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C-reactive protein response is higher in early than in late ovarian hyperstimulation syndrome

Kati V.M. Korhonen [a,*], Hanna M. Savolainen-Peltonen [a,b], Tomi S. Mikkola [a,b], Aila E. Tiitinen [a], Leila S. Unkila-Kallio [a]

[a] Obstetrics and Gynecology, University of Helsinki, and Helsinki University Hospital, 00290 Helsinki, Finland
[b] Folkhälsan Research Center, Biomedicum Helsinki, 00290 Helsinki, Finland

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ABSTRACT

Objectives: Many *in vitro* fertilization (IVF) complications are inflammatory by nature, some of which are even life-threatening. We evaluated the response of C-reactive protein (CRP) in IVF complications, especially in early and late ovarian hyperstimulation syndrome (OHSS), to support clinical decision making in gynecological emergency policlinics.

Study design: In a prospective two-year study at Helsinki University Hospital, Finland, we recruited patients with IVF complications including moderate or severe OHSS ($n = 47$ patients: 36 early and 14 late OHSS cases), or other IVF complications ($n = 13$). As controls, we recruited women in an uncomplicated IVF cycle ($n = 27$). Serial blood samples (CRP, blood count, platelets, albumin, estradiol, creatinine, and electrolytes) were collected from patients upon admission to the emergency polyclinic and during and after treatment on the ward, and from the controls prior, during, and after the IVF protocol. All samples were categorized according to oocyte pick-up (OPU). The statistics included comparisons between and within the study groups, and receiver-operating characteristic (ROC) curve analysis for diagnostic accuracy of CRP for early OHSS at emergency polyclinics.

Results: On admission, CRP did not differentiate OHSS from other IVF complications, but CRP was higher in early (median 21; IQR 8–33 mg/L) than in late (6; 3–9 mg/L, $p = 0.001$) OHSS. In ROC analysis for CRP (12 mg/L), the area under the curve (AUC) was 0.74 ($p = 0.001$) with sensitivity of 69% and specificity of 71% for early OHSS. CRP was significantly higher (28; 10–46 mg/L) in patients with early OHSS two days after oocyte pick-up (OPU) than in the controls (5; <3–9 mg/L, $p < 0.001$). The level normalized by 12 days, similarly to the controls. On the ward, the peak CRP was higher if early OHSS was complicated with infection (108; 49–166 mg/L) than without infection (20; 8–32 mg/L, $p = 0.001$). Late OHSS was associated with hypoalbuminemia (19.6; 16.2–23.1 g/L, $p < 0.001$) and thrombocytosis (494; 427–561 E9/L, $p = 0.004$; comparisons to early OHSS).

Conclusions: Early OHSS associates with a distinct rise in CRP level beyond that induced by uncomplicated oocyte pick-up, whereas the CRP levels in late OHSS are comparable to those in the control cycles. CRP identifies, but cannot distinguish IVF complications.

Introduction

The complications of *in vitro* fertilization (IVF) treatment include ovarian hyperstimulation syndrome (OHSS), intra-abdominal hemorrhage, ovarian torsion, spontaneous cyst rupture, infections and thromboembolism [1]. Many of these complications involve inflammation and quite similar symptoms consisting of abdominal pain, distension, diarrhea, vomiting, fever and/or dyspnea. The most prevalent complication is the potentially life-threatening OHSS that emerges in around 0.5–5% of IVF cycles [2]. Ultrasonography reveals enlarged cystic ovaries and intra-abdominal fluid. However, data on the role of laboratory tests in differential diagnosis of these complications are scarce.

Early OHSS is triggered by injected human chorionic gonadotrophin (hCG), and the symptoms usually start within a week after oocyte pick-up (OPU), whereas late OHSS is associated with early production of hCG due to pregnancy with symptoms exaggerating

* Corresponding author at: PO Box 140 (Haartmaninkatu 2), FIN-00290 Helsinki, Finland. Fax: +358 9 4717 4801.
E-mail address: kati.korhonen@fimnet.fi (Kati V.M. Korhonen).

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from 10 days after OPU onwards [3]. Based on the clinical symptoms and laboratory findings, OHSS is classified as mild, moderate, severe, or critical [4]. Hematocrit is considered the best indicator of the severity of the syndrome [5], but leukocytosis, hypoproteinemia, and hyponatremia also associate with severe forms of OHSS [6]. Ovarian torsion and the rupture of an ovarian cyst may occur with OHSS, with symptoms of unilateral pain and anemia [7,8]. Described risk factors for OHSS include young age, polycystic ovarian syndrome [9], high antral follicle count and anti-Müllerian hormone level [10], but OHSS is still difficult to predict and prevent [11,12].

C-reactive protein (CRP), an acute phase protein produced by the hepatocytes, is a marker of systemic inflammation, tissue damage, and/or infection [13]. CRP measurement is of value in differential diagnosis for bacterial and viral infections and postoperative complications [14]. CRP has been suggested to exclude concomitant infection in OHSS [7]. However, the effect of OPU on CRP in high-response IVF cycles and the role of CRP in the differential diagnosis of IVF complications are unclear. The aim of this study was to assess the CRP response in conjunction with other routine laboratory parameters as an indicator of IVF complications, especially early OHSS.

