

Assessment of serum estradiol effect on cervical cytomorphological changes in infertile women undergoing IVF/ICSIRasha S. Abd-Al-Fatah¹, Estabraq AR. Al-wasiti^{2*}, Ban Juma'a Qasim³**Abstract**

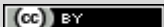
Women undergoing IVF procedures tend to have high levels of estradiol hormone because of the drugs used to stimulate egg production, and this may lead to display cervical cytomorphological changes & may affects pregnancy outcome in IVF cycles. The aim of the study is to correlate serum estradiol level on preovulatory day in women undergoing IVF/ICSI with cytomorphological changes in cervix and pregnancy test result. In this prospective case-control study, a total 100 cases were included 50 case group and 50 control group both in age range between (20-44) First blood sample to test serum estradiol taken on day 2 of menstrual cycle in both groups and second blood sample taken in preovulatory in both case and control group. Serum estradiol measured by Minividas. Cervical pap smear taken in preovulatory day in both case and control groups and stained with conventional pap stain then assessed according to Bethesda system 2001. There is non-significant correlation between serum estradiol in preovulatory day and appearance of abnormality in pap smear reports (P value=0.9). There is non-significant correlation between serum estradiol in preovulatory day and pregnancy test result (P value =0.5). In conclusion, serum estradiol does not have an association with IVF outcome and does not affect pap smear outcome.

Keywords: Estradiol; Preovulatory; IVF/ICSI

*Corresponding Author: Estabraq AR. Al-wasiti

¹Ministry of Health²Department of Chemistry and Biochemistry/College of Medicine, Al-Nahrain University³Department of Pathology and Forensic Medicine/College of Medicine, Al-Nahrain University

Received October 15, 2016; accepted January 11, 2017; published February 15, 2017

Copyright © 2017 EA. This is article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. **Introduction**

Estrogen has a predictable effect on the cells of the cervix and the presence of high level estrogen can be determined on the Pap smear [1]. The difference between a healthy pregnancy and an unsuccessful in vitro fertilization (IVF) attempt may be less than few nanograms of estrogen. And the tiniest

variations in a woman's estrogen levels may help to explain why up to 70% of healthy embryos fail to implant themselves in the uterus because it may alter embryo implantation and the necessary genetic process at the implantation site in the uterus and can drastically shorten the fertility window

[2]. During IVF cycles, the endometrium and embryo are exposed to supra-physiological concentrations of estradiol during ovarian stimulation, which could influence pregnancy outcomes [2].

Patients, materials and methods

Serum estradiol (E2) measurement:

In this study two blood samples taken from each patient in case and control groups.

In case group first blood sample taken in day two of menstrual cycle and second blood sample taken in preovulatory day (HCG day) which was usually reported from patient's data in IVF/ICSI operation. In control group 1st blood sample taken in the second day of menstrual cycle (CD2) and 2nd blood sample taken in preovulatory day (HCG day) according to U/S assessment of dominant follicle. The blood is centrifuged for 10 minutes then 200 microliters serum used to measure serum E2 using minividas which takes about 1 hour for each group of exam.

Estradiol blood test [3 ,4, 5]

*Alternative Names: E2 test

Test instructions: [3]

Instruct the patient to temporarily stop taking certain medicines that may affect test results. These medicines include:

- Birth control pills
- Antibiotics such as ampicillin or tetracycline
- Corticosteroids
- DHEA (a supplement)

- Estrogen
- Medicine to manage mental disorders (such as phenothiazine)
- Testosterone

