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Establishment and validation of a score to predict ovarian response to stimulation in IVF

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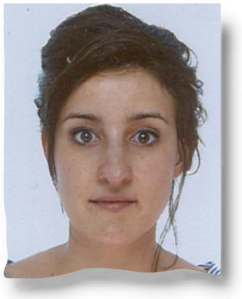

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KEY MESSAGE

A score, integrating clinical and biological parameters, can predict ovarian response and can be useful for customizing IVF treatments.

A B S T R A C T

This study aimed to integrate clinical and biological parameters in a score able to predict ovarian response to stimulation for IVF in gonadotrophin-releasing hormone (GnRH) antagonist protocols. A progressive discriminant analysis to establish a score including the main clinical and biological parameters predicting ovarian response was performed by retrospectively analysing data from the first ovarian stimulation cycle of 494 patients. The score was validated in a prospectively enrolled, independent set of 257 patients undergoing their first ovarian stimulation cycle. All ovarian stimulations were performed using a combination of GnRH antagonist and recombinant FSH. Ovarian response was assessed through ovarian sensitivity index (OSI). Parameters from the patients' database were classified according to correlation with OSI: the progressive discriminant analysis resulted in the following calculation: score = 0.192 – (0.004 × FSH (IU/l)) + (0.012 × LH:FSH ratio) + (0.002 × AMH (ng/ml)) – (0.002 × BMI (kg/m^2)) + (0.001 × AFC) – (0.002 × age (years)). This score was significantly correlated with OSI in the retrospective (r = 0.599; P < 0.0001) and prospective (r = 0.584; P < 0.0001) studies. In conclusion, the score including clinical and biological parameters could explain 60% of the variance in ovarian response to stimulation.

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https://doi.org/10.1016/j.rbmo.2017.09.011

Please cite this article in press as: Clelia Chalumeau, Jessika Moreau, Nicolas Gatimel, Clementine Cohade, Florence Lesourd, Jean Parinaud, Roger Leandri, Establishment and validation of a score to predict ovarian response to stimulation in IVF, Reproductive BioMedicine Online (2017), doi: 10.1016/j.rbmo.2017.09.011

Introduction

Ovarian stimulation with gonadotrophins is a key step in IVF. The response to stimulation varies widely from patient to patient and at the extremes leads either to excessive responses with the risk of hyperstimulation syndrome (OHSS) or to poor response with low results (Honnma et al., 2012; La Marca and Sunkara, 2014; La Marca et al., 2014). Therefore, there is a need for personalization of treatments to avoid cycle cancellation for inadequate response to gonadotrophins (La Marca and Sunkara, 2014).

The ovarian response is linked to the ovarian reserve (OR), defined as the number of antral follicles which can be stimulated by gonadotrophins. Its assessment is of great value to determine the prognosis of fertility treatments and the choice of protocol to be used in assisted reproductive technologies (Verhagen et al., 2008). OR can be evaluated by two direct parameters: antral follicle count (AFC) and serum anti-Müllerian hormone (AMH). These have been reported to have the best predictive value of ovarian response (Lan et al., 2013; Nelson et al., 2015). Indirect parameters, such as age and FSH, have also been shown to influence the level of response to gonadotrophins (El-Shawarby and Khalaf, 2009; Oehninger et al., 2015). Other parameters such as body mass index (BMI) (Ozekinci et al., 2015), tobacco smoking (Freour et al., 2012) or alcohol consumption (Nardo et al., 2007) can also influence ovarian response to stimulation for IVF. Therefore, ovarian response appears to be multiparametric and there is a need to integrate all parameters to benefit the choice of gonadotrophin starting dose. Such a study has already been performed by La Marca et al. (2012) for agonist protocols. The present study aimed to establish a score predicting the response in antagonist protocols, including parameters influencing ovarian response, by the use of a progressive discriminant analysis.

