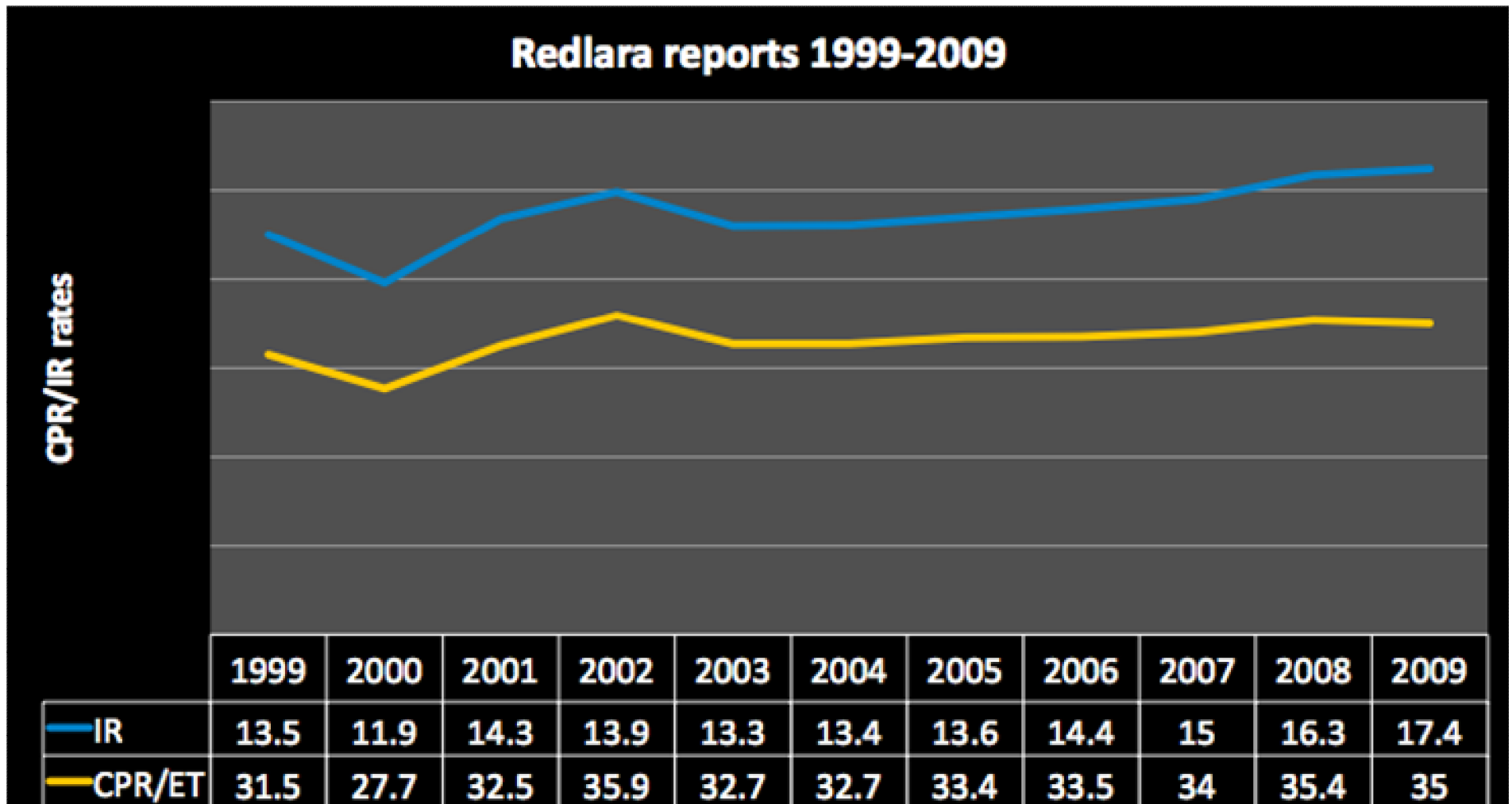


Clinical Decisions to Effectively Maximize Treatment Outcomes



Dr. Marcos Horton
Co-Director and Founder
Pregna Medicina Reproductiva
Past-President
Argentinian Society for Reproductive
Medicine
Buenos Aires, Argentina

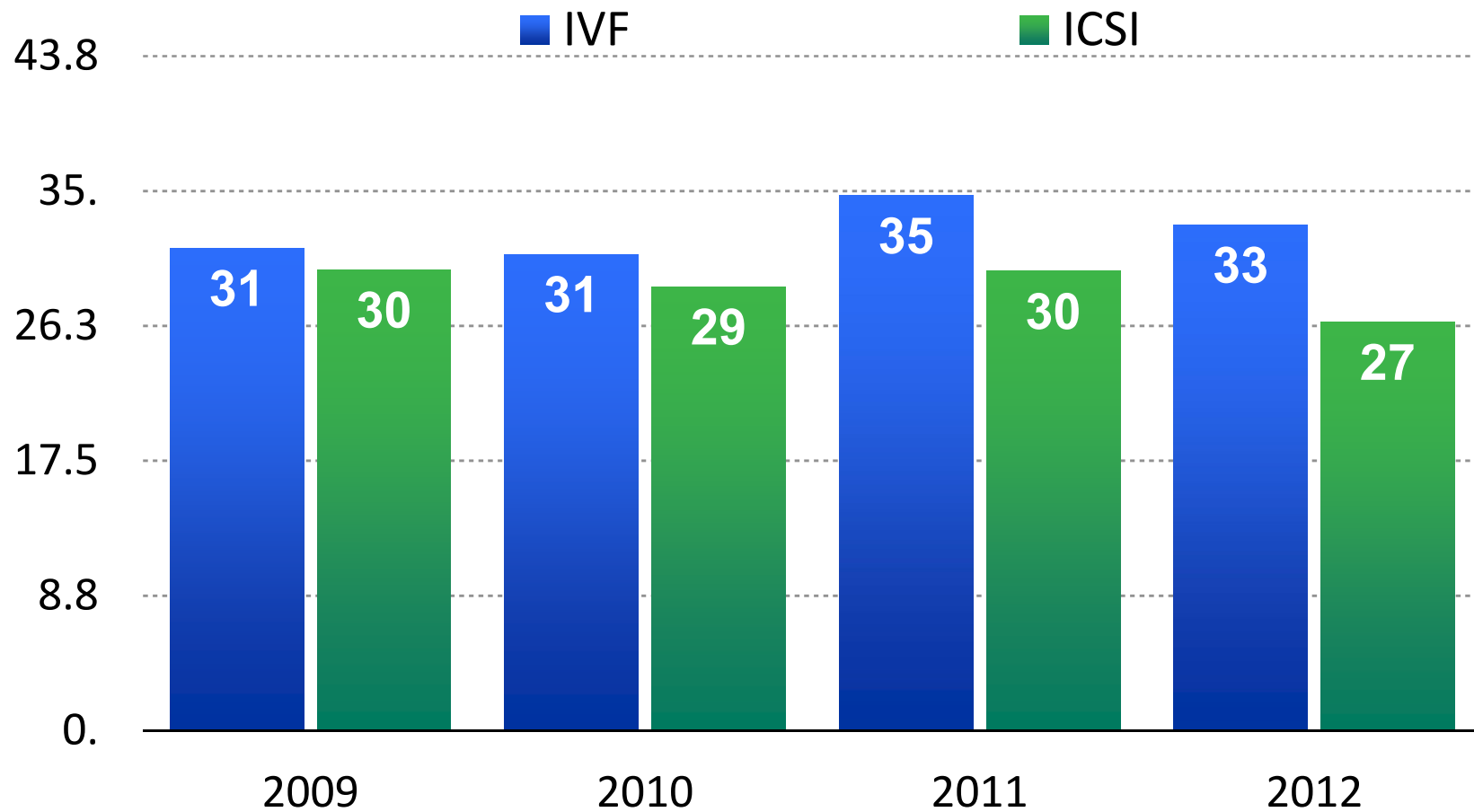
Despite Continuous Improvements in ART Clinical Results are Similar



REDLARA 2012

| Table 2. Clinical pregnancy rate and delivery rate IVF/ICSI (*) cycles in 2012. | | | |
|---|----------------------|---------------------------------|-----------------------|
| ART procedure | Oocyte pick up (OPU) | Clinical pregnancy rate per OPU | Delivery rate per OPU |
| ICSI | 25,420 | 26.5% | 20.9% |
| IVF | 4,404 | 32.8% | 26.5% |

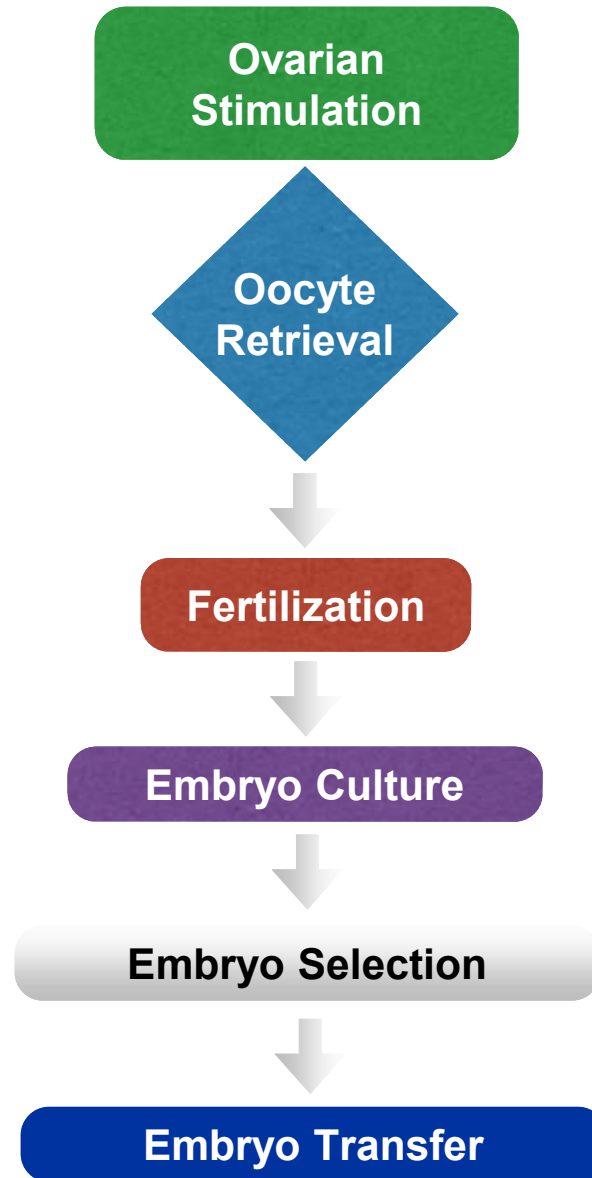
(*) one case was labeled as "other"



How to Optimize Results?

