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An AMH-based FSH dosing algorithm for OHSS risk reduction in first cycle antagonist protocol for IVF/ICSI

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ABSTRACT

The study assessed the impact of an AMH algorithm for FSH dosing in 589 patients to maintain pregnancy rates while minimizing OHSS rates in 1st antagonist cycles for IVF. Patients with low AMH < 12 pmol/L (n = 203) had maximal stimulation with corifollitropin, patients with AMH 12–32 pmol/L (n = 256) had standard stimulation with 150 IU/day of rFSH and patients with AMH > 32 pmol/L (n = 130) had minimal stimulation with 112 IU/day of HP-hMG. The proportion of patients with targeted (5–14) number of oocytes at retrieval was: Low AMH 42%, intermediate AMH 76% and high AMH 67% ($p < 0.001$). Low responses (≤ 4 oocytes) was found in 55%, 16% and 26% ($p < 0.001$) in the low, intermediate and high AMH group, respectively. Excessive responses (≥15 oocytes) was found in 2.5%, 6.2% and 6.1% in the low, intermediate and high AMH groups, respectively. Despite the high proportion of low responses, the ongoing pregnancy rates in the high AMH group was 41% per started cycle. A total of 14 patients had OHSS preventive actions like agonist triggering (n = 12) and/or cryopreservation of all embryos (n = 4) and all avoided OHSS. Three (0.5%) patients were admitted to hospital with severe OHSS, and all occurred after hCG triggering and all cases were late OHSS in relation to pregnancy. All were in the high AMH group after aspiration of 10–15 follicles.

The conclusion is that among high AMH patients, low dose HP-hMG will limit the mean number of oocytes, without compromising pregnancy rates. The OHSS risk will be low, but as long as transfer after hCG triggering is used OHSS will occur unless a cut-off for OHSS preventive actions as low as 10–15 follicles is used.

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Introduction

Ovarian hyperstimulation syndrome (OHSS) is a serious complication to ovarian stimulation for women undergoing IVF treatment [1–3]. The risk is reported to be approximately 3% among women with an expected normal ovarian response and up to 30% in high risk patients [4–6]. The risk of OHSS has been accurately assessed in closely monitored large multicentre trials. Thus, a study including 731 women undergoing IVF in the long agonist protocol using 225 units of FSH per day found an OHSS risk (moderate/severe) of 3% [7]. Another study using an antagonist protocol and stimulation with 150 IU of FSH per day in 749 patients below 35 years, also observed 3% with moderate to severe OHSS [8]. A large randomized study of 1506 patients treated with corifollitropin versus 200 IU rFSH per day in a GnRH antagonist protocol found moderate to severe OHSS in 4.1% and 2.7% for the corifollitropin-alfa and rFSH group, respectively [9]. A number of studies, including recent register data sets from the United States and Sweden, have shown a close correlation between the number of oocytes and the risk of OHSS. The more oocytes the higher the risk [10,11].

The risk of OHSS may be reduced through several approaches. A shift from long agonist protocol to antagonist protocol will reduced the OHSS risk [12]. Additionally, individualized FSH dosing where low FSH doses are given to patients of high risk of OHSS may reduce the risk [13,14] and finally secondary prevention with agonist triggering and cryopreservation of all embryos, may lower the OHSS risk [4]. The rationale for individualized FSH dosing, as phrased by Magnusson et al. [11], is to keep the "balance between efficacy and safety" [14,23].

In order to try to reduce the OHSS risks and maintain pregnancy rates we changed our approach to ovarian stimulation in 2014 and implemented Anti-Müllerian hormone (AMH) as a biomarker for ovarian stimulation [15,16]. This was done by segmenting 1st cycle patients into 3 groups given maximum, standard or low dose of FSH stimulation according to their AMH levels. The purpose was to achieve as constant a number of oocytes as possible, irrespective of

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AMH levels. Our target was to achieve around 10 oocytes, with a range from 5–14. Additionally, we changed to the antagonist protocol and used GnRH agonist triggering for patients with excessive responses. The primary end-points of the present study were 1) the proportion of patients with an optimal response, defined as 5–14 retrieved oocytes and 2) the occurrence of OHSS and OHSS preventive measures in the three AMH groups.

Materials and methods

Study design

This is a prospective cohort study of 589 patients undergoing their 1st treatment cycle in antagonist protocol at the Fertility Clinic, Rigshospitalet, Copenhagen University Hospital from January 2014 to June 2017. All included patients were stimulated according to an AMH-based FSH dosing-algorithm.

