Ovarian hyperstimulation syndrome: an analysis of patient characteristics in the Asian population

Rajesh H, Lee W Y, Fook-Chong S, Yu S L

ABSTRACT

Introduction: We aimed to identify the variables associated with ovarian hyperstimulation in Asian patients and compare them with western standards.

Methods: This is a retrospective case record analysis of 79 patients with ovarian hyperstimulation at a tertiary restructured hospital.

Results: Gonadotropin doses resulting in hyperstimulation did not vary between long and antagonist cycles in women less than 35 years with polycystic ovaries (PCO). Mean oestradiol levels at hyperstimulation were not different between PCO and non-PCO patients in a long cycle. Hyperstimulation was mostly due to higher starting doses. Total follicle counts of more than 20 on Day 5–7 after stimulation may be predictive of subsequent hyperstimulation. Hyperstimulation tended to be more severe in lean PCO patients, and prophylactic albumin helped to reduce its severity.

Conclusion: Gonadotropin doses at stimulation should start at 150 iu or less in women below 35 years of age, with a step up of 37.5 iu, as necessary. Transfer should be abandoned in the presence of high oestradiol levels (more than 5,000 pg/ml), when the total number of intermediate and large follicle count exceeds 30 on the day of oocyte retrieval, or when more than 19 eggs are retrieved. Variables in the Asian population appear to be similar to those in the western population.

Keywords: oestradiol level, follicle count, gonadotropin dose, *in vitro* fertilisation, ovarian hyperstimulation syndrome

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INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is a combination of ovarian enlargement due to multiple ovarian cysts and an acute fluid shift out of intravascular space. The pathophysiology is not clearly understood, but it is thought to be due to cytokines and vascular endothelial growth factor triggered by human chorionic gonadotropin (hCG). This may result in haemoconcentration and third-space accumulation of fluid, leading to complications such as thromboembolic episodes, hypovolaemic shock, renal failure, acute respiratory distress syndrome and death. Early OHSS is associated with an excessive ovarian response to gonadotropin stimulation, whereas late onset is a result of endogenously produced hCG from an implanting pregnancy.[1]

Polycystic ovarian syndrome patients, younger age and women with a lower body mass index (BMI) seem to be at a higher risk of developing OHSS. The oestradiol cut-off level to prevent OHSS is thought to be 4,000–4,500 pg/ml.[2,3] Various studies have suggested that more than 15–20 follicles at oocyte retrieval is associated with OHSS.[1,2,4] Prediction of ovarian hyperstimulation has been derived predominantly from the western literature. Although the characteristics may be similar in the Asian population, this has not been sufficiently analysed. The aim of our study was to identify the variables associated with ovarian hyperstimulation in our patient profile and to develop preventive strategies.

METHODS

This was a retrospective case analysis of patients who developed moderate or severe OHSS during *in vitro* fertilisation (IVF) at the Centre for Assisted Reproduction (CARE) at Singapore General Hospital. A total of 79 patients were identified over a period of five years (2002–2007) and their case records were retrieved. Patient characteristics (age, BMI), ultrasonographic features of polycystic ovary (PCO) or non-polycystic ovary (NPCO), antral follicle count, intermediate follicle count, oestradiol level on decision day, gonadotropin dose and pregnancy outcomes if a fresh transfer was attempted were analysed. Analysis was done using the Statistical Package for the Social Sciences (SPSS Inc, Chicago, IL, USA). Comparison between groups

Department of Obstetrics and Gynaecology, Singapore General Hospital, Outram Road, Singapore 169608

