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Original Article

Effect of low-dose aspirin on the development of ovarian hyperstimulation syndrome and outcomes of assisted reproductive techniques in the women with PCOS, a randomized double-blinded clinical trial

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ABSTRACT

Objective: Ovarian hyperstimulation syndrome (OHSS) is a major complication of assisted reproductive technologies (ART). Polycystic ovary syndrome (PCOS) is a risk factor for OHSS. The aim of this randomized clinical trial (RCT) was to study the effect of low-dose aspirin (LDA) on the development of OHSS and ART outcomes in PCOS during ART.

Materials and methods: This double-blinded placebo controlled RCT was performed on 232 PCOS infertile women in their first ART cycles during 2010–2016. LDA and placebo capsules were prepared, packed and specified by code numbers in similar shapes. One package was given to every woman and asked to take one capsule/day since the 21st day of her cycle prior to the gonadotropin stimulation. Gonadotropin releasing hormone agonist long protocol and triggering by human chorionic gonadotropin were used. Development of moderate to severe OHSS and their ART outcomes were documented then the codes were broken and data analyzed. Chi-square and Mann–Whitney U tests were used for the statistical analyses.

Results: Eighteen cases that did not follow the study design were excluded. 214 cycles remained for the final analyses with 109 cases in LDA and 105 in the placebo group. Rate of the moderate to severe OHSS in LDA group was 34.9% compared to 30.5% in placebo group ($P = 0.494$). Fertilization rate was 71.8% vs 65.1% ($P = <0.001$) and the mean number of grade III embryos were 3.28 ± 3.53 vs 1.46 ± 1.42 ($P = 0.014$) in LDA and placebo groups, respectively. The mean number of the oocytes in different grades, total and frozen embryos also implantation and clinical pregnancy rates were not different between the groups.

Conclusion: Moderate to Severe OHSS was not decreased but fertilization rate and the mean number of poor quality embryos were increased in LDA arm.

Registration number: IRCT 201105216541N1.

Introduction

Ovarian hyper stimulation syndrome (OHSS) is the most serious and life-threatening complication of controlled ovarian stimulation (COS) during assisted reproductive technology (ART). OHSS is characterized by ovarian enlargement, increased vascular permeability, intravascular volume depletion, accumulation of fluid in the third spaces and increased risk of thrombosis. The risk factors of OHSS include young age, polycystic ovary syndrome (PCOS) and

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elevated serum estradiol (E2) or anti-mullerian hormone (AMH) levels [1–3]. OHSS is classified to mild, moderate, severe and critical grades [1,3,4]. The incidence of moderate OHSS is reported to be 3–10% and for the severe form is 0.5–2% during all IVF cycles [5,6].

PCOS affects 15% of the reproductive age women and as the most common cause of anovulatory infertility [7] is diagnosed by the revised Rotterdam criteria [8]. The risk of OHSS is higher in PCOS women when treated by gonadotropins [3,9]. Even low-dose gonadotropins in PCOS lead to a higher number of growing follicles, higher serum E2 levels and OHSS [9–11]. These findings are explained by the presence of more FSH receptors on the granulosa cells of PCOS patients induced by higher androgenic stimulations, hyper-insulinemia and elevated IGF1 levels that cause higher vascular endothelial growth factor (VEGF) gene expression [12–14]. It is reported that high E2 levels plus high human chorionic gonadotropin (HCG) levels lead to over expression of several inflammatory cytokines and interleukins (IL-8 and IL-6), increased plasma renin activity and angiotensin II levels, increased VEGF, platelet hyper stimulation and platelet activation [15]. Several methods are suggested to prevent OHSS such as coasting, reducing or eliminating HCG by replacing it with Gonadotropin-releasing hormone (GnRH) during antagonist cycles, freezing all embryos, administration of calcium, albumin, dopamine agonists or non-steroidal anti-inflammatory drugs (NSAIDS) like low-dose aspirin (LDA) [16] and meloxicam [17,18].