During the study period, a total of 888 patients met the inclusion criteria and 589 (66%) were treated according to the AMH-based FSH-dosing algorithm and thus included in the study. A total of 299 patients were not stimulated according to the algorithm primarily due to individual treatment preferences. However, the 299 patients did not differ from the 589 included patients in terms of age, AMH, antral follicle count (AFC), BMI and indication for treatment.

AMH-based FSH-dosing algorithm

Patients with low AMH < 12 pmol/L were stimulated with a weight-adjusted dose of Elonva® according to labelling: women >60 kg received 150 μg and women <60 kg received 100 μg. Patients with an intermediate AMH 12–32 pmol/L received standard stimulation with rFSH (Follitropin-alfa or -beta) 150 IU/day, and patients with high AMH > 32 pmol/L were stimulated with Menopur® (HP-hMG) 112 IU/day. The FSH dose was fixed the first seven days of stimulation. After seven days of stimulation, the FSH dose could be adjusted based on sonographic assessment. The standard criteria of at least 3 follicles ≥17 mm was used for triggering of ovulation with 6500 IU of Ovitrelle. Triggering with the GnRH agonist Suprefact® 0,5 mg was used in cases with excessive response having a high risk of OHSS. No specific cut-off in terms of an expected number of oocytes was applied, but, as a guide, agonist-triggering was used if there were >25 follicles >12 mm. Oocyte retrieval was done 36 h after hCG or GnRH agonist administration, and transfer was done at day 2 or day 5. Patients who were triggered with a GnRH agonist additionally received 1500 IU hCG at the day of oocyte retrieval except in four cases where it was clinically indicated to perform cryopreservation of all embryos/blastocysts. Luteal support was given using vaginal progesterone Lutinus® 100 mg 3 times daily for 2 weeks. Lutinus® OHSS was classified according to the NICE accredited OHSS guideline from The Royal College of Obstetricians and Gynaecologists (RCOG) [21]. All patients with OHSS requiring clinic attention were examined and treated by the 1st author.

AMH analysis

Until June the 1st 2015, serum AMH was measured using the Immunotech RIA AMH/MIS kit. After June the 1st, 2015, the fully automated AMH Assay (Elecsys,) was used. AMH analyses were performed using the Immunotech assay in 216 patients and the Elecsys assay in 373 patients. We have previously analysed over 400 samples with both assays and found a conversion factor of 0.8 i.e. AMH values measured with Elecsys were 0.8 of the value obtained with Immunotech. Therefore, the cut off level between low, intermediate and high AMH in the first 216 patients included until June the 1st 2015 were 15 and 40 pmol/L whereas the cut off were 12 and 32 pmol/L in the 373 patients included after June the 1st 2015. Values are expressed as measured by the Elecsys assay.

Statistical analysis

All data were prospectively collected and recorded in an SSPS version 22 and STATA 13.1. Data was presented as number (percentage) for categorical data; mean ± standard deviation (SD) for normally distributed data; and median (interquartile range (IQR) or range as specified) for non-normally distributed data. Analyses were performed using the nonparametric independent-samples Kruskal-Wallis test for non-normally distributed continuous variables and one-way ANOVA for normally distributed continuous variables. The Chi-square test or Fisher's exact test was used when analyzing categorical variables. Linear regression analysis was used when estimating the relationship between continuous variables and logistic regression applied for binary outcome variable. Age was categorized as follows: 20–29, 30–34, and 35–40 years; and age groups used in the age-adjusted analyses.

The study was approved by the Danish Patient Safety Authority (Number 3-3013-2242/1).

Results

Baseline characteristics of the 589 patients are shown in Table 1. As seen, 203 (34.5%) were in the low AMH group, 256 (43.5%) in the intermediate and 130 (22.0%) in the high AMH group. Median (interquartile range) AMH in the three AMH groups was 6.0 (4.0–8.6), 20.0 (16.0–24.8), and 48.0 (40.8–62.4) pmol/L ($p < 0.001$).

