The value of anti-Müllerian hormone measurement in the long GnRH agonist protocol: association with ovarian response and gonadotrophin dose adjustments

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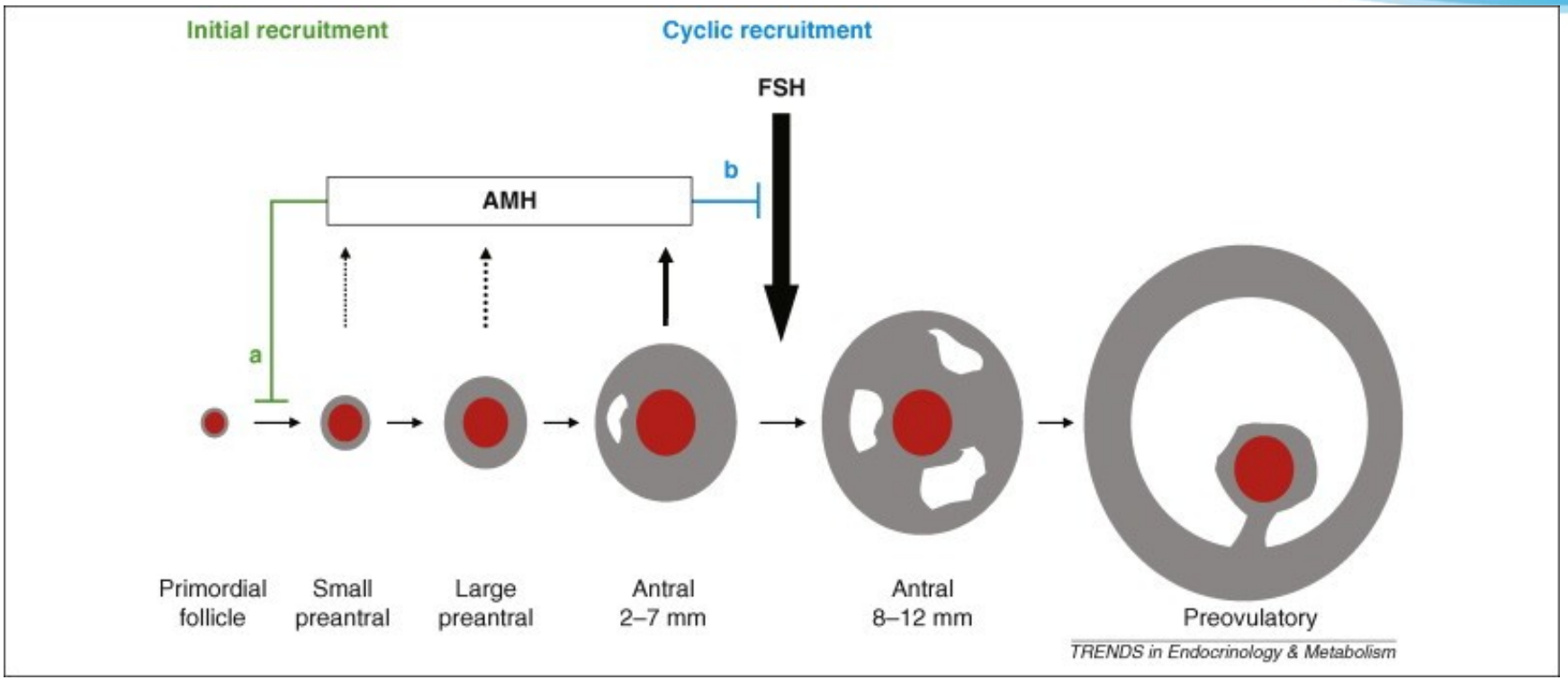
Introduction
AMH(anti-Müllerian hormone)

- a glycoprotein belonging to the transforming growth factor-b superfamily (Cate et al, 1986)
- In women, produced solely by the ovarian granulosa cells
  - low in *primary follicles* but increases to maximal levels in *pre-antral* and *small antral follicles* (up to 6-7 mm in diameter)
  - gradually declines as follicles increase further in size
  - becomes undetectable at a stage where FSH-dependent follicular growth has been initiated
  - not expressed in atretic follicles

Introduction

AMH (anti-Müllerian hormone)



Introduction

AMH (anti-Müllerian hormone)

- plays a role in the control of follicle growth via paracrine and autocrine effects
- inhibits the recruitment of resting follicles from the primordial follicle pool (Durlinger et al., 1999;Carlsson et al., 2006)
- decreases the sensitivity of small antral follicles to FSH (Durlinger et al., 2001)

Introduction

AMH (**anti-Müllerian hormone**)

- The serum level of AMH is a marker of the ovarian reserve
- the number of *antral follicles* has been shown to correlate more strongly with serum AMH than with the serum level of FSH (Fanchin et al., 2003a)
- AMH appears to be the earliest endocrine marker of ovarian aging (de Vet et al., 2002)

Introduction

AMH (anti-Müllerian hormone)