Evidence shows that increased platelet activation correlates with elevated VEGF levels and other platelet-derived vasoactive substances. Activated platelets release calcium and produce serotonin, histamine, platelet derived growth factor and arachidonic acid [16]. Arachidonic acid is converted to thromboxane A2 (TXA2) by the cyclooxygenase enzyme in the platelets. Cyclooxygenase enzyme is irreversibly inhibited in the platelets by all dosages of aspirin or acid salicylic acid (ASA) and decreases the production of TXA2 to less than 80% [19]. Cyclooxygenase enzyme also converts arachidonic acid to prostacyclin (PGI2) in the endothelial cells that is best inhibited at 324 gr daily doses of aspirin. So, LDA (50–150 mg/day) increases the ratio of PGI2/TXA2 in the plasma by interfering TXA2 production. While PGI2 is a vasodilator and TXA2 is the most potent vasoconstrictor in the body. Finally LDA prevents vasoconstriction, platelet aggregation and thromboembolic complications [20,21].

Based on the mentioned mechanisms and few previous studies [16,18,22,23] we hypothesized that LDA may prevent platelet activation, release of platelet derived vasoactive substances and probably decreases the rate of OHSS. We designed this randomized controlled trial (RCT) to evaluate the effect of LDA on developing moderate to severe OHSS and their ART outcomes in PCOS patients.

Material and methods

232 infertile PCOS women aged between 18 and 40 years in their first ART cycles during 2010–2016 at Ghadir-Mother and child hospital affiliated to Shiraz University of Medical Sciences and Omid-Persian Gulf center affiliated to Bushehr University of medical sciences, were enrolled in this double-blind, placebo-controlled RCT (Registration Number: IRCT 201105216541N1). This study was approved by the scientific and ethics committee of Shiraz University of Medical Sciences (Reference number: ct-89-5522).

PCOS was diagnosed according to the modified Rotterdam criteria [8]. The women with history of gastritis, gastrointestinal bleeding or hypersensitivity to aspirin or abnormal semen parameters (according to WHO 2010 criteria) [24] were not included since the beginning. 232 PCOS women were randomized to two groups based on a randomization table. Both LDA (100 mg aspirin) and placebo capsules were prepared in the same shape and packed separately by the pharmacist affiliated to the pharmaceutical division of Shiraz University of Medical Sciences. The pharmacist specified every package containing forty aspirin or placebo capsules by a code number. The double-blinded nature of the study was explained to the women, written consent forms were signed by them and then a package with a specific code number was given to each patient. So, neither the patient nor the physician knew which package contained aspirin or the placebo. The patients were instructed to ingest one capsule after the lunch every day starting from the 21st day of their menstrual cycle prior to the cycle that was planned to start gonadotropins.

ART cycles were conducted for all of the patients by the long GnRH agonist protocol as following: Administration of GnRH agonist (0.3 mg Buserelin Acetate SC; Suprefact, Sanofi-Aventis, Germany) from the 21st day of previous menstrual cycle till the day of HCG triggering. One ampule of FSH (Fostimon, 75 IU, SC, IBSA pharmaceutical, Italy) and one ampule of human menopausal gonadotropin (HMG) (Merional, 75 IU, IM, IBSA pharmaceutical, Italy) were started from the 2nd day of the cycle. The number and size of the follicles were monitored by transvaginal ultrasound (TVU) scan every 2–3 days, starting from the 6th day of the menstrual cycle (in which the gonadotropins were started). E2 levels were measured and the gonadotropin dosages were adjusted individually. HCG triggering (5000–10,000 IU, Pregnyl, Merk, Germany) was used for the final oocyte maturation when at least 2–3 follicles sized 17 mm in diameter were seen by TVU. Serum LH and E2 levels were measured on the HCG triggering day and were documented. Ovum-pickup was performed 36 h after HCG injection. The number and grading of the denuded oocytes was reported by the embryologist as following: 1-immature GVs, 2- MI oocytes and 3- mature MII oocytes [25]. Fertilization rate was calculated by the percentage of the embryos that were developed with two pro-nucleuses at 16–18 h after IVF/ICSI from the total oocytes exposed to sperms. Three days after retrieval of the oocytes the number and quality of the resultant embryos were recorded. The embryos were classified based on the standard scoring method to the grades of I, II and III, where I indicates the best quality and III shows the lowest quality embryo [26]. Fresh embryo transfers were performed 3 days after the ovum pick up under ultrasound guide. Luteal phase support was started by administration of progesterone (100 mg, IM; Iran hormone, Iran) for 3 days followed by vaginal progesterone (Cyclogest 400 mg,; Actavis, UK) every 12 h till 8 weeks of gestation. Implantion rate was defined as the percentage of the implanted gestational sacs from the total transferred embryos. Clinical Pregnancy was confirmed by detection of gestational sac and fetal heart at 4–5 weeks after transfer of the embryo. Pregnancy rate was defined as percentage of pregnant women from the women who underwent ART.

