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ARTICLE

Anti-Müllerian hormone for the assessment of ovarian response in GnRH-antagonist-treated oocyte donors

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Abstract Evidence regarding the role of anti-Müllerian hormone (AMH) among oocyte donors is limited and only involves gonadotrophin-releasing hormone (GnRH)-agonist-treated donors. This trial assessed the predictive ability of AMH for ovarian response among 108 oocyte donors treated with an antagonist protocol. In multivariate linear regression analysis, both AMH and age were independently associated with ovarian response (unstandardized coefficients 0.904 and −0.378, respectively). In receiver operating characteristic curve analysis, AMH performed better than age, but was a modest predictive marker for low (≤6 oocytes) and excessive (>20 oocytes) ovarian response (area under the curve (AUC) 0.643 and 0.695, respectively). Similarly, a multivariate logistic model including AMH and age was also modest (AUC 0.651 and 0.697 for low and excessive responders, respectively). The predictive ability of AMH did not significantly alter when different thresholds were adopted, such as <4 oocytes for low response and >25 for excessive response (AUC 0.759 and 0.724, respectively). Among oocyte donors treated with a GnRH-antagonist protocol, although AMH was correlated with the number of oocytes retrieved, it demonstrates a modest ability in discriminating women with low or excessive ovarian response.

KEYWORDS: anti-Müllerian hormone, AMH, GnRH antagonist, oocyte donation, oocyte donors, ovarian response

Introduction

Oocyte donation has become an increasingly used fertility treatment. The number of cycles using donor oocytes represents approximately 12% of all assisted reproduction cycles in the USA (Centers for Disease Control and Prevention, 2008). Nonetheless, despite the increase in cycles utilizing donated oocytes and the significant effect that this

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may have for couples that are unable to conceive after assisted reproduction treatment with autologous oocytes, the financial burden related to donation remains high (Gorrill et al., 2001). First of all, managing an oocyte donor screening programme requires a great deal of time and effort and is associated with significant cost (Gorrill et al., 2001). Most women who express initial interest in the programme do not become active donors, with >70% voluntarily withdrawing from the screening process and almost 20% finally failing medical or psychological screening (Gorrill et al., 2001). Furthermore, the financial compensation of oocyte donors appears to represent a significant amount of money (Anonymous, 2007) with specific authorities even suggesting an increase in the compensation given (O'Dowd, 2010). Therefore it appears that appropriate selection of oocyte donors is of paramount importance for the proper and more cost-efficient functionality of an oocyte donation programme.

Donors' characteristics and ovarian reserve tests have been utilized to predict the level of ovarian response in oocyte donation cycles. Whereas donors' basal FSH concentrations were not associated with response to stimulation and final oocyte outcome (Barton et al., 2010), antral follicle count (AFC; Melo et al., 2009b) and age (Barton et al., 2010) appear to be correlated with the level of ovarian response.

Recently, anti-Müllerian hormone (AMH), an ovarian reserve marker proven to predict ovarian response in infertile patients (Broer et al., 2009, 2011; Gnoth et al., 2008; Nelson et al., 2007), was assessed in oocyte donors. Only two retrospective studies examined the efficacy of AMH as a predictive marker for impaired and excessive response to stimulation among oocyte donors and these were performed in patients treated with a gonadotrophin-releasing hormone (GnRH)-agonist protocol (Nakhuda et al., 2010; Riggs et al., 2011). Whereas the results were promising regarding the predictive ability of the marker for hyper-response, contradictory findings were reported regarding the accuracy of AMH in the prediction of impaired ovarian response.

Taking into account the lack of a significant amount of evidence regarding the role of AMH in oocyte donors, and the fact that the GnRH-antagonist protocol is increasingly used for the treatment of oocyte donors (mainly due to the fact that in combination with agonist triggering it totally eliminates the likelihood of ovarian hyperstimulation syndrome) (Galindo et al., 2009; Melo et al., 2009a), the current study attempted to examine the role of AMH as a predictor of the number of oocytes retrieved among donors treated with GnRH antagonists. It therefore performed a retrospective cohort trial and assessed whether AMH may be considered as a useful marker to predict lower and excessive ovarian response in oocyte donors treated with GnRH antagonists and therefore may serve as factor that could tailor the selection process for an oocyte donation programme.

