

DOI: <http://dx.doi.org/10.18203/2320-1770.ijrcog20194344>

Original Research Article

## Serum estradiol level on the day of ovulation trigger and pregnancy outcomes in in-vitro fertilisation-intracytoplasmic sperm injection cycles

Avani Pillai\*, Fessylouis T., Ramesh P., Parvathy T., Aparna N.

Department of Reproductive Medicine and Surgery, Amrita Institute of Medical Sciences, Kochi, Kerala, India

**Received:** 23 July 2019

**Accepted:** 30 August 2019

**\*Correspondence:**

Dr. Avani Pillai,  
E-mail: [avanimj@gmail.com](mailto:avanimj@gmail.com)

**Copyright:** © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

### ABSTRACT

**Background:** There is conflicting evidence with regards to the impact of supraphysiologic estradiol levels in in-vitro fertilisation-intracytoplasmic sperm injection (IVF-ICSI) cycles on pregnancy outcomes such as oocyte quality, implantation, and clinical pregnancy. The objective of our study was to evaluate the effect of serum estradiol levels on the day of ovulation trigger on pregnancy outcomes in IVF-ICSI cycles.

**Methods:** We performed a retrospective cohort study, which included eighty-three women who underwent IVF-ICSI and experienced fresh embryo transfer (ET) over one year period. The women included in the study were divided into four groups according to the serum estradiol level on the day of ovulation trigger; Group I: <2000pg/ml, Group II: 2000-3000pg/ml, Group III: 3000-4000pg/ml and Group IV: >4000pg/ml. The outcome measures including number of oocytes retrieved, MII (metaphase II) oocytes, fertilization rate, embryo quality, overall pregnancy rate, implantation rate and clinical pregnancy rate were compared among these four groups.

**Results:** The total number of oocytes, MII oocytes as well as good quality embryos significantly increased from group 1 to group 4. The implantation rate was lowest in group 4 compared to all other groups, although not statistically significant. There was no significant difference in overall and clinical pregnancy rate between the groups.

**Conclusions:** Serum estradiol level shows a positive correlation with the number of oocytes retrieved and good quality embryos. A higher estradiol level does not have a significant negative impact on the implantation rate, overall or clinical pregnancy rate.

**Keywords:** Embryo transfer Embryo quality, Implantation, Oocyte

### INTRODUCTION

Assisted Reproductive technique (ART) has become the treatment of choice in indicated cases of female infertility and male sterility. The use of ART is steadily increasing and according to the report by National ART Registry of India (NARI), the number of IVF-ICSI cycles in India have increased exponentially over the last decade.<sup>1</sup> In-vitro fertilisation- intracytoplasmic sperm injection (IVF-

ICSI) uses controlled ovarian hyperstimulation (COH) to produce a large number of follicles in the ovaries and obtain a big cohort of mature oocytes during the cycle, thus increasing the chances of successful outcome of the treatment. Since Estradiol (E2) is secreted primarily from the granulosa cells of the ovarian follicle, serum estradiol levels rises significantly throughout the COH treatment. E2 levels can be increased more than 10-fold in IVF cycles over natural cycles.<sup>2</sup> Measurement of serum E2 in

IVF-ICSI cycles is used to assess the ovarian response to COH and also predict ovarian hyperstimulation syndrome (OHSS). Serum estradiol plays a key role in the regulation of uterine preparation for embryo implantation, through stimulation of endometrial proliferation and enhancement of uterine and endometrial perfusion.<sup>3,4</sup>

