THE PERIODIC COMET OF POR: THE NOVEL POSEIDON CLASSIFICATION

Sandro C. Esteves,
Androfert - Andrology & Human Reproduction Clinic
Campinas, Brazil

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Disclosures

- Receipt of honoraria for lectures from Besins, Lilly, Gedeon Richter, and Merck

Educational objectives

- Describe the rationale for the POSEIDON criteria in stratifying low prognosis patients and how the criteria can be used to optimally manage these patients undergoing IVF
- Explain the development of the novel ART calculator, its concise role, and the current version of the calculator tool
- Review the latest validation data for implementation of the calculator in predicting POSEIDON markers

Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number POSEIDON group

Alviggi C. Italy | **Humaidan P.** Denmark | **Buhler K.** Germany | **Andersen C.** Denmark | **Fischer R.** Germany | **Esteves S.** Brazil | **Ubaldi F.** Italy | **Conforti A.** Italy | **Sunkara S.** UK | **Polyzos N.** Spain | **Galliano D.** Spain | **De Placido G.** Italy

Fertility and Sterility

June 2016 Volume 105, Issue 6, Pages 1452–1453

A new more detailed stratification of low responders to ovarian stimulation: from a poor ovarian response to a low prognosis concept

Poseidon Group, Alviggi C, et al. Fertil Steril. 2016;105:1452-3.

Why?

Little progress has been achieved in the clinical management of patients with reduced ovarian reserve or poor ovarian response to OS

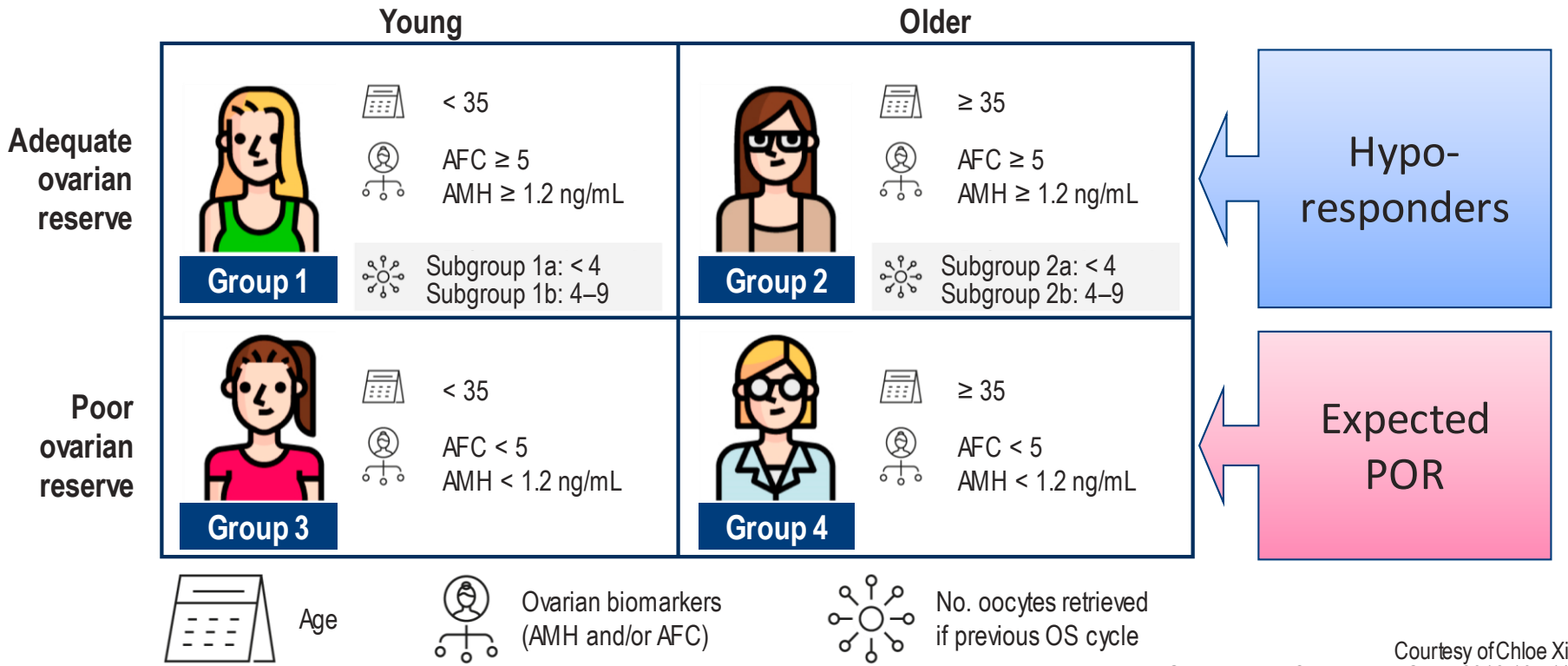
- Wide heterogeneity in POR definition
- Existing definitions group patients with diverse clinical characteristics and prognosis into same “box”

- Difficult to draw valid conclusions from existing trials
- Insufficient evidence to support the use of any particular intervention
- Lack of guidance for clinicians
- Patient frustration

OS, ovarian stimulation; POR, poor ovarian reserve.

Poseidon Group, Alviggi C, et al. Fertil Steril. 2016;105:1452-3.

POSEIDON criteria: low prognosis groups

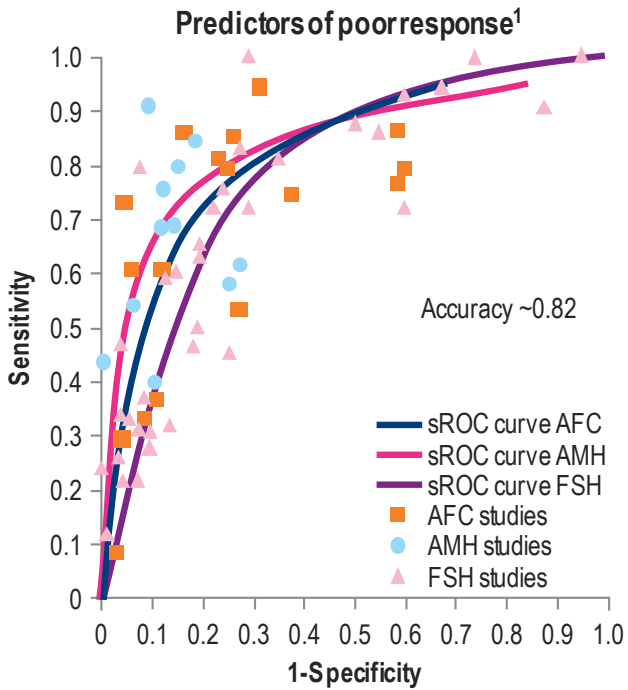


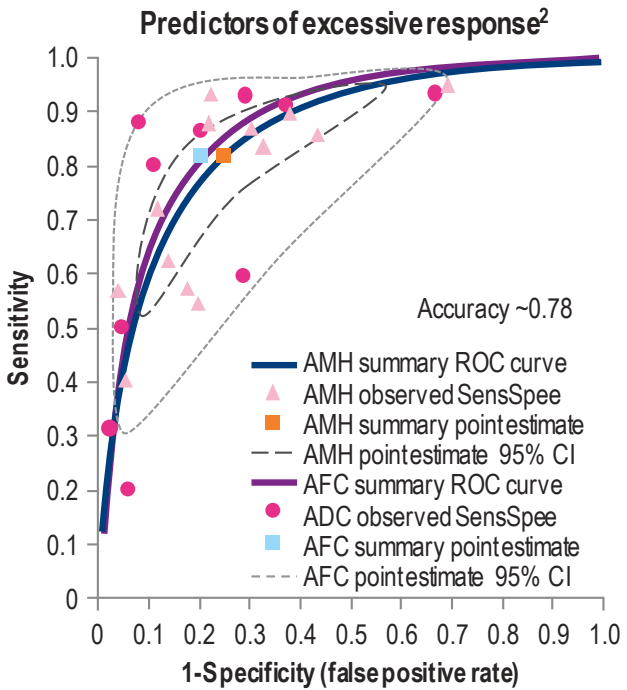
AFC, antral follicle count; AMH, anti-Müllerian hormone.