Results

*Serum E2 in preovulatory day and its effect on IVF outcome

There is non-significant correlation between serum estradiol in preovulatory day and pregnancy test result (P value =0.5) as shown in table 4.1 Highest positive pregnancy test found in patients with serum estradiol range (1290-1878) where 6 patients (12%) out of 13 patient (26%) in this estradiol levels has positive pregnancy test, as shown in table 4.1. Worst pregnancy test found in patients with serum estradiol above 3056 because zero patients (0%) out of 3 patients (6%) in this hormone level has positive pregnancy rate as shown in table 4.1. One patient (2%) out of 9 patients (18%) with serum estradiol level below 700 gives positive pregnancy rate, as shown in table 4.1. Three patients (6%) out of 12 patients (24%) with serum estradiol level range (701-1289) has positive pregnancy test, as shown in table 4.1. Also Three patients (6%) out of 8 patients (16%) in serum estradiol range (1879-2466) has positive pregnancy test, as shown in table 4.1. And 2 patients (4%) out of 5 patients (10%) with serum estradiol range (2467-3055) has positive pregnancy test, as shown in table 4.1.

Table 4.1

Correlations between S.E2 in preovulatory day and IVF outcome

		pregnancy test		Total	P Value
		+ve	-ve		
serum E2day HCG	112-700	1	8	9	0.5
	701-1289	3	9	12	
	1290-1878	6	7	13	
	1879-2466	3	5	8	
	2467-3055	2	3	5	
	3056-3644	0	1	1	
	4234-4822	0	2	2	
Total		15	35	50	

*Correlation between serum estradiol in preovulatory day and pap smear result in case group

There is non-significant correlation between serum estradiol in preovulatory day and appearance of abnormality in pap smear reports (P value=0.9) as shown in table 4.2 and figure 4.1. However pap smear abnormality appears to be reduced when serum estradiol raised above 3000 because no case (0%) was reported with ASC-US when serum estradiol raised above 3056 .as shown in table 4.2 and in figure 4.1. While 3 patients (6%) out of 9 patients with serum estradiol < 700 was reported with ASC-US as shown in table 4.2 and in figure 4.1. And 3 patients (6%) out of 12 patients (24%)

with serum estradiol range (701-1289) reported with ASC-US, as shown in table 4.2 and in figure 4.1. Two patients (4%) out of 13patients (26%) with serum estradiol range (1290-1878) reported with ASC-US. as shown in table 4.2 and in figure 4.1. Two patients (4%) out of 8 patients (16%) with serum estradiol range (1879-2466) reported with ASC-US as shown in table 4.2 and in figure 4.1. And one patient (2%) out of 5 patients (10%) with serum estradiol range (2467-3055) reported with ASCUS. as shown in table 4.2 and in figure 4.1.

Table 4.1S

E2 in preovulatoryday and pap smear in case group

Serum E2day HCG * pap						P value
		pap			Total	
		NILM	ASC-US	Inadequate		
Serum E2 day HCG	112 -700	5	3	1	9	0.9
	701-1289	8	3	1	12	
	1290-1878	11	2	0	13	
	1879-2466	6	2	0	8	
	2467-3055	4	1	0	5	
	3056-3644	1	0	0	1	
	4234-4822	2	0	0	2	
Total		37	11	2	50	