Material and methods

This prospective cohort study of IVF patients was conducted at Helsinki University Hospital, Department of Obstetrics and Gynecology, Finland in 2006–08, approved by the local Ethical Committee. The study complies with the Strobe criteria [15]. Sixty-five women with OHSS symptoms were recruited from the outpatient emergency polyclinic with informed consent. We excluded five patients with mild OHSS, as only moderate and severe forms do need special care and treatment [4,9]. Thus we had 60 *acute patients*, with referral either from private clinics (68%) or from our IVF unit. Forty-seven patients had OHSS, and 13 some other IVF complication. Three patients had admissions both as early and late OHSS, resulting in 50 OHSS cases: 36 (72%) early and 14 (28%) late OHSS (Fig. 1).

Data on patient characteristics, medical history, infertility treatments, and symptoms were retrieved through a structured questionnaire and medical records. The physician on duty did a gynecological and ultrasound examination, an X-ray in the case of dyspnea, and made the decisions about hospitalizing (n = 47, 78%) or discharging the patient, treatment with intravenous fluids, drainage of ascites and pleural fluid. A voluntary follow-up visit a week after discharge was offered to those hospitalized (n = 42, 89%).

OHSS was combined with another diagnosis in eight cases (four pelvic and two urinary infections, two suspected ovarian torsions). Fever (≥38 °C) with intense abdominal pain was regarded as an infection. The severity of OHSS was graded by common criteria [4] and we identified the symptomatically worst day during hospitalization (dyspnea, fever, diminished diuresis, maximum waist circumference, weight, and drainage of ascites or pleural fluid).

As *controls*, we recruited 30 infertile women, from our IVF unit with informed consent, who had a possible risk factor (Table 1) for developing OHSS [16] when signing up for their IVF cycle or at timing of OPU. All women were treated with a standard (reduced doses) long gonadotrophin releasing hormone agonist protocol [17], as the antagonist protocol had not yet been introduced in practice at our IVF unit. Three patients developed OHSS, resulting in 27 controls.

All blood samples were categorized as days after OPU (OPUd). Samples including serum and plasma for freezing (−80 °C) were collected from the *acute patients* on admission, daily or every other day on the ward, and at the follow-up visit; and from the *controls* prior (mid-luteal phase), repeatedly during (10th day of stimulation, OPU, OPU2, OPU7, OPU14) and after IVF cycle (OPU35).

All parameters were measured with accredited methods at the Helsinki University Hospital Laboratory (HUSLAB). For CRP

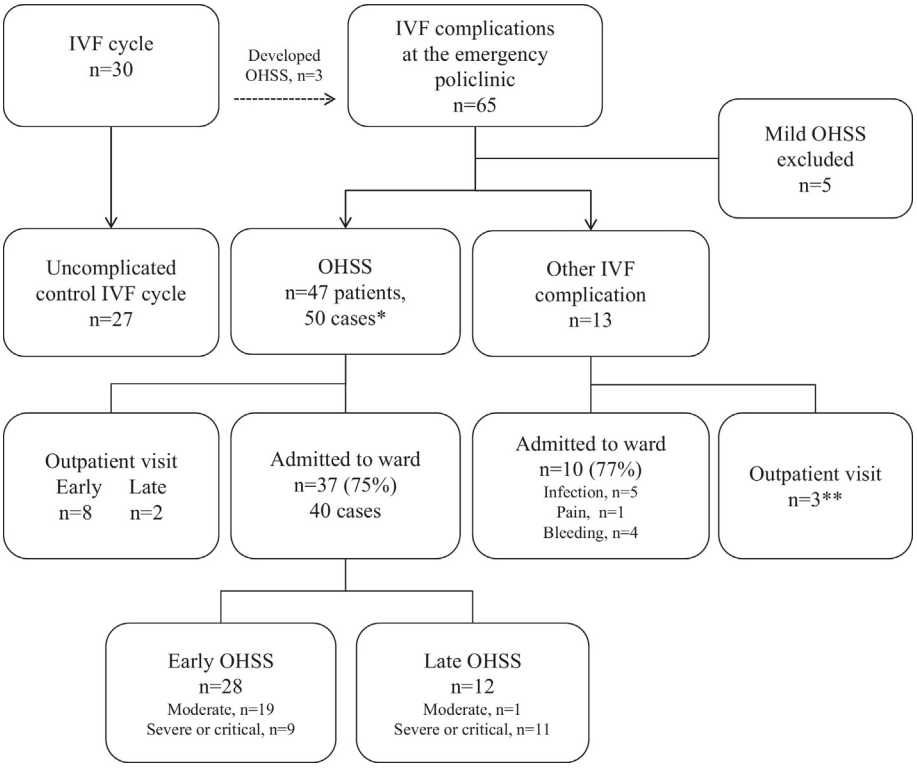

Fig. 1. Flow-chart of the recruitment and classification of patients in the study. IVF: *in vitro* fertilization; OHSS, ovarian hyperstimulation syndrome. *Three patients had both early and late OHSS. **Gastroenteritis or unexplained pain.

Table 1
The patient characteristics. The data are expressed as number of patients (%), or mean ± standard deviation.

