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Calcium gluconate infusion is not as effective as dopamine agonists in preventing ovarian hyperstimulation syndrome

N. TURKTEKIN[1], C. KARAKUS[2], R. OZYURT[3]

[1]Nisantası University, Vocational School, Operating Room Services Department, Istanbul, Turkey
[2]Vocational School of Health Services, Beykent University, Istanbul, Turkey
[3]Istanbul IVF-Center, Istanbul, Turkey

Abstract. – OBJECTIVE: The aim of the study was to compare the effectiveness of calcium gluconate and cabergoline therapy in the prevention of ovarian hyperstimulation syndrome (OHSS).

PATIENTS AND METHODS: Eight hundred and forty-five women who underwent GnRH antagonist protocol and at high risk for developing OHSS were divided into two groups, those given cabergoline (n=435) or calcium gluconate (n=410). In cabergoline group, 0.5 mg of cabergoline was administered once daily p.o. starting on the day of ovulation trigger and continued until the following 8 days. In calcium gluconate group, intravenous calcium gluconate was administered daily for four days starting on the day of oocyte pickup (OPU). 10 ml of 10% calcium gluconate solution was dissolved in 200 ml of physiological saline and administered by intravenous route within 40 minutes. Infusion was started within the first 30 minutes following the OPU and continued on the 1st, 2nd and 3rd days after OPU.

RESULTS: Mild OHSS was developed in 367 (89%) patients receiving calcium gluconate infusion, while 251 patients (57%) in the cabergoline group developed mild OHSS. The frequency of mild OHSS in the calcium group was significantly higher than the cabergoline group ($p<.001$). Moderate OHSS was observed in 32 people (7.8%) in the calcium gluconate group, while it was observed in 184 people in the cabergoline group (42.3%). Calcium gluconate infusion significantly reduced the development of moderate OHSS compared to cabergoline therapy ($p<.001$). Severe OHSS developed in 11 patients (2.7%) in the calcium gluconate group, while severe OHSS did not develop in those given cabergoline (0%, $p<.001$). Clinical pregnancy, live birth and abortion rates were similar in the two groups. When logistic regression analysis was performed, a significant correlation was found between age, BMI, AMH, the number of antral follicle count, OHSS history, paracentesis, progesterone on the day of hCG, 2 PN zygotes, and HbA1c levels and the development of OHSS. No correlation was found between the use of metformin or cetrotide and the development of OHSS.

CONCLUSIONS: Calcium gluconate treatment is not effective in the prevention of OHSS.

Key Words:
OHSS, Calcium gluconate, Cabergoline, PCO.

Introduction

Although assisted reproductive technologies (ART) have helped many infertile couples get pregnant it paved the way for ovarian hyperstimulation syndrome (OHSS) which is iatrogenically created by the clinician and puts maternal life at risk. OHSS is a systemic disease characterized by abdominal swelling and tenderness secondary to a sudden increase in vascular permeability due to volume overgrowth of the ovaries that occur during controlled ovarian stimulation cycles. The main causes OHSS are unknown. It is characterized by an increase in the synthesis of vascular endothelial growth factor (VEGF). Additionally, due to multi-follicular, intravascular fluid in the ovarian vessels is directed to the third space and forms the typical findings of the OHSS[1-3]. The increase in the amount of fluid shifting to the third spaces also determines the outcome of the OHSS. The follow-up and treatment of the syndrome becomes more difficult as a result of pre-renal azotemia and deterioration in hematological parameters due to the accumulation of fluid in the third spaces. Although spontaneous development of OHSS depending on FSH receptor mutation has been reported, it is believed that the main mech-

Corresponding Author: Nurettin Turktekin, MD; e-mail: drnturktekin@gmail.com

anism underlying OHSS is the use of high-dose gonadotropins for controlled ovarian stimulation (COS)[2]. The use of human chorionic gonadotrophin (hCG) also increases the risk of OHSS. Supraphysiological levels are another risk factor for OHSS[3].