- The serum AMH level shows only minimal fluctuations during the menstrual cycle (La Marca et al., 2006)
  - reflecting the continuous noncyclic growth of pre-antral and small antral follicles (independent of FSH)
- the serum level of AMH displays a high inter-cycle Reproducibility
  - a single blood sample is sufficient for a reliable assessment of the ovarian reserve, compared with three measurements for FSH (Fanchin et al., 2005)

Introduction

AMH (anti-Müllerian hormone)

- AMH to be superior to the age of the patient and measurements of FSH, estradiol and inhibin B on cycle day 2–3 in predicting oocyte yield in IVF (La Marca et al., 2010)
- serum AMH levels have been demonstrated to decrease gradually during the follicular phase in both pituitary-desensitized GnRH agonist cycles (Fanchin et al., 2003b; La Marca et al., 2004) and GnRH antagonist cycles (Lee et al., 2010)

Materials and Methods : study population

- retrospective analysis of data derived from a randomized, active-controlled, assessor-blind, multicentre, multinational trial
- patients (n = 731) undergoing IVF after stimulation with
  - HP-hMG (Menopur; Ferring Pharmaceuticals A/S, Copenhagen, Denmark)
  - rFSH (follitropin alfa, Gonal-F; Merck Serono, Geneva, Switzerland)

Materials and Methods : study population

- Inclusion criteria
  - tubal factor infertility
  - unexplained infertility
    - endometriosis stage I/II
    - mild semen abnormalities not requiring ICSI
  - Age : 21 ~ 37
  - BMI : 18~29 kg/m2
  - FSH within normal limits (1-12 IU/l)
  - Regular menstrual cycles of 21-35 days which were presumed to be ovulatory and a willingness to accept transfer of one or two embryos.

Materials and Methods : study population

- Exclusion criteria
  - polycystic ovary syndrome
  - endometriosis stage III/IV
  - partners with severe male factors requiring ICSI

Materials and Methods : study protocol

- Patients underwent COS following down-regulation with a GnRH agonist in a long protocol
- Pituitary suppression (triptorelin acetate, 0.1 mg/day S.C.) was initiated 5–7 days before the estimated start of next menses and continued until the end of gonadotrophin administration
- Prior to start of ovarian stimulation, the antral follicle count (AFC; follicles <2 mm) was recorded by TVU of the ovaries by one or more operators at the clinics and follicular development was monitored after 5 days of treatment and thereafter at least every 2 days

Materials and Methods : study protocol

- Stimulation with HP-hMG or rFSH was started at a dose of 225 IU/day for the first 5 days and was followed by individual dose-adjustments according to the patient's follicular response as exclusively measured by TVU.
- The daily dose could either be increased or decreased by 75 IU per adjustment and not changed more frequently than every fourth day.
- Recombinant hCG (choriongonadotrophin alfa, Ovitrelle; Merck Serono), 250 mg S.C., was used to induce final follicular maturation when ≥ 3 follicles of ≥ 17 mm in diameter were observed and was administered 36+2 h before planned oocyte retrieval.

Materials and Methods : study protocol

- The target for the ovarian stimulation was set to be 7–15 oocytes
  - reasonable chances (25%) of pregnancy
  - the risk of developing moderate/severe ovarian hyperstimulation syndrome (OHSS) is low in patients with ≤15 oocytes (Arce et al., 2005)
- Cycle cancellation :
  - at the day of hCG administration were either
    - inability to reach the hCG criterion, or
    - >25 follicles with a diameter of ≥10 mm

Materials and Methods : study protocol

- A top-quality embryo (TQE) was defined as
  - 4~5 cells on Day 2,
  - ≥7 cells on Day 3, equally-sized blastomeres and ≤20% fragmentation on Day 3 and no multinucleation
- The transfer of one or two embryos was done on Day 3 after oocyte retrieval

Materials and Methods : study protocol

- Vaginal progesterone gel of 90 mg/day 8%
  - for luteal support
  - from the day of embryo transfer
  - until the confirmation of clinical pregnancy (5–6 weeks after embryo transfer) or negative serum hCG test (13–15 days after embryo transfer)

Materials and Methods : Collection and handling of serum

- Blood samples for AMH : Days 1 ,6 and the last day of stimulation, the day of oocyte retrieval.
- Day 1 : before the start of gonadotrophin administration
- Day 6 and last stimulation day: at least 8 h after the previous gonadotrophin dose.
- Centrifuged : 10 min, 1800g.
- Stored : at –18C or colder at the clinic for a maximum of 2 weeks before transfer to –70C and subsequent analysis at a central laboratory.
- The sera were only thawed once.

Materials and Methods : Collection and handling of FF

- patients who had oocyte retrieval.
- Fluid was collected from one follicle of ≥17 mm from which an oocyte was retrieved.
- Fluid was preferably collected from the first follicle aspirated and from follicles where flushing had not been performed.
- Centrifuged : 10 min, 1000g .
- Fluids that were found to be contaminated by RBC or flushing medium were not included.

