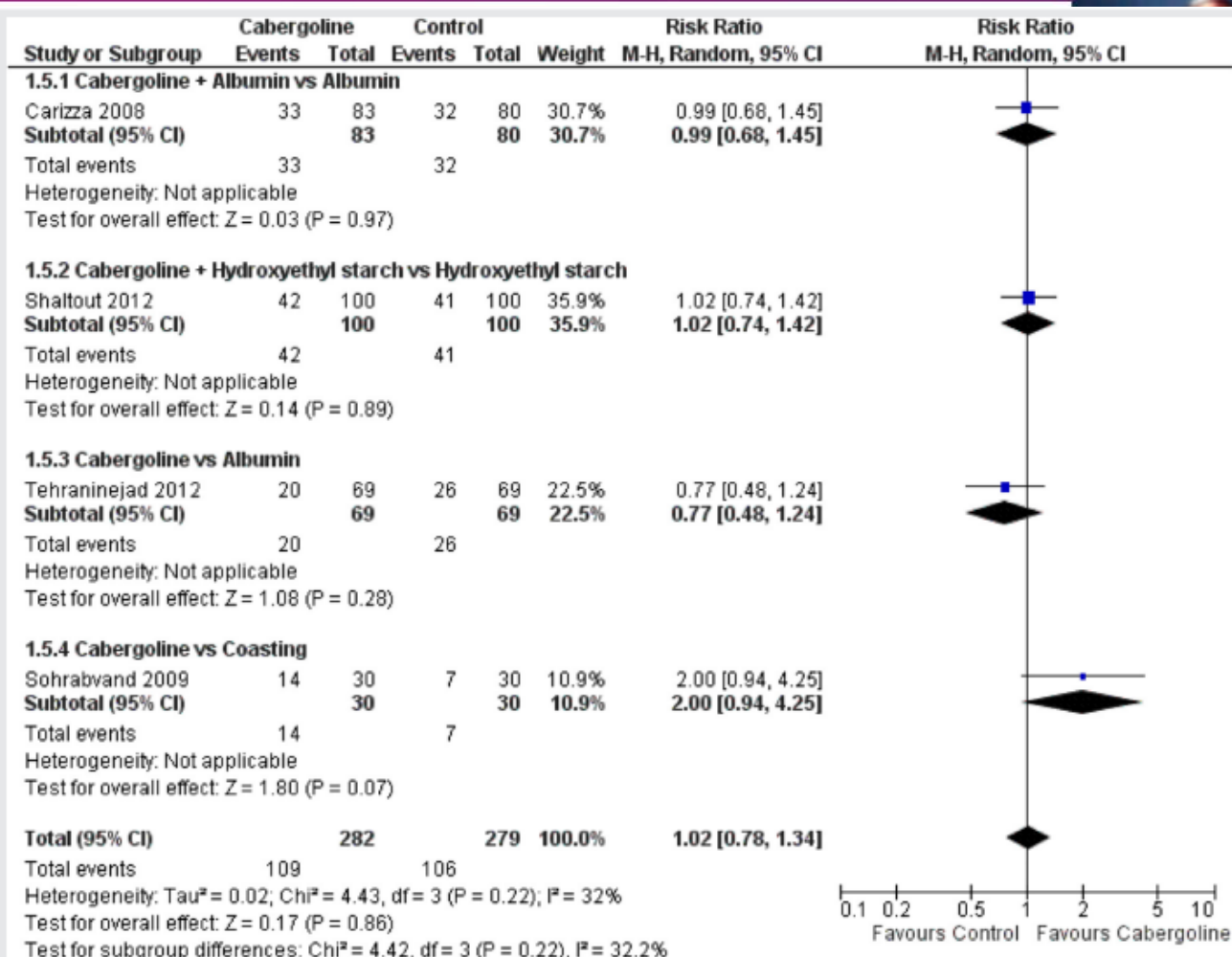
Total (95% CI)		408		450	100.0%	0.38 [0.29, 0.51]
Total events	46		127			
Heterogeneity: $\tau^2 = 0.00$; $\text{Chi}^2 = 4.21$, $\text{df} = 6$ ($P = 0.65$); $I^2 = 0\%$						
Test for overall effect: $Z = 6.49$ ($P < 0.00001$)						
Test for subgroup differences: $\text{Chi}^2 = 3.84$, $\text{df} = 5$ ($P = 0.57$), $I^2 = 0\%$						



Forest plot for moderate or severe ovarian hyperstimulation syndrome per allocated woman. CI = confidence interval; M-H = Mantel-Haenszel.

