Arch Gynecol Obstet (2012) 285:857–862
DOI 10.1007/s00404-011-2090-8

REPRODUCTIVE MEDICINE

The effects of peak and mid-luteal estradiol levels on in vitro fertilization outcome

Özlem Moraloğlu · Esra Ayşın Tonguc · Murat Özel · Gülnur Özakşit · Turgut Var · Esma Sarikaya

Received: 31 May 2011 / Accepted: 12 September 2011 / Published online: 22 September 2011

Abstract
Purposes To evaluate the role of peak E2 level and its ratio to mid-luteal E2 level on implantation and clinical pregnancy rates in patients undergoing IVF cycles.
Methods A retrospective study was designed covering 106 patients who were admitted to IVF Unit between June and October 2008. The patients were divided into two groups with respect to peak E2 levels. Ovulation induction has been done via standard long agonist protocol. Blood samples were drawn on the day of (hCG) administration and 8 days after embryo transfer for serum E2, progesterone measurements.
Results The mean peak E2 level was 2,697.4 ± 1,453 pg/ml (range 684–4,983 pg/ml. The number of retrieved oocytes, luteal E2 level, peak E2 level and E2 ratio were significantly higher in E2 >2,500 group, however, the implantation rate was significantly lower in this group.
There were statistically significant differences in peak E2 levels, luteal E2 levels, retrieved oocytes, E2 ratios; of the women who got pregnant and did not get pregnant, all the above parameters were significantly higher in non-pregnant group. According to E2 ratios, the clinical pregnancy rate was highest in group 1 and significantly lowest in group 3.
Conclusion This study has shown that the high E2 level and mid-luteal decline of E2 which were defined as peak E2 level/mid-luteal E2 level were predictive for implantation rate in IVF cycles.

Ö. Moraloğlu · E. A. Tonguc (✉) · M. Özel · G. Özakşit · T. Var · E. Sarikaya
Department of Reproductive Endocrinology, Zekai Tahir Burak Women's Health Research and Education Hospital, Tunali Hilmi Cad. Binnaz Sok. No: 1/5 Kavaklidere, Ankara 06100, Turkey
e-mail: esratonguc@yahoo.com

Keywords Peak estradiol · Mid-luteal estradiol · E2 ratio · IVF outcome

Introduction

Establishment of pregnancy in human IVF requires transfer of morphologically adequate embryos into the uterus. This is achieved by the retrieval of multiple cumulus-oocyte complexes (COC) after ovarian stimulation. Ovarian stimulation is necessary for multiple follicular developments and is accompanied by supraphysiological serum estradiol levels. Assessment of the role of estradiol levels for IVF outcome has been the focus of interest for many years.

At present, the importance of supraphysiological estradiol levels on the day of hCG administration for the probability of pregnancy in IVF remains unclear [1]. The role of estradiol in the luteal phase is also not clear and it is suggested that it only plays a permissive role [2, 3].

Significantly lower implantation and pregnancy rates were shown in cycles with high serum estradiol concentrations on the ovulatory (hCG) day [4–6]. The proposed mechanism of possible adverse effects of elevated estradiol levels is the altered endometrial receptivity [5–9]. Valbuena et al. [10] suggested that high E2 levels are deleterious to embryo adhesion in vitro, mainly because they have a direct toxic effect on the embryo that may occur at the cleavage stage. On the contrary, Bianco et al. concluded that elevated E2 levels in donors were not found to affect pregnancy outcome in oocyte donation cycles. This suggests elevated E2 levels do not compromise oocyte quality or embryo development in vitro, but that elevated E2 levels may diminish endometrial receptivity [11].

The impact of elevated E2 levels on the day of hCG administration (and of a high number of retrieved oocytes) in the subgroup of IVF patients known as "high responders" on implantation during assisted reproduction has been the subject of debate. Various studies showed that the different threshold levels above which a patient could be defined as a high responder make the meaningful interpretation confusing. High responders were defined variously in these studies as patients who had a peak E2 level of >3,000 pg/ml [7], >15 retrieved oocytes [5, 8] or >10 retrieved oocytes [9, 12].

Sharara and Mc Clamrock [3] found that the ratio of the day of hCG estradiol to mid-luteal estradiol was highly predictive of successful outcome in IVF-embryo transfer. The ongoing pregnancy and implantation rates (PR and IR, respectively) were significantly impaired if the above ratio was >5. They postulated that the endometrial integrity might become compromised when there was a dramatic decline in estradiol concentrations around the mid-luteal period as reflected by a high ratio.

