MJMR, Vol. 34, No. 1, 2023, pages (186-195).

Open Access
ISSN:2682-4558

Research Article

Effect of early intake versus known standard intake of cabergoline in prevention of development of OHSS in patients undergoing ICSI cycles

Alaa Gamal Abd El-Azeem[1], Mohamed Ahmed Mohamed[1], Mohamed Rabi Osman[1], Hashim Faris Mohamed[1]

[1] Department of Obstetrics and Gynaecology, Faculty of Medicine, Minia University, Minia, Egypt

DOI: 10.21608/mjmr.2022.166720.1198

Abstract

Background: Ovarian hyper stimulation syndrome (OHSS) is a complication resulting from administration of human chorionic gonadotrophin (hCG) in assisted reproduction technology (ART) treatment. Most cases are mild, but forms of moderate or severe OHSS appear in 3% to 8% of in vitro fertilisation (IVF) cycles. Recently, early adminstration of dopamine agonist (cabergoline) used as a preventive intervention for OHSS in women at high risk of OHSS who are undergoing ICSI cycles. The aim of the study is to assess the influence of timing of cabergoline initiation on prevention of OHSS. **Methods:** This was a clinical trial study including eighty patients with high risk for ovarian hyperstimulation attended to the infertility clinic/ center of Obstetrics and Gynaecology department, Minia University Maternity hospital and in private centers between April 2019 and April 2020 and undergoing ovulation induction using GnRH agonist down regulation protocol for ICSI cycles. Patients were divided into two groups according to the drug regimen used for OHSS risk prevention. **Results:** There is no statistically significant difference between early administration and standard administration groups as regard the age and BMI. There is no statistically significant difference between early administration and standard administration groups as regard cycle cancelation, clinical pregnancy and 1st time abortion. OHSS was statistically significant higher in standard administration than early administration group. **Conclusion:** early administration of cabergoline might be an effective approach for prophylaxis against OHSS.

Key Words: OHSS, cabergoline, Gonadotrophin Injection.

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a dangerous iatrogenic complication of ovulation induction[(1)]. Though it is a rare [(2)] or an uncommon[(3)] condition its true incidence is difficult to delineate as a strict consensus definition is lacking[(3)]. The incidence ranges from of 33% in mild cases to 3-6% in moderate cases while reaching only 1-2% in severe cases[(4,5).] These severe cases are life-threatening conditions that could be fatal. Furthermore, the pathophysiology of this condition is not fully clear, understanding it helps identifying preventive and treating modalities [(6).]

The syndrome almost always presents either up to 8 days after hCG administration in susceptible patients (early onset) or during early pregnancy, 9 or more days after hCG administration related to pregnancy induced hCG production(late onset[(7)]. Early OHSS can to some extent be predicted by pre-ovulatory indices of ovarian response, in time to institute preventive measures such as cancellation

[8]. Late OHSS does not relate strongly to pre-ovulatory ovarian response, making it difficult for clinicians to identify the cycles in which it is likely to occur [2,9].

Clinical features of OHSS include a spectrum of findings, such as ovarian enlargement, ascites, haemoconcentration, hyper-coagulability, and electrolyte imbalances. Pleural effusion, acute renal insufficiency, and venous thrombo-embolism occur in severe cases. A classification of OHSS symptoms was adopted by ASRM.[3]. Human chronic gonadotropine hCG administration for the final follicular maturation and ovulation triggering is the knock-out stimulus for OHSS. This leads to over expression of vascular endothelial growth factor VEGF in the ovary, and release of vasoactive angiogenic substances or mediators that increase capillary permeability. Subsequently, fluid shift from the intra- to the extravascular spaces with acute third-space fluid sequestration occurs. This causes hemoconcentration with reduced organ perfusion, alterations in blood coagulation and the resulting risk of thromboembolism and leakage of fluid into the peritoneal cavity and lungs [3,6 ,10,11].