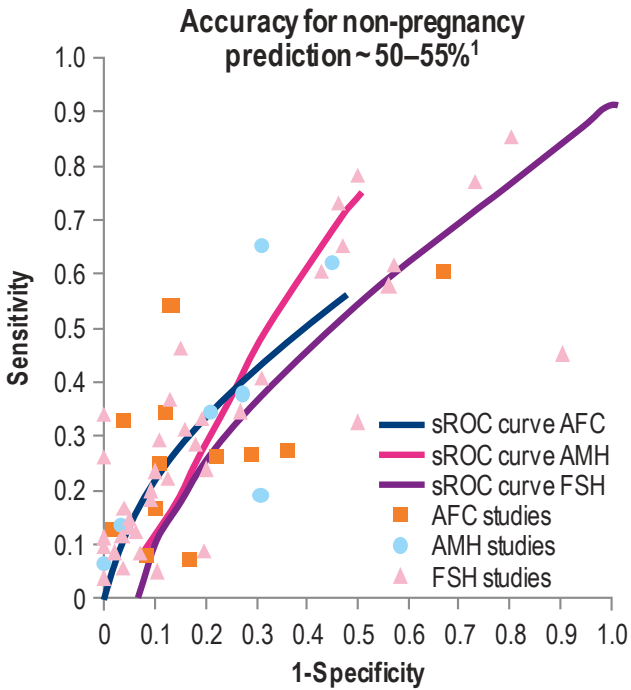
Courtesy of Chloe Xilinas.
Poseidon Group, Alviggi C, et al. Fertil Steril. 2016;105:1452-3.
Humaidan P, et al. F1000Res. 2016;5:2911.

AFC and AMH predict ovarian response but not LBR

AFC~AMH > FSH > Age



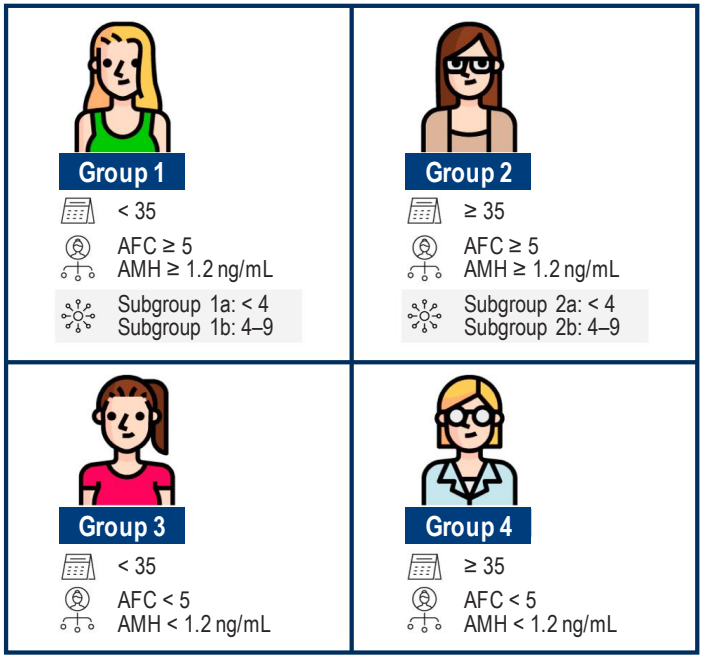


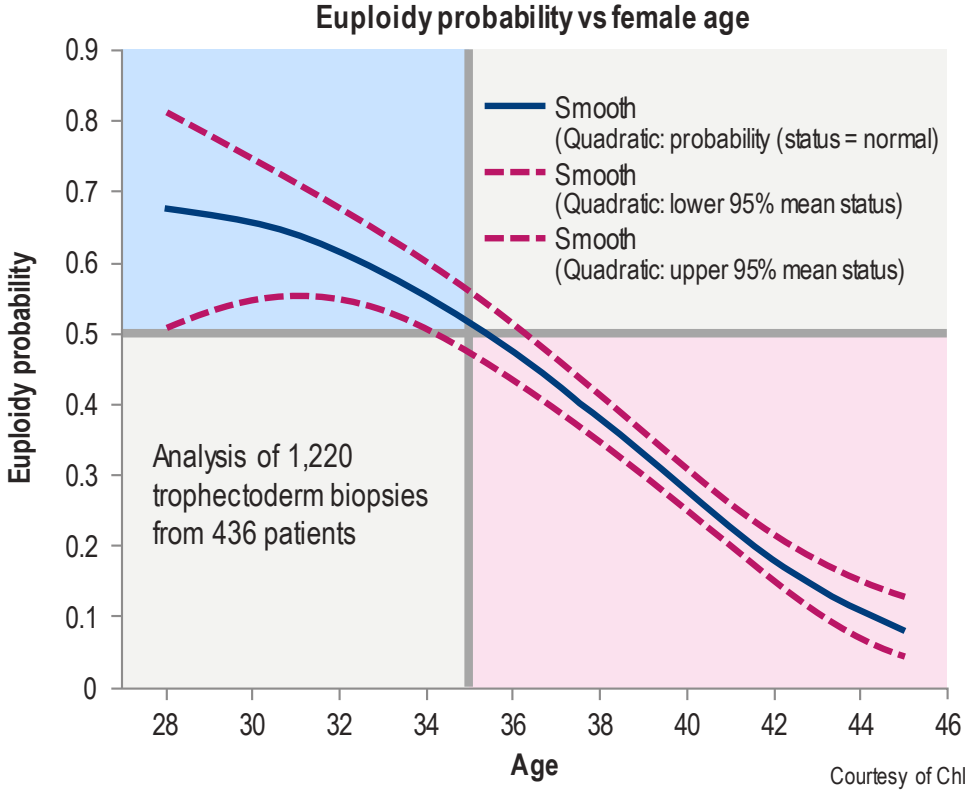


LBR, live birth rate;
sROC, summary receiver operating characteristics.

1. Modified from: Broer SL, et al. Fertil Steril. 2009;91:705-14.
2. Modified from: Broer SL, et al. Hum Reprod Update. 2011;17:46-54.

Female age affects oocyte and embryo genetic competence ≥ 35 years: blastocyst euploidy probability < 50% overall

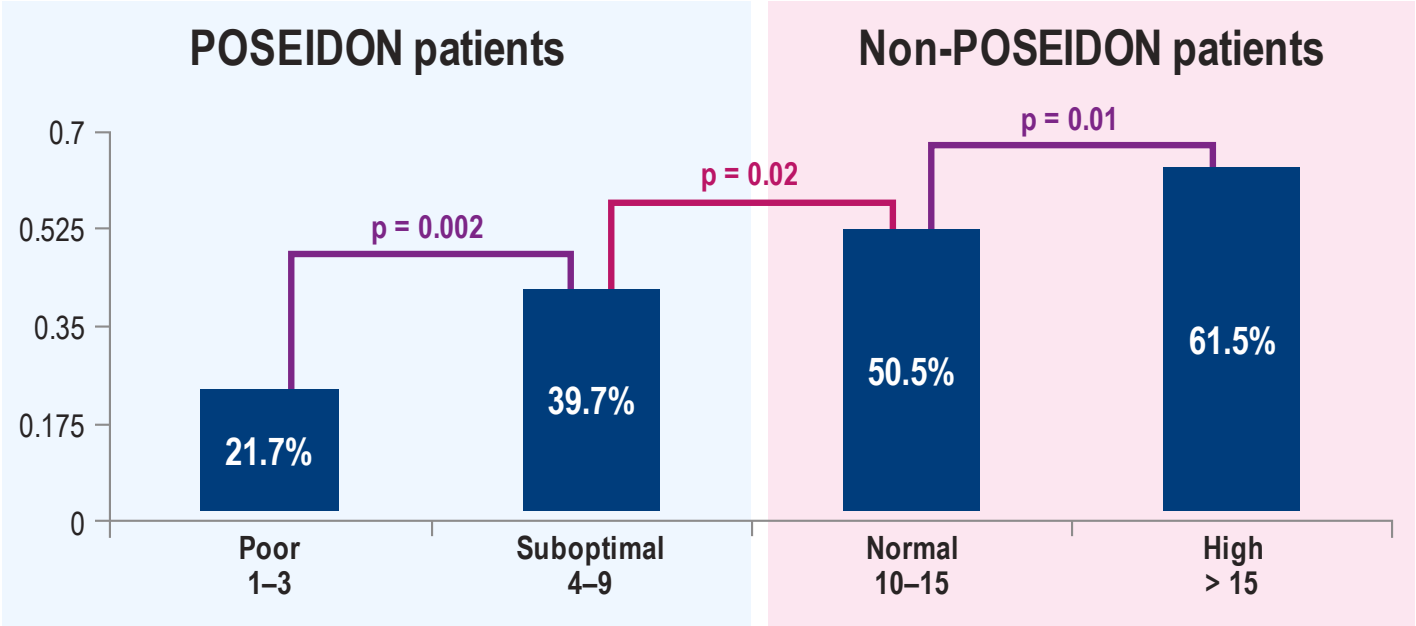




Courtesy of Chloe Xilinas.