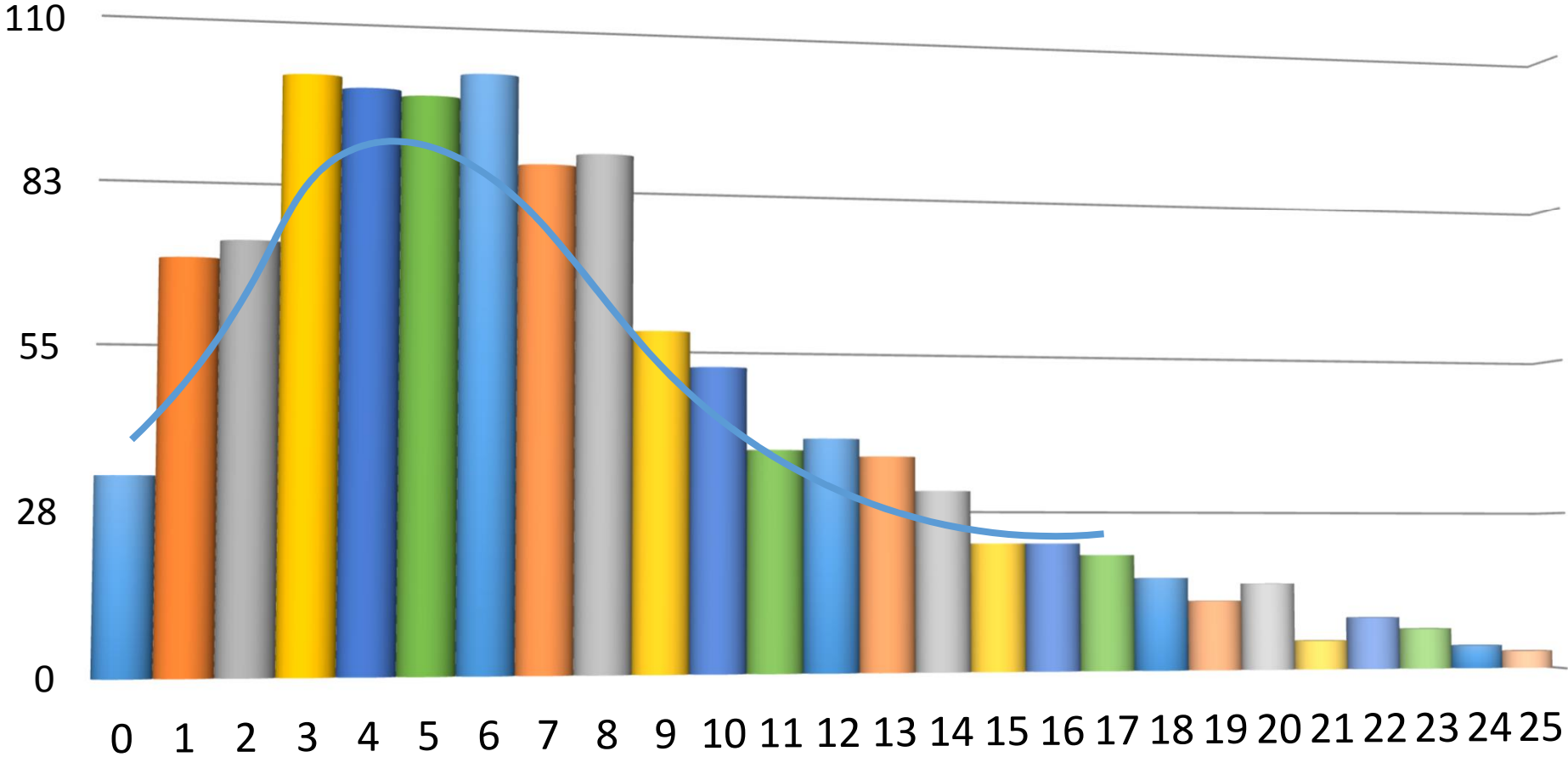


ART is a Multi-Step Process



Ovarian Stimulation

Eggs retrieved, N=1135, 2014



What is Normal? How Do We Individualize?



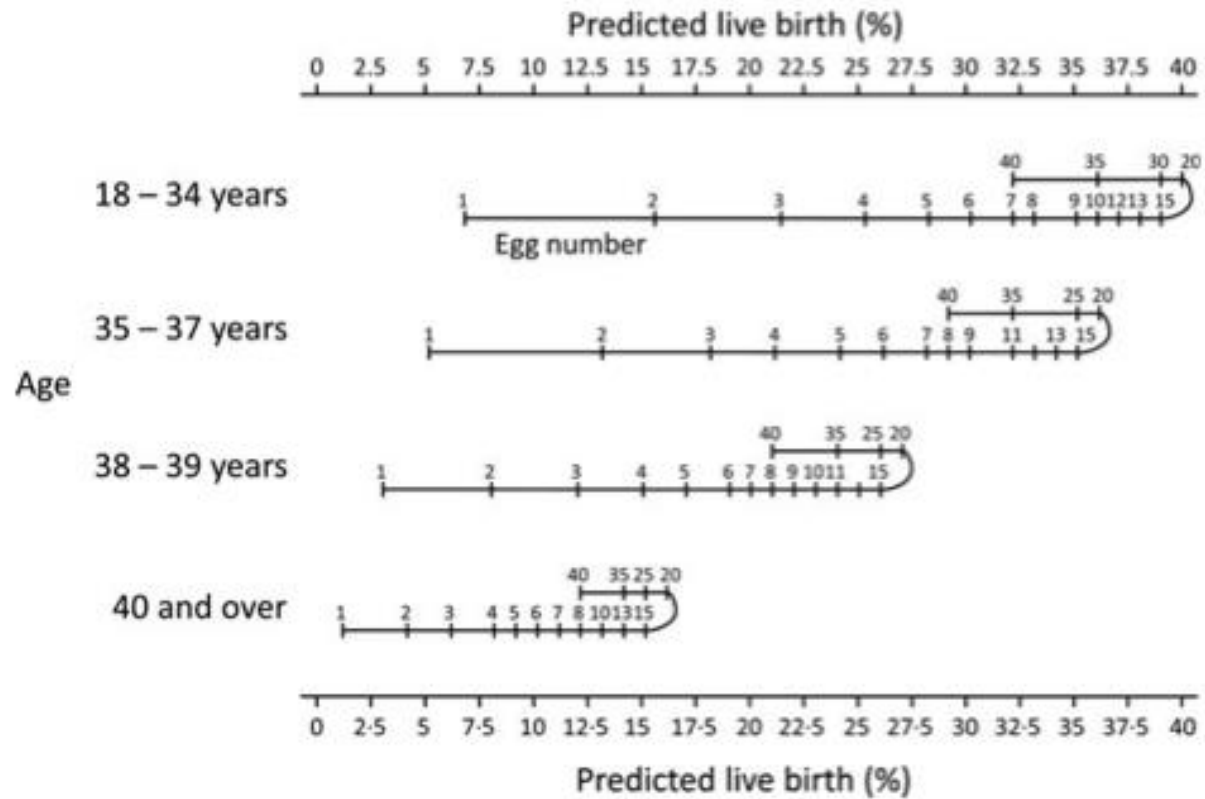


Figure 5 Nomogram to calculate predicted live birth probability given egg number and age.