Patients in the risk group for OHSS should be well managed. Otherwise, thromboembolic events, respiratory distress, liver or renal failure may occur[4]. Women with polycystic ovary syndrome (PCOS) or having many follicles during COS are in the high risk for OHSS[3,5]. The development of OHSS can be prevented by using the following methods in patients in the risk group for OHSS: (i) individualization of COS protocols and individual adjustment of gonadotropin dose, (ii) ovulation trigger with GnRH agonists, (iii) coasting by reducing or cutting the dose of gonadotropins, (iv) cycle cancellation or freezing embryos, (v) use of plasma expanders.

A recent comprehensive review[6] has shown that dopamine agonists are effective in reducing the occuring of OHSS. In full compliance with this, cabergoline, a dopamine agonist, is highly effective in the treatment of OHSS. By inhibiting the phosphorylation of VEGF receptor, cabergoline decreases vascular permeability and prevents new vessel formation[7,8]. However, since cabergoline acts only through VEGFR, VEGF secretion continues and a complete recovery in the course of OHSS is not possible[9]. The increase in VEGF synthesis due to the activation of the renin-angiotensin-aldosterone system contributes to the formation of OHSS by increasing the permeability of the ovarian vessels. Abnormality in the fluid-electrolyte balance leads to a decrease in intracellular calcium, leading to the continuation of VEGF production by increasing adenylyl cyclase-mediated cyclic adenosine monophosphate (cAMP)-renin synthesis[10]. Due to all these mechanisms, both VEGF synthesis and VEGFR-2 activation must be blockedin order to prevent the development of OHSS. Increasing intracellular calcium blocking cAMP-mediated VEGF secretion is a new method to prevent OHSS. Hence, there are several studies[11,12] investigating the effect of calcium gluconate therapy in patients with OHSS. The most important limitation of previous studies is the small number of participants. Therefore, this study was planned to determine the incidence of early onset OHSS development in 845 high-risk patients for OHSS who received calcium gluconate infusion or cabergoline. Clinical pregnancy, miscarriage, and live birth rates were recorded.

Patients and Methods

This study was conducted in accordance with the Declaration of Helsinki and informed consent was obtained from all participants at the time of enrollment. The sample size of the study was calculated with the Mann-Whitney test with the effect size of 0.50%, power of 80% and maximum acceptable type 1 error of 5%. A total of 845 patients at high risk for developing OHSS were included the study. Participants were divided into two groups as those who received calcium gluconate (n=410) or those who received cabergoline treatment (n=435). Women with PCOS had a high antral follicle (>24) or AMH (> 3.4 ng/ml)[13,14]. Development of 18 or more follicles larger than 12 mm in diameter was set as the criterion for inclusion in the high-risk group for OHSS in PCOS patients. Patients with high serum estradiol levels, excessive growth of follicles (≥25) or a large number of retrieved oocytes (≥24) during COS were included in this group. Serum estradiol levels above 3500 pg/mL on the day of ovulation trigger were considered in the high-risk group for OHSS[13,15]. Those with a history of OHSS in their previous trials were also considered in the risk group for OHSS and included in the study. Patients with overt endocrinopathy of the thyroid and adrenal glands, especially diabetes mellitus, were excluded. Likewise, patients with a history of acute or chronic renal or liver disease, chronic obstructive pulmonary disease, hypertension, bleeding diathesis, and patients with a systemic disease were excluded.

In cabergoline group, 0.5 mg of cabergoline was administered once daily p.o. starting on the day of ovulation trigger and continued until the following 8 days. Calcium gluconate infusion was started within the first 30 minutes following the oocyte pick-up in the other 410 patients in the high-risk group for OHSS. Then, infusion was continued on the 1st, 2nd and 3rd days after OPU. 10 ml of 10% calcium gluconate solution was dissolved in 200 ml of physiological saline and administered by intravenous route within 40 minutes. A detailed protocol on dissolution and administration of calcium gluconate can be found elsewhere[16].