	Control cycle[a]	Early OHSS	Late OHSS	Other IVF complication	
n	27	36	14	13	*p*-Value
Age (years)	34.0 ± 2.4*	31.6 ± 4.4*	34.5 ± 3.6	34.1 ± 4.1	0.019
BMI (kg/m^2)	23.6 ± 3.5	22.2 ± 3.2	21.6 ± 2.7	23.3 ± 3.9	0.284
Smoking	2 (7)	1 (3)	1 (7)	2 (15)	0.477
Duration of Infertility (years)	4.6 ± 2.8	4.2 ± 2.4	2.8 ± 1.3	4.6 ± 3.3	0.181
Etiology					0.110
Male	4 (15)	9 (25)	5 (36)	0	
Female	6 (22)	9 (25)	6 (43)	6 (46)	
Combined	7 (26)	8 (22)	0	1 (8)	
Unexplained	10 (37)	8 (22)	3 (21)	6 (46)	
Ovum donor	0	2 (6)	0	0	
Risk factor[b]	21 (78)	22 (61)	4 (29)	4 (31)	0.004

Abbreviations: OHSS, ovarian hyperstimulation syndrome; IVF, *in vitro* fertilization; BMI, body mass index.
[a] Inclusion criteria: previous OHSS; previous cycle cancelation due to high response; a prior IVF cycle with ≥15 follicles; a young woman with male or unexplained infertility starting her first cycle.
[b] Previous OHSS, anovulation, polycystic ovary syndrome, BMI < 20 kg/m^2, or age < 25.
Group differences were analyzed by using one-way ANOVA for parametric variables; Kruskal–Wallis tests for nonparametric variables; and Chi-Square test for categorical variables; *$p < 0.05$.

particle-enhanced immunoturbidimetric assay (Tina-quant C-Reactive Protein Gen.3®, Roche Diagnostics, Rotkreuz, Switzerland) on a Modular Analyzer® (Hitachi Ltd., Tokyo, Japan) was used; detection limit 3 mg/L.

We analyzed the data using SPSS for Windows® (version 18). Values above or below the detection limit were given an arbitrary value, either twice the upper detection limit or 0.5 times the lowest detection limit, respectively. Distribution of the variables was assessed by the Shapiro–Wilk test. Statistical tests between and within the groups are specified in the Tables and Figures. For correlations, we used Pearson's or Spearman's coefficient tests. Data are expressed as median; inter-quartile range (IQR) or mean ± standard deviation (SD) unless otherwise stated. The level of significance was $p < 0.05$.

The main outcome measure was CRP. *Post hoc* power analysis revealed that at OPU2 we had 93% power ($1 - \beta$) to detect the difference in the CRP levels between the controls and early OHSS when the α-level was set at 0.05. The diagnostic accuracy of CRP for early OHSS at the emergency polyclinic was analyzed by receiver-operating characteristic (ROC) curve analysis and expressed as the area under the curve (AUC).

Results

The clinical characteristics of the study groups were otherwise comparable, but patients with early OHSS were younger than the controls (Table 1). All patients were generally healthy, asthma being the most common complaint (7%). A known risk factor for OHSS (Table 1) was associated with early OHSS ($p = 0.04$ *vs.* late OHSS). The severe or critical forms of OHSS were more frequent with late than early OHSS (79% *vs.* 25%, $p = 0.001$). Early OHSS was characterized by a higher number of follicles and retrieved oocytes, as well as preventive procedures (more antagonist cycles, lower cumulative doses of gonadotrophins, and fewer embryo transfers) than the other groups (Table 2).

The symptomatically worst day on the ward with early OHSS was OPU5 (range 2–8); OPU16 (13–32) with late OHSS; and OPU2 (0–8) with other IVF complications. Eight patients were febrile, four of whom had early OHSS with infection, the rest with other IVF complications. Twelve patients received antibiotics: eight with early OHSS, one with late OHSS, and three with other IVF complications. Three patients underwent laparoscopy: one with early OHSS and ovarian torsion and two as intra-abdominal bleedings.

Table 2
The treatment characteristics. The data are indicated as patient number (%) or median (inter-quartile range).

	Control cycle	Early OHSS	Late OHSS	Other IVF complication	
n	27	36	14	13	*p*-Value
Agonist protocol	27 (100)	23 (64)	11 (79)	9 (69)	0.006
Starting FSH dose (IU)	150 (137–163)	150 (125–175)	150 (109–191)	163 (138–188)	0.070
Cumulative FSH dose (IU)	1500 (1275–1725)	1288 (1063–1513)	1688 (1175–2201)	2000 (1325–2675)	0.002
Triggering dose (IU)					<0.001
hCG 5000	9 (33)	33 (92)	7 (50)	6 (46)	
hCG 10,000	18 (67)	3 (8)	7 (50)	6 (46)	
GnRH analog	0	0	0	1 (8)	
Luteal support[a]	26 (96)	19 (53)	14 (100)[b]	10 (77)	<0.001
Follicles at OPU	19 (12–26)	37 (27–47)	21 (18–24)	16 (11–21)	<0.001
Ovum count	11 (7–16)	20 (13–27)	17 (16–19)	11 (9–13)	<0.001
Transferred embryos					0.014
No transfer	1 (4)	17 (47)	0	3 (23)	
One embryo	25 (93)	18 (50)	11 (79)	9 (69)	
Two embryos	1 (4)	1 (3)	3 (21)	1 (8)	
Pregnancy rate	12 (46)	7 (37)	14 (100)	6 (60)[c]	0.002

Abbreviations: OHSS, ovarian hyperstimulation syndrome; IVF, *in vitro* fertilization; FSH, follicle stimulating hormone; hCG, human chorionic gonadotrophin; ET, embryo transfer; OPU, ovum pick-up; GnRH, gonadotrophin releasing hormone.
[a] Vaginal progesterone after embryo transfer.
[b] One patient had additional hCG.
[c] One twin pregnancy.
Group differences were analyzed by using one-way ANOVA for parametric variables; Kruskal–Wallis test for nonparametric variables; and Chi-Square test for categorical variables.

Table 3
Laboratory parameters on admission according to the study group. The data are expressed as median (inter-quartile range) if not otherwise stated.