Materials and methods

Eligible patients

Oocyte donors between 18 and 36 years old who underwent ovarian stimulation and oocyte retrieval between 2009 and 2011 were included in this study. This study was approved by the ethical committee of the UZ Brussel.

All donors had normal menstrual cycles between 25 and 35 days. Women with polycystic ovaries, grade III or IV endometriosis, previous ovarian surgery or with basal FSH concentrations >15 mIU/ml were excluded from the oocyte donation programme. All eligible oocyte donors were treated with an antagonist protocol (Orgalutran; MSD, Oss, The Netherlands; or Cetrotide; Merck Serono, Geneva, Switzerland) starting from day 6 of stimulation, while ovarian stimulation was performed with rFSH (Puregon; MSD; or Gonal-F; Merck Serono) or urinary FSH (Fostimon; Mithra Pharmaceuticals, Liege, Belgium) at a dose ranging from 150 to 225 IU from cycle day 2 onwards, depending on the age and body mass index (BMI) of each donor. Ovulation triggering was performed with either 0.2 mg of GnRH agonist (Decapeptyl; Ipsen NV, Merelbeke, Belgium) for the majority of the donors (85%) while the rest received 10,000 IU human chorionic gonadotrophin.

All donors' files were retrospectively reviewed and AMH values that were obtained during the preliminary examination prior to stimulation, irrespective of the day of the menstrual cycle and based on the convenience of the donor, were recorded. In addition, other baseline characteristics such as age and BMI were also recorded, given that previous trials have shown that among IVF patients treated with a GnRH antagonist, age and BMI are related to insufficient ovarian response to mild stimulation (Verberg et al., 2007).

Anti-Müllerian hormone assay

Serum AMH was determined by the Immunotech AMH enzyme immunoassay (Beckman Coulter, Marseilles, France). The intra- and inter-assay coefficients of variation were <9.5% (3.3 ng/ml). Functional sensitivity of the assay was 0.35 ng/ml.

Outcome measures

The main outcome measures were to determine whether AMH values are related to the degree of ovarian response. Additional outcomes were to determine the predictive ability of AMH in order to predict low and excessive response to stimulation. This study defined oocyte donors with ≤6 oocytes retrieved at oocyte retrieval as low responders and those with >20 oocytes retrieved as excessive responders.

The thresholds of 6 oocytes for low ovarian response and 20 oocytes for excessive response were adopted in accordance with the threshold values used in previous published trials that assessed the value of AMH as a predictor of low ovarian response in GnRH-agonist-treated donors (Nakhuda et al., 2010; Riggs et al., 2011). Furthermore, a mean number of 6 oocytes per recipient results in a good ongoing pregnancy in this study centre (43.5%; Stoop et al., 2011), and this threshold further represents the minimal demand for entering the programme for a future donation.

Statistical analysis

Baseline characteristics (AMH, FSH, BMI and age) and results related to response (total stimulation dose required and

days of stimulation) were compared for the three categories of ovarian response (low, normal and excessive response). The analysis used the Kruskal–Wallis test due to the lack of normality in the distribution of the results.

In addition, Pearson correlation coefficients were calculated in order to evaluate whether ovarian response (number of oocytes retrieved) is associated with AMH and basal FSH values and the age of the donors. Variables associated with the number of oocytes retrieved ($P < 0.1$) were included in a multivariate linear regression model to identify the unstandardized coefficients and 95% confidence interval (CI) for factors independently related to the oocyte retrieval rate.

Receiver operating characteristic (ROC) curves were constructed for each of the parameters tested in order to assess the sensitivity and specificity of AMH in predicting low response (≤6 oocytes) and hyper-response (>20 oocytes) to stimulation. Parameters that were found to significantly correlate with ovarian response were entered into a multivariate logistic regression model and ROC curves were constructed for this model.