The diagnosis and classification of OHSS was made as described by Golan et al[17]. The presence of enlarged ovaries accompanied by nausea, vomiting, abdominal distension and pelvic pain was defined as mild OHSS. Ovarian size varying between 5 and 12 cm in sonographic measurement was accepted as enlargement of the ovaries. In

addition to mild OHSS findings, the presence of ascite in the pelvis and abdomen in ultrasonography was considered as moderate OHSS. Severe OHSS was diagnosed in patients with clinically evident ascitic fluid in pleural and pericardial spaces and respiratory distress in addition to moderate OHSS findings. Patients with increased hematocrit levels (>45%), decreased renal perfusion and urine output (<600 mL/24 h), and increased liver enzymes were also considered to have severe OHSS and were hospitalized. Participants in both groups managed on an out-patient basis with daily ultrasonographic and clinical examination to evaluate the development of OHSS after OPU. Biochemical and hematological parameters were followed closely. Patients hospitalized for severe OHSS were observed in terms of fluid, electrolyte balance, and their urine output was recorded. The amount of ascitic fluid evacuated in cases who underwent paracentesis was recorded.

Women with mild or moderate OHSS were hospitalized if clinical and laboratory findings worsened. Patients were kept under follow-up until complete improvement in OHSS symptoms was achieved. In order to prevent development of OHSS, no embryo transfer was performed to the patients in both groups. Embryos of the participants were frozen and stored on the 3rd or 5th day. Frozen embryo transfer was performed in patients recovering from OHSS.

Primary outcome of our study was to determine the incidence and type of OHSS development in the treatment groups. Secondary outcome was to compare clinical pregnancy, miscarriage, and live birth rates between the groups. Clinical pregnancy was defined as evidence of a gestational sac, confirmed by ultrasound examination. The loss of fetus before 20 weeks of gestation was defined as miscarriage. After recording the previous OHSS history of the women in both groups, whether they used metformin or antagonists, whether abdominal paracentesis was performed, and the number of collected oocytes were also recorded. Following the recording of the demographic data, the laboratory and embryological data, especially the hematocrit and AMH values, were also recorded. The contributions of demographic, laboratory, clinical and embryological findings to the development of OHSS were analyzed one by one using multiple logistic regression analysis (OR, 95% - CI).

Statistical Analysis

SPSS 23.0 (IBM Corp., Armonk, NY, USA) package program was used for statistical analysis of the data. The normal distribution properties of the variables were examined using the Shapiro-Wilk test. Chi-square and Fischer's exact test were used to compare categorical variables. The Mann-Whitney-U test was used in groups that did not fit the normal distribution. Multiple logistic regression analysis was used to determine the factors affecting the development of OHSS. Categorical measurements were given as numbers and percentages, while continuous measurements were given as median and minimum-maximum. $p<0.05$ was considered statistically significant in all tests.

Results

Median age ($p<.001$), platelet counts ($p<.001$), and HTC values ($p<.001$) of cabergoline group were significantly lower than those treated with calcium gluconate. However, in addition to the number of follicle ($p<.001$) and oocyte ($p<0.001$), the number of IVF attempt ($p<.001$), BMI ($p<.001$), AMH ($p<.01$), HbA1C values ($p<.001$), gonadotropin usage time ($p<.001$) and dose ($p<.001$), E2 and progesterone values on the day of hCG ($p<.001$, $p<.001$) MI ($p<.001$) and MII oocyte ($p<.001$), 2 PN zygote ($p<.001$), cleavage stage ($p<.001$) and blastocyst stage embryo ($p<.001$) were significantly higher in those treated with cabergoline than those treated with calcium treatment **(Supplementary Tables I and II)**.

The history of OHSS was significantly higher in the cabergoline group than in the calcium group ($p<.001$). The need for paracentesis was higher in those given cabergoline than those given calcium ($p<.001$). The number of patients using metformin due to PCOS was significantly higher in the cabergoline group than in the calcium group ($p<.001$). Similarly, GnRH antagonist use after OPU was significantly higher in those taking cabergoline than those taking calcium ($p<.004$). During OPU, the number of eggs collected below 20 and between 20-40 was higher in the calcium group, while the number of eggs between 40-60 and above 60 was significantly higher in the cabergoline group ($p<.001$) **(Supplementary Table II)**.

