ORIGINAL ARTICLE

Eastern Journal of Medicine

East J Med 31(4): 858-864, 2026
DOI: 10.5505/ejm.2026.70481

Protective Effect of Silymarin in an Experimental Rat Model of Ovarian Hyperstimulation Syndrome

Ersin Onat[1*], Deniz Dirik[1], Ahmet Ufuk Kömüroğlu[2]

[1]*Department of Obstetrics and Gynecology, Van Yüzüncü Yıl University, Faculty of Medicine, Van, Turkey*
[2]*Department of Basic Medical Sciences, Faculty of Medicine, Van Yüzüncü Yıl University, Van, Turkey*

ABSTRACT

This study aimed to evaluate the effect of silymarin on the concentrations of angiopoietin-2 (ANGPT-2), angiopoietin-1 (ANGPT-1), vascular endothelial growth factor-A (VEGF-A), and tumor necrosis factor-alpha (TNF-α) in an ovarian hyperstimulation syndrome (OHSS) model.

Thirty-two 22-day-old female Wistar Albino rats were assigned to four groups: control, OHSS, OHSS + silymarin, and silymarin. The OHSS model was induced by pregnant mare serum gonadotropin (PMSG) followed by human chorionic gonadotropin (hCG). Silymarin was administered at a dose of 50 mg/kg. All animals were sacrificed on postnatal day 28. Serum and follicular fluid levels of VEGF-A, ANGPT-1, ANGPT-2, and TNF-α were measured using enzyme-linked immunosorbent assay. Biochemical parameters were evaluated. Statistical analysis was performed using one-way analysis of variance followed by Tukey post-hoc testing.

In the OHSS group, serum VEGF-A and ANGPT-1 levels were significantly increased, whereas ANGPT-2 levels were significantly decreased compared with controls ($p < 0.001$). In the OHSS + silymarin group, VEGF-A and ANGPT-1 levels showed a decreasing trend, while ANGPT-2 levels demonstrated an increasing trend; however, some changes did not reach statistical significance. TNF-α levels in serum and follicular fluid did not differ significantly among groups (serum: $p = 0.270$; follicular fluid: $p = 0.360$). Albumin and total protein levels were lower in the control group compared with the other groups ($p < 0.001$).

In this OHSS model, silymarin reduced VEGF-A and ANGPT-1 levels while increasing ANGPT-2. As a pilot proof-of-concept study, these findings suggest a modulatory role of silymarin in OHSS-related angiogenic imbalance. Larger studies and clinical trials are required to confirm these results.

Keywords: Angiopoietin, OHSS, silymarin, VEGF-A

Introduction

Ovarian hyperstimulation syndrome (OHSS), which has an incidence of roughly 0.3–5%, has become a significant complication due to the extensive use of assisted reproductive technologies (1,2). OHSS is a clinical condition characterized by systemic effects such as ascites, pleural effusion, and hemoconcentration resulting from increased vascular permeability during the luteal phase or early pregnancy (3). Although the etiology of OHSS has not been fully elucidated, it is generally accepted that the underlying mechanism involves controlled ovarian hyperstimulation with exogenous hormones followed by exposure to LH and hCG (4).

Increased angiogenesis and the ensuing rise in vascular permeability are important mechanisms in the etiology of OHSS. Angiopoietin-1 (ANGPT-1), Angiopoietin-2 (ANGPT-2), and VEGF-A are crucial for this pathogenesis. Furthermore, one of the main mediators in the pathophysiology of OHSS is tumor necrosis factor-alpha (TNF-α) (5). According to reports, 36 hours after hCG administration, VEGF levels in follicular fluid are roughly 100 times higher than those in serum or peritoneal fluid (4). Endothelial permeability and barrier function are significantly regulated by ANGPT-1 and ANGPT-2 (6). By attaching to intercellular junction proteins in individuals at risk of OHSS, ANGPT-1 is believed to promote pathophysiological angiogenesis (7). Another crucial factor is TNF-α, which is generated locally in the corpus luteum and influences angiogenic activity during the luteal phase (8).