But despite significant increase in the number of oocytes in IVF-ICSI cycles, implantation rates are only 7-9% compared to 0-33% in natural cycles.<sup>5</sup> This may be possibly attributed to the supraphysiological E2 levels in IVF-ICSI cycles which cause alterations in both the endometrial receptivity and oocytes/embryo quality. High E2 levels at the time of implantation may cause altered synchrony between the embryo and endometrium, impair endometrial response to trophoblastic invasion and have a negative impact on endometrial receptivity.<sup>6</sup> Various studies have been performed to assess the effect of serum E2 levels on the day of ovulation trigger on the reproductive outcome in IVF-ICSI cycles. Some studies have suggested that high serum E2 concentration resulting from excessive ovarian response adversely affect the outcomes of assisted reproduction.<sup>7,8</sup> On the contrary, other studies report that high serum E2 concentrations do not appear to alter endometrial receptivity or pregnancy outcomes.<sup>9-11</sup> Thus, there is conflicting evidence with regards to the impact of E2 levels in IVF-ICSI cycles on pregnancy outcomes such as oocyte quality, fertilization rate, embryo quality, implantation, and clinical pregnancy. The objective of our study is to evaluate the effect of serum estradiol levels on the day of ovulation trigger on pregnancy outcomes in IVF-ICSI cycles.

## METHODS

This was a retrospective cohort study performed at an ART centre of a tertiary care university teaching hospital for a period of one year from October 2017 to September 2018. A total of eighty-three women who underwent IVF-ICSI with their own eggs and experienced fresh embryo transfer (ET) during this period were included in the study.

Controlled ovarian hyperstimulation was individualized between the patients and done using long agonist protocol or antagonist protocol based on the patient's characteristics. In long agonist protocol, pituitary down regulation was done using leupride acetate depot 3.75mg in the luteal phase or after 15 days of combined oral contraceptive pills (OCP). Ovarian stimulation was commenced after at least one week of down regulation and after beginning of menstruation. In antagonist protocol, OCP's were administered in the previous cycle and gonadotropins were started from day 2 or 3 of the cycle. The starting dose of gonadotropins [recombinant Follicle stimulating hormone (FSH) and/or human menopausal gonadotropin (hMG)] was individualized according to age, antral follicle count, anti-mullerian

hormone (AMH) levels, body mass index (BMI) and previous cycles, if present for both the protocols of IVF. Thereafter the dose was adapted according to the ovarian response to treatment. In antagonist protocol, fixed regimen was used where cetrorelix 0.25mg was added after 5 days of gonadotropin injections. The final oocyte maturation was achieved with 10,000 IU of human chorionic gonadotropin (HCG) trigger when at least 2 or more follicles reached a diameter of  $\geq 17$ mm. Serum estradiol, leutinising hormone (LH) and progesterone levels were measured on the day of ovulation trigger.

Ultrasound guided transvaginal oocyte retrieval was performed  $36 \pm 1$  hours after ovulation trigger. Total number of oocytes and MII (metaphase II) oocytes were noted. These were micro injected by spermatozoa (ICSI was done) in a labeled microinjection dish on the heated stage of an inverted phase contrast microscope under 200 x magnifications within 2-4 hours of oocytes retrieval. Normal fertilization was determined 16-20 hours after ICSI by presence of two pronuclei. Fertilization rate is percentage of transformation of micro injected oocytes into two pronuclei.<sup>12</sup> Embryos grading was performed on day 2 by (Association for the study of biology of reproduction) ASEBIR consensus scheme for scoring cleavage stage embryos.<sup>13</sup> Up to four embryos were transferred in the uterine cavity under trans-abdominal ultrasound guidance on day 2 (majority) or day 3 of embryo culture. Result was confirmed by a quantitative analysis of serum  $\beta$  HCG concentration on 14 day after embryo transfer and a cut-off level of 50mIU/ml was used to define pregnancy. Subsequently, ultrasound was performed after 6 weeks of gestation to confirm number of sacs implanted and viability.

For the purpose of analysis, the women included in the study were divided into four groups according to the serum estradiol level on the day of ovulation trigger; Group I: <2000 pg/ml, Group II: 2000-3000 pg/ml, Group III: 3000 -4000 pg/ml and Group IV: >4000 pg/ml. The demographic parameters such as age, body mass index (BMI), duration of infertility, indication for IVF-ICSI were compared among these four groups.

The outcome measures including number of oocytes retrieved, MII oocytes, fertilization rate, embryo quality, overall pregnancy rate, implantation rate and clinical pregnancy rate were compared among these four groups.