	Early OHSS	Late OHSS	Other IVF complication	*p*-Value	Control cycle	*p*-Value vs early OHSS
n	36	14	13		27	
Days after OPU	OPU3 (1–8)[a]	OPU13 (8–17)[a]	OPU2 (0–7)[a]		OPU2-3	
CRP (mg/L)	21 (8–33)[#]	6 (3–9)[#]	3 (<3–27)	0.009	5 (<3–22)	<0.001
WBC (E9/L)	13.6 (11.4–15.8)	11.7 (9.9–13.5)	12.1 (8.9–15.3)	0.191	9.5 (5.4–13.5)	<0.001
HCT (%)	41 (38–44)[*]	43 (37–48)[*2]	38 (34–42)[*,*2]	0.030	39 (34–43)	0.038
PLC (E9/L)	256 (214–298)[#]	343 (271–415)[#,#2]	218 (180–257)[#2]	<0.001	257 (191–485)	0.912
E2 (nmol/L)	9.6 (5.8–13.4)[#]	7.3 (5.4–9.2)[**]	3.4 (1.2–5.6)[#,**]	<0.001	3.7 (1.2–9.3)	<0.001
Alb (g/L)	35.1 (32.1–38.1)	32.3 (29.4–35.3)[#]	37.4 (35.5–39.3)[#]	0.002	N.A.	
Na (mmol/L)	135 (132–138)	136 (134–138)	136 (134–136)	0.370	N.A.	

Abbreviations: OHSS, ovarian hyperstimulation syndrome; IVF, *in vitro* fertilization; OPU, ovum pick-up; CRP, C-reactive protein; WBC, white blood cell count; HCT, hematocrit; PLC, platelet count; E2, estradiol; Alb, albumin; Na, sodium, N.A. not available.
Normal ranges: CRP < 3 mg/L; WBC 3.4–8.2 E9/L; HCT 35–46%; PLC 150–360 E9/L; Alb 36–48 g/L; Na 137–145 mmol/L.
[*2/#2]: 2 indicates another pair differing with similar (* or #) significance in the comparison.
[a] Median (range).
Group differences were analyzed by one-way ANOVA followed by Tukey or Games Howell *post hoc* tests for parametric variables; Kruskal–Wallis test and Mann–Whitney *U* test for non-parametric variables. $^{*}p \leq 0.05$, $^{**}p \leq 0.01$, and $^{\#}p \leq 0.001$.

On admission, the CRP level was significantly higher in patients with early than late OHSS or the controls (Table 3). The CRP levels did not differ between agonist and antagonist protocol treated patients (data not shown), and did not correlate with the oocyte count in early OHSS. If early OHSS was accompanied with signs of infection, the CRP was higher (55; 29–80 mg/L) than without infection (16; 6–27 mg/L, $p = 0.002$), similarly to other infectious IVF complications (38; 4–73 mg/L, $p = 0.48$). In the ROC analysis, the AUC was 0.74 ($p = 0.001$) with sensitivity of 69% and specificity of 71% for a cut-off CRP of 12 mg/L for early OHSS.

Hematocrit levels exceeded 45% in seven of 20 (35%) severe/critical cases. Platelet count (PLC) levels were higher with late than early OHSS or other complications (Table 3). Thrombocytosis correlated to the severity of OHSS ($r = 0.31$, $p = 0.04$). Hypoalbuminemia was worse in severe/critical OHSS (31.4; 29.6–33.3 g/L) than in moderate OHSS (36.8; 34.0–39.6 g/L, $p < 0.001$).

In control IVF cycles (Fig. 2) CRP levels increased from undetectable at mid-luteal phase to a peak of 5 (<3–9) mg/L at OPU2 ($p = 0.001$) followed by a decrease to 3 (<3–6) mg/L at OPU7 ($p = 0.03$), and to undetectable at OPU14. CRP did not correlate with BMI and the levels were similar in pregnant and non-pregnant patients (data not shown). Of the other parameters, hematocrit, white blood cell count, PLC, and albumin varied significantly, but within normal limits. CRP level at OPU, (but not at OPU2), correlated to the ovum count ($r = 0.42$, $p = 0.03$).

When analyzing CRP in the course of the disease (OPU-related data, Fig. 3), the CRP level in early OHSS was higher than in the controls at OPU2 (28; 10–46 mg/L, $p < 0.001$), and OPU7 (17; 9–25 mg/L, $p = 0.001$, without infection), and reached control levels at discharge (11; <3–23 mg/L). In late OHSS, the CRP level peaked to 8 (<3–18) mg/L, decreased to 6 (<3–11) mg/L at discharge, and was 7 (3–11) mg/L at the follow-up visit. Peak CRP was the highest when early OHSS was complicated with infection (108; 49–166 mg/L; without infection 20; 8–32 mg/L, $p < 0.001$), (Fig. 4). BMI or the drainage of ascites ($n = 23$, 59%) or pleural fluid ($n = 5$, 13%) had no systematic effect on the CRP level. CRP levels after OPU were not affected by IVF treatment outcome (data not shown).

The mean PLC exceeded that of the controls after OPU10 in both late OHSS and in the other IVF complications groups. Plasma albumin levels at OPU7 in early OHSS were lower than in the controls ($p < 0.001$) and remained lower during the entire follow-up. The most serious hypoalbuminemia occurred in late OHSS at OPU16-21 (Fig. 3).

Comments

This prospective study shows that the majority of IVF complications, within a week after OPU, are associated with an elevated CRP response beyond the level induced by OPU, whereas in late OHSS, the CRP response is more stable.