Rapid increases or elevated levels of estrogen (>2500 pg/mL), previously considered a key determinant in OHSS pathophysiology, are now regarded primarily as predictive markers (9). Similarly, low progesterone levels may also be

*Corresponding Author: Dr. Ersin Onat, Department of Obstetrics and Gynecology, Faculty of Medicine, Van Yüzüncü Yıl University, Campus of Dursun Odabaş Medical Center, 65080 Tuşba, Van, Turkey
E-mail: adar.onat@gmail.com, Tel: +90 544 508 77 05
ORCID ID: Ersin Onat: 0000-0002-6153-241X, **Deniz Dirik:** 0000-0002-5169-4052, **Ahmet Ufuk Kömüroğlu:** 0000-0002-0371-9251
Received: 19.03.2026, **Accepted:** 29.07.2026

predictive of OHSS (10). Numerous biochemical markers associated with OHSS have been investigated (11–13). There is no definitive treatment specific to OHSS, and current management is largely based on supportive care.

Silymarin has anti-angiogenic properties (14) and inhibits inflammatory cytokine release, thereby reducing both TNF signaling pathways and TNF expression (15). This flavonoid has been employed in the management of diverse inflammatory conditions owing to its anti-inflammatory, anti-angiogenic, and antioxidant properties. Silymarin's capacity to inhibit crucial cytokines implicated in the pathophysiology of OHSS, particularly TNF-α and VEGF-A, which are vital for angiogenesis, indicates its potential to ameliorate the clinical progression of OHSS (14). However, no studies directly investigating the effect of silymarin on OHSS have been reported in the literature. We therefore sought to investigate the possibility that silymarin's anti-angiogenic and anti-inflammatory qualities could stop the onset of OHSS.

Materials and Methods

This study conducted at the Van Yüzüncü Yıl University Experimental Animal Research Center, adhering to the Guide for the Care and Use of Laboratory Animals issued by the United States National Institute of Health. The Animal Ethics Committee at Van Yüzüncü Yıl University gave its approval (Decision No: 2021/02.10; Date: 25.02.2021). During the study, every effort was made to lessen the animals' pain. Van Yüzüncü Yıl University Scientific Research Projects Commission (TTU-2021-9478) helped with the study project.

OHSS model was created utilizing 32 female Wistar Albino rats aged 22 days. A computer-based random number table was used to randomize the groups, and the people who did the analyses didn't know which group they were in. The sample size was determined based on the anticipated effect size in VEGF-. It was found that 8 animals per group and A levels with 80% power and α=0.05 were enough.

1. Control group: An intraperitoneal administration of 0.9% NaCl solution was given between postnatal days 22 and 26.

2. OHSS group: 10 IU of PMSG was given under the skin for four days in a row, starting on postnatal day 22. On postnatal day 26, a single dose of 30 IU of hCG was given under the skin.

3. OHSS + Silymarin group: Along with the OHSS protocol, silymarin was given by mouth through gavage at a dose of 50 mg/kg, 30 minutes before and 8 hours after hCG was given. Silymarin was prepared as a suspension in 0.5% carboxymethylcellulose solution immediately before administration. The 50 mg/kg dose was selected based on prior experimental studies demonstrating effective anti-inflammatory and anti-angiogenic activity at this dose level in rodent models.

4. Silymarin group: Silymarin (50 mg/kg) was administered orally via gavage in 2 doses at 8-hour intervals on postnatal day 26.

All animals were euthanized under anesthesia on postnatal day 28. The OHSS group showed a lot of swelling in the ovaries and more fluid in the peritoneum.

