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Correlation Between Vascular Endothelial Growth Factor (VEGF) and Ovarian Hyperstimulation Syndrome (OHSS); A Retrospective Study

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1. Abstract

Purpose: In the context of in vitro fertilization treatment ovarian hyperstimulation syndrome can lead to a serious illness. Its pathogenesis is not fully understood, but is associated with several cytokines, enzymes and growth factors. VEGF is considered among others to be a significant factor. The aim of the present study was to investigate whether there are correlations between VEGF serum concentrations and clinical and biochemical parameters of ovarian hyperstimulation syndrome. Thus, VEGF could be used as a clinical parameter of ovarian hyperstimulation syndrome.

Methods: Three patient groups were formed in which VEGF measurements were performed. In the first group, patients with ovarian hyperstimulation syndrome after stimulation treatment and hospitalization were examined. In the second group, patients with stimulation for in vitro fertilization but without OHSS were considered and in the third group, patients without stimulation treatment were recorded. The groups were comparatively statistically evaluated.

Results: There was a clear association between the VEGF scores and duration of hospitalization in the diseased patients. The VEGF determinations did not differentiate between stimulated patients with and without ovarian hyperstimulation syndrome. However, there was a significant difference between stimulated and unstimulated patients.

Conclusion: The determination of VEGF seems to be of limited use as a clinically useful parameter for the assessment and prognosis of ovarian hyperstimulation syndrome. Methodological weakness of the retrospective study design should be a reason for caution in interpreting the results.

2. Keywords: In-vitro-Fertilization; Ovarian Hyperstimulation Syndrome; Vascular Endothelial Growth Factor (VEGF); Cytokines; Reproductive Medicine; Gonadotropins

3. Introduction

Ovarian hyperstimulation syndrome is a potentially life-threatening condition, which can occur as part of an in vitro fertilization treatment [1].

Over the past 10 years, severe ovarian hyperstimulation syndromes have been reported less frequently. The German IVF Register (D.I.R) for example recorded 0.32% overstimulation syndromes grade III (WHO classification) in 2008. In 2017, the share was only 0.2%. This can be attributed for example to the increasing use of the antagonist

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protocol (from 31.8% to 64.2%), which allows the possibility of final oocyte maturation with GnRH analogues [2]. In combination with cryopreservation of fertilized oocytes, almost complete avoidance of serious ovarian hyperstimulation syndromes is possible [3-5]. In order to avoid the fragmentation of the cycle and an OHSS, modified protocols [6] are used with low dose of HCG [7], estradiol and progesterone [8,9].

Despite all approaches, patients with ovarian hyperstimulation syndrome continue to be hospitalized. Thus, in a 2015 survey of the Federal Statistical Office, 1533 cases were recorded with the ICD N98 [10], which is a considerable deviation from the D.I.R. reports.

4. Aetiology and Clinic

Pathogenesis is based on a multifactorial event [11] but so far, its aetiology has not been completely understood yet [12]. However, there is a direct correlation between the use of gonadotropins for stimulation and HCG for final oocyte maturation or HCG increase as a consequence of early pregnancy [12,13]. HCG can be seen as the main trigger for development of OHSS [14]. Sporadic ovarian hyper stimulation syndromes can be attributed to FSH and LH receptor mutation [15-18] or hypothyroidism [19]. However, rare cases of OHSS have also been reported after stimulation with clomiphene citrate [20,21].

The predisposing factors and risks for the development of severe OHSS include young age, normal BMI [22,23], PCO [24] ethnicity, high oocyte reserves [25,26], the use of a long protocol (GnRH protocol) [27], about 15-20 diagnosed follicles >10 mm-13 mm before final oocyte maturation [21], an estradiol level in the serum 12.850 pmol/L, more than 20 won oocytes [28-30] and the onset of pregnancy, especially of a multiple pregnancy [22]. An elevated inhibin A and B level has also been described [31].