The purpose of this retrospective study was to examine the effects of the peak and mid-luteal E2 levels, and the degree of decline in E2 levels from its peak level (on the day of hCG injection) to the lower levels of mid-luteal phase (day eight of hCG injection), as it is reflected by the E2 ratio (E2 level on the day of hCG injection/E2 on the day eight of hCG injection), on clinical PRs in an IVF-embryo transfer program.

Material and method

Of the patients who underwent IVF-ET at the outpatient clinic of Zekai Tahir Burak Woman's Health Education and Research Hospital IVF Unit between June and October 2008, 106 normal and high responders to the first cycle of COH with GnRH-agonist were included in the study. Approval for the study was obtained from the local ethics committee of the hospital. Data were obtained from patient records.

Patients with unexplained infertility, ovulatory dysfunction, male and tubal factors were included in the study. For the patients included in the study, the causes of infertility were male factor 34.9% ($n = 37$), tubal factor 14.1% ($n = 15$), ovulatory dysfunction 14.1% ($n = 15$), and unexplained in 36.7% ($n = 39$) of cases.

Study inclusion criteria included:

1. A basal FSH hormone level <10 IU/L
2. Age between 19–38
3. Long protocol with GnRH-a and rFSH
4. First cycle of IVF treatment.

Exclusion criteria were poor responders (women who achieved an E2 level <500 pg/ml on the day of hCG administration and/or women in whom <5 oocytes were retrieved), endometriosis patients, frozen-thawed cycles and other stimulation protocols.

The patients were divided into two groups with respect to peak E2 levels (Group 1: <2,500 pg/ml, Group 2: >2,500 pg/ml). Also the patients were compared of the women who got pregnant and did not get pregnant and the patients were divided into three groups with respect to E2 ratios (peak E2 level/mid-luteal E2 level) (Group 1 = 0.6–2.5, Group 2 = 2.5–5, Group 3 = >5). A comparison between the groups was made regarding ovarian stimulation characteristics, fertilization, implantation and pregnancy rates.

All the patients received oral contraceptive pills starting 3 weeks previously to ensure ovarian quiescence. Subcutaneous 0.5 mg/dl Leuprolid acetate (Lucrin daily flacon, 1 mg Abott, Cedex, İstanbul) was used for the inhibition and it was started from mid-luteal phase of previous menstrual cycle. The ovarian stimulation was initiated when serum estradiol levels were lower than 50 pg/ml and follicles smaller than 10 mm. rFSH (Gonal F, Serono laboratories, Boulogne, France) was used for ovarian stimulation based 225 IU initiation dose on the 3rd day of vaginal bleeding. After the initiation of gonadotrophin stimulation, the dosage of lucrin was reduced to 0.25 mg/dl and continued until the day of oocyte retrieval. Dose alterations were performed on 4th day of stimulation and continuing days according to sonographic findings and E2 levels. Once three follicles, at least 18 mm in diameter, were observed, ovulation was induced by intramuscular injection of 10,000 IU hCG (Pregnyl-Organon). Oocyte pick up (OPU) was performed 34–36 h after hCG injection. Embryos were transferred from 72 to 78 h after OPU by Wallace catheter (Edwards-Wallace Catheter; Marlow Technologies, Willoughby, OH) under ultrasonography guidance. Luteal phase support was achieved with a vaginal progesterone gel (Crinone gel 8%, Ares-Serono SA, Geneva, Switzerland) beginning from the OPU day and continued at least until pregnancy was ruled out by a negative serum hCG measurement.

The biochemical pregnancy rate was detected with the confirmation of positive serum hCG 2 weeks after ET. The implantation rate was the proportion of embryo transferred resulting in an intrauterine gestational sac. Clinical pregnancies were detected with the confirmation of positive fetal cardiac activities by transvaginal sonography on sixth gestational week. Blood samples were drawn on the hCG day and on the eighth day of embryo transfer (ET) for E2 (peak and mid-luteal E2, respectively) and progesterone levels. E2 ratio was defined as peak E2 level/mid-luteal E2 level [3]. Miscarriage was defined as a loss of a clinical pregnancy before the 13th week of gestation.