All of the women were observed for the signs and symptoms of OHSS. Development of OHSS was proved according to the presence of the clinical, laboratory and ultrasound features. The cases of mild OHSS with abdominal distention, bloating and ovaries $\leq$5 cm are observed in a large number of ART cycles without clinical significance and were not included among the OHSS cases in this study. All of the affected patients with moderate, severe and critical grades are considered as OHSS in this study. Moderate OHSS is diagnosed with abdominal pain, ultrasonographic measurements of ovarian sizes between 5 and 12 cm and any amount of ascites. Severe OHSS is diagnosed when ascites is clinically detectable with marked abdominal discomfort, liver dysfunction, dyspnea, hypotension, oliguria, hyponatremia and hyperkalemia. Critical grades are diagnosed when end-organ morbidities like acute respiratory distress syndrome, thromboembolic complications or renal failure are identified and the patients need Intensive care unit (ICU) admission [27,28].

After data collection the code numbers were broken by the pharmacist and the data were analyzed. Eighteen women who did

not exactly follow the study design were excluded. Among the excluded cycles 8 belonged to LDA group and 10 belonged to the placebo group. Finally 214 cycles remained for analyses, 109 cycles with LDA and 105 cycles with placebo. The consort diagram shows the details (Fig 1).

The patients were observed for the possible complications of LDA ingestion such as gastrointestinal (GI) or intra peritoneal bleeding with ovum pickups.

Statistical analysis

Data were analyzed by statistical package for social sciences for windows software (SPSS Version 22, Chicago, IL, USA). The specific distribution of data was checked by kolmogorov-Smirnov test and since data were not normally distributed, Mann–Whitney U-test was used to compare the means of the variables. OHSS frequency also fertilization, implantation and clinical pregnancy rates were compared between the groups using chi-square test. P-value < 0.05 was considered statistically significant.

Results

Final analysis was performed on 214 women, 109 cases took LDA and 105 cases took placebo. The demographic characteristics of the patients also LH and E2 levels on the triggering days and the number of oocytes underwent IVF or ICSI had no statistically significant difference between the two groups (Table 1).

Comparison of the number and quality of the obtained oocytes and resultant embryos showed no statistically significant difference between the groups except for the mean number of grade III as poor quality embryos that was significantly higher in LDA group (Table 2).

There was no case of critically ill OHSS in this study who needed ICU admission in both of the case and control groups. The frequency of moderate and severe OHSS was 34.9% in LDA group compared to 30.5% in the placebo group that was not statistically significant Clinical Pregnancy rate was higher in LDA arm (28.4% vs 22.9%) but was not statistically significant. Fertilization rate was significantly higher in LDA arm ($p < 0.001$) (Table 3).

No complications related to LDA administration such as GI or internal bleeding after ovum pickups were detected in both arms of this study.

Discussion

This study was performed on 232 infertile PCOS women candidate for their first IVF cycles as a high-risk population for OHSS and ART outcomes during GnRH-agonist protocol. This RCT mainly aimed to address the probable effect of LDA on development of OHSS in PCOS. Prevention of OHSS as the most dramatic complication of ART has been one of the most important and challenging topics for the years before introduction of GnRH antagonists [1–3]. GnRH agonist protocols, with pituitary down regulation and HCG triggering with resultant higher VEGF production leads to the highest risk of OHSS development [29]. Historically it was about 2001 when Ludwig and colleagues reported a significant reduction of OHSS with the GnRH-antagonist protocols in Cetrorelix arm but no reduction by ganirelix arm in a meta-analysis [30]. Since then GnRH-antagonists are commonly used for the prevention of premature LH surge followed by GnRH-agonists triggering instead of HCG to make the IVF cycles much more controllable for OHSS [17,31]. However still several clinicians prefer to use GnRH-agonist protocols to obtain oocytes and embryos with higher qualities [32].