The glycoprotein VEGF (Vascular Endothelial Growth Factor) plays a key role in the pathophysiology of OHSS [32,33]. The family of VEGF proteins are classified into different subtypes A-E and PIGF (Phosphatidylinositol-glycan biosynthesis class F protein, a placenta growth factor) [34] and they are also involved in major neovascularization [35], organ and tumour signalling processes [36-38]. Splicing produces various biologically active isoforms [39].

VEGF binds to receptors of endothelial cells [34] and various immune cells [40]. It contributes to an increased cell division rate, angiogenesis and loosening of the cell assemblage, which is essential for the physiological processes of the corpus luteum [34,41], endometrial and placental development and embryogenesis. HCG triggering increases the expression of VEGF mRNA in the luteinized granulosa cells [42,43]. In addition, renin and its associated renin-angiotensin-aldosterone system and other secreted cytokines [44-46] are described in association with OHSS formation [47,48].

An important pathophysiological phenomenon is fluid displacement from the intravascular space [11], which leads to ascites, pleural effusion and, in rare cases, pericardial effusion. In severe cases, an anasarca can be observed.

With the discharge of protein-rich fluid with sometimes hemodynamically relevant volumes, further extravasation occurs, resulting in hypotension and tachycardia [49]. With hemodynamic disorder, renal perfusion may be impaired [22,50]. Protein losses as well as renal dysfunction can lead to a severe electrolyte imbalance with hyponatraemia and hyperkalaemia. Frequently, hepatic metabolic disorders and pancreatic enzyme changes are also observed [51].

Intravascular fluid loss results in altered blood rheology and haemoconcentration, which is associated with a significant increasing risk of thrombosis [52,53]. The occurrence on anatomically unusual vessels must be considered (arm vessels). Brain infarcts were also observed in rare cases [54]. However, the effects of the cytokines on the

endothelial cells may also contribute to the increased risk of thrombosis. The immobilization of the patient is exacerbated by abdominal and pulmonary symptoms [30,55].

Abdominal complications, in addition to mechanical obstruction by ascites of the urinary tract [56], may occur in the form of a massive enlargement of the ovaries, which may be associated with adnexal torsion and subsequent organ failure [57].

The manifestation of symptoms can range from very minor complaints to intensive care-related illnesses. Over time, various gradual classification systems have been designed, which are based on three increasing degrees [58]. A corresponding proposal for the degrees of severity of OHSS is shown in Table 1.

Table 1: Classification of the OHSS according to [79].

Severity	Grade	Symptoms
Mild	1	- Abdominal distension - Malaise
	2	- Characteristics of grade 1 + Nausea and vomiting and / or diarrhea + Enlargement of the ovaries to 5 cm-12 cm
Moderate	3	Characteristics of mild OHSS + Sonographic evidence of ascites
Severe	4	Characteristics of moderate OHSS + Clinical evidence of ascites and / or pleural effusion or dyspnea
	5	All characteristics from grade 1-4 + changes of blood: • Hemoconcentration with • Increase in blood viscosity • Coagulation disorders • Reduced renal perfusion/function

The extent to which an OHSS has an influence on the pregnancy is still unclear. Gestational diabetes, pregnancy-induced hypertension, preterm birth and birth weight are discussed [59,60].

5. Question

The aim of this retrospective study was to find out if there are indications for correlations between VEGF serum concentration and clinical and biochemical parameters of ovarian hyper stimulation syndrome. Thus, VEGF could be used as a clinical parameter of ovarian hyper stimulation syndrome.

6. Material and Methods

The data evaluation complied with the principles of the Helsinki Declaration. The investigation of surplus material for the purpose of scientific research is defined in the general terms and conditions of the Mainz University Medical Centre.

The processing of the data was anonymized and the evaluation was carried out on the basis of excess material for diagnostic laboratory tests, which was cryopreserved under the precondition of subsequent laboratory evaluation and the patient's consent.