Laboratory analysis

The serum levels of E2, FSH, and LH that were studied with Electrochemiluminescence Immunoassay "ECLIA" (Roche) were intended to use on Elecsys and cobas e 601 immunoassay analyzers. The analysis sensitivity of the assay was 5 pg/ml and linear interval of test was 500–4,300 pg/ml for estrogen. E2 levels were assayed with intra- and interassay coefficients of variation of <3.3 and <4.9%, respectively. FSH sensitivity assay 0.13 mIU/ml, range assay 0.13–200 mIU/ml, sensitivity assay 5% was measured. For serum FSH measurement,the intra-and interassay coefficients of variation were <2.8 and <4.5%, respectively.

Statistical analysis

Continuous data were expressed as mean ± SD and were analyzed with 2-sample *t* test and Mann–Whitney rank sum test. Categorical data were analyzed with Chi-square test or Fisher's exact test where appropriate. All statistical analysis was performed by SPSS 15.0 package (SPSS, Chicago, IL, USA).

A probability value of <0.05 represented statistical significance.

Power analysis

We estimated 48 patients per group would be needed to show ±1 difference in E2 ratio was defined as peak E2 level/mid-luteal E2 level with in groups, assuming a statistical power of 95% at an alpha level of 0.05. Power analysis was performed using NCSS-PASS package program.

Results

The mean (± SD) patient age was 30.5 ± 5.9 years (range 19–38 years). The mean body mass index was 24.9 ± 3.2 kg (range 18.6–37.2 kg). The mean basal FSH level was 7.8 ± 2.2 IU/L (range 0.2–10 IU/L). The mean number of oocytes retrieved was 10.1 ± 4.4 (range 5–35). The mean peak E2 level was 2,697.4 ± 1,453 pg/ml (range 684–4,983 pg/mL).

Comparing E2 <2,500 pg/ml and E2 >2,500 pg/ml, there were no statistically significant differences in age, serum basal FSH level, fertilization rate, number of replaced embryos and PRs. The number of retrieved oocytes, luteal E2, peak E2 and E2 ratio were significantly higher in E2 >2,500 pg/ml group, however, the implantation rate was significantly lower in this group (Table 1).

Figure 1 shows a sharp decline in the mid-luteal E2, in group >2,500 pg/ml. There were statistically significant differences in peak E2 levels, luteal E2, retrieved oocytes, E2 ratio; of the women who got pregnant and did not get pregnant, all the above parameters were significantly higher in non-pregnant group (Table 2).

When the patients were divided into three groups with respect to E2 ratios (Group 1 = 0.6–2.5, Group 2 = 2.5–5, Group 3 = >5). It was seen that a great majority of the patients (92.4%) were in groups 1 and 2. The clinical

Table 1 Outcome of IVF in 106 women grouped according to their peak E2 response as high responders or normal responders

Variable	E2 Level		*P* value
	<2,500 pg/ml ($n = 57$)	≥2,500 pg/ml ($n = 49$)	
Age (years)	31.45 ± 5.99	29.53 ± 5.78	NS
FSH level (IU/ml)	7.55 ± 2.60	6.70 ± 1.89	NS
Dose of total gonadotrophins usage (IU)	2,858 ± 1,332	2,434 ± 1,149	NS
Peak E2 level (pg/ml)	1,746.5 ± 345.2	3,834.6 ± 1,284.3	<0.001
Progesterone level on day of hCG administration (ng/ml)	0.84 ± 0.36 (0.2–13)	1.88 ± 4.47 (0.2–30)	NS
Progesterone level on day 8 of hCG administration (pg/ml)	52.32 ± 15.52 (0.2–60)	58.07 ± 8.92 (0.6–60)	<0.05
E2 level on day 8 of hCG administration (pg/ml)	1,148.7 ± 602.9	1,417.8 ± 538.9	<0.05
No. of retrieved oocytes	8.2 ± 3.3	12.9 ± 5.7	<0.001
Fertilization rate (%)	70.2 ± 26.1	72.6 ± 24.3	NS
No. of embryos transferred	2.8 ± 0.9	2.9 ± 0.8	NS
No. of clinical pregnancies/Number of women (%) (PRs)	17/57 (29.8)	19/49 (38.8)	NS
Abortus ratio (%)	15 (26.3)	11 (22.4)	NS
No. of implanted embryos/Number of embryos transferred (%) (IRs)	40/160 (25.0)	20/144 (13.9)	<0.05
Estradiol ratio (peak E2/Mid-luteal E2)	1.9 ± 0.9	2.8 ± 1.3	0.001