The most important of these mediators is vascular endothelial growth factor (VEGF). VEGF is a vasoactive mediator which increases capillary permeability. VEGF has been found to be expressed in human ovaries and is expressed at a higher level in the granulosa cells [12]. It has been observed that VEGF mRNA levels increases after human chorionic gonadotropin (hCG) administration in granulosa cells and the elevated levels of the secreted proteins have been detected in serum, plasma, and peritoneal fluids in women at risk or with OHSS. VEGF stimulates new blood vessel development and vascular hyperpermeability by interacting with its VEGF receptor 2 (VEGFR2)[13,14]. Other factors that have been implicated include angotensin II, interleukin-6, insulin like growth factor 1 IGF-1, epidermal growth factor, transforming growth factor a and b, basic fibroblast growth factor, platelet driven growth factor interleukin 1b and others which can act directly or indirectly via VEGF [3].

No definite cure for this syndrome [15], prevention is considered as an essential and vital issue. Every attempt should be done to identify those at high risk. Two types of prevention have been suggested; primary prevention (before ovarian stimulation) and secondary prevention after ovarian stimulation.[2]. Many preventive approaches have been used for its prevention including using antagonist rather than agonists for ovulation induction, triggering ovulation with agonist, metformin administration, intravenous albumin, cabergoline, corticosteroids, aspirin, coasting, cryopreservation and others, but the reports are conflicting and many of them have not been critically evaluated [2,3].

There is growing evidence that the ergot derivative; cabergoline which is a potent dopamine receptor agonist on D2 administration reduces incidence and severity of OHSS.[3] Dopamine agonists prevent the phosphorylation of VEGFR2 and reduce the in vitro and in vivo release of vasoactive angiogenic agents. As a result, vascular permeability is also reduced. Consequently, dopamine agonist at a daily dose of 0.5 mg has been supposed to be a potential new strategy to prevent OHSS and reduce its severity.[16]

Results obtained with animal models[17] and the safe clinical profile of dopamine agonists, have led to studies on humans.[16] Many studies have evaluated cabergoline as a preventive strategy to reduce the incidence of OHSS using varying doses and regimens[2,3,10] Effectiveness of cabergoline in reduction of the incidence of OHSS was reported in a group of women with the polycystic ovarian syndrome and hyperprolactinemia[18]. Also, safety of cabergoline use during infertility treatment: fertilization, implantation and pregnancy rates were similar to matched controls.[19] Four systematic reviews and meta-analyses have revealed that cabergoline reduces the

incidence of moderate/severe OHSS without affecting implantation, pregnancy and miscarriage rates.[20-23] Two Cochrane reviews reported that the quality of evidence regarding the use dopamine agonist versus placebo in prevention of ovarian hyperstimulation ranged from very low to moderate.[15,24] On the other hand, others reported that there is good evidence that dopamine agonist administration starting at the time of hCG trigger for several days reduce the incidence of OHSS (grade A)[3].

Various cabergoline administration protocols were reported in different studies. Doses were ranging from 0.25 mg- 0.5 mg and were started either from day of HCG triggering or day of oocyte retrieval.[16-23 & 25-28] Cabergoline was continued form two days in one study[27] and up to 8 days in most studies[25,28] or as long as three weeks in one study [26] . Alveizer et al.,[25] gave 0.5 mg cabergoline daily for 8 days from the day of HCG injection. Carriza et al.,[26] gave 0.5 mg cabergoline daily for 3 weeks from the day after oocyte retrieval. Salah Edeen and Alhelou[27] used 0.5 mg cabergoline oral on 2 successive days and repeated after 1 week starting from the day of HCG. Shaltout et al.,[28] used 0.25 mg cabergoline daily for 8 days from the day of HCG injection.

The influence of timing of cabergoline initiation on prevention of OHSS is currently under study.

Patients and Methods

This study was an interventional comparative clinical trial including eighty patients with high risk for ovarian hyperstimulation attended to the infertility clinic/center of Obstetrics and Gynaecology department, El Minia University Maternity hospital, El Minia, Egypt and in private centers and undergoing ovulation induction using GnRH agonist down regulation protocol for ICSI cycles. Patients were divided into two groups according to the drug regimen used for OHSS risk prevention. The study was conducted between April 2019 and April 2020 after approval of the study protocol by the Ethical Committee of and all participants will sign an informed written consent form.

Inclusion criteria: (high risk for OHSS)

1. Female less than 35 years old.
2. Previous history of sever OHSS.
3. Patient undergoing ovulation induction by GnRH Agonist down regulation protocol
4. Presence of >18 oocytes11 mm or more in diameter at any day of the stimulation cycle before HCG trigger.
5. Ovary size >10cm.
6. Serum estradiol >3500 pg/ml on the day of HCG administration.