In this study the women's baseline characteristics and the mean number of the oocytes that underwent IVF or ICSI had no statistical difference between the two groups indicating that the final results could not be affected by the mentioned factors.

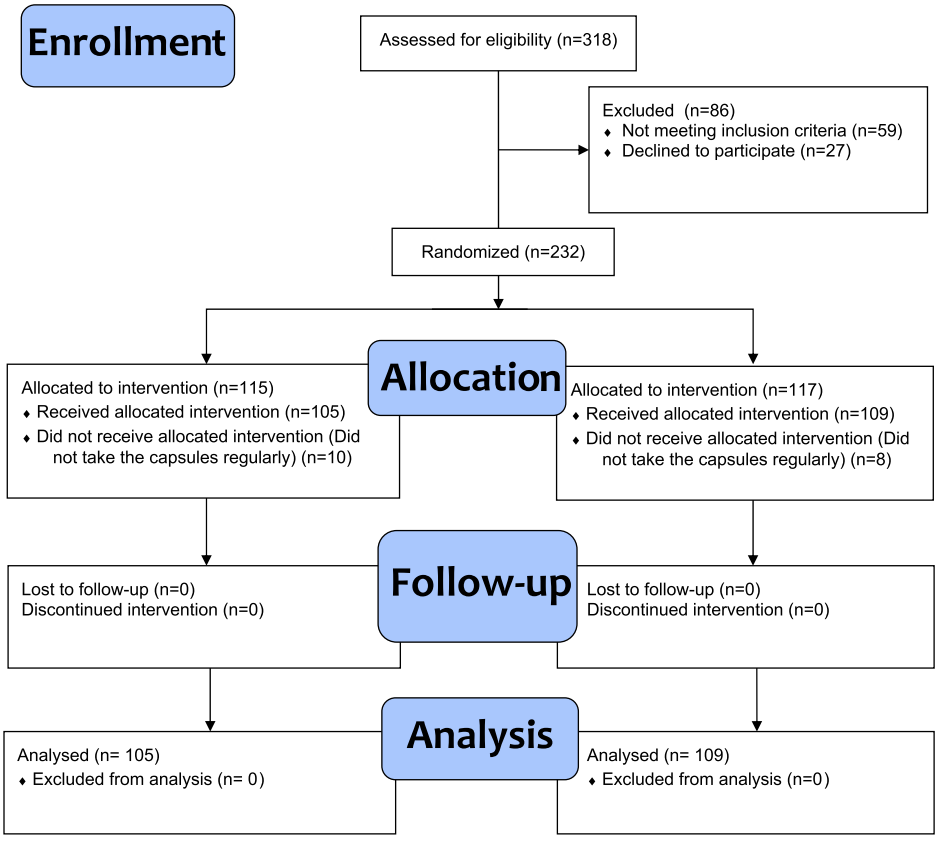

Fig. 1. Consort diagram for the study group.

Table 1
Comparison of the demographic data, LH and estradiol on the triggering day and ART methods between the groups.

Variable	LDA group N = 109	Placebo group N = 105	P-value
Age (year)	28.72 ± 4.25	28.51 ± 4.72	0.691
Duration of infertility (year)	7.49 ± 4.78	6.82 ± 4.18	0.421
LH (IU/L) on triggering day	2.33 ± 3.36	2.11 ± 2.02	0.771
Estradiol (pg/ml) on triggering day	2178.07 ± 1108.40	2113.60 ± 1226.70	0.687
Cancelation	0.06 ± 0.25	0.08 ± 0.28	0.599
Number of the oocytes underwent IVF	4.2 ± 2.96	3.75 ± 2.82	0.517
Number of the oocytes underwent ICSI	8.32 ± 4.91	8.00 ± 5.31	0.656

IVF: In-vitro fertilization. ICSI: Intra-cytoplasmic sperm injection. Data are presented as mean ± SD. p value < 0.05 is significant.

Table 2
Comparison of the mean number of the oocytes and embryos with different grades between the groups.