Rajesh H, MBBS, MRCOG
Consultant

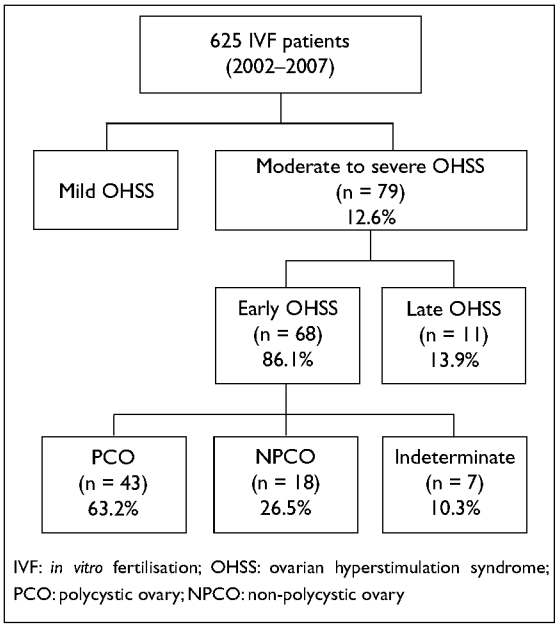
Lee WY, MD
Medical Officer

Yu SL, MBBS, MMed, FRCOG
Senior Consultant

Department of Clinical Research

Fook-Chong S, BSc MSc, CStat
Senior Biostatistician

Correspondence to:
Dr Hemashree Rajesh
Tel: (65) 8123 1053
Fax: (65) 6225 3464
Email: hemashree rajesh@yahoo.com



IVF: *in vitro* fertilisation; OHSS: ovarian hyperstimulation syndrome; PCO: polycystic ovary; NPCO: non-polycystic ovary

Fig. 1 Chart shows the distribution of patients.

was done using the Mann-Whitney test for continuous variables and chi-square test for categorical variables. Pearson's correlation coefficient was reported as a measure of correlation between the number of large follicles and oestradiol.

Ovarian hyperstimulation was classified according to Golan's classification.[5] In our setting, moderate hyperstimulation is managed on an outpatient basis, while severe hyperstimulation patients are admitted for treatment. Patients were further subdivided into those with early-onset hyperstimulation (symptomatic at 0–9 days) and late-onset (after the initial nine-day period) hyperstimulation. Patients with long cycle and antagonist cycles were included. Depending on the patient characteristics (e.g. weight, presence of PCO), follicle-stimulating hormone (FSH) levels on Day 2, ovarian volume and antral follicle count, a team of IVF specialists decided on the final dose and the best cycle (long vs. antagonist) for each patient at a weekly meeting. Follicular count was evaluated using ultrasonography (US) between Day 5 and 7 after gonadotropin stimulation. In cases of poor recruitment, the individual clinician would increase the gonadotropin dose. An increase of 37.5 iu was considered appropriate, while any further increase was documented to be too high. In patients in whom there was substantial recruitment, the clinician was at liberty to lower the dose. The sum of gonadotropin dose averaged over the days of stimulation was considered as the net average dose administered to the individual per day.

Table I. Mean dose of gonadotropin among polycystic ovary patients (n = 43).

Age (yrs)	Mean gonadotropin dose ± SD (iu)		p-value
	Long cycle	Antagonist cycle	
< 35 (n = 37)	204.2 ± 66.2[a]	168.3 ± 74.8[b]	0.134
> 35 (n = 6)	285.0 ± 33.5[c]	300.0[d]	1.000

[a] n = 28, [b] n = 9, [c] n = 5, [d] n = 1
SD: standard deviation

A subsequent follicular count was performed on the day when hCG was administered to facilitate oocyte retrieval. All measured follicles were classified as small (< 8 mm), intermediate (≥ 8 to < 14 mm) and large (≥ 14 mm) according to their size. Based on the Rotterdam criteria, US was used to determine the polycystic nature of the ovaries. The ovaries were classified as indeterminate in some individuals who had a US done prior to 2003 and where the number of follicles could not be counted clearly. Oestradiol level was measured on the day a decision was made to administer hCG, which could be the same day as hCG administration or 1–2 days earlier.

RESULTS

We performed 625 IVF cycles between 2002 to 2007. A total of 79 patients with moderate to severe OHSS were analysed. Among this group of patients, 68 patients had early OHSS, which accounted for an incidence of 10.9% (68/625). This also included nine patients who had prophylactic albumin anticipating OHSS (and thereafter were asymptomatic) and two who had prophylactic albumin with no further records at our hospital. Taking into account these patients, the actual incidence of patients with early OHSS was 9.1%. About one-third of PCO and NPCO patients had severe OHSS. Severe OHSS presented significantly later than moderate ovarian hyperstimulation after oocyte retrieval (severe 3.82 days, moderate 2.25 days, p = 0.004). The median duration of admission for severe OHSS was four days. 63% of the 79 patients with moderate to severe OHSS were Chinese, while the remaining were a mixture of other Asian nationalities (Malay, Indian and Eurasian). 68 (86.1%) of the 79 patients had early OHSS (0–9 days after hCG administration). Among the early OHSS patients, 43 (63.2%) were diagnosed with PCO on US, 18 (26.5%) with NPCO and seven (10.3%) were indeterminate (Fig. 1). There was no significant difference in the mean dose of gonadotropin associated with hyperstimulation in patients with or without PCO (208.3 ± 72.4 iu vs. 232.2 ± 65.4 iu, p = 0.182).