When the groups were compared in terms of the incidence of OHSS **(Supplementary Table II)**, the frequency of mild OHSS was significantly higher in the calcium group than in the cabergoline group (89.5% *vs.* 57.7%, $p<.001$). Moderate OHSS was observed in 184 people in the cabergoline group (42.3%), while it was observed in

32 women (7.8%) in the calcium group, and the difference between the two groups was statistically significant ($p<.001$). Severe OHSS was detected in 11 individuals in the calcium group (2.7%), while it was not detected in anyone in the cabergoline group (0%). The difference between the two groups in terms of severe OHSS was statistically significant ($p<.001$). There was no significant difference between the two groups in terms of clinical pregnancy (52.4% *vs.* 55.2%, $p<.44$), frequency of miscarriages (2% *vs.* 3.4%, $p<.208$) and live birthrates (47.8% *vs.* 50.8%, $p<.409$).

Two different methods were used to examine the factors affecting OHSS **(Supplementary Tables III and IV)**. In the first method, multiple logistic regression analysis was performed by including all parameters, including the OHSS history, into the model. In the second method, other parameters were included without adding the OHSS story to the model. In the regression analysis by adding the history of OHSS **(Supplementary Table III)**, age 0.8 fold (OR=0.851), number of follicle 1.0 fold (OR=1.077), BMI 1.0-fold (OR=1.076), AMH 0.8-fold (OR=0.869), the number of MI oocyte 1.3 fold (OR =1.342), the number of MII oocyte 1.2-fold (OR=1.221), OHSS history 177-fold (OR=177.304), paracentesis 152-fold (OR=152.050), number of oocyte (<20) 18-fold, number of oocyte (20-40) 72-fold, and severity of OHSS 5.3 fold contributed to the development of OHSS. In addition to use of metformin or cetrotideafter OPU, clinical pregnancy, live birth and miscarraige rates did not affect the development of OHSS.

In the regression analysis without adding OHSS history **(Supplementary Table IV)**, age 0.8-fold (OR=0.830), number of follicles 1.0-fold (OR=1.086), number of trials 1.4-fold (OR=1.475), BMI 1.1-fold (OR=1.125), AMH 0.8-fold (OR=0.872), HbA1C 1.3-fold (OR=1.328), progesterone on the day of hCG 1.1-fold (OR=1.140), MI oocyte 1.3-fold (OR=1.310), MII oocyte 1.2-fold (OR=1.256), 2 PN zygotes 0.8-fold (OR=0.855), paracentesis 138-fold (OR=138.057), the number of oocytes (<20) 19-fold, the number of oocyte (20-40) 83-fold, and OHSS severity 4.9-fold (OR=4.927) were contributing to the development of OHSS. Clinical pregnancy and live birth rates did not contribute to the development of OHSS. In the regression analysis without OHSS, the number of IVF attempt, HbA1c, hCG day P4 value, and the number of 2 PN zygotes also contributed to the development of OHSS.

Discussion

OHSS is an iatrogenic complication of assisted reproductive techniques, characterized by increased arteriolar vasodilation and impaired permeability, resulting in a shift of intrasvascular fluid to the extravascular space[13]. Since mild form OHSS is seen in approximately one third of IVF cycles, preventive measures are directed towards preventing the development of moderate and severe OHSS. Severe OHSS develops about 2-3% of cycles[15,18]. A recent Cohrane review has listed the following seven methods for preventing the development of OHSS; Use of metformin in women with PCOS, use of GnRH antagonist protocol or clomiphene citrate for COS, use of dopamine agonist for VEGFR-2 blockade, use of volume expanders for hypovolemia, coasting, and use of progesterone for luteal phase support[16]. However, neither method alone or in combination has been able to provide complete prevention. For this reason, research continues to develop new methods and medications to prevent OHSS.

By makinghypovolaemic hyponatremia and haemoconcentration OHSS reduces intracellular calcium and increases cAMP-mediated-renin-angiotensin II-VEGF release[19]. The continuation of VEGF synthesis due to hypocalcemia is also an obstacle to fully recover from OHSS. Calcium gluconate infusion has been introduced to prevent VEGF synthesis and development of OHSS by blocking the renin-angiotensin II-VEGF pathway[10,11,12,20]. When the literature was reviewed, five studies[11,12,20-22] aiming to prevent the development of OHSS were found by infusing calcium gluconate in patients at high risk for OHSS **(Supplementary Table V)**. While calcium infusion was used in all of these five studies, either cabegoline or placebo was used in the patients in the control group. In only one study, calcium infusion was used in combination with other preventive methods. As a common result of all studies calcium gluconate infusion prevented the moderate and severe OHSS, equivalent to cabergoline. When compared with placebo, calcium gluconate infusion significantly reduced the progression of both moderate and severe OHSS[11,12,20-22].