Esteves SC, et al. Panminerva Med. 2019;61:3-10.

Low prognosis owing to decreased number of oocytes and thus lower CLBR

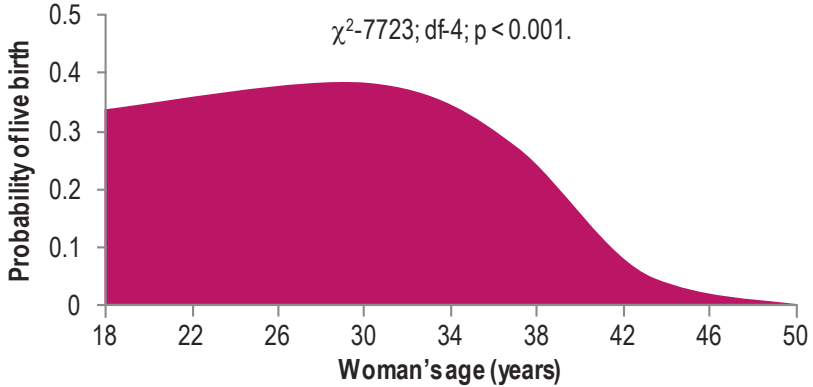


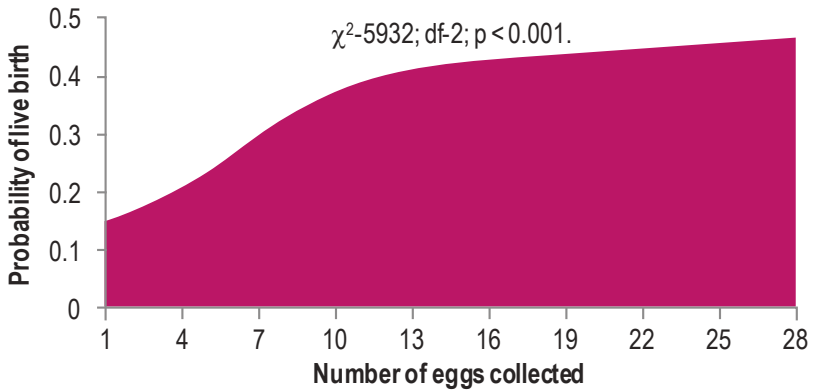
Age-adjusted CLBR strongly influenced by oocyte number

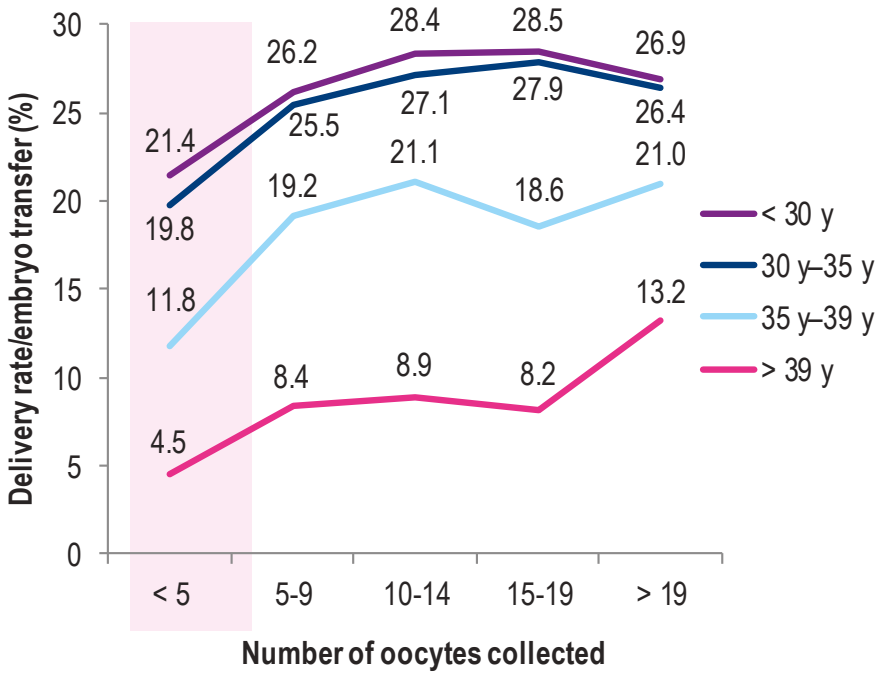
Age adjusted (OR 0.9; 95% CI 0.9–1.01).
CLBR, cumulative LBR.

Drakopoulos P, et al. Hum Reprod. 2016;31:370-6.

Only female age and number of oocytes can predict LBR

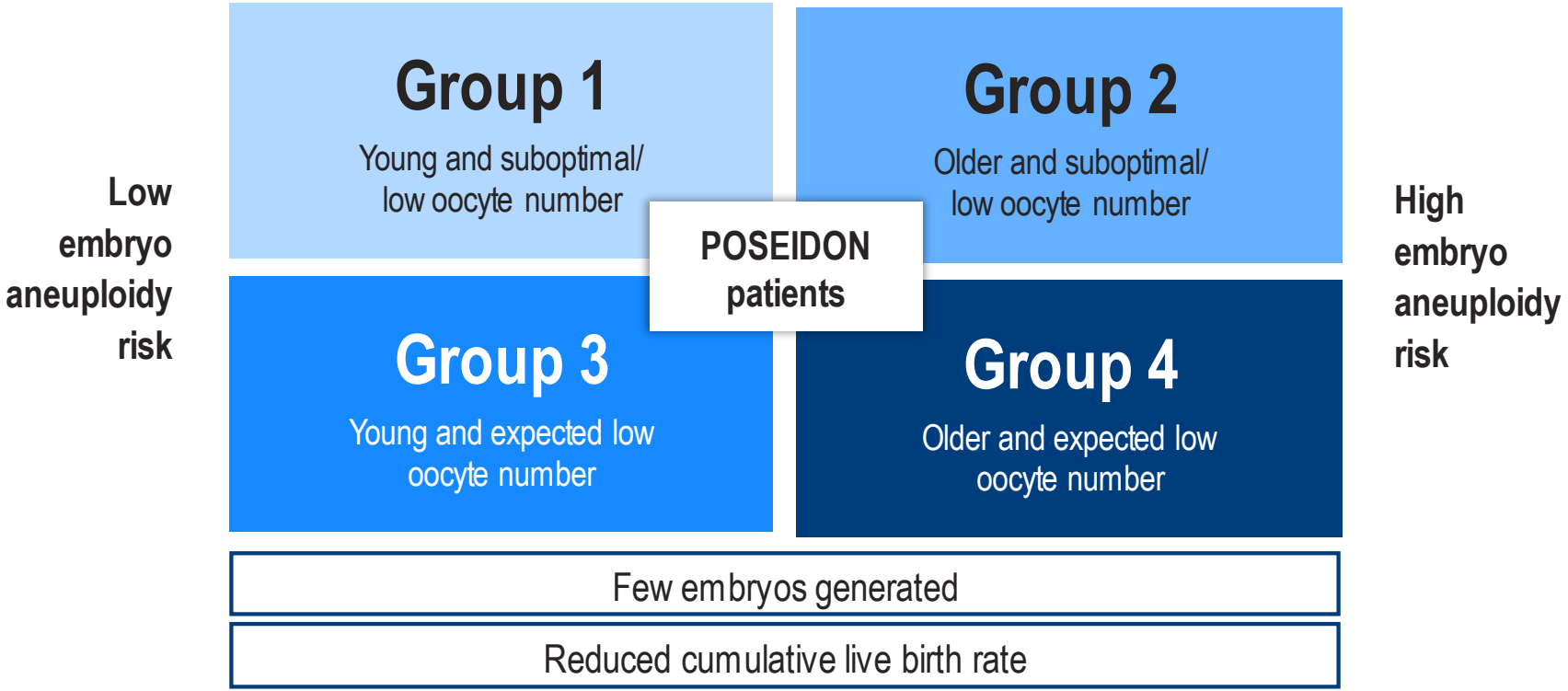






df, degrees of freedom; y, years.