The following three groups were formed:

1. Case group: Hospitalized OHSS-patients.
2. Control group 1: stimulated patients without OHSS.
3. Control group 2: unstimulated, non-pregnant patients.

6.1. Case Group

In the period between 2011 and 2014, 31 inpatients with OHSS and their corresponding cryopreserved samples were listed in the Mainz University Hospital and their basic parameters and clinical status were documented.

Initially, age, date of hospital admission, body height in cm, degree of OHSS at admission [1-5], time between follicular puncture or HCG administration and time of inpatient admission were recorded. Appearance of OHSS was divided into Early Onset (hospital admission 1-9 days after follicular puncture) and Late Onset (>9 days after follicular puncture). This was supplemented by recording the weight measurement in kg and haematocrit determination in %. To obtain a representative BMI, the lowest weight was chosen during inpatient stay.

During hospitalization two samples for VEGF measurement were taken. The first blood sample was from the date of hospital admission and the second during the highest signs of haemoconcentration as determined by the haematocrit. In addition, nine of the OHSS-treated patients had serum samples before ovulation induction and 14 days after embryo transfer, as these patients were treated at the Fertility Centre of the Mainz University Women's Hospital. For these patients at time of embryo transfer there were no clinical signs of OHSS observed.

6.2. Control Group 1

The first control group was obtained from the fertility centre at the University Women's Hospital Mainz by matched pair method but without development of OHSS. We included and compared only patients with similar age, year of treatment and sample measurement, BMI, male infertility as reason for fertility treatment, similar medication for stimulation, downregulation and final oocyte maturation. 31 patients could be selected for the matching procedure. The examined cryopreserved samples had been taken on the day of final oocyte maturation and 14 days after embryo transfer. These patients did not develop any signs of OHSS in between. 62 individual samples were examined.

6.3. Control group 2

The second control group included women who had no stimulation treatment and were not pregnant. Here, 31 patients from the fertility centre of the University Women's Clinic Mainz were recorded for whom a diagnostic laboratory examination was carried out during the consultation. The matching procedure was analogous to control group 1.

6.4. Determination of VEGF

To obtain the serum, it was centrifuged after coagulation and the samples were cryopreserved. For the determination of VEGF, room temperature was maintained and the measurement was carried out without interruption according to the procedure described below.

The in-house laboratory measured the samples with the Human VEGF Quantikine® Elisa kit from R&D Systems GmbH, Wiesbaden Germany. It is a sandwich solid phase enzyme immunoassay. The monoclonal antibody-coated microtiter plates are re-incubated for 2 hours. After two hours of incubation with the sample, washing and addition of one VEGF conjugate followed. After further washing steps, the appropriate substrate solution was coated, incubated and after addition of a stop solution, the colour change is measured at 450 nm using a calibrated microtiter plate photometer (Multiscan FC, Thermo Fisher Scientific, Massachusetts, USA). In each case, a standard and control measured value was investigated parallel to the test sample, with the result that the standard curve was used to determine the concentration using the 4-parameter equation.

6.5. Statistical Evaluation

The evaluation of the data was carried out explorative, whereby the p-values are to be interpreted descriptively. This also resulted from the variety of tests. A multiple test correction did not occur.

In the case group mean, median, standard deviation, skewness, standard skewness, minimum and maximum, as well as the frequency distribution of age, BMI (from the lowest weight during the whole inpatient stay), inpatient length of stay and time interval between follicular aspiration and inpatient admission were determined. Furthermore, for the duration of the inpatient stay mentioned statistical parameters were calculated on the bases of the maximum haematocrit, the maximum weight difference, the mean serum VEGF concentration and the maximum serum VEGF concentration.

Furthermore, in the case group onset type of OHSS (early or late onset), the presence of ascites or pleural effusion, the necessity of ascites- and/or pleural puncture, the need for analgesic therapy and the onset of pregnancy were recorded to illustrate the clinical condition of the patients as far as possible.