Leitao. Cabergoline for OHSS prevention. *Fertil Steril* 2014.

Cabergoline: OHSS and clinical pregnancy



Forest plot for clinical pregnancy per allocated woman. Abbreviations as in Figure 1.

Leitao. Cabergoline for OHSS prevention. Fertil Steril 2014.

Characteristics from OHSS cycles when fresh embryos were transferred or all of the embryos were cryopreserved (Fertility Medical Group - our data)



Cycles' Characteristics	Freeze all	Fresh embryo transfer	P
Number of cycles	123	153	
Number of patients	114	141	
Patient's age	32.6 ± 2,8	33.4 ± 2.9	0.431
Estradiol level (E2) on trigger day	4543± 2232	3326 ± 1657	0.003
Total dose of FSH for COS	2147 ± 606	2298 ± 756	0.456
Aspirated follicles	38.3 ± 14,7	37.9 ± 6.9	0.645
Retrieved oocytes	28.2 ± 10,9	27.4 ± 11.2	0.352
Retrieved oocytes rate	73.5%	73.1%	0.652
MII number	20.8 ± 8,0	20.4 ± 6.7	0.546
MII rate	73.8%	74.5%	0.336
Normal fertilization rate	80.7%	77.7%	0.451
Number of cryopreserved embryos	9.3 ± 4.6	5.2 ± 3.1	<0.0001

General characteristics from OHSS cycles when all of the embryos were cryopreserved (Fertility Medical Group - our data)



Embryo thawing cycles	Freeze all
Number of cycles	155
Number of patients	114
Patient's age on cryopreservation	32.2 ± 3.7
Patient's age on thawing	32.5 ± 3.6
Time of cryopreservation (mo)	3.0 ± 3.8
Thawing embryos	5.3 ± 2.4
Viable embryos after thawing	4.9 ± 2.2
Viable embryos rate	92.5%
Number of transferred embryos	2.2 ± 0.6

Number of thawing cycles from ovarian hyperstimulation syndrome cycles

Number of thawing cycles	Patients	Cycles
1 cycle	78	78
2 cycles	31	62
3 cycles	5	15
total	114	155

Clinical outcomes from OHSS when fresh embryos were transferred or all of the embryos were cryopreserved
(Fertility Medical Group - our data)



Cycle's outcomes	Freeze all (n=123)	Fresh embryo transfer (n=153)	P
Clinical pregnancy rate	49.0%	41.5%	0.004
Single pregnancy rate	67.2%	68.7%	0.589
Twin pregnancy rate	31.1%	28.1%	0.384
Triplet pregnancy rate	1.6%	0	0.754
Miscarriage rate	15.8%	15.6%	0.789
Implantation rate	38.6%	24.8%	0.028
Cumulative pregnancy rate	62.3%	-	
Estimated cumulative pregnancy rate	68.4%	55.7%	0.049

Characteristics from ovarian OHSS when the trigger was performed by using hCG or GnRH agonist (Fertility Medical Group - our data)