Exclusion criteria: (low risk for OHSS)

1. Female more than 35 years old
2. Patient with single ovary.
3. Patient undergoing ovulation induction by antagonist protocol.
4. Presence of < 18 oocytes during oocyte retrieval or at any time before HCG trigger.
5. Ovary size <10cm.
6. Serum estradiol <3500 pg/ml on the day of HCG administration.

All patients will be subjected to:

1. History taking (name, age, duration of infertility, type of infertility male or female factor, previous history of OHSS)
2. Clinical examination.
3. Ultrasound scanning.
4. Investigations (CBC, HCT value, liver and kidney functions, E2 level)
5. β-hCG was checked 15 days after embryos transfer.

A long protocol was used for ovulation induction starting with subcutaneous daily injections of triptorelin acetate 300 micrograms decapeptyle, on Day 21 of the preceding cycle. Urinary FSH (fostimon) and HMG (merional) injections were administered at the first day of the subsequent cycle, at an initial dose of 150 IU; the doses were subsequently adjusted on the basis of responses and monitoring with transvaginal scan, and serum estradiol levels. The duration of stimulation was tailored according to the response with serial estradiol estimations and Ultrasound scans that will be performed on alternate days between Days 5 and 10 of the cycle and as necessary thereafter.

Once the decision to administer HCG was taken, patients were immediately allocated into two randomized groups; 40 patients each according to the drug regimen used for OHSS prevention (using computer-generated tables):

Group A (group I) (n=40) (Early administration group) The drug regimen consists of cabergoline oral tab 0.5 mg (Dostinex, Pfizer Australia Pty ltd) that was administered daily starting from the day of peak serum estradiol level and optimum follicle number that were fulfilled the criteria for successful hyperstimulation – whatever this day is -) and continued till the day of ovum retrieval and for more 8 days after .

Group B (group II) (n=40) (Standard administration group). The drug regimen consists of cabergoline oral tab 0.5 mg (Dostinex, Pfizer Australia Pty ltd) that was administered daily starting from the day of ovum retrieval for 8 days after.

Follow up

Patients were followed up according to the standard protocol for ICSI. Primary outcome variables were efficacy and safety. Efficacy of each regimen was recorded as the success in the prevention of OHSS. Safety was recorded as the presence or absence of side effects. Secondary outcome variables were pregnancy rate, live-birth rate….etc. All patients were assessed every week after retrieval and for 8 weeks to determine early clinical or ultrasound evidence of OHSS. The occurrence and severity of OHSS was defined according to the classification described by Golan et al.,[5]

.

The presence of OHSS is defined in accordance with the Golan 5 grade system and women who at least are at grade 2 of this classification (Mild) considered as OHSS cases and will experience abdominal distention and discomfort, nausea and vomiting and/or diarrhea and enlargement of ovaries(5-12cm). In Moderate forms, ultrasound evidences of ascites will be observed and severe OHSS accompany with clinical signs of ascites, hydrothorax, breathing disorders, hemoconcentration, coagulopathy and renal perfusion decrease.

Complaints of abdominal discomfort, nausea, vomiting and ultrasound evidence of enlarged ovaries (5–12 cm) and/ or the detection of ascites defined the occurrence of moderate OHSS. The presence of clinically evident ascites and/or hydrothorax, increased blood viscosity and coagulation abnormality or laboratory Investigation of increased hematocrite level (>45%) or decreased S. albumin (<35 g/l) defined the occurrence of severe OHSS. Patients with severe OHSS will be hospitalized. Onset of OHSS within 9 days of ovulatory trigger is defined as early onset OHSS while beyond 9 days is defined as late onset OHSS. Clinical and ultrasound examinations will be performed on the day of embryo transfer, then weekly to detect the occurrence of OHSS.

All patients will be instructed to contact us if they experi-enced difficulty in breathing, recurrent vomiting, decreased urine volume, dizziness on standing, abdominal pain, enlargement of the abdomen, and rapid weight gain and were examined as needed. Women will be monitored on an outpatient basis via phone contact and visits until menstruation occurred or until fetal heart activity was detected in pregnant patients. The primary outcome is an evaluation of the development of OHSS in the partici-pants. Implantation rate and clinical pregn-ancy rate were secondary outcomes.