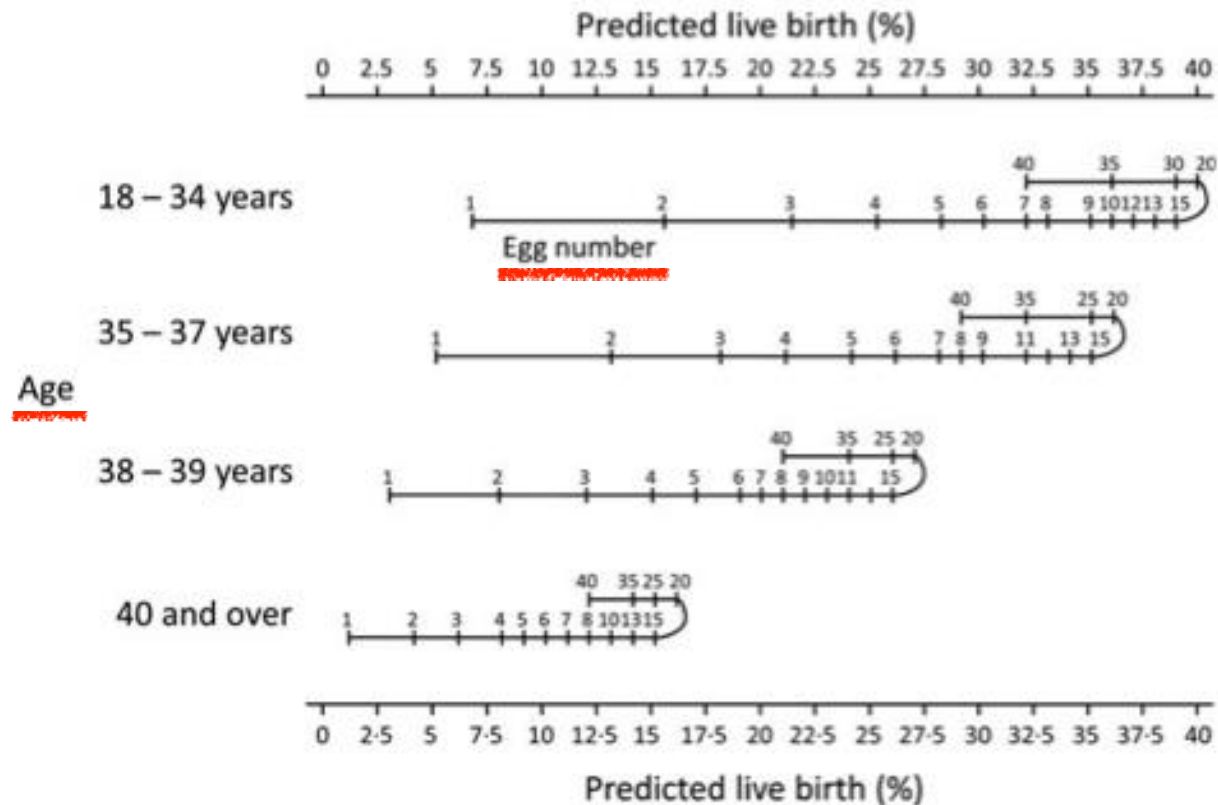
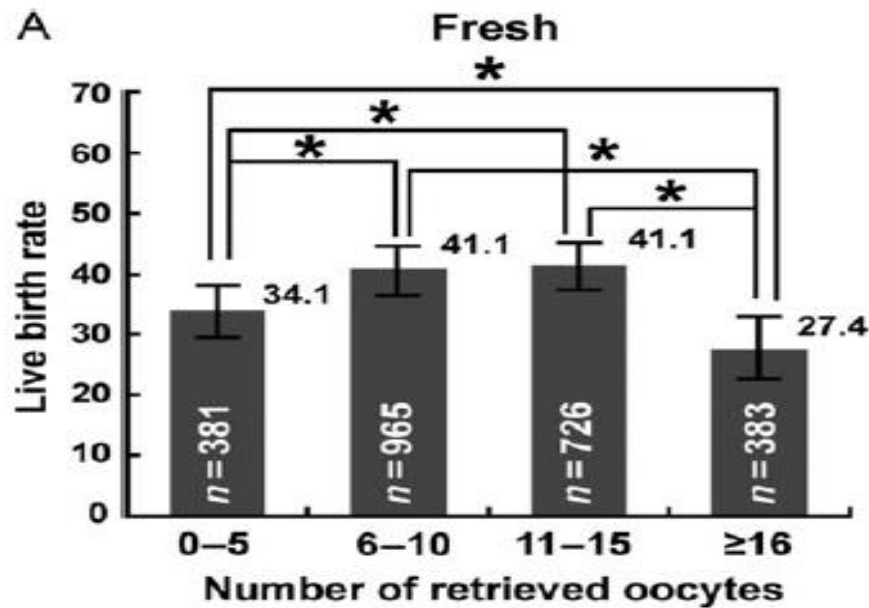


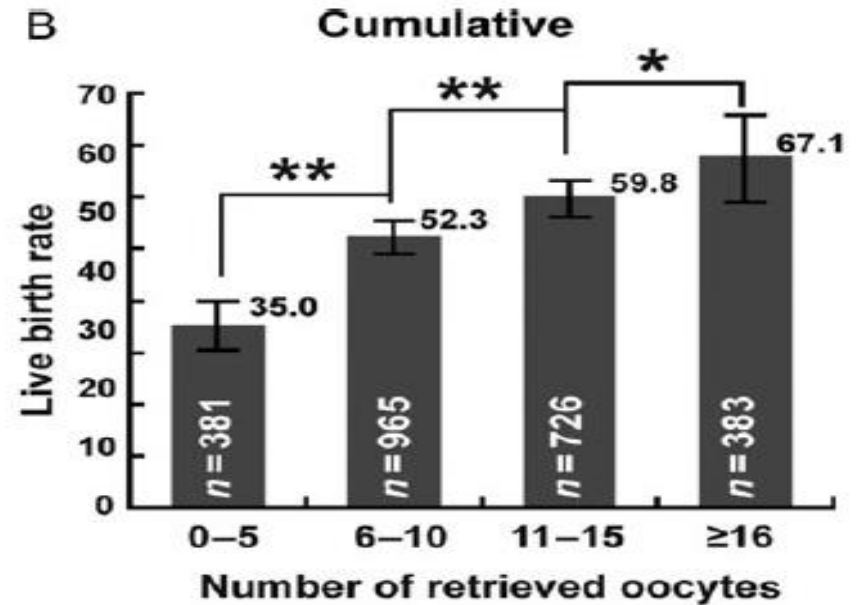
Figure 5 Nomogram to calculate predicted live birth probability given egg number and age.

Reproductive Performance & # Eggs

Pts 18-34 years old
Normal BMI



69%



69%

Clinical outcomes in relation to the daily dose of recombinant follicle-stimulating hormone for ovarian stimulation in *in vitro* fertilization in presumed normal responders younger than 39 years: a meta-analysis

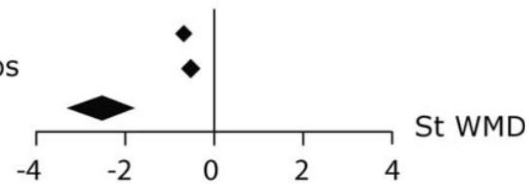
10 RCT
comparing
different rFSH
starting doses
N=1952 cycles

**M.D. Sterrenburg^{1,*}, S.M. Veltman-Verhulst¹, M.J.C. Eijkemans^{1,2},
E.G. Hughes³, N.S. Macklon^{1,4}, F.J. Broekmans¹, and B.C.J.M. Fauser¹**

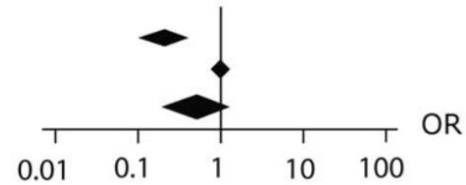
¹Department of Reproductive Medicine and Gynaecology, University Medical Centre Utrecht, Heidelberglaan 100, Utrecht 3584 CX, The Netherlands ²Julius Centre for Health Sciences and Primary Care, University Medical Centre, Utrecht, The Netherlands ³Department of Obstetrics and Gynaecology, McMaster University, Hamilton, Ontario, Canada ⁴Department of Obstetrics and Gynaecology, University of Southampton, Southampton, UK

A 100 IU/d versus 200 IU/d

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

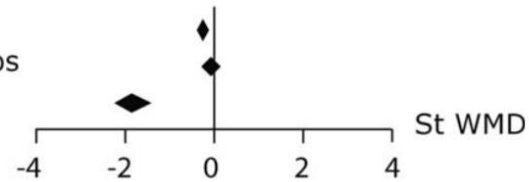


Chance of OPU
 Chance of pregnancy
 Chance of OHSS



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

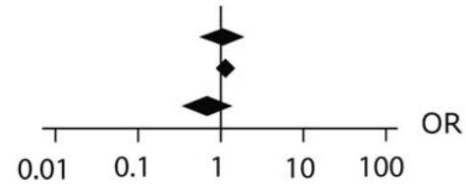
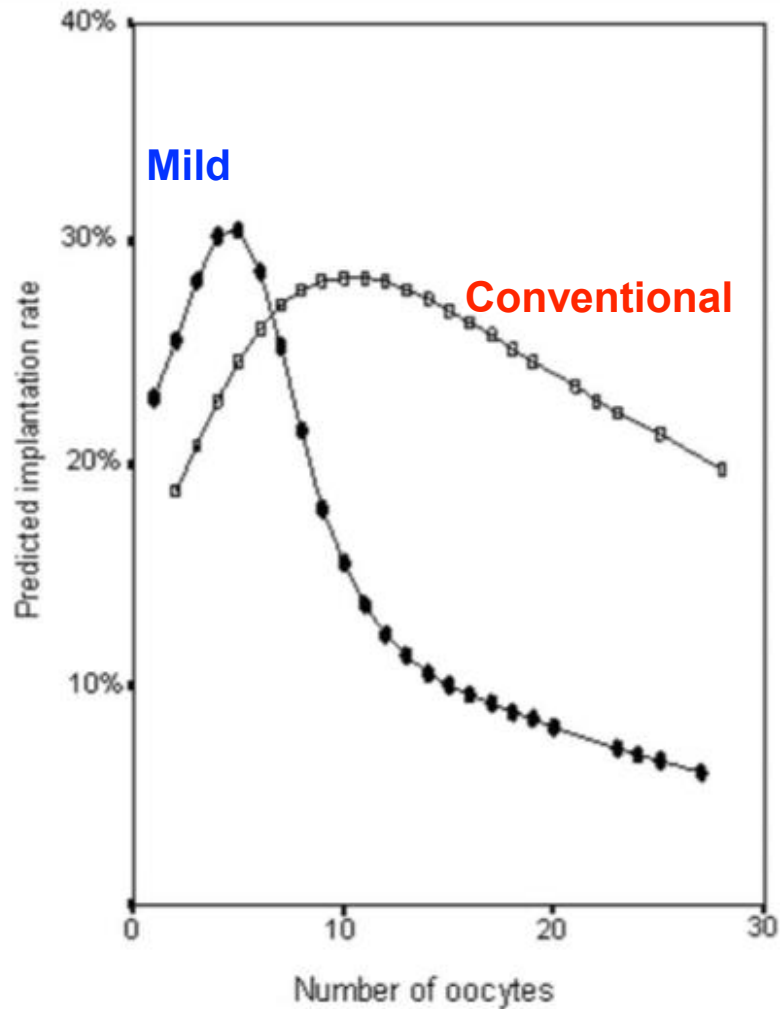


Figure 8 Summary all parameters; **(A)** Comparison A: 100 versus 200 IU/day; **(B)** Comparison B: 150 versus 200–250 IU/day. St WMD, standardized weighted mean difference; OR, odds ratio; OPU, ovum pick up; OHSS, ovarian hyperstimulation syndrome.

