

Ovarian Hyperstimulation Syndrome: Experience of a Reproductive Medicine Center 2005-2011



Síndrome de Hiperestimulação Ovárica: Experiência de um Centro de Medicina da Reprodução 2005-2011

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ABSTRACT

Introduction: Ovarian Hyperstimulation Syndrome is a complication of controlled ovarian hyperstimulation during cycles of Assisted Medical Reproduction. The objective of this work was to analyze those cycles to achieve a better knowledge of this pathology, namely risk factors and strategies for prevention and treatment of Ovarian Hyperstimulation Syndrome.

Materials and Methods: Retrospective analysis of 4870 ART cycles (2005 - 2011), with moderate (27) and severe (24) Ovarian Hyperstimulation Syndrome. Data was analyzed for patients' characteristics, stimulation protocol, embryologic and clinical outcomes, and treatment performed.

Results: In Ovarian Hyperstimulation Syndrome groups the mean ages and the doses of rFSH + HMG were lower, and the serum E2 levels, doses of HCG, number of oocytes retrieved as well as the rates of blastocyst, biochemical and clinical pregnancy, implantation, newborns, very preterm birth and newborns with low and very low weight were significantly higher. Patients with severe Ovarian Hyperstimulation Syndrome were hospitalized and received only support measures with no complications.

Discussion: Ovarian Hyperstimulation Syndrome is associated with conditions that can bring risk to the fetus, namely prematurity and low birth weight, so the pregnancy should be carefully monitored in these cases.

Conclusions: Young age is a risk factor for Ovarian Hyperstimulation Syndrome and high serum E2 levels may predict a higher risk too and thus should induce the adoption of prevention strategies.

Keywords: Ovarian Hyperstimulation Syndrome; Reproductive Techniques, Assisted.

RESUMO

Introdução: A Síndrome de Hiperestimulação Ovárica é uma complicação da hiperestimulação controlada do ovário realizada nos ciclos de reprodução medicamente assistida. O objetivo deste trabalho foi efetuar uma análise desses ciclos, para melhor compreensão daquela patologia, nomeadamente fatores de risco, formas de prevenção e tratamento da mesma e suas consequências.

Materiais e Métodos: Análise retrospectiva de 4870 ciclos de reprodução medicamente assistida (2005 - 2011) com Síndrome de Hiperestimulação moderado (27) e grave (24). Foram estudados, os dados das características dos doentes, protocolos de estimulação, resultados embriológicos e clínicos, e tratamento efetuado.

Resultados: No grupo com Síndrome de Hiperestimulação Ovárica a idade média foi inferior, a dose de rFSH + HMG foi mais baixa e os níveis de estradiol foram mais elevados. Nos grupos com Síndrome de Hiperestimulação, as taxas foram significativamente superiores para o número médio de ovócitos e blastocistos obtidos, de gravidez bioquímica e clínica, de implantação e de recém-nascidos. O parto muito pré-termo e a proporção de recém-nascidos com peso baixo e muito baixo foram superiores no grupo com Síndrome de Hiperestimulação Ovárica. As doentes com Síndrome de Hiperestimulação Ovárica grave foram hospitalizadas tendo apenas sido necessária medicação de suporte.

Discussão: A Síndrome de Hiperestimulação Ovárica foi associada a condições de risco para o feto, nomeadamente prematuridade e baixo peso ao nascimento, devendo manter-se uma vigilância apertada da gravidez nestes casos.

Conclusão: A idade jovem constitui um fator de risco de Síndrome de Hiperestimulação Ovárica e o nível de estradiol elevado foi preditor do mesmo, devendo levar à adoção de estratégias de prevenção.

Palavras-chave: Síndrome de Hiperestimulação Ovárica; Técnicas de Reprodução Assistida.

INTRODUCTION

Ovarian Hyperstimulation Syndrome (OHSS) is based on an excessive answer triggered by therapeutic ovarian controlled hyperstimulation during Assisted Reproductive Techniques (ART) cycles by *in vitro* fertilisation (IVF) and intracytoplasmic sperm injection (ICSI)¹. It represents one of the most important iatrogenic complications of ART.²

It is characterised by ovarian cystic expansion

associated with ascites, due to an increase of peritoneal capillary patency.³ It may present with a wide clinical spectrum of manifestations ranging from mild to moderate symptomatology. These are characterised by abdominal discomfort, non-tense abdominal distension, nausea, vomiting and diarrhea, requiring only clinical supervision¹ and occur in approximately 5% of hormonal stimulation