Ovarian responses

The median number (IQR) of aspirated oocytes was 8 [4–10] in women aged <30 years (n = 123); 7 [5–11] in women aged 30–34 years (n = 223); and 5 [3–8] in women aged ≥35 years (n = 235) There was no significant difference in the number of aspirated oocytes in women aged <30 years versus women aged 30–34 years ($p = 0.9$), but women aged ≥35 years had a significantly lower number of oocytes aspirated($p < 0.001$). In women receiving maximal and intermediate simulation, the ovarian response was associated with both serum-AMH (Coefficient: 0.44, 95% CI: 0.44, CI: 0.29;0.58 and 0.13, CI: 0.04;0.22) and female age (-0.18, CI: -0.29; -0.07 and -0.15, CI: -0.27; -0.04). To the contrary, the ovarian response was independent of both AMH ($p = 0.5$) and age ($p = 0.8$) in women receiving minimal stimulation. However, the chance of the defined optimal response was independent of age irrespective of the stimulation protocol (maximal $p = 0.053$; intermediate $p = 0.2$; and minimal stimulation $p = 0.5$). Only in women receiving maximal stimulation did AMH affect the chance of an optimal response (1.3, CI: 1.2;1.5, $p < 0.001$).

Table 2 shows response parameters and clinical outcome in the three AMH groups. The targeted number of 5–14 oocytes was achieved in 76%, 42% and 67% in the intermediate, low and high AMH group. In the unadjusted analysis, the chance of achieving the 5–14 oocytes was significantly reduced in women with low (OR 0.21, 95% CI: 0.14;0.32, $p < 0.001$) as well as high AMH (OR 0.61, 95% CI: 0.38;0.97, $p = 0.04$) compared with women with intermediate AMH. In the multivariate analyses adjusted for BMI and age, a significant interaction between AMH and age group was observed. In women aged <30 years, high AMH was associated with a reduced chance of an optimal response (aOR: 0.27, CI: 0.11;0.64, $p = 0.003$), whereas low AMH was not (aOR: 0.47, CI: 0.14; 1.51, $p = 0.20$). In women aged ≥30 years, low AMH was associated with a reduced chance of an optimal response (aOR: 0.20, CI: 0.13; 0.32,

Table 1
Baseline characteristics of 589 patients treated with an AMH based stimulation algorithm in their first IVF/ICSI cycle.

Serum AMH (pmol/L) groups	<12 Elonva 100/150 μg	12-32 rFSH 150 IU	>32 Menopur 112.5 IU	All	P- value
Hormone stimulation					
Number of patients, n (%)	203 (34.5)	256(43.5)	130 (22.0)	589 (100)	
Age (Years) mean ± SD	35.2 ± 3.6	32.2 ± 4.2	31.5 ± 3.9	33.1 ± 4.2	0.000
AMH (Anti-Müllerian horm.) median (IQR)	6.0 (4.0 – 8.6)	20.0 (16.0 – 24.8)	48.0 (40.8 – 62.4)	18.0 (8.1 – 28.8)	0.001
AFC (Antral follicle count) mean ± SD	7.9 ± 3.9	19.8 ± 6.3	41.4 ± 12.3	23.1 ± 7.5	0.000
Weight (kg) mean ± SD	66.6 ± 12.5	64.8 ± 10.4	61.7 ± 8.2	64.4 ± 10.4	0.003
BMI (kg/m^2) mean ± SD	23.5 ± 3.9	23.3 ± 3.4	22.3 ± 2.6	23.2 ± 3.5	0.006
Causes of infertility					
Anovulation, n (%)	2 (0.9)	7 (2.7)	51 (39.2)	60 (10.2)	
Tubal factor, n (%)	10 (4.9)	15 (5.9)	4 (3.0)	29 (4.9)	
Uterine factor, n (%)	6 (3.0)	5 (1.9)	2 (1.6)	13 (2.2)	
Endometriosis, n (%)	16 (7.9)	10 (3.9)	2 (1.6)	28 (4.7)	
Single women, n (%)	33 (16.3)	25 (9.8)	8 (6.2)	66 (11.2)	
Male factor, n (%)	74 (36.5)	127 (49.6)	48 (36.9)	249 (42.3)	
Unexplained, n (%)	62 (30.5)	67 (26.2)	15 (11.5)	144 (24.5)	

Data are described with means and standard deviation or median (interquartile range (IQR). Kruskal-Wallis test; one-way ANOVA A *p-value* < 0.05 was considered statistically significant.

Table 2
Cycle characteristics and outcome in relation to the AMH-based FSH stimulation algorithm.