Finally, for generalization purposes, the diagnostic accuracy of AMH was further examined through the construction of ROC curves at different thresholds such as <4 oocytes for poor ovarian response, as proposed by the Bologna criteria (Ferraretti et al., 2011) and >25 oocytes for excessive ovarian response.

All analyses were performed using the Statistics Package for Social Sciences version 19.0 (SPSS, USA).

Results

Patients' baseline characteristics

Overall 108 donors were included in the analysis. The median age of the participants was 28 years and the mean BMI was 22.9 kg/m^2. The mean number of oocytes retrieved was 13.9 ± 7.8, and the women were stimulated for a median period of 10 days with a median total gonadotrophin dose of 1700 IU. Four different starting doses of gonadotrophins were utilized (150, 175, 200 and 225 IU), chosen according to age and BMI; nonetheless, the mean number of oocytes retrieved did not significantly differ among those groups.

Table 1 shows the patients' characteristics according to the level of ovarian response. As shown, the only parameter that differed significantly among the three categories for ovarian response was the AMH concentration ($P = 0.012$).

AMH, basal FSH and age in relation to ovarian response

AMH concentrations among oocyte donors showed a weak positive correlation with the number of oocytes retrieved with Pearson correlation coefficient (R 0.412, $P < 0.0001$). Donors' basal FSH did not correlate with the level of ovarian response (R −0.040), whereas age showed a significant but weaker correlation than AMH (R −0.252, $P = 0.009$). When using a multivariate linear regression model, both age and AMH were independently correlated with the number of oocytes retrieved; nonetheless, AMH was again the most significant factor which was correlated to the level of ovarian response (unstandardized coefficients and 95% CI 0.904, 0.511 to 1.297, $P < 0.0001$) compared with age (−0.378, −0.673 to −0.083, $P = 0.012$). This is more clearly reflected using standardized correlation coefficients, according to which AMH showed a higher correlation with the number of oocytes retrieved compared with age (R 0.440, $P < 0.0001$; and −0.138, $P = 0.012$, respectively).

AMH and predictive ability of ovarian response

This study further examined whether AMH, basal FSH and age may be useful in the prediction of low or excessive response to stimulation. All the above parameters were plotted in ROC curves and results are presented in Figure 1. Although it appears that AMH has a higher area under the curve (AUC) compared with age for both low and excessive responders, the value is still low compared with previous trials either in donors (Nakhuda et al., 2010; Riggs et al., 2011) or in IVF/intracytoplasmic sperm injection patients (Broer et al., 2009, 2011; Gnoth et al., 2008; Nelson et al., 2007). The predictive ability of AMH for either low or excessive

Table 1 Baseline characteristics according to the level of ovarian response.

	≤6 oocytes	*7–20 oocytes*	*>20 oocytes*
Patients	16	73	19
Demographics			
Age (years)	28 (25–30)	29 (25–32)	25 (21–32)
BMI (kg/m^2)	22.6 ± 1.8	23.2 ± 4.0	20.9 ± 2.6
Endocrinological profile			
Basal FSH values (mIU/ml)	7.2 ± 3.3	6.5 ± 3.0	5.6 ± 2.4
AMH values (ng/ml)[a]	3.22 ± 1.3	4.3 ± 2.6	7.3 ± 5.6
Stimulation characteristics			
Stimulation days	10 (9–11)	10 (9–11)	9 (9–10)
Total gonadotrophin dose (IU)	1925 (1575–2325)	1750 (1500–2212.50)	1600 (1350–1900)

Values are *n*, median (interquartile range) or mean ± SD.
AMH = anti-Müllerian hormone; BMI = body mass index.
[a]Values are statistically significantly different ($P = 0.012$).