Materials and Methods : Analytical methods for the variables measured in serum and FF

- Serum and FF AMH analysis was performed batch wise in a single laboratory (hormone laboratory at Universitair Ziekenhuis, Brussels) to minimize variability
- AMH was measured with the Immunotech Beckman Coulter AMH ELISA kit (A11893)
- The intra-assay and inter-assay coefficients of variation were ,9.5%
- Functional sensitivity of the assay was 2.5 pmol/l

  (1 ng/ml = 7.14 pmol/l)

Materials and Methods : Analytical methods for the variables measured in serum and FF

- Serum was analysed for other endocrine variables by a central laboratory using
  - electrochemiluminescence immunoassays
    - FSH, LH, hCG
  - chemiluminescent immunometric assays
    - estradiol, progesterone, SHBG
  - radioimmunoassays
    - androstenedione, total testosterone
-

Materials and Methods : Analytical methods for the variables measured in serum and FF

- The sensitivity [and total imprecision (coefficient of variation, CV)] of the validated analytical methods were as follows
  - FSH ,0.1 IU/l (,6%),
  - LH ,0.1 IU/l(,6%),
  - hCG ,0.1 IU/l (,8%),
  - estradiol 55 pmol/l (10%),
  - Progesterone 0.6 nmol/l (,8%),
  - SHBG 0.02 nmol/l (10%),
  - Androstenedione 0.08 nmol/l (10%)
  - Total testosterone 0.17 nmol/l (5%)

Materials and Methods : Analytical methods for the variables measured in serum and FF

- The sensitivity (and total imprecision, CV) were as follows:
  - FSH ,0.1 IU/l (,5%),
  - LH 0.1 IU/l (,5%),
  - hCG ,0.1 IU/l (,8%),
  - estradiol 18 pmol/l (,5%),
  - Progesterone 0.095 nmol/l (,5%),
  - SHBG 0.35 nmol/l (,5%),
  - Androstenedione 0.13 nmol/l (,12%),
  - total testosterone 0.1 nmol/l (,8%),
  - cortisol 20 nmol/l (,8%),
  - cortisone 4 nmol/l (,10%),
  - inhibin A 1.0 ng/l (9%),
  - VEGF ,9.0 ng/l (7%)
  - IGF-1 0.105 nmol/l (10%)

Results

Serum AMH at the start of the stimulation

- 731 patients who initiated COS
  - 623 patients had serum AMH measurements on stimulation day 1
    - 314 patients treated with HP-hMG
    - 309 patients treated with rFSH

Table I Patient demographics, baseline characteristics and serum endocrine concentrations at the start of the stimulation.

Variable	All[a] ($n = 623$)	HP-hMG[a] ($n = 314$)	rFSH[a] ($n = 309$)
Baseline			
Age (years), mean (SD)	30.8 (3.3)	30.8 (3.2)	30.8 (3.4)
Weight (kg), mean (SD)	62.1 (8.4)	62.8 (8.5)	61.3 (8.3)
BMI (kg/m^2), mean (SD)	22.3 (2.6)	22.5 (2.7)	22.1 (2.6)
Duration of infertility (years), mean (SD)	3.9 (2.2)	3.9 (2.3)	3.9 (2.2)
Primary cause of infertility			
Tubal infertility, *n* (%)	213 (34%)	116 (37%)	97 (31%)
Mild male factor, *n* (%)	59 (9%)	29 (9%)	30 (10%)
Other (incl. endometriosis I/II), *n* (%)	65 (10%)	31 (10%)	34 (11%)
Unexplained infertility, *n* (%)	286 (46%)	138 (44%)	148 (48%)
Duration of GnRH agonist before the start of stimulation (days)	15.1 (4.0)	15.1 (4.1)	15.1 (3.9)
Day 1 of stimulation			
Mean ovarian volume (ml)	4.3 (3.0, 5.9)	4.4 (3.1, 5.9)	4.3 (2.9, 5.9)
AFC	10 (7, 14)	10 (7, 14)	10 (7, 14)
21–29 years	11 (7, 16); $n = 209$	11 (8, 16); $n = 105$	10 (7, 16); $n = 104$
30–34 years	10 (7, 14); $n = 316$	9 (7, 14); $n = 165$	10 (7, 14); $n = 151$
35–37 years	10 (7, 14); $n = 94$	10 (7, 14); $n = 42$	9 (7, 14); $n = 52$
FSH (IU/l)	3.7 (2.9, 4.7)	3.7 (2.9, 4.7)	3.8 (3.0, 4.7)
LH (IU/l)	1.9 (1.4, 2.7)	1.8 (1.3, 2.7)	2.0 (1.5, 2.6)
Progesterone (nmol/l)	1.2 (0.9, 1.5)	1.2 (0.9, 1.5)	1.1 (0.9, 1.5)
Androstenedione (nmol/l)	4.1 (3.1, 5.4)	4.3 (3.1, 5.5)	3.9 (3.0, 5.1)
Total testosterone (nmol/l)	0.6 (0.5, 0.9)	0.6 (0.5, 0.9)	0.6 (0.4, 0.8)
SHBG (nmol/l)	55 (42, 71)	56 (40, 72)	55 (42, 69)
Free androgen index	1.1 (0.7, 1.7)	1.2 (0.8, 1.8)	1.1 (0.7, 1.7)
AMH (pmol/l)	26.0 (16.8, 37.4)	25.5 (17.2, 36.1)	26.6 (16.4, 37.9)
21–29 years	30.7 (20.1, 44.8); $n = 210$	30.7 (20.7, 46.6); $n = 106$	30.7 (18.7, 41.4); $n = 104$
30–34 years	25.1 (16.3, 37.2); $n = 317$	24.3 (16.3, 34.0); $n = 165$	26.5 (16.4, 38.9); $n = 152$
35–37 years	19.0 (11.9, 27.9); $n = 96$	19.7 (13.3, 27.9); $n = 43$	18.4 (11.5, 27.9); $n = 53$