Modified from: McLernon DJ, et al. BMJ. 2016;355:i5735.
De Geyter C, et al. Swiss Med Wkly. 2015;145:w14087.


Low embryo aneuploidy risk
Group 1
Young and suboptimal/ low oocyte number
Group 2
Older and suboptimal/ low oocyte number
POSEIDON patients
Group 3
Young and expected low oocyte number
Group 4
Older and expected low oocyte number
High embryo aneuploidy risk
Few embryos generated
Reduced cumulative live birth rate

Validation study: POSEIDON classification

- Study investigating frequency of patients according to POSEIDON criteria
  - Brazil, Turkey, Vietnam
- Assessment includes the number of embryos according to POSEIDON classification, CLBR based on ICMART definition

[Unpublished data not available]

ICMART, International Committee Monitoring Assisted Reproductive Technologies.

Unpublished data.

What is new in POSEIDON?

- Introduced the concept of “low prognosis” in ART
- Combined oocyte quality and quantity for identification and stratification of the “low prognosis” patient
- Included “hypo-responders” as a distinct category of “low prognosis” patients
- **Introduced an intermediate marker of success in ART: the ability to retrieve the number of oocytes needed to obtain at least one euploid blastocyst for transfer in each patient**

Poseidon Group, Alviggi C, et al. Fertil Steril. 2016;105:1452-3.
Humaidan P, et al. F1000Res. 2016;5:2911.

ORIGINAL RESEARCH ARTICLE Provisionally accepted The full-text will be published soon. Notify me

Front. Endocrinol. | doi: 10.3389/fendo.2019.00099

A novel predictive model to estimate the number of mature oocytes required for obtaining at least one euploid blastocyst for transfer in couples undergoing in vitro fertilization/intracytoplasmic sperm injection: The ART Calculator

 Sandro C. Esteves[1*], José F. Carvalho[2],  Fabiola C. Bento[1] and Jonathan Santos[3]

[1]Androfert, Andrology and Human Reproduction Clinic, Brazil

[2]Statistika Consulting, Brazil

[3]CliniSYS, Brazil

ART Calculator development

- ART database (CliniSYS IVF®) for infertile couples who underwent IVF/ICSI with the intention of having trophectoderm biopsy for PGT-A

  PGT-A for reasons of AMA, severe male factor, recurrent miscarriage, repeated implantation failure, and patients concerned about the euploidy status of their embryos

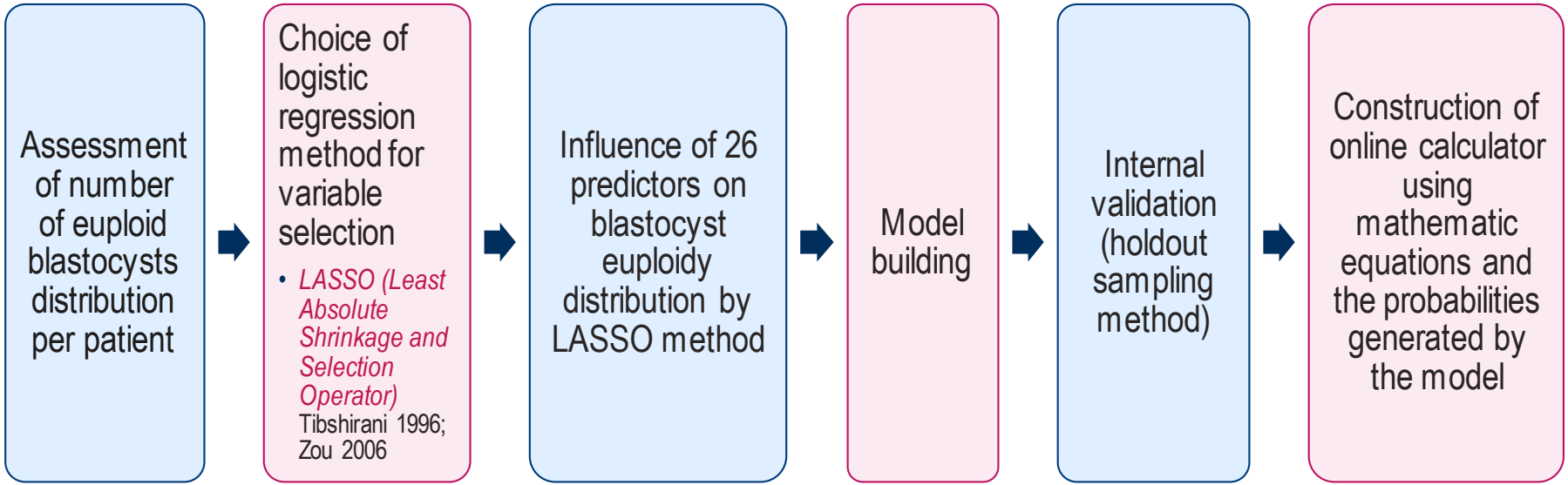
- **347** couples
- **2,520** mature oocytes
- **882** blastocysts

Characteristics	Mean; frequency
Infertility duration, years	7
Female age, years	38.9
Male age, years	42.4
BMI, female, kg/m^2	24.5
BMI, male, kg/m^2	27.6
Infertility factor, n (%):	
Male factor	117 (33.8)
Unexplained	63 (18.2)
Female	69 (19.9)
> 1 type	98 (28.1)
AFC, n	6.7
AMH, ng/mL	1.39
Semen parameters:	
Sperm count, M/mL	30.5
Total motility, %	63.4
Sperm morphology, %	2.9
DFI, %	21.6
Azoospermia, n (%):	65 (18.7)
Non-obstructive	44
Obstructive	21
Conventional OS, n (%):	304 (87.6)
rFSH monotherapy	111
rFSH + rLH	193
Minimal stimulation, N (%)	43 (12.4)
Total gonadotropin dose, IU	
Conventional	3,145
Minimal	525
Sperm source for ICSI, n (%):	
Ejaculate	391 (71.5)
Epididymis	27 (4.9)
Testicle	129 (23.6)
Oocyte and embryo parameters:	
Oocytes retrieved, n	8.2
Mature (MII) oocytes, n	6.3
Fertilized oocytes (2PN), n	4.3
Blastocysts, n	2.1
Euploid blastocysts, n	0.74
Euploid blastocysts, %	34.8

2PN, 2 pronuclei; AMA, advanced maternal age; DFI, DNA fragmentation index; ICSI, intracytoplasmic sperm injection; MII, metaphase II; PGT-A, PGT for aneuploidy; rFSH, recombinant follicle-stimulating hormone; rLH, recombinant luteinizing hormone.

Esteves SC, et al. Front Endocrinol (Lausanne). 2019;10:99.