To obtain reliable interpretation of CRP levels in women under IVF treatment we recruited women with clinical risk factors for OHSS. We detected that retrieval of multiple follicles and oocytes induced a peak in CRP at two days after OPU, doubling the pre-treatment level. This CRP response is probably due to the tissue damage and inflammation induced by OPU, ovulation and formation of multiple corpora lutei, and is well in line with earlier studies showing a rise from the day of hCG injection to OPU [18,19] and to the day of embryo transfer [20]. Contrary to some studies [21,22], we found a significant decrease, instead of an increase, in CRP from OPU2 to OPU7. As the half-life of CRP is around 19 h [13], the decrease we found is well in line with the postoperative decline after uncomplicated abdominal surgery [14]. Probably less traumatic OPU and the use of vaginal, not intramuscular, luteal support explain the difference between the studies.

The two to three times higher CRP levels in early OHSS than in the controls, is in line with one earlier study [23]. However, distinguishing early OHSS from infective complications at the emergency polyclinic is difficult. This is also reflected in the ROC/AUC analysis (cut-off value CRP 12 mg/L) for early OHSS, as infections usually exceed this level. Further, fever (>38 °C) has been associated with early severe OHSS in up to half of the patients [24] making the differential diagnosis of infections more complicated. Thus, the decision of antibiotic treatment requires follow-up and consideration of other risk factors for infection, such as puncture of endometriomas or tubal disease, as well as results of urine and possibly blood cultures. However, there is clinical need to search for novel biomarkers for infections [25].

The majority of our severe cases had late OHSS with low CRP levels. The association between severity and late OHSS agrees with a previous study [26]. Another study [27] explained the severity with multiple pregnancies, which was not a factor in this study with mostly singletons. Patients with late OHSS had noticeably less clinical risk factors for OHSS than those with early OHSS, in line with an earlier study [26], further emphasizing the distinct nature of these two forms of OHSS.

In our series, one patient had early OHSS with a rising CRP level from 100 to 150 mg/L (OPU2-4), but no signs of clinical infection or other complications. She had an uneventful surveillance without antibiotics. Another patient with previous mild asthma was treated on the internal medicine ward as pneumonia due to severe breathing difficulties and pleural fluid before diagnosing late OHSS, highlighting the accurate diagnostics and knowledge of OHSS symptoms in emergency polyclinics.

Hemoconcentration (hematocrit ≥45%) as a traditional marker of severe OHSS is arguable as only one third of our patients met this

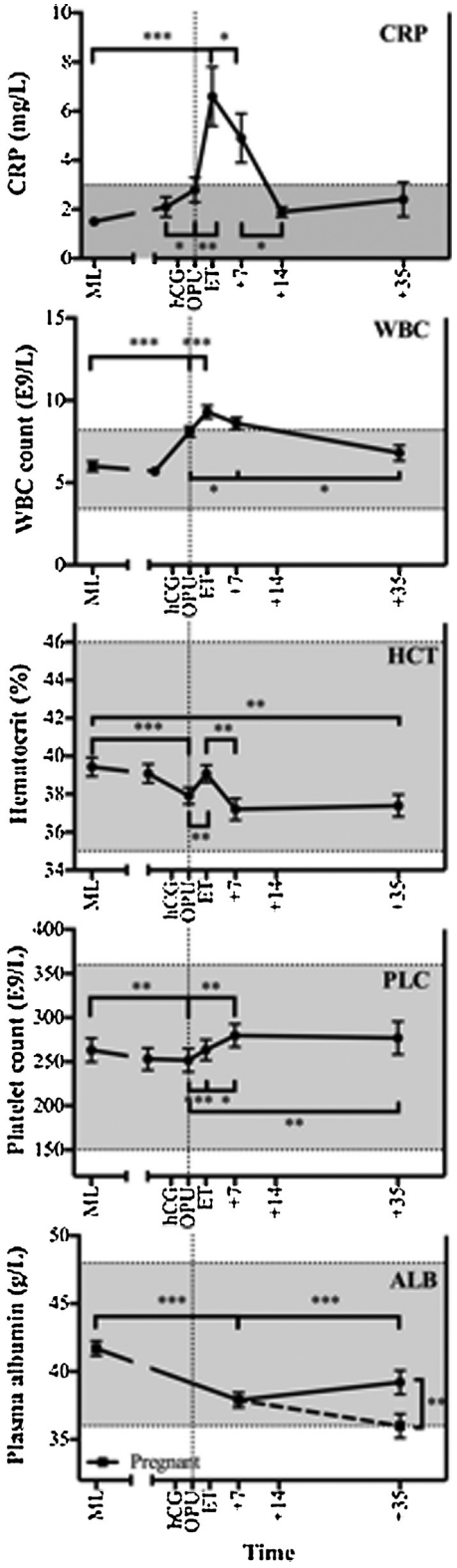

Fig. 2. C-reactive protein (CRP), white blood cell count (WBC), hematocrit (HCT), platelet count (PLC), and plasma albumin (Alb) levels during uncomplicated IVF cycle in women at risk of developing ovarian hyperstimulation syndrome (OHSS). Time points are the mid-luteal phase (ML) prior suppression, one to three days before human chorionic gonadotrophin injection (hCG), ovum pick-up (OPU), embryo transfer (ET), and the days after oocyte retrieval (OPUd). The gray area indicates the normal range of the laboratory values. Albumin levels are shown in pregnant (dashed line) and non-pregnant women. No other pregnancy related findings existed. Pairwise analyses were done by repeated measures ANOVA or Wilcoxon signed rank test. The data are expressed as mean ± standard error of mean; $^{*}p < 0.05$, $^{**}p \leq 0.01$, and $^{***}p \leq 0.001$.