In the control groups mean, median, standard

deviation, skewness, standard skewness, minimum and maximum were analyzed for VEGF concentrations.

In the case of a linear relationship, the correlation using the Pearson correlation coefficient was otherwise calculated using the Spearman correlation coefficient.

Statistical analyses were performed with normal distribution (Shapiro-Wilk test: $p > 0.05$) using the T test for independent samples and in the absence of normal distribution by Mann-Whitney U test. Before evaluation with the T-test, variance heterogeneity was excluded in the Levène test.

7. Results

7.1. Case Group

Within the case group with 31 patients, about 64.5% of the patients were ≤ 35 years old. 66.67% were normal weight with a BMI ≤ 25 kg / m^2. The average time between puncture and inpatient admission was 12.84 days and the inpatient stay was 8.58 days. The average maximum haematocrit value was 42.97%, the maximum weight difference averaged 3 kg. The maximum VEGF serum value determined during hospitalization was 3201.89 pg/ml and averaged 417.65 pg/ml. Of these, 67.7% had a late onset OHSS.

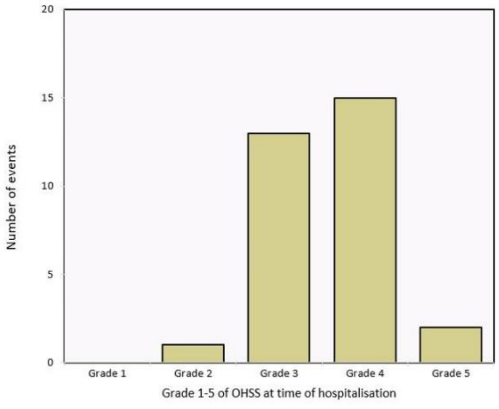

Figure 1: OHSS grade at time of hospitalisation.

From 25 patients, where pregnancy tests were obtainable, 22 got pregnant. 67.7% of the case group had a late onset OHSS and 32.3% an early onset OHSS. 96.8% of those affected had ascites and 16.1% had pleural effusions, of which 12.9% of the ascites and no pleural effusion had to be punctured. 61.3% of patients needed analgesic treatment.

Correlation analysis showed no correlation between VEGF means and age, inpatient length of stay, haematocrit maxima and maximum weight difference. The BMI only showed a weak negative correlation.

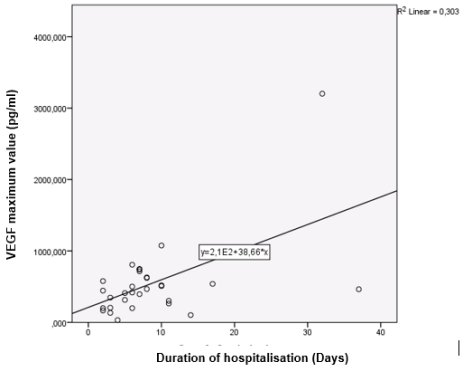

Figure 2: Correlation between VEGF maximum values and hospital stay.

The correlation coefficients for the VEGF maxima with respect to age, BMI and haematocrit maxima only showed a weak negative and for the maximum weight difference a weak positive tendency. Only for the inpatient length of stay there was an indication for a positive correlation ($p = 0.001$).

The OHSS grade as well as the onset types showed no correlation to the measured VEGF values. Also, evidence for a correlation between OHSS grade and hospital stay was weak.

7.2. Comparison of Groups

Both, VEGF mean values and maximum values, showed higher values in control group 1 than in control group 2.

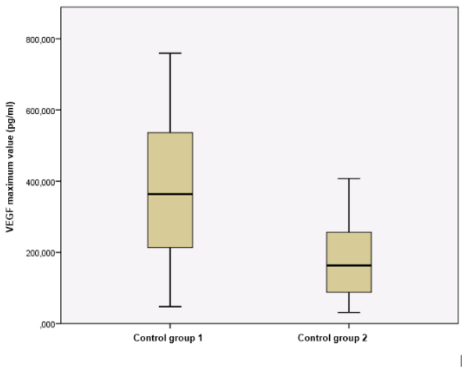

Figure 3: Comparison of VEGF measurements (maximum values) between the control groups.