Materials and methods

Patients

A retrospective and prospective cohort were included in this study. The retrospective cohort (n = 494) included all patients meeting the inclusion criteria and having their first ovarian stimulation in 2014 and 2015. Patient characteristics are summarized in **Table 1**. The prospective cohort (n = 257) was a different group of patients who met the same inclusion criteria and had their first stimulation in the first semester of 2016. These patients were recruited on the first day of ovarian stimulation. All patients (n = 761) who had their first follicular puncture for IVF in 2014, 2015 and the first semester of 2016 in the Department of Reproductive Medicine of the Toulouse University Hospital entered the study, whatever the cause of infertility. Patients were included in the study if the delay between the evaluation of OR (AFC and AMH, FSH, LH and oestradiol) and IVF was less than 1 year. Out of the 761 patients, 32 had polycystic ovaries. Because the main evaluation parameter was the number of collected oocytes, attempts in which the follicle puncture appeared difficult were excluded from the study. Only the first stimulation cycle for each patient was studied.

OR was evaluated by AFC (2–10 mm using a 2D 7.5 MHz probe) and AMH (Beckman, AMH Genll kit). All hormone measurements (AMH, FSH, LH and oestradiol) were conducted in the same laboratory (ART Centre of the Toulouse University Hospital), using the same methods, between cycle day 2 and 4.

Data were extracted from the ART Centre patient database. This database was approved by the French National Commission for Information Technology and Civil Liberties (CNIL) to be used for clinical research. Patients are aware that their data can be used for anonymous clinical studies unless they specifically state otherwise. According to a recent French law (2016–1537), non-interventional studies, such as from clinical databases, do not need to be submitted to an ethical committee.

Table 1 – Demographic data in the retrospective and prospective studies.

	Retrospective study N = 494	Prospective study N = 257
Age	33.7 ± 4.2	34.1 ± 4.1
FSH (IU/l)	7.3 ± 2.2	7.4 ± 2.2
LH (IU/l)	5.9 ± 2.5	6.0 ± 2.5
LH:FSH	0.86 ± 0.43	0.86 ± 0.42
Oestradiol (pg/ml)	37 ± 17	43 ± 24
AMH (ng/ml)	3.3 ± 2.9	3.3 ± 2.8
BMI (kg/m^2)	22.9 ± 3.4	22.7 ± 3.5
AFC	22 ± 11	21 ± 11
Time between OR assessment and stimulation (months)	6.7 ± 2.7	7.1 ± 2.6
Smokers (%)	98 (20)	53 (21)
Tobacco consumption (cig/day) (range)	0–20	0–20
Stimulation length (days)	11.6 ± 2.7	11.7 ± 2.2
Total number of injected rFSH units	2149 ± 958	2299 ± 955
Mean daily number of injected rFSH units	187 ± 76	198 ± 76
Number of collected oocytes	9.4 ± 4.9	10.6 ± 5.1
Ovarian response (number of collected oocytes/100 mean daily rFSH IU)	6.2 ± 4.5	6.7 ± 4.6
Number of ICSI (%)	332 (67)	199 (77)
Origin of sperm (%)		
Husband	427 (86.4)	236 (91.8)
Ejaculated fresh	30 (6.1)	10 (3.9)
Ejaculated frozen	2 (0.4)	2 (0.8)
Urinary frozen	18 (3.6)	4 (1.6)
Epididymal frozen	3 (0.6)	3 (1.2)
Testicular frozen	14 (2.8)	2 (0.8)
Donor		
Number of obtained embryos	5.1 ± 3.5	5.7 ± 3.7
Number of transferred embryos	1.6 ± 0.8	1.7 ± 0.9
Number of pregnancies (%)	154 (31)	70 (27)
Ongoing pregnancies (%)	121 (24)	48 (19)

Values expressed as mean ± SD, n (%) or range.
AFC = antral follicle count; AMH = anti-Müllerian hormone; BMI = body mass index; ICSI = intracytoplasmic sperm injection; rFSH = recombinant FSH.