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cycles.⁴ More serious clinical signs, frequently requiring hospitalisation are described in about 2% of the cycles.⁵ In turn, these are characterised by severe abdominal pain, incoercible vomiting, tension ascites, hypovolaemia with hypotension, dyspnea, oliguria or anuria, fluid-electrolyte imbalance, haemoconcentration and abnormal liver function tests and may be as severe as to include hepatorenal syndrome or ARDS, with hospitalisation in Intensive Care.¹ In the literature, there are well described rare cases of thrombosis mainly, but not exclusively, in patients with thrombotic predisposition: jugular and subclavian veins combined thrombosis,⁶ intracranial venous sinus thrombosis⁷ and left medial cerebral artery thrombosis causing, in the described cases, irreversible neurological damage.⁸

Two mortal cases of perforation of duodenal ulcer are also described in this context.^{9,10} There are even described mortality rates of approximately three deaths per 100.000 IVF cycles completed¹¹ which, although low, should in fact be non-existent, as they represent a direct consequence of the infertility treatment performed. Therefore, it is most important to recognize the risk factors for development of OHSS, in order to allow adequate strategies and, whenever these fail, the best possible treatment, which should be tailored to each individual case.

Therefore, one of the aims of this work consisted in the analysis of characteristics of patients submitted to ICSI and IVF cycles, including cycles in which OHSS has developed, trying to identify potential risk factors for its development, to be considered when a woman starts a hormone stimulation cycle. Furthermore, we evaluated and compared laboratorial and clinical results obtained in these cycles (namely pregnancy and possible complication rates, as abortion or birth defects) to those cycles in which OHSS did not occur. We also completed a revision of the hormone stimulation protocols applied in the cycles that were included in the study and their possible relation with OHSS development. Finally, we briefly describe the treatment that has been performed in the severe OHSS cases and its results (namely complications that occurred and time of hospitalisation required for patient's recovery).

MATERIAL AND METHODS

Patient database have been used after informed and written consent, according to the Portuguese National Assisted Medical Procreation Law (*Lei Nacional de Procriação Medicamente Assistida*) (Law number 32/2006, from 26th July) and the Portuguese National Assisted Medical Procreation Council (*Conselho Nacional de Procriação Medicamente Assistida*) (CNPMA, 2008) criteria.

Participants

The present study consists in a retrospective analysis of IVF and ICSI cycles performed between January 2005 and October 2011 (3.978 ICSI cycles and 893 IVF cycles in total) in a Reproductive Medicine Center, complicated by the occurrence of moderate to severe OHSS. The

remaining ICSI and IVF cycles performed in that period have been included as a control group, including those with mild OHSS. One ICSI cycle has been excluded from the study, after a testicular biopsy revealed the absence of spermatozoa or spermatids.

OHSS classification

OHSS has been considered as (i) mild when clinical signs only include weight increase, thirst, abdominal discomfort and/or mild distension, with an ovarian diameter lower than 5 cm; (ii) moderate in patients which additionally present nausea and vomiting, abdominal distension without tension or pain, dyspnea and/or ascites (identified by ultrasound), with an ovarian diameter between 5 - 12 cm, but when no hospitalisation is required and (iii) severe when a third space fluid collection is identified, a hydrothorax and/or tension ascites is present, when there is evidence of intravascular fluid loss, haemoconcentration, hypovolaemia, oliguria and/or hepatorenal syndrome, with an ovarian diameter over 12 cm and when hospitalisation is required.^{12,13}

Data

In all the cycles, we analysed data concerning patient characteristics, stimulation protocols, embryological and clinical results. Data was retrieved from the Center computerized database. Information concerning treatment received by OHSS patients and period of hospitalisation was obtained through hospital medical records or, when these were not available or insufficient, by telephone interview with the patients. Data concerning gestation period and newborn weight followed the American Society criteria for ART.¹⁴

Stimulation protocol

Controlled ovarian hyperstimulation was more frequently performed using an antagonist (cetorelix: Merck-Serono, Geneva, Switzerland; ganirelix: Organon, Oss, Holland), the agonist protocol being performed in the remaining patients (buserelin: Sanofi Aventis, Frankfurt, Germany). Recombinant follicle stimulating hormone (rFSH-beta: Organon; rFSH-alfa: Merck-Serono) was used for stimulation, with human menopausal gonadotropin (HMG: Ferring, Kiel, Germany) added infrequently. HMG was used in isolation in only a few patients. Ovulation induction was performed with urinary chorionic gonadotropin (HCG: Organon).

Statistical analysis

Data was analysed using IBM SPSS Statistics 20 software. Averages were compared using *t* test for independent samples. Categorical variables were analysed using descriptive statistics and Qui-square test, with continuity correction. Fisher exact test was used when contingency tables contained values inferior to 5. All statistical performed tests were 2-tailed and a *p* value of < 0.05 was considered to be statistically significant.

Table 1: Patient characteristics.