Table II. Mean estradiol levels associated with early ovarian hyperstimulation syndrome among PCO and NPCO patients.

Diagnosis	Mean estradiol level ± SD (pg/ml)†	p-value
PCO		0.45
Long cycle (n = 33)	*6,009 ± 2,651	
Antagonist cycle (n = 10)	4,834 ± 1,854	
NPCO		0.889
Long cycle (n = 17)	*5,391 ± 2,857	
Antagonist cycle (n = 1)	4,109	

* p = 0.25 when comparing long cycle between PCO and NPCO.
†1 pg/ml = 3.671 pmol/L
SD: standard deviation; PCO: polycystic ovary; NPCO: non-polycystic ovary

Table III. Degree of hyperstimulation between patients with PCO and NPCO.

Degree of hyperstimulation	No. of patients (%)		
	PCO (n = 43)	NPCO (n = 18)	Total (n = 61)
Moderate	26 (60.5)	13 (72.2)	39 (63.9)
Severe	16 (37.2)	5 (27.8)	21 (34.4)
Unknown	1 (2.3)	-	1 (1.6)

PCO: polycystic ovary; NPCO: non-polycystic ovary

Among patients with PCO age < 35 years, the average gonadotropin dose associated with hyperstimulation in a long cycle was higher than that associated with an antagonist cycle, athough it was not statistically significant (204.2 ± 66.2 iu vs. 168.3 ± 74.8 iu, p = 0.134). The doses were comparable among PCO patients age > 35 years (285.0 ± 33.5 iu vs. 300.0 iu, p = 1.000) (Table I).

We aimed to have a standard dose or a step-up regime in the cycle. 50% of the 68 patients with early OHSS did not have any change initiated in the starting dose. 22.1% of the patients had an initial high starting dose, which was decreased in the cycle. In 23.5% of patients, the dose was stepped up by 50 iu in the cycle, resulting in hyperstimulation, while 2.9% of patients had their dose increased by 37.5 iu, which resulted in hyperstimulation. Only one (1.5%) patient was coasted. The mean oestradiol levels at hyperstimulation in patients with a long cycle were comparable in patients with PCO and NPCO (6,009 ± 2,651 pg/ml vs. 5,391 ± 2,857 pg/ml, p = 0.25). Among patients with PCO, there was no significant difference in the mean oestradiol levels associated with hyperstimulation in a long cycle compared to an antagonist cycle (6,009 ± 2,651 pg/ml vs. 4,834 ± 1,854 pg/ml, p = 0.45) (Table II). There was no statistically significant difference in the degree of hyperstimulation between PCO and NPCO patients (p = 0.600). Severe hyperstimulation occurred in 37.2% of patients with PCO and 27.8% of patients with NPCO, while the figures for the moderate group were 60.5% and 72.2%, respectively (Table III).

A significantly higher number of active follicles on US monitoring between Day 5 and Day 7 of the cycle and a higher number of mature follicles in patients with PCO were observed. The total number of follicles on Day 7 US, which was characteristic of OHSS, was significantly higher in PCO patients than NPCO patients (28.6 ± 9.1 vs. 20.3 ± 8.0, p = 0.001). Follicles that were already recruited (> 8 mm) on Day 7 US were not significantly different in the two groups (11.5 ± 7.4 vs. 10.0 ± 5.5, p = 0.579). The indeterminate group was excluded from this analysis. At peak stimulation, a significantly higher average number of large follicles (> 14 mm) was noted in PCO patients compared to NPCO patients (17.6 ± 6.5 vs. 13.0 ± 4.24, p = 0.010). There was a trend toward significantly higher number of intermediate follicles in PCO patients compared to NPCO patients (15.1 ± 6.0 vs. 12.3 ± 7.9, p = 0.079). There was no significant difference in the number of small follicles (< 8 mm) between the two groups (3.6 ± 5.1 vs. 3.1 ± 2.59, p = 0.791). The average number of small, intermediate and large follicles was not associated with the grade of OHSS (p = 0.934, 0.754 and 0.437, respectively).