Serum-AMH, groups Hormonstimulation	<12 Elonva 100/150 μg	12-32 rFSH 150 IU	>32 Menopur 112.5 IU	all	P-value
Patients, n (%)	203(34.5)	256(43.5)	130 (22.0)	589	
Stimulation duration (days) mean±SD	8.5±1,7	8.5±1.3	9.6±2.2	8.8±1.7	0.3
hCG triggering, n (%)	203(100.0)	251(98.0)	123(94.6)	577(98.0)	
GnRH triggering, n (%)	0(0)	5(2.0)	7(5.4)	12(2.0)	
Cycles converted to IUI, n (%)	3(1.5)	4(1.6)	1(0.8)	8(1.4)	0.9
Number of follicles aspirated, median (IQR)	5.9±4.9	9.7±4.2	9.6±5.2	8.4±4.5	0.000
Number of retrieved oocytes, median (IQR)	4.0 (3.0-6.0)	8.0 (5.0-11.0)	7.0 (4.0-10.0)	6.0 (4.0-10.0)	0.001
Oocyte retrievals, patients, n, (%)	200(98.5)	252(98.4)	129(99.2)	581(98.7)	0.9
Number of patients with oocytes, n ≤4 (%)	110(55.0)	41(16.0)	34(26.2)	185(31.5)	0.001
Number of patients with oocytes, n 5 – 14 (%)	85(41.8)	195(76.2)	87(66.9)	367(62.3)	0.001
Number of patients with oocytes, n 15 – 20 (%)	4(2.0)	13(5.0)	6(4.6)	23(3.9)	0.14
Number of patients with oocytes, n >20 (%)	1(0.5)	3(1.2)	2(1.5)	6(1.0)	0.63
Embryo transfer, n (% of oocyte retrievals)	148(74.0)	218(86.1)	105(81.4)	470(80.9)	0.005
Dual transfers, n (%)	22(10.8)	15(5.9)	6(4.6)	43(7.3)	
Embryos cryopreserved, mean ± SD (range)	0.3±0.4	0.4±0.5	0.4±0.5	0.4±0.5	
Positive hCG, n (% of started cycles)	48(23.7)	94(36.7)	61(46.9)	203(34.5)	0.001
Positive hCG, n (% of transfer)	48(32.4)	94(43.3)	61(58.1)	203(443.2)	0.001
Ongoing pregnancies, n (% of started cycles)	28(13.8)	65(25.4)	53(40.8)	146(24.8)	0.001
Ongoing pregnancies, n (% of transfer)	28(18.9)	65(30.0)	53(50.5)	146(31.1)	0.001
Twins, n (% ongoing pregnancies)	3(1.5)	0(0.0)	0(0.0)	3(0.5)	
GnRH, Freeze all, HCG and OHSS					
GnRH-triggering to prevent OHSS, n (%)	0(0)	1(0.4)	7(5.4)	8(1.4)	
GnRH-triggering and freeze-all to prevent OHSS, n (%)	0(0)	4(1.6)	0(0)	4(0.7)	
HCG-triggering and freeze-all to prevent OHSS, n (%)	0(0)	0(0)	2(1.5)	2(0.3)	
HCG-triggering and OHSS, n (%)	0(0)	0(0)	3(2.3)	3(0.5)	
Preventive measures or OHSS (total), n (%)	0(0)	5(2.0)	12(9.2)	17(2.9)	

1) Statistics, comment in text.
2) Data are described with means and standard deviation or median (interquartile range (IQR)). Fisher 's exact test, Chi-square test, Kruskal-Wallis test one-way ANOVA.

$p < 0.001$), while high AMH was not (aOR: 0.79, CI: 0.44; 1.43, $p = 0.44$).

An excessive response, defined as ≥15 retrieved oocytes, occurred in 2.5%, 6.4% and 6.2% in the low, intermediate and high AMH groups, respectively. There was no significant difference in the risk of having an excessive response across the three AMH groups neither in the unadjusted nor in the adjusted logistic regression analysis.

In the unadjusted analyses, both low and high AMH were associated with an increased risk of having ≤4 oocytes retrieved, but again a significant interaction with age was observed. Women aged <30 with a high AMH were more likely to have a low response than women of the same age with an intermediate AMH (aOR: 4.30, CI: 1.69;10.9), whereas low AMH (aOR: 1.54, CI: 0.41;5.87) was not associated with of a low response in this age group. In women aged ≥30, low AMH (aOR: 7.30, CI: 4.45;11.96) was an independent predictor of low response, whereas high AMH was not (aOR: 1.35, CI: 0.70; 2.64).