Values are median (IQR) unless otherwise indicated.
[a]Patients with AMH measurement at the start of stimulation.

Results

Serum AMH at the start of the stimulation

Correlation :

- Negative : between serum AMH at the start of the stimulation /age (r = −0.25)
- Positively : AFC (r = 0.35, P < 0.001)
- Weak :
  - age /AFC (r = −0.08, P = 0.046)
  - (r ≤ 0.15) at the start of the stimulation between Serum AMH and serum concentrations of FSH, LH, estradiol, progesterone, androstenedione, SHBG, total testosterone and free androgen index.

Results

Serum AMH during the stimulation

- The serum AMH concentration decreased gradually during COS and showed similar dynamic changes in both treatment groups, although a significantly (P , 0.001) larger reduction was noted during stimulation with rFSH than with HP-hMG.

Results
Serum AMH during the stimulation

- The median AMH (IQR) concentration was decreased
  - In the rFSH group,
    - 30% to 18.6 (12.8, 27.5) pmol/l on Day 6 of stimulation
    - 55% to 11.9 (8.1, 16.9) pmol/l on the last day of stimulation
  - In the HP-hMG group
    - 16% to 21.4 (14.9, 32.7) pmol/l on Day 6
    - 46% to 13.7 (10.3, 19.6) pmol/l on the last day of stimulation in the HP-hMG group.

Results

Serum AMH during the stimulation

- Day1 , Day 6 and the last day of stimulation ($p < 0.001$)
  - HP-hMG group: r = 0.91 and 0.82
  - rFSH group: r = 0.93 and 0.84
- The magnitude of the decreases in serum AMH from baseline to stimulation day 6 as well as during the whole stimulation period was correlated ($P < 0.001$) with the number of follicles $\geq$10 mm on Day 6 and on the last stimulation day
  - HP-hMG group: r= 0.33 and 0.51
  - rFSH group: r = 0.38 and 0.57

Results

Serum AMH association with endocrine values

- AMH concentrations at the start of stimulation
  - Serum estradiol and androstenedione on Day 6 (P , 0.001)
    - HP-hMG group: r = 0.38 and 0.31, respectively
    - rFSH group: r =0.58 and 0.34, respectively
  - the last stimulation day and on the day of oocyte retrieval respectively, of serum estradiol
    - HP-hMG group: r = 0.45 and 0.49, respectively
    - rFSH group: r = 0.55 and 0.53, respectively

Results

Serum AMH association with endocrine values

- androstenedione
  - HP-hMG group: r = 0.50 and 0.52,respectively;
  - rFSH group: r = 0.49 and 0.49, respectively),
- total testosterone
  - HP-hMG group: r = 0.40 and 0.44, respectively;
  - rFSH group:r ¼ 0.36 and 0.39, respectively)
- The serum progesterone concentration
  - at oocyte retrieval was also significantly (P , 0.001)correlated with serum AMH measured at the start of the stimulation
    - HP-hMG group: r = 0.39; rFSH group: r = 0.50)

Results

Serum AMH association with endocrine values

- Correlations between serum AMH at the start of the stimulation and all other endocrine variables in serum measured on Day 6 or at the end of the stimulation were
- <0.30.
- Similar relationships between AMH and endocrine variableswere observed when using AMH concentrations on Day 6 or at the end of stimulation instead of AMH at the start of the stimulation

Results

Serum AMH association with ovarian response

- The median (IQR) number of oocytes retrieved was significantly (P, 0.001) higher in the rFSH group compared with the HP-hMG group: 11 (8, 16) versus 9 (6, 13).
- The serum concentrations of AMH on stimulation days 1, 6 and last day were all significantly (P , 0.001) positively correlated with the number of oocytes retrieved. In both treatment groups, the correlations were stronger for basal AMH (HP-hMG: r = 0.48; rFSH: r = 0.62) than for AMH on Day
- 6 (HP-hMG: r = 0.42; rFSH: r = 0.58) or AMH on the last day
- (HP-hMG: r = 0.35; rFSH: r =0.48)