Ovarian stimulation

All patients had an ovarian stimulation for an IVF/intracytoplasmic sperm injection (ICSI) using a protocol combining recombinant FSH (rFSH) (Gonal F® Merck, Lyon, France or Puregon® MSD, Boulogne, France) and gonadotrophin-releasing hormone (GnRH) antagonist (Cetrotide® 0.2 mg, Merck, Lyon, France or Orgalutran®, MSD,

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Table 2 – Correlations between ovarian response (number of collected oocytes/mean daily rFSH dose) and the different clinical and biological parameters.

	Pearson coefficient (r)	P-value
Age	0.335	<0.0001
BMI	0.164	<0.001
Tobacco consumption	0.002	NS
FSH	0.306	<0.0001
LH	0.170	<0.0001
LH:FSH	0.336	<0.0001
Oestradiol	0.069	NS
AMH	0.415	<0.0001
AFC	0.454	<0.0001

AFC = antral follicle count; AMH = anti-Müllerian hormone; BMI = body mass index.

Boulogne, France). The daily rFSH starting dose (75–300 IU/day) was subjectively chosen by physicians according to age, BMI and OR. On stimulation day 6, the rFSH doses were adapted according to the results of ovulation monitoring (oestradiol and ultrasonographic evaluation). Ovulation was triggered using recombinant human chorionic gonadotrophin (rHCG) (Ovitrelle®, Merck, Lyon, France) when at least three follicles ≥18 mm were obtained. Follicular punctures were performed 36 h after HCG injection. Ovarian response was assessed through the ratio number of recovered oocytes/100 mean daily rFSH IU (ovarian sensitivity index) (Carre et al., 2016; Huber et al., 2013).

Statistical analysis

Using the data from the retrospective cohort we first studied the individual correlations of each parameter with ovarian response. Secondly, we performed a progressive discriminant analysis using all the parameters found to be significantly correlated with ovarian response to establish a predictive score. FSH starting dose was not included in the model. Thirdly, to verify the value of this score it was applied to the prospective cohort. Statistical analyses were performed using Statview software (SAS Institute, Cary, NC, USA). Data are means ± SD. Correlations were made using Pearson coefficients.

Table 4 – Evolution of the correlation coefficient (r) during the progressive discriminant analysis.

Parameters	r
AFC	0.454
AFC + age	0.512
AFC + age + FSH	0.550
AFC + age + FSH + BMI	0.578
AFC + age + FSH + BMI + LH:FSH ratio	0.593
AFC + age + FSH + BMI + LH:FSH ratio + AMH	0.599

AFC = antral follicle count; AMH = anti-Müllerian hormone; BMI = body mass index.

Results

Individual correlations with ovarian response

As shown in **Table 2**, the parameters showing the highest correlation with ovarian response were AFC, AMH, LH to FSH ratio, age and FSH. Some parameters were also correlated with each other (**Table 3**), such as AFC with AMH ($r = 0.663$), AMH with LH ($r = 0.415$), while others such as age and AMH ($r = 0.173$) or FSH and AFC ($r = 0.241$) were weakly correlated.

Results of the progressive discriminant analysis

To integrate the parameters into a score taking into account their predictive value and the correlations between them, a progressive discriminant analysis was performed (**Table 4**) which allowed the calculation of an ovarian response score as follows: 0.192 – (0.004 × FSH (IU/l)) + (0.012 × LH:FSH ratio) + (0.002 × AMH (ng/ml)) – (0.002 × BMI (kg/m^2)) + (0.001 × AFC) – (0.002 × age (years)). Oestradiol, LH and tobacco consumption were not included in the score due to a lack of additional value. **Figure 1** shows the correlation of the score with the response ($r = 0.599$; $P < 0.0001$).

Application of the score to an independent population

When applied to an independent population (prospective study) of 257 patients, the score had a similar correlation with the ovarian response ($r = 0.584$; $P < 0.0001$).

Table 3 – Correlations between clinical and biological parameters.