Pregnancies

The ongoing pregnancy rates per started cycle in the three AMH groups were 13.8%, 25.4% and 40.8% respectively ($p < 0.001$). The chance of achieving an ongoing pregnancy was reduced in women with low AMH irrespective of her age group (age-adjusted OR: 0.55, CI: 0.33;0.93, $p = 0.024$), whereas high AMH was associated

with an increased chance of achieving an ongoing pregnancy (age-adjusted OR: 1.97, CI: 1.25;3.10, p = 0.003). High AMH remained an independent predictor of an ongoing pregnancy after adjustment for age group, BMI, and number of retrieved oocytes (aOR: 2.17, CI: 1.36;3.45, p = 0.001) whereas low AMH was not (aOR: 0.67, CI: 0.39;1.14, p = 0.14).

Ohss

Table 3 shows detailed individual data of the 17 patients out of the 589 (2.9%) who had either OHSS (n = 3) or preventive actions (n = 14) towards OHSS such as GnRH agonist triggering and cryopreservation of all embryos. Among the 17 patients, Table 3 also shows that the 5 patients in the 12–32 AMH group had 13–30 follicles aspirated and 12–28 eggs were retrieved. In 4 of these 5 cases freeze all was done. None of the 5 patients developed early OHSS. The remaining 12 patients all had AMH > 32, between 10 and 32 follicles were aspirated and 8–29 eggs retrieved. The three cases of clinically significant OHSS all came from this group. They had 12–15 follicles before triggering All had received triggering with hCG, had 10–15 follicles aspirated and 9–13 eggs retrieved. All three got pregnant and all 3 were hospitalized. Two had ascites drainage.

Discussion

The basis for our use of the AMH based FSH dosing algorithm for individualization was to “up-dose” patients predicted to have a low response and “down-dose” those predicted to be at risk for excessive responses. The response to ovarian stimulation was associated with age in women with similar AMH receiving maximal and intermediate stimulation, respectively. However, in women receiving minimal stimulation, the response was unaffected by increasing age. Furthermore, the chance of an optimal response was independent of the age-increase in women with similar AMH in all stimulation protocols. This indicate that the individualized approach based on AMH eliminate the age-dependent response to some extent. The highest proportion that responded “on target” was in the intermediate 12–32 pmol/L AMH range where 76% of the patients had 5–14 eggs. This is consistent with the recent large study, using AMH and body weight as a response predictor [14] showing that patients with an AMH around 20–30 pmol/L is the group that most often achieve the targeted number of oocytes. For this group of patients, the recommended standard dose of rFSH 150 [22] indeed seems appropriate.

In terms of avoiding excessive responses in the high-risk patients, use of low-dose hMG stimulation in antagonist cycles provided a mean of 7 oocytes, only 6.1% developed an excessive (≥15 eggs) response and the ongoing singleton pregnancy rate per started cycle of 41% was good. Combined, these data indicate an efficient and safe stimulation for patients with high AMH, but it is noteworthy that despite the overall modest responses all three cases with severe OHSS were found in the high AMH group, despite the mild stimulation and use of Menopur instead of rFSH. Menopur is known to give less eggs compared to recombinant FSH [8] and may have a better benefit/risk ratio compared to rFSH in patients at high risk of OHSS [23]. Additionally, compared to the long agonist protocol, the antagonist protocol gives less eggs and reduce the OHSS risk to around half [24]. The main concern with the low dose approach is that further lowering in high AMH patients is likely to give an unacceptable high proportion of subnormal responses. In the present study (Table 2) 26% of the high AMH patients already had a subnormal (≤ 4 eggs) response. In patients with a risk of being hyper responders based on their AFC, dosing with 100 IU/day of rFSH also caused a similar proportion of patients with subnormal responses [29].

However, in women aged <30, high AMH was in fact associated with an increased risk of a poor response indicating that the algorithm could have compromised the pregnancy chance in some individuals’ due to a too cautious stimulation. Defining the optimal low dose of FSH for presumed hyperresponders therefore remains a challenge, but based on our study and the OPTIMIST trial [29], doses ranging between 125–137.5 IU/day may be better choices.

We used corifollitropin to maximize the FSH dose and thus the response in “low-AMH patients”. The rationale for this is that corifollitriopin is equivalent to around 300 IU of rFSH and this is believed to represent maximal stimulation. In the present study none of the corifollitropin stimulated 1st cycle patients developed OHSS or needed any interventions to avoid this. In contrast among unselected patients around 4% will develop moderate to severe OHSS after treatment with corifollitropin [30].