VEGF mean on average was higher in the case group (238.12 pg/ml) than in control group 2, which statistically was a recordable difference ($p < 0.001$; $t(42.292) = 5.349$).

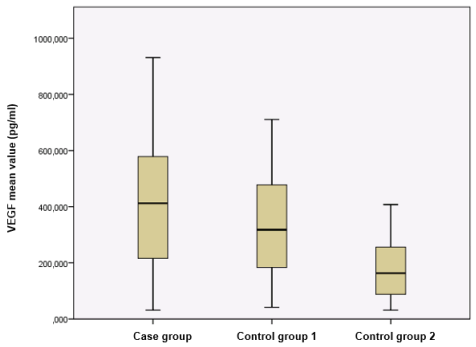

Figure 4: Comparison of VEGF measurements (mean) between case group and control groups.

For the comparison of the VEGF mean values between case group and control group 1, no statistically meaningful statement was made ($p = 0.095$, $t(57.614) = 1.697$). Likewise, the tendencies of the VEGF maximum values were not different in comparison.

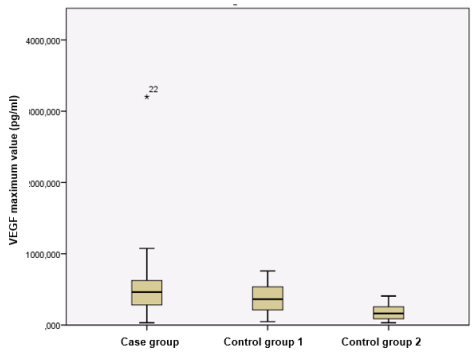

Figure 5: Comparison of VEGF measurements (maximum values) between case and control groups.

8. Discussion

Among women diagnosed with OHSS, age and BMI correlated with the expected risk factors, with higher prevalence among younger women and those of normal weight [22,23,61]. In line with the known data, inpatients showed a higher incidence of late onset events [62] and pregnancies [22,63]. This correlates with HCG of ongoing pregnancy. The incidence of ascites and concomitant weight gain and, to a lesser extent, pleural effusions in the case group are consistent with general observations on OHSS [11].

Regarding the age of the case group patients and VEGF values, no meaningful connection could be found in this work. We found only a slight tendency for younger OHSS patients to reach the slightly higher VEGF maximum level during their inpatient stay, which was not significant.

With regard to haematocrit, which showed a positive correlation in various studies [64,65], there was no increase in the examined patients- only in a few cases. This may lead to the fact that some patients have already started therapy when they were first measured.

For the body mass index, no meaningful correlation could be found in the VEGF measurements, but a slight positive correlation between maximum weight gain during hospital stay and maximum VEGF level could be observed, which correlates with known data. But it must be relativized by missing confirmation in the correlation analysis of VEGF means and weight gain.

This can be explained by the fact that BMI was measured at hospitalization, where patients already had a fluid retention affecting their bodyweight. The missing significant correlation with the above measurements must be seen as a result of methodology of this retrospective study, where standardized data collection is missing, especially before an OHSS.

Interestingly, in contrast to existing studies [66], there was no correlation between the severity of OHSS and the measured VEGF. Patients with higher grade OHSS did not show statistically significant higher serum VEGF concentrations as patients with less severe overstimulation at the time of inpatient admission. As 96% of the patients in the case group developed ascites, a possible bias of misleading use of OHSS classification system can be neglected. Statistical analysis of the available data did not reveal any meaningful differences in VEGF measurements

between patients with early onset and those with late onset OHSS.