Our results, on the other hand, were similar to the literature data at some points and completely different at other points. Mild OHSS was developed in 367 patients receiving Calcium gluconate infusions, while 251 patients in the cabergoline group developed mild OHSS. Mild OHSS frequency detected in the calcium group was sig-

nificantly higher than the cabergoline group. In previous studies[20-22], moderate and severe OHSS incidences were compared and mild OHSS was not taken into account because it occurs in approximately 30% of normal cycles. In our study, mild OHSS was detected in 89% of the cases in the calcium group and in 73% of the cases in the cabergoline group, and these data are significantly higher than the literature data (30%). The high incidence of mild OHSS, despite calcium and cabergoline treatment, can be interpreted as both drugs reduce the transition from mild form OHSS to moderate or severe OHSS.

Moderate OHSS was detected in 32 women (7.8%) in the calcium gluconate group, while moderate OHSS was observed in 184 people (42.3%) in the cabergoline group. Calcium infusion significantly reduced the development of moderate OHSS compared to cabergoline therapy ($p<.001$). The reason why cabergoline cannot sufficiently reduce moderate OHSS can be attributed to its partial inhibition of VEGFR2. Cabergoline inhibits VEGFR2 phosphorylation in the ovaries, thus preventing VEGF from binding to this receptor to some extent. However, since this is not a complete receptor blockade, luteal angiogenesis continues despite decreased permeability, which prevents a complete recovery in OHSS[23]. In the group given calcium gluconate, increased calcium levels may have reduced the development of moderate OHSS by preventing the release of cAMP-mediated-renin-angiotensin II-VEGF[10].

While severe OHSS developed in 11 patients (2.7%) in the calcium gluconate group, severe form of OHSS did not develop in the cabergoline group (0%, $p<.001$). Since the frequency of moderate OHSS is low in those taking calcium gluconate, some of the mild forms may have turned into severe OHSS. Despite Calcium treatment, we can explain the development of severe OHSS in 11 patients with juxtaglomerular cells (JG) dysfunction. Calcium and cAMP regulate the release of renin in the JG apparatus. Increase in cAMP and decrease in calcium in JG cells increase the release of renin. Calcium reduction activates calcium-inhibitable isoforms of adenylyl cyclase (types V and/or VI) in JG cells. Type V or VI adenylyl cyclase firstly increases cAMP level and subsequently both renin and VEGF secretion[10]. Calcium gluconate, which we use in the prevention of OHSS, inhibits calcium-inhibitable isoforms of adenylyl cyclase by increasing JG cell calcium and prevents the release of cAMP-mediated-renin-angiotensin II-VEGF[10]. We do not know whether calciumlevels in the circulation or, more importantly, in the juxtaglomerular cells, decrease in OHSS patients. Fluid shift and electrolyte imbalance in the extravascular space due to OHSS may cause hypocalcemia. Increased level of the calcium-inhibitable isoform adenylyl cyclase-V in the juxtaglomerular cell is required for hypocalcemia to stimulate renin release[10]. Since cAMP signals are compartmentalized in JG cells, every stimulus that leads to an increase in cAMP does not result in renin release. While PTH increases cAMP release in JG cells, it does not affect renin secretion. This is because PTH activates non-calcium-sensitive adenylate cyclases, which does not cause renin release[24]. Comprehensive studies[24,25]comparing serum and urine calcium and renin levels in high-risk women with PCOS for OHSSneed to answer this question. Administering calcium gluconate treatment in OHSS patients with hypoclaemia seems to be a more logical approach. It has been reported that infants born to mothers under OHSS prevention therapy are not different from healthy controls in terms of neonatal respiratory distress syndrome[26,27].