	BMI	Tobacco consumption	FSH	LH	LF:FSH	Oestradiol	AMH	AFC
Age	0.034	0.066	0.068	0.043	0.095[a]	0.130[b]	0.173[c]	0.230[d]
BMI		0.048	0.116[b]	0.042	0.027	0.100[b]	0.001	0.011
Tobacco consumption			0.130[b]	0.080	0.030	0.005	0.007	0.070
FSH				0.242[d]	0.325[d]	0.129[b]	0.237[d]	0.241[d]
LH					0.778[d]	0.003	0.415[d]	0.274[d]
LH:FSH						0.111[a]	0.483[d]	0.362[d]
Oestradiol							0.064	0.132[b]
AMH								0.663

Values are the Pearson coefficient (r).
AFC = antral follicle count; AMH = anti-Müllerian hormone; BMI = body mass index.
[a] $P < 0.05$;
[b] $P < 0.01$;
[c] $P < 0.001$;
[d] $P < 0.0001$.

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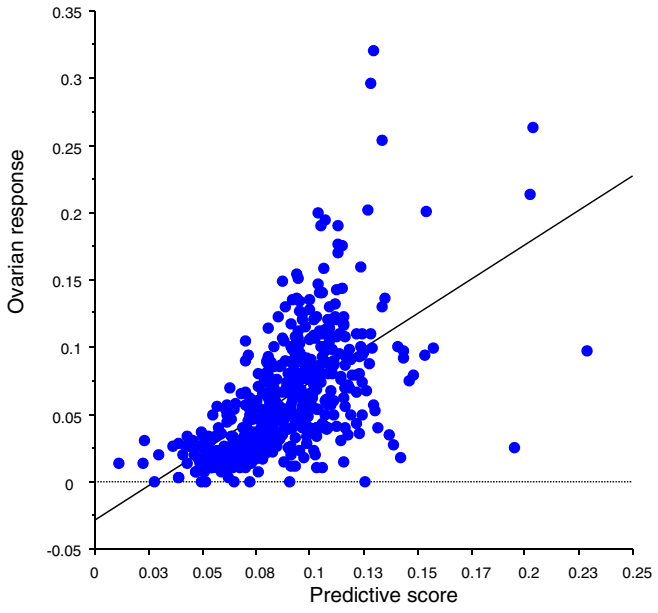

Figure 1 – Correlation between ovarian response and predictive score (r = 0,599; $P < 0.0001$).

Discussion

From the tested clinical and biological parameters, AMH and AFC had the highest correlations with ovarian response. This has been widely reported by other authors. Indeed, Patrelli et al. (2012) reported a good correlation between AMH levels and the number of collected oocytes (r = 0.643) after stimulation with high doses of rFSH (225–450 IU/day). In their meta-analysis, Broer et al. (2011) showed that, for the prediction of excessive ovarian response, AMH had 82% sensitivity and 76% specificity. For poor responders, Burks et al. (2015) have shown that an AMH lower than 0.5 ng/ml permitted discrimination between successful and unsuccessful stimulation with 83% sensitivity and 71% specificity.

Using a receiver operating characteristics (ROC) curve, AFC has also shown the ability to predict a high ovarian response (area under the curve (AUC) = 0.882) as a low response (AUC = 0.882) (Oehninger et al., 2015). Contrary to our findings, Nelson et al. (2015) found a better predictive value of AMH versus AFC for oocyte yield. It should be noted that in the Nelson study, 19 assisted reproductive technology centres participated. Because AFC has been shown to have important inter-observer variations (Iliodromiti et al., 2014), this discrepancy could be explained by the fact that our study was performed in a single centre with only a few operators.

We found a high correlation between AFC and AMH (r = 0.663); however, it was lower than that found in the study by Tadros et al. (2016), where the correlation coefficient was as high as 0.83. The high correlation reported by Tadros et al. (2016) can be explained by the fact that all AFC were performed by the same physician, increasing the accuracy of the test. In our study, although all AMH measurements were performed in the same laboratory, using the same kit, the ultrasonographical examinations were performed by different clinicians with different probes and devices, which explains the lower correlation between AMH and AFC. Indeed, Scheffer et al. (2002) found a good intra- and inter-observer reproducibility, but using the same probe and apparatus. Moreover, in the study by Tadros et al. (2016), the correlation between AMH and AFC varies among the AFC, being lower in intermediate AFC, and thus depends on the studied population.