Variable	LDA group	Placebo group	P-value
Total number of retrieved oocytes	10.92 ± 6.27	10.73 ± 6.05	0.819
GV oocytes	1.60 ± 1.00	2.11 ± 1.95	0.108
MI oocytes	2.15 ± 1.90	2.22 ± 2.13	0.754
MII oocytes	9.02 ± 5.32	8.34 ± 5.42	0.194
Total Embryos	7.31 ± 4.73	6.42 ± 4.13	0.187
Grade I Embryo	3.29 ± 2.25	3.76 ± 2.49	0.169
Grade II embryo	2.66 ± 0.62	2.38 ± 1.55	0.197
Grade III embryo	3.28 ± 3.53	1.46 ± 1.42	0.014
Frozen Embryos	5.85 ± 5.69	4.44 ± 4.08	0.147

M: Metaphase. GV: germinal vesicle. Data are presented as mean ± SD. p value <0.05 is significant.

Incidence of the moderate and severe OHSS in PCOS women during IVF using GnRH-agonist long protocol is reported to be as high as 26.7% to even 60% in the literature. This wide range seems to represent the fact that the standard OHSS classification system might have the pitfall and is differently interpretable by different researchers [33,34]. Importantly, ovarian size as the most easily measurable item for the diagnosis and prevention of OHSS in the early years of ovulation induction has lost its significance for ART cycles. Ovarian size with the cut-off point of ≥5 cm was used in many of the previous studies and also in our study as standard value for the diagnosis of moderate OHSS and ≥12 cm for the diagnosis of severe OHSS [27,28]. However Mathur R et al. suggested the ovarian size of 8–12 cm for the diagnosis of moderate OHSS [35] that is basically considered for the classifications of OHSS by Royal College of Obstetricians and Gynecologists (RCOG) [36].

In our study the rate of moderate to severe OHSS in the PCOS women was calculated to be 34.9% for the LDA and 30.5% for the placebo groups. In 2008 Revelli and colleagues performed a randomized study on the normo-responders and high responders by the administration of 100 mg/day asprin plus 10 mg/day prednisolone versus no adjunct therapy, starting from the first day of the IVF cycle. Their results showed a lower rate of severe OHSS among the treated patients (1.7% vs. 6.5%) [23]. It should be noticed that they included normal or high responder women, started medications from the first day of the IVF cycles and co-administered prednisolone that might have changed the response due to its anti-inflammatory effects [37].

Another RCT published on 2010 by Varnagy and colleagues compared 100 mg daily aspirin with no adjuvant treatment started form the first day of ART cycles with GnRH agonist protocol in an unselected group of IVF patients and reported that the incidence of severe or critical OHSS in the high-risk group receiving LDA was lower (0.25% vs 8.4%) [16]. They defined the high-risk group as previous history of OHSS, PCOS or age> 30 years. Our study is different in the method of patient selection and starting day of drug administration. Moreover Varnagy and colleagues included only the severe or critically-ill patients who needed hospitalization while we included all moderate to severe OHSS affected women, which means a larger group and there was no case of critically ill woman among none of our study groups.

Moini and colleagues published an RCT at 2006 that was performed to study the effect of LDA on implantation and pregnancy rates in unselected IVF cycles with GnRH agonist long protocol. They concluded that Implantation and pregnancy rates were not different but the mean number of the follicles and OHSS were decreased in the group who received LDA [22]. However other study reports did not confirm the lower number of retrieved follicles with LDA during ART cycles. Even though the starting day of LDA administration was the same as ours in Moini and colleagues' study but still the study group was different.

The American Society for Reproductive Medicine (ASRM) Practice Committee released a guideline published on the prevention and treatment of moderate and severe OHSS [3] and concluded that based on only one single randomized trial and another study [16,23] there is only fair evidence on the effectiveness of aspirin for the prevention of OHSS with grade B of evidence. To the best of our knowledge our study is the first double-blinded, placebo-controlled RCT, on PCOS women during ART to evaluate the effect of LDA on the development of moderate to severe OHSS during GnRH-agonist long protocol.

Similar to all of the above reports we did not find any statistically significant difference between the two groups for the number of GV, MI, MII oocytes, the total number of produced embryos and frozen embryos. Grade III or the low quality embryos, were significantly more produced in LDA group. This finding may indicate that while LDA could not affect directly the number and quality of the oocytes in our study, but possibly adversely affected the developmental potency of the embryos by resulting in poorer quality embryos.