We utilized commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kits designed for Rattus norvegicus to quantify the levels of angiopoietin-1 (ANGPT-1), vascular endothelial growth factor-A (VEGF-A), angiopoietin-2 (ANGPT-2), and tumor necrosis factor-α (TNF-α) in rat samples. We used the following kits: ANGPT-1 (Cat. No.: YLC0172RA, Shanghai YL Biotech Co., Ltd, Shanghai, China) VEGF-A (Cat. No.: YLC0205RA, Shanghai YL Biotech Co., Ltd, Shanghai, China), ANGPT-2 (Catalog No.: YLC0173RA, Shanghai YL Biotech Co., Ltd, Shanghai, China), and TNF-α (Catalog No.: YLC0208RA, Shanghai YL Biotech Co., Ltd, Shanghai, China) The tests were done exactly as the makers said to do them. For ANGPT-1, the analytical detection range was 3.125–200 pg/mL; for VEGF-A and TNF-α, it was 15.625–1000 pg/mL; and for ANGPT-2, it was 188–12000 pg/mL. The assays were able to detect ANGPT-1 at a level of 1.36 pg/mL, VEGF-A and TNF-α at a level of 5.4 pg/mL, and ANGPT-2 at a level of 0.09 ng/mL. For all kits, the intra-assay and inter-assay coefficients of variation were less than 10% and 12%, respectively. After the assay procedures were finished, a microplate reader measured absorbance at 450 nm, and the concentrations of the analytes were figured out using the standard curves that went with them.

We used an automated clinical chemistry analyzer (ARCHITECT c16000, Abbott Diagnostics, USA) to check the levels of estradiol, progesterone, serum albumin, total protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, and creatinine. All measurements on serum samples were made in

accordance with the manufacturer's instructions and standard laboratory procedures.

Primary and secondary outcome measures.

The principal outcome was the alteration in serum VEGF-A levels subsequent to silymarin treatment in the experimental OHSS model. Secondary outcomes comprised other angiogenic markers (serum and follicular fluid ANGPT-1, ANGPT-2 and TNF-α), biochemical and hormonal parameters, and macroscopic OHSS findings.

Statistical Analysis: We used Version 20.0 of IBM SPSS Statistics for Windows to do the statistical analyses. The Shapiro-Wilk test looked at how normal the data distribution was, while Levene's test looked at how similar the variances were. We used one-way ANOVA and then Tukey's post hoc test for variables that were normally distributed. We used the Kruskal-Wallis test and then Dunn's post hoc test with Bonferroni adjustment for variables that were not normally distributed. Results are presented as mean ± SD or median (interquartile range) as appropriate. A p-value below 0.05 was considered statistically significant. All continuous variables assessed in this study (serum and follicular fluid VEGF-A, ANGPT-1, ANGPT-2, TNF-α; albumin, total protein, ALT, AST, urea, creatinine, estradiol, and progesterone) satisfied the normality assumption per the Shapiro-Wilk test; accordingly, one-way ANOVA followed by Tukey's post hoc test was uniformly applied. The distribution status of each variable is indicated in the footnotes of the respective tables.

Results

Table 1 shows the serum levels of VEGF-A, ANGPT-1, ANGPT-2, and TNF-α among the study groups.

The OHSS group had significantly higher serum VEGF-A levels than the control and silymarin groups ($p < 0.001$). Serum VEGF-A levels were lower in the OHSS + silymarin group compared to the OHSS group, but this difference was not statistically significant (Figure 1).

The OHSS group showed significantly higher serum ANGPT-1 levels and lower ANGPT-2 levels compared to the control, silymarin, and OHSS + silymarin groups (ANGPT-1: $p = 0.002$; ANGPT-2: $p < 0.001$) (refer to Figure 2). There were no significant differences in serum ANGPT-2 levels between the control, silymarin, and OHSS + silymarin groups. Serum TNF-α levels were not significantly different between groups.

Albumin, total protein, ALT, AST, urea, creatinine, estradiol, and progesterone levels were all measured (see Table 2). The control group had significantly lower serum albumin and total protein levels than the other groups ($p < 0.001$). No significant differences in albumin or total protein levels were found between the OHSS, OHSS + silymarin, and silymarin groups. The OHSS and OHSS + silymarin groups showed significantly higher serum estradiol and progesterone levels than the control and silymarin-only groups (estradiol: $p < 0.001$; progesterone: $p = 0.001$). There were no significant intergroup differences in ALT, AST, urea, or creatinine levels.