A positive correlation was noted between the number of large follicles and oestradiol (r = 0.517) (Fig. 2). No correlation was observed between the number of small and intermediate follicles and oestradiol. Out of the 43 PCO patients in our study, the BMI of only 35 patients were recorded. There was no significant difference in BMI or severity of hyperstimulation between PCO and NPCO patients. 40% of patients with PCO had a BMI > 23 compared to only 14.3% of those with a BMI < 19. However, there was a trend toward a more severe degree of hyperstimulation in PCO patients with a lower BMI compared to those with a higher BMI. Severe hyperstimulation in those with BMI < 19 was 60%, BMI 19.1–23 was 50% and BMI > 23 was 21.4%. (p = 0.076) (Table IV).

Out of the 61 PCO and NPCO patients who had OHSS, 51 (83.6%) were aged ≤ 35 years and 10 (16.4%) were aged ≥ 36 years. A reduction in the severity of hyperstimulation was observed when prophylactic albumin was administered. 26.2% of patients who

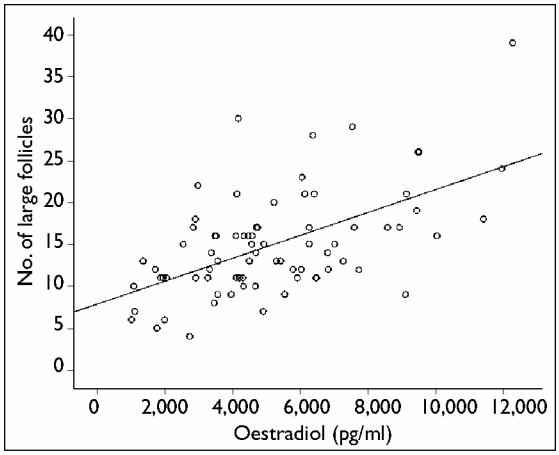


Fig. 2 Graph shows the correlation between the number of large follicles and oestradiol.

Table IV. Degree of hyperstimulation in different BMI groups among PCO patients.

Degree of hyperstimulation	No. of patients (%)			Total
	BMI < 19	BMI 19.1–23	BMI > 23.1	
Moderate	2 (40.0)	8 (50.0)	11 (78.6%)	21
Severe	3 (60.0)	8 (50.0)	3 (21.4%)	14
Total	5	16	14	35

BMI: body mass index; PCO: polycystic ovary

Table V. Severity of OHSS among patients who received albumin and those who did not.

Type of OHSS	No. of patients (%)		
	Albumin	No albumin	Total
Moderate	31 (73.8)	13 (54.2)	44 (66.7)
Severe	11 (26.2)	11 (45.8)	22 (33.3)
Total	42	24	66

OHSS: ovarian hyperstimulation syndrome

received prophylactic albumin had severe OHSS compared to 45.8% of patients who did not receive albumin (p = 0.103) (Table V).

43 patients had an embryo transfer, as they were thought to be suitable and OHSS was not anticipated. Embryo transfer was also performed in 16 patients who were given albumin prophylactically, but they were subsequently found to be well. There was a 25% incidence of pregnancy, the majority of which occurred in patients who subsequently had OHSS compared to those who did not (29.6% vs. 18.8%). 23.5% of these patients had luteal phase hCG supplementation. The hCG probably contributed to the aggravation of symptoms and resulted in symptoms of hyperstimulation in these patients, contributing to an increased OHSS rate. 90% of patients who presented with OHSS later than nine days became pregnant. 50% of these patients had twins, which contributed to the OHSS.

DISCUSSION

OHSS may lead to complications such as hypovolaemic shock, thromboembolism, hepatorenal failure, acute respiratory distress syndrome and death. These are iatrogenic complications of a non-vital treatment and can be detrimental. It is therefore important to identify the causes and risk factors associated with OHSS in order to minimise its risk. OHSS may be classified as demonstrated in Table VI.[5]

An analysis of several large series encompassing 11,342 treatment cycles showed that the incidence of moderate and severe OHSS was 3.4% and 0.8%, respectively.[6] Delvigne and Rozenberg reported an incidence of 0.5%–5% for severe OHSS.[7] The pregnancy rate in hyperstimulated cycles was threefold higher than that in non-hyperstimulated cycles. Mild OHSS does appear to be beneficial in improving pregnancy rates.[8] However, severe hyperstimulation worsens pregnancy outcome in addition to the various complications mentioned earlier, with a higher rate of multiple gestation, miscarriage, low birth weight, prematurity, pregnancy-induced hypertension, gestational diabetes mellitus and placenta abruption.[9] In our study, we analysed patients with moderate to severe OHSS in order to determine the risk factors and minimise adverse outcomes in this group. Factors that should be considered include gonadotropin doses, high serum oestradiol concentrations immediately prior to hCG administration, US findings of polycystic ovary morphology, follicle count, BMI and age.