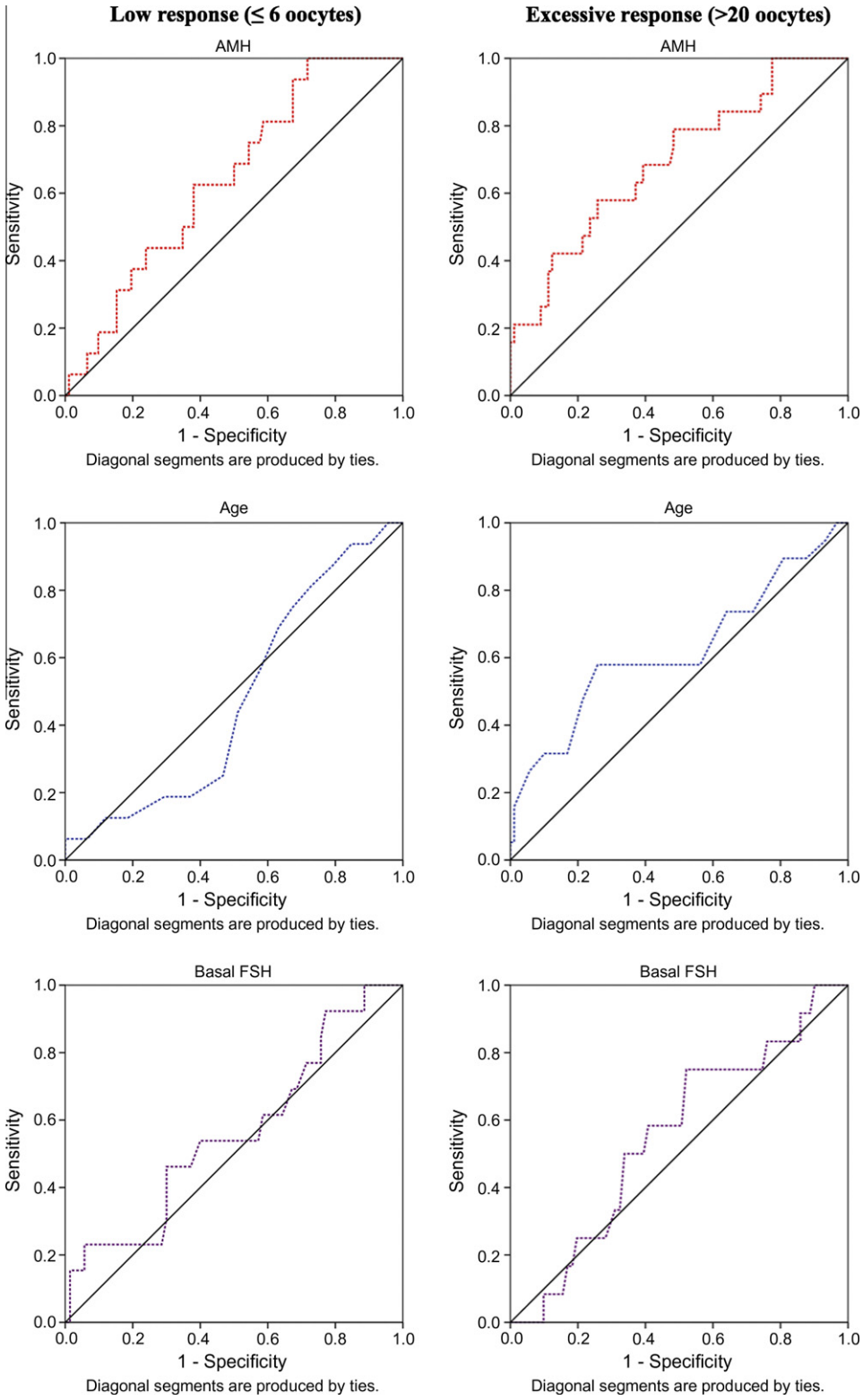

Figure 1 Receiver operating characteristic curves for anti-Müllerian hormone, age and basal FSH for the prediction of low response (≤6 oocytes) and excessive response (>20 oocytes).

ovarian response appears to be modest, as shown in the ROC curves constructed (AUC 95% CI, 0.643, 0.513 to 0.773 for low ovarian response (≤6 oocytes); 0.695, 0.564 to 0.826, $P = 0.008$) for excessive response (>20 oocytes).