Fertilization rate was estimated by number of fertilized oocytes per number of microinjected oocytes. Overall pregnancy rate was calculated by the number of patients with biochemical/clinical pregnancy divided by the number of patients who had embryo transfer. Implantation rate was defined as the number of embryos which have produced ultrasonographic evidence of an intrauterine gestational sac per the total number of embryos transferred into the uterine cavity.

Clinical pregnancy was determined by the ultrasound evidence of fetal heartbeat. Clinical pregnancy rate was calculated as the number of patients with clinical pregnancy divided by the number of patients who had embryo transfer.

**Statistical analysis**

Statistical analysis was performed using linear regression for continuous outcome and logistic regression for binary outcome with backward selection to compare the groups

using statistical software SAS 9.4. A p value <0.05 was considered significant.

**RESULTS**

The baseline demographic characteristics such as age and duration of infertility and indications for ART were comparable between all the four groups. The mean age of the patients in our study was 32.19±4.81 years. There was a significant variation in the BMI between the study groups. Women in group 2 (E2 level -2000-3000 pg/ml) had higher BMI compared to other groups (Table 1).

**Table 1: Comparison of the baseline demographic parameters of the study groups.**

Parameters	Group 1 (n=18)	Group 2 (n=15)	Group 3 (n=24)	Group 4 (n=26)	P value
Age (years)	32.48±4.98	32.40±4.48	31.41±3.09	32.65±6.17	0.826
BMI (kg/m <sup>2</sup> )	24.57±3.10	28.64±6.28	23.50±2.49	23.82±3.09	<0.001*
Duration of infertility (years)	6.72±4.52	7.13±2.46	7.46±3.28	7.19±2.49	0.912
<b>Indication for ART</b>					
Poor ovarian reserve (n, %)	9 (50)	4 (26.7)	1 (4.2)	6 (23.1)	0.008*
Male factor (n, %)	3 (16.7)	5 (33.3)	4 (16.7)	7 (26.9)	0.554
Pelvic factor (n, %)	2 (11.1)	4 (26.7)	15 (62.5)	8 (30.8)	0.004*
PCO (n, %)	0	0	0	2 (7.7)	0.213
Unexplained (n, %)	4 (22.2)	2 (13.3)	4 (16.7)	3 (11.5)	0.801

\*P value is statistically significant; BMI, body mass index; ART, assisted reproductive technique; PCO, polycystic ovary

**Table 2: Comparison of the ovarian reserve tests among the groups.**

Test	Group 1 (n=18)	Group 2 (n=15)	Group 3 (n=24)	Group 4 (n=26)	P value
Baseline FSH (IU/ml)	6.31±3.61	5.96±2.0	6.52±2.54	6.09±1.85	0.902
Baseline E2 (pg/ml)	45.54±23.20	41.58±12.07	64.18±29.53	54.01±28.33	0.03*
AMH (ng/ml)	2.30±2.45	2.58±1.70	4.80±3.75	5.29±4.62	0.015*
AFC (n)	8.44±4.79	7.13±3.09	13.25±3.68	13.65±5.59	<0.001*

\* P value is statistically significant; FSH, follicle stimulating hormone; E2, estradiol; AMH, anti-Mullerian hormone; AFC, antral follicle count.

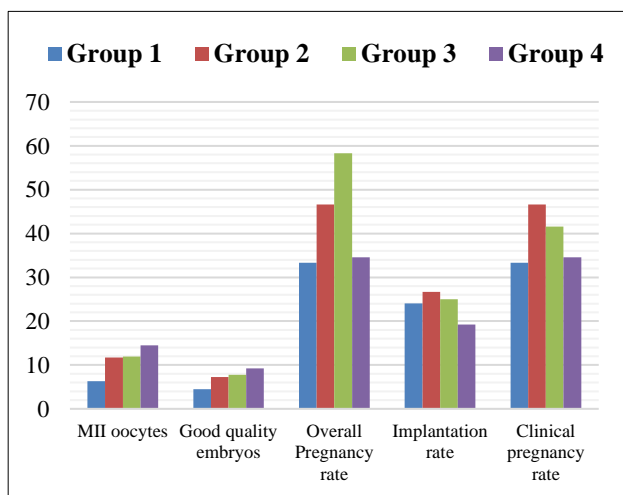
**Table 3: Comparison of the IVF-ICSI outcome between the study groups.**