Outcome According to Ovarian Response

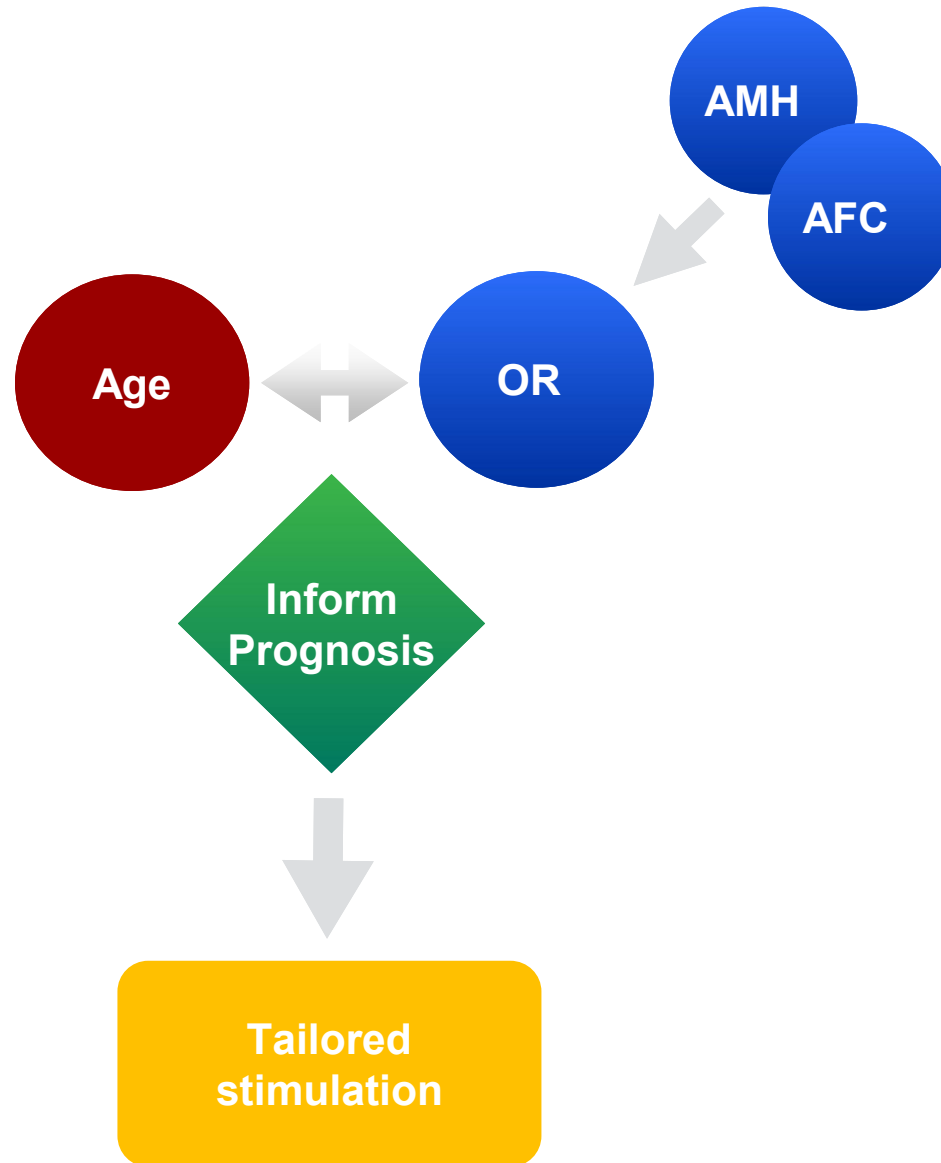


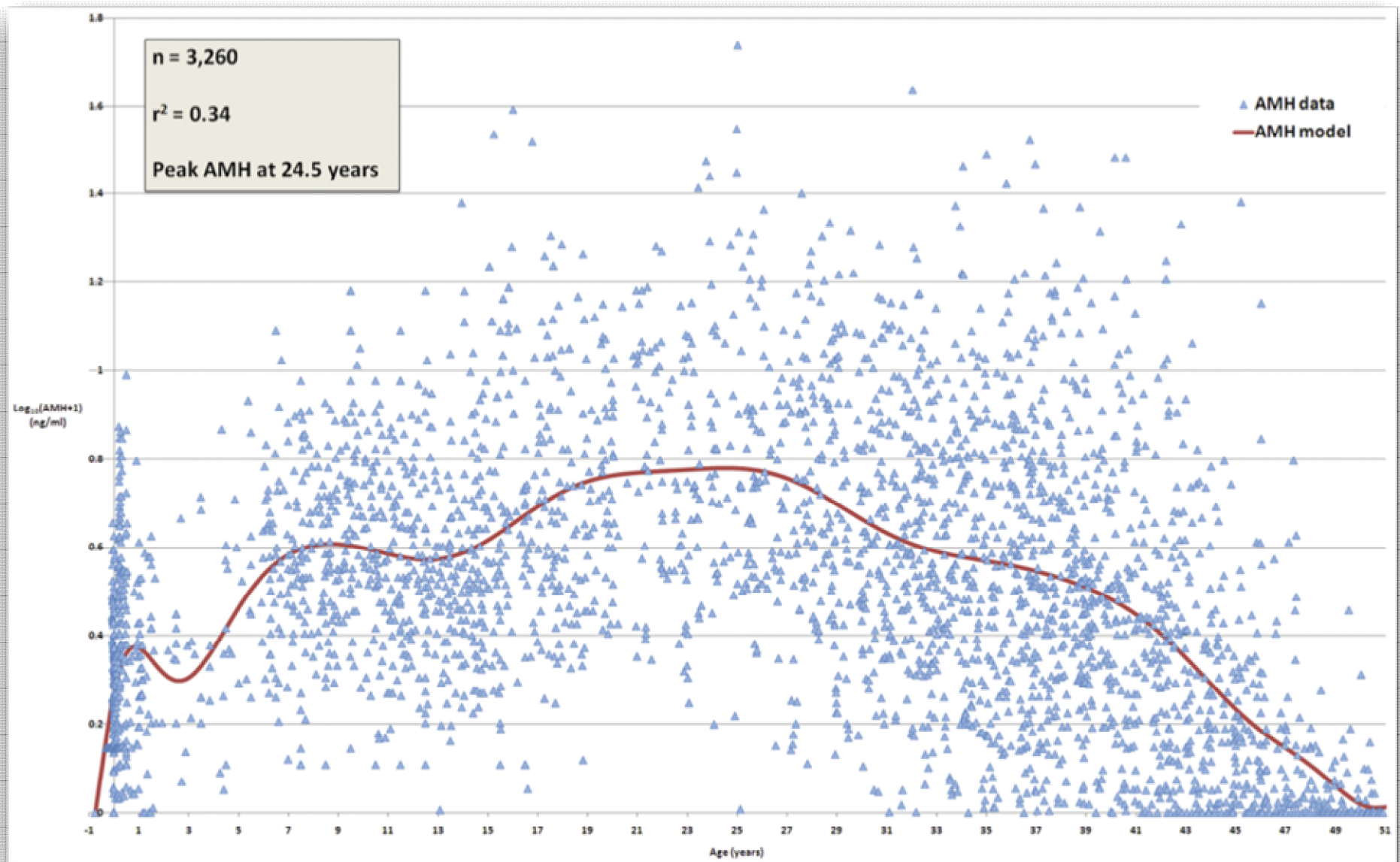
Meta-analysis
3 RCTs
N=592 first IVF cycles

“Tailored Stimulation”