Parameter	ICSI		IVF	
	Control cycles	OHSS cycles	Control cycles	OHSS cycles
Cycles	3947	30	872	21
Female age (years)	35.0 ± 4.5 (18 - 48)	32.2 ± 3.5 ^a (25 - 40)	34.0 ± 4.1 (21 - 52)	33.9 ± 3.1 (29 - 40)
Male age (years)	36.8 ± 5.8 (20 - 66)	33.2 ± 3.7 ^a (27 - 41)	35.5 ± 5.0 (24 - 60)	35.8 ± 4.3 (27 - 44)
Infertility duration (years)	4.0 ± 3.2 (0 - 23)	3.0 ± 2.1 (1 - 10)	3.7 ± 2.9 (1 - 22)	3.7 ± 2.3 (1 - 11)
Number of tries	1.6 ± 0.9 (1 - 8)	1.4 ± 0.7 (1 - 3)	1.3 ± 0.7 (1 - 6)	1.1 ± 0.4 (1 - 2)
Female karyotype (%)				
Normal karyotype	3835 (97.2)	30 (100)	854 (97.9)	19 (90.5)
Mosaics				
- Turner Syndrome	63 (1.6)		9 (1.0)	1 (4.8)
- Others	5 (0.1)		3 (0.3)	
Translocations				
- Robertsonian	6 (0.1)		2 (0.2)	
- Reciprocal	26 (0.7)		3 (0.3)	
Others	12 (0.3)		1 (0.1)	1 (4.8)
Male karyotype (%)				
Normal karyotype	3832 (97.1)	29 (96.7)	842 (96.6)	
Klinefelter Syndrome				
- 47, XXY pure	26 (0.7)		21 (2.4)	
- Mosaics	9 (0.2)			
Other mosaics	3 (0.1)			21 (100)
Translocations				
- Robertsonian	18 (0.5)		1 (0.1)	
- Reciprocal	32 (0.8)			
Others	27 (0.7)	1 (3.3)	8 (0.9)	
Infertility causes (%)				
- Male factor	3403 (86.2)	27 (90)	497 (57)	9 (42.9)
- Ovulatory factor	511 (12.9)	3 (10)	145 (16.6)	5 (23.8)
- Endometriosis	291 (7.4)	3 (10)	95 (10.9)	3 (14.3)
- Uterine factor	370 (9.4)	1 (3.3)	70 (8)	3 (14.3)
- Tubal factor	249 (6.3)	2 (6.7)	142 (16.3)	3 (14.3)
- Non-determined	69 (1.7)	1 (3.3)	62 (7.1)	2 (9.5)
- Other causes	224 (5.7)	1 (3.3)	45 (5.2)	3 (14.3)
Pure male factor (%)	2284 (57.9)	19 (63.3)	306 (35.1)	3 (14.3) ^a
Pure female factor (%)	241 (6.1)	1 (3.3)	108 (22.7)	6 (28.6)

Values expressed as average ± standard deviation (variation), except for those parameters otherwise indicated

^a Statistically significant difference between OHSS group and control group.

* Ovarian Hyperstimulation Syndrome

RESULTS

The present study included 3.978 ICSI cycles and 893 IVF cycles performed in our Medical Center over the past seven years. OHSS development occurred in 31 (0.78%) ICSI cycles and in 21 (2.35%) IVF cycles. Among ICSI cycles with OHSS development, 18 (58.1%) were considered moderate, representing a global incidence of 0.45% and the remaining 13 (41.9%) were considered severe, representing 0.33% of the cycles. IVF cycles were complicated by 10 cases of moderate OHSS (47.6%) and 11 cases of severe OHSS (52.4%), representing an incidence of 1.12% and 1.23%, respectively. One of the ICSI cycles with moderate OHSS was cancelled after a testicular biopsy revealed the absence of spermatozoa or spermatid count and therefore the study only included the remaining 30 OHSS cases.

In what concerns patient characteristics (Table 1), we observed that both members of the couple were on average younger in the ICSI cycle group with OHSS. There were no differences between both groups in the duration of

infertility and number of treatment attempts, as well as in the frequencies of specific infertility causes. In contrast, in IVF cycles, a higher proportion of a pure masculine infertile factor was observed in the control group (35.1) vs. the OHSS group (14.3). There were no significant differences in what concerned feminine (2.84% in ICSI cycles and 2.06% in IVF cycles) and masculine (2.91% in ICSI cycles and 3.44% in IVF cycles) karyotype abnormalities when compared to the control group. Of note, in the OHSS group, there was a single case of masculine reciprocal translocation in ICSI cycles and isolated cases of Turner syndrome and feminine deletion in IVF cycles were recorded.

There were no significant differences between ICSI and IVF cycles with respect to any of the following spermogram parameters: spermatozoa count, morphology, progressive motility, vitality or hypo-osmolarity test. Spermatozoa were obtained by aspiration or testicular biopsy (each one completed in just one OHSS cycle, representing a total of 6.6% of the cases). There were also no significant

Table 2: Stimulation data.