Analysis of follicular fluid samples revealed higher VEGF-A and TNF-α levels in the OHSS group and lower ANGPT-2 levels compared to the other groups, but these differences were not statistically significant (VEGF-A: $p = 0.190$; ANGPT-2: $p = 0.290$; TNF-α: $p = 0.360$). Follicular fluid ANGPT-1 levels were similar across all groups ($p = 0.910$; Table 3).

Discussion

Ovarian hyperstimulation syndrome (OHSS) is the most serious iatrogenic side effect of ovarian stimulation and can even kill you in very rare cases. Clinically, it is marked by ovarian enlargement, abdominal tenderness, and distension due to abrupt elevations in vascular permeability and fluid migration into the extravascular space. The development of OHSS occurs as an iatrogenic adverse effect of high-dose gonadotropins used for ovarian stimulation (16). Angiogenesis, one of the key steps in its pathogenesis, is activated by proangiogenic factors such as VEGF, TNF-α, and ANGPT-1, while being inhibited by antiangiogenic factors including ANGPT-2 and angiostatin (17).

Vascular endothelial growth factor (VEGF), which is produced by multiple follicles in response to ovarian stimulation, is a key factor in the pathogenesis of OHSS (5). The heparin-binding protein family includes VEGF, which promotes both angiogenesis and vascular permeability (18). Its ability to cause extravasation of protein-rich fluid from the intravascular space accounts for almost all clinical manifestations of OHSS (19). Patients with OHSS have been found to have elevated VEGF-A levels in both serum and ascitic fluid, which is consistent with our findings (18). In another study conducted in rats, VEGF-A levels in peritoneal fluid were found to be

Table 1: Comparison of Serum VEGF-A, ANGPT-1, ANGPT-2, and TNF-α Levels Among The Study Groups

	Control (n=8) Mean ± SD	OHSS (n=8) Mean ± SD	OHSS+S (n=8) Mean ± SD	Silymarin (n=8) Mean ± SD	p value
VEGF-A (pg/mL)	32.71±6.01c	51.86±4.60 a	46.07±7.03a,b	39.03±4.25b,c	0.001
ANGPT-1 (pg/mL)	47.09±11.19c	66.16±5.70 a	62.69±11.32a,b	50.01±9.27b,c	0.002
ANGPT-2 (pg/mL)	168.82±13.78a	106.24±22.44b	173.68±42.45 a	176.68±24.56 a	0.001
TNF-α (pg/mL)	110.90±23.28a	89.38±14.29a	97.12±16.97a	108.99±39.18 a	0.270

Abbreviations: VEGF-A, vascular endothelial growth factor-A; ANGPT-1, angiopoietin-1; ANGPT-2, angiopoietin-2; TNF-α, tumor necrosis factor-alpha; OHSS, ovarian hyperstimulation syndrome; OHSS+S, OHSS + Silymarin group. Data are presented as mean ± SD. All variables conformed to normal distribution (Shapiro-Wilk test); one-way ANOVA followed by Tukey's post hoc test was applied. Groups sharing the same superscript letter (a, b, or c) are not significantly different from each other (Tukey HSD, $p > 0.05$)

Table 2: Distribution of Biochemical and Hormonal Parameters Among The Study Groups

	Control	OHSS	OHSS+S	Silymarin	p value
Albumin (g/dL)	3.92±0.16b	4.23±0.13a	4.33±0.15a	4.41±0.14a	0.001
T.protein (g/dL)	4.88±.24b	5.59±0.34a	5.73±0.13a	5.58±0.20a	0.001
ALT (IU/L)	21.70±4.55a	20.54±3.09a	20.66±3.61a	23.10±2.55a	0.480
AST (IU/L)	127.41±7.27a	101.73±5.73b	95.63±5.74b	102.06±5.97b	0.090
Urea (mg/dl)	52.18±3.20a	40.66±4.97c	46.33±3.91b,c	48.38±3.51a,b	0.070
Creatinine	0.21±0.03a	0.20±0.031a	0.24±0.03a	0.23±0.035a	0.220
Estrodiol (pg/mL)	14.03±3.16b	103.72±7.53a	102.20±6.34a	18.48±2.49b	0.001
Progesterone (pg/mL)	3.01±1.38c	28.93±4.57b	75.72±10.99a	71.45±10.59a	0.001