When logistic regression analysis was performed, a significant correlation was found between age, BMI, AMH, number of antral follicles and oocytes, OHSS history, paracentesis, P4 level on the day of hCG, 2 PN zygotes, and HbA1c level and the development of OHSS. No correlation was found between the use of metformin or cetrotide and the development of OHSS. Similarly, clinical pregnancy, live birth and abortion rates did not affect the development of OHSS. Miscarriage, clinical pregnancy and live birth rates were found to be similar in the cabergoline and calcium gluconate treatment group. Likewise, there was no significant difference between the two groups in terms of late-onset OHSS development. Despite the adequacy in the number of cases, our study has some limitations. The inhomogeneity of treatment groups seems to be the main problem. It would be better if the outcomes of babies born to mothers with OHSS could be given. Despite all these limitations, the high number of cases increases the clinical importance of our study.

Conclusions

Our results were quite different when compared with the other five studies using calcium gluconate for the prevention of OHSS in the literature. Although the results of patients in the cabergoline group were consistent with the literature we showed

that calcium gluconate treatment did not prevent the development of severe OHSS. Considering the high number of participants, we can say that calcium gluconate infusion is not very effective in the prevention of OHHS. However, our results need to be confirmed with extensive studies.

Ethics Approval and Consent to Participate

The study was performed according to the guidelines of the Helsinki Declaration on human experimentation and ethical approval was received. Informed consent was obtained from all participants at the time of enrollment.

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Authors' Contributions

N.T., C.K. and R.O. conceived, designed and performed the study procedures; C.K., N.T. and R.O analyzed the data and contributed reagents and materials; N.T. wrote the paper.

Conflicts of interest

The authors declare no conflicts of interest.

References

1) Agrawal R, Tan SL, Wild S, Sladkevicius P, Engmann L, Payne N, Bekir J, Campbell S, Conway G, Jacobs H. Serum vascular endothelial growth factor concentrations in in vitro fertilization cycles predict the risk of ovarian hyperstimulation syndrome. Fertil Steril 1999; 71: 287-293.
2) 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: 486-489.
3) Delbaere A, Smits G, De Leener A, Costagliola S, Vassart G. Understanding ovarian hyperstimulation syndrome. Endocrine 2005; 26: 285-290.
4) Braat D, Bernardus R, Gerris J. Anonymous reports of lethal cases of ovarian hyperstimulation syndrome. In: Gerris J, Olivennes F, Delvigne A editor(s). Ovarian Hyperstimulation Syndrome. London: Informa UK Limited 2006: 59-66.
5) Mathur RS, Akande AV, Keay SD, Hunt LP, Jenkins JM. Distinction between early and late ovarian hyperstimulation syndrome. Fertil Steril 2000; 73: 901-907.
6) Mourad S, Brown J, Farquhar C. Interventions for the prevention of OHSS in ART cycles: an overview of Cochrane reviews. Cochrane Database Syst Rev 2017: 23; CD012103.
7) Bates DO, Harper SJ. Regulation of vascular permeability by vascular endothelial growth factors. Vascul Pharmacol 2002; 39: 225-237.
8) Gomez R, Gonzalez-Izquierdo M, Zimmermann RC, Novella-Maestre E, Alonso-Muriel I, Sanchez-Criado J, Remohi J, Simon C, Pellicer A. Low-dose dopamine agonist administration blocks vascular endothelial growth factor (VEGF)-mediated vascular hyperpermeability without altering VEGF receptor 2-dependent luteal angiogenesis in a rat ovarian hyperstimulation model. Endocrinology 2006; 147: 5400-5411.
9) Ata B, Yakin K, Alatas C, Urman B. Dual renin-angiotensin blockage and total embryo cryopreservation is not a risk-free strategy in patients at high risk for ovarian hyperstimulation syndrome. Fertil Steril 2008; 90: 531-536.
10) Ortiz-Capisano MC, Ortiz PA, Harding P, Garvin JL, Beierwaltes WH. Decreased intracellular calcium stimulates renin release via calcium-inhibitable adenylyl cyclase. Hypertension 2007; 49: 162-169.
11) Naredi N, Karunakaran S. Calcium gluconate infusion is as effective as the vascular endothelial growth factor antagonist cabergoline for the prevention of ovarian hyperstimulation syndrome. J Hum Reprod Sci 2013; 6: 248-252.
12) Naredi N, Singh SK, Lele P, Nagraj N. Severe ovarian hyperstimulation syndrome: Can we eliminate it through a multipronged approach? Med J Armed Forces India 2018; 74: 44-50.
13) Practice Committee of the American Society for Reproductive Medicine. Electronic address: ASRM@asrm.org; Practice Committee of the American Society for Reproductive Medicine. Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. Fertil Steril 2016; 106: 1634-1647.
14) Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004; 19: 41-47.
15) Papanikolaou EG, Pozzobon C, Kolibianakis EM, Camus M, Tournaye H, Fatemi HM, Van Steirteghem A, Devroey P. Incidence and prediction of ovarian hyperstimulation syndrome in women undergoing gonadotropin-releasing hormone antagonist in vitro fertilization cycles. Fertil Steril 2006; 85: 112-120.
16) Yakovenko SA, Sivozhelezov VS, Zorina IV, Dmitrieva NV, Apryshko VP, Voznesenskaya JV. Prevention of OHSS by intravenous calcium. Hum Reprod 2009; 24 Suppl 1: i61.
17) Golan A, Ronel R, Herman A, Soffer Y, Weinraub Z, Caspi E. Ovarian hyperstimulation syndrome:

An update review. ObstetGynecolSurv 1989; 44: 430-440.

18) Humaidan P, Nelson SM, Devroey P, Coddington CC, Schwartz LB, Gordon K, Frattarelli JL, Tarlatzis BC, Fatemi HM, Lutjen P, Stegmann BJ. Ovarian hyperstimulation syndrome: review and new classification criteria for reporting in clinical trials. Hum Reprod 2016; 31: 1997-2004.

19) Guo JL, Zhang DD, Zhao Y, Zhang D, Zhang XM, Zhou CQ, Yao SZ. Pharmacologic Interventions in Preventing Ovarian Hyperstimulation Syndrome: A Systematic Review and Network Meta-Analysis. Scientific reports 2016; 6: 190-193.

20) El-Khayat W, Elsadek M. Calcium infusion for the prevention of ovarian hyperstimulation syndrome: a double-blind randomized controlled trial. FertilSteril 2015; 103: 101-105.

21) Fouda UM, Elshaer HS, Youssef GG, Hanafy A, Mehrem WM, Youssef MA, Farouk M, Nabil H. Cabergoline versus calcium infusion in the prevention of ovarian hyperstimulation syndrome: a randomised controlled study. J Obstet Gynaecol 202; 16: 1-5.

22) Gurgan T, Demirol A, Guven S, Benkhalifa M, Girgin B, Li TC. Intravenous calcium infusion as a novel preventive therapy of ovarian hyperstimulation syndrome for patients with polycystic ovarian syndrome. Fertil Steril 2011; 96: 53-57.

23) Soares SR, Gomez R, Simon C, Garcia-Velasco JA, Pellicer A. Targeting the vascular endothelial growth factor system to prevent ovarian hyperstimulation syndrome. Hum Reprod Update 2008; 14: 321-333.

24) Atchison DK, Harding P, Cecilia Ortiz-Capisano M, Peterson EL, Beierwaltes WH. Parathyroid hormone stimulates juxtaglomerular cell cAMP accumulation without stimulating renin release. Am J Physiol Renal Physiol 2012; 303: 1157-1165.

25) Celik O, Aydin S, Celik N, Ugur K, Yavuzkir S, Hatirnaz S, Yardim M, Celik S. Molecular role of peptides/proteins in subfertility of polycystic ovarian syndrome. Cell Mol Biol (Noisy-le-grand) 2019; 65: 32-40.

26) Gurel S, Erel O. The Relevant Relationship Between Umbilical Cord Blood Gas and Acid Base Analysis and Dynamic Thiol (Sh)/Disulphide (S-S) Balance in Neonatal Babies with Different Perinatal Risks and Newborn Diseases, Iran J Pediatr 2020; 3: e102793.

27) Gurel S. Respiratory Distress in Newborn. Aegean J Med Sci 2019; 1: 38-41.