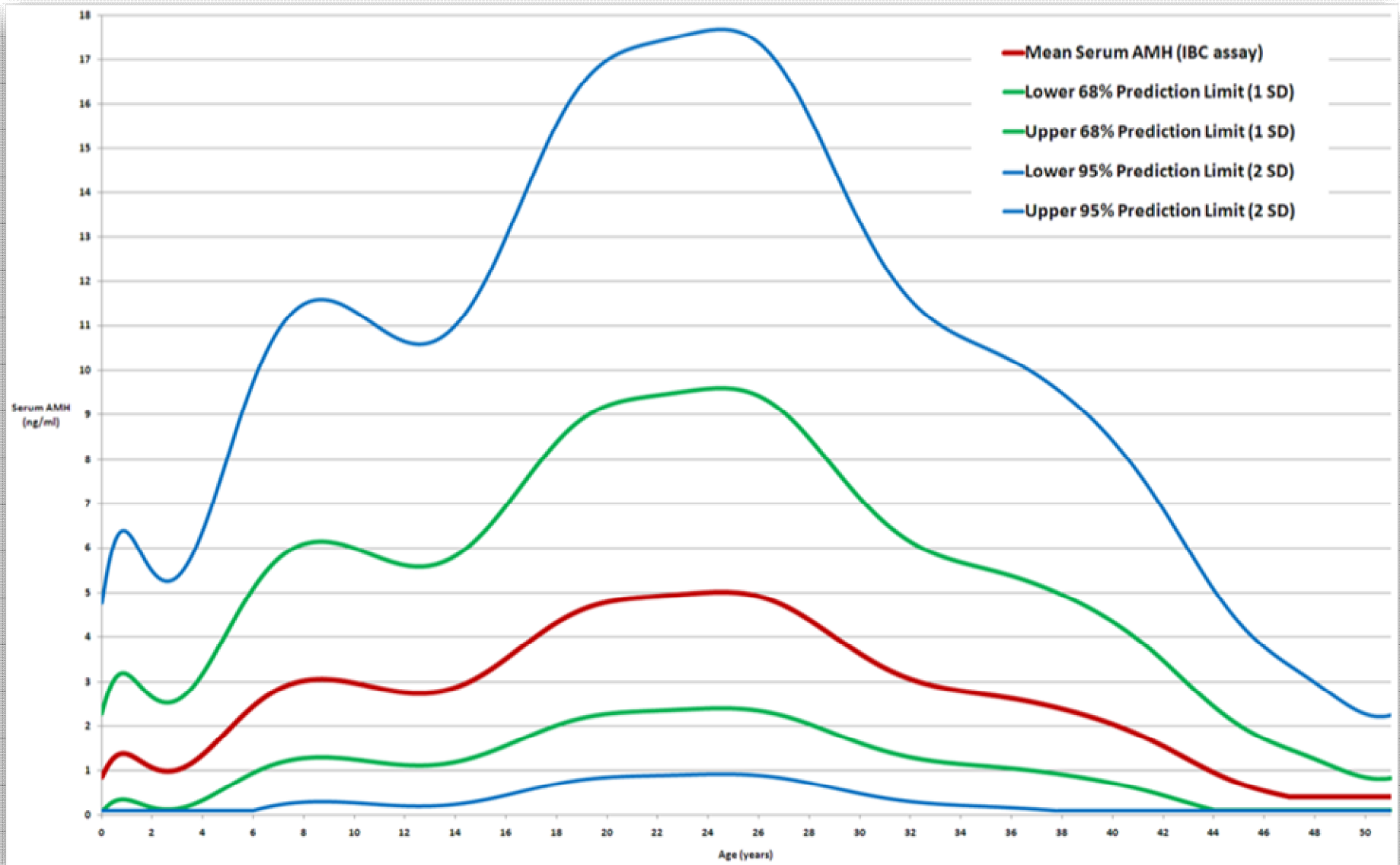


Clinical Decisions Start with the Basics

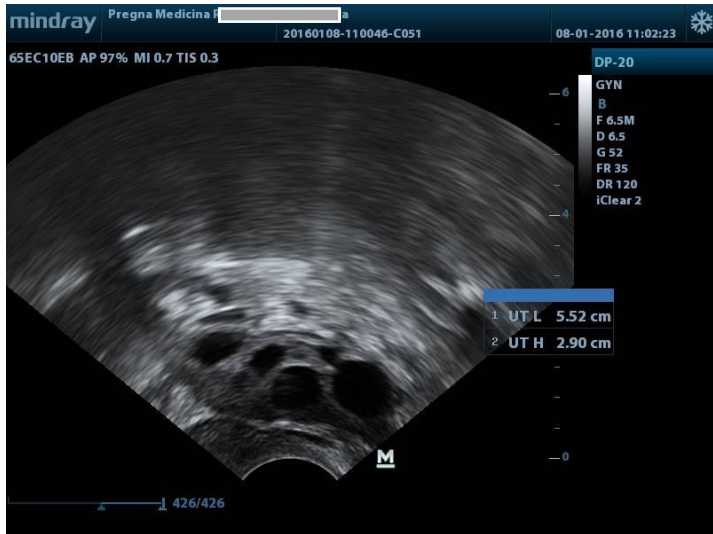
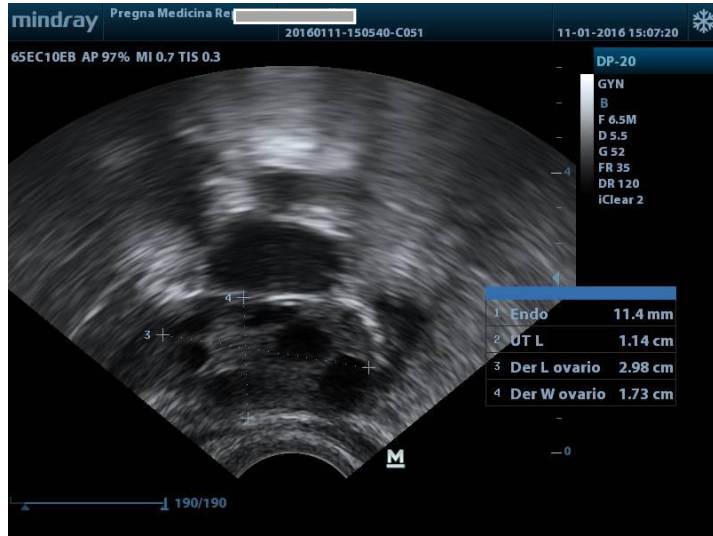




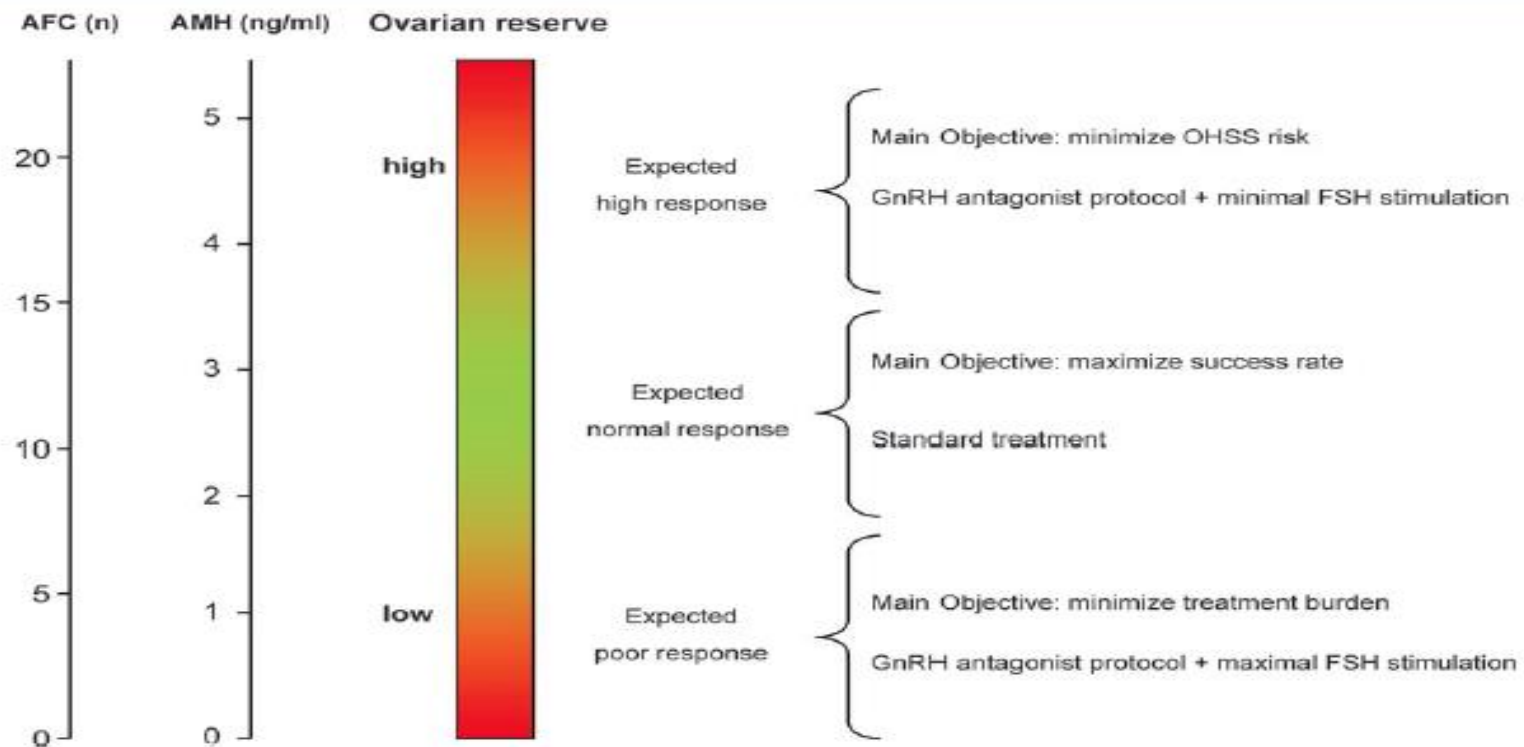
A Validated Model of Serum Anti-Müllerian Hormone from Conception to Menopause. Kelsey, et al. *PLoS ONE*. July 2011



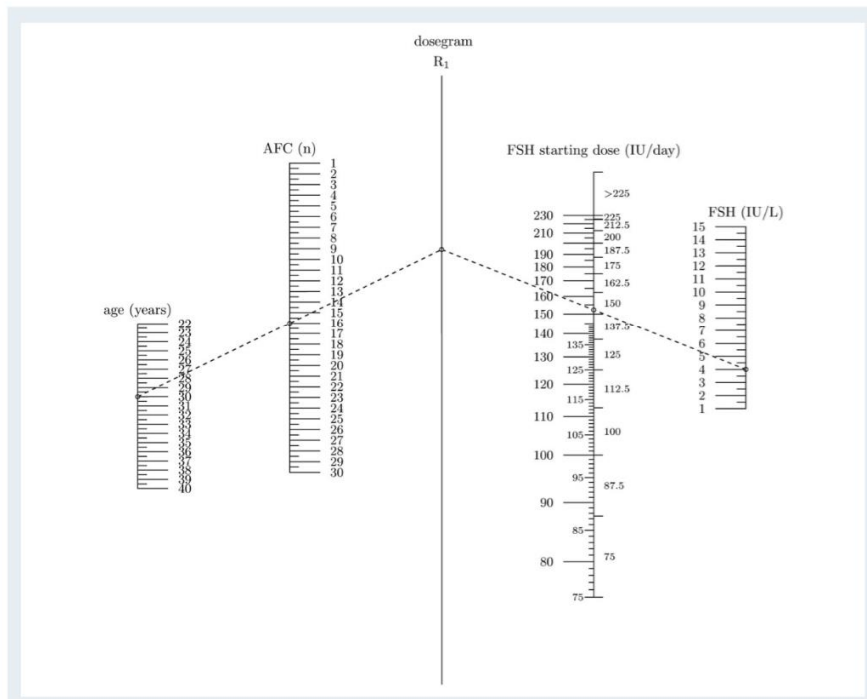
A Validated Model of Serum Anti-Müllerian Hormone from Conception to Menopause. Kelsey, et al. *PLoS ONE*. July 2011