Parameter	ICSI		IVF	
	Control cycles	OHSS cycles	Control cycles	OHSS cycles
Basal FSH (mIU/mL)	7.3 ± 4.1 (0.1 - 86.7)	6.6 ± 2.2 (2.5 - 13.5)	6.6 ± 3.6 (0.1 - 55.3)	6.3 ± 1.9 (3.5 - 11.3)
Stimulation protocol (n; %)				
- Antagonist	3034 (89.5)	27 (90.0)	692 (92.9)	21 (100.0)
- Agonist	356 (10.5)	3 (10)	53 (7.1)	
Total rFSH dose (IU/mL)	1573 ± 608.2 (300 - 7200)	1322.5 ± 608.2 (800 - 2700)	1493.4 ± 501.4 (600 - 3600)	1221.3 ± 319 ^a (800 - 1800)
Total HMG dose (IU/mL)	2220 ± 1018.3 (1200 - 5400)		1680 ± 812.6 (750 - 3375)	
Total rFSH + HMG dose (IU/mL)	2834.6 ± 1057.2 (750 - 9000)	1717.5 ± 742.9 ^a (925 - 3225)	2519.4 ± 985.7 (875 - 6875)	2362.5 ± 843 (1275 - 3225)
Stimulation duration (days)	8.5 ± 1.7 (1 - 19)	8.5 ± 1.4 (7 - 11)	8.3 ± 1.5 (5 - 15)	7.9 ± 1.6 (6 - 12)
Estradiol measurement at the time of HCG administration (pg/mL)	1246.3 ± 891.1 (1 - 14630.4)	1707.9 ± 646.5 ^a (455.7 - 3142)	1337.3 ± 863.8 (7.3 - 8213)	1594.6 ± 504.5 (885 - 2706.4)
Ovulation triggering (n; %)				
- HCG	2756 (98.1)	15 (100)	544 (96.6)	12 (100)
HCG dose (IU/mL)	9612.1 ± 1874.6 (5000 - 15000)	10000 ± 0 ^a (10000 - 10000)	9364.6 ± 1780.5 (5000 - 15000)	10000 ± 0 ^a (10000 - 10000)

Values expressed as average ± standard deviation (variation), except for those parameters otherwise indicated

^a Statistically significant difference between OHSS and control groups, Ovarian Hyperstimulation Syndrome (OHSS).

Table 3: Embryological results.

Parameter	ICSI		IVF	
	Control cycles	OHSS cycles	Control cycles	OHSS cycles
Cycles (n)	3947	30	872	21
Number of oocyte obtained (n)	29716	324	7475	232
Average number of oocyte obtained/cycle	7.53 ± 4.8 (0 - 36)	10.8 ± 4.1 ^a (3 - 19)	8.57 ± 4.6 (0 - 34)	11 ± 4.2 ^a (6 - 21)
MII (n)	24251	257	6981	208
2PN (n)	16841	189	4824	155
MI/number of oocyte obtained (n; %)	24251 / 29716 (81.6)	257 / 324 (79.3)	6981 / 7475 (93.4)	208 / 232 (89.7) ^a
Oocyte immaturity rate (n; %)	5465 / 29716 (18.4)	67 / 324 (20.7)	494 / 7475 (6.6)	24 / 232 (10.3) ^a
Fertilisation rate (n; %)	16841 / 24251 (69.4)	189 / 257 (73.5)	4824 / 6981 (69.1)	155 / 208 (74.5)
Cleavage rate (n; %)	16483 / 16841 (97.9)	182 / 189 (96.3)	4732 / 4824 (98.1)	153 / 155 (98.7)
Blastocyst rate (%)	4030 / 16841 (23.9)	75 / 189 (39.7) ^a	1694 / 4824 (35.1)	81 / 155 (52.3) ^a
Transferred embryo type (n; %)				
- 2-4 cells	824 (11.9)	2 (3.8)	120 (7.5)	
- 5-17 cells	3436 (49.5)	14 (26.9) ^a	670 (42.1)	11 (28.2)
- Morula	286 (4.1)	1 (1.9)	60 (3.8)	1 (2.6)
- Compactation	446 (6.4)	3 (5.8)	67 (4.2)	1 (2.6)
- Blastocyst	1945 (28)	32 (61.5) ^a	673 (42.3)	26 (66.7) ^a

Values expressed as average ± standard deviation (variation), except for those parameters otherwise indicated.

^a Statistically significant difference between OHSS group and control group;

* Ovarian hyperstimulation syndrome (OHSS);

† Metaphase II (MII);

‡ Two pro-nucleus (2PN);

§ Maturity rate (n° MII/n° oocyte obtained); Immaturity rate [(n° oocyte - n° MII) / n° oocyte]; Fertilisation rate (2PN/MII); Cleavage rate (Obtained embryo number/2PN); Blastocyst rate (blastocyst number/2PN).