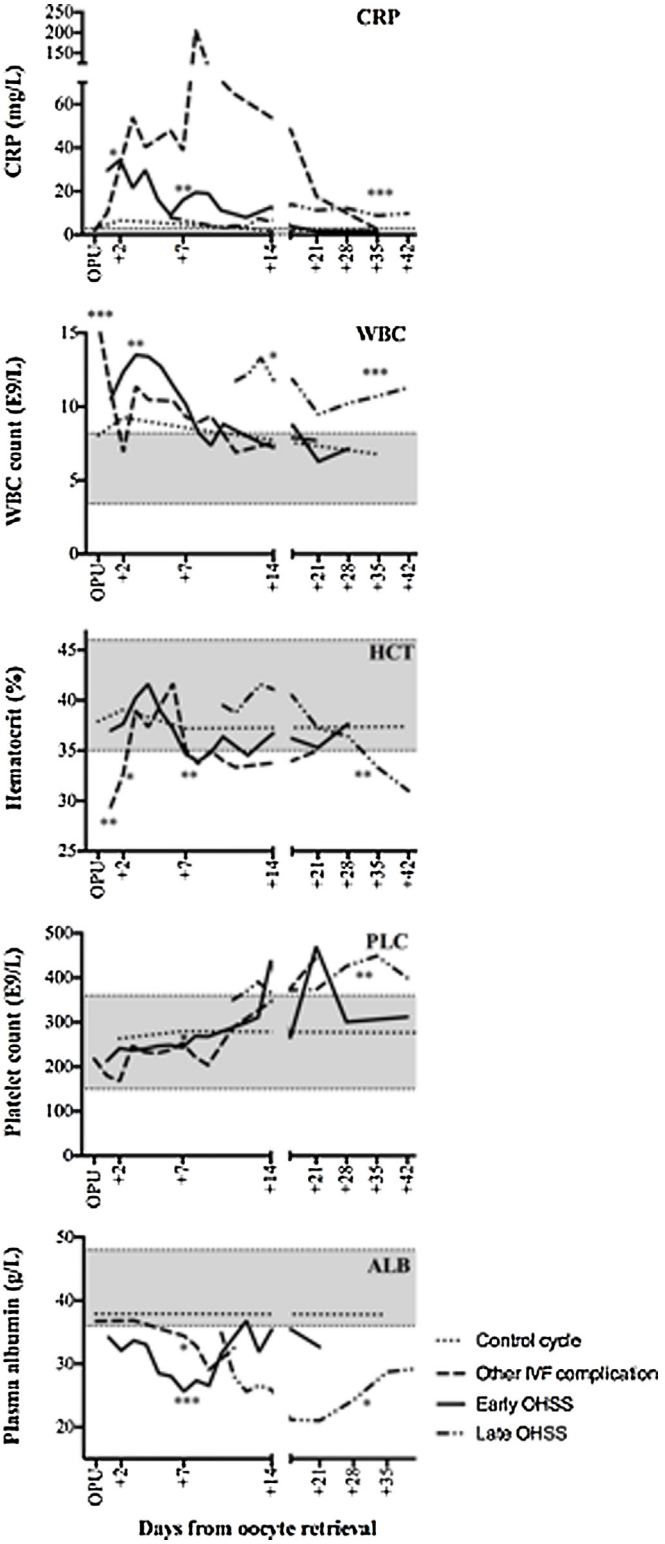

Fig. 3. C-reactive protein (CRP), white blood cell count (WBC), hematocrit (HCT), platelet count (PLC), and plasma albumin (Alb) levels after oocyte pick-up (OPU), during the course of early and late ovarian hyperstimulation syndrome (OHSS), other IVF complications, or during uncomplicated IVF cycle. The OHSS cases complicated with infection were excluded from the analysis. The gray area indicates the normal range of the laboratory values. Group differences were analyzed by Student's *t*-test or Mann–Whitney *U*-test. The data are expressed as mean ± Standard Error of Mean; $^{*}p < 0.05$, $^{**}p \leq 0.01$, and $^{***}p \leq 0.001$ (compared with uncomplicated IVF cycle).