Table 3
Comparison of the moderate and severe OHSS and ART outcomes between the groups.

Variable	LDA group N/total (%)	Placebo group N/total (%)	P-value
Moderate and severe OHSS	38/109 (34.9%)	32/105 (30.5%)	0.494
Fertilization rate	797/1109 (71.87%)	675/1036 (65.15%)	<0.001*
Implantation rate	33/82 (40.24%)	25/63 (39.68%)	0.945
Clinical Pregnancy rate	31/109 (28.4%)	24/105 (22.9%)	0.350

OHSS: Ovarian hyper stimulation syndrome. Data are presented as number/total (%). *P value < 0.05 is significant.

In our study the implantation, and clinical pregnancy rates were not significantly different between the LDA and placebo groups. However the fertilization rate was statistically higher in the LDA group. Effectiveness of LDA to improve the outcome of ART is still controversial. A systematic review and meta-analysis was published at 2012 that was conducted on 17 RCTs and did not support the effectiveness of LDA to improve the outcomes of IVF/ICSI [38]. Also by another meta-analysis Siristatidis and colleagues showed that ART outcomes were not statistically affected by LDA [39]. However a recently published meta-analysis conducted on 13 RCTs showed that LDA may improve the pregnancy rates with ART [40].

During this study no woman developed GI or internal bleeding in both arms. We believe that administration of LDA is well tolerated by the women during ART cycles as had been previously concluded [41].

LDA is proven to be effective for the prevention of preeclampsia and intra uterine growth restriction in the high-risk pregnant women by increasing uterine blood flow or uteroplacental perfusion and decreasing vascular resistance [42,43]. Theoretically the same mechanism might be functional to improve folliculogenesis, fertilization and implantation by increasing the vascular blood flow in the ovaries and uterus but the study results on these topics are not consistent.

Shifting from the long agonist protocol to antagonist protocol with agonist triggering as a revolution towards a safe ovulation induction, has provided the best evidence (Grade A) to prevent OHSS. Metformin also imposes good evidence (Grade A) to decrease the risk of OHSS in PCOS patients [1,3,17]. Basically these measures help to reduce the release of vasoactive substances and reduce platelet activation and vascular permeability and development of OHSS free clinics. But still it is a fact that every PCOS patient should be treated individually in ART cycles to gain the best outcome and the least complications.

These data show that OHSS is not decreased but fertilization rate is increased by LDA. Also low quality embryos with grade III were more produced with LDA.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Author's contribution

B.N.J., J.Z., S.A., A.Z.; Contributed in the study design, data collection, data analysis and interpretation. E.R., Z.A. P.K.: Contributed in the data collection, data analysis and interpretation. All authors participated in the critical revision and approval of the final draft before submission.