Results

Serum AMH association with outcome

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Disscussion

- The lower decline in serum AMH and the higher AMH concentration in FF at oocyte retrieval in the HP-hMG group compared with the rFSH group can be readily explained by the less pronounced follicle growth observed during the initial stimulation and the lower number of follicles/oocytes retrieved after stimulation with HP-hMG

Disscussion

- The stronger correlation between serum AMH at the start of the stimulation and the serum estradiol concentration on stimulation day 6 in the rFSH group compared with the HP-hMG group may reflect the early estrogenization of a larger fraction of follicles recruited in the rFSH group

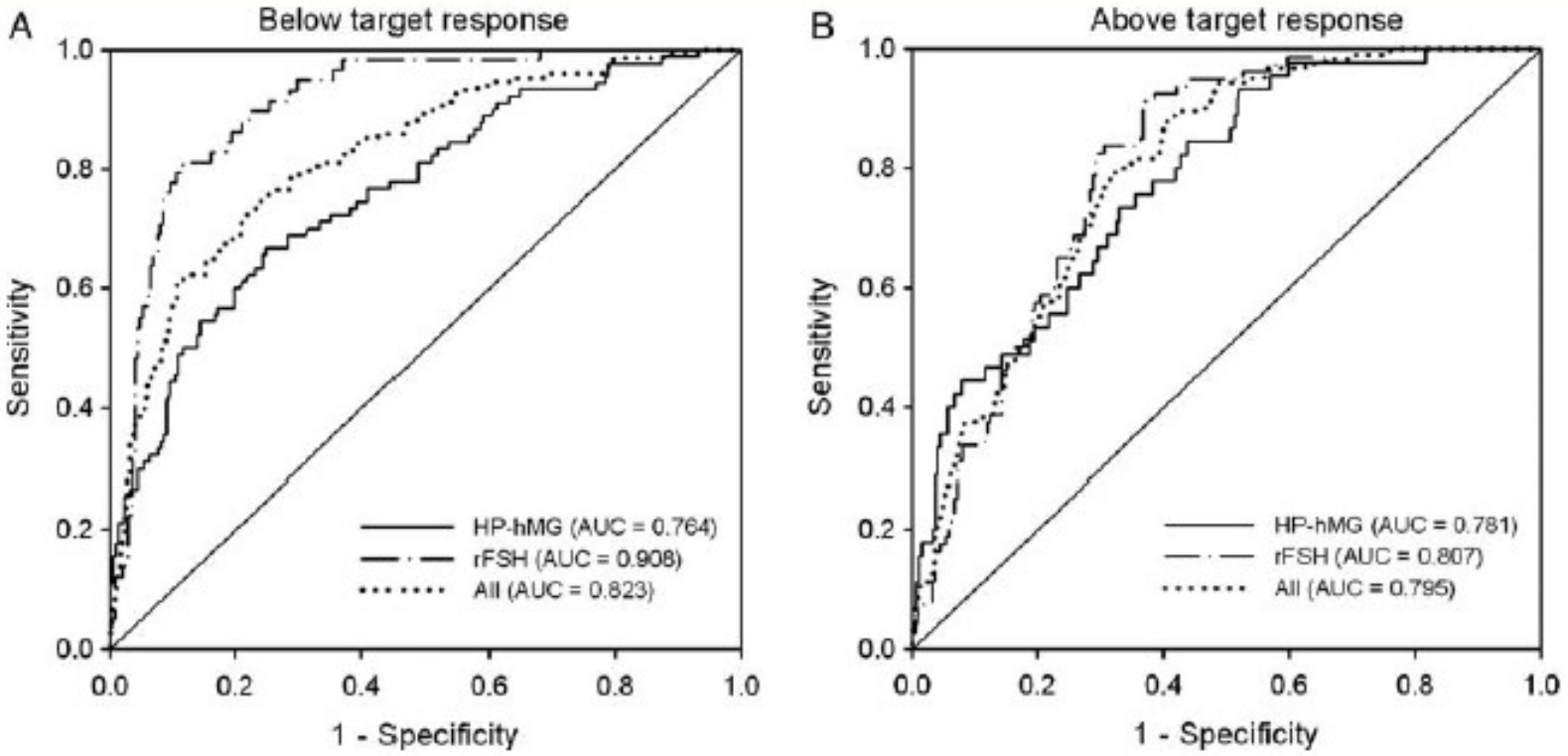

Figure 1 ROC curve analysis showing the predictive value of serum AMH at the start of the stimulation for the estimation of number of oocytes at retrieval below (<7) (A) and above (>15) the target (B) after COS in patients treated with HP-hMG or rFSH in the long GnRH agonist protocol. The diagonal line is the reference line of no discrimination (AUC = 0.5). Cut-off values for response below the target were 21.2 pmol/l for HP-hMG (sens. 66.7%, spec. 75.2%) and 16.4 pmol/l for rFSH (sens. 81.0%, spec. 88.3%). The cut-off values for response above the target were 29.8 pmol/l for HP-hMG (sens. 73.3%, spec. 67.0%) and 29.5 pmol/l for rFSH (sens. 82.5%, spec. 70.4%).