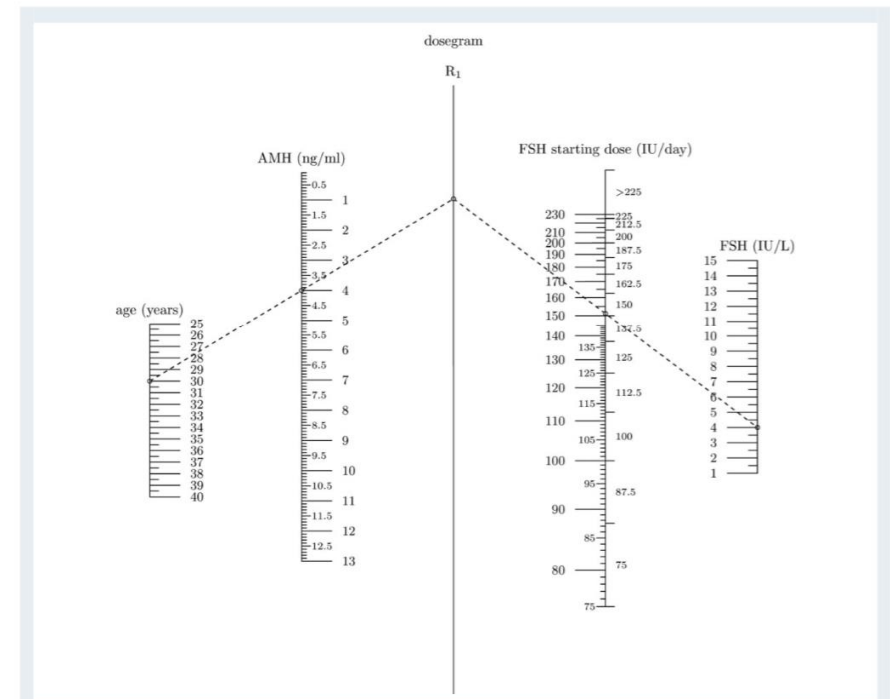
Predicting Ovarian Response: Diagnosis



Starting Dose: The “Dosogram” Based on AFC & AMH



Downloaded from <http://humrep.oxfordjournals.org/> by guest on



- Prevents OHSS
- Predicts Response
- Cost Effective

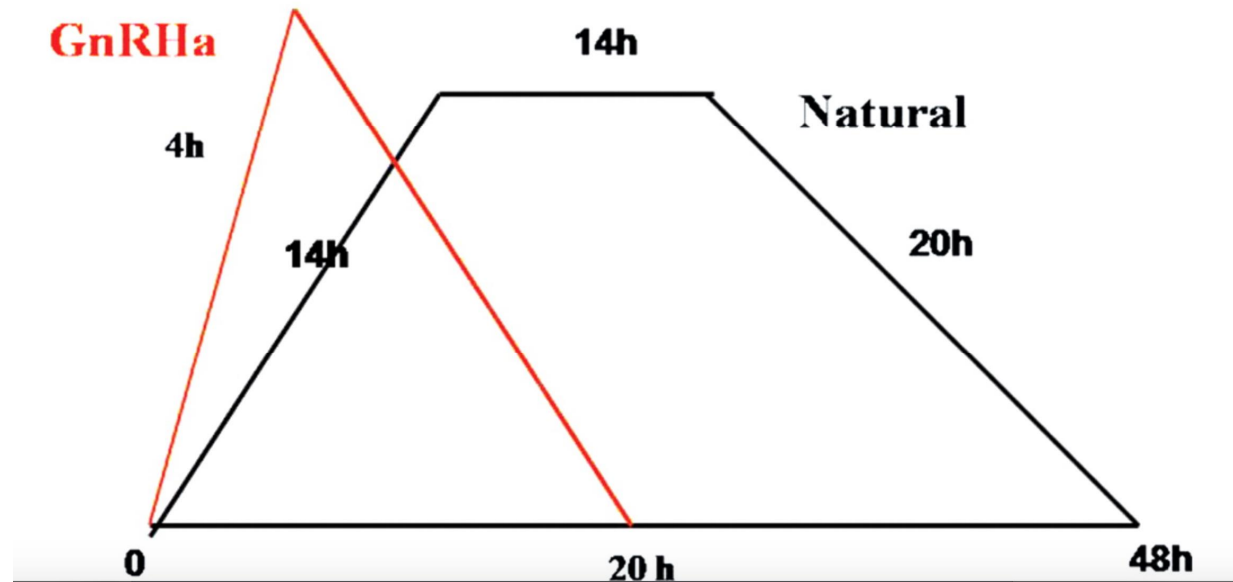
Menu

| | GnRH Agonist | | | GnRH Antagonist | | | No GnRH Analogue | |
|--|--------------|-------|------------|-----------------|------|---------------------|------------------|---------|
| | Long | Short | Microflare | Standard | Mild | Modified Natural | Mini | Natural |
| r-FSH | | | | | | | | |
| HMG | | | | | | | | |
| r-FSH+LH | | | | | | | | |
| Others: Clomiphene Letrozole Testosterone Estrogen | | | | | | | | |



GnRHa Triggering

LH-surge after GnRHa triggering versus natural cycle



- " OHSS
- " Freeze all+approach (check P levels!)
- " Fertility preservation
- " Egg donation

Timing of hCG Trigger



Prolonging oocyte in vitro culture and handling time does not compensate for a shorter interval from human chorionic gonadotropin administration to oocyte pickup

Fertility & Sterility.
2015;103(1):72-75

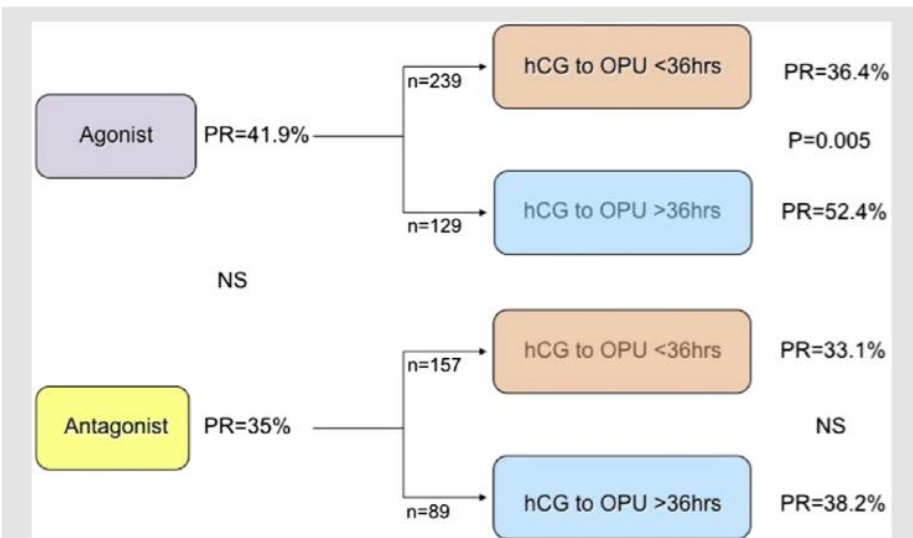
Jamieson et al. *Fertil Steril.*
1991;56:93. 97.

Bokal et al. *Hum Reprod.*
2005;20:1562. 1568.

Raziel et al. *Fertil Steril.* 2006;
86:583. 587.

Roni Garor, M.Sc., Yoel Shufaro, M.D., Ph.D., Naomi Kotler, B.Sc., Dania Shefer, M.Sc., Natalia Krasilnikov, M.Sc., Avi Ben-Haroush, M.D., Haim Pinkas, M.D., Benjamin Fisch, M.D., Ph.D., and Onit Sapir, Ph.D.

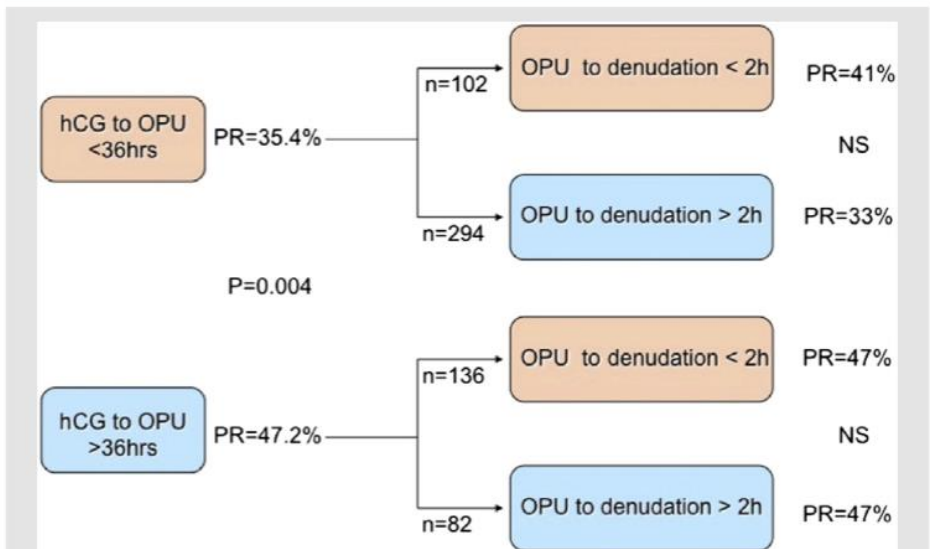
FIGURE 1



Clinical pregnancy rates (PR) by type of pituitary suppression in cycles with <36-hour or >36-hour hCG–OPU interval. A longer interval led to a significantly better reproductive outcome in GnRH agonist cycles.

Garor. *OPU and ICSI intervals and ART outcome. Fertil Steril* 2015.

FIGURE 2



Clinical pregnancy rates (PR) by OPU–denudation interval (more or less than 2 hours) in cycles with <36-hour or >36-hour hCG–OPU intervals.


Garor. *OPU and ICSI intervals and ART outcome. Fertil Steril* 2015.

ICSI for All?

Advantages

- Standardization & task organization in ART labs
- Uniformity (variability, checkpoints in time-lapse)
- "Mastering" the technique for personnel training in other invasive procedures (blastomere & trophoctoderm biopsy, assisted hatching, fragment removal, cytoplasmic transfer, etc.)