Parameters	Group 1 (n=18)	Group 2 (n=15)	Group 3 (n=24)	Group 4 (n=26)	P value
Oocytes (mean±SD)	7.83±7.41	15.53±5.91	13.50±4.86	19.90±9.39	<0.001*
MII oocytes (mean±SD)	6.33±6.18	11.73±5.72	11.91±5.25	14.46±9.54	0.005*
Fertilization rate (%)	88.78	80.29	76.63	82.21	0.051
<b>Embryo quality</b>					
Grade A (mean±SD)	3.0±3.2	5.0±2.2	5.7±3.2	6.0±5.5	0.083
Grade B (mean±SD)	1.4±2.1	2.3±1.4	2.0±1.0	3.2±1.2	0.001*
Good quality embryos (Grade A+B) (mean±SD)	4.44±4.36	7.26 ± 2.71	7.75 ± 3.75	9.19 ± 5.72	0.009*
Embryos transferred (mean±SD)	2.38 ± 0.97	2.73 ± 0.70	2.66 ± 0.48	3.03 ± 0.66	0.031
Overall pregnancy rate (n; %)	6 (33.3)	7 (46.6)	14 (58.3)	9 (34.6)	0.283
Implantation rate (mean±SD)	24.06 (37.13)	26.65 (30.06)	24.98 (35.77)	19.21 (27.74)	0.888
Clinical pregnancy rate (n; %)	6 (33.3)	7 (46.6)	10 (41.6)	9 (34.6)	0.827

\* P value is statistically significant; MII, Metaphase II

On comparing the ovarian reserve tests between the groups, baseline FSH levels were comparable between the four groups. Groups 3 and 4 showed higher E2 levels at the beginning of stimulation compared to groups 1 and 2. AMH levels varied significantly between the groups, with group 1 having lowest and group 4 having the highest value. AFC was almost twice in groups 3 and 4 when compared to Groups 1 and 2 (Table 2).

Number of oocytes retrieved was significantly higher in Group 4 when compared to other groups. The total number of MII oocytes significantly increased from Group 1 to Group 4, correlating positively with levels of E2. The fertilization rate was comparable between all the groups with no statistically significant difference. Interestingly, although the number of Grade A embryos showed a non-significant increase from Group 1 to Group 4, the number of Grade B embryos was significantly higher in Group 4. This resulted in the total number of good quality embryos (Grade A+B) to be highest in Group 4 (p=0.009). The overall pregnancy rate showed a step-wise rise from Group 1 to Group 3 but declined in Group 4. This was despite the fact that the E2 levels, number of oocytes retrieved and number of embryos transferred gradually increased from Group 1 to Group 4. The implantation rate was lowest in Group 4 compared to all other groups, although not statistically significant (Table 3). The clinical pregnancy rate, overall pregnancy rate and implantation rate showed an interesting trend of being higher in Groups 2 and 3 and comparatively lower in groups 1 and 4 (Figure 1).



**Figure 1: Comparison of four groups based on E2 levels and their pregnancy related outcomes.**

## DISCUSSION

Our study showed an increase in the total number of oocytes, MII oocytes and good quality embryos (grade A+B) with higher serum E2 level. However, there was no significant difference in clinical pregnancy rate and implantation rate between the four groups.