Table 4: Clinical results (Pregnancies and Births).

Parameter	ICSI		IVF	
	Control cycles	OHSS cycles	Control cycles	OHSS cycles
ET cycles (n)	3606	29	832	21
Total transferred embryos (n)	6937	52	1590	39
Average number of transferred embryos (n; % of ET cycles)	6937 / 3606 (1.9)	52 / 29 (1.8)	1590 / 832 (1.9)	39 / 21 (1.9)
Biochemical pregnancy (n; % of ET cycles)	1518 / 3606 (42.1)	27 / 29 (93.1) ^a	477 / 832 (57.4)	21 / 21 (100) ^a
Clinical pregnancy (n; % of ET cycles)	1303 / 3606 (36.1)	26 / 29 (89.7) ^a	418 / 832 (50.2)	21 / 21 (100) ^a
Ectopic pregnancy (n; % of ET cycles and CP)	23 / 3606 (0.6) 23 / 1303 (1.8)	1 / 29 (3.4) 1 / 26 (3.8)	8 / 832 (1) 8 / 418 (1.9)	1 / 21 (4.8) 1 / 21 (4.8)
Single pregnancy (n)	961	17	274	12
Twin pregnancy (n; % of CP)	334 / 1303 (25.6)	9 / 26 (34.6)	141 / 418 (33.7)	8 / 21 (38.1)
Triplet pregnancy (n; % of CP)	8 / 1303 (0.6)		3 / 418 (0.7)	1 / 21 (4.8)
Abortion (n; % of CP)	199 / 1303 (15.3)	4 / 26 (15.4)	47 / 418 (11.2)	1 / 21 (4.8)
Eutocic delivery (n)	253	3	78	3
Dystocic delivery (n; % of total deliveries)	630 / 883 (71.3)	11 / 14 (78.6)	198 / 276 (71.7)	10 / 13 (76.9)
Implantation rate (n; % of ET cycles)	1636 / 6937 (23.6)	34 / 52 (65.4) ^a	559 / 1590 (35.2)	31 / 39 (79.5) ^a

Values expressed as average \pm standard deviation (variation), except for those parameters otherwise indicated.

^a Statistically significant difference between OHSS and control groups;

* Ovarian Hyperstimulation Syndrome (OHSS);

† Embryo Transfer (ET);

‡ Clinical Pregnancy (CP);

§ Implantation Rate (gestational sacs number/transferred embryo number).

differences between the use of these techniques and the ejaculated sperm obtained in both groups.

In what concerns ovarian stimulation (Table 2), in ICSI cycles from the control group, rFSH was administered in 2.088 (61.6%), rFSH + HMG in 1.280 (37.8%) and HMG in 20 (0.6%) of the patients. In OHSS group, rFSH was used in 20 (66.7%) and rFSH + HMG in 10 (33.3%) of the cases, in the absence of HMG. The average total dose of rFSH + HMG used was lower in the OHSS group.

In the control group of IVF cycles, rFSH was used in 540 (72.5%), rFSH + HMG in 195 (26.2%) and HMG in 10 (1.3%) of the patients. In the OHSS group, rFSH was used in 17 (81.0%) and rFSH + HMG in 4 (19.0%) of the cases, all in the absence of HMG. The average total dose of rFSH administered was lower in OHSS group and there were no significant differences in stimulation duration.

The stimulation protocol performed was of the antagonist type in the majority of patients with only a small percentage having received the agonist protocol in ICSI cycles complicated with OHSS. There were no significant differences between the groups.

In all OHSS cases, the drug used for ovulation triggering was HCG. The dose of HCG used in the OHSS group was significantly higher than the one used in the control groups and estradiol measured on the day of HCG administration was higher in the ICSI-OHSS group.

In what concerns embryological results (Table 3), the

average number of oocytes retrieved per cycle was higher in the OHSS groups. Immaturity rate was higher in IVF-OHSS group. There were no significant differences in fertilisation and cleavage rates between the groups.

The rate of blastocyst was significantly higher in the OHSS groups. In the same way, transferred embryo type was significantly different in both groups, with a higher proportion of transferred blastocyst in the OHSS groups. In both groups, the majority of transferred embryos were of good quality (A and B), both in ICSI and IVF cycles (96% in the control group vs. 100% in the OHSS group, in both cycles).