Anti-Müllerian hormone concentrations and age, which were found to be significantly correlated with ovarian response in the multivariate linear regression model, were entered in a multivariate logistic regression and ROC curves

were constructed. According to the analysis, the predictive value of the multivariate model including age and AMH for predicting low and excessive response was also limited (AUC 0.651, 0.521 to 0782, $P = 0.054$; and 0.697, 0.557 to 0.837, $P = 0.007$), respectively.

Finally, sensitivity analysis was performed for different, more robust thresholds for low and excessive ovarian response. Although the AUC for predicting poor response at a threshold value of <4 oocytes was higher (0.759), the 95% CI was wide (0.488 to 1.000) and the *P*-value was not significant, suggesting that the predictive ability of the test is limited; furthermore these results were based on only three oocyte donors with ≤ 3 oocytes retrieved and therefore they should be interpreted with caution. On the contrary, AMH has shown a slightly higher accuracy for predicting excessive response at a threshold of >25 oocytes (AUC 0.724, 0.510 to 0.938, $P = 0.036$).

The lack of predictive ability of AMH for different categories of ovarian response is clearly demonstrated in the scatterplot created (**Figure 2**), according to which it appears that there is a significant overlap for AMH values between low, normal and excessive ovarian responders, in such a way that a clear cut-off concentration is impossible to identify. Furthermore, an interesting observation is that the majority of the oocyte donors with low AMH values, e.g. <2.0 ng/ml, had >6 oocytes retrieved (ranging from 8 to 17), and therefore were considered normal responders (**Figure 2**).

Discussion

This is the first study, as far as is known, to examine the efficacy of AMH in the prediction of ovarian response for oocyte donors treated with a GnRH-antagonist protocol. According to the results, AMH is significantly correlated with ovarian response; however, this correlation is of medium strength, whereas its ability as a marker to predict excessive or low response to stimulation in these donors is modest. Although AMH values do perform better than basal FSH values or age, the AUC in the ROC curves constructed for the prediction of low or excessive response is below 0.7. Therefore, in oocyte donors treated with a GnRH-antagonist protocol, AMH does not appear to be a reliable marker for guiding the patient selection process for oocyte donation programmes.

Only two previous trials have been published regarding the predictive ability of AMH among oocyte donors. A previous retrospective study has shown that AMH has a high predictive ability both for low and excessive ovarian response (Riggs et al., 2011), whereas another study supported that although AMH has modest predictive ability for low ovarian response it might be a useful tool in the donor selection process due to the fact that it may predict hyper-response (Nakhuda et al., 2010). The current results are in agreement with the results obtained by Nakhuda et al. (2010), although it appears that AMH performs less well in oocyte donors treated with GnRH antagonists, given that the current study was unable to provide evidence that AMH has a high ability to predict low or hyper-response.

One explanation for this modest predictive ability of AMH may be the fact that the current trial used a different down-regulation protocol with a GnRH antagonist compared with the other trials, which involved only women treated with a GnRH-agonist protocol. Therefore the difference between the two protocols may be the cause of the difference of the predictive ability of the AMH. The difference between those two protocols may be related to the difference in their potency regarding the number of oocytes retrieved, given that agonist down-regulation results in a higher number of oocytes (Kolibianakis et al., 2006). For example in agonist-treated donors, due to the higher mean number of oocytes retrieved, differences between low and