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; OHSS+S, OHSS + Silymarin group. Data are presented as mean ± SD. All variables conformed to normal distribution (Shapiro-Wilk test); one-way ANOVA followed by Tukey's post hoc test was applied. Superscript letters (a, b, c) denote statistically significant post hoc groupings (Tukey HSD, $p < 0.05$); superscript letters are only applied to variables with statistically significant overall ANOVA results ($p < 0.05$). For AST ($p = 0.09$) and Urea ($p = 0.07$), group comparisons did not reach statistical significance; post hoc letter designations were removed accordingly

significantly higher in the OHSS group compared to controls (20). The findings of our study are consistent with these results.

It has been shown that ANGPT-1, ANGPT-2, and their receptor Tie-2 may participate in ovarian angiogenesis during folliculogenesis in rat ovaries (21). In women who develop OHSS, follicular fluid ANGPT-1 levels were reported to be significantly increased compared to those who did not develop OHSS, while ANGPT-2 levels remained unchanged. This finding suggests that ANGPT-1 may promote pathophysiological angiogenesis in OHSS patients (22). In another rat study, ANGPT-2 levels were not significantly different between the control and OHSS groups (23). Our study found that serum ANGPT-1 levels were significantly higher and serum ANGPT-2 levels were significantly lower in the OHSS group than in the control group. In follicular fluid, ANGPT-1 levels in the OHSS group were comparable to those in other groups. Silymarin administration to OHSS-induced rats resulted in elevated ANGPT-2 levels in follicular fluid.

TNF-α is essential in the development and selection of antral follicles (8). Research indicates that serum TNF-α levels are markedly increased in

Table 3: Comparison of Follicular Fluid VEGF-A, ANGPT-1, ANGPT-2, and TNF-α Levels Among The Study Groups

	Control (n=8)	OHSS (n=8)	OHSS+S (n=8)	Silymarin (n=8)	p Value
VEGF-A (pg/mL)	70.80±13.52a	86.49±8.30a	75.67±19.13a	69.00±13.58a	0.190
ANGPT-1 (pg/mL)	80.85±15.21a	85.07±26.00 a	84.14±23.16a	79.45±17.71a	0.910
ANGPT-2 (pg/mL)	320.23±41.02a	272.58±70.22 a	301.21±47.98a	332.28±61.26 a	0.290
TNF-α (pg/mL)	134.41±19.89 a	166.70±35.53 a	145.43±50.48 a	134.84±44.37a	0.360

Abbreviations: VEGF-A, vascular endothelial growth factor-A; ANGPT-1, angiopoietin-1; ANGPT-2, angiopoietin-2; TNF-α, tumor necrosis factor-alpha; OHSS+S, OHSS + Silymarin group. Data are presented as mean ± SD. All variables conformed to normal distribution (Shapiro-Wilk test); one-way ANOVA followed by Tukey's post hoc test was applied. No statistically significant differences were observed among groups for any follicular fluid variable ($p > 0.05$); accordingly, no post hoc letter designations are shown