Clinical results analysis (Table 4) showed no significant differences in the transferred average number of embryos per embryo transfer (ET) cycle between the groups. Biochemical and clinical pregnancy success rates by ET cycle were higher in the OHSS groups. There were no differences between the groups in ectopic, twin and triplet pregnancy rates (nor in the total number of multiple pregnancies). In what concerns the type of birth, there was a predominance of dystocic delivery in all groups (for ICSI, 0.38% / ET cycles in the OHSS cases and 0.17% / ET cycles in control cases; for IVF, 0.48% / ET cycles in OHSS cases and 0.24% / ET cycles in control cases; for all cases, 0.42% / ET cycles in OHSS cases and 0.19% / ET cycles in control cases). Implantation rate was higher in the OHSS groups. There was no difference in the proportion of abortions for

Table 5. Clinical Results (Newborn Frequency and Complications).

Parameter	ICSI		FIV	
	Control cycles	OHSS cycles	Control cycles	OHSS cycles
Newborn (<i>n</i> ; % of ET cycles)	1087 / 3606 (30.1)	19 / 29 (65.5) ^a	358 / 832 (43)	18 / 21 (85.7) ^a
Female (<i>n</i>)	549	9	172	9
Male (<i>n</i>)	532	10	186	9
Male/Female Ratio	0.97	1.11	1.08	1
Pregnancy time (weeks)				
(<i>n</i> ; %):	37.5 ± 2.6 (22 - 43)	36.1 ± 3.6 (27 - 40)	37.1 ± 2.9 (24 - 42)	37.8 ± 2.1 (33 - 41)
< 28 (Extremely preterm birth)	8 (0.9)	1 (7.1)	6 (2.2)	
< 32 (Very preterm birth)	38 (4.3)	6 (42.9) ^a	16 (5.8)	
< 37 (Preterm birth)	204 (23.1)	6 (42.9)	73 (26.4)	2 (15.4)
37-42 (Term birth)	675 (76.5)	8 (57.1)	203 (73.6)	11 (84.6)
> 42 (Post-term birth)	3 (0.3)			
Weight at birth (grams)				
(<i>n</i> ; %):	2745.4 ± 705 (440 - 5010)	2217.7 ± 854 ^a (814 - 3990)	2645.7 ± 677.5 (600 - 4460)	2749.6 ± 585.8 (1730 - 3800)
< 1000 (extremely low)	25 (2.3)	2 (10.5)	10 (2.9)	
< 1500 (very low)	67 (6.3)	5 (26.3) ^a	24 (6.9)	
< 2500 (low)	332 (31.1)	12 (63.2) ^a	118 (33.7)	8 (44.4)
2500 - 4000 (normal)**	725 (67.8)	7 (36.8) ^a	231 (66)	10 (55.6)
> 4000	12 (1.1)		1 (0.3)	
Birth defects				
Live births (<i>n</i> ; % of total deliveries)				
- Major birth defects	17 / 883 (1.9)		10 / 276 (3.6)	
- Minor birth defects	10 / 883 (1.1)			
Chromosomal abnormalities				
Live births (<i>n</i> ; % of total deliveries)	3 / 883 (0.3)		1 / 276 (0.4)	

Values expressed as average ± standard deviation (variation), except for those parameters otherwise indicated.

^a Statistically significant difference between OHSS group and control group;

* Ovarian Hyperstimulation Syndrome (OHSS);

† Embryo transfer (ET);

** Normal: weight within the normal range for newborns.

clinical pregnancy between the groups.

In what concerns newborns (NB) and complications (Table 5), the proportion of NB per ET cycle was significantly higher in OHSS groups, with a male/female ratio of approximately 1 in all groups. There were no significant differences in the pregnancy average time in weeks between both groups. However, in ICSI-OHSS cycles, less than 32 weeks pregnancy proportion was significantly higher. Average weight at birth was lower in the ICSI-OHSS group, with a higher proportion with very low and low weight.

As far as birth defects and chromosomal abnormalities, these were only identified in the control groups. Chromosomal abnormalities found in NB in ICSI cycles included one case of trisomy 21, two NB with Robertsonian translocations and one with reciprocal translocation. In IVF cycles, there was only one NB with trisomy 21.

With regard to hospitalised patients, only 24 severe OHSS cases were admitted in the Hospital, with a hospitalisation average of 8.2 days (5 - 15). All patients presented on admission with fatigue, nausea, abdominal distension and discomfort. Of note, there was no vomiting or dyspnea and bowel movements remained unchanged. There was also no anaemia, no fever and the patients remained normotensive. The exams showed haemoconcentration and an increase in ovarian volume, with on average for the right ovary of 7.89