Table II Baseline, stimulation and outcome variables grouped by AMH quartiles at the start of the stimulation.

Variable	AMH quartiles												P-value (AMH)	P-value (treatment)
	<P25[a]			P25–P50[b]			>P50–P75[c]			>P75[d]				
	All (*n* = 155)	HP-hMG (*n* = 73)	rFSH (*n* = 82)	All (*n* = 156)	HP-hMG (*n* = 86)	rFSH (*n* = 70)	All (*n* = 157)	HP-hMG (*n* = 79)	rFSH (*n* = 78)	All (*n* = 155)	HP-hMG (*n* = 76)	rFSH (*n* = 79)		
Serum AMH at the start of stimulation (pmol/l)[e]														
Mean IQR	12.4 (10.1, 15.2)	13.5 (10.6, 15.4)	12.1 (9.3, 14.8)	21.3 (18.5, 23.6)	21.2 (18.8, 23.3)	21.6 (18.3, 23.7)	31.7 (28.8, 34.3)	30.6 (28.7, 33.6)	33.2 (28.9, 35.1)	50.3 (41.1, 60.6)	50.3 (42.3, 61.0)	50.3 (40.9, 60.2)		
Age (years)[f]	32.0 (3.4)	32.2 (3.3)	31.8 (3.5)	30.8 (3.3)	30.6 (3.3)	31.1 (3.2)	30.5 (3.2)	30.6 (3.0)	30.3 (3.5)	29.9 (3.0)	29.9 (2.9)	30.0 (3.1)	<0.001[g]	0.952[g]
AFC[e]	7 (5, 10)	7 (5, 11)	7 (4, 9)	10 (7, 14)	10 (7, 13)	12 (7, 14)	11 (8, 16)	11 (8, 16)	11 (8, 16)	11 (8, 18)	12 (8, 20)	11 (8, 16)	<0.001[g]	0.868[g]
FSH at the start of stimulation (IU/l)[e]	4.0 (3.0, 5.1)	3.6 (3.0, 5.0)	4.2 (3.0, 5.2)	3.8 (3.0, 4.6)	4.0 (3.2, 4.8)	3.4 (3.0, 4.4)	3.7 (3.1, 4.6)	3.7 (3.1, 4.4)	3.7 (3.0, 4.7)	3.4 (2.7, 4.4)	3.2 (2.6, 4.4)	3.6 (2.8, 4.4)	0.084[g]	0.382[g]
Dose adjustment on stimulation day 6													<0.001[h]	0.034[h]
Decrease, *n* (%)	2 (1)	1 (1)	1 (1)	7 (4)	4 (5)	3 (4)	10 (6)	6 (8)	4 (5)	37 (24)	13 (17)	24 (30)		
No change, *n* (%)	75 (48)	34 (47)	41 (50)	104 (67)	56 (65)	48 (69)	123 (78)	55 (70)	68 (87)	104 (67)	55 (72)	49 (62)		
Increase, *n* (%)	78 (50)	38 (52)	40 (49)	45 (29)	26 (30)	19 (27)	24 (15)	18 (23)	6 (8)	14 (9)	8 (11)	6 (8)		
Gonadotrophin dose on stimulation day 6 (IU)[f]	262 (40)	263 (40)	261 (40)	243 (39)	244 (40)	242 (39)	232 (34)	236 (40)	227 (27)	214 (42)	220 (39)	208 (43)	<0.001[g]	0.047[g]
Number of treatment days[f]	11.2 (2.4)	11.5 (2.6)	10.9 (2.1)	10.2 (1.5)	10.1 (1.6)	10.3 (1.5)	10.2 (1.4)	10.5 (1.5)	9.9 (1.2)	9.8 (1.5)	10.0 (1.5)	9.7 (1.5)	<0.001[g]	0.042[g]
Total gonadotrophin dose (IU)[f]	2874 (942)	2975 (1022)	2783 (860)	2452 (578)	2432 (620)	2476 (526)	2341 (467)	2452 (554)	2229 (325)	2130 (426)	2199 (438)	2063 (406)	<0.001[g]	0.025[g]
Cycle cancelled														
Poor response, *n* (%)	13 (8)	7 (10)	6 (7)	2 (1)	2 (2)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	<0.001[h]	0.127[h]
High response, *n* (%)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	1 (1)	0 (0)	1 (1)	7 (5)	3 (4)	4 (5)	<0.001[h]	0.278[h]
Early OHSS (moderate/severe), *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	7 (5)	3 (4)	4 (5)	<0.001[h]	0.982[h]
Oocytes retrieved (OR)[e]														
Mean IQR	6 (5, 9)	6 (4, 9)	6 (5, 9)	10 (7, 12)	8 (7, 11)	11 (8, 13)	12 (8, 16)	11 (7, 15)	13 (11, 18)	14 (10, 18)	12 (9, 16)	15 (11, 20)	<0.001[g]	<0.001[g]
According to target													<0.001[h]	<0.001[h]
Below target (<7 oocytes), *n* (%)	92 (60)	45 (63)	47 (57)	32 (21)	22 (26)	10 (14)	18 (12)	17 (22)	1 (1)	6 (4)	6 (8)	0 (0)		
Within target (7–15 oocytes), *n* (%)	60 (39)	26 (36)	34 (41)	109 (70)	57 (66)	52 (74)	93 (60)	48 (61)	45 (58)	83 (55)	46 (61)	37 (48)		
Above target (>15 oocytes), *n* (%)	2 (1)	1 (1)	1 (1)	15 (10)	7 (8)	8 (11)	45 (29)	14 (18)	31 (40)	63 (41)	23 (31)	40 (52)		
TQEs[f]	0.6 (0.9)	0.5 (0.9)	0.7 (1.0)	0.9 (1.3)	1.0 (1.1)	0.9 (1.5)	1.1 (1.6)	1.0 (1.4)	1.2 (1.7)	1.4 (2.1)	1.5 (2.3)	1.3 (2.0)	<0.001[g]	0.830[g]
TQE/OR (%)[f]	8.6 (14.9)	8.4 (16.5)	8.8 (13.5)	9.5 (13.2)	10.9 (13.5)	7.8 (12.7)	9.3 (11.9)	9.9 (12.5)	8.6 (11.3)	10.2 (15.0)	11.9 (17.3)	8.4 (12.1)	0.290[g]	0.094[g]
Ongoing pregnancy, *n* (%)	29 (19)	9 (12)	20 (24)	52 (33)	26 (30)	26 (37)	39 (25)	26 (33)	13 (17)	41 (26)	25 (33)	16 (20)	0.915[h]	0.374[h]