Disadvantages

- Overlapping tasks overwhelming
 - Burden to human resources
 - Security? (physiological barriers bypassed)
 - Follow up in high risk population confusing
 - Cost-efficacy?
 - No evidence of benefit in CPR, IR or LBR
- 

REDLARA 2012

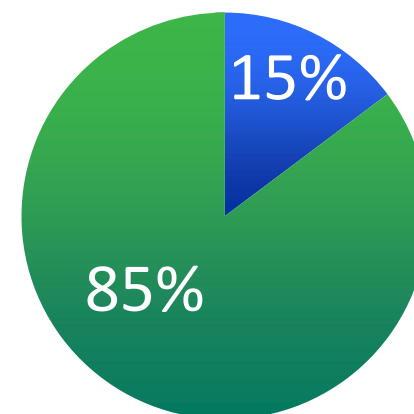


Table 1. Assisted Reproduction technology procedures and access in 2012

| Country | Number of clinics | Assisted reproductive techniques | | | | | | | Access (*****) |
|--------------|-------------------|----------------------------------|--------------|---------------|---------------|--------------|--------------|---------------|----------------|
| | | IVF/ICSI initiated cycles (*) | IVF (**) | ICSI (**) | FET(***) | OD | FP(****) | Total | |
| Argentina | 25 | 6,461 | 504 | 5,515 | 3,027 | 1,543 | 429 | 11,031 | 1,193 |
| Bolivia | 1 | 215 | 148 | 62 | 14 | 8 | 923 | 237 | 96 |
| Brazil | 57 | 16,030 | 1,070 | 13,937 | 4,252 | 1,170 | 0 | 21,452 | 447 |
| Chile | 8 | 1,563 | 131 | 1,321 | 549 | 197 | 48 | 2,309 | 595 |
| Colombia | 11 | 977 | 293 | 622 | 262 | 247 | 13 | 1,486 | 139 |
| Ecuador | 6 | 608 | 216 | 324 | 165 | 154 | 107 | 927 | 254 |
| Guatemala | 1 | 100 | 38 | 62 | 7 | 17 | 0 | 124 | 37 |
| Mexico | 27 | 3,345 | 1,222 | 2,017 | 1,046 | 1,140 | 114 | 5,531 | 196 |
| Nicaragua | 1 | 91 | 46 | 41 | 0 | 9 | 0 | 100 | 67 |
| Panama | 1 | 245 | 7 | 192 | 86 | 33 | 9 | 364 | 452 |
| Peru | 6 | 1,264 | 298 | 875 | 430 | 547 | 114 | 2,241 | 308 |
| Dominican R. | 2 | 80 | 42 | 35 | 5 | 26 | 0 | 111 | 48 |
| Uruguay | 2 | 293 | 20 | 233 | 77 | 46 | 2 | 416 | 585 |
| Venezuela | 7 | 585 | 369 | 184 | 153 | 259 | 5 | 997 | 148 |
| Total | 155 | 31,857 | 4,404 | 25,420 | 10,073 | 5,396 | 1,764 | 47,326 | 367.0 |

(*) initiated cycles; (**) oocyte pick ups; (***) includes the transfer of own and donated oocytes; (****) initiated fertility preservation cycles; (*****) number of cycles/million of women 15-45 years

Randomized Controlled Trial Did Not Show Benefits Using ICSI in Non-Male Factor Infertility

435 non-male factor cycles

Multicentric (4 clinics) randomized

- . IVF N= 224

- . ICSI N= 211

- . Implantation rate > IVF than ICSI

(95/318 [30%] vs 72/325 [22%]; RR 1.35 [95% CI 1.04-1.76]).

- . Pregnancy rates also higher in IVF vs. ICSI

(72 [33%] vs 53 [26%]; RR 1.17 [0.97-1.35]).

- . Work load time in the lab much lower in IVF

(22.9 [SD 12.1] vs 74.0 [38.1] min; 95% CI for difference 45.6-56.6).

Publication: 2003
Revised: August 2010

Intra-cytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in couples with non-male subfertility (Review)

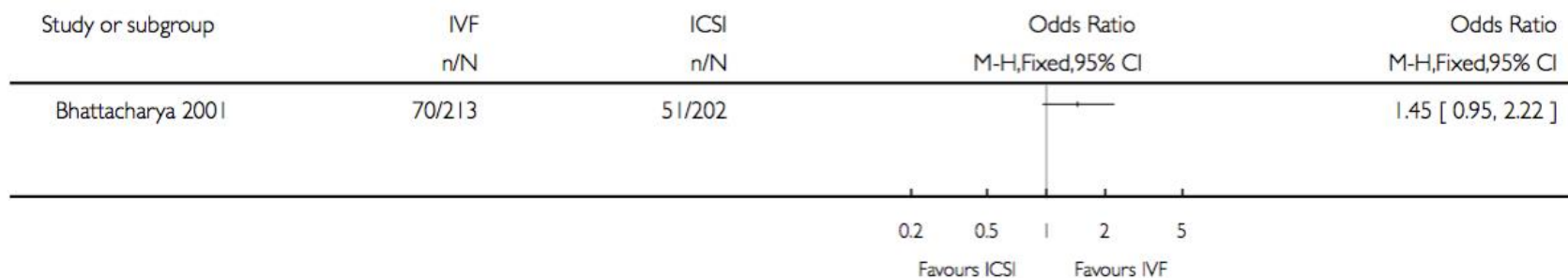
van Rumste MME, Evers JLH, Farquhar C

Analysis 1.1. Comparison 1 ICSI versus IVF, Outcome 1 Pregnancy rate.

Review: Intra-cytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in couples with non-male subfertility

Comparison: 1 ICSI versus IVF

Outcome: 1 Pregnancy rate



To Hatch or Not to Hatch?



Cochrane
Library

Cochrane Database of Systematic Reviews

Published 2013

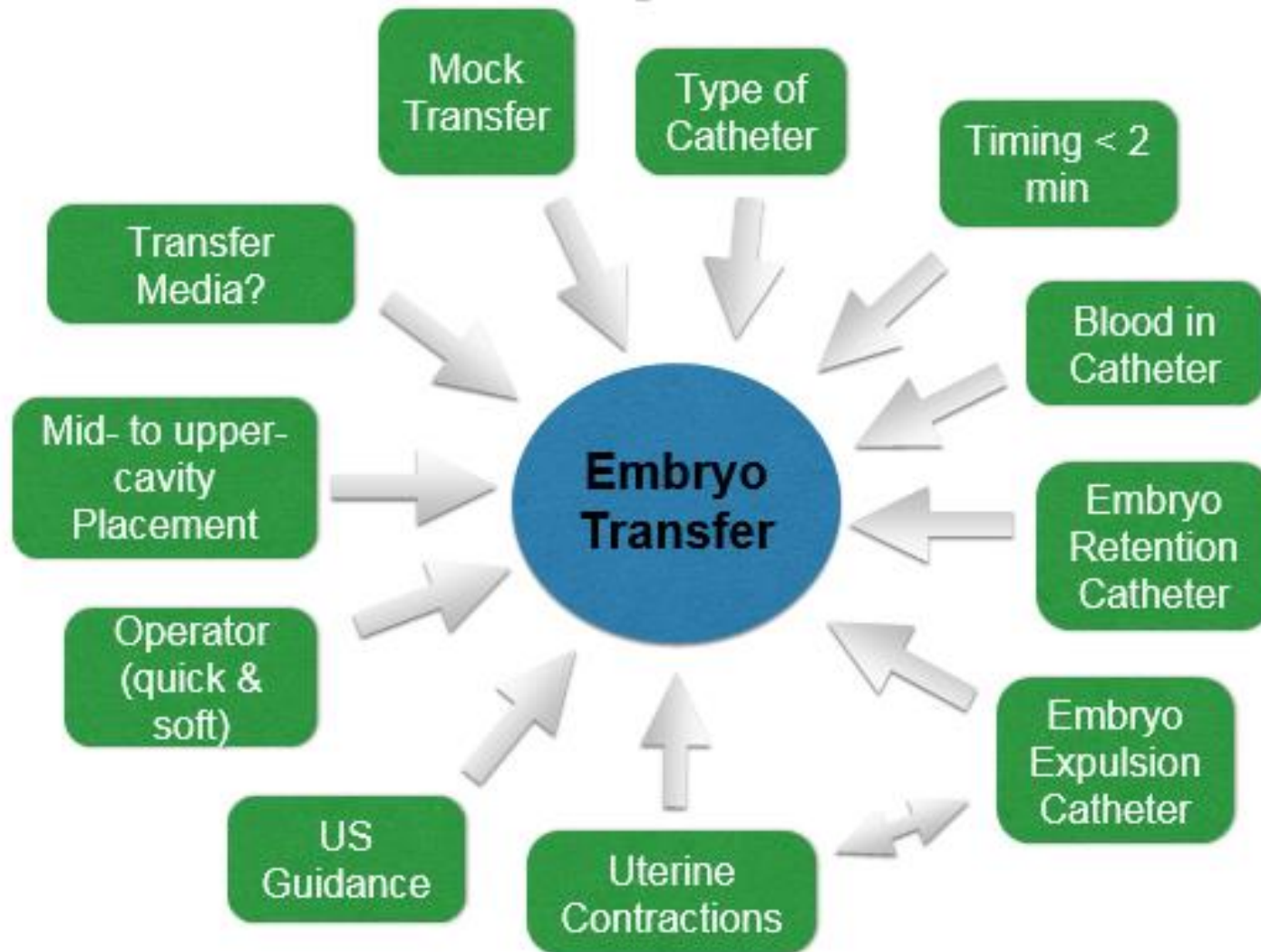
Assisted hatching on assisted conception (in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI)) (Review)

Carney SK, Das S, Blake D, Farquhar C, Seif MM, Nelson L

Slight increase in PR's, although evidence is low to moderate and LBR's were reported in only a few studies, more data needed.

A subgroup of recurrent failed IVF could benefit.

Embryo Transfer: a Critical Step



Importance of embryo transfer technique in maximizing assisted reproductive outcomes

Fertility & Sterility.
2016;15(4):855-860.

William B. Schoolcraft, M.D.