We only found a positive significant correlation for the length of inpatient stay and VEGF maximum values, which could speak for the expected increased activity and could be related to the severity of the disease or the needed treatment. This in turn confirms the relationship between the disease and the VEGF

Furthermore, OHSS patients of the case group were compared with control group 1 consisting of similarly stimulated women, who in turn had not developed overstimulation syndrome after stimulation and HCG trigger. The differences in the VEGF mean and maximum values were statistically evaluated. Here we found no statistically significant differences. Nevertheless, OHSS patients showed a slight tendency of higher VEGF values than the control group patients. It should be mentioned that such contradictory findings are also present in literature [38,67-71] and indicates a possibly low clinical relevance of VEGF measurements in clinical routine [72], which is also confirmed by various studies [62,73-76].

We included control group 2 to show VEGF levels in patients without stimulation and OHSS. By introducing this group, we wanted to demonstrate VEGF level differences to patients with stimulation and with and without OHSS. A clearly higher level of VEGF was demonstrated in the case group and the control group 1 in comparison to control group 2. As we found no clear differences between the case group and the control group 1, stimulation is a mandatory factor, which matches the aetiology of OHSS [66,77]. Contradictory results possibly can be explained by an insufficient amount of measurements of VEGF. More frequent and strict standardized measurements could give a more detailed insight of discrete VEGF secretion alterations, which were limited by the retrospective study design as investigations were done on surplus material of emergency patients. This can also be applied to the biometric and biochemical data evaluation, which can be improved by a prospective study design. Another possible reason for bias could be the limited reproducibility due to the single centre design.

Besides methodical weaknesses of the study, other individual factors for angiogenesis should be assumed, which induces OHSS. These could be other cytokines and genetic predispositions as the patient has a clear risk for recurrence in other treatment cycles. We think that VEGF is only a part in the development of OHSS and cannot explain the origin of OHSS alone. Based on the results further investigation with consideration of the number of follicles before puncture, determination of the isoforms, FSH-LH receptor analyses, further cytokines and the VEGF mRNA content of the granulosa cells would be meaningful to obtain more precise statements on the VEGF measurement. Thus, due to the extensive context of VEGF, a sole clinical determination does not seem to be helpful.

9. Summary

Compared to other studies on VEGF, the number of patients included is relatively large. However, it is a retrospective evaluation, without standardized protocols for the carried-out investigations. VEGF plays an important role in the development of ovarian hyper stimulation syndrome. For now, it seems to be of limited use as a clinical parameter for assessment and prognosis of the disease [78,79]. Although it can be demonstrated more often in comparison with unstimulated patients, but it is difficult, due to the considerations made here, to use it as a simple instrument of detection. So individualized and risk-adapted therapies currently cannot be derived. Prospective studies with larger number of patients are needed to clarify a possible benefit of VEGF in the clinical routine.

10. Ethics Approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the 1964 Helsinki declaration and

its later amendments or comparable ethical standards. According to the understanding of the investigators a vote by the ethics commission of the Rheinland-Pfalz regional medical association was not obtained, because it was a retrospective data analysis and patients of the Mainz University Medical Centre were informed and questioned by means of standard information (see § 14 AVB, hospital brochure or outpatient admission contract) and whether they agree with the anonymous use of so-called surplus material for research purposes or not. If approved, the material can be used for a specific research project without having to submit an application to the ethics committee and without having to reassert the patient.

Consent to participate Informed consent was obtained from all individual participants included in the study.

11. Consent for Publication

By participating in the study, the participants also agreed to anonymize publication.

Availability of data and material

Data and material is stored at Mainz University Medical Center in accordance with medical retention requirements.

12. Authors' Contribution

Michael Amrani, Co Researcher and author of this article

Julia Birkenbach, Researcher and author of dissertation

Christine Skala, Co Researcher and expert for dissertation

Rudolf Seufert, Co Researcher and expert for dissertation

Ruth Gomez, Co Researcher and supervisor

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