Results

The study was conducted between April 2019 and April 2020 in private centers on 80 patients seeking for ICSI included in the study according to inclusion criteria.

There is no statistically significant difference between early administration and standard administration groups as regard the age and BMI.

There is no statistically significant difference between early administration and standard administration groups as regard

cycle cancelation, clinical pregnancy and 1st time abortion. OHSS was statistically significant higher in standard administration than early administration group.

Table (1): Comparison of age and BMI of the studied groups

		Early administration No. = 40	Standard administration No. = 40	t	P-value	Sig.
Age (year)	Range	20 – 35	20 – 35	1.753•	0.084	NS
	Median [IQR]	27.5 [4]	26 [8]			
	Mean ± SD	27.925 ± 3.450	26.200 ± 5.120			
BMI	Range	25 – 35	25 – 32	1.979•	0.051	NS
	Median [IQR]	29 [3]	27.5 [4]			
	Mean ± SD	29.125 ± 2.524	28.000 ± 2.562			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
•: independent student t test

Table (2): Comparison of type of infertility characteristics of the studied groups

		Early administration No. = 40	Standard administration No. = 40	t/x^2	P-value	Sig.
Type of Infertility	Male	12 (30%)	8 (20%)	7.040*	0.071	NS
	Female	13 (32.5%)	12 (30%)			
	Combined	3 (7.5%)	12 (30%)			
	Unexplained	12 (30%)	8 (20%)			
Infertility Duration (years)	Range	2 – 12	2 – 13	1.397•	0.166	NS
	Median [IQR]	6 [4.75]	3 [8]			
	Mean ± SD	6.625 ± 2.837	5.500 ± 4.230			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
•: independent student t test, chi square test

Table (3): Comparison of treatment outcome of the studied groups

		Early administration	Standard administration	X^2	P-value	Sig.
		No. = 40	No. = 40			
OHSS	No	23 (57.5%)	8 (20%)	16.787*	0.002	HS
	Mild	7 (17.5%)	10 (25%)			
	Moderate	6 (15%)	10 (25%)			
	Severe	4 (10%)	4 (10%)			
	Critical	0 (0%)	8 (20%)			
Cycle cancelation	Yes	4 (10%)	8 (20%)	1.569*	0.210	NS
	No	36 (90%)	32 (80%)			
Clinical pregnancy	Yes	18 (45%)	16 (40%)	0.323*	0.570	NS
	No	18 (45%)	12 (30%)			
1st trimester abortion	Yes	3 (7.5%)	4 (10%)	0.157*	0.692	NS
	No	37 (92.5%)	36 (90%)			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
•: chi square test

Discussion

OHSS is the most serious complication of COS and is potentially fatal, so optimization of prophylactic measures will reduce morbidity and mortality in ART clinics. Prophylactic strategies include; using the antagonist protocol, decreasing starting gonadotropin dose, metformin, coasting, cycle cancelation, cryopreservation of all embryos, in vitro maturation, calcium gluconate and infusion of plasma expanders [29].

In high responders, GnRH agonist trigger in antagonist protocol is the most effective strategy to prevent or at least significantly decrease OHSS [30].

However, it is associated with severe luteal phase insufficiency leading to very poor reproductive outcome [31]. So, to improve the reproductive outcome, options include freezing-all embryos and cycle segmentation or, dual trigger in which lower doses of HCG are used in addition to the GnRH agonist [32].

This study investigated whether the timing of cabergoline administration affects the rate of OHSS in high-risk patients.

To the best of our knowledge, this is the first study that looked specifically at when cabergoline was initiated in a cycle using agonist protocol, with the primary outcome being OHSS rates.

In 2013 a study has been done, and all women received a “long protocol,” which employs a GnRH agonist to prevent premature ovulation and necessitates the use of hCG to trigger the final oocyte maturation [33].

Also in our study we used “long protocol,” and trigger with (5,000-10,000) IU hCG) for final oocyte maturations. To avoid luteal phase insufficiency in these cycles [34].