The age of the patient at the time of follicular puncture showed a good correlation with the ovarian response. This could be partially due to the link between age and OR (AMH and AFC), as previously described by Cui et al. (2014). However, age appeared to have an additional predictive value in our study. This added value was also shown in the study by Oehninger et al. (2015) for high as well as for low response.

BMI had a significant but low correlation with the ovarian response, similar to that reported by Ozekinci et al. (2015), in which study the total dose of injected FSH increased with increasing BMI. This can be explained by a lower bioavailability of FSH after subcutaneous (SC) injection in obese patients. Indeed, Steinkampf et al. (2003) reported a high negative correlation between BMI and extent of absorption (AUC) after 300 IU of rFSH was injected subcutaneously (r = –0.526; $P < 0.05$).

In the current study, basal serum FSH levels were linked to the response, mainly by their correlation with AMH and AFC. However, the polymorphisms of FSH receptors are also implied in the fact that when FSH levels increase there is a need for higher doses of gonadotrophins for stimulation (Desai et al., 2013; Lazaros et al., 2013).

The LH to FSH ratio is positively correlated to the response, as previously reported by Brodin et al. (2009), who showed that the ovarian sensitivity to FSH is higher when the ratio is high than when it is normal or low.

Because many parameters have an influence on ovarian response and since some of them are closely or partially linked, only a score including all predictive factors with weighted values can be a good predictor, but the predictive value remains limited. Previously, a nomogram based on age, AMH and day 3 FSH was proposed to predict the FSH starting dose before an agonist protocol (La Marca et al., 2012), but this only explained 30% of the variability in ovarian sensitivity (r = 0.31). Nevertheless, a randomized trial of the use of this nomogram for agonist protocols allowed an optimal response of 63% to be obtained versus 42% in the control group (Allegra et al., 2017). In our study, even if the combination of parameters allowed a significant increase in the correlation coefficient, it remained relatively low (r = 0.6), suggesting that other parameters were involved. For instance, we have recently described how environment, and especially air quality, impacts on ovarian sensitivity (Carre et al., 2016). Another explanation could be that the ovarian sensitivity index (OSI) is based on the number of recovered oocytes, which can be influenced not only by the ovarian response but also by the accessibility of follicles to transvaginal puncture and the willingness of physicians to retrieve oocytes from small follicles. Moreover, Rombauts et al. (2015) have shown inter-cycle variations of ovarian responses in the same patients, using the same FSH doses, which can be at the origin of low correlations between a patient's parameters and OSI. Therefore, the score must be used as a guide but not as an absolute parameter to choose the FSH starting dose. It can be used by classifying the predicted response according to the score percentiles. For instance, the starting dose could be 100 IU per day if the score is higher than the 75th percentile, 150 IU between the 75th and the 50th, 200 IU between the 50th and the 25th and 300 IU when it is lower than the 25th. However, the value of individualization of the FSH starting dose is controversial, because in the Optimist study, van Tilborg et al. (2012) claim the importance of individualization in a cost-efficiency evaluation, while Nyboe Andersen *et al.* (2017) found no

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improvement in efficiency and safety of individualized dosing according to pre-treatment patient characteristics. Moreover, as for all scores, the one we described must be adapted for each assisted reproductive technology centre because most parameters can vary among practitioners (Arvis et al., 2012).

ARTICLE INFO

Article history:
Received 9 May 2017
Received in revised form 6 September 2017
Accepted 14 September 2017
Declaration: The authors report no financial or commercial conflicts of interest.

Keywords:
Anti-Müllerian hormone
Antral follicle count
FSH
Gonadotrophin-releasing hormone antagonist protocol
Ovarian reserve
Ovarian stimulation

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Please cite this article in press as: Clelia Chalumeau, Jessika Moreau, Nicolas Gatimel, Clementine Cohade, Florence Lesourd, Jean Parinaud, Roger Leandri, Establishment and validation of a score to predict ovarian response to stimulation in IVF, Reproductive BioMedicine Online (2017), doi: 10.1016/j.rbmo.2017.09.011