cm³ (5.5 - 10) and on average for the left ovary of 6.9 cm³ (6.3 - 8.2). A diagnosis of late (after a positive βHCG) and severe OHSS was reached. Patients were evaluated by vaginal touch, speculum examination, ultrasound (which showed moderate to voluminous ascites, with no abnormality in bowel loops and normal uterus and adnexa). Haematocrit, serum ions, liver function, renal function and coagulation parameters were evaluated during hospitalisation. Patients were rehydrated (in order to reduce haemoconcentration) and required furosemide (in order to improve diuresis, as fluid therapy may actually increase the risk of ascites and pleural effusion and in view of the association of OHSS with increased vascular permeability, which results in increased intra-abdominal pressure when renal function may be compromised). Enoxaparine was administered in patients who were breastfeeding. Ascites and pleural effusion were evaluated by abdominal ultrasound extension to the lung surface. Most patients reported miction difficulties on admission and required urinary catheterisation with urinary output and fluid balance monitoring. No other complications were observed during hospital admission and therefore neither thoracocentesis nor paracentesis/culdocentesis were required. Admission lasted from 2 to 15 days and upon discharge patients were advised rest, fluid restriction, appropriate nutrition and paracetamol for analgesia. Even

though it did not prove necessary, a specific recommendation was made for immediate return to the Hospital should any sign of deterioration arise. There was also no need for re-hospitalisation in the literature review performed.

DISCUSSION

Patients who develop OHSS were globally younger in ICSI than in IVF cycles, a finding already described in previous studies.^{15,16} This relation is probably due to the fact that in both groups younger patients have a higher number of recruitable follicles and a higher gonadotropin receptor density, developing a more intense response to gonadotropin.¹⁷ Male age was also lower, a fact that might be related to a tendency for couples to be within the same age group.

In the present study, there were no significant differences between the groups in what concerns infertility causes. This finding is not in agreement with a revision in 214.219 ICSI/IVF cycles, 1.523 with moderate OHSS and 655 with severe OHSS, where a relation was found between OHSS development and tubal and ovulatory factors, including Polycystic Ovary Syndrome (PCOS)¹⁵.

PCOS was already related with OHSS in previous studies¹⁸ in which only severe OHSS cases were included in the OHSS group (165) and another study¹⁹ where 24 moderate OHSS and 29 severe OHSS were described. This association is probably due to the presence of an increased ovarian sensitivity to gonadotropin in PCOS. In a systematic review which included 10 studies, there was a relation between PCOS and OHSS.²⁰ In addition, there was also a lower proportion of patients with reduced ovarian reserve in the group that developed OHSS.¹⁵ In the present study (51 cases, 24 severe), it is likely that a lower number of OHSS cycles may explain the lack of association with PCOS. On the other hand, the discrepancy between our results and those that have been described may be explained by the fact that our classification of infertility due to ovulatory disorders included not only PCOS patients, but also other ovulatory problems. The latter may be associated to a lower ovarian sensitivity to gonadotropin action and therefore inversely related with OHSS development. Furthermore, the association between female pathology as cause of infertility and OHSS development found in the referred studies may also be explained by a lower pure masculine factor cycle proportion in the IVF-OHSS group.

In the present work, there were no significant differences between groups in what concerns stimulation protocols but this study only included three ICSI-OHSS cases using an agonist protocol. A Cochrane systematic review made in 2006, including 29 trials,²¹ revealed a 2% lower OHSS incidence when using an antagonist vs. an agonist protocol. A more recent revision²² involving 45 randomised clinical trials showed an incidence difference of 2.7%. This was due to an OHSS incidence reduction by half when the antagonist was compared to the agonist protocol and a lower probability of cycle cancelling due to high risk of OHSS development. In another randomised clinical trial²³ it was also shown that

the antagonist protocol was associated to a lower OHSS incidence. One possible explanation for higher safety of the antagonist protocol may be the immediate action of the drug, its administration being indicated specifically for the suppression of premature and spontaneous LH release, thereby reducing the stimulation duration and secondary effects due to hypoestrogenemia.²⁴

In the present study (4.871 cycles), we found no significant differences between the groups in the use of rFSH, HMG or both, in agreement with a meta-analysis of seven randomised clinical trials²⁵ involving 2.159 patients. The average total dose of rFSH + HMG used was lower in the ICSI-OHSS group, as well as the average total dose of rFSH administered in the IVF-OHSS group. A meta-analysis²⁶ demonstrated that the OHSS development risk increases significantly with daily FSH doses higher than 200 IU and with average stimulation duration of 8.5 days, corresponding to a total dose of 1.700 IU. This apparent inversion of the expected results may be related to the fact that in this study, as a preventative measure, we performed a reduction of the administered dose in patients that were judged to present a OHSS development risk.

Estradiol quantification on the day of HCG administration revealed a higher value in the ICSI-OHSS group, what is in agreement with a prospective study²⁷ and with the observation that the OHSS development is usually associated with an increase in estradiol levels.²⁸

All OHSS cases underwent ovulation induction with HCG. Several studies showed a lower OHSS incidence using a GnRH agonist.²⁹⁻³¹ The higher incidence in our study may thus be explained by the longer half-life of HCG, remaining high until six days after administration. In a revision study,³³ as well as in a prospective study of 102 oocyte donors with high OHSS development risk,³⁴ the authors concluded that using a GnRH agonist as ovulation inductor results in a total absence of OHSS. In addition, a retrospective study demonstrates that HCG dose reduction may result in a reduction of OHSS incidence.³⁵ In the present study, the administered HCG dose in the OHSS group was significantly higher.