[a]<16.8 pmol/l.
[b]16.8–26.0 pmol/l.
[c]26.1–37.4 pmol/l.
[d]>37.4 pmol/l.
[e]Median (IQR).
[f]Mean (SD).
[g]ANCOVA.
[h]Logistic regression.

Discussion

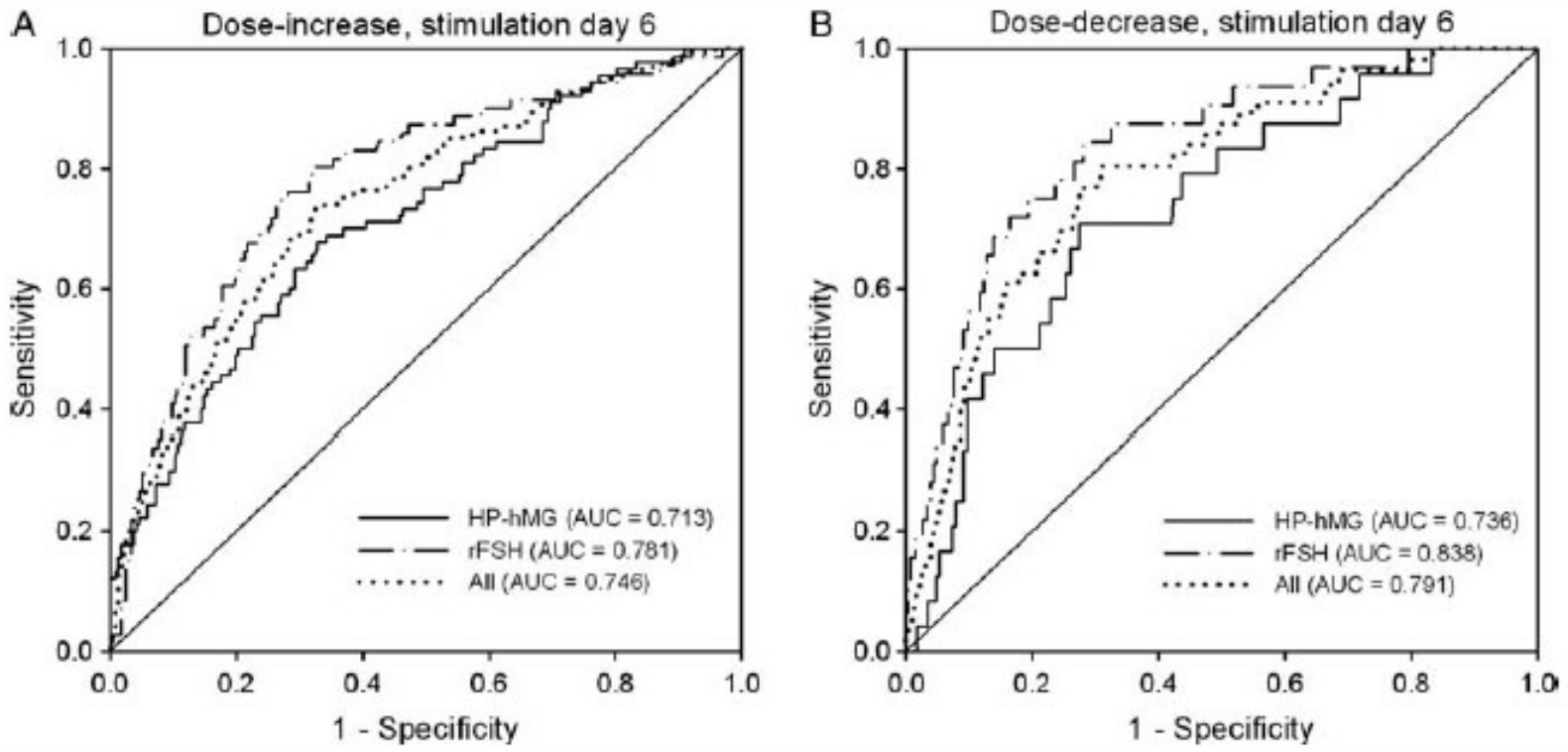

Figure 2 ROC curve analysis showing the predictive value of serum AMH at the start of the stimulation for the need for a gonadotrophin-dose increase (A) or decrease (B) on stimulation day 6 in patients treated with HP-hMG or rFSH in the long GnRH agonist protocol. All patients had received starting doses of 225 IU/day for the first 5 days. The diagonal line is the reference line of no discrimination (AUC = 0.5). Cut-off values for