Cabergoline was found to decrease the risk of OHSS in rats via inhibition of VEGFR2-dependent vascular permeability. Another mechanism of action is via decreasing follicular fluid mediators which might have a role in OHSS [35].

Various studies have evaluated the efficacy of cabergoline as a preventive measure for OHSS.

A previous study reported that the higher dose of cabergoline prevents an increase in the severity of OHSS and its prolongation following the occurrence of pregnancy [36].

Another study observed the effect of cabergoline in the prevention of OHSS in women at risk undergoing IVF/ICSI treatment cycles. It was observed that prophylactic treatment with the dopamine agonist, cabergoline, significantly reduced the incidence of OHSS in women at high risk undergoing IVF/ICSI treatment[37].

Guvendag et al., [38] showed that cabergoline significantly decreases the follicular fluid levels of antimullarian hormone, insulin like growth factor, Inhibin B and hepatocyte growth.

A study compared cabergoline therapy to coasting concluded that, 8 days cabergoline therapy started from hCG administration is a very effective way to reduce moderate–severe OHSS without compromising pregnancy rates in patients at risk of developing OHSS [39].
Another study compared prophylactic cabergoline therapy to prophylactic intravenous human albumin, concluded that cabergoline was more effective and less costly than human albumin in the prevention of OHSS in high-risk patients [40].

Tehraninejad et al.,[41] in 2006 conducted a study on rats to test the effect of cabergoline on luteal progesterone levels. They found that serum progesterone levels and luteal apoptosis remained unchanged, suggesting the absence of a luteolytic effect of cabergoline.

Randomized high-risk patients for either starting cabergoline on the day of hCG or the day of oocyte retrieval. The study showed that both regimens were equally effective in prophylaxis against OHSS, meanwhile, implantation and pregnancy rates were comparable [42].

Conclusion

To the best of our knowledge, there is no published data on starting cabergoline before the day of hCG administration. So, based on observation that VEGF expression in human granulosa cells starts before hCG administration, we postulated that early administration of cabergoline might be an effective approach for prophylaxis against OHSS. In the present work, cabergoline was administrated to high risk patients when the fulfilling the inclusion criteria. This can occur even with starting induction.

Our results showed that this approach is effective in prevention of early OHSS without compromising pregnancy rates.

References

1. kumar, P., Sait, S.F., Sharma, A., Kumar M., Ovarian hyperstumulation syndrome J. Hum. Reprod. Sci. 2011, 4, pp 70-75
2. Sallam, H.H., Ezzeldin F., Sallam, N. H. Prevention of OHSS. An evidence-based approach. WARM 2010, S17-18
3. 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(7), 1634-1647
4. R.S. Morris, C. Miller, L. Jacobs, K. Miller Conservative management of ovarian hyperstimulation syndrome J. Reprod. Med., 40 (1995), pp. 711-714
5. Golan, R. Ron-El, A. Herman, Y. Soffer, Z. Weinrau b, E. Caspi Ovarian hyperstimulation syndrome: an update review Obstet. Gynecol. Surv., 44 (1989), pp. 430-440
6. Busso, C.E., Soares, S.R., Pellicer A., mangment of ovarian hyperstimulation syndrome- UpToDate 2018.
7. Lyons CA. Wheeler CA. Frishman GN, Hackctl RJ, Scifcr DB and Hanning RVJ Early and late presentation of the ovarian hypcrstimulation syndrome: two distinct entities with different risk factors. Hum Reprod 1994; 9, 792-799.