In the present study, the average number of obtained oocytes was higher in the OHSS group, both in ICSI (10.8 vs. 7.53) and in IVF (11 vs. 8.57) cycles, in agreement with retrospective studies (13 vs. 10)³⁶ and (13 vs. 9)³⁷ which is in keeping with the fact that a high number of follicles obtained by aspiration is a good predictive factor for early OHSS development.

Blastocyst rate and transferred blastocyst proportion was significantly higher in the OHSS groups. In ICSI cycles, this may have been attributed to embryo transfer being predominantly performed on the fifth day. However, in IVF cycles, embryos were mainly transferred on the fifth day in both OHSS positive and negative groups. Therefore, the higher blastocyst proportion should not be exclusively related to the transfer day, but rather to a relationship between embryo maturation frequency to blastocyst and OHSS development.

In the present work, both biochemical and clinical pregnancy were higher in OHSS groups, as in several previous studies,¹⁵ as pregnancy increases frequency, duration and severity of OHSS symptoms.¹ In fact, in a retrospective study, the comparison between the clinical characteristics of patients who develop early and late OHSS, revealed that the conception cycle was the main cause of late OHSS, as opposed to OHSS which occurs earlier and is mainly related to gonadotropin stimulation.³⁸ These authors remark that the sustained action of HCG increased due to pregnancy might be related with longer duration and higher severity of late vs. early OHSS, implying a higher magnitude and duration of the granulosa cell stimulation.³⁷ Implantation rate was higher in OHSS groups, related with a similar transferred embryo average number with a higher number of gestational sacs. The same result has been obtained in a prospective study that suggested that OHSS severity increases the number of gestational sacs, independently of the moment in which it starts, confirming the hypothesis that a higher severity of late OHSS might be due to a pregnancy effect.³⁷

Contrary to one study,¹⁵ we did not find any significant differences in multiple pregnancy rate between the groups. However, a faster and more sustained increase in HCG levels occurs in multiple pregnancy.³⁹ In our work, the number of transferred embryos, a risk factor for multiple pregnancy development, was not significantly associated with OHSS development.

In the present study, higher prematurity rates and low weight at birth have been found in the OHSS group, in agreement with other results.⁴⁰ In another study, a relation between OHSS development and low weight at birth, but not with prematurity was found.¹⁵ Higher prematurity rates have however been observed.³⁶ There are still no data that support a pathogenic association between prematurity and OHSS, except when there is a high prevalence of multiple pregnancies and in fact, in the present work, there are no significant differences between both groups. The higher rate of low weight at birth in the OHSS group might be explained by OHSS induction of placental developmental abnormalities and gestational hypertension and these have been observed at a higher prevalence in patients that develop OHSS.³⁶

We observed no significant differences in abortion rate between the groups, as in other previous studies.^{19,36} A multicentric study that found a higher abortion rate reported a higher number of multiple pregnancies.³⁶

In our work, birth defects only occurred in a small percentage of newborns in the control group, corresponding approximately, in ICSI cycles (1.9% *major* and 1.1% *minor*), to those found by another study.⁴² The latter was

observational and analysed congenital birth defects after ICSI cycles between 1994 - 1997, in 13 reproductive medicine centers (five public and eight private) which found 2.2% *major* and 1.2% *minor* abnormalities. Although the birth defect rate that we obtained in IVF cycles was slightly higher (3.6%), this difference was not statistically significant. In another study,⁴³ there was also no significant differences in birth defect rates between ICSI and IVF cycles, with a *major* birth defect rate of 3.8% in IVF cycles, in agreement with the present work. The chromosomal abnormality rate found in live births from the control group of 0.3% in ICSI cycles and 0.4% in IVF cycles did not exceed the 0.92% rate obtained for general population.⁴⁴

During hospitalisation, no patient presented any relevant clinical signs or required re-hospitalisation, in agreement with a literature review.

CONCLUSIONS

When starting an ART cycle, young age and estradiol levels seem to be relevant risk factors for OHSS, alerting the physician for this possible complication and allowing for adoption of adequate preventative measures. OHSS is also positively associated with laboratory and clinical results obtained during ART cycles, with a higher average oocyte number, biochemical and clinical pregnancy, implantation, as well as a higher proportion of newborn. However, beyond maternal risk, OHSS may also cause foetal abnormalities, namely prematurity and low weight at birth, for which we recommend close pregnancy supervision.

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CONFLICT OF INTERESTS

All authors declare that there are no conflicts of interest concerning the present manuscript.

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