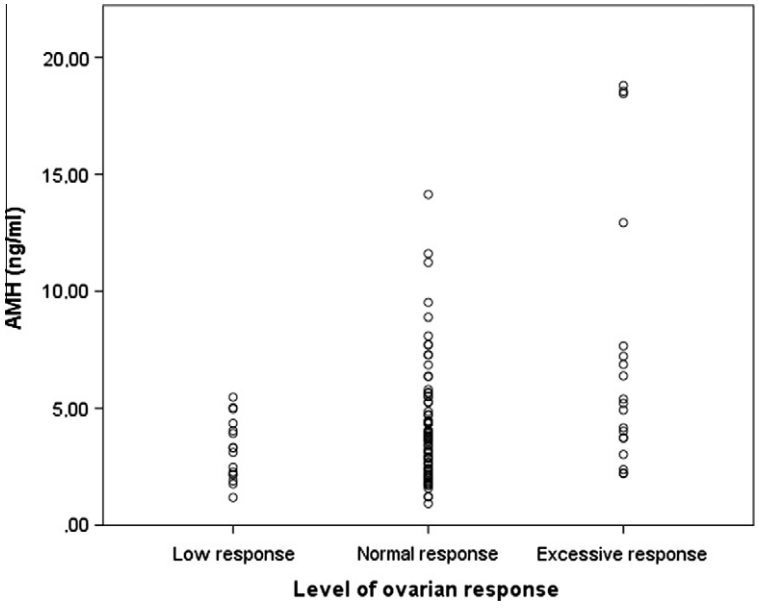

Figure 2 Scatterplot for the distribution of anti-Müllerian hormone values according to the level of ovarian response (low, normal and excessive response).

high responders are more clearly demonstrated and this is reflected in the ROC curves. On the contrary, in a GnRH-antagonist protocol, which is a milder stimulation protocol and results in fewer oocytes, the difference in the mean number of oocytes between donors who exhibit a lower or an excessive response is not so robust as in agonist protocols. Therefore, although AMH in antagonist-treated donors is significantly associated with the degree of ovarian response, this association is not very strong and it does not appear to have a really high predictive ability for low or excessive response. The current results appear to support such a hypothesis, given that the mean number of oocytes retrieved here was 13.9 whereas for donors treated with GnRH agonist in the reports by Riggs et al. (2011) and Nakhuda et al. (2010), considerably higher mean numbers of oocytes were retrieved, 17 and 21 respectively. This is further reflected in a previous trial comparing the serum AMH concentrations among GnRH-agonist and -antagonist cycles, which has shown that although no difference exists in serum AMH values between agonist and antagonist-treated women, the number of oocytes retrieved is significantly higher in the agonist group (Lee et al., 2008).

Another potential explanation for this modest association of AMH with ovarian response in this trial may simply be the age and the fertility background of oocyte donors compared with infertile patients. Given the fact that donors are women of younger age with no specific infertility problems reported, it is likely that these women may have a substantially better ovarian reserve compared with infertile women. Consequently, and given that AMH basically reflects the ovarian reserve pool of the patient, in younger healthy donors AMH may not be such a reliable marker for predicting ovarian response as it is among infertile women. This may be further supported by the fact that, in this dataset, even donors with low AMH values were more likely to experience a normal rather than an impaired response to ovarian stimulation, whereas most AMH values ranged between 1 and 8 ng/ml, values that may be considered normal in most centres. The latter observation suggests that, although AMH may not predict low or excessive response within the range of normal women, it does not exclude the possibility that the test may show a good predictive ability in a more variable population.

Finally, other potential reasons for the poor outcomes may be the sampling timing or the assay itself. In younger women, AMH concentrations may show a substantial (random) variation across the menstrual cycle (Hehenkamp et al., 2006); nevertheless, in general, random fluctuation of AMH concentrations through a full menstrual cycle is extremely small (Hehenkamp et al., 2006; Tsepelidis et al., 2007), while the intra-cycle variation of AMH is even smaller than the intra-cycle variation of AFC (van Disseldorp et al., 2010). In addition, AMH assay may be related to the outcome observed. The current study determined serum AMH using the Immunotech AMH enzyme immunoassay, whereas one of the previous studies used the Diagnostic Systems Laboratories assay (Nakhuda et al., 2010). Given that initial studies comparing the two assays have shown that AMH concentrations measured with the DSL assay were 4–5-fold lower compared with the Immunotech assay (Bersinger et al., 2007; Freour et al., 2007), the lack of difference may be attributed to the assay itself. However, a major advantage of the use of the Immunotech assay is that the new AMH Gen II assay, which will fully replace both assays soon, has been calibrated identically to the old Immunotech assay (Nelson and La Marca, 2011), a fact which makes the current results easier to replicate in the future with the use of the new AMH assay.