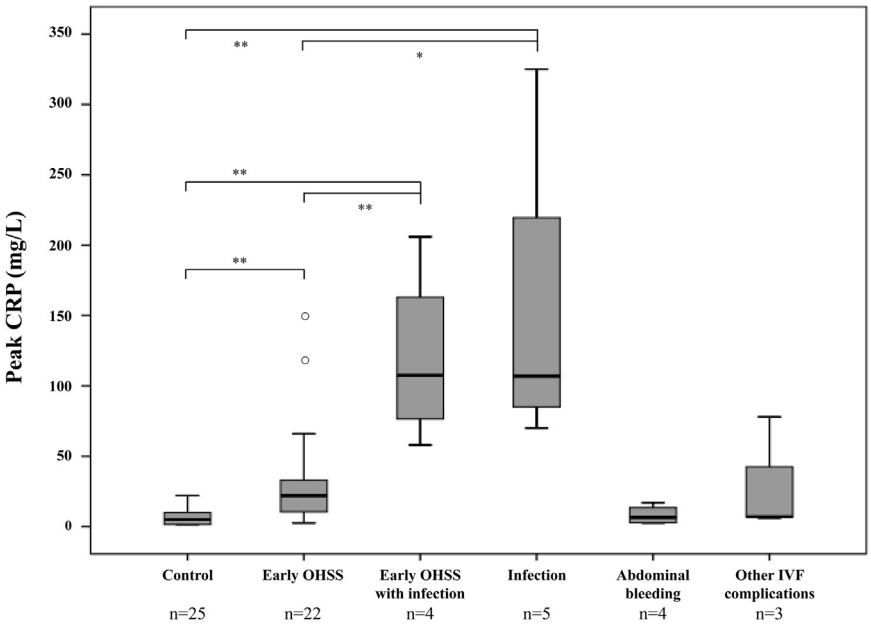

Fig. 4. Peak C-reactive protein (CRP) levels in the early IVF complications. The box represents the inter-quartile range, the line inside indicates the median CRP, and the whiskers represent the first and fourth quartile. ○ Represents the outliers. OHSS, ovarian hyperstimulation syndrome; OPU, oocyte pick-up. Group differences were analyzed by Kruskall–Wallis and Mann–Whitney *U* test. $^{*}p \leq 0.01$, $^{**}p \leq 0.001$ between the groups or compared with uncomplicated IVF cycle.

criterion on admission. This is probably due to the current recommendation to take care of fluid balance during IVF treatment, especially with OHSS symptoms. To our knowledge, only little is known about platelet levels during OHSS or the IVF cycle, although platelets are known to have a role in corpus luteum formation [28]. Our finding of elevated PLC levels from 10 days to over a month after OPU, especially in late OHSS, and the association of PLC level and the severity of the syndrome may relate to inflammatory, interleukin-6 induced PLC formation from bone marrow [29], as elevated interleukin-6 levels have been detected in OHSS [30]. However, thrombocytosis as a marker of hemoconcentration [7] was not supported, as hemodilution and thrombocytosis occurred simultaneously in patients with late OHSS.

A limitation of our study is the small number of IVF complications other than OHSS to evaluate the differences in laboratory parameters in those. It can also be argued that we miss data on the anti-Müllerian hormone in risk factor assessment for OHSS, as it was not in general use at that time. Additionally, the control IVF cycles give no data from antagonist cycles and agonist triggering, a current method used to prevent imminent OHSS [31,32]. However, we think, that the reduced dose agonist cycles show us the best reference levels for emergency polyclinics, as antagonist cycles are supposed to induce less systemic inflammation [19,33]. Further, we could compare most samples of acute patients to the controls after OPU up to OPU14 and at OPU35. To our knowledge, comparisons with this extent have not been reported. We also reached all the most severe IVF complications of the area at our tertiary clinic.

IVF complications offer a diagnostic challenge to the clinician on duty. Knowledge of the day of admission according to OPU and the progress of the preceding IVF protocol is of utmost importance for interpreting laboratory results when evaluating possible IVF complications. Caution is also needed in the interpretation of CRP level with obesity and pregnancy, as these conditions have been associated with elevated levels of inflammatory markers [34–36]. However, the possibility of OHSS, early or late, should always be considered.

In conclusion, without other signs of infection, elevated CRP indicates follow-up, but is not an indication to prescribe antibiotics. We suggest that, a clinically elevated CRP level (>10 mg/L) in the first week after OPU is indicative for early OHSS and/or infection in IVF patients, whereas later, increased platelet count and hypoalbuminemia in patients with embryo transfer, support the diagnosis of late OHSS. Any of these findings, with or without hemoconcentration, indicates follow-up.

Conflict of interest

Our study has been supported by Helsinki University Hospital Research Funds, the State Funding for University Level Research, Serono research grant, The Foundation of Paulo, The Jane and Aatos Erkko Foundation. The study sponsors had no influence on the study design or the reporting. The authors have no competing interests to declare. H.S-P. has received funding for a congress trip from Finox Biotech.

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References

[1] Klemetti R, Sevón T, Gissler M, Hemminki E. Complications of IVF and ovulation induction. Hum Reprod 2005;20:3293–300.
[2] Delvigne A, Rozenberg S. Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review. Hum Reprod Update 2002;8:559–77.
[3] Mathur RS, Akande AV, Keay SD, Hunt LP, Jenkins JM. Distinction between early and late ovarian hyperstimulation syndrome. Fertil Steril 2000;73:901–7.
[4] Golan A, Weissman A. Symposium: Update on prediction and management of OHSS. A modern classification of OHSS. Reprod Biomed Online 2009;19:28–32.
[5] Fábregues F, Balasch J, Manau D, et al. Haematocrit, leukocyte and platelet counts and the severity of the ovarian hyperstimulation syndrome. Hum Reprod 1998;13:2406–10.
[6] Myrianthefs P, Ladakis C, Lappas V, et al. Ovarian hyperstimulation syndrome (OHSS): Diagnosis and management. Intensive Care Med 2000;26:631–4.
[7] Delvigne A, Rozenberg S. Review of clinical course and treatment of ovarian hyperstimulation syndrome (OHSS). Hum Reprod Update 2003;9:77–96.