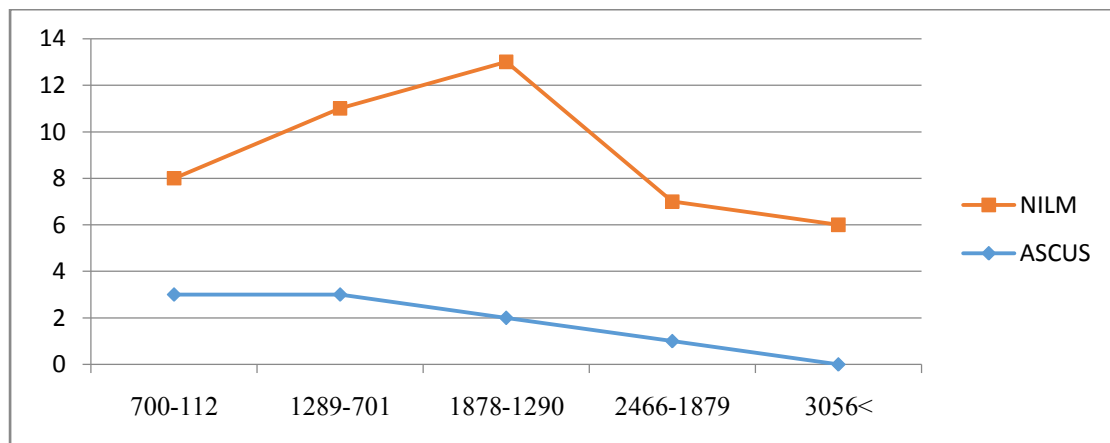


Figure 4.1

Distribution of pap smear result in relation to S.E2 level in preovulatory day

Discussion

Correlation of preovulatory Serum estradiol in and IVF outcome in case group

There is no correlation in serum estradiol in preovulatory day (i.e day of HCG) and IVF outcome but it was shown that higher pregnancy rate reported in serum estradiol range (1290-1878) and the higher the S.E2 the higher number of ova pickup but the relation between serum estradiol to serum progesterone in day of HCG was reported by Lin, *et al* [6] in which the number of oocytes was the most significant factor relating to s. Progesterone concentration. So by using milder stimulation approach to produce fewer oocytes in next cycle will overcome the high serum Progesterone and high S.E2 concentration, this is in keeping that most clinicians consider each patient's general condition including age, ovarian reserve and availability of cryopreservation in the IVF center.

Correlation between preovulatory serum estradiol and pap smear result in case group

In this study There was no significant correlation between serum estradiol in day of HCG and appearance of abnormality in pap smear but even it appear that intraepithelial lesion are zero when s. estradiol raised above 3000 pg/ml and it was reported in (12%) of cases when hormone estradiol where below 1289, this is compared with another study conducted by Boon [7] who observed that estrogen receptor was absent in cancer cells, and

in many cases increased in the tumor microenvironment (the area around the tumor that helps it grow) the cases where from the general population and not from IVF patients while it was reported by Foster [8] that high levels of estrogen are associated with cancer of the breast, uterus and cervix and with cystic breast disease, uterine fibroids and endometriosis; with heavy bleeding and premenstrual syndrome; with depressed thyroid function; and with fluid retention and weight gain. Also the study did in general population not in IVF patients.

Conclusion

Serum estradiol does not has an association with IVF outcome and does not affect pap smear outcome. Careful regulation of estrogen levels may offer a new way to improve the success of IVF procedures since no pregnancy happened in our study when serum estradiol exceed 3000 pg/ml.

Competing interests

Authors declare that we have no competing interests.

References

1. Nichols H. Estrogen is the primary female sex hormone. Among other roles, it promotes the development and maintenance of female characteristics in the human body. MNT 206.
2. National Academy of Science. Estrogen affects IVF success Web MD, 2016
3. Borawski D, Bluth MH. Reproductive function and pregnancy. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by

- Laboratory Methods. 22nd ed. Philadelphia, PA: Elsevier Saunders; 2011:chap 25.
4. Carmina E, Stanczyk FZ, Lobo RA. Laboratory assessment. In: Strauss JF, Barbieri RL, eds. Yen and Jaffe's Reproductive Endocrinology. 7th ed. Philadelphia, PA: Elsevier Saunders; 2014:chap 34.
 5. Gruber HA, Farag AF. Evaluation of endocrine function. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 22nd ed. Philadelphia, PA: Elsevier Saunders; 2011:chap 24.
 6. Lin Y, Lan K, Huang F, et al. Reproducibility and clinical significance of pre-ovulatory serum progesterone level and progesterone/estradiol ratio on the day of human chorionic gonadotropin administration in infertile women undergoing repeated in vitro fertilization cycles. *Reproductive Biology and Endocrinology* 2015;**13**:41.
 7. Boon J. Study redefines role of estrogen in cervical cancer. National Cancer Institute (NCI) and the University of Oklahoma Health Sciences Center 2015.
 8. Foster J. Natural protection against estrogen overload. 2000.