A major strength of this study is that it is the first, as far as is known, to assess the value of AMH for the prediction of ovarian response in GnRH-antagonist-treated oocyte donors. This may indeed be very important, considering that the use of GnRH antagonists among oocyte donors is rapidly increasing, due to the fact that treatment with an antagonist protocol and ovulation triggering with a GnRH agonist leads to the elimination of ovarian hyperstimulation syndrome among oocyte donors (Melo et al., 2009a). Furthermore, taking into account the wide age range of oocyte donors enrolled (18–36 years), the facts that the FSH threshold for including oocyte donors was relatively high (15 mIU/ml) and that the number of oocytes retrieved did not significantly differ among patients treated with different starting doses of FSH (150–225 IU), suggest that the likelihood of patients' selection bias may have been considerably reduced.

However, several limitations do exist and need to be highlighted. As women with basal FSH >15 mIU/ml were not included in this cohort of oocyte donors, it is possible that this selection may have added to the lower accuracy of AMH for predicting low ovarian response; however, its effect would have probably been detrimental given that oocyte donors are in general women of younger age without fertility problems. The same concerns may also arise for the fact that the gonadotrophin starting dosage was adapted according to patients' age and BMI (150–225 IU), a policy which may have also flawed the relationship between test and outcome; nevertheless, given that the specific strategy was adopted for the whole subset of patients (irrespective of the presumed ovarian response), it is rather unlikely that this may have influenced the results.

In addition, this study is a retrospective cohort trial with all the limitations that may be related to the retrospective study design. Nonetheless, given that no prospective trial has been published regarding the role of AMH in oocyte donors and that this is the first trial assessing AMH among donors treated with an antagonist protocol, it may be of value for further research in this field. Another caveat is that the impact of AFC on the level of ovarian response was not assessed and there was no attempt to correlate AMH values with AFC. Previous trials have shown that AFC is a marker that can serve as a good predictor for ovarian response among oocyte donors and can improve the selection of oocyte donors for inclusion in an egg donation programme (Melo et al., 2009b). However, given the retrospective design and the fact that ultrasound scans were performed by several different physicians, the current study decided not to include this outcome due to the presence of inter-observer variability which might have seriously biased the results. Finally, there was no attempt to correlate the concentrations of AMH with the final pregnancy outcome among recipients. Although other investigators have done so in previous studies, such an attempt here would have been considerably flawed given the fact that oocytes are partially used for fresh and egg bank donation. As egg

banking for oocyte donation was introduced in the study centre during the observation period, the mixed use of fresh and cryopreserved oocytes and the learning curve associated with vitrification would have limited the evaluation of the relationship between AMH and pregnancy rates (Dessolle et al., 2009).

The implication derived from this trial is that AMH predictive ability may be completely different in GnRH-antagonist-treated donors. Although AMH is associated with ovarian response, it shows a limited predictive ability for low or excessive response to stimulation. As shown by the AUC in ROC curves, the diagnostic accuracy of serum AMH concentrations cannot be considered as a marker that may safely guide the selection process of candidate donors for oocyte donation programmes. Given that among the group of women included, even those with relatively low AMH values (e.g. $<$2.3 ng/ml) had $>$20 oocytes retrieved, whereas others with relatively high values (e.g. $>$5.5 ng/ml) had $<$6 oocytes retrieved, it is rather unlikely that such a test may help to triage women suitable for oocyte donation. Nonetheless, it should be acknowledged that these results are based on retrospective data. Therefore, a future prospective trial is essential. Furthermore, given that the vast majority of the trials assessing AMH among infertile patients undergoing IVF/intracytoplasmic sperm injection included only patients treated with a GnRH-agonist protocol, it would be of interest to investigate whether AMH shows the same high predictive ability in antagonist-treated infertile patients or whether it simply performs worse in the antagonist setting.

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