Age is one of the most important prognostic determinants of IVF-ICSI outcome. The mean age of the women in all the four groups of our study were similar. Women in Group 2 had significantly higher mean BMI as well as lower AMH and basal E2 levels compared to the other groups. Increasing adiposity may impact ovarian reserve, and Monica et al demonstrated a negative correlation between BMI and AMH.<sup>14</sup> They reported that obese women had significantly lower AMH levels compared to their non-obese counterparts. Another prospective study by Rehman et al, reported that overweight women with BMI  $\geq 26$  Kg/m<sup>2</sup> had significantly decreased levels of E2 on day 2 as well as on the day of HCG.<sup>15</sup>

In our study the ovarian reserve tests (AMH and AFC) showed an upward trend being lowest in Group 1 and highest in Group 4. This finding was similar to that reported in other studies. Issac et al in an analytic review to differentiate the clinical profiles of patients and assess the response to ovarian stimulation and success of ART concluded that ovarian reserve tests correlate significantly with ovarian response to stimulation and thus estradiol levels on the day of trigger.<sup>16</sup> Lee et al, found that AMH and E2 levels on day of HCG were significant predictors of ovarian response and thus OHSS.<sup>17</sup> Another prospective study by Fiçicioglu et al, demonstrated an association between serum AMH and E2 levels with ovarian response but no difference in pregnancy success rate.<sup>18</sup>

## Oocyte retrieved

Our study showed a significant positive correlation between E2 levels  $>4000$ pg/ml on the day of ovulation trigger and the number of oocytes retrieved ( $19.9 \pm 9.39$ ). This finding has also been replicated in other studies. Kara et al, performed a cross sectional study on the association of serum E2 levels on the day of hCG with IVF- ICSI outcome and found that women who had E2 levels  $>4000$  pg/ml had significantly higher number of number of oocytes retrieved ( $17.2 \pm 4.4$ ) compared to other groups.<sup>19</sup> Blazar et al, compiled the data from 1901 consecutive cycles to determine the impact of serum E2 at the time of hCG administration on the probability of resultant ongoing pregnancy and found the mean number of oocytes retrieved increased in linear fashion with rising peak serum E2 at all levels.<sup>20</sup> Joo et al, did a retrospective study of E2 levels on the day of hCG and IVF outcome in 455 fresh IVF-ET cycles.<sup>21</sup> They observed that significantly higher number of oocytes were retrieved in the group with serum E2 levels  $>4000$  pg/ml ( $15.3 \pm 6.6$ ) compared to other groups. Arslan et al, conducted a retrospective to investigate the effect of the cumulative exposure to estradiol (E2) during the follicular phase on IVF outcome.<sup>22</sup> There was a significant difference between groups regarding the total number of oocytes recovered and the number of frozen embryos with the highest values observed in the group with E2 exposure  $>90^{\text{th}}$  percentile.

### **Fertilization rate**

It has been postulated that despite groups with increased E2 levels have higher number of oocytes and MII oocytes recovered, the percentage of fertilization remain similar.<sup>22</sup> This was comparable to our study in which fertilization rates among the four groups were not significantly different. Wu et al, retrospectively reviewed 274 IVF cycles and divided the patients into five groups according to their peak E2 levels on hCG day.<sup>23</sup> Though the number of oocyte retrieved in group 5 were more, the oocyte fertilization and embryo cleavage rates were not significantly different among these five groups. Mittal et al, did a retrospective study in which the subjects were grouped by serum E2 levels per mature follicle.<sup>24</sup> They did not observe any significant difference in the fertilization rates between the study groups. Valbuena et al reviewed data on ovarian stimulation and endometrial receptivity and found no effect of serum E2 levels on the day of hCG on the fertilization rate and embryonic quality.<sup>25</sup>

### **Good quality embryos**

Our study showed significant rise in the good quality embryos (grade A+B) with the rise in E2 levels on the day of ovulation trigger. In a retrospective analysis of 330 consecutive fresh oocyte donation cycles, Pena et al, showed that elevated E2 levels were associated with a larger number of oocytes and embryos and high-grade embryos.<sup>26</sup> Higher peak E2 levels directly correlated with a greater number of oocytes retrieved, embryos formed and higher average embryo quality scores. Ng et al, classified patients as per E2 levels on day of hCG.<sup>27</sup> The proportion of transferable embryos was not reduced in Group C (with highest E2 levels) when compared to those of Groups A and B. They concluded that excessive ovarian response does not compromise oocyte and embryo quality. Papageorgiou et al, in a retrospective study with 905 cycles showed better IVF outcome expressed as number of oocytes, total embryos obtained and number of high grade embryos which were significantly better for patients with E2 above the 90<sup>th</sup> percentile on the day of hCG.<sup>28</sup> Pregnancy rates were higher for high responders, but the difference did not reach statistical significance.