ART Calculator development roadmap

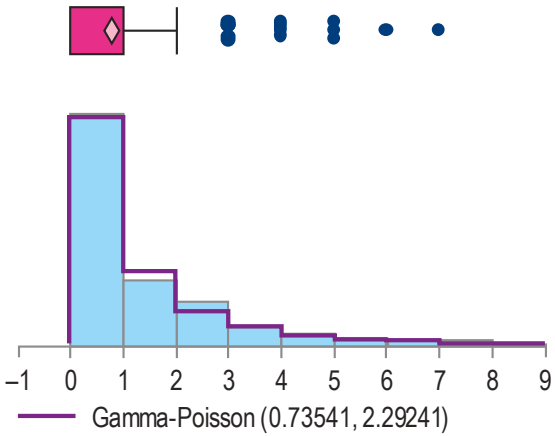


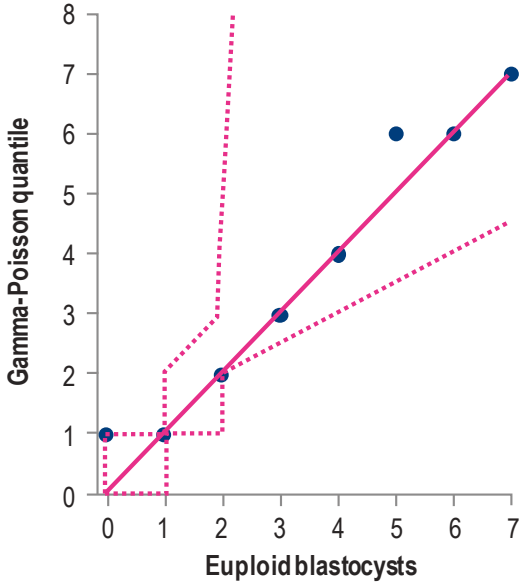
Esteves SC, et al. Front Endocrinol (Lausanne). 2019;10:99.

ART Calculator development roadmap

1. Distribution of number of euploid blastocysts per patient followed a negative binomial (gamma-Poisson)

- Suggests that, for a given woman, the events related to mature oocytes turning into euploid blastocyst are independent (i.e. embryos and oocytes are independently distributed concerning the ploidy status)





Type	Parameter	Estimate	Lower 95%	Upper 95%
Location	Lambda	0.7354086	0.5922671	0.9153501
Overdispersion	Sigma	2.2924108	1.7883531	3.0878009

Esteves SC, et al. Front Endocrinol (Lausanne). 2019;10:99.

ART Calculator development roadmap

2. Generalized regression and variable selection by the LASSO method (using the negative binomial distribution for the response variable "*number of euploid blastocysts*") to select predictors for blastocyst euploidy

- *Female age*
- *Type of sperm used for ICSI (testicular sperm from NOA men)*
- *MII oocytes*

Term	Estimate	SE	Wald χ^2	Prob > χ^2	Lower 95%	Upper 95%
(Intercept)	−1.586739	0.81916	3.752062	0.0527	−3.19227	0.0187992
SpermSource [Ejaculate-Testicular/NOA]:female age-39.4904	**−0.203824**	**0.04861**	**17.57654**	**< 0.0001**	**−0.2991**	**−0.10853**
Male age, years	0	0	0	1.0000	0	0
BMI, female	0	0	0	1.0000	0	0
BMI, male	0.015738	0.02808	0.314088	0.5752	−0.03930	0.0707809
AMH	0	0	0	1.0000	0	0
AFC	0	0	0	1.0000	0	0
Baseline FSH	0	0	0	1.0000	0	0
Female infertility	−0.129911	0.79867	0.026457	0.8708	−1.69529	1.4354721
POR associated	0	0	0	1.0000	0	0
Male factor associated	0	0	0	1.0000	0	0
Sperm count	0	0	0	1.0000	0	0
Sperm motility	0	0	0	1.0000	0	0
Sperm morphology	0	0	0	1.0000	0	0
Sperm DNA fragmentation index (DFI)	0	0	0	1.0000	0	0
OS type (CONVENTIONAL-MINIMAL]	0	0	0	1.0000	0	0
Gonadotropins [recFSH+recLH-None]	0	0	0	1.0000	0	0
Gonadotropins [recFSH alone-recFSH+recLH]	0	0	0	1.0000	0	0
Gonadotropins [recFSH alone-None]	0	0	0	1.0000	0	0
Gonadotropin dose	0	0	0	1.0000	0	0
Sperm status for ICSI [FRESH-FROZEN-THAWED]	0	0	0	1.0000	0	0
Oocyte status [FRESH-FROZEN-THAWED]	0	0	0	1.0000	0	0
MII oocytes	**0.080924**	**0.01626**	**24.76903**	**< 0.0001**	**0.04905**	**0.112794**
Dispersion	0.000011	0.17383	4.067e-7	0.9995	−0.34059	0.3408134

Statistics:
Response: ≥ 1 euploid blastocysts
Distribution: negative binomial
Estimation method: adaptive LASSO with validation column
Mean model link: Log
Dispersion model link: Identity

NOA, non-obstructive azoospermia.

Esteves SC, et al. Front Endocrinol (Lausanne). 2019;10:99.

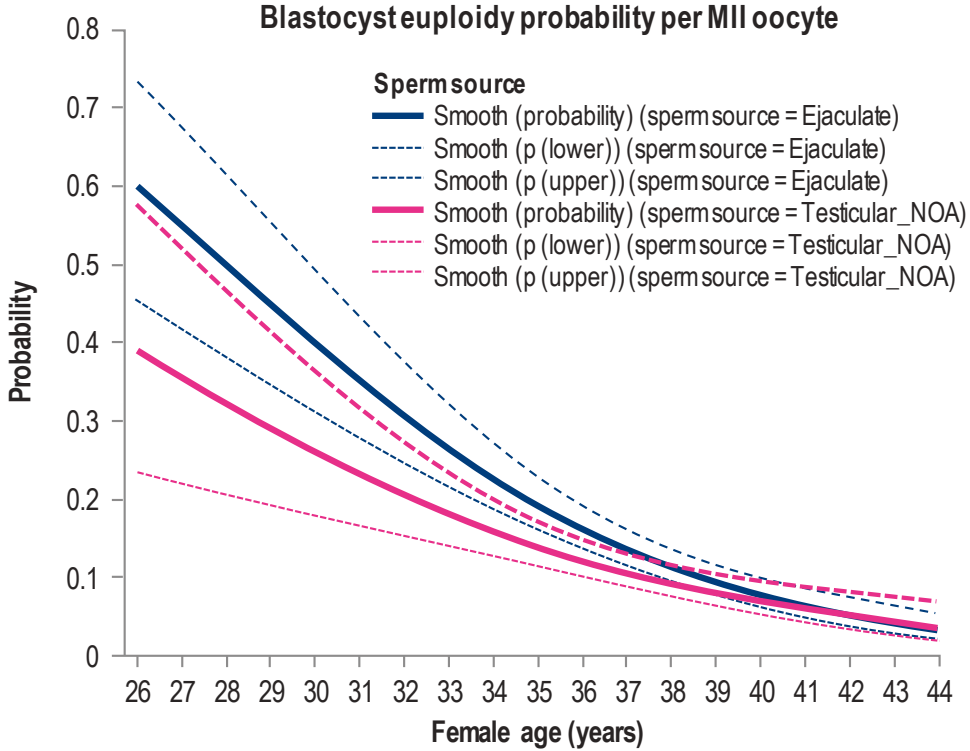
Development of ART Calculator roadmap

3. Model building

Equation
Y = a+b [Sperm = "Ejaculate"] +c [Sperm = Ejaculate](FemaleAge-38.9066) + d [Sperm=Testicular_NOA](FemaleAge-38.9066),
where $p = \left(\frac{1}{1+e^{-y}}\right)$

Term	Estimate	SE	Wald χ^2	Prob > χ^2
(Intercept)	−2.6518	0.117	371.96	< 0.0001
spermSource [EJACULATE]: (ageFemale-37.9384)	−0.2045	0.026	57.63	< 0.0001
spermSource [TESTICULAR_ NOA]:(ageFemale-37.9384)	−0.1530	0.035	18.65	< 0.0001
spermSource [Ejaculate]	0.2231	0.117	3.61	0.0574

Statistics:
Response: euploid blastocyst given MII oocytes
Distribution: binomial
Estimation method: nominal logistic fit
Mean model link: Logit
Area under the curve: 0.71589



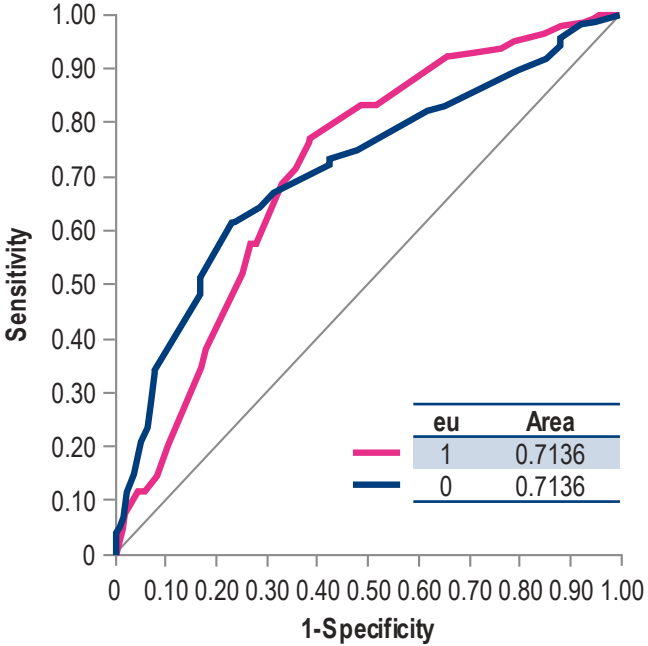
Esteves SC, et al. Front Endocrinol (Lausanne). 2019;10:99.