8. Hancock KW, Stitch SR, Oakey R, Scott JS, Levell MJ and Ellis PR Ovulation induction. Problems of prediction of response to gonadal-rophin. Lancet 1970;2,482-485.
9. Mathur RS, Akande AV, Kcay SD ct al., Late onset OHSS after ovarian stimulation is poorly predicted by peak ocstradiol concentration and number of oocytes collected. Hum Reprod 1997; 12 (Abslr Book I), R-229.
10. Soares SR, Gómez R, Simón C, García-Velasco JA, Pellicer A. Targeting the vascular endothelial growth factor system to prevent ovarian hyperstimulation syndrome. Hum Reprod Update 2008;14:321-33.
11. D.D. Braat, J.M. Schutte, R.E. Bernar dus, T.M. Mooij, F.E. van LeeuwenMaternal death related to IVF in the Netherlands 1984–2008 Hum. Reprod., 25 (2010), pp. 1782-1786
12. Naredi N, Talwar P, Sandeep K. VEGF antagonist for the prevention of ovarian hyperstimulation syndrome: Current status. Med J Armed Forces India 2014;70:58-63
13. Wang TH, Horng SG, Chang CL, Wu HM, Tsai YJ, Wang HS, et al., Human chorionic gonadotropin-induced ovarian hyperstimulation syndrome is associated with up-regulation of vascular endothelial growth factor. J Clin Endocrinol Metab 2002;87: 3300-8.
14. Gille H, Kowalski J, Li B, Le Couter J, Moffat B, Zioncheck TF, et al., Analysis of biological effects and signaling properties of Flt-1 (VEGFR-1) and KDR (VEGFR-2). Areassessment using novel receptor-specific vascular endothelial growth factor mutants. J Biol Chem 2001;276: 3222-30.
15. Tang, H., Mourad, S., Zahi., S., Hart, R. J., Dopamine agonists to prevent ovarian hyperstim,ulation syndrome in women undergoing assisted repro-duction technology Cochrane Database of systemic reviews. 2016 issue 11
16. Shaltout A, Shohyab A, Youssef MA. Can dopamine agonist at a low dose reduce ovarian hyperstimulation syndrome in women at risk undergoing ICSI treatment cycles? A randomized controlled study. Eur J Obstet Gynecol Reprod Biol 2012;165:254-8.
17. Ata B, Seyhan A, Orhaner S, Urman B. High dose cabergoline in management of ovarian hyperstimulation syndrome. Fertil Steril 2009;92:1168.e1-4.
18. E. Papaleo, N. Doldi, L. DeSantis, G. Marelli, E. Marsiglio, S. Rofena, A. F errari Cabergoline influences ovarian stimulation in hyperprolactinaemic patients with polycystic ovary syndrome Hum. Reprod., 16 (2001), pp. 2263-2266 CrossRefView Record in ScopusGoogle Scholar
19. C. Alvarez, I. AlonsoMuriel, G. Garcí a, J. Crespo, J. Bellver, C. Simón, A. P ellicer Implantation is apparently unaffected by the dopamine agonist Cabergoline when administered to pre-vent ovarian hyperstimulation synd-rome (OHSS) in women undergoing ART. A pilot study Hum. Reprod., 22 (2007), pp. 3210-3214
20. V.M. Leitao, R.M. Moroni, L.M. Sek, C.O. Nastri, W.P. Martins Cabergoline for the prevention of ovarian hyper-stimulation syndrome: systematic review and meta-analysis of rando-mized controlled trials Fertil. Steril., 101 (2014), pp. 664-675
21. M. Baumgarten, L. Polanski, B. Camp bell, N. Raine-Fenning Do dopamine agonists prevent or reduce the severity of ovarian hyperstimulation syndrome in women undergoing assisted repro-duction? A systematic review and meta-analysis Hum. Fertil. (Camb.), 16 (2013), pp. 168-174
22. H. Tang, T. Hunter, Y. Hu, S.D. Zhai, X. Sheng, R.J. Hart Cabergoline for preventing ovarian hyperstimulation syndrome Cochrane Database Syst. Rev., 15 (2) (2012), p. CD008605
23. M.A. Youssef, M. VanWely, M.A. Ha ssan, H.G. AlInany, M. Mochtar, S. K hattab, *et al.*Can dopamine agonists reduce the incidence and severity of OHSS in IVF/ICSI treatment cycles? A systematic review and meta-analysis Hum. Reprod. Update, 16 (2010), pp. 459-466