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References

[1] Boothroyd C, Karia S, Andreadis N, Rombauts L, Johnson N, Chapman L, et al. Consensus statement on prevention and detection of ovarian hyperstimulation syndrome. Aust N Z J Obstet Gynaecol 2015;55(6):523–34.
[2] 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;1:CD012103.
[3] Practice Committee of the American Society for Reproductive Medicine. Electronic address, A.a.o. and M. Practice Committee of the American Society for Reproductive, Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. Fertil Steril 2016;106(7):1634–47.
[4] Vloeberghs V, Peeraer K, Pexsters A, D'Hooghe T. Ovarian hyperstimulation syndrome and complications of ART. Best Pract Res Clin Obstet Gynaecol 2009;23(5):691–709.
[5] D'Angelo A, Brown J, Amso NN. Coasting (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome. Cochrane Database Syst Rev 2011;6:CD002811.
[6] Gunnala V, Melnick A, Irani M, Reichman D, Schattman G, Davis O, et al. Sliding scale HCG trigger yields equivalent pregnancy outcomes and reduces ovarian hyperstimulation syndrome: analysis of 10,427 IVF-ICSI cycles. PLoS One 2017;12(4), e0176019.
[7] Fauser BC, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril 2012;97(1):28–38.e25.
[8] Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81(1):19–25.
[9] Qu J, Che Y, Xu P, Xia Y, Wu X, Wang Y. The higher response of vascular endothelial growth factor and angiotensin-II to human chorionic gonadotropin in women with polycystic ovary syndrome. Int J Fertil Steril 2015;8(4):373–8.
[10] Rasool S, Shah D. Fertility with early reduction of ovarian reserve: the last straw that breaks the Camel's back. Fertil Res Pract 2017;3:15.
[11] Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. Fertil Steril 2008;89(3):505–22.
[12] Geva E, Jaffe RB. Role of vascular endothelial growth factor in ovarian physiology and pathology. Fertil Steril 2000;74(3):429–38.
[13] Baptiste CG, Battista MC, Trottier A, Baillargeon JP. Insulin and hyperandrogenism in women with polycystic ovary syndrome. J Steroid Biochem Mol Biol 2010;122(1–3):42–52.
[14] Miele C, Rochford JJ, Filippa N, Giorgetti-Peraldi S, Van Obberghen E. Insulin and insulin-like growth factor-I induce vascular endothelial growth factor mRNA expression via different signaling pathways. J Biol Chem 2000;275(28):21695–702.
[15] Nastri CO, Ferriani RA, Rocha IA, Martins WP. Ovarian hyperstimulation syndrome: pathophysiology and prevention. J Assist Reprod Genet 2010;27(2–3):121–8.
[16] Varnagy A, Bodis J, Manfai Z, Wilhelm F, Busznyak C, Koppan M. Low-dose aspirin therapy to prevent ovarian hyperstimulation syndrome. Fertil Steril 2010;93(7):2281–4.
[17] Namavar Jahromi B, Parsanezhad ME, Shomali Z, Bakhshai P, Alborsi M, Moein Vaziri N, et al. Ovarian hyperstimulation syndrome: a narrative review of its pathophysiology, risk factors, prevention, classification, and management. Iran J Med Sci 2017:1–13.
[18] Quintana R, Kopcow L, Marconi G, Young E, Yovanovich C, Paz DA. Inhibition of cyclooxygenase-2 (COX-2) by meloxicam decreases the incidence of ovarian hyperstimulation syndrome in a rat model. Fertil Steril 2008;90:1511–6.
[19] Rubinstein M, Marazzi A, Polak de Fried E. Low-dose aspirin treatment improves ovarian responsiveness, uterine and ovarian blood flow velocity, implantation, and pregnancy rates in patients undergoing in vitro fertilization: a prospective, randomized, double-blind placebo-controlled assay. Fertil Steril 1999;71(5):825–9.
[20] Choudhury A, Freestone B, Patel J, Lip GY. Relationship of soluble CD40 ligand to vascular endothelial growth factor, angiopoietins, and tissue factor in atrial fibrillation: a link among platelet activation, angiogenesis, and thrombosis? Chest 2007;132(6):1913–9.
[21] Zhang X, Wang Z, Wang Z, Zhang Y, Jia Q, Wu L, et al. Impact of acetylsalicylic acid on tumor angiogenesis and lymphangiogenesis through inhibition of VEGF signaling in a murine sarcoma model. Oncol Rep 2013;29(5):1907–13.
[22] Moini A, Zafarani F, Haddadian S, Ahmadi J, Honar H, Riazi K. Effect of low-dose aspirin therapy on implantation rate in women undergoing in-vitro fertilization cycles. Saudi Med J 2007;28(5):732–6.
[23] Revelli A, Dolfin E, Gennarelli G, Lantieri T, Massobrio M, Holte JG, et al. Low-dose acetylsalicylic acid plus prednisolone as an adjuvant treatment in IVF: a prospective, randomized study. Fertil Steril 2008;90(5):1685–91.
[24] World Health Organization, D.o.R.H.a.R.. WHO laboratory manual for the examination and processing of human semen. 5th ed. 2010. p. 286. Geneva.
[25] Veeck LL. Oocyte assessment and biological performance. Ann N Y Acad Sci 1988;541:259–74.
[26] Steer CV, Mills CL, Tan SL, Campbell S, Edwards RG. The cumulative embryo score: a predictive embryo scoring technique to select the optimal number of embryos to transfer in an in-vitro fertilization and embryo transfer programme. Hum Reprod 1992;7(1):117–9.
[27] Gardner DKWA, Howles CM, Shoham Z. Severe ovarian hyperstimulation syndrome. In: Textbook of assisted reproductive technologies laboratory and clinical perspectives. 3rd ed. London: informa; 2009. p. 759–72.
[28] Aubuchon M, Burney RO, Schust DJ, Yao MWM. Infertility and assisted reproductive technology. In: Berek JS, editor. Berek & novak's gynecology. 15th ed. Philadelphia: Lippincott Williams & Wilkins; 2012. p. 1133–89.
[29] Guimera M, Morales-Ruiz M, Jimenez W, Balasch J. LH/HCG stimulation of VEGF and adrenomedullin production by follicular fluid macrophages and luteinized granulosa cells. Reprod Biomed Online 2009;18(6):743–9.
[30] Ludwig M, Katalinic A, Diedrich K. Use of GnRH antagonists in ovarian stimulation for assisted reproductive technologies compared to the long protocol. Meta-analysis. Arch Gynecol Obstet 2001;265(4):175–82.