### **Implantation and pregnancy rate**

Authors found that the implantation rate dropped with higher levels of E2 (>4000pg/ml) although this was not statistically significant. Sharara et al, evaluated the impact of elevated peak E2 levels and a high number of retrieved oocytes on the implantation in patients undergoing assisted reproductive techniques in a retrospective study of 106 IVF cycles.<sup>10</sup> There were no statistically significant differences in implantation rate or pregnancy rate between normal and high responders implying elevated peak E2 levels and high oocyte yield are not detrimental to IVF outcome. This was comparable

to our study which did not show any statistically significant decline in the implantation and pregnancy rate with high E2 levels on the day of HCG. Similarly, Wu et al, observed that although the pregnancy and implantation rates decreased with E2 levels >5,000 pg/mL, there were no statistically significant differences between these five groups.<sup>23</sup> In the study by Blazar et al, implantation rates increased steadily with increasing levels of peak E2 until a plateau of approximately 17% at levels 2500 pg/mL was reached and there was no significant change thereafter.<sup>20</sup> Ongoing pregnancy rates also showed similar trend with increasing levels of peak E2, until a plateau was reached at approximately 2500 pg/mL.

Paulson et al, studied the effects of controlled ovarian hyperstimulation (COH) on endometrial receptivity during in vitro fertilization (IVF) by comparing embryo implantation data of non-anonymous donor oocyte program with those of standard IVF.<sup>29</sup> The implantation rates per individual embryo were significantly higher in donor cycles (with lower E2 levels) than in standard IVF (35% versus 10.7%). Clinical and ongoing pregnancy rates per cycle were likewise higher in the donor group than in the standard IVF group (67% versus 39%, and 61% versus 30%, respectively). They concluded that COH with higher E2 levels inhibits embryo implantation after IVF by decreasing endometrial receptivity, which is an important factor in IVF pregnancy success. Arslan et al, showed that the implantation and pregnancy rates in cycles with highest levels of E2 AUC (>90<sup>th</sup> percentile) were significantly lower than in patients with a normal E2 response.<sup>22</sup> Similar results were observed for the implantation rate (24.8% versus 12.9% in the normal E2 group versus highest group, respectively, P < 0.05). Joo et al, showed that serum E2 levels have a concentration-dependent effect on the pregnancy outcome, suggesting an optimal range of E2 level 3000-4000 pg/mL for women <38 years for achieving a successful pregnancy.<sup>21</sup> Kosmas et al, did a systematic review of the studies evaluating the association of serum estradiol levels on the day of trigger with the IVF outcome.<sup>30</sup> They concluded that currently there is lack of high-quality evidence to support or refute the value of E2 determination on the day of hCG administration for pregnancy achievement in IVF cycles.

The effect of supraphysiologic E2 levels on the oocyte quality and endometrial receptivity and if so, the cut-off of estradiol levels which affects the IVF outcome remains controversial. Some recommend robust stimulation to include not only retrieval of a greater number of oocytes but also improved implantation and pregnancy rates, at least until peak E2 levels of 2500. Any adverse impact on endometrial histology may possibly be overcome by a more robust patient response to stimulation.<sup>20</sup> Some patients may benefit from mild stimulation protocols which would avoid very high estradiol levels in the cycle. More robust multicentric RCTs are required to study the effects supraphysiological E2 on the pregnancy outcome and mark the cut off levels of E2 above which fresh

embryo transfer should be avoided and ‘freeze all technique’ implemented to avoid the detrimental effects of high E2 levels on the endometrium.