Administration of gonadotropin according to an individually adjusted regimen is associated with lower risk of OHSS. The average dose of gonadotropin associated with hyperstimulation in a long cycle and antagonist cycle was comparable (204 iu vs. 168 iu). 50% of the patients with early OHSS from our group received the same dose throughout, while 23.5% had their low dose increased by 50 iu, 22.1% had high starting dose and 2.9% had their low dose increased by 37.5 iu. We suggest increasing gonadotropin by 37.5 iu instead of 50 iu in patients at high risk of ovarian hyperstimulation. Oestradiol is a useful parameter for monitoring gonadotropin cycles, as it reflects the size of the granulosa or luteal cell mass. The absolute safe limit of oestradiol levels for hCG trigger is still not clear. Haning et al study suggested that hCG may be given as long as oestradiol is < 4,000 pg/ml.[3]

Table VI. Classification of OHSS.

Severity	Grade	Clinical features
Mild	1	Abdominal distention causing discomfort
	2	Grade 1 disease plus gastrointestinal symptoms (nausea, vomiting or diarrhoea) and ovarian enlargement from 5–12 cm
Moderate	3	Features of mild OHSS plus ascites
Severe	4	Features of moderate OHSS plus ascites or hydrothorax, ovarian enlargement > 12 cm, oliguria with normal serum creatinine
	5	All of the above plus a change in blood volume, increased blood viscosity (Hct > 45%, WBC > 15,000), raised serum creatinine and liver dysfunction

OHSS: ovarian hyperstimulation syndrome; Hct: haematocrit; WBC: whole blood count

A study conducted on 2,524 IVF cycles suggested that the combination of a threshold of ≥ 18 follicles and/or oestradiol ≥ 5,000 pg/ml yields a sensitivity rate of 83%, with 84% specificity for severe OHSS.[1] We found that the mean oestradiol associated with hyperstimulation in a long cycle of an NPCO patient was 5,391 pg/ml and that in a PCO patient was 6,009 pg/ml. Both are comparable and similar to findings in the western literature.

There was no significant difference in gonadotropin dose associated with hyperstimulation, oestradiol concentrations, BMI and severity of OHSS between PCO and NPCO patients. The number of follicles on Day 5–7 was significantly higher in PCO patients than in NPCO patients who subsequently developed OHSS. However, there was no statistically significant difference in the degree of hyperstimulation between patients with PCO and NPCO. The number and size of follicles may be a predictor of OHSS. Various studies have suggested that having > 15–20 follicles is associated with OHSS.[1,2,4] Blankstein et al reported that the presence of more than four large (≥ 14 mm) follicles is significantly correlated with the occurrence of OHSS. Patients with one large follicle and fewer than four intermediate follicles as well as those with less than six follicles in total did not develop OHSS.[10] In our study, the number of follicles associated with OHSS for PCO patients was 28, while that for NPCO patients was 20 ($p = 0.001$). This is slightly higher than values reported in the western literature.

The distribution of follicular categories may affect the severity of OHSS. Blankstein et al suggested that an increase in the fraction of small functioning follicles correlated with a higher risk of developing severe OHSS. In severe OHSS, most of the preovulatory follicles (54.7%) were small (< 9 mm) follicles. Mild OHSS was characterised by a higher number (68.7%) of intermediate (9–15 mm) follicles. The study also reported that women with near equal distribution of the three follicular groups did not develop OHSS.[10] In our study, however, the average number of small, intermediate and large follicles was not associated with the grade of OHSS. We found a positive correlation between the number of large follicles and oestradiol, but no correlation between the number of small and intermediate follicles and oestradiol was observed. Oestrogen may have a lower predictive value, as the release of vasoactive factors can be directly associated with the number of follicles but not with oestrogen, which is possibly due to the difference in the metabolic pathway of their synthesis.[1] Therefore, oestradiol may not be as reliable as the number of follicles in predicting the risk of OHSS.