Development of ART Calculator roadmap

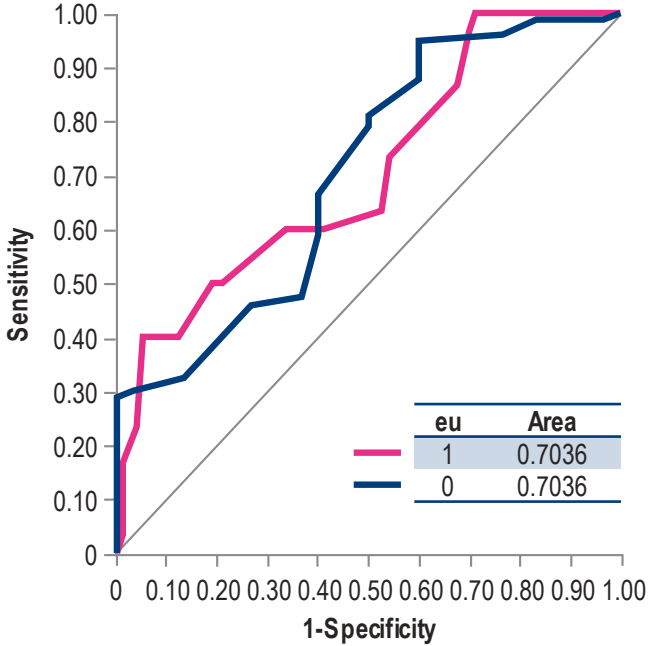
4. Model validation

The similarity between the ROC curves indicates the model is internally validated

ROC curve on training data (80% of the data)



ROC curve on validation data (20% of the data)



Esteves SC, et al. Front Endocrinol (Lausanne). 2019;10:99.

ART Calculator development roadmap

5. Construction of online calculator

The probability of success is denoted by π. Its complement, $1-\pi$, is the risk, i.e. the probability of having no euploid blastocyst despite achieving the estimated number of mature oocytes

It uses the formula to compute the minimum number of mature oocytes and its associated uncertainty (95% CI)

$$n \geq \frac{log(1-\pi)}{log(1-p)}$$

The 95% CIs for "p" were obtained from the logistic regression

The calculator computes the value of "p", given the female age and sperm source (and type of azoospermia)

Esteves SC, et al. Front Endocrinol (Lausanne). 2019;10:99.

ART Calculator development

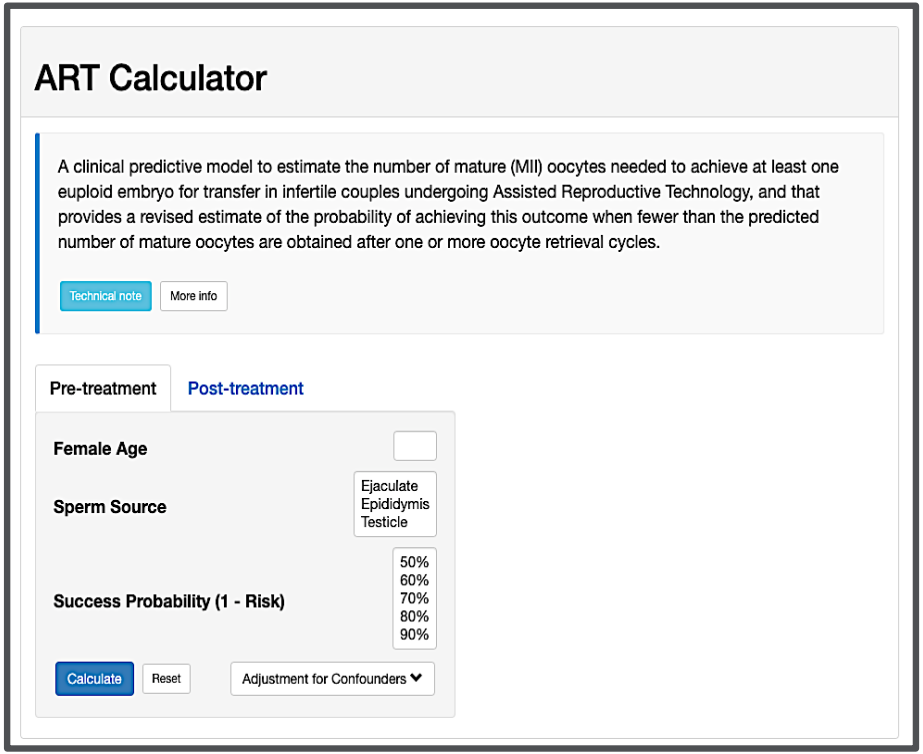
Two types of predictions

Pre-treatment

Estimate the minimum number of mature oocytes to achieve ≥ 1 euploid blastocyst for transfer in infertile couples undergoing IVF/ICSI

Post-treatment

Provide a revised estimate of the probability of achieving ≥ 1 euploid blastocyst when fewer than the predicted number of mature oocytes are obtained after ≥ 1 oocyte retrieval cycles



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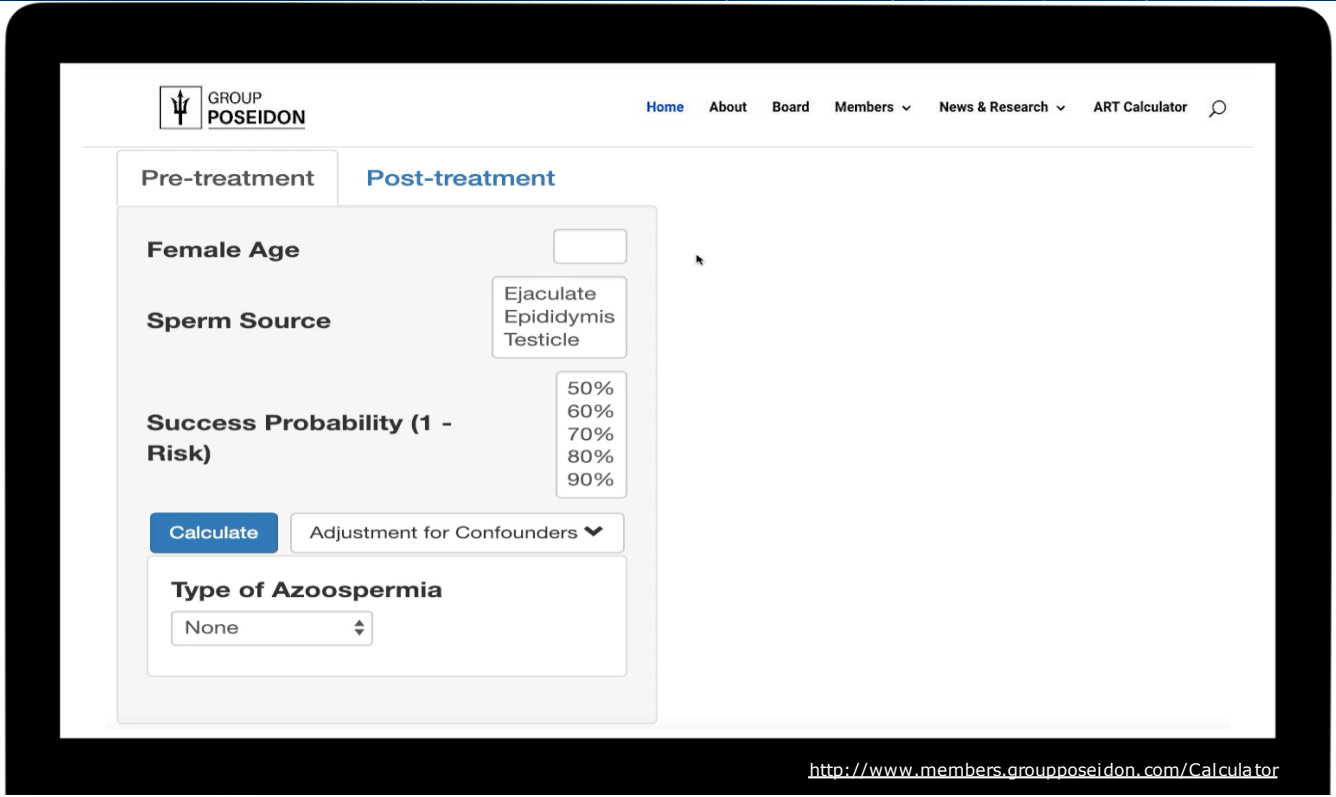
The easy way