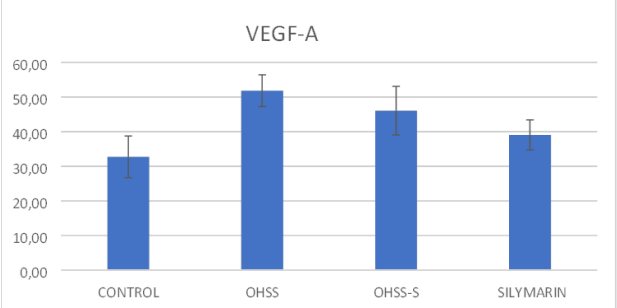

Fig. 1. Distribution of serum VEGF-A levels among groups

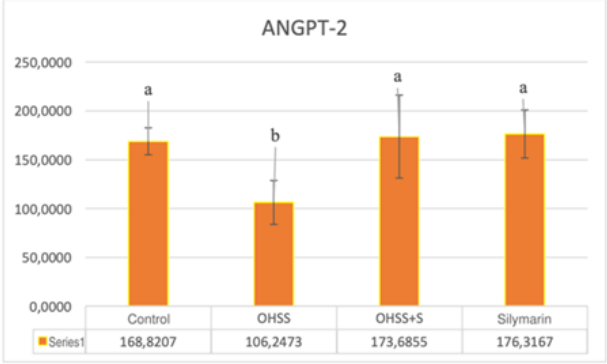

Fig.2. Distribution of serum ANGPT-2 levels among groups

women undergoing IVF treatment who subsequently develop OHSS (24). In our study, while serum TNF-α levels were reduced in the OHSS group relative to the control group, this discrepancy was not statistically significant ($p = 0.270$). Likewise, follicular fluid TNF-α levels were elevated in the OHSS group compared to the control group; however, this disparity was not statistically significant.

Elevated estrogen, previously identified as a significant element in the pathophysiology of OHSS, is now regarded mainly as a predictive marker rather than a causative agent (9). Likewise, low progesterone levels may also serve as a predictive marker for OHSS (10). Numerous biochemical markers have been investigated in patients diagnosed with OHSS, yielding heterogeneous results. Due to increased vascular permeability in OHSS, fluid leakage into the extravascular space accompanied by hypoalbuminemia may occur (11). Some studies have reported decreased creatinine levels (12), while others found no significant differences in liver enzyme levels (13). In contrast to the literature, our study demonstrated lower albumin and total protein levels in the control group compared to the other groups. This unexpected finding may be attributable to the physiological immaturity of the control animals; at postnatal day 28, immature rats may exhibit lower baseline hepatic protein synthesis compared to gonadotropin-stimulated counterparts. Additionally, gonadotropin-induced metabolic activation and the established hepatoprotective properties of silymarin may have contributed to relatively higher albumin and total protein concentrations in the treated groups. This finding is unlikely to reflect clinically meaningful hypoalbuminemia, given the absence of hepatic or renal dysfunction across all groups, and should be

interpreted in the context of the developmental age of the experimental animals. The phytoestrogenic effects of silymarin, along with its reported influence on FSH and LH, may explain the observed increase in progesterone levels in the silymarin group; however, this finding requires confirmation by further studies (25). No significant differences were observed among groups in terms of ALT, AST, urea, or creatinine levels.

Silymarin has long been used in the treatment of liver diseases such as liver cirrhosis and chronic hepatitis. It is also known to suppress TNF-α induction. Based on these findings, the effects of silymarin are thought to be associated not only with antioxidant and anti-inflammatory mechanisms but also with modulation of the VEGF/ANGPT balance. It has been reported that silymarin reduces diabetes-induced VEGF secretion and normalizes angiogenic responses in a human brain microvascular endothelial cell line (HBEC-5i) (26). Other studies have demonstrated inhibitory effects of silymarin on angiogenesis and apoptosis (27). Additionally, silymarin suppresses TNF-α induction (15). In our study, administration of silymarin to OHSS-induced rats (OHSS+S group) resulted in decreased VEGF-A levels in both serum and follicular fluid; however, this reduction was not statistically significant when compared with the OHSS group. Increasing the sample size may render this effect statistically significant. No significant differences were observed between the OHSS and OHSS+S groups regarding TNF-α levels in either serum or follicular fluid.

This research possesses numerous limitations. The restricted sample size diminishes the statistical power and generalizability of the results. Second, the results are based on an animal model, and extrapolation to clinical practice should be approached with caution. Additionally, animal models may not fully reflect human physiology. The applied protocol involved a single dose and a limited time frame; therefore, studies evaluating different doses and treatment durations are required to support these findings. Furthermore, the analyses were limited to VEGF-A, ANGPT-1/2, and TNF-α, while other important vascular mediators such as IL-6, IL-8, and nitric oxide were not included. Consequently, larger-scale experimental and clinical studies are needed for these findings to be considered clinically meaningful and translatable into practice.