## CONCLUSION

Our study was pragmatic and authors used logistic regression analysis to account for confounding variables. Our study had limitations due to its retrospective design and authors may not have found statistical significance in certain outcome measures due to relatively small sample size. To conclude, higher serum estradiol level on day of ovulation trigger is associated with an increase in the number of oocytes, MII oocytes and embryo quality. The implantation rate was lowest with serum estradiol level above 4000pg/mL, although this was not statistically significant. There was no significant difference in overall and clinical pregnancy rate between the groups.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

## REFERENCES

1. Malhotra N, Shah D, Pai R, Pai HD, Bankar M. Assisted reproductive technology in India: A 3 year retrospective data analysis. *J Hum Reprod Sci.* 2013;6(4):235-40.
2. Pittaway DE, Wentz AC. Evaluation of the exponential rise of serum estradiol concentrations in human menopausal gonadotropin induced cycles. *Fertil Steril.* 1983;40:763-7.
3. Liu SM, Zheng YZ, Wang HB, Sun ZY, Zhen JR, Shen K, et al. Factors associated with effectiveness of treatment and reproductive outcomes in patients with thin endometrium undergoing estrogen treatment. *Chin Med J.* 2015;128:3173-7.
4. Wang XM, Jiang H, Zhang WX, Li Y. The effects of growth hormone on clinical outcomes after frozen-thawed embryo transfer. *Int J Gynaecol Obstet.* 2016;133:347-50.
5. Pelinck MJ, Hoek A, Simons AH, Heineman MJ. Efficacy of natural cycle IVF: a review of the literature. *Hum Reprod Update.* 2002;8:129-39.
6. Chen CD, Chen SU, Chou CH, Chen MJ, Wen WF, Wu SY, et al. High estradiol concentrations induce heat shock protein 70 expression and suppress nuclear factor kappa B activation in human endometrial epithelial cells. *Biol Reprod.* 2016;95:87.
7. Simon C, Cano F, Valbuena D, Remohi J, Pellicer A. Clinical evidence for a detrimental effect on uterine receptivity of high serum oestradiol concentrations in high and normal responder patients. *Hum Reprod.* 1995;10:2432-7.
8. Yu Ng EH, Yeung WS, Yee Lan Lau E, So WW, Ho PC. High serum oestradiol concentrations in fresh IVF cycles do not impair implantation and pregnancy rates in subsequent frozen-thawed embryo transfer cycles. *Hum Reprod.* 2000;15:250-5.
9. Levi AJ, Drews MR, Bergh PA, Miller BT, Scott RT. Controlled ovarian hyperstimulation does not adversely affect endometrial receptivity in in vitro fertilization cycles. *Fertil Steril.* 2001;76:670-4.
10. Sharara FI, McClamrock HD. High estradiol levels and high oocyte yield are not detrimental to in vitro fertilization outcome. *Fertil Steril.* 1999;72:401-5.
11. Testart J, Belaisch-Allart J, Forman R, Gazengel A, Strubb N, Hazout A, et al. Influence of different stimulation treatments on oocyte characteristics and in-vitro fertilizing ability. *Hum Reprod.* 1989;4:92-7.
12. Rosen MP, Shen S, Shen S, Rinaudo PF, Huddleston HG, McCulloch CE, et al. Fertilization rate is an independent predictor of implantation rate. *Fertil Steril.* 2010;94(4):1328-33.
13. Balaban B, Brison D, Calderón G, Catt J, Conaghan J, Cowan L, et al. The Istanbul consensus workshop on embryo assessment: proceedings of an expert meeting. *Hum Reprod.* 2011;26:1270-83.
14. Pasternak MC, Christos P, Spandorfer SD. The relationship between body mass index and anti-mullerian hormone levels in reproductive-age women; is there a negative correlation? *Fertil Steril.* 2018;109(3):53.
15. Rehman R, Hussain Z, Faraz N. Effect of estradiol levels on pregnancy outcome in obese women. *J Ayub Med Coll Abbottabad.* 2012;24:3-5.
16. Kligman I, Rosenwaks Z. Differentiating clinical profiles: predicting good responders, poor responders, and hyperresponders. *Fertil Steril.* 2001;76:6.
17. Lee TH. Serum anti-mullerian hormone and estradiol levels as predictors of ovarian hyperstimulation syndrome in assisted reproduction technology cycles. *Human Repro.* 2008;23(1):160-7.
18. Cem Fiçioğlu, Kutlu T, Baglam E, Bakacak Z. Early follicular antimüllerian hormone as an indicator of ovarian reserve. *Fertil Steril.* 2006;85:3.
19. Kara M, Kutlu T, Sofuoglu K, Devranoglu B, Cetinkaya T. Association between serum estradiol level on the hCG administration day and IVF-ICSI outcome. *Iran J Reprod Med.* 2012;10:53-8.
20. Blazar AS, Hogan JW, Frankfurter D, Hackett R, Keefe DL. Serum estradiol positively predicts outcomes in patients undergoing in vitro fertilization. *Fertil Steril.* 2004;81(6):1707-9.
21. Joo BS, Park SH, An BM, Kim KS, Moon SE, Moon HS. Serum estradiol levels during controlled ovarian hyperstimulation influence the pregnancy outcome of in vitro fertilization in a concentration-dependent manner. *Fertil Steril.* 2010;93:442-6.
22. Arslan M, Bocca S, Arslan EO, Duran HE, Stadtmauer L, Oehninger S. Cumulative exposure to high estradiol levels during the follicular phase of IVF cycles negatively affects implantation. *J Assist Reprod Genet.* 2007;24(4):111-7.
23. Wu CH, Kuo TC, Wu HH, Yeh GP, Tsai HD. High serum estradiol levels are not detrimental to in