Values are mean ± SD unless otherwise indicated as *NS* not significant

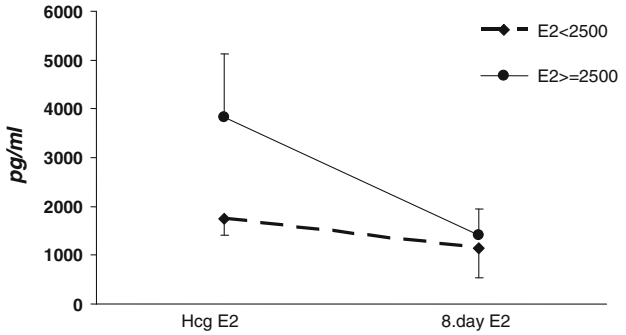

Fig. 1 Decline in the mid-luteal E2, in group >2,500 pg/ml and <2,500 pg/ml groups

pregnancy rate was highest in group 1 and significantly lowest in group 3. The mean mid-luteal progesterone (hCG day-8) levels of these three groups were statistically significantly different, and a statistical relationship to group 1 with a p value of 0.001 was found (Table 3).

A total number of 60 clinical pregnancies were noted with 3 missed abortions and 4 extra uterine pregnancies. In 4 women with a peak E2 level ≥2,500 pg/mL, moderate degree ovarian hyper stimulation syndrome (OHSS) was observed (7.8%). They recovered fully with expectant management, but they did not conceive.

Discussion

High serum E2 concentrations may be detrimental to the implantation and pregnancy rates in IVF treatment. The effect of such supraphysiologic E2 levels on the IVF-ET outcome has been the subject of many researches in the literature [13–17]. In a retrospective study by Pellicer et al. [9], where gonadotrophins without clomiphene citrate were used, a negative effect was observed based on numerous oocytes retrieved from 97 patients, constituting the first study in the GnRH agonist era. The patients in this study were divided into three groups based on the number of oocytes retrieved: 1–5, 6–10 and >10. When compared to women who had 1–5 oocytes retrieved, IRs were significantly reduced in the 6–10 oocytes retrieval group. Both fertilization rates and IRs were significantly lower in women with >10 oocytes [9]. Among women who had >10 retrieved oocytes, peak E2 levels were significantly higher as well as E2 levels on days 1 and 2 after hCG administration. The researchers suggested that impaired embryo quality may be the cause of the lower IRs and PRs [9]. Makkar et al. [18] demonstrated that a high serum E2 level caused a decrease interleukin-11 and interleukin-6 expression in the peri-implantation endometrium and the lower IRs and PRs in the high responders may due to this reduction.

Table 2 Demographic and cycle characteristics of patients with or without established pregnancy

Variable	Pregnant (n = 60) mean ± SD	Non-pregnant (n = 46) mean ± SD	P value
Age (years)	30.40 ± 5.87	30.71 ± 5.78	0.960
BMI	25.13 ± 3.12	24.63 ± 3.49	0.441
No. of antral follicle	9.23 ± 4.47	11.56 ± 4.88	<0.05
FSH level (IU/ml)	7.55 ± 2.50	6.64 ± 1.99	<0.05
Peak E2 level (pg/ml)	2,322.8 ± 1,241.7	3,219.2 ± 1,405.0	<0.001
No. of retrieved oocytes	9.1 ± 5.1	12.0 ± 4.6	<0.01
No. of 2PN	5.2 ± 4.2 (median = 4)	7.32 ± 3.82 (median = 7)	<0.001
No. of embryo fertilized	2.87 ± 0.95	2.87 ± 0.81	0.987
No. of G1 embryo	1.18 ± 1.26 (median = 1.00)	0.67 ± 0.73 (median = 1.00)	0.073
Fertilization rate (%)	71.3 ± 24.8	71.3 ± 26.0	0.991
E2 level on day 8 of hCG administration (pg/ml)	1,343.1 ± 890	1,897.5 ± 1,176	<0.05
Estradiol ratio (peak E2/mid-luteal E2)	2.1 ± 1.1	2.9 ± 1.1	<0.05

Table 3 Pregnancy and implantation rates in 106 patients grouped according to their E2 ratios (Group 1 = 0.6–2.5, Group 2 = 2.5–5, Group 3 = >5)

Variable	Group 1 (n = 69)	Group 2 (n = 29)	Group 3 (n = 8)	P value
No. of clinical pregnancies/Number of women (%) (PRS)	28/69 (40.6)	7/29 (24.1)	1/8 (12.5)	<0.05
Progesterone value on day 8 of hCG administration	55.7 ± 12.2 (0.2–60)	33.3 ± 21 (0.6–60)	25 ± 20 (0.8–60)	0.001

High responders were defined as women who had >15 retrieved oocytes by the same group of researchers [5, 8]. Simon et al. [5] studied 59 high responders, and 105 normo-responders (≤15 oocytes) and concluded that although fertilization rates did not change, there was a distinctive decrease of IRs and PRs in high responders. Then, they established peak estradiol threshold levels as, 1,770 pg/ml for high responders and 2,200 pg/ml for normo-responders, above which IRs and PRs were significantly decreased in both groups [5]. When peak E2 levels exceeded 2,500 pg/ml among all cycles, IRs and PRs decreased significantly, independent of the number of retrieved oocytes [5].

Similarly, in this study, when the patients were divided into two groups according to their peak E2 levels, there were no significant differences in PRs, but implantation rate was significantly lower in >2,500 pg/ml group. These results are similar to the results of the study by Sharara et al. [13].

We also evaluated the ratio of peak estradiol/mid-luteal estradiol considering earlier studies [2, 3, 6, 14] investigating the effects of mid-luteal estradiol levels in pre-implantation period on IVF outcome. It was seen that a great majority of the patients (92.4%) were in groups 1 and 2. The clinical pregnancy rate was highest in group 1 and significantly lowest in group 3. A sharp decline in the mid-luteal E2, defined in our study as peak estradiol to mid-luteal estradiol ratio higher than 5, resulted in lower pregnancy rate, which was also confirmed by other studies [3, 6, 14].

Also the patients were evaluated of the women who got pregnant and did not get pregnant. There were significant difference between the peak E2 levels, the luteal E2 levels, E2 ratios of the pregnant patients and the patients in whom pregnancy was not achieved. All the above parameters were significantly higher in non-pregnant group.

While initially the success of IVF outcome used to be associated with E2 level, it was soon resolved that E2/oocyte ratio may be another important parameter in a successful COH cycle.

But, there is no accepted optimal E2/oocyte ratio yet [1, 4, 19]. In a recent study, Var et al. [20] concluded that, IVF success may be increased with a strategy to keeping the E2/oocyte ratio above 100 pg/ml in IVF cycles.

There may be a threshold for peak E2 level and E2 ratio above which IRs and PRs are negatively affected, and this threshold level is likely to be much higher than 2,500–3,000 pg/ml and E2 ratio higher than 5 resulted in lower pregnancy rate, which was also confirmed by other studies [1, 3, 6, 14]. Some researchers believe that IVF outcome is not reduced until peak E2 is >5,000 pg/ml, as previously reported [4, 13, 21, 22].

Friedler et al. concluded that only marked E2 decline (>98%) might influence the miscarriage rate, especially in high responder group therefore neither the significant decline of mid-luteal E2 nor the absolute serum concentration of E2 were detrimental to IVF-ET outcome and their accepted threshold for peak E2 level was 2,500 pg/ml [23, 24].

On the contrary, Joo et al. concluded that the serum E2 levels during COH influenced the IVF outcome in a concentration-dependent manner. They suggested that the optimal range of E2 levels were 3,000–4,000 pg/ml for women <38 years and 2,000–3,000 pg/ml for women ≥38 years [25].

Conclusion

This study has shown that the high E2 level and mid-luteal decline of E2 which were defined as peak E2 level/mid-luteal E2 level were predictive for implantation rate in IVF cycles. Larger randomized controlled clinical trials are still needed to discover the effect of the E2 level on ART.

Conflict of interest None.

References

1. Kosmas IP, Kolibianakis EM, Devroey P (2004) Association of estradiol levels on the day of hCG administration and pregnancy achievement in IVF: a systematic review. Hum Reprod 11: 2446–2453
2. Hung EYN, Yeung WSB, Lau EYL, So WWK, Ho PC (2000) A rapid decline in serum oestradiol concentrations around the mid-luteal phase had no adverse effect on outcome in 763 assisted reproduction cycles. Hum Reprod 9:1903–1908
3. Sharara FI, McClamrock HD (1999) Ratio of oestradiol concentration on the day of human chorionic gonadotrophin administration to mid-luteal oestