CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

Intérêt de l'évaluation de la réserve ovarienne dans le bilan et la prise en charge d'une infertilité

Collège de Gynécologie
Paul Barrière - Carole Splingart - Thomas Fréour

Orléans Avril 2013

Déclarations d'intérêt

Les auteurs ne déclarent aucun conflit d'intérêt relatif à ce sujet

La réserve ovarienne
- *Définition* -

NOMBRE (et qualité)
des ovocytes
présents dans les follicules primordiaux
du cortex ovarien
à un instant donné.

Stock folliculaire

- Au 7ème mois de grossesse : 6 à 7 millions d'ovocytes
- A la naissance : entre 600 000 et 2 millions de follicules
- A 19 ans : 300 000 follicules
- A 50 ans : 1 500 follicules

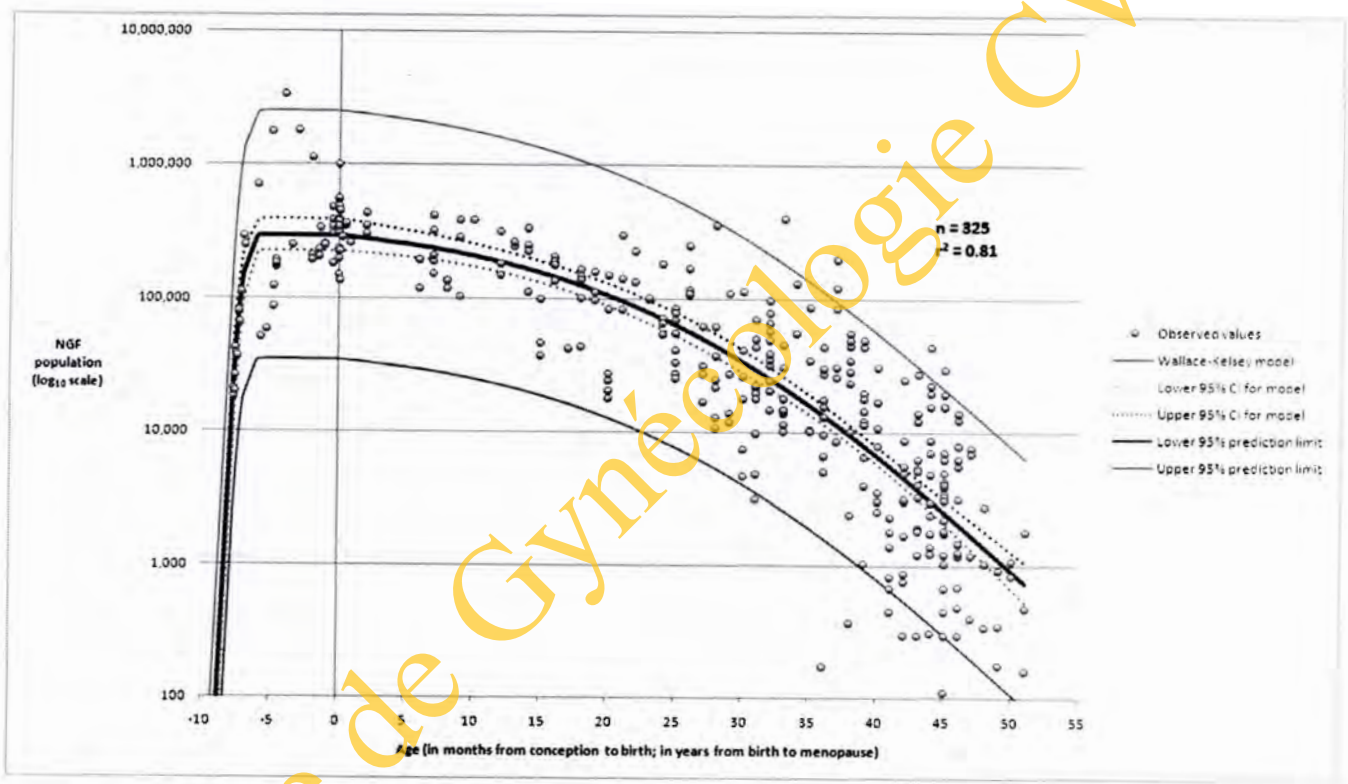


Figure 1. The model that best fits the histological data. The best model for the establishment of the NGF population after conception, and the subsequent decline until age at menopause is described by an ADC model with parameters $a = 5.56$ (95% CI 5.38–5.74), $b = 25.6$ (95% CI 24.9–26.4), $c = 52.7$ (95% CI 51.1–54.2), $d = 0.074$ (95% CI 0.062–0.085), and $e = 24.5$ (95% CI 20.4–28.6). Our model has correlation coefficient $r^2 = 0.81$, fit standard error = 0.46 and F-value = 364. The figure shows the dataset (n = 325), the model, the 95% prediction limits of the model, and the 95% confidence interval for the model. The horizontal axis denotes age in months up to birth at age zero, and age in years from birth to 51 years.
doi:10.1371/journal.pone.0008772.g001

Le dogme initial

- Le stock folliculaire est définitivement constitué avant la naissance à la 34ème semaine
- Stock assez stable dans l'enfance

Néo ovogénèse

- Poursuite du débat

Tilly and Telfer

Mol Hum Reprod 2009

Normile Science 2009

White et al Nat Med 2012

Woods and Tilly Fer Ster 2012

Woods et al Plos Genet 2012

Woods et al Reprod Sci 2013(1)

Woods et al Reprod Sci 2013(2)

Woods and Tilly Semin Reprod Med 2013

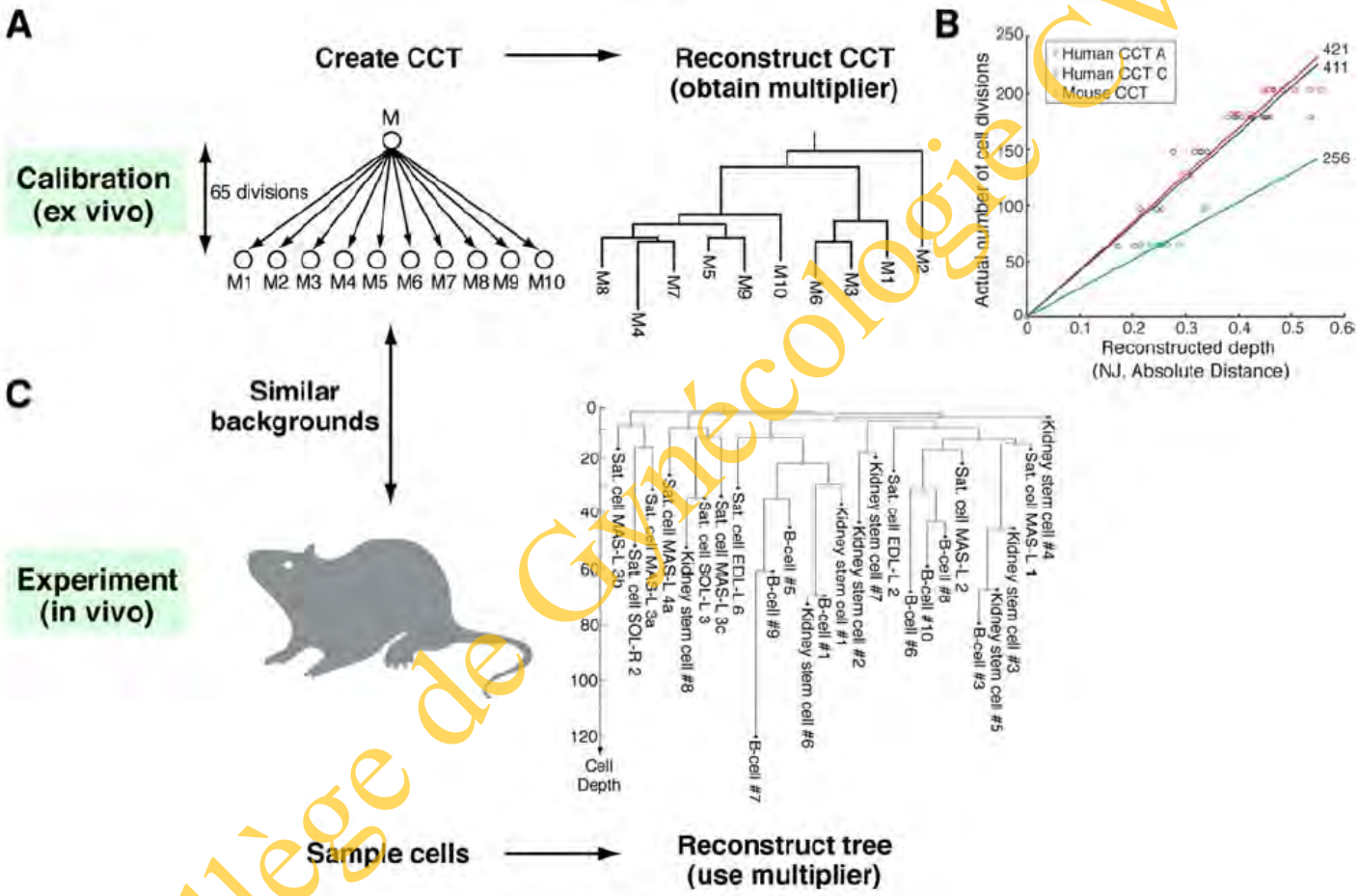
OPEN ACCESS Freely available online

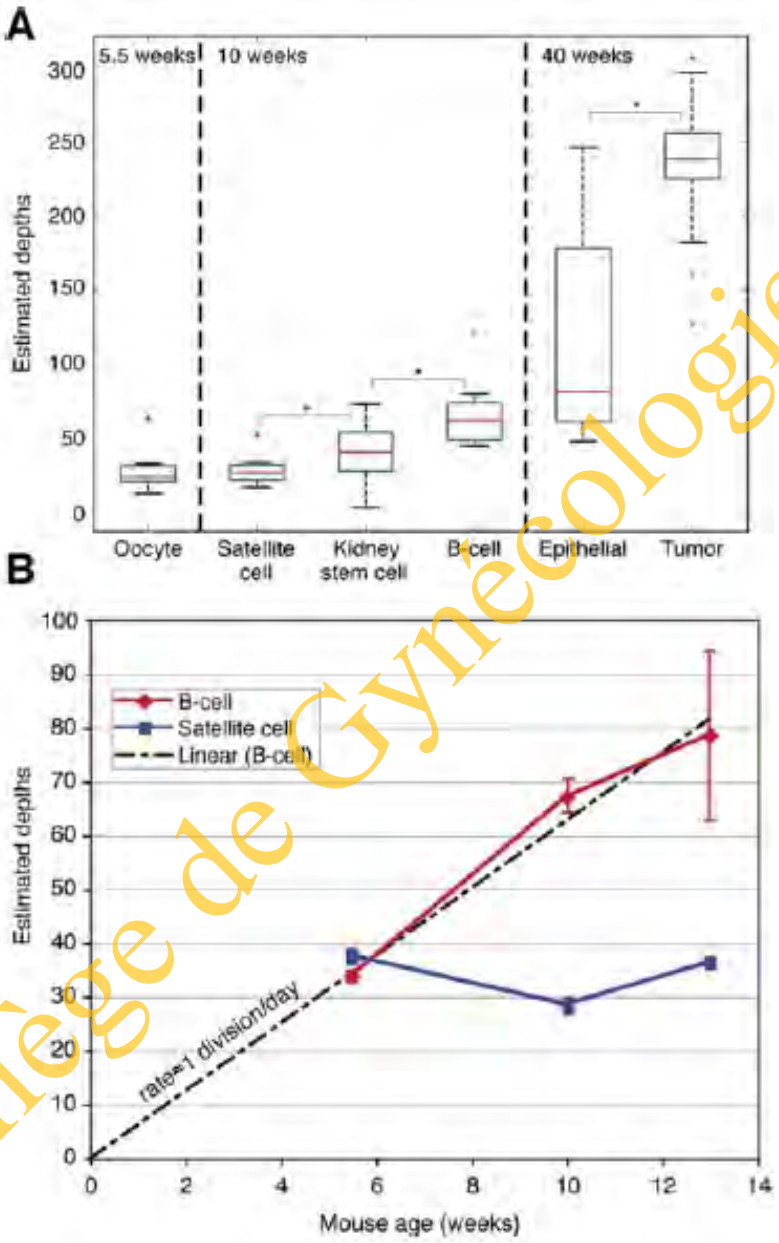
PLoS COMPUTATIONAL BIOLOGY

Estimating Cell Depth from Somatic Mutations

Adam Wasserstrom[1], Dan Frumkin[1], Rivka Adar[1], Shalev Itzkovitz[2], Tomer Stern[2], Shai Kaplan[1], Gabi Shefer[3], Irena Shur[3], Lior Zangi[4], Yitzhak Reizel[5], Alon Harmelin[6], Yuval Dor[7], Nava Dekel[5], Yair Reisner[4], Dafna Benayahu[3], Eldad Tzahor[5], Eran Segal[2], Ehud Shapiro[1,2]*

1 Department of Biological Chemistry, Weizmann Institute of Science, Rehovot, Israel, **2** Department of Computer Science and Applied Mathematics, Weizmann Institute of Science, Rehovot, Israel, **3** Department of Cell and Developmental Biology, Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel, **4** Department of Immunology, Weizmann Institute of Science, Rehovot, Israel, **5** Department of Biological Regulation, Weizmann Institute of Science, Rehovot, Israel, **6** Department of Veterinary Resources, Weizmann Institute of Science, Rehovot, Israel, **7** Department of Cellular Biochemistry and Human Genetics, The Hebrew University-Hadassah Medical School, Jerusalem, Israel





- Clusters de CGP à partir de leurs progéniteurs
- Migration incohérente dans les 2 ovaires
- Pas de corrélation entre le lignage et la position physique des ovocytes

Dekel et al, 2011

Formation des follicules primordiaux

- Nombreux facteurs impliqués
  - Zfx (Luoh et al 97)
  - Daz 1a Luoh(Ruggin et al 97)
  - Fig alpha (Soyal et al 00)
  - MSH5, DMC1, NGF (Dissen et al 01)
  - SPO 11 (Di Giacomo et al 05)
  - Notch (Trombly et al 09)

Sortie quotidienne du stock et entrée en croissance

Primaire ↳ Secondaire

- Taux de croissance, prépubertaire : 1 à 3%
- Après la puberté :
  - 20 ans : 35/jour
  - 30 ans : 30/jour
  - 40 ans : 9/jour

Pour une ovulation par cycle

Rôle de l'ovocyte

Sortie du stock

Croissance et différenciation du follicule

-Facteurs activateurs :

GD9, Fox03

BMP 15 (GDF 9b), Kit Ligand

-Facteurs inhibiteurs :

Foxl2, AMH

JCEM ONLINE

Hot Topics in Translational Endocrinology—Endocrine Research

Genes Involved in Initial Follicle Recruitment May Be Associated with Age at Menopause

Marlies Voorhuis, Frank J. Broekmans, Bart C. J. M. Fauser, N. Charlotte Onland-Moret, and Yvonne T. van der Schouw

SNP du gène AMHR2 et du gène BMP15 associés à l'âge de la ménopause naturelle

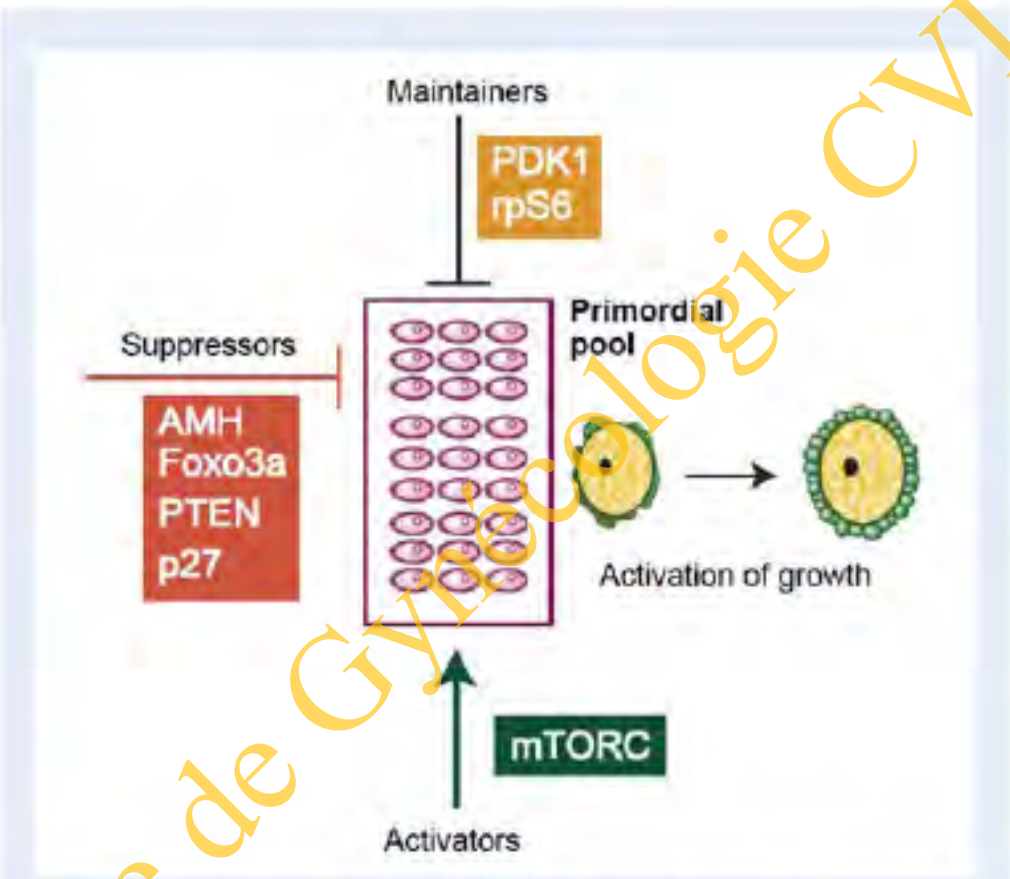
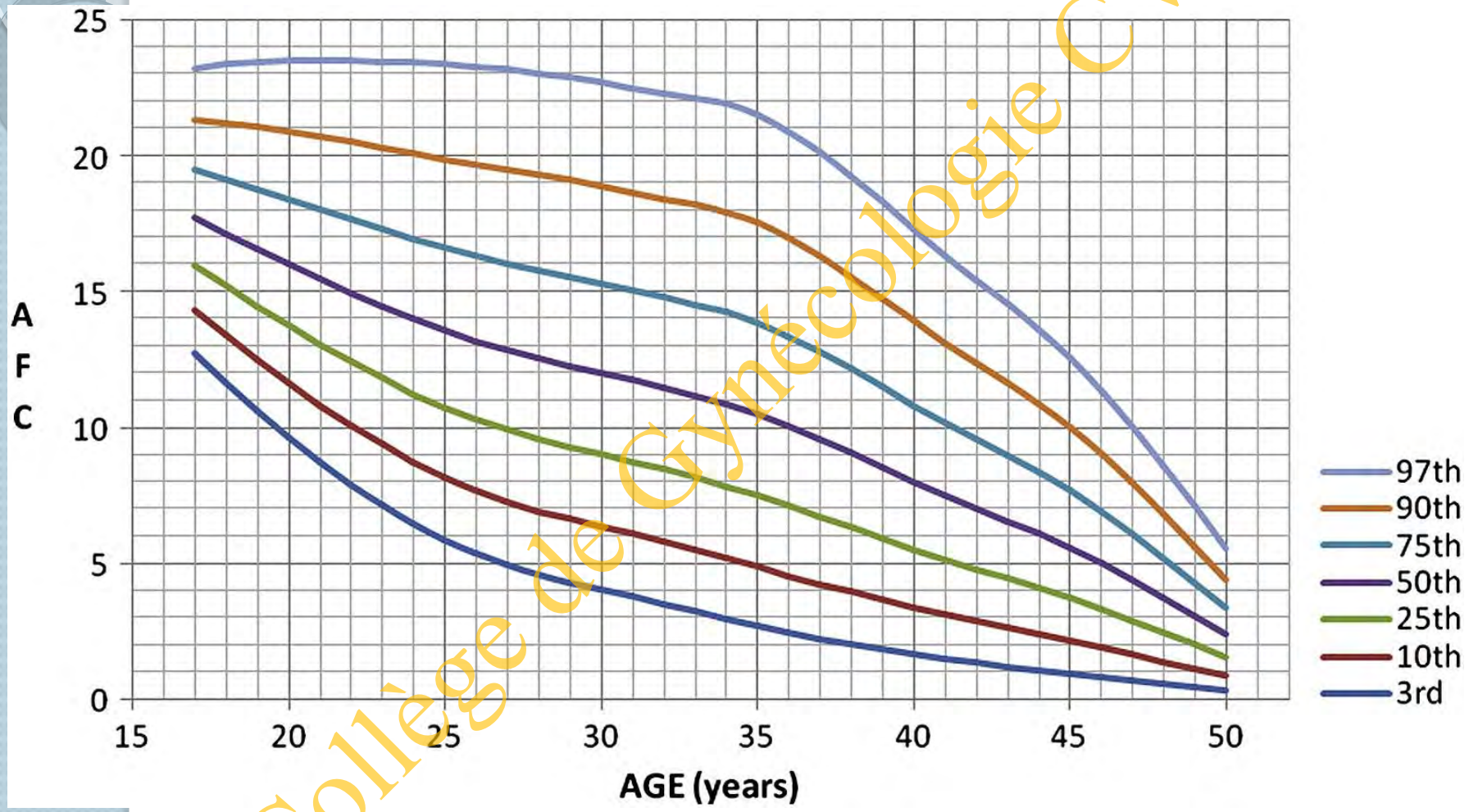


Figure 3 Mechanisms underlying activation of quiescent follicles. A summary of some of the components of the PI3K pathway that have been implicated in maintaining health of the primordial pool (black bar) and either suppressing (orange bar) or activating (green arrow) the initiation of growth. These details have been gathered through knockout mouse models (see Reddy *et al.*, 2010 for review).



Almog B et al, F&S, 2011

TABLE 3

Percentiles of antral follicle count, age of switching rate, and age of poor antral follicle count (eight or fewer).

Percentile of AFC	Age (y) of switching rate	Age (y) of AFC ≤8
3rd	26	22
10th	28	26
25th	32	34
50th	NA	42
75th	34	45
90th	36	48
97th	38	49

Note: AFC = antral follicle count; NA = not applicable.

Almog. Age-related normogram for antral follicle count. Fertil Steril 2011.

Almog B et al, F&S, 2011

Le Vieillissement ovarien

- Altérations qualitatives de l'ovocyte liées à l'âge

- Voies de signalisation des :
  - TGF-beta Sma/mab
  - Insulin/IGF1

Luoh et al Cell 2010

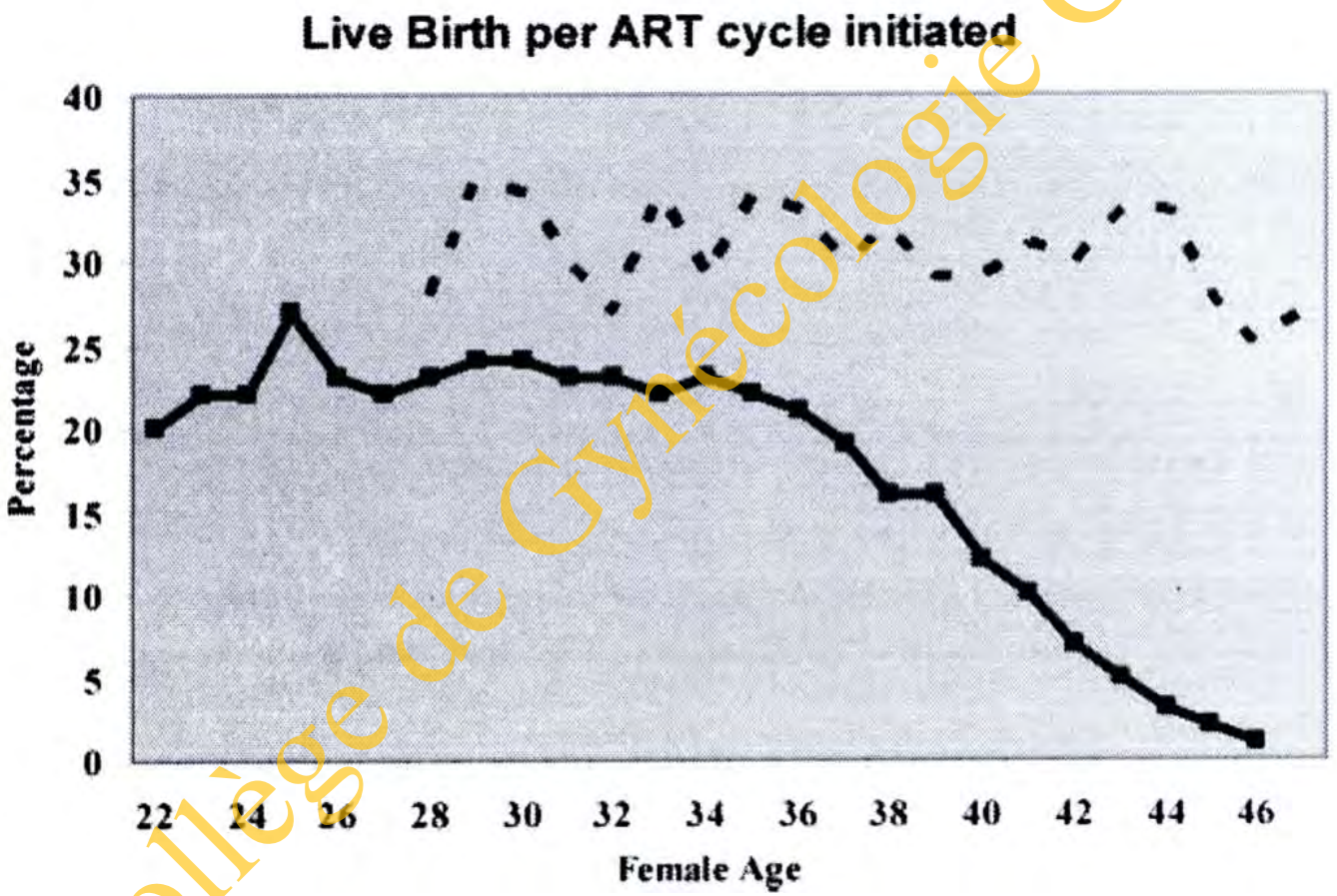
Le Vieillissement ovarien

Altérations qualitatives de l'ovocyte liées à l'âge

- Effets sur :
  - La fécondabilité de l'ovocyte
  - La ségrégation chromosomique
  - Les mécanismes de réparation de l'ADN
  - L'intégrité du cycle cellulaire
  - Le fonctionnement mitochondrial

- Effets indépendants de la régulation de la croissance et non autonomes à l'ovocyte

Luo et al Cell 2010



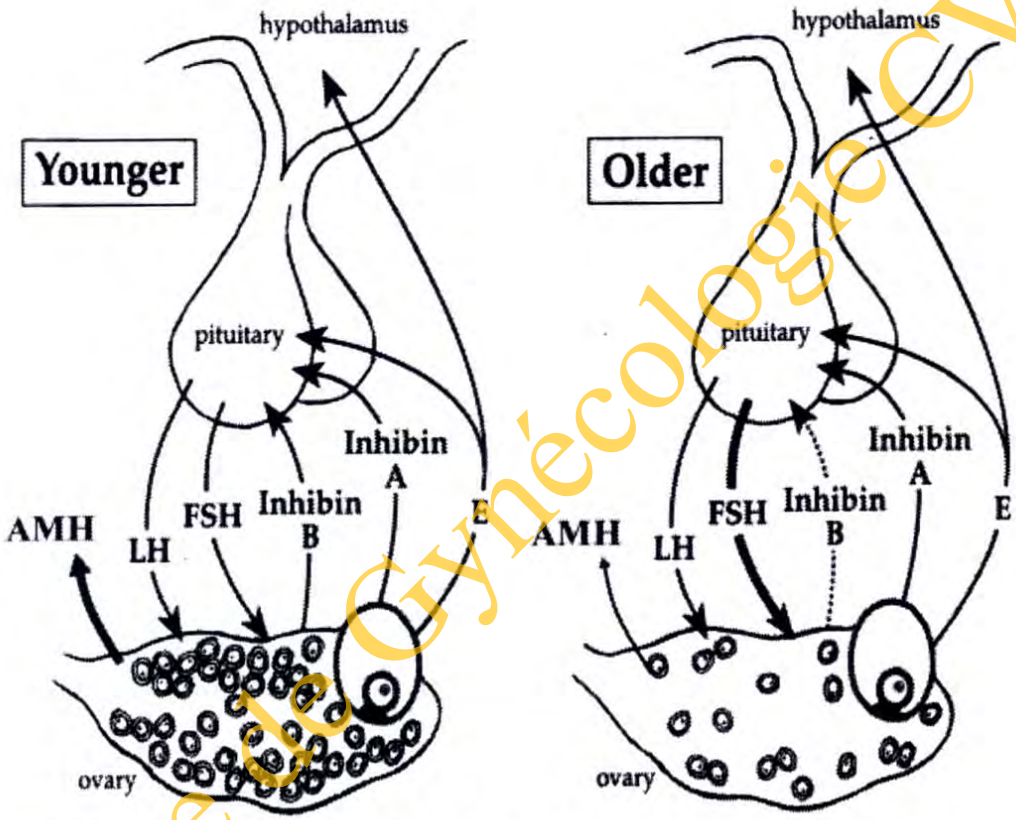


FIG. 13. Schematic illustration of the changes in ovarian follicle reserve with increasing female age and the effect of these quantitative changes upon several ovarian and hypothalamo-pituitary endocrine factors. Graph was adapted from Soules *et al.* (330).

Mesures de la Réserve ovarienne

- Estimation liée à l'âge

- Directe : biopsie ovarienne
  - Imprécise sur un fragment
  - Agressive
  - Adhésiogène

Mesures de la Réserve ovarienne Indirectes

- Biologiques
- Échographiques

Mesures biologiques de la réserve ovarienne

FSH / E2 :

- Variabilité intercycle
- Intérêt pronostique discuté en FIV

Bancsi et al, Fertil Steril 2003

Nelson et al, Human Reprod 2007

Lee et al, Human Reprod 2008

MacTavish et al, Endoc 2007

- Élévation tardive dans l'IOP

Mesures biologiques de la réserve ovarienne

AMH :

- Faible variation inter et intra-cycle
- Bonne corrélation au CFA
- Aspect qualitatif de la réserve ovarienne

Lie Fong et al,RBMonline 2008

Rôle de l'AMH

-Rôle inhibiteur sur le recrutement primaire

-Modulation du recrutement cyclique en diminuant la sensibilité des follicules à la FSH

-Inhibition de la stéroïdogénèse

-Baisse des récepteurs à la LH

-transcription de l'AMH stimulée par la FSH in vitro *(Taieb et al, Mol Endoc, 2011)*

Tableau 11 : Etude longitudinale chez 50 femmes prélevées annuellement, et dosage de l'AMH (kit DSL), inhibine B, FSH et E2 dans les années qui ont précédé la dernière menstruation.
(Sowers et al, 2008).

* Le kit de dosage de l'**AMH** commercialisé par DSL donne des concentrations 4.6 fois plus faibles que celles données par le kit Immunotech / Beckman (voir le paragraphe «Analytique»).

	1993-94 Moy ± DS	1994-95 Moy ± DS	1995-96 Moy ± DS	1997-98 Moy ± DS	1998-99 Moy ± DS	1999-2000 Moy ± DS
AMH ng/ml	0.626 ± 0.51	0.462 ± 0.37	0.335 ± 0.30	0.104 ± 0.10	0.112 ±0.10	0.086± 0.08
Inhibine B pg/ml	69.8 ± 45	54.3 ± 43	50.4 ± 37	28 ± 21	30 ±55	23 ± 24
FSH UI/L	8 ±2.4	7.6 ± 3.7	7.7 ± 4.9	16.4 ± 15.8	18.6 ± 15	21.5 ± 18
E2 pg/ml	58.9 ±24	72 ± 36	65.1 ± 44	66 ± 59	57.1 ± 48	57 ± 31

CONTROVERSES SUR L'INTÉRÊT DE L'AMH DANS LA PRÉVISION DU VIEILLISSEMENT OVARIEN

Human Reproduction, Vol.26, No.11 pp. 2925–2932, 2011
Advanced Access publication on August 16, 2011 doi:10.1093/humrep/der271

human reproduction

DEBATE *Reproductive endocrinology*

Anti-Müllerian hormone—is it a crystal ball for predicting ovarian ageing?

Justine Shuhui Loh[1] and Abha Maheshwari[2,*]

[1]Department of Obstetrics and Gynaecology, Aberdeen Royal Infirmary, NHS Grampian, Aberdeen AB25 2ZL, UK [2]Department of Obstetrics and Gynaecology, Division of Applied Health Sciences, University of Aberdeen, Aberdeen AB25 2ZL, UK

Table I WHO criteria for screening[a].

The condition sought should be an important health problem for the individual and community
There should be an accepted treatment or useful intervention for patients with the disease
The natural history of the disease should be adequately understood
There should be a latent or early symptomatic stage
There should be a suitable and acceptable screening test or examination
Facilities for diagnosis and treatment should be available
There should be an agreed policy on whom to treat as patients
Treatment started at an early stage should be of more benefit than treatment started later
The cost should be economically balanced in relation to possible expenditure on medical care as a whole
Case finding should be a continuing process and not a once and for all project

[a] Wilson and Jungner 1968 cited in Mak *et al.* (1998, p. 646).

OPEN ACCESS Freely available online

PLoS one

A Validated Model of Serum Anti-Müllerian Hormone from Conception to Menopause

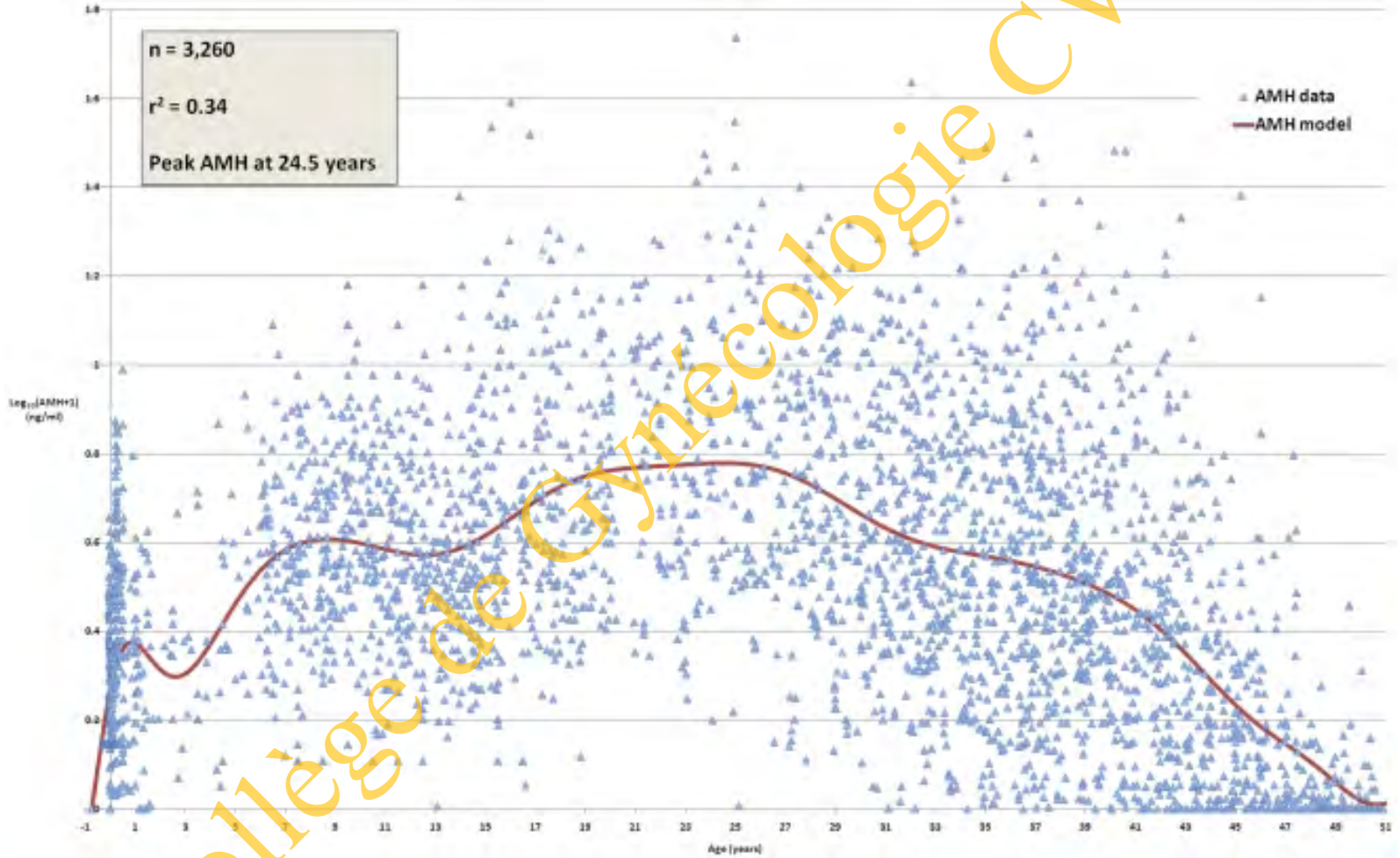
Thomas W. Kelsey[1], Phoebe Wright[2], Scott M. Nelson[3], Richard A. Anderson[4], W. Hamish B. Wallace[5]*

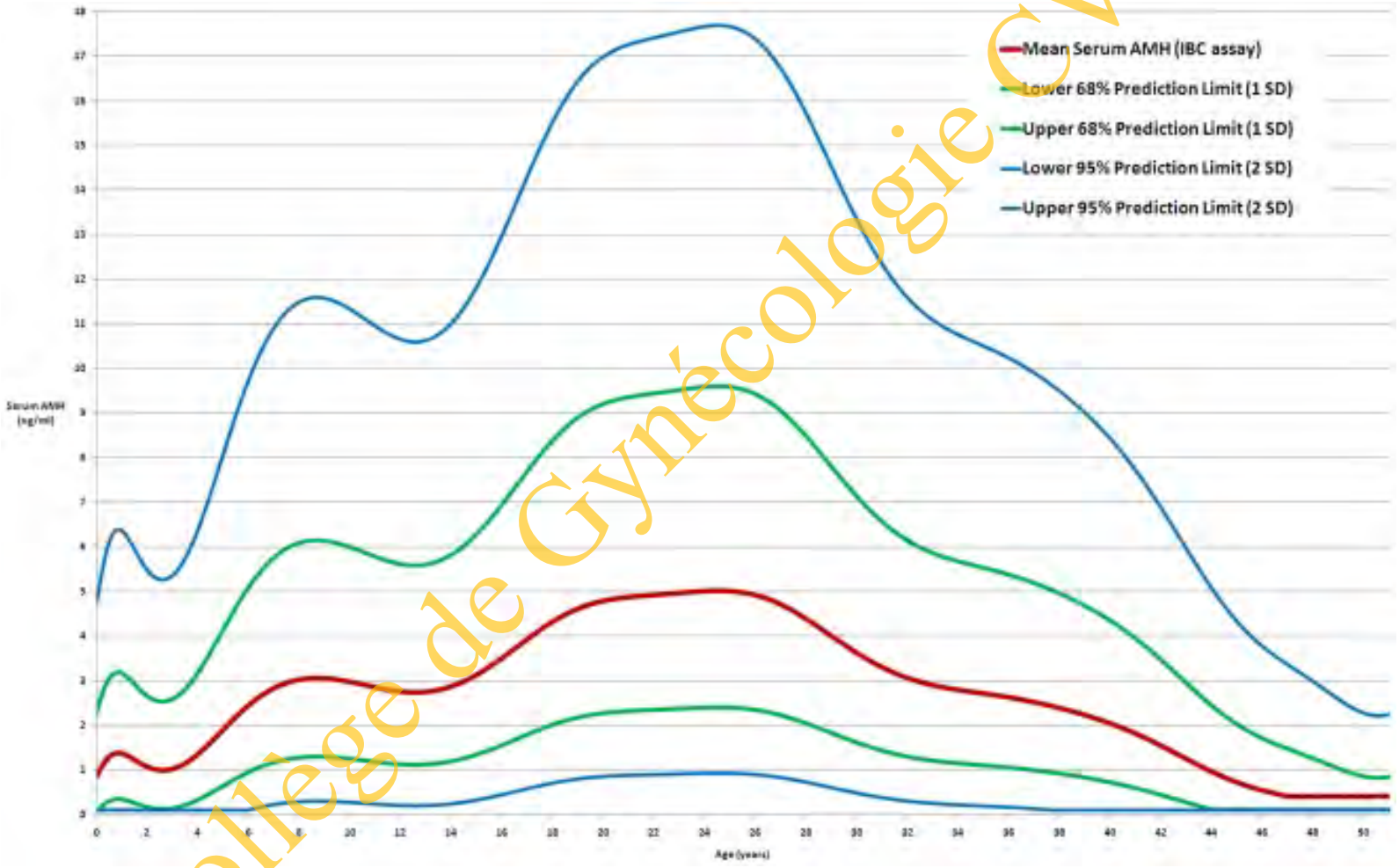
1 School of Computer Science, University of St. Andrews, St. Andrews, Scotland, United Kingdom, **2** University of Edinburgh, Edinburgh, Scotland, United Kingdom, **3** Centre for Population and Health Sciences, University of Glasgow, Glasgow, Scotland, United Kingdom, **4** MRC Centre for Reproductive Health, University of Edinburgh, Edinburgh, Scotland, United Kingdom, **5** Division of Reproductive and Developmental Sciences, University of Edinburgh, Edinburgh, Scotland, United Kingdom

Le taux d'AMH est aussi le reflet de la réserve ovarienne, c'est a dire des follicules primordiaux et du taux d'entrée en croissance

Kelsey et al, Plos One 2011

Kelsey et al, Mol Hum Reprod 2011





Gynecological Endocrinology, 2011, 1-4, Early Online

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DOI: 10.3109/09513590.2011.593666

informa
healthcare

RESEARCH ARTICLE

The ovarian follicular pool and reproductive outcome in women

A. La Marca, E. Papaleo, G. D'Ippolito, V. Grisendi, C. Argento, A. Volpe

Mother-Infant Department, Institute of Obstetrics and Gynecology, University of Modena and Reggio Emilia, Italy and (EP) Centro Natalità, Gynecological-Obstetrics Department, San Raffaele Hospital, Vita-Salute San Raffaele, Milano, Italy

- 8 études compilées
- Disponibilité de l'histoire de reproduction et de l'histologie ovarienne
- Patientes évaluées en réserve ovarienne supérieure ou inférieure à la moyenne de leur âge

Conclusion : pas de relation évidente entre quantité et qualité du pool folliculaire

Nomogram for the decline in serum antimüllerian hormone: a population study of 9,601 infertility patients

Scott M. Nelson, Ph.D.,[a] *Martina C. Messow, Dipl. Stat.,*[b] *A. Michael Wallace, Ph.D.,*[c] *Richard Fleming, Ph.D.,*[a,d] *and Alex McConnachie, Ph.D.*[b]

La diminution de la concentration sérique en AMH liée à l'âge peut être décrite par un nomogramme construit à partir d'une équation quadratique

Anti-Müllerian Hormone Predicts Menopause: A Long-Term Follow-Up Study in Normoovulatory Women

S. L. Broer, M. J. C. Eijkemans, G. J. Scheffer, I. A. J. van Rooij, A. de Vet, A. P. N. Themmen, J. S. E. Laven, F. H. de Jong, E. R. te Velde, B. C. Fauser, and F. J. M. Broekmans

Évaluation des cycles et du statut ménopausique chez 257 femmes normo-ovulatoires de 21 à 46 ans, 11 ans après un dosage d'AMH

- AMH corrélée à l'âge ultérieur de la ménopause

- AMH hautement prédictive de la datation de la ménopause

Human Reproduction Update, Vol.19, No.1 pp. 67–83, 2013
Advanced Access publication on October 26, 2012 doi:10.1093/humupd/dms043

human reproduction update

The ageing ovary and uterus: new biological insights

S.M. Nelson[1,*], E.E. Telfer[2], and R.A. Anderson[3]

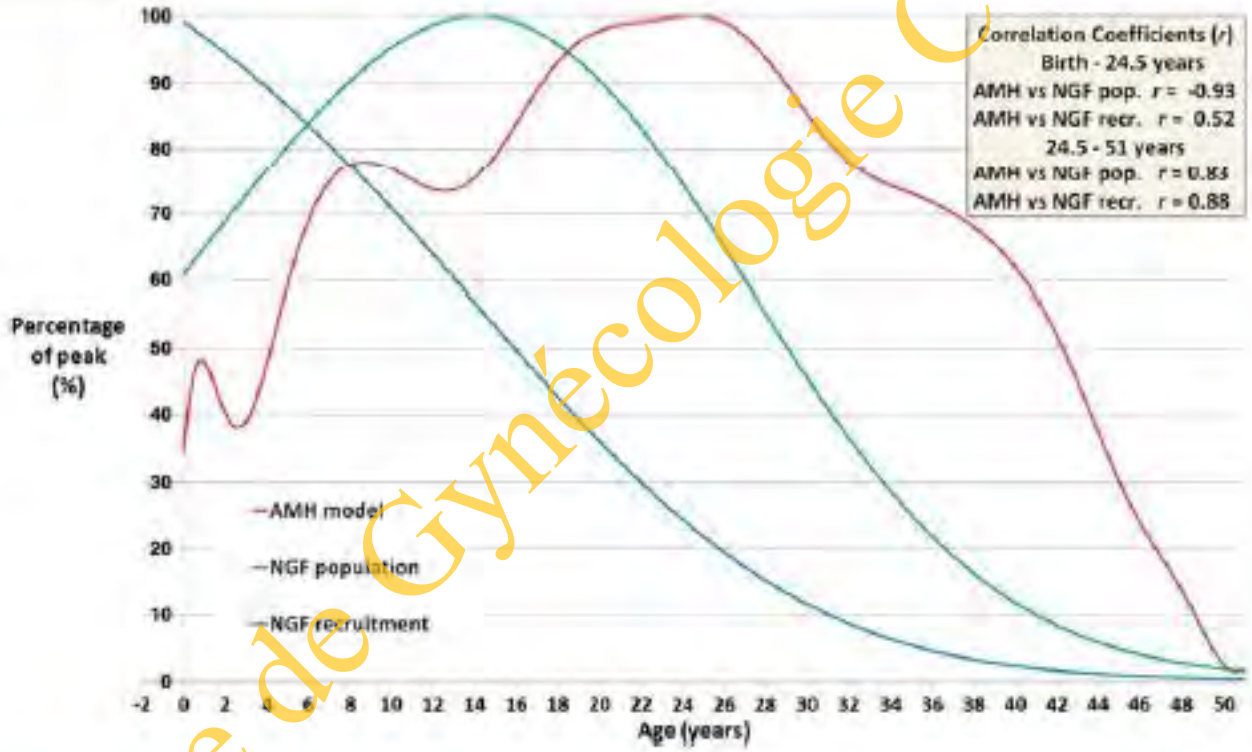
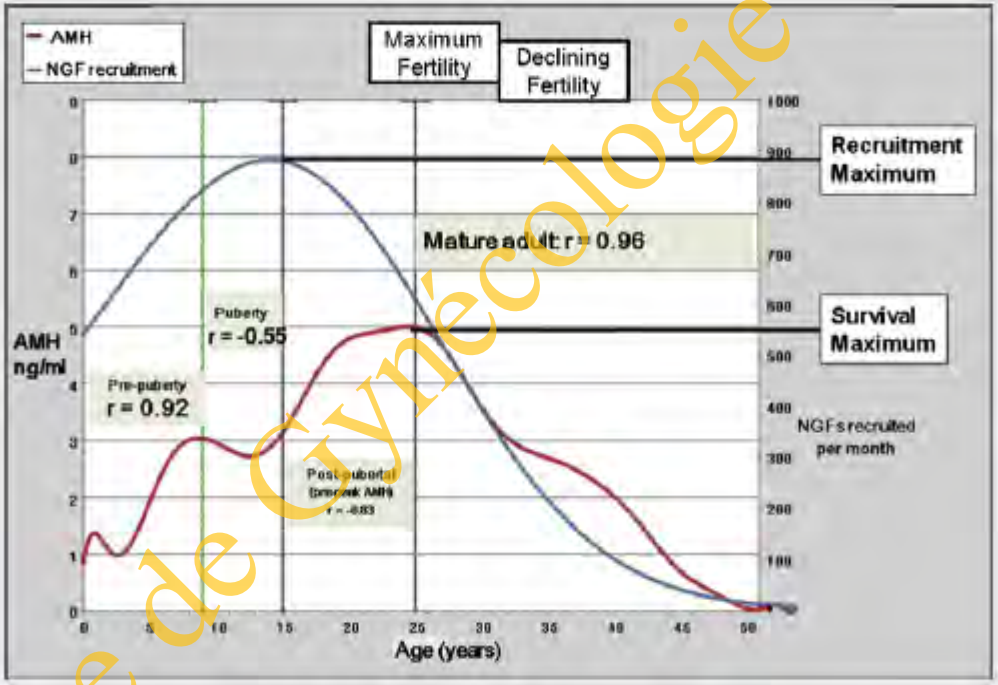


Figure 4 Comparison of serum AMH concentrations with NGF population and with NGF recruitment. The red line is the log-unadjusted validated AMH model (Kelsey et al., 2012), peaking at 24.5 years. The blue line denotes the decline in NGF population (Wallace and Kelsey, 2010), with peak population at 18–22 weeks gestation. The green line denotes the numbers of NGFs recruited towards maturation population (Wallace and Kelsey, 2010), with peak numbers lost at age 14.2 years on average. Each quantity has been normalized so that the peak occurs at 100%. Correlation coefficients (r) are given for AMH concentrations against the other two curves for birth to 24.5 years and for 24.5–51 years. Reproduced with permission from Kelsey et al. (2012).

Interpreting human follicular recruitment and antimüllerian hormone concentrations throughout life

Richard Fleming, Ph.D.,[a,e] Tom W. Kelsey, Ph.D.,[b] Richard A. Anderson, M.D., Ph.D.,[c] W. Hamish Wallace, M.D.,[d] and Scott M. Nelson, Ph.D.[e]

Fertility and Sterility® Vol. 98, No. 5, November 2012



Antimüllerian hormone (AMH) and follicular recruitment profile across the lifespan. Comparison of serum concentrations of AMH with recruitment rates of nongrowing follicles (NGF). The red line is the log-unadjusted validated AMH model (8), showing a peak at 24.5 years. The blue line denotes the numbers of NGFs recruited per month toward the maturation population of follicles (7), with peak numbers lost at age 14.2 years on average. Correlation coefficients (r) are given for AMH concentrations against follicular recruitment for each developmental phase; from birth to puberty (age 9 years), during puberty (9–15 years), postpuberty (15–25 years), and mature adults (>25 years). The phases of human fertility described by te Velde and Pearson (20) have been incorporated.

Fleming. Folliculogenesis, AMH, and human fertility. Fertil Steril 2012.

AMH ET RÉPONSE OVARIENNE EN FIV

Current Opinion in
Obstetrics and Gynecology

The role of anti-Mullerian hormone assessment in assisted reproductive technology outcome

Broer, Simone L[a]; Mol, BenWillem[b]; Dólleman, Madeleine[a]; Fauser, Bart C[a]; Broekmans, Frank JM[a]

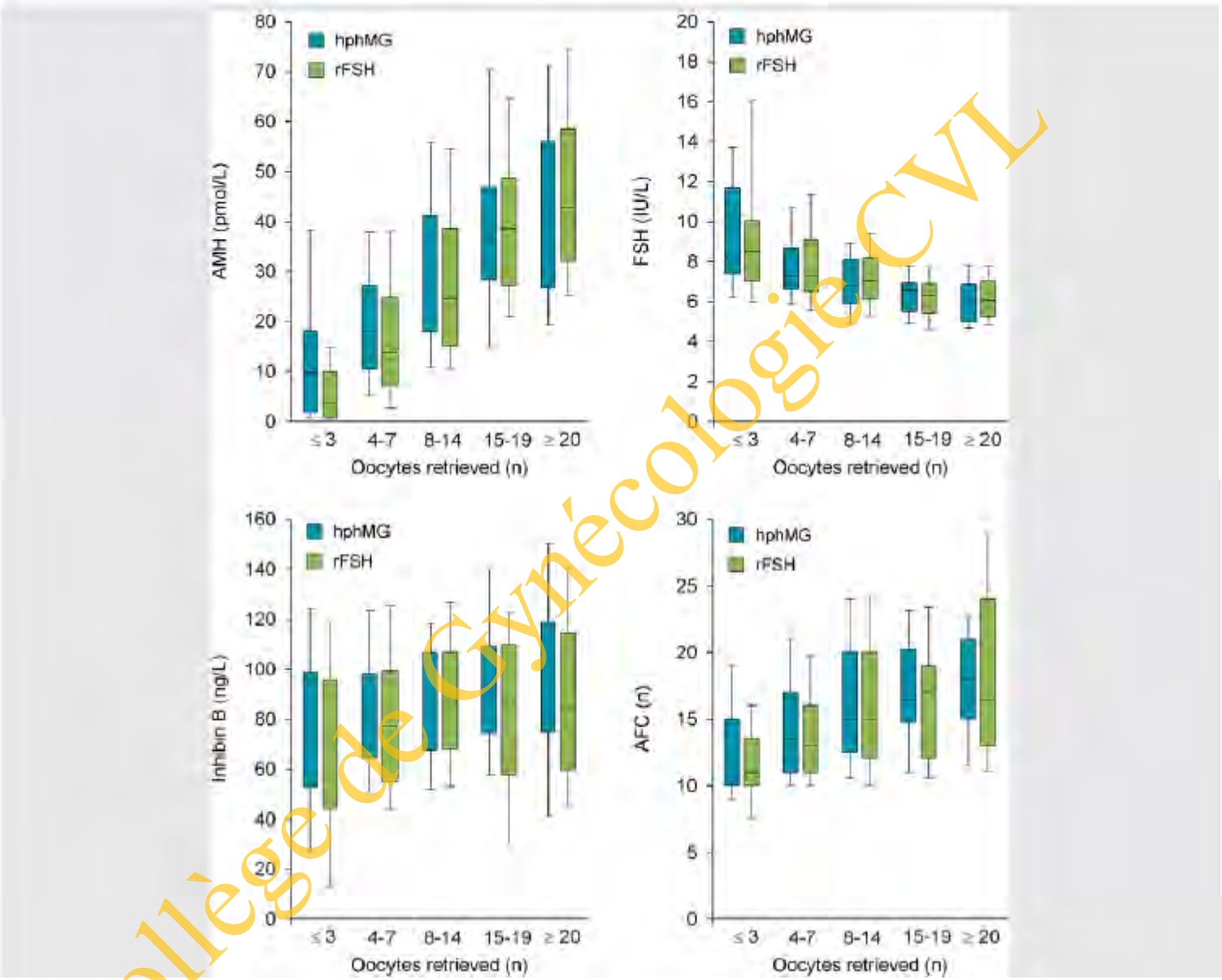
L’AMH prédit les extrêmes de la réponse ovarienne en stimulation pour FIV mais ne peut être encore utilisée pour prédire les résultats.

L’AMH permet l’individualisation des traitements

Antimüllerian hormone in gonadotropin releasing-hormone antagonist cycles: prediction of ovarian response and cumulative treatment outcome in good-prognosis patients

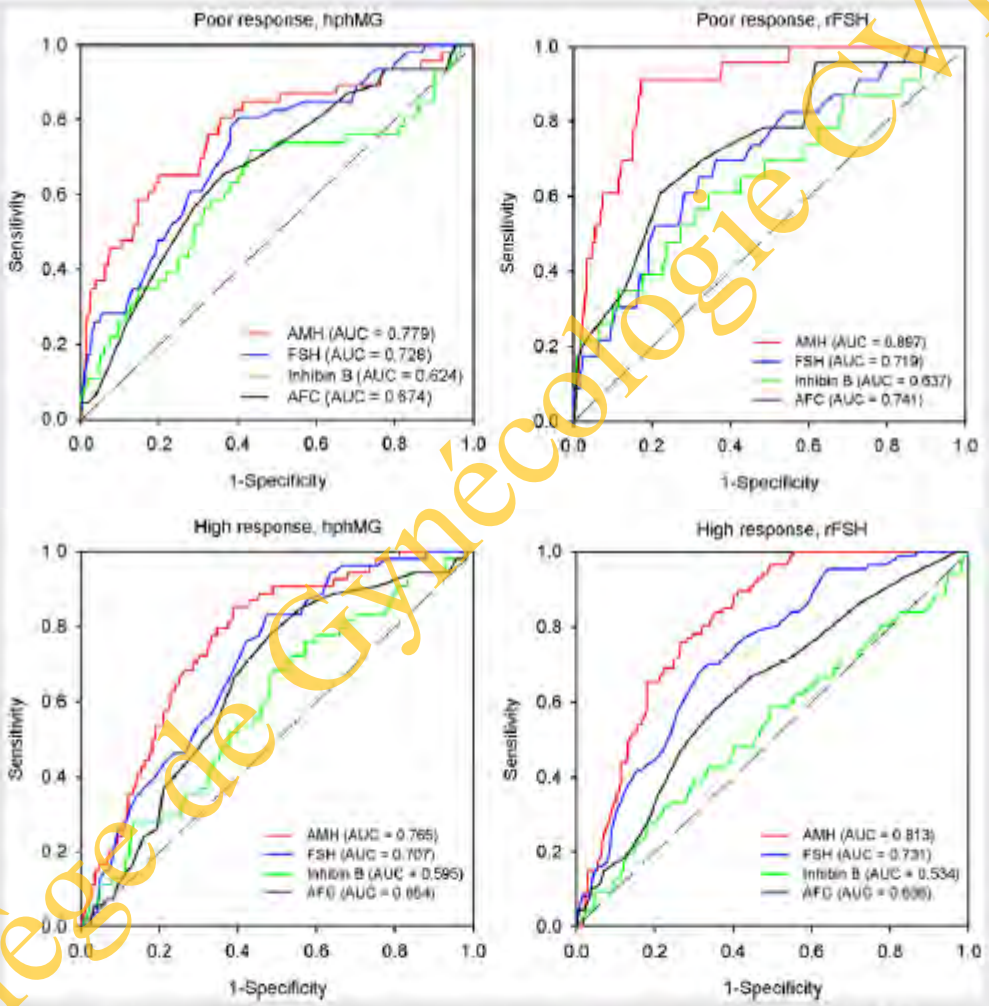
Joan-Carles Arce, M.D., Ph.D.,[a] Antonio La Marca, M.D., Ph.D.,[b] Bjarke Mirner Klein, Ph.D.,[c] Anders Nyboe Andersen, M.D.,[d] and Richard Fleming, Ph.D.[e]

Fertility and Sterility® Vol. ■, No. ■, ■ 2013



Box and whisker plots for antimüllerian hormone (AMH), follicle-stimulating hormone (FSH), inhibin B, and antral follicle count (AFC) at start of stimulation in patients with various numbers of oocytes retrieved after stimulation with highly purified human menopausal gonadotropin (hphMG) or recombinant FSH in a gonadotropin-releasing hormone (GnRH) antagonist protocol. Values are median (*lines*), 25th–75th percentile (*boxes*), and 10th–90th percentile (*whiskers*). hphMG: ≤3 (n = 47), 4–7 (n = 124), 8–14 (n = 145), 15–19 (n = 38), ≥ 20 (n = 18); recombinant FSH: ≤3 (n = 25), 4–7 (n = 112), 8–14 (n = 147), 15–19 (n = 55), ≥ 20 (n = 30).

Arce. AMH, oocytes, and cumulative live births. Fertil Steril 2013.



Receiver operating characteristic (ROC) curve analysis showing the predictive values of antimüllerian (AMH), follicle-stimulating hormone (FSH), inhibin B, and antral follicle count (AFC) at start of stimulation for estimation of poor ovarian response (≤3 oocytes retrieved or cycle cancellation due to poor response) and high response (≥15 oocytes retrieved or cycle cancellation due to excessive response), respectively, after controlled ovarian stimulation in patients treated with highly purified human menopausal gonadotropin (hphMG) or recombinant FSH in a gonadotropin-releasing hormone (GnRH) antagonist protocol. The diagonal line is the reference line of no discrimination (area under the curve = 0.5).

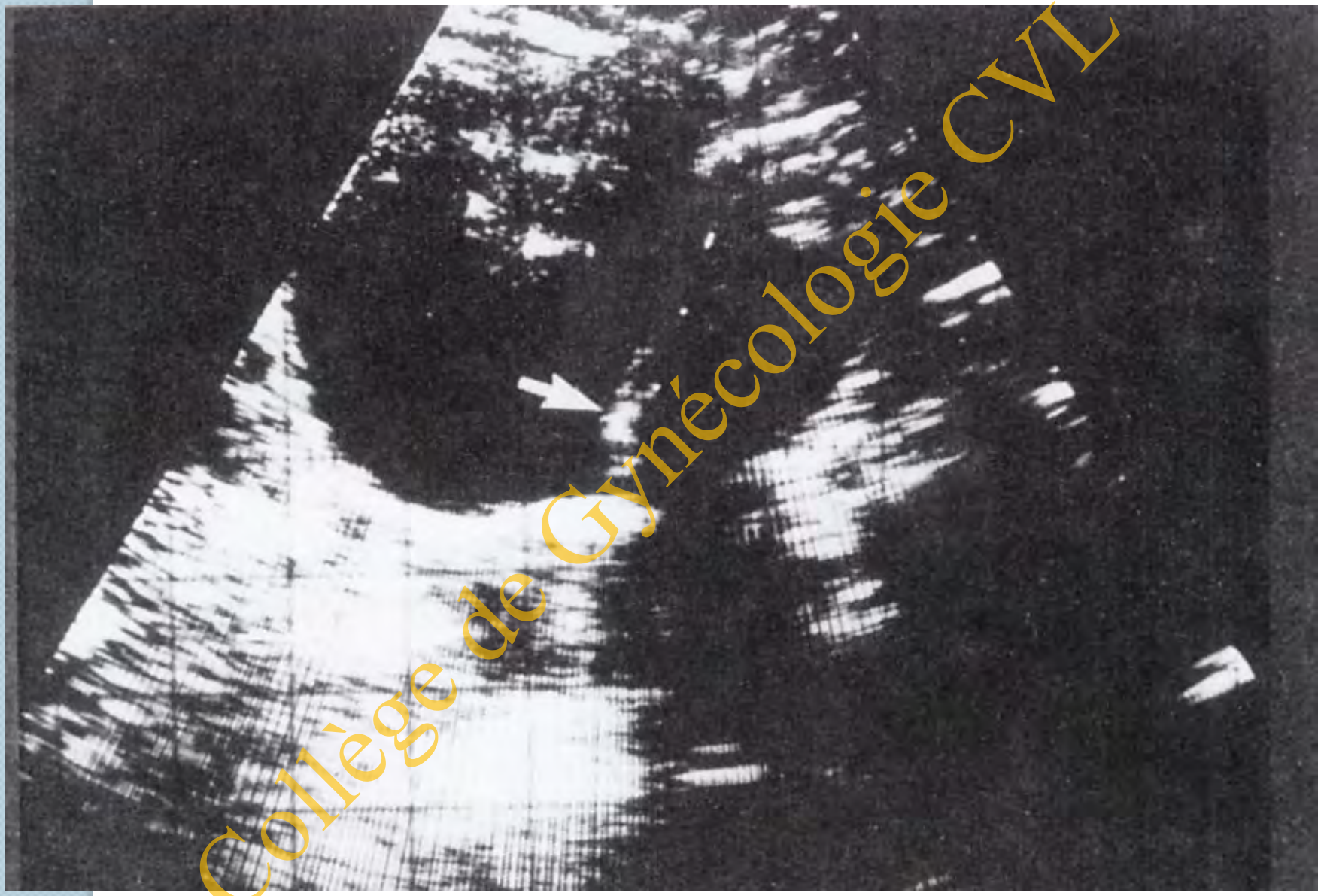
Arce. AMH, oocytes, and cumulative live births. Fertil Steril 2013.

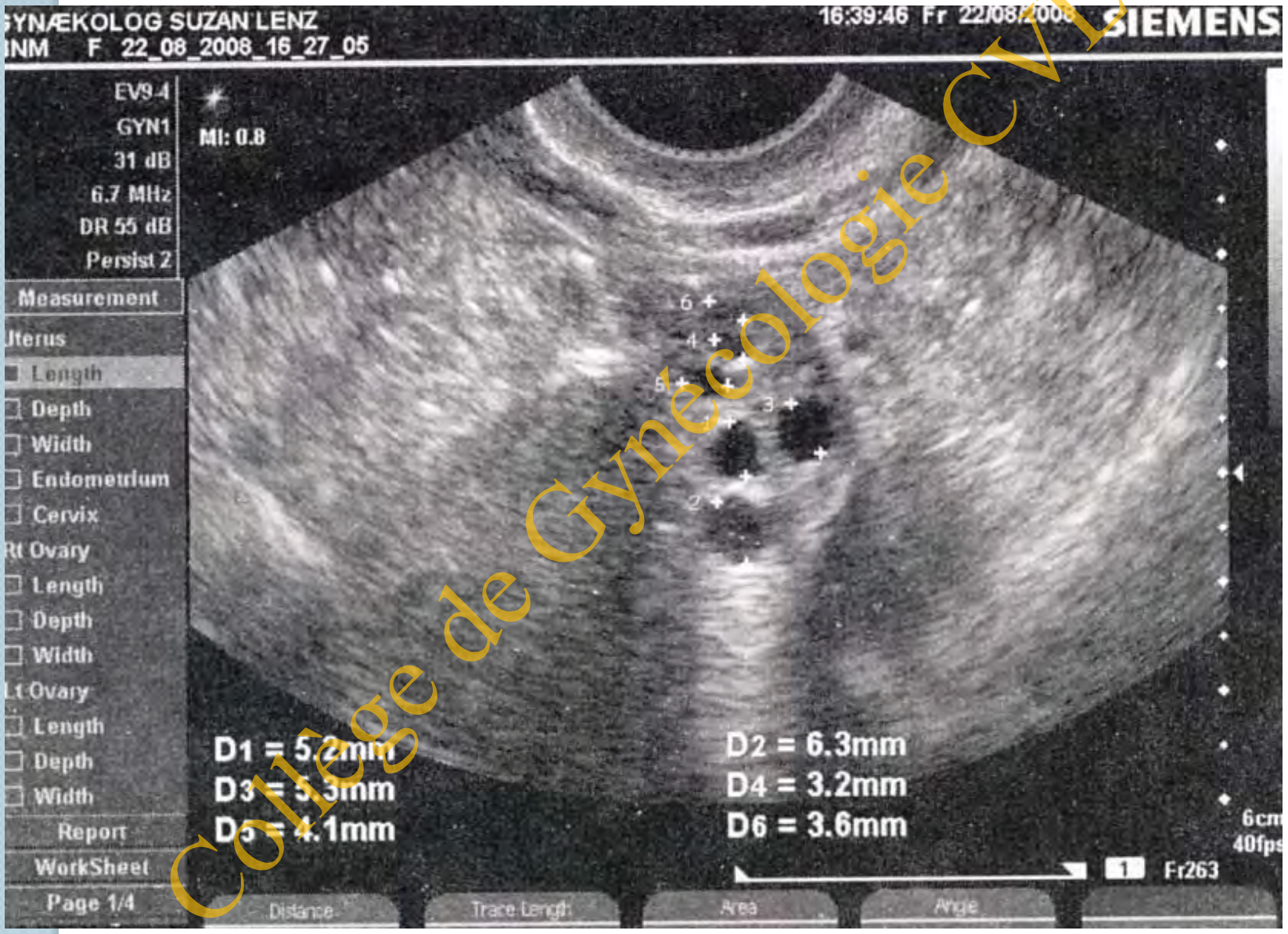
There is a positive relationship between AMH and oocyte yield in GnRH antagonist cycles, and AMH is the best predictor for identifying patients with poor and high ovarian response. The positive association between AMH and cumulative live-birth rates after fresh and cryopreserved cycles reflects the availability of more oocytes/ blastocysts, not higher quality.

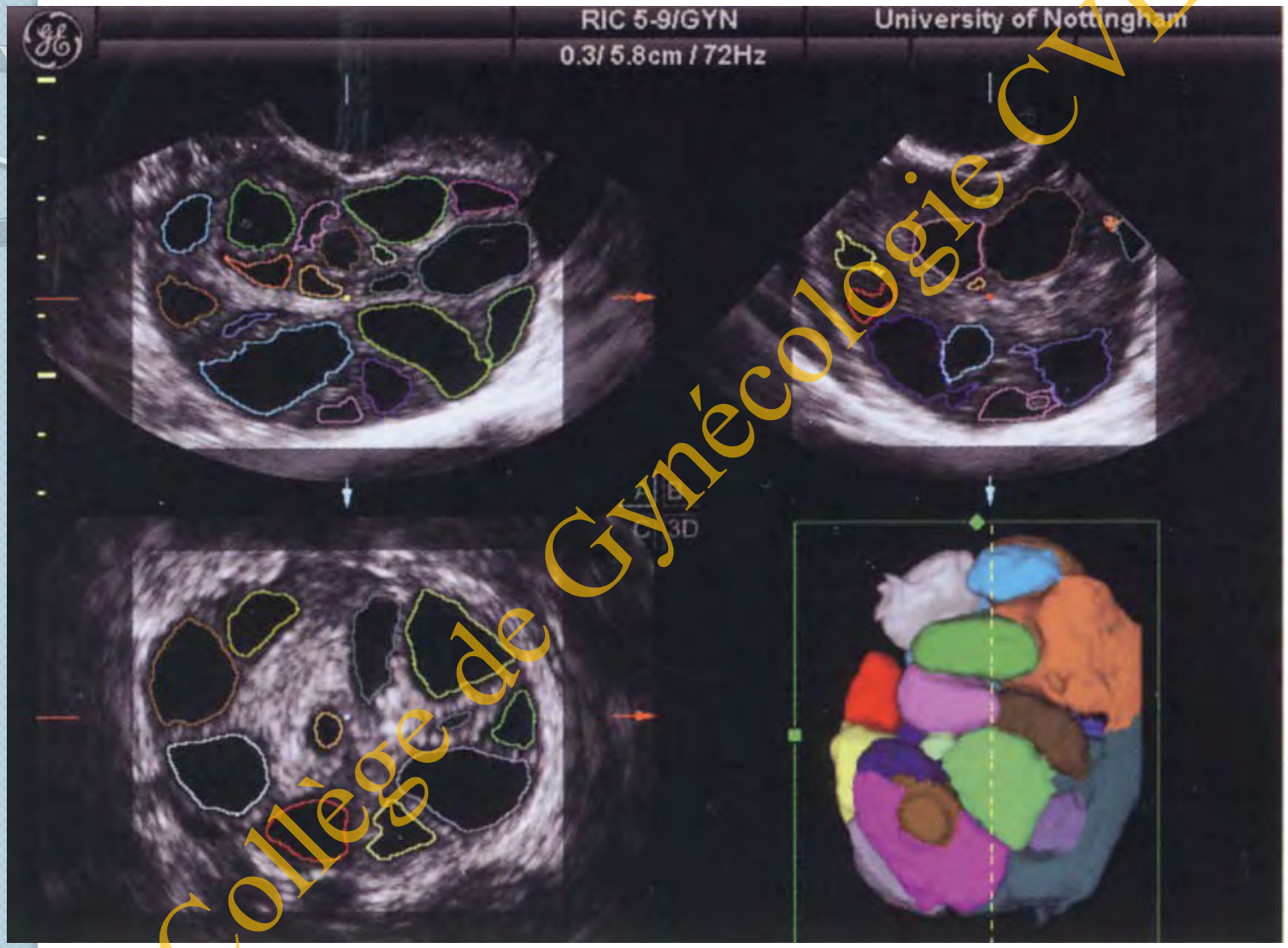
Mesures échographiques de la réserve ovarienne

Le Compte de Follicules Antraux (CFA)

- Opérateur et matériel dépendant
- Intérêt pronostique confirmé (Verhagen et al, 2008)
- Bonne reproductibilité (Jayapraskasm et al, 2007)
- Recommandations : J2 à J4 ou après down-regulation (Lenz et al, 2008)



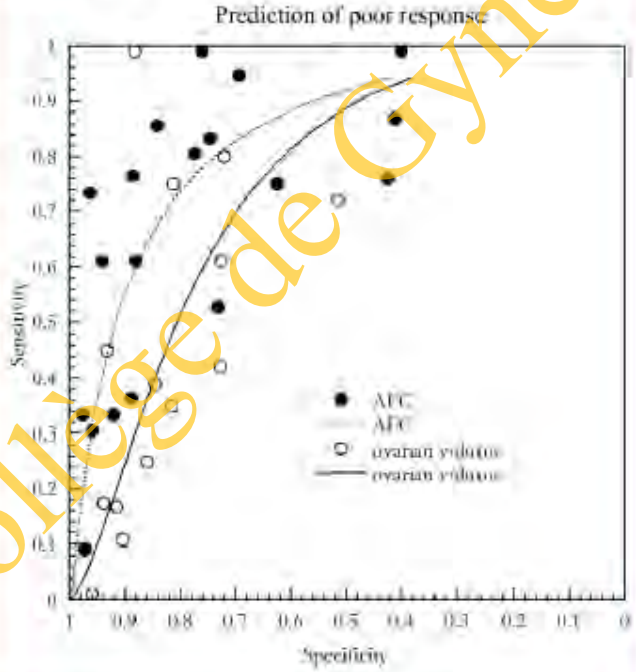




Le volume ovarien : intérêt prédictif inférieur au CFA pour la réponse ovarienne (*Hendriks et al, Fertil Steril 2007)*

FIGURE 1

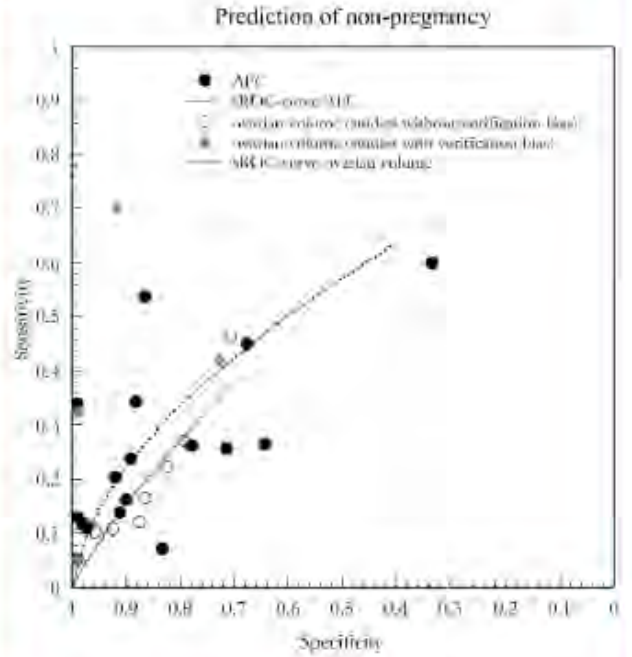
Receiver operating characteristic of studies on ovarian volume and AFC in their capacity to predict the occurrence of poor ovarian response in IVF. From each study, all cutoff points are plotted. Summary ROC curves for both ovarian volume and AFC are given: the *solid line* represents the summary of the ROC curve for ovarian volume, and the *dotted line* represents the summary ROC curve for AFC.



Hendriks. Meta-analysis of ovarian volume. Fertil Steril 2007.

FIGURE 2

Receiver operating characteristic of studies on ovarian volume and AFC in their capacity to predict the occurrence of nonpregnancy in IVF. From each study, all cutoff points are plotted. Summary ROC curves for both ovarian volume (after exclusion of studies with verification bias) and AFC are given: the *solid line* represents the summary of the ROC curve for ovarian volume, and the *dotted line* represents the summary ROC curve for AFC.



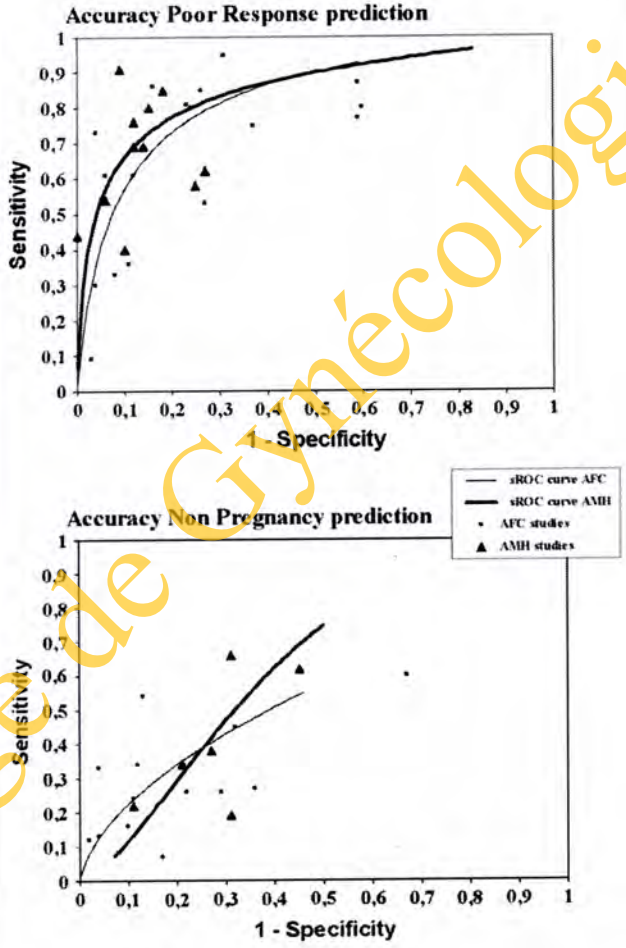
Hendriks, Meta-analysis of ovarian volume. Fertil Steril 2007.

Parmi les follicules en croissance :

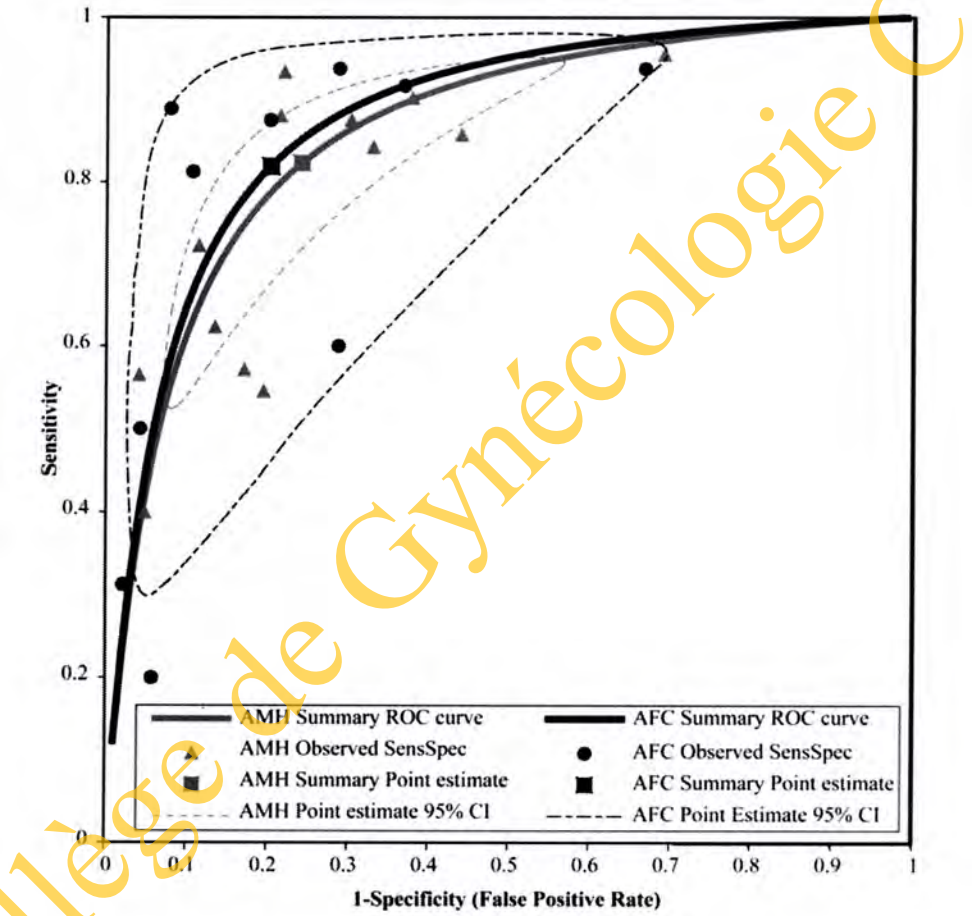
- Concentrations différentes d'AMH intrafolliculaires (Andresen et al, JCEM, 2008)
- Taille et sensibilité à la FSH différentes
- Compétence ovocytaire et aptitude au développement embryonnaire différentes
- Hétérogénéité des tailles augmentant avec l'âge (Grynberg et al, Fertil Steril, 2008)
- Pas de preuve que le plus grand et le plus sensible à la FSH soit le plus compétent

FIGURE 1

Accuracy of poor response and nonpregnancy predictions. AFC = antral follicle count; AMH = antimullerian hormone; ROC = receiver operating characteristic.



Broer. AMH in IVF outcome prediction. Fertil Steril 2009.



CFA marqueur de la quantité et de la qualité des ovocytes

(y compris dans le PCO)

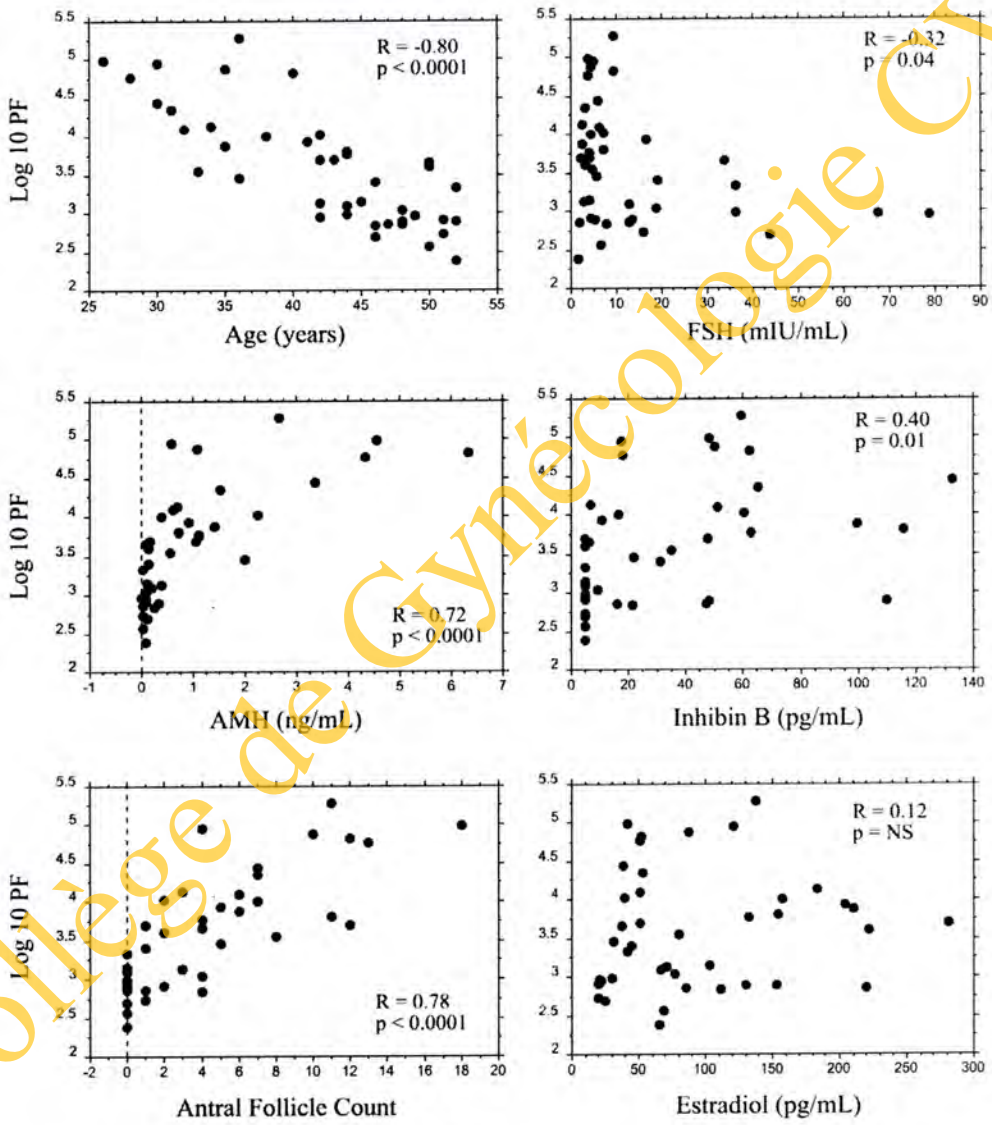
(Holte et al, Fertil Steril, 2011)

Corrélation établie entre les marqueurs indirects et le nombre absolu de follicules primordiaux à l'histologie

HANSEN et al Fertil Steril 2011

FIGURE 1

Scatterplots and correlations (Pearson correlation coefficients) for log 10 primordial follicle (PF) counts versus ovarian reserve test results and chronological age.



Hansen. Primordial follicle number and markers of ovarian function. Fertil Steril 2011.

Human Reproduction Update, Vol.17, No.1 pp. 46–54, 2011
Advanced Access publication on July 28, 2010 doi:10.1093/humupd/dmq034

human reproduction update

AMH and AFC as predictors of excessive response in controlled ovarian hyperstimulation: a meta-analysis

S.L. Broer [1,*], M. Dólleman [1], B.C. Opmeer [2], B.C. Fauser [1], B.W. Mol [3], and F.J.M. Broekmans [1]

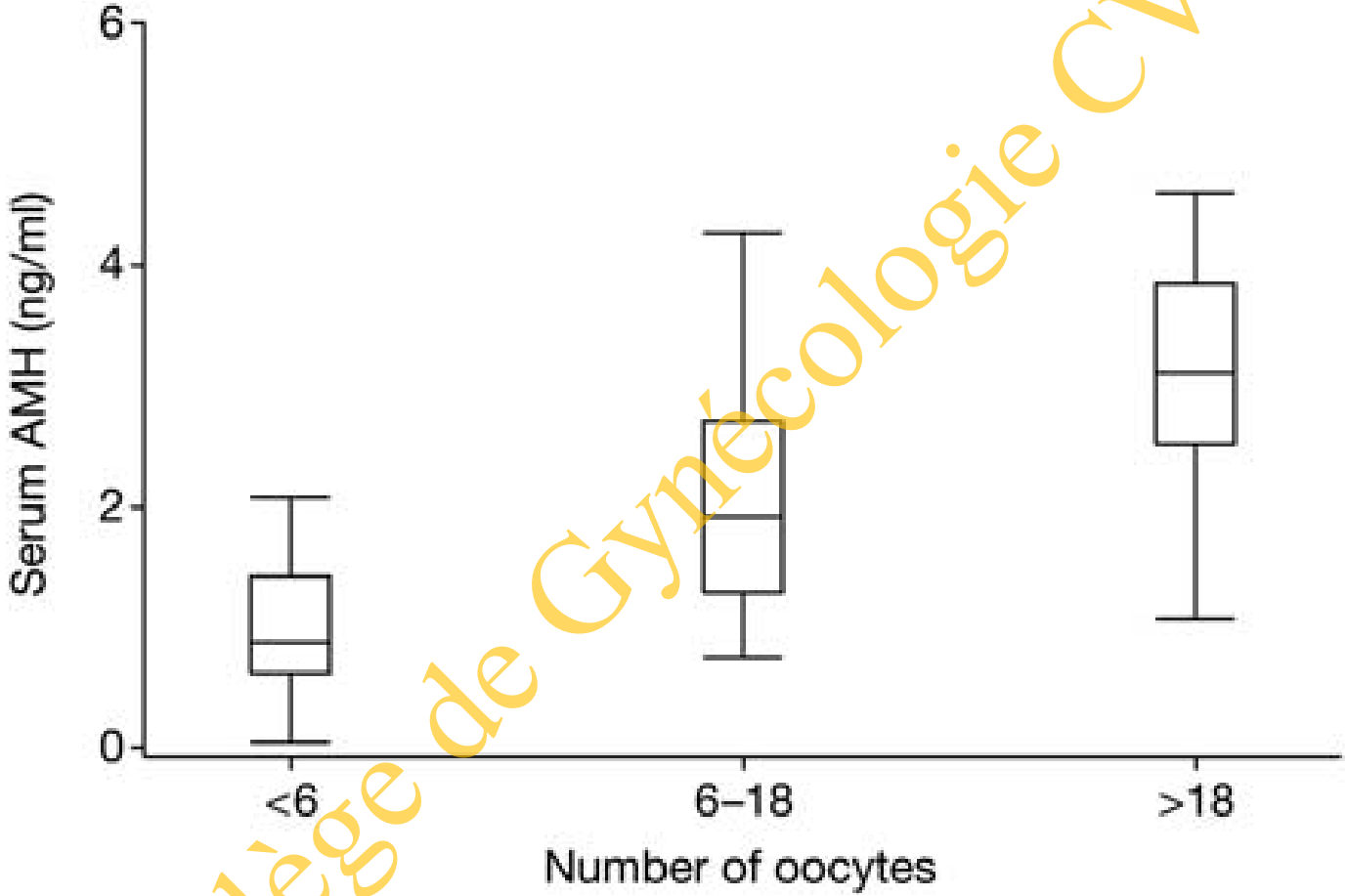
[1]Department of Reproductive Medicine and Gynecology, University Medical Center, room F05.126, P.O. Box 85500, 3508 GA Utrecht, The Netherlands [2]Department of Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam, The Netherlands [3]Department of Obstetrics and Gynecology, Academic Medical Center, Amsterdam, The Netherlands

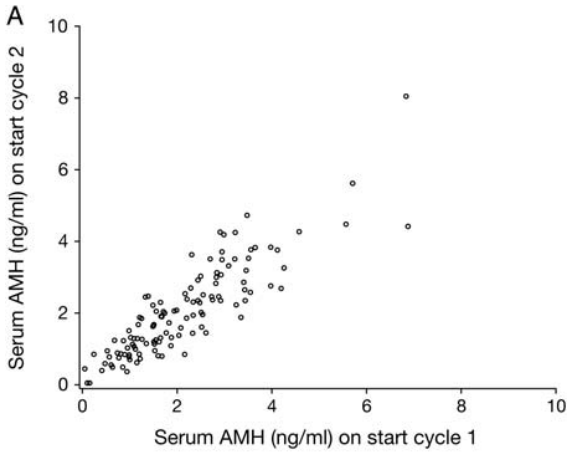
Human Reproduction, Vol.26, No.12 pp. 3413–3423, 2011
Advanced Access publication on September 27, 2011 doi:10.1093/humrep/der318

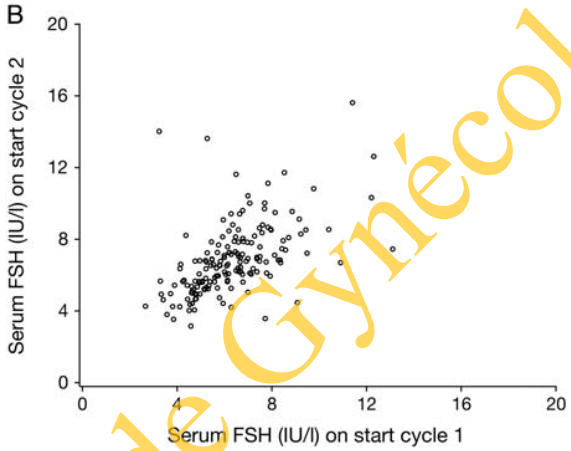
human reproduction ORIGINAL ARTICLE *Reproductive endocrinology*

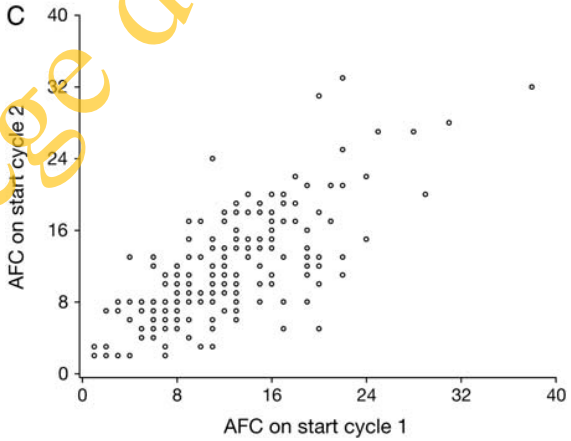
Predictive factors of ovarian response and clinical outcome after IVF/ICSI following a rFSH/GnRH antagonist protocol with or without oral contraceptive pre-treatment

A. Nyboe Andersen[1], H. Witjes[2], K. Gordon[3], and B. Mannaerts[4,*] on behalf of the Xpect investigators[†]









Human Reproduction Update, Vol.19, No.1 pp. 26–36, 2013
Advanced Access publication on November 27, 2012 doi:10.1093/humupd/dms041

human reproduction update

Added value of ovarian reserve testing on patient characteristics in the prediction of ovarian response and ongoing pregnancy: an individual patient data approach

Simone L. Broer[1,2,*‡], Jeroen van Disseldorp[1,2‡], Kimiko A. Broeze[1,2], Madeleine Dolleman[1,2], Brent C. Opmeer[1,2], Patrick Bossuyt[1,2], Marinus J.C. Eijkemans[1,2], Ben-Willem J. Mol[1,2], and Frank J.M. Broekmans[1,2] on behalf of the IMPORT study group[**]

Table II Univariable and multivariable models of age and ORT in the prediction of poor response and ongoing pregnancy.

	Poor response prediction				Ongoing pregnancy prediction			
	OR	95% CI	*P*-value	Variance RI	OR	95% CI	*P*-value	Variance RI
Univariable models								
Age (per year)	1.12	1.08–1.17	<0.001	0.412	0.94	0.89–0.99	0.011	0.441
FSH (per IU/l)	1.27	1.19–1.35	<0.001	0.559	0.98	0.92–1.04	0.477	0.537
AFC (per N)	0.77	0.73–0.82	<0.001	0.235	1.00	0.97–1.03	0.951	0.554
AMH (per ng/ml)	0.50	0.41–0.60	<0.001	0.440	1.09	0.96–1.24	0.197	0.462
Multivariable models								
Age and FSH				0.320				0.430
Age (per year)	1.12	1.07–1.17	<0.001		0.94	0.89–0.99	0.013	
FSH (per IU/l)	1.26	1.18–1.34	<0.001		0.99	0.93–1.05	0.632	
Age and AFC				0.192				0.476
Age (per year)	1.07	1.02–1.11	0.007		0.93	0.89–0.98	0.020	
AFC (per N)	0.78	0.74–0.83	<0.001		0.99	0.96–1.02	0.625	
Age and AMH				0.321				0.393
Age (per year)	1.08	1.03–1.13	0.001		0.94	0.89–0.99	0.017	
AMH (per ng/ml)	0.54	0.44–0.66	<0.001		1.06	0.93–1.21	0.373	

Results of random intercept logistic regression model in the prediction of poor response or ongoing pregnancy. For the prediction of a poor response, the multivariable analyses showed that all three ORT add predictive information to female age alone.

Female age is the strongest predictor of ongoing pregnancy. All three ORT show a very small or absent predictive effect in the prediction of an ongoing pregnancy. Multivariable analyses show that all three ORT do not add predictive information to female age alone in the prediction of an ongoing pregnancy. *P*-values reflect whether the variable plays a significant role in the model.

The column 'Variance RI' denotes the estimated variance of the random intercept in the random intercept logistic model. Its square root is the estimated standard deviation (SD), and may be interpreted on the logistic scale. A 1 SD difference in the population of studies corresponds to an increase in the Odds on the outcome (poor response and ongoing pregnancy, respectively) of exp (SD).

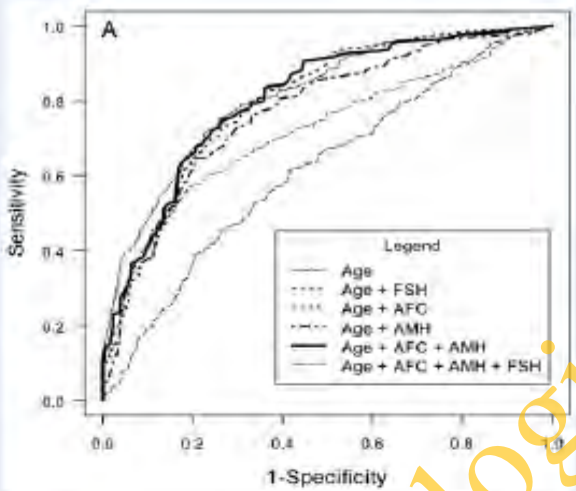
Table III AUCs of prediction models of age and ORTs for the prediction of a poor response and ongoing pregnancy.

	Three-test study group				Total study group			
	AUC	95% CI	*P*-value	*n*	AUC	95% CI	*P*-value	*n*
Poor response prediction								
Univariable models								
Age	0.61	0.54–0.68	NA	617	0.60	0.57–0.64	NA	4034
FSH	0.68	0.61–0.74	0.051	617	0.66	0.62–0.69	0.004	3652
AFC	0.76	0.70–0.82	<0.001	617	0.73	0.69–0.77	<0.001	2118
AMH	0.78	0.72–0.84	<0.001	617	0.81	0.77–0.84	<0.001	1274
Multivariable models								
Age and FSH	0.71	0.65–0.78	<0.001	617	0.69	0.66–0.72	<0.001	3652
Age and AFC	0.79	0.73–0.85	<0.001	617	0.76	0.72–0.80	<0.001	2118
Age and AMH	0.77	0.70–0.83	<0.001	617	0.80	0.76–0.84	<0.001	1274
Age and AMH and AFC	0.80	0.74–0.86	<0.001	617	0.80	0.74–0.86	<0.001	618
Age and AMH and AFC and FSH	0.81	0.75–0.86	<0.001	617	0.81	0.75–0.86	<0.001	617
Ongoing pregnancy prediction								
Univariable models								
Age	0.57	0.47–0.66	NA	420	0.56	0.54–0.59	NA	5207
FSH	0.53	0.43–0.62	0.348	420	0.54	0.51–0.58	0.084	3521
AFC	0.50	0.40–0.59	0.100	420	0.52	0.48–0.57	0.612	1977
AMH	0.55	0.45–0.64	0.630	420	0.58	0.51–0.64	0.495	1008
Multivariable models								
Age and FSH	0.58	0.48–0.67	0.195	420	0.60	0.57–0.64	0.116	3521
Age and AFC	0.58	0.48–0.67	0.247	420	0.57	0.52–0.61	0.709	1977
Age and AMH	0.57	0.48–0.67	0.753	420	0.59	0.53–0.65	0.415	1008
Age and AMH and AFC	0.59	0.49–0.68	0.371	420	0.59	0.49–0.68	0.341	421
Age and AMH and AFC and FSH	0.58	0.49–0.68	0.414	420	0.58	0.49–0.68	0.414	420

AUC, area under the curve; ORT, ovarian reserve test; AMH, anti-Müllerian hormone; AFC, antral follicle count; FSH, follicle stimulating hormone.

Poor response prediction. In the univariable analysis, it is shown that both AMH and AFC have a high accuracy, while FSH only has a moderate accuracy. In the multivariable models, the added value to the AUC of an ORT on female age is shown; the *P*-value indicates whether this added value is significant in comparison to age alone. All ORT show a significant rise in the AUC. Moreover, the added value of adding several ORTs to female age is shown. The model including age, AFC and AMH reached the maximum predictive power. This level of accuracy, however, is also obtained when using a two factor model in the total study group

Ongoing pregnancy. In the univariable analysis, it is shown that age is the strongest predictor compared with the single ORTs. The multivariable analysis shows that no single or combined ORT adds substantial predictive power to age alone. This is shown in the three tests study group, as well as in the total study group.



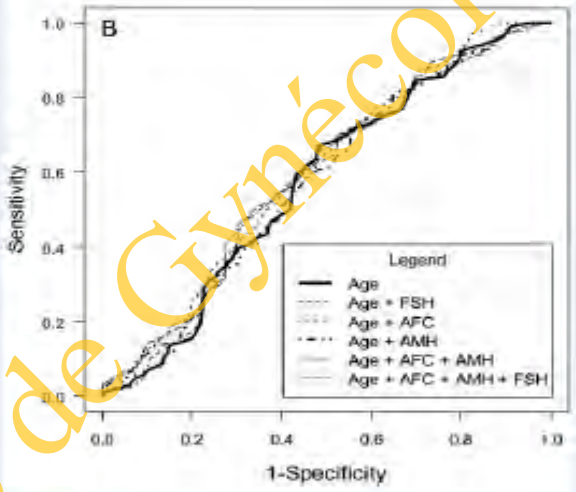
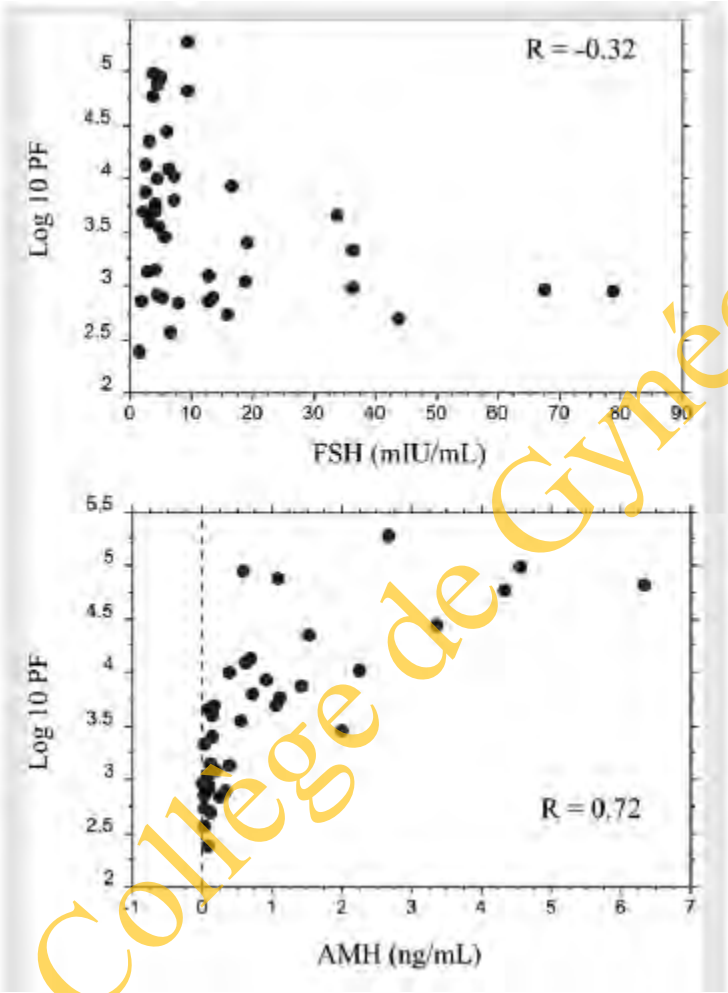


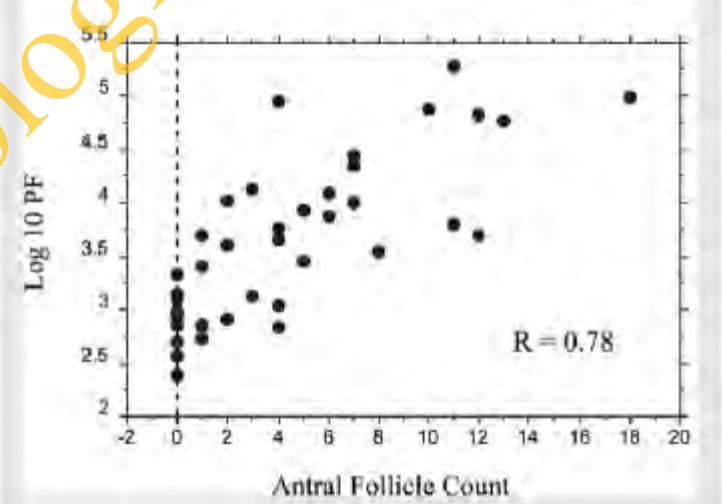
Figure 3 ROC curves of age and ORT in the prediction of poor response and ongoing pregnancy. (**A**) Poor response prediction based on age and ORT. The ROC curves of age or age combined with a single or more ORT are depicted. The ROC curves for 'Age + AMH', 'Age + AMH + AFC' and 'Age + AMH + AFC + FSH' run toward the upper left corner, indicating a good capacity to discriminate between normal and poor responders at certain cut-off levels. (**B**) Ongoing pregnancy prediction based on age and ORT. The ROC curves age or age combined with one or more ORT run almost parallel to or even cross the $X = Y$ line, indicating that the tests are useless for pregnancy prediction. AFC, antral follicle count; AMH, anti-Müllerian hormone; FSH, follicle stimulating hormone; ORT, ovarian reserve test; ROC, receiver-operating characteristic.

Biomarkers of ovarian response: current and future applications

Scott M. Nelson, Ph.D.

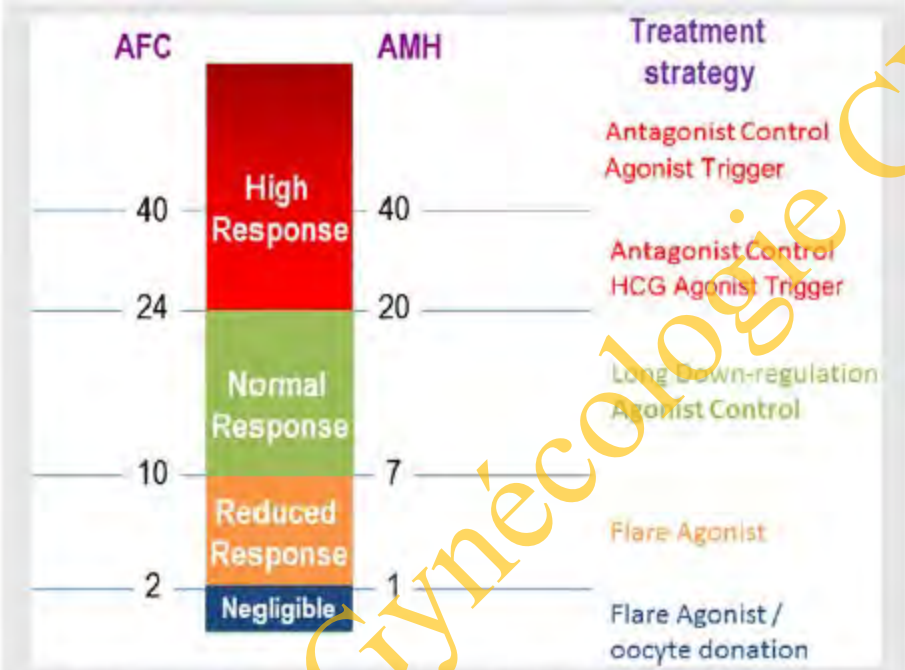
Fertility and Sterility® Vol. 99, No. 4, March 15, 2013





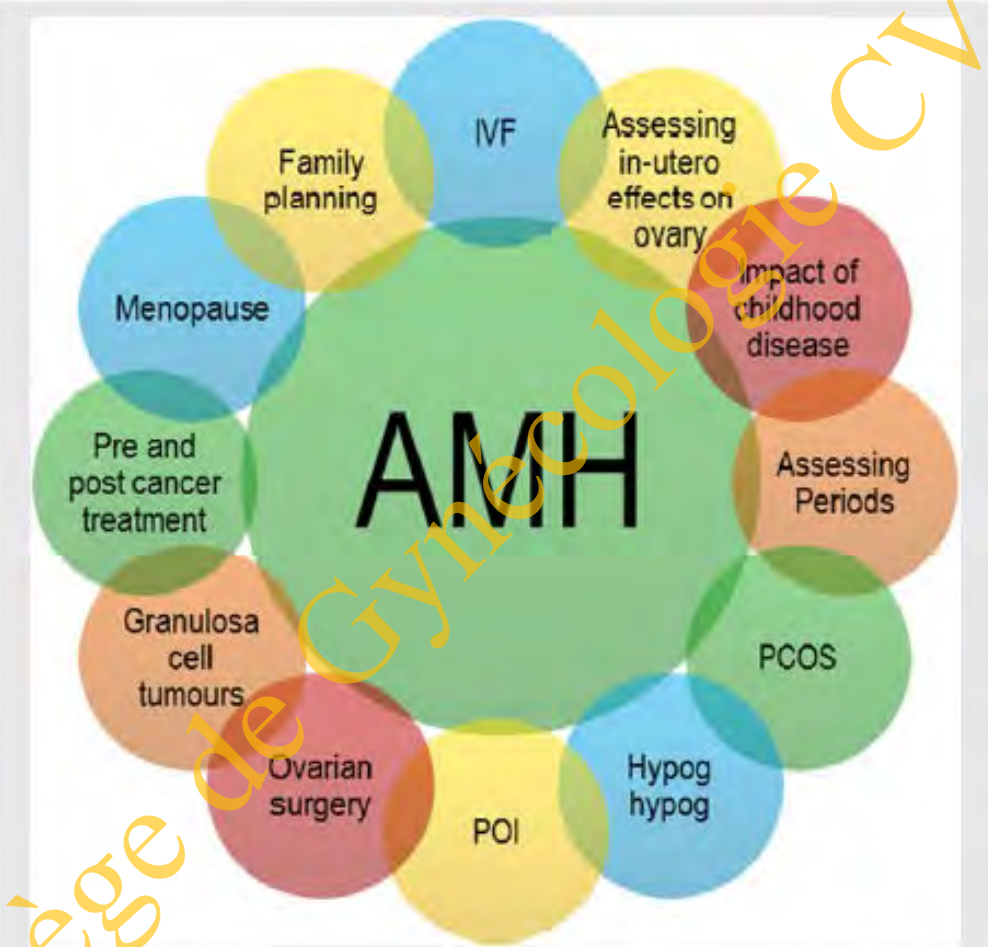
Scatter plots and correlations (Pearson correlation coefficients) for log 10 primordial follicle (PF) counts versus ovarian reserve test results. Adapted with permission from Hansen et al., 2011 (2).

Nelson. Biomarkers of ovarian response. Fertil Steril 2013.



Antimüllerian hormone (AMH) stratified individualization of treatment as used by the author. Ovarian response categories dictate risk, and treatment strategies are designed to minimize risk while maximizing oocyte yield within each response category. Negligible response means that the conventional criteria for triggering (three follicles ≥17 mm) is unlikely to be achieved. For all antagonist cycles with an excessive response, an agonist trigger is adopted. The AMH measurements are for the AMH Gen II assay, and the values are in pmol/L. The suggested antral follicle count (AFC) thresholds are based on the correlation of AMH and AFC and associated response category literature (30, 65).

Nelson. Biomarkers of ovarian response. Fertil Steril 2013.



Potential clinical applications of antimüllerian hormone (AMH) by health-care providers. IVF = in vitro fertilization; PCOS = polycystic ovary syndrome; hypog hypog = hypogonadotrophic hypogonadism; POI = premature ovarian insufficiency.

Nelson. Biomarkers of ovarian response. Fertil Steril 2013.

Our current ability to predict ovarian response has been transformed in recent years with the recognition of the strong linear relationships of AMH and AFC with ovarian reserve. The automation of the AMH assay will be a major step forward and allow rapid access to estimation of the ovarian reserve to all health-care providers. Inevitably, ovarian biomarkers will continue to develop dramatically, with the integration of novel discovery platforms and computational medicine. However, while we await these developments, we can ensure that we harness the collective power of the currently available biomarkers to ensure optimal patient care and true personalization of ovarian stimulation.

ET LA GÉNÉTIQUE ?

Human Reproduction, Vol.27, No.2 pp. 594–608, 2012
Advanced Access publication on November 24, 2011 doi:10.1093/humrep/der391

human reproduction ORIGINAL ARTICLE *Reproductive genetics*

Genetic variants and environmental factors associated with hormonal markers of ovarian reserve in Caucasian and African American women

Sonya M. Schuh-Huerta[1,2,*], Nicholas A. Johnson[3], Mitchell P. Rosen[4], Barbara Sternfeld[5], Marcelle I. Cedars[4], and Renee A. Reijo Pera[1,2]

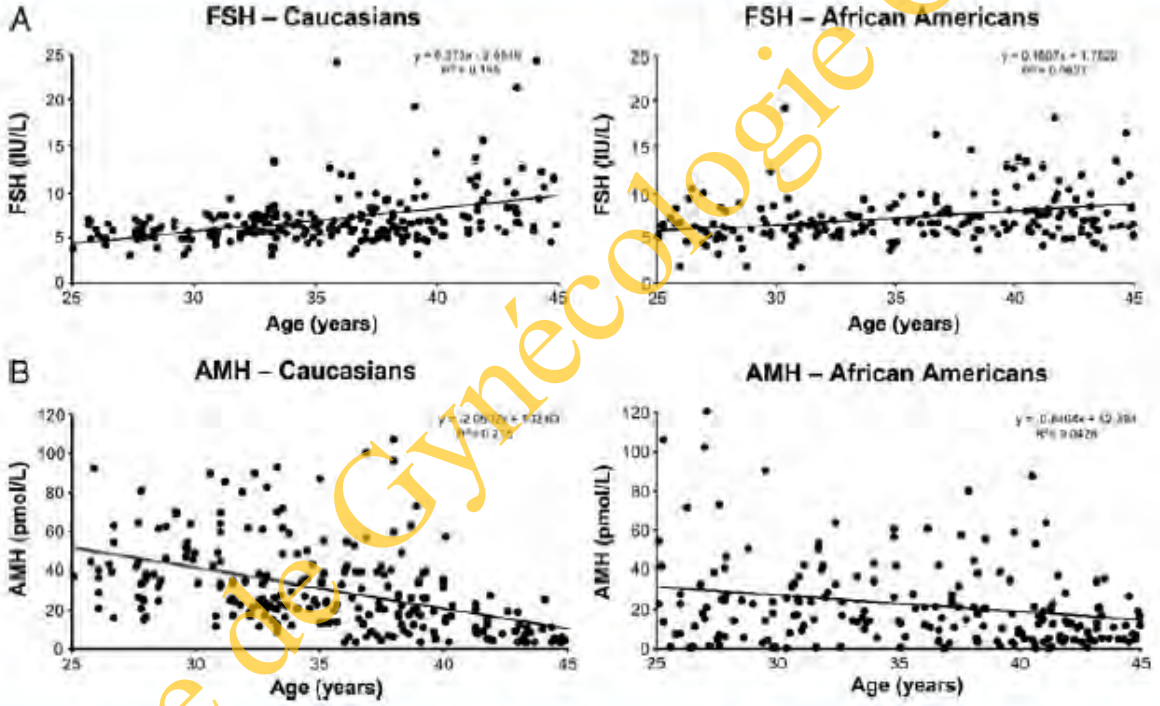


Figure 1 Measurements of FSH and AMH versus age in women of the entire study population. Total serum concentrations of FSH and female age in Caucasian and African American women indicate that FSH increases with age in both ethnic groups (**A**). Total serum concentrations of AMH versus age indicate that AMH decreases with age but is highly variable between women and is more variable among African American women (**B**). The corresponding correlation coefficients (R^2) and linear equations are shown ($n = 200–232$ women).

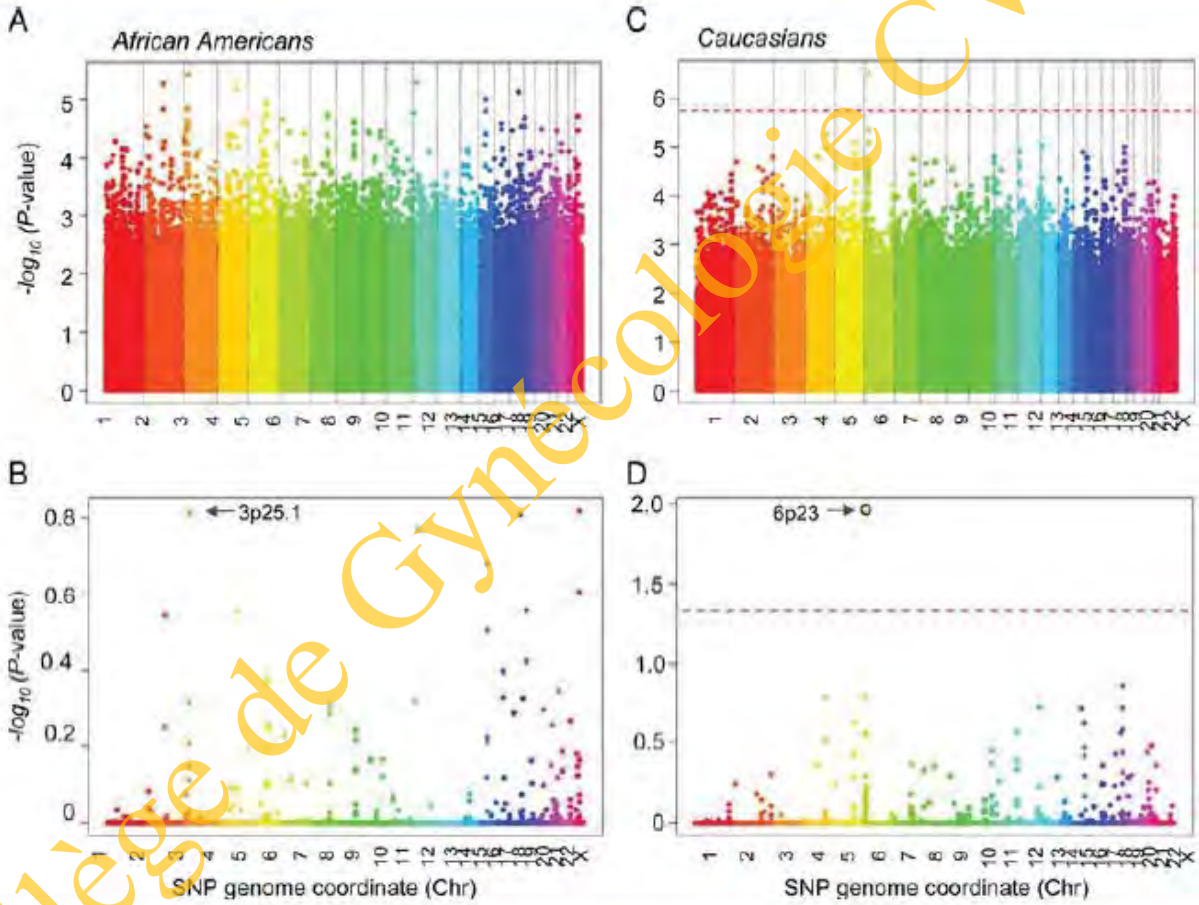


Figure 3 Summary of GWA results for AMH by chromosome showing Manhattan plots of the uncorrected (**A** and **C**) and corrected (**B** and **D**) *P*-values of the Fisher's exact test in the African American (A and B) and Caucasian (C and D) populations. Each point represents a SNP from the single SNPs and haplotype tests of association remaining after QC and SNP filtering (677 261 in the Caucasian cohort and 738 185 in the African American cohort). The red dashed lines indicate *P*-values of 1.5×10^{-6} (uncorrected) and 0.05 (corrected), chromosome-wide significance level.

Table IV Associations between FSH- and AMH-related SNPs and AFC in African American and Caucasian women.

SNP[a]	Race	Gene	Alleles[b]	MAF	FSH/AMH genotype effect (concentration)[c]	AFC genotype effect (follicles)[d]	*P*-value[e]
rs6543833	Afr Amer	*MYADML*	**G**/C	0.27	−0.62 ± 0.34 (FSH)	+1.09 ± 0.32	1.85×10^{-3} (9.25×10^{-3})*
rs12465811	Afr Amer	*MYADML*	**T**/G	0.32	−0.38 ± 0.24 (FSH)	+0.94 ± 0.25	1.31×10^{-3} (6.55×10^{-3})*
rs9875589	Afr Amer	*TPRXL*	A/**C**	0.46	+14.02 ± 3.72 (AMH)	+4.88 ± 0.63	3.68×10^{-5} (1.84×10^{-4})*
rs12295403	Afr Amer	*TMEM86A*	**T**/G	0.10	+16.67 ± 5.11 (AMH)	+5.17 ± 0.86	3.34×10^{-3} (1.67×10^{-2})*
rs11255291	Afr Amer	*ITIH2*	**T**/C	0.25	−1.34 ± 0.22 (FSH)	+1.31 ± 0.36	0.211 (1)
rs6488619	Caucasian	*GRIN2B*	C/**T**	0.25	+1.16 ± 0.33 (FSH)	+0.55 ± 0.049	0.104 (0.416)
rs10061804	Caucasian	*NPR3*	**T**/C	0.28	+2.05 ± 0.80 (FSH)	+1.44 ± 0.30	0.310 (1)
rs12213875	Caucasian	*JARID2*	**A**/G	0.37	+13.82 ± 4.18 (AMH)	+3.08 ± 0.52	0.0514 (0.206)
rs9396503	Caucasian	*JARID2*	**T**/G	0.37	+14.92 ± 4.60 (AMH)	+3.74 ± 0.66	0.0415 (0.166)

$P < 0.05$ for four out of five FSH/AMH-associated SNPs also associated with AFC, compared with 0.34 (<1) expected by chance.

[a]SNPs at each locus are those associated with serum FSH or AMH levels, rather than those with the strongest signal for follicle number.

[b]Alleles are shown as minor/major allele; bold indicates the effect allele.

[c]The difference in mean (±SEM) serum FSH levels (IU/l) or AMH levels (pM) for a given genotype.

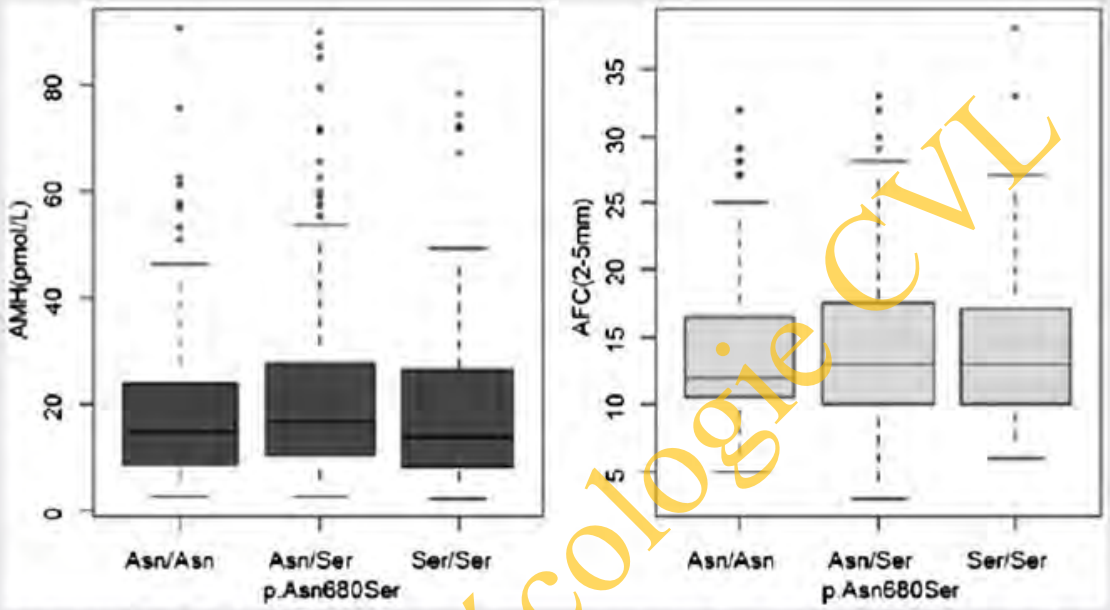
[d]The difference in mean (±SEM) number of follicles for the corresponding genotype calculated from the regression analysis.

[e]*P*-values are based on the Fisher's exact test for SNP association with the hormone; parentheses denote corrected *P*-values; *$P < 0.05$.

Polymorphisms in gonadotropin and gonadotropin receptor genes as markers of ovarian reserve and response in in vitro fertilization

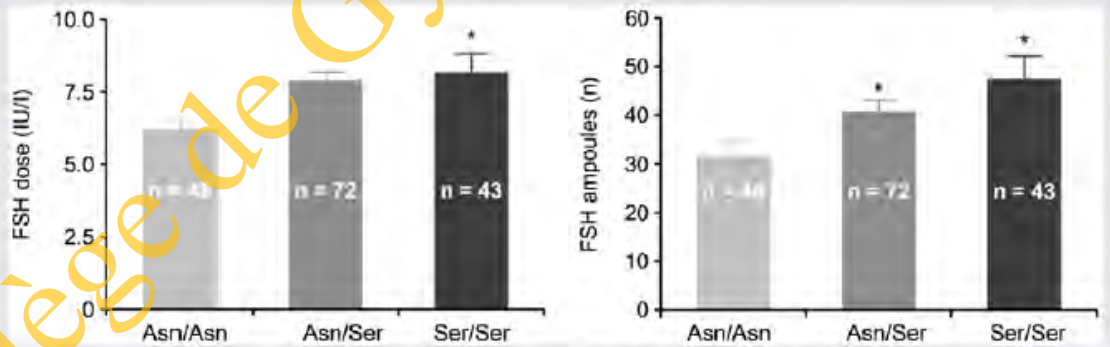
Antonio La Marca, M.D., Ph.D.,[a] Giovanna Sighinolfi, M.D.,[a] Cindy Argento, M.D.,[a] Valentina Grisendi, M.D.,[a] Livio Casarini, M.D.,[b,c] Annibale Volpe, M.D.,[a] and Manuela Simoni, M.D.[b,c,d]

Fertility and Sterility® Vol. 99, No. 4, March 15, 2013



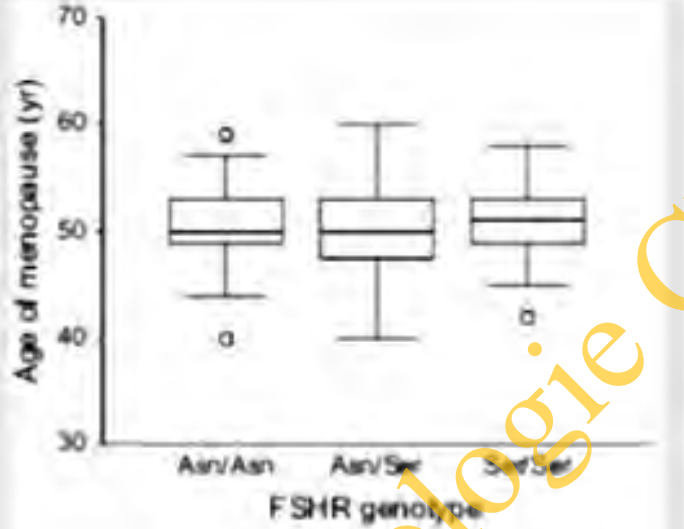
Women (n = 421) were genotyped for *FSHR* 680 polymorphisms. There were no significant differences in serum AMH levels and AFC between the different polymorphisms (modified from reference [33] with permission).

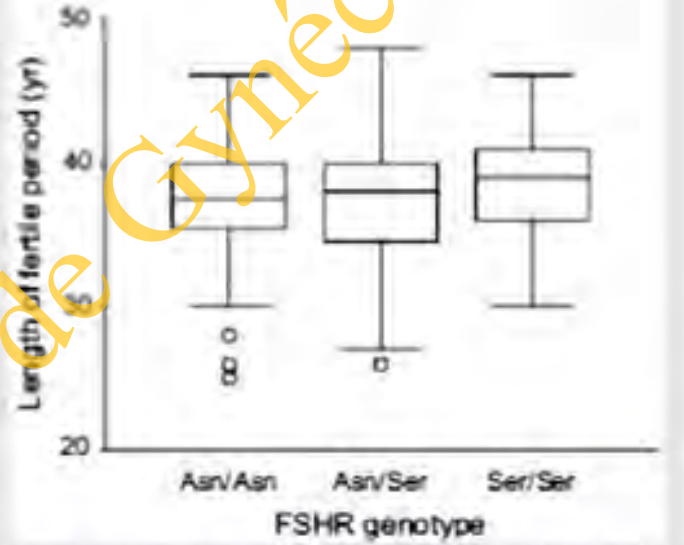
La Marca. Genetic polymorphisms and ovarian reserve. Fertil Steril 2013.



Basal FSH levels and ampules of FSH used in COS for patients with variants of the *FSHR*. In women using assisted reproductive technology, the distribution was 45% for the wild-type (Asn/Asn), 29% for the heterozygote (Asn/Ser), and 26% for the homozygote (Ser/Ser). Although peak E_2 levels, numbers of preovulatory follicles, and numbers of retrieved oocytes were similar in the three groups, basal FSH levels were significantly higher for carriers of the Ser variant. Furthermore, both the heterozygotes and homozygotes required significantly more FSH during COS compared with the wild-type group (*$P < .05$ vs. other groups) (modified from reference [106]).

La Marca. Genetic polymorphisms and ovarian reserve. Fertil Steril 2013.





Age of menopause (top) and duration of fertility (low) in 251 postmenopausal Italian women genotyped for *FSHR* gene polymorphism at codon 680. The *box plots* indicate the first and third quartiles, with the *horizontal line* representing the median; the *error bars* correspond to percentiles 10 and 90, and extreme values are represented by *circles* (modified from reference [67] with permission).

La Marca. Genetic polymorphisms and ovarian reserve. Fertil Steril 2013.

La mesure de la réserve ovarienne est-elle un préalable à l'AMP ?

- « No single test » *(Carvhalo et al, 2008)*
- Adapter la prise en charge dans le temps
- Adapter la posologie

(Popovic-Todovic, Hum Reprod 2003

Klinkert et al, Hum Reprod 2005; Lenz et al, 2008

Etude Consort Serono 2007)

- « Donner des follicules à la FSH plutôt que de la FSH aux follicules » *(Fanchin 2008)*
- Prédictabilité de la réponse ultérieure après la réponse au 1er cycle *(Hendriks et al, 2008)*

Les recommandations (RPC 2010)

- En présence de signes d'appel vers une baisse de la réserve ovarienne :
  - Âge>35 ans, cycles courts et/ou irréguliers, antécédents familiaux de ménopause précoce, antécédents personnels d'agression ovarienne

  → *Faire un bilan de RO chez la femme consultant pour infertilité, même si pas de recours à l'AMP prévu d'emblée*

- En l'absence de ces signes :
  - *pas de bilan de RO*
  - *sauf en cas de recours à l'AMP pour une autre raison*

- Marqueurs validés : FSH et E2 en 1ère intention, *AMH et/ou CFA en cas de doute pour confirmation*

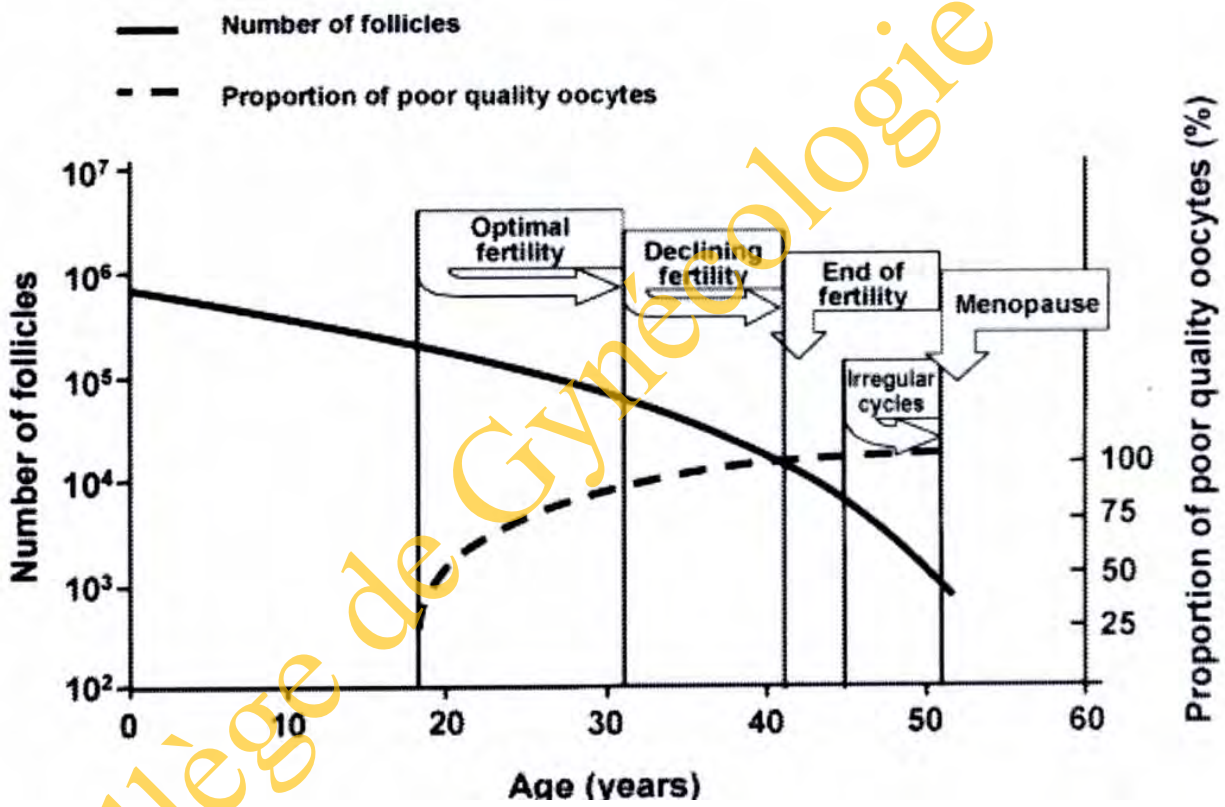
EN PRATIQUE …

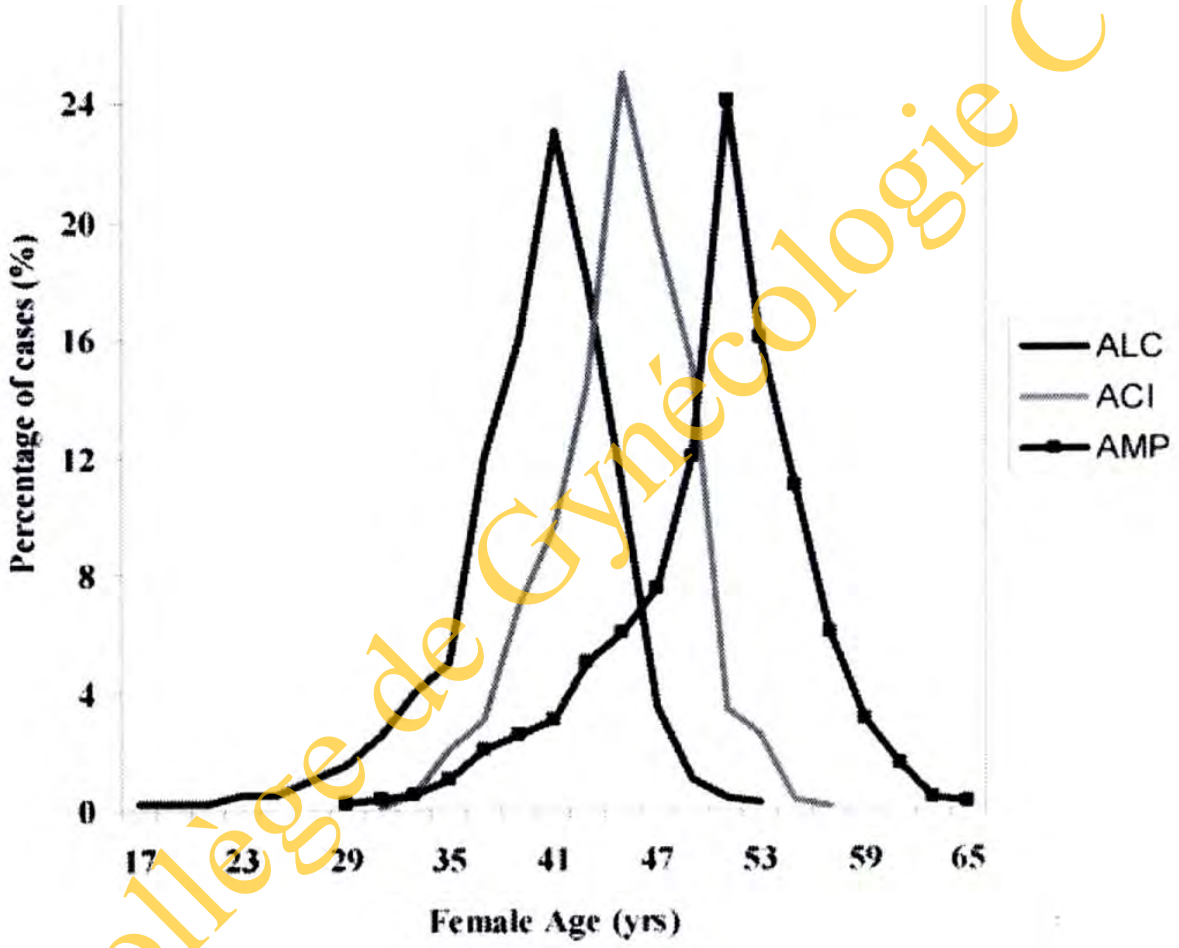
De la puberté à la ménopause :

normofertile

↓ hypofertile

↓ stérile





CONCLUSION

- Constitution d'un stock de follicules primordiaux à la 34ème semaine, puis assez stable dans la petite enfance
- Néo-ovogenèse efficace très peu probable
- Évaluation des outils de mesure en cours d'optimalisation
- Optimaliser la gestion du temps
- Individualisation des traitements