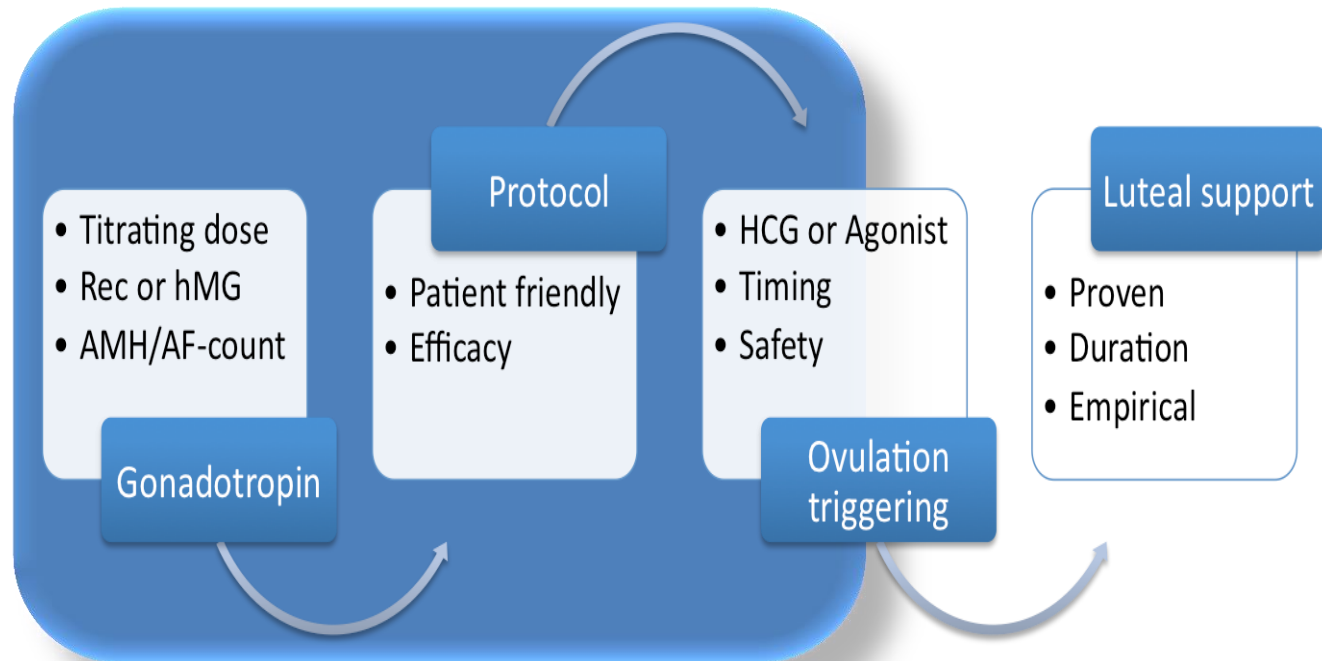
Cycles' Characteristics	hCG	GnRH agonist	P
Number of cycles	49	74	
Number of patients	45	69	
Patient's age	31.8 ± 3.8	31.9 ± 3.6	0.887
Estradiol level (E2) on trigger day	4039 ± 2112	5328 ± 3036	0.006
Total dose of FSH for COS	2259 ± 714	2067 ± 481	0.101
Aspirated follicles	34.5 ± 11,7	41.3 ± 17.9	0.015
Retrieved oocytes	25.3 ± 9,6	30.8 ± 11.3	<0.001
Retrieved oocytes rate	73.4%	74.5%	0.59
MII number	19.6 ± 7.8	22.0 ± 8.1	0.123
MII rate	77.2%	71.3%	<0.001
Normal fertilization rate	79.3%	84.0%	0.011
Number of cryopreserved embryos	9.2 ± 4.5	9.9 ± 4.9	0.422

Clinical outcomes from OHSS cycles when the trigger was performed by using hCG or GnRH agonist (Fertility Medical Group - our data)



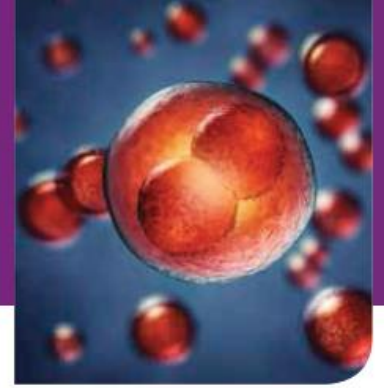
Cycle's outcomes	hCG (n=49)	GnRH agonist (n=74)	P
Clinical pregnancy rate	44.90%	51.35%	0.483
Single pregnancy rate	75.0%	76.9%	0.856
Twin pregnancy rate	26.1%	29.7%	0.585
Triplet pregnancy rate	4.35%	0	0.935
Miscarriage rate	29.7%	14.6%	0.164
Implantation rate	39.0%	37.1%	0.885
Cumulative pregnancy rate	53.0%	59.5%	0.483

If we would like to have an OHSS Free IVF Clinic



Individualization of IVF treatment

Conclusion



- ✓ Multiple strategies can be applied in patients under risk of OHSS depending on the situation:
 - ✓ Define ovarian reserve with AMH and/or AFC according to convenience
 - ✓ Utilize rFSH in low doses delivered in small increments by devices with proven precision
 - ✓ Antagonists cycles must be preferred and triggered with agonists
 - ✓ If fresh embryo transfer render risks of late OHSS, freeze all

- ✓ In cycles triggered with agonists intensify luteal phase support

Obrigado!! Gracias!! Thank You!!



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