Individual hormone stimulation based on several parameters may also be used to optimize ovarian response [25]. In the PIVET algorithm the dose of FSH administration was based on several parameters in terms of day-2 FSH, AMH, AFC, BMI, age and smoking. Indeed, the purpose of the PIVET algorithm was similar to

Table 3
Baseline and cycle characteristics in 17 patients out of 589 started cycles in relation to ovarian hyperstimulation syndrome (OHSS), GnRH agonist triggering and Freeze-all to prevent OHSS.

Patients[a], n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
AMH 12-32													+	+	+	+	+
AMH>32	+	+	+	+	+	+	+	+	+	+	+	+					
Age (years)	**30**	**37**	**30**	**31**	**33**	**35**	**27**	**37**	**27**	**27**	**27**	**29**	**29**	**27**	**32**	**27**	**30**
Weight	**81**	**48**	**58**	**57**	**61**	**63**	**52**	**67**	**53**	**50**	**61**	**58**	**72**	**52**	**54**	**63**	**73**
BMI	**27**	**19**	**20**	**22**	**20**	**23**	**19**	**23**	**20**	**18**	**22**	**23**	**22**	**20**	**21**	**23**	**24**
AMH-pmol/L	**82**	**78**	**120**	**199**	**80**	**77**	**42**	**39**	**34**	**83**	**62**	**42**	**28**	**27**	**26**	**22**	**24**
AFC	**50**	**40**	**60**	**50**	**80**	**60**	**25**	**34**	**24**	**55**	**60**	**22**	**25**	**23**	**40**	**20**	**30**
Stim. days	**11**	**9**	**8**	**7**	**8**	**7**	**15**	**9**	**16**	**7**	**14**	**9**	**11**	**10**	**9**	**8**	**9**
hCG-trigg.	+	+					+	+	+								
GnRH-trigg.			+	+	+	+				+	+	+	+	+	+	+	+
Follic. ≥12 mm	**21**	**24**	**25**	**28**	**35**	**26**	**15**	**12**	**13**	**27**	**27**	**26**	**27**	**28**	**29**	**31**	**30**
Follicl. ASP	**20**	**24**	**12**	**25**	**32**	**20**	**15**	**12**	**10**	**20**	**15**	**12**	**13**	**25**	**20**	**30**	**24**
Oocytes	**16**	**23**	**8**	**10**	**29**	**13**	**13**	**9**	**10**	**16**	**12**	**10**	**12**	**19**	**15**	**28**	**21**
Transfer			+	+	+	+	+	+	+	+	+	+					+
Freeze all	+	+											+	+	+	+	
Positive hCG				_	+	+	+	+	+	_	_	+					+
Ongoing. preg.					+	+	+	+	+			+					+
Severe, OHSS							+	+	+								

Statistics, see comments in the text.
[a] Patients, in total 17.

our AMH based algorithm, both aiming to minimize the risk of OHSS, without reducing the pregnancy rates [26–28]. Our algorithm has the advantage that it is based on a single parameter that may facilitate the use by clinicians in practice.

Despite the individualized stimulation, a total of 14 patients had preventive actions taken to avoid OHSS, and three (0.5%) patients were admitted to hospital with severe OHSS. All three OHSS cases occurred after hCG triggering, all were late OHSS in relation to pregnancy and all occurred in the high AMH group.

We used agonist triggering in a total of 12 patients, but not to those 3 that finally developed OHSS. Indeed those 3 cases had only 10, 12 and 15 follicles aspirated, so agonist triggering was not considered indicated and used by the clinicians. Our conclusion is that among high AMH patient, a low dose of HP-hMG will keep the OHSS risk low, the pregnancy rates will be good, but as long as hCG triggering is used, OHSS will occur. If the three cases of OHSS in the present study should have been prevented, agonist triggering and/or freeze all should have been done in all cases with more than 10 follicles. Therefore, even if we had used the OHSS predictive cut-offs of 19 follicles or more $\geq$11 mm on the day of hCG suggested by Geisinger et al study [31], we would not have prevented OHSS in these 3 cases. According to the study by Tarlatzi et al, we might have avoided an OHSS of the three patients as one of them had 15 follicles [32].

In conclusion, our findings suggest that an AMH-algorithm can be used to select the starting dose of FSH and it allows appropriate stimulation with low risk of OHSS, but OHSS will occur in hCG exposed cycles.

Disclosure statement

No potential conflict of interest was reported by the authors.

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