Esteves SC, et al. Front Endocrinol (Lausanne). 2019;10:99.

ART Calculator: external validation study

- ART database for infertile couples undergoing IVF/ICSI and PGT-A
- Study is designed to assess the ability of the ART Calculator to predict the minimum number of MII oocytes needed to achieve ≥ 1 euploid blastocyst in infertile patients undergoing IVF/ICSI

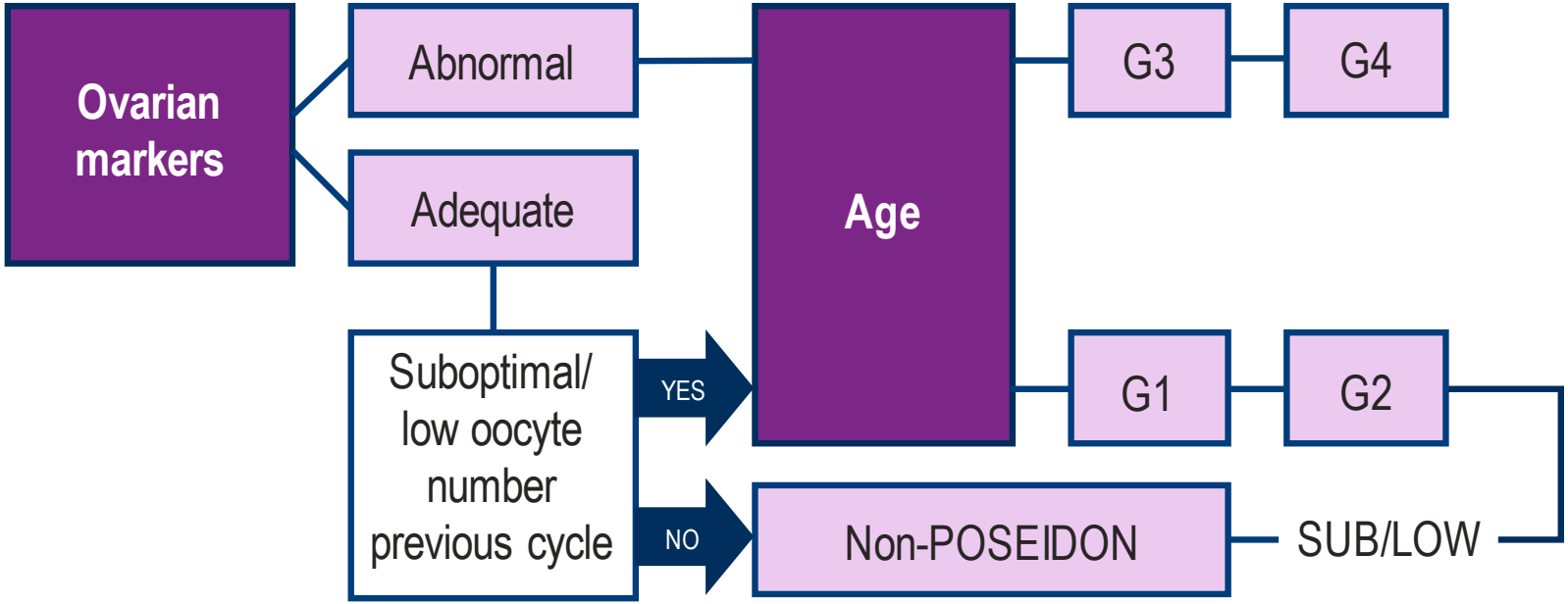
[Unpublished data not available]

Unpublished data.

Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number

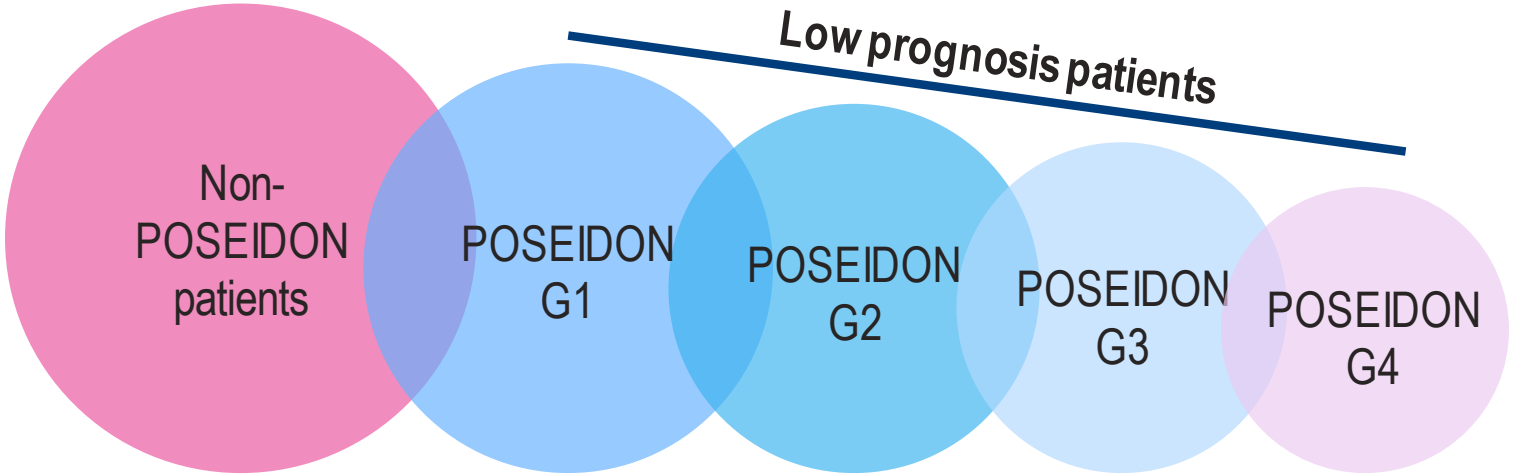
STEP 1	STEP 2	STEP 3
POSEIDON-based stratification	Estimate the minimum number of mature oocytes needed to have at least one euploid blastocyst for transfer	Patient-oriented treatment strategy to achieve the individualized oocyte number

POSEIDON patient stratification system:
ovarian biomarkers, age, number of oocytes if previous cycle



Poseidon Group, Alviggi C, et al. Fertil Steril. 2016;105:1452-3.
Humaidan P, et al. F1000Res. 2016;5:2911.
Haahr T, et al. Reprod Biol Endocrinol. 2018;16:20.

POSEIDON-based stratification



Andersen CY, et al. (editors). Research topic frontiers in endocrinology. Available from: https://www.frontiersin.org/research-topics/6849/poseidons-stratification-of-low-prognosis-patients-in-art-the-why-the-what-and-the-how. Accessed May 2019.