[31] Alama P, Bellver J, Vidal C, Giles J. GnRH analogues in the prevention of ovarian hyperstimulation syndrome. Int J Endocrinol Metab 2013;11(2):107–16.
[32] Murber A, Fancsovits P, Ledo N, Gilan ZT, Rigo Jr J, Urbancsek J. Impact of GnRH analogues on oocyte/embryo quality and embryo development in in vitro fertilization/intracytoplasmic sperm injection cycles: a case control study. Reprod Biol Endocrinol 2009;7:103.
[33] Kaur H, Krishna D, Shetty N, Krishnan S, Srinivas M, Rao KA. A prospective study of GnRH long agonist versus flexible GnRH antagonist protocol in PCOS: Indian experience. J Hum Reprod Sci 2012;5(2):181–6.
[34] Lainas TG, Sfontouris IA, Zorzovilis IZ, Petsas GK, Lainas GT, Alexopoulou E, et al. Flexible GnRH antagonist protocol versus GnRH agonist long protocol in patients with polycystic ovary syndrome treated for IVF: a prospective randomised controlled trial (RCT). Hum Reprod 2010;25(3):683–9.
[35] Mathur R, Evbuomwan I, Jenkins J. Prevention and management of ovarian hyperstimulation syndrome. Curr Obstet Gynaecol 2005;15:132–8.
[36] Royal college of obstetricians and gynaecologists. The management of ovarian hyperstimulation syndrome. 3rd ed. London: NICE; 2016. p. 1–22.
[37] Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. Mol Cell Endocrinol 2011;335(1):2–13.
[38] Dentali F, Ageno W, Rezoagli E, Rancan E, Squizzato A, Middeldorp S, et al. Low-dose aspirin for in vitro fertilization or intracytoplasmic sperm injection: a systematic review and a meta-analysis of the literature. J Thromb Haemost 2012;10(10):2075–85.
[39] Siristatidis CS, Basios G, Pergialiotis V, Vogiatzi P. Aspirin for in vitro fertilisation. Cochrane Database Syst Rev 2016;11:CD004832.
[40] Wang L, Huang X, Li X, Lv F, He X, Pan Y, et al. Efficacy evaluation of low-dose aspirin in IVF/ICSI patients evidence from 13 RCTs: a systematic review and meta-analysis. Medicine (Baltimore) 2017;96(37), e770.
[41] Gelbaya TA, Kyrgiou M, Li TC, Stern C, Nardo LG. Low-dose aspirin for in vitro fertilization: a systematic review and meta-analysis. Hum Reprod Update 2007;13(4):357–64.
[42] Ali MK, Abbas AM, Yosef AH, Bahloul M. The effect of low-dose aspirin on fetal weight of idiopathic asymmetrically intrauterine growth restricted fetuses with abnormal umbilical artery Doppler indices: a randomized clinical trial. J Matern Fetal Neonatal Med 2017:1–6.
[43] Haapsamo M, Martikainen H, Rasanen J. Low-dose aspirin reduces uteroplacental vascular impedance in early and mid gestation in IVF and ICSI patients: a randomized, placebo-controlled double-blind study. Ultrasound Obstet Gynecol 2008;32(5):687–93.