[8] Vloeberghs V, Peeraer K, Pexsters A, D'Hooghe T. Ovarian hyperstimulation syndrome and complications of ART. Best Pract Res Clin Obstet Gynaecol 2009;23:691–709.
[9] Humaidan P, Quartarolo J, Papanikolaou EG. Preventing ovarian hyperstimulation syndrome: guidance for the clinician. Fertil Steril 2010;94:389–400.
[10] Broer SL, Dólleman M, Opmeer BC, Fauser BC, Mol BW, Broekmans FC. AMH and AFC as predictors of excessive response in controlled ovarian hyperstimulation: a meta-analysis. Hum Reprod Update 2011;7:46–54.
[11] Alama P, Bellver J, Vidal C, Giles J. GnRH analogues in the prevention of ovarian hyperstimulation syndrome. Int J Endocrinol Metab 2013;11:107–16.
[12] Nastri CO, Teixeira DM, Moroni RM, Leitão VMS, Martins WP. Ovarian hyperstimulation syndrome: pathophysiology, staging, prediction and prevention. Ultrasound Obstet Gynecol 2015;45:377–93.
[13] Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest 2003;111:1805–12.
[14] Adamina M, Steffen T, Tarantino I, Beutner U, Schmied BM, Warschkow R. Meta-analysis of the predictive value of C-reactive protein for infectious complications in abdominal surgery. Br J Sur 2015;102:590–8.
[15] http://www.strobe-statement.org
[16] Delvigne A, Kostyla K, De Leener A, et al. Metabolic characteristics of women who developed ovarian hyperstimulation syndrome. Hum Reprod 2002;17:1994–6.
[17] Tiitinen A, Halttunen M, Härkki P, Vuoristo P, Hyden-Granscog C. Elective single embryo transfer: the value of cryopreservation. Hum Reprod 2001;16:1140–4.
[18] Wunder DM, Kretschmer R, Bersinger NA. Concentrations of leptin and C-reactive protein in serum and follicular fluid during assisted reproductive cycles. Hum Reprod 2005;20:1266–71.
[19] Orvieto R, Volodarsky M, Hod E, et al. Controlled ovarian hyperstimulation using multi-dose gonadotropin-releasing hormone (GnRH) antagonist results in less systemic inflammation than the GnRH-agonist long protocol. Gynecol Endocrinol 2007;23:494–6.
[20] Liu B, Zhang L, Guo RW, Wang WJ, Duan XQ, Liu YW. The serum level of C-reactive protein in patients undergoing GnRH agonist protocols for in vitro fertilization cycle. Clin Exp Obstet Gynecol 2014;41:190–4.
[21] Almagor M, Hazav A, Yaffe H. The levels of C-reactive protein in women treated by IVF. Hum Reprod 2004;19:104–6.
[22] Seckin B, Ozaksit G, Batioglu S, Ozel M, Aydogan M, Senturk B. The relationship between the change in serum high sensitivity C-reactive protein levels and IVF success. Gynecol Endocrinol 2012;28:418–21.
[23] Levin I, Gamzu R, Pauzner D, et al. Elevated levels of CRP in ovarian hyperstimulation syndrome: An unrecognised potential hazard? BJOG 2005;112:952–5.
[24] Abramov Y, Elchalal U, Schenker JG. Febrile morbidity in severe and critical ovarian hyperstimulation syndrome: a multicentre study. Hum Reprod 1998;13:3128–31.
[25] Quenot J, Luyt C, Roche N, et al. Role of biomarkers in the management of antibiotic therapy: an expert panel review II: Clinical use of biomarkers for initiation or discontinuation of antibiotic therapy. Ann Intensive Care 2013;3:1–17.
[26] Mathur RS, Akande AV, Keay SD, Hunt LP, Jenkins JM. Distinction between early and late ovarian hyperstimulation syndrome. Fertil Steril 2000;73:901–9.
[27] Lee KH, Kim SH, Jee BC, et al. Comparison of clinical characteristics between early and late patterns in hospitalized patients with ovarian hyperstimulation syndrome. Fertl Steril 2010;93(7):2274–80.
[28] Furukawa K, Fujiwara H, Sato Y, et al. Platelets are novel regulators of neovascularization and luteinization during human corpus luteum formation. Endocrinology 2007;148:3056–64.
[29] Burmester H, Wolber E, Freitag P, Fandrey J, Jelkmann W. Thrombopoietin production in wild-type and interleukin-6 knockout mice with acute inflammation. J Interferon Cytokine Res 2005;25:407–13.
[30] Wei L, Chou C, Chen M, et al. The role of IL-6 trans-signaling in vascular leakage: Implications for ovarian hyperstimulation syndrome in a murine model. J Clin Endocrinol Metab 2013;98:E472–84.
[31] Youssef MA, Van Der Veen F, Al-Inany HG, et al. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology. Cochrane Database Syst Rev 2014;10:CD008046.
[32] Toftager M, Bogstad J, Bryndorf T, et al. Risk of severe ovarian hyperstimulation syndrome in GnRH antagonist versus GnRH agonist protocol: RCT including 1050 first IVF/ICSI cycles. Hum Reprod 2016;0:1–12.
[33] Orvieto R, Zagatsky I, Yulzari-Roll V, La Marca A, Fisch B. Substituting human chorionic gonadotropin by gonadotropin-releasing hormone agonist to trigger final follicular maturation, during controlled ovarian hyperstimulation, results in less systemic inflammation. Gynecol Endocrinol 2006;22:437–40.
[34] Visser M, Bouter LM, McQuillan GM, et al. Elevated C-reactive protein levels in overweight and obese adults. JAMA 1999;282(22):2131–5.
[35] Sacs GP, Seyani L, Lavery S, Trew G. C-reactive protein levels are raised at 4 weeks gestation. Hum Reprod 2004;19(4):1025–30.
[36] CohenY, Ascher-Landsberg J, Cohen A, Lessing B, Grisaru D. The role of C-reactive protein measurement as a diagnostic aid in early pregnancy. EJOG 2014;176:64–7.