Colorado Center for Reproductive Medicine, Lone Tree, Colorado

- “ Pregnancy rates & provider at embryo transfer.
Hearns-Stokes et al. Fertil Steril. 2000 Jul;74(1):80-6.
- “ Transfer technique and catheter choice.
Ghazzawi et al. Hum Reprod. 1999 Mar;14(3):677-82.
- “ Ultrasound-guided soft catheter embryo transfers.
Wood et al. Hum Reprod. 2000 Jan;15(1):107-12.
- “ Immediate ambulation after embryo transfer: a prospective study.
Bar-Hava et al. Fertil Steril. 2005;Mar;83(3):594-7.
- “ Minimizing embryo expulsion after et: a randomized controlled study.
Mansour R. et al. Hum Reprod. 2005;Jan 20(1):170-4.
- “ Embryo transfer technique.
Mansour RT et al. Hum Reprod. 2002;May 17(5):1149-53.
- “ Comparison between catheters for ultrasound-guided embryo transfer.
Karande V et al. Fertil Steril. 2002;Apr 77(4):826-30

Mock Transfer Protocol

- A mock transfer is scheduled during workup previous to IVF.
- A soft catheter is passed under US guidance, and if passage is negative, other catheters are tried.
- If negative a second appointment is scheduled with an assistant, and explore the need of adjuvant maneuvers, anesthesia, instrumentation, or sedative medication.
- If negative a diagnostic hysteroscopy is scheduled

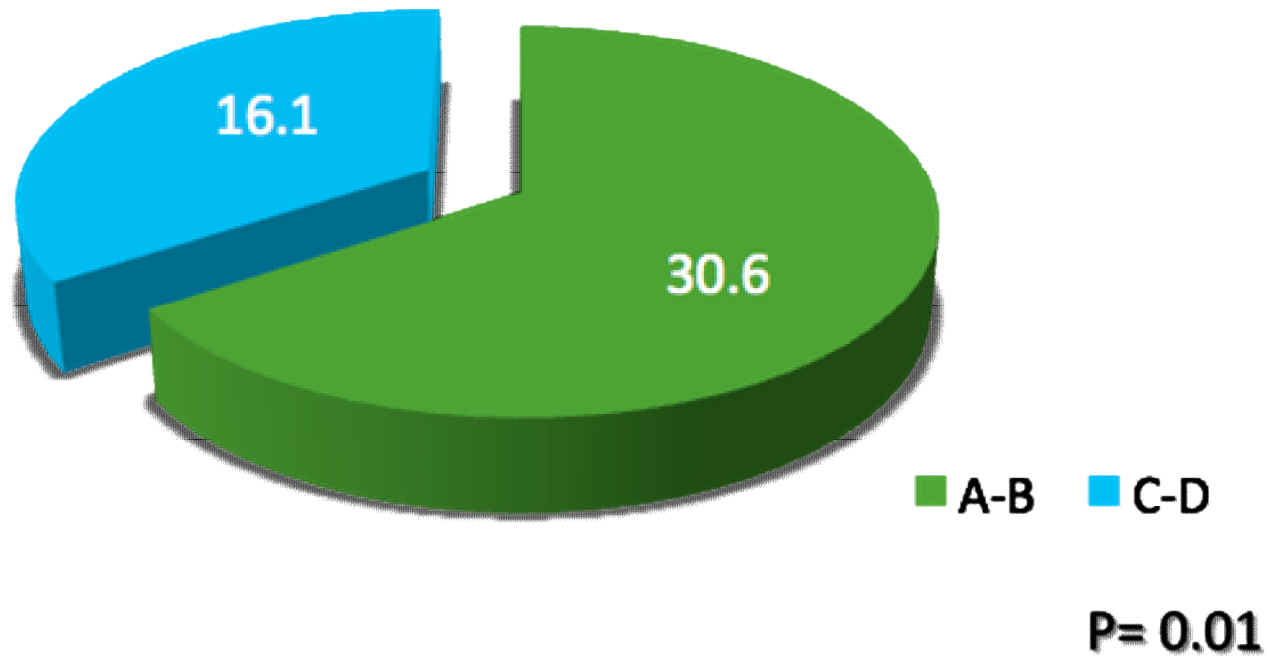
Transfer Protocol

- “ Full bladder & Ultrasound guidance
- “ Assistant checks mock transfer
 - “ Positive: proceed with instructions to biologist
 - “ Negative: perform MT up to internal os
- “ Vaginal wash with saline + cervical os with culture media
- “ Biologist checks identity with the patient
- “ Biologist loads embryo/s with a witness
- “ Soft catheter used (COOK Echotip soft pass)
- “ Smooth ejection and slow backup
- “ Total procedure lasts < 2 min
- “ Patient walks back to the room
- “ 10 minutes bed rest

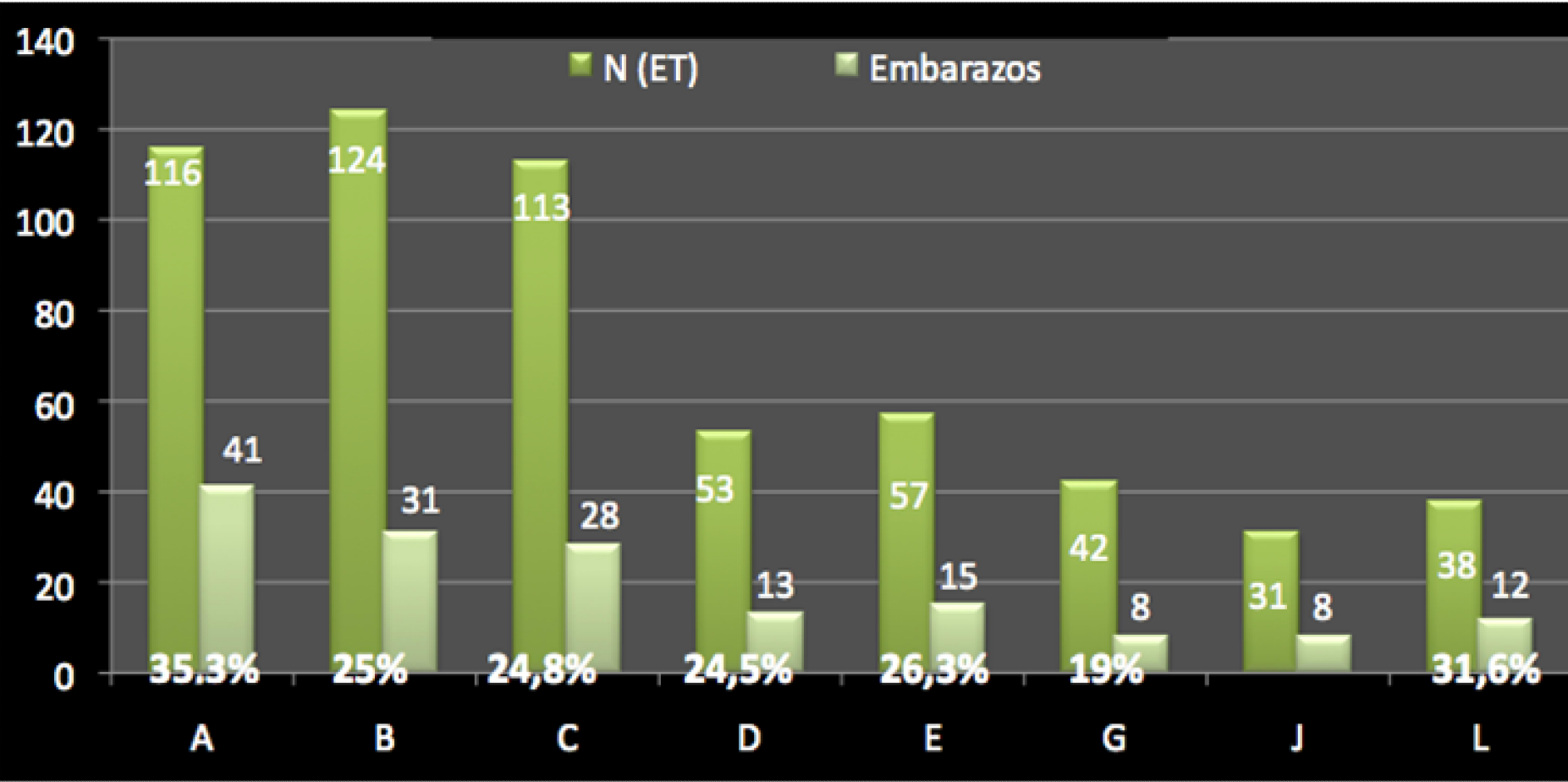
Embryo Transfer: Classification

| ET | US | Full Bladder | Mid 1/3 | Fundal touch | See discharge | Ejection Speed | Catheter removal | Blood tip | Embryo retention | Time <2 min | Catheter change |
|----|-----|--------------|---------|--------------|---------------|----------------|------------------|-----------|------------------|-------------|-----------------|
| A | YES | YES | YES | NO | YES | SMOOTH | SLOW | NO | NO | YES | NO |
| B | YES | YES | YES | NO | YES | REGULAR | MEDIUM | NO | NO | YES | Y/N |
| C | YES | YES | Y/N | Y/N | Y/N | FAST | FAST | Y/N | Y/N | Y/N | Y/N |
| D | NO | NO | NO | YES | NO | FAST | FAST | YES | Y/N | NO | YES |

Pregnancy Rate and Type of Transfer



Pregnancy Rates per Clinician



Clinical Decisions to Maximize Outcome

- Tailor stimulation dosing to improve PR's and decrease OHSS

Use dosograms

- Use protocols with GnRH antagonists

Equal PR's & Almost 0% OHSS

- Check P levels on day of hCG

If > 1.5-1.6 freeze all

- Trigger with GnRH agonists when possible

Freeze all cycles, egg donors, oocyte vitrification cycles

Clinical Decisions to Maximize Outcome

- IVF for non-male factor & ICSI for male factor, or as a tool in:

Thawed eggs, PGS, HIV,
Frozen sperm

- Schedule OPU @ 36 hs. or more

Could improve PR's especially in
agonist cycles

- Culture to the blastocyst stage ideally

More checkpoints to assess the
embryo

- Use Time Lapse Systems?

Could improve outcome added to
other markers

Clinical Decisions to Maximize Outcome

- Establish mock transfer & real transfer protocols:

Improves PR's & improves differences between clinicians

- Freeze-all cycles?

Still not clear from RCT

- Perform assisted hatching?

May be beneficial for RIF

- Offer CCS

RCT show improvement in OPR's, IR's, and reduces TTP

Clinical Decisions to Effectively Maximize Treatment Outcomes

Dr. Marcos Horton
Co-Director and Founder
Pregna Medicina Reproductiva
Past-President
Argentinian Society for Reproductive Medicine
Buenos Aires, Argentina