Among patients with early OHSS in our study, 1.5% had coasting. Coasting refers to the withholding of administration of hCG until serum oestradiol falls to a lower range, typically 3,000 pg/ml. However, it should not be initiated if the leading follicles have a diameter < 15–18 mm, and the duration should be limited to less than four days. Coasting appears to lower the risk of OHSS, with < 2% incidence of severe OHSS, and at the same time gives a satisfactory fertilisation and pregnancy rate.[11] GnRH agonist increases follicular recruitment and is associated with a higher incidence of OHSS. A study performed in Milan showed that a GnRH agonist cycle has considerably higher recorded cases of OHSS as compared to a GnRH antagonist cycle (27.6% vs. 11.5%). There was also a statistically significant increase in the total number of follicles with diameter > 10 mm and in oestradiol levels in a GnRH agonist cycle.[12] Most of our 68 patients with early OHSS were on an agonist long cycle (56 vs. 12). This suggests that agonist long cycle may contribute to a higher risk of OHSS. However, the Cochrane meta-analysis of five prospective randomised studies suggested that the incidence of severe OHSS was not associated with the type of analogue used.[13]

There was a trend toward greater severity in the

degree of hyperstimulation in patients with a lower BMI compared to those with a higher BMI (severe hyperstimulation was observed in 60%, 50% and 21.4% of PCO patients whose BMI was < 19, 19–23 and > 23, respectively). A study of 5,019 IVF and intracytoplasmic sperm injection treatments showed that increased BMI is associated with increased FSH requirement, fewer collected oocytes and increased risk of insufficient follicle development during ovarian stimulation.[14] This suggests that being overweight or obese may attenuate response to gonadotropin stimulation and may be one of the reasons for the lower risk of developing OHSS. However, lean body weight and BMI have been found to be unreliable risk factors for OHSS.[15]

Among our PCO patients, younger patients required a lower mean gonadotropin dose for both long and antagonist cycles than older patients (Table I). Younger patients, similar to patients with lower BMI, have a larger number of recruitable follicles and a higher density of gonadotropin receptors, thus rendering them more responsive to gonadotropins. Older women may have a lower risk of OHSS due to diminished follicles or possibly, a lower responsiveness to gonadotropins. Most of our PCO or NPCO patients who developed OHSS belonged to a younger age group of ≤ 35 years (83.6%), while those > 35 years of age made up just 16.4%. The higher-than-average incidence of OHSS in our study can be attributed to the fact that the majority of our patients were below 35 years of age. A study of 101 patients conducted in Austria found significantly lower body weight in the group of women who developed OHSS, but found no relationship between age and OHSS.[16]

In conclusion, the variables appear to be similar in both Asian and western populations. The average gonadotropin dose associated with hyperstimulation was 204.2 iu in a long cycle and 168.3 iu in an antagonist cycle in women below 35 years of age. This conforms to the western standard of 150 iu. We suggest increasing gonadotropin by 37.5 iu instead of 50 iu in patients at high risk of ovarian hyperstimulation. The mean estradiol associated with hyperstimulation in a long cycle in a PCO patient was 6,009 pg/ml (22,059 pmol/L), while that in an NPCO patient was 5,391 pg/ml (19,790 pmol/L). No significant difference in the gonadotropin dose associated with hyperstimulation, oestradiol concentrations, severity and BMI was found between PCO and NPCO patients. The mean number of follicles on Day 5–7 US in patients who subsequently developed OHSS was significantly higher in PCO than in NPCO (28 vs. 20) patients. PCO may contribute to a higher risk of OHSS; however, there was no statistically significant difference in the degree of hyperstimulation between patients with PCO and NPCO. A total follicle count of > 20 on Day 5–7 US may be predictive of subsequent hyperstimulation. Transfer should be abandoned in the presence of high oestradiol levels (> 5,000 pg/ml ≈ 18,000 mmol/L) when the total number of intermediate and large follicle count exceeds 30 on the day of oocyte retrieval, or when the oocyte retrieval exceeds 19 eggs. Hyperstimulation may be more severe as BMI decreases. Prophylactic albumin may be considered to reduce the incidence of hyperstimulation.

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