In this pilot proof-of-concept study, the administration of Silymarin in an experimental model of OHSS led to the modulation of critical angiogenic mediators, evidenced by decreased levels of VEGF-A and ANGPT-1, alongside elevated levels of ANGPT-2. These effects transpired without notable alterations in TNF-α concentrations, indicating that silymarin predominantly affects angiogenic balance rather than inflammatory cytokine activity. These initial findings indicate that silymarin may require additional investigation as a potential modulatory agent in OHSS; however, more extensive experimental and clinical studies are necessary before any conclusive therapeutic implications can be drawn.

References

1. Selter J, Wen T, Palmerola KL, Friedman AM, Williams Z, Forman EJ. Life-threatening complications among women with severe ovarian hyperstimulation syndrome. Am J Obstet Gynecol 2019; 220(6): 575.e1-575.e11.
2. Cenksoy C, Ozcan-Cenksoy P, Erdem O, Sancak B, Gursoy R. A potential novel strategy, inhibition of vasopressin-induced VEGF secretion by relcovaptan, for decreasing the incidence of ovarian hyperstimulation syndrome in the hyperstimulated rat model. Eur J Obstet Gynecol Reprod Biol 2014; 174: 86-90.
3. Aboulghar MA, Mansour RT, Serour GI, Sattar MA, Amin YM, Elattar I. Management of severe ovarian hyperstimulation syndrome by ascitic fluid aspiration and intensive intravenous fluid therapy. Obstet Gynecol 1993; 81(1): 108-111.
4. Busso CE, Soares SR, Pellicer A. Pathogenesis, clinical manifestations, and diagnosis of ovarian hyperstimulation syndrome UpToDate. 2019.
5. Guzeloglu-Kayisli O, Kayisli UA, Taylor HS. The role of growth factors and cytokines during implantation: endocrine and paracrine interactions. Semin Reprod Med 2009; 27(1): 62-79.
6. Eklund L, Saharinen P. Angiopoietin signaling in the vasculature. Exp Cell Res 2013; 319(9): 1271-1280. doi: 10.1016/j.yexcr.2013.03.011
7. Scotti L, Abramovich D, Pascuali N, Durand LH, Irusta G, de Zúñiga I, Tesone M, Parborell F. Inhibition of angiopoietin-1 (ANGPT1) affects vascular integrity in ovarian hyperstimulation syndrome (OHSS). Reprod Fertil Dev 2016; 28(6): 690-699.
8. Galvão AM, Ferreira-Dias G, Skarzynski DJ. Cytokines and angiogenesis in the corpus luteum. Mediators Inflamm 2013; 2013: 420186.