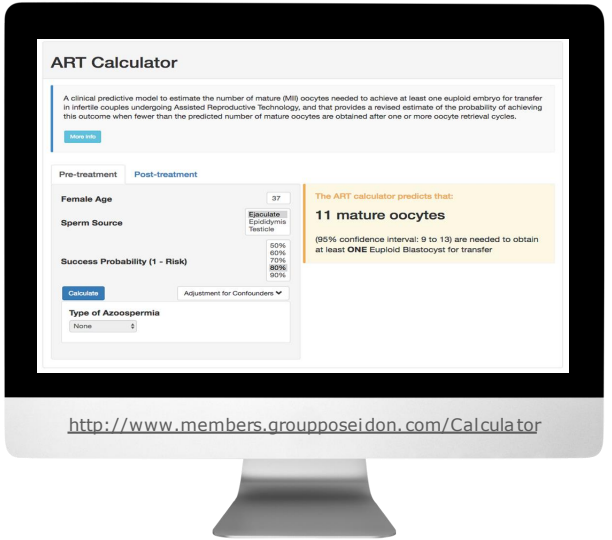
Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number

POSEIDON-based stratification

STEP 1

Estimate the minimum number of mature oocytes needed to have at least one euploid blastocyst for transfer

STEP 2



http://www.members.groupposeidon.com/Calculator

Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number

STEP 1	STEP 2	STEP 3
POSEIDON–based stratification	Estimate the minimum number of mature oocytes needed to have at least one euploid blastocyst for transfer	Patient-oriented treatment strategy to achieve the individualized oocyte number

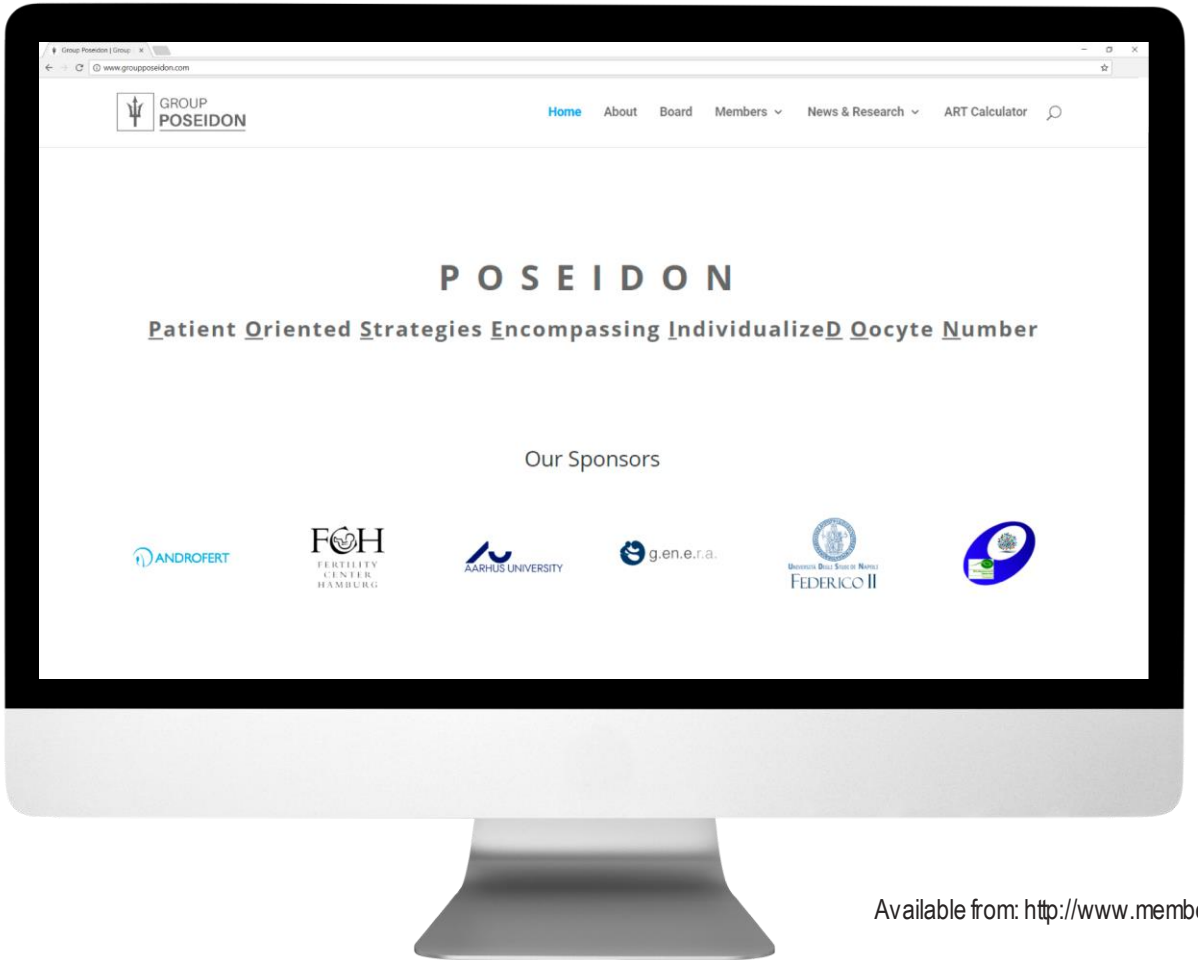
The most optimal treatment strategy is planned with the mindset to achieve the POSEIDON marker of success

- GnRH analogue regimen
- Gonadotropin dose and drug type
- Trigger strategy
- Adjuvant therapy
- Combined strategies (AccuVit, DuoStim, etc.)
- Personalized use of laboratory technology
- Personalized luteal phase support

iART

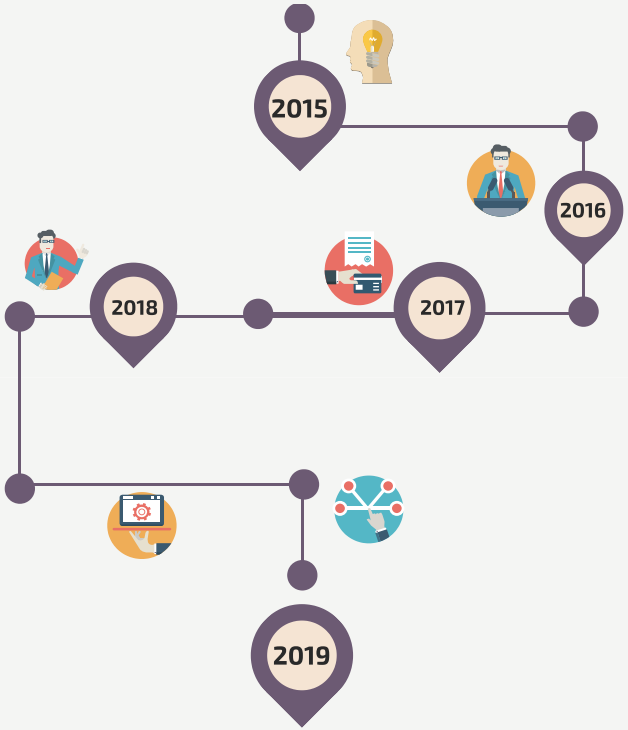
Improve care and reduce time to live birth

www.groupposeidon.com



Available from: http://www.members.groupposeidon.com/Calculator. Accessed May 2019.

THE (BRIEF) HISTORY OF POSEIDON GROUP



GROUP POSEIDON

01 **46 members**

17 countries & 4 continents
(Italy, Denmark, Germany, Spain, Portugal, France, Greece, Israel, Romenia, Russia, Croatia, Brazil, Mexico, Argentina, Uruguay, India, Vietnam, Taiwan, UAE

02 **Dedicated educational website**
www.groupposeidon.com

03 **Online ART Calculator**
Prediction tool to calculate the minimum number of mature oocytes needed to obtain at least 1 euploid blastocyst for transfer in patients undergoing IVF/ICSI

04 **ART Calculator External Validation**
Investigator-sponsored study

05 **Dedicated Research Topic**
Open access articles' collection
Frontiers in Endocrinology (Reproduction)

06 **Over 15 peer-reviewed papers***
Reviews, original articles, perspective articles, letters, etc. (*Pubmed)

07 **Meetings, Oral & Poster presentations**
Excemed, ESHRE, SBRA

08 **Over 50 lectures across the globe**

09 **Two clinical trials***
*clinicaltrials.gov (May 2019)

10 **This space is yours**
Join us!