- vitrofertilization outcome. *Taiwan J Obstet Gynecol.* 2007;46:54-9.
24. Mittal S, Gupta P, Malhotra N, Singh N. Serum estradiol as a predictor of success of in vitro fertilization. *J Obstet Gynaecol India.* 2014;64:124-9.
  25. Valbuena D, Jasper M, Remohí J, Pellicer A, Simón C. Ovarian stimulation and endometrial receptivity. *Hum Reprod.* 1999;14(Suppl 2):107-11.
  26. Peña JE, Chang PL, Chan LK, Zeitoun K, Thornton MH, Sauer MV. Supraphysiological estradiol levels do not affect oocyte and embryo quality in oocyte donation cycles. *Hum Reprod.* 2002;17(1):83-7.
  27. Ng EH, Lau EY, Yeung WS, Ho PC. Oocyte and embryo quality in patients with excessive ovarian response during in vitro fertilization treatment. *J Assist Reprod Genet.* 2003;20(5):186-91.
  28. Papageorgiou T, Guibert J, Goffinet F, Patrat C, Fulla Y, Janssens Y, et al. Percentile curves of serum estradiol levels during controlled ovarian stimulation in 905 cycles stimulated with recombinant FSH show that high estradiol is not detrimental to IVF outcome. *Hum Reprod.* 2002;17:2846-50.
  29. Paulson RJ, Sauer MV, Lobo RA. Embryo implantation after human in vitro fertilization: importance of endometrial receptivity. *Fertil Steril.* 1990;53:870-4.
  30. Kosmas IP, Kolibianakis EM, Devroey P. Association of estradiol levels on the day of hCG administration and pregnancy achievement in IVF: a systematic review. *Hum Reprod.* 2004;19:2446-53.

**Cite this article as:** Pillai A, Fessylouis T, Ramesh P, Parvathy T, Aparna N. Serum estradiol level on the day of ovulation trigger and pregnancy outcomes in in-vitro fertilisation-intracytoplasmic sperm injection cycles. *Int J Reprod Contracept Obstet Gynecol* 2019;8:3834-40.