9. Nastri CO, Ferriani RA, Rocha IA, Martins WP. Ovarian hyperstimulation syndrome: pathophysiology and prevention. J Assist Reprod Genet 2010; 27(2-3): 121-128.
10. Baser E, Aydogan-Kirmizi D, Ozelci R, Aldemir O, Dilbaz B, Dilbaz S, Moraloglu-Tekin O. Neutrophil:lymphocyte and estradiol:progesterone ratios as predictive markers for ovarian hyperstimulation syndrome (OHSS). Reprod Fertil Dev 2022; 34(3): 343-349.
11. Elmahal M, Lohana P, Anvekar P, Menda MK, Arti. Hyponatremia: an untimely finding in ovarian hyperstimulation syndrome. Cureus 2021; 13(7): e16556.
12. Rekola M, Korhonen K, Unkila-Kallio L, Alfthan H, Stefanovic V, Tiitinen A, Mikkola TS, Savolainen-Peltonen H. Serum erythropoietin level is increased during stimulation for IVF but not in OHSS. Reprod Biol Endocrinol 2024; 22(1): 14.
13. Qi T, Hu Y, Liu M, Tian L, Peng Z, Xu H, Zhang C. Abnormal alanine aminotransferase levels in patients with moderate or severe ovarian hyperstimulation result in an increased risk of obstetric complications. Int J Gynaecol Obstet 2023; 162(3): 913-921.
14. Jiang C, Agarwal R, Lü J. Anti-angiogenic potential of a cancer chemopreventive flavonoid antioxidant, silymarin: inhibition of key attributes of vascular endothelial cells and angiogenic cytokine secretion by cancer epithelial cells. Biochem Biophys Res Commun 2000; 276(1): 371-378.
15. Aggarwal BB. Signalling pathways of the TNF superfamily: a double-edged sword. Nat Rev Immunol 2003; 3(9): 745-756.
16. Delbaere A, Smits G, Olatunbosun O, Pierson R, Vassart G, Costagliola S. New insights into the pathophysiology of ovarian hyperstimulation syndrome: what makes the difference between spontaneous and iatrogenic syndrome? Hum Reprod 2004; 19(3): 486-489.
17. Rajabi M, Mousa SA. The role of angiogenesis in cancer treatment. Biomedicines 2017; 5(2): 34.
18. Farkas B, Boldizsar F, Bohonyi N, Farkas N, Marczi S, Kovacs GL, Bodis J, Koppan M. Comparative analysis of abdominal fluid cytokine levels in ovarian hyperstimulation syndrome (OHSS). J Ovarian Res 2020; 13(1): 11.
19. Geva E, Jaffe RB. Role of vascular endothelial growth factor in ovarian physiology and pathology. Fertil Steril 2000; 74(3): 429-438.
20. Hortu I, Karadadas E, Ozceltik G, Tavmergen E, Tavmergen-Goker EN, Yigitturk G, Erbas O. Oxytocin and cabergoline alleviate ovarian hyperstimulation syndrome (OHSS) by suppressing vascular endothelial growth factor (VEGF) in an experimental model. Arch Gynecol Obstet 2021; 303(4): 1099-1108.
21. Abramovich D, Rodriguez-Celin A, Hernandez F, Tesone M, Parborell F. Spatiotemporal analysis of the protein expression of angiogenic factors and their related receptors during folliculogenesis in rats with and without hormonal treatment. Reproduction 2009; 137(2): 309-320.
22. Scotti L, Abramovich D, Pascuali N, de Zúñiga I, Oubiña A, Kopcow L, Lange S, Owen G, Tesone M, Parborell F. Involvement of the ANGPTs/Tie-2 system in ovarian hyperstimulation syndrome (OHSS). Mol Cell Endocrinol 2013; 365(2): 223-230.
23. Pascuali N, Scotti L, Oubiña G, de Zúñiga I, Gomez-Peña M, Pomilio C, Saravia F, Tesone M, Abramovich D, Parborell F. Platelet-derived growth factor-B restores vascular barrier integrity and diminishes permeability in ovarian hyperstimulation syndrome. Mol Hum Reprod 2020; 26(8): 585-600.
24. Chistyakova GN, Remizova II, Gazieva IA, Chermyaninova OV. Immunological and hemostasiological disorders in women with ovarian hyperstimulation syndrome. Gynecol Endocrinol 2014; 30(Suppl 1): 39-42.
25. Moosavifar N, Mohammadpour AH, Jallali M, Karimiz G, Saberi H. Evaluation of effect of silymarin on granulosa cell apoptosis and follicular development in patients undergoing in vitro fertilization. East Mediterr Health J 2010; 16(6): 642-645.
26. Alhusban A, Alkhazaleh E, El-Elimat T. Silymarin ameliorates diabetes-induced proangiogenic response in brain endothelial cells through a GSK-3β inhibition-induced reduction of VEGF release. J Diabetes Res 2017; 2017: 1256169.
27. Attia GM, Elmansy RA, Algaidi SA. Silymarin decreases the expression of VEGF-A, iNOS, and caspase-3 and preserves the ultrastructure of cardiac cells in doxorubicin-induced cardiotoxicity in rats: a possible protective role. Int J Clin Exp Med 2017; 10(2): 4158-4173.