24. Mourad S., Brown., J., Farquhar,C., Interventions for the prevention of ohss in ART cycles: an overview of Cochrane reviews. Cochrane Database of systemic reviews. 2017. Issue 1.
25. Alvarez C, Marti-Bonmati L., Novella-Maestre E Sanz R., Gomez Fernandez-Sanchez M Simon C Pellicer., A Dopamine agonist cabergoline reduces hemoconcentration and ascites in hyperstimulated women undergoing assisted reproduction *J Clin Endocrinol Metab* 2007, vol.92 (pg.2931- 2937)
26. Carizza C., Abdelmassih V., Abdelmassih S., Ravizzini Salgueiro L Salgueiro PT Jine LT Nagy P Abdelmassih R Cabergoline reduces the early onset of ovarian hyperstimulation syndrome: a prospective randomized study *Reprod Biomed Online* 2008, vol. 17 (pg. 751- 755)
27. Salah Edeen AMR Alhelou YM Can cabergoline prevent ovarian hyperstimulation syndrome in PCO patients undergoing gonadotropin stimulation? Comparative study with prednisolone Abstracts of the 25th Annual Meeting of ESHRE 28 June–1 July 2009 Amsterdam, The Netherland
28. Shaltout A Shohayeb A Eid M Abbas S Role of cabergoline in preventing ovarian hyperstimlation syndrome in high risk intracytoplasmic sperm injection (ICSI) patients and effect on outcome Abstracts of the 25th Annual Meeting of ESHRE 28 June–1 July 2009 Amsterdam, The Netherland.
29. 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(1):44–50.
30. Dosouto C, Haahr T, Humaidan P. Gonadotropin-releasing hormone agonist (GnRHa) trigger – state of the art. Reprod Biol 2017;17(1):1–8.
31. Fatemi HM, Polyzos NP, van Vaerenbergh I, Bourgain C, Blockeel C, Alsbjerg B, et al., Early luteal phase endocrine profile is affected by the mode of triggering final oocyte maturation and the luteal phase support used in recombinant follicle-stimulating hormone–gonadotropin-releasing hormone antagonist in vitro fertilization cycles. Fertil Steril 2013; 100:742–7.
32. Devroey P, Polyzos NP, Blockeel C. An OHSS-free clinic by segmentation of IVF treatment. Hum Reprod 2011; 26(10):2593–7.
33. Seow KM, Lin YH, Bai CH, Chen HJ, Hsieh BC, Huang LW, et al., Clinical outcome according to timing of cabergoline initiation for prevention of OHSS: a randomized controlled trial. Reprod Biomed Online 2013; 26(6): 562–8.
34. Humaidan P. Luteal phase rescue in high-risk OHSS patients by GnRHa triggering in combination with low-dose HCG: a pilot study. Reprod Biomed Online 2009;8(5):630–4
35. Soares SR, Gómez R, Simón C, Garcیa-Velasco JA, Pellicer A. Targeting the vascular endothelial growth factor system to prevent ovarian hyperstimulation syndrome. Hum Reprod Update 2008; 14:321–
36. Ata B, Seyhan A, Orhaner S, Urman B. High dose cabergoline in management of ovarian hyperstimulation syndrome. Fertil Steril 2009 Sep; 92(3):1168.e1-1168.e4.
37. Kilic N, Ozdemir O, Başar HC, Demircan F, Ekmez F, Yucel O. Cabergoline for preventing ovarian hyperstimulation syndrome in women at risk undergoing in vitro fertilization/ intracytoplasmic sperm injection treat-ment cycles: a randomized controlled study. Avicenna J Med 2015 Oct-Dec;5(4): 123-127.
38. Guvendag Guven ES, Dilbaz S, Duraker R, Mentese A, Cinar O, Ozdegirmenci O. The effect of cabergoline on folicular microenvironment profile in patients with high risk of OHSS. Gynecol Endocrinol 2013;29 (8):749–53.
39. Esinler I, Bozdag G, Karakocsok mensuer L. Preventing ovarian hyperstimulation syndrome: cabergoline versus coasting. Arch Gynecol Obstet 2013; 288(5):1159–63.

40. Tehraninejad ES, Hafezi M, Arabipoor A, Aziminekoo E, Chehrazi M, Bahmanabadi A. Comparison of cabergoline and intravenous albumin in the prevention of ovarian hyperstimulation syndrome: a randomized clinical trial. J Assist Reprod Genet 2012;29(3):259–64.
41. Gomez R, Gonzalez-Izquierdo M, Zimmer-mann 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; 147:5400–11.
42. Seow KM, Lin YH, Bai CH, Chen HJ, Hsieh BC, Huang LW, et al. Clinical outcome according to timing of cabergoline initiation for prevention of OHSS: a randomized controlled trial. Reprod Biomed Online 2013;26(6): 562–8.