increased dose were 23.0 pmol/l for HP-hMG (sens. 67.8%, spec. 67.1%) and 21.4 pmol/l for rFSH (sens. 74.6%, spec. 73.6%). The cut-off values for decreased dose were 32.4 pmol/l for HP-hMG (sens. 70.8%, spec. 72.6%) and 37.4 pmol/l for rFSH (sens. 75.0%, spec. 80.7%).

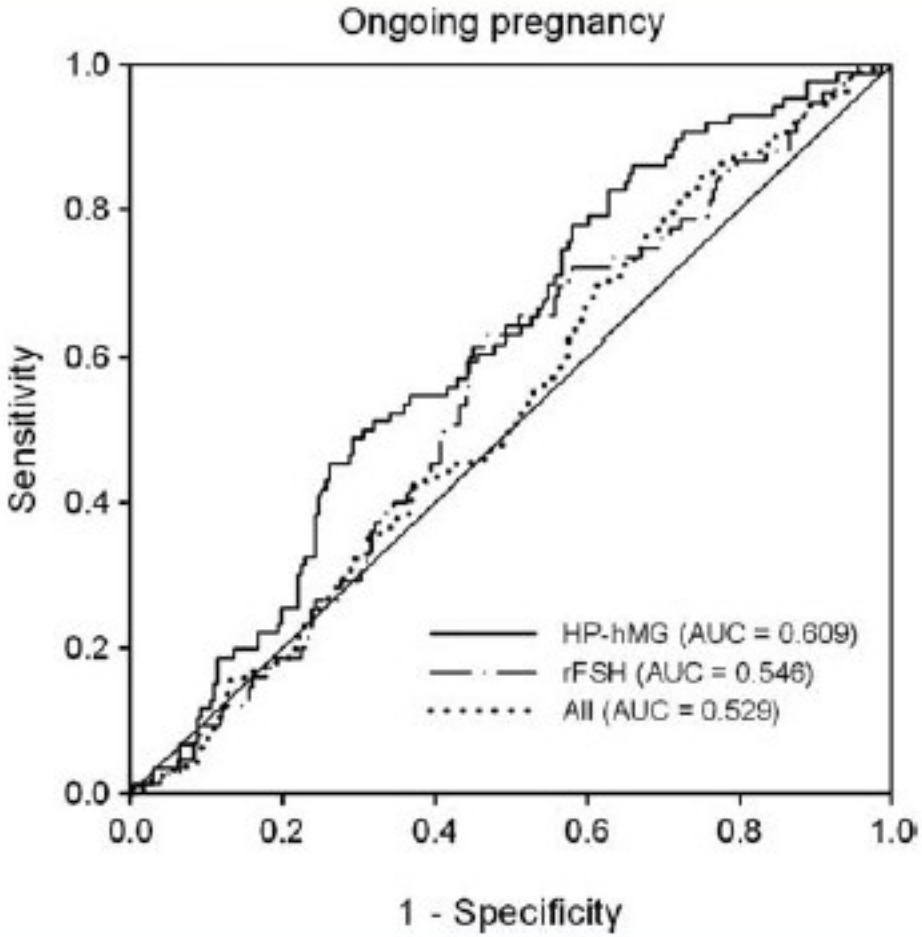

Figure 3 ROC curve analysis showing the predictive value of serum AMH at the start of the stimulation for ongoing pregnancy in patients treated with HP-hMG or rFSH in the long agonist protocol. The diagonal line is the reference line of no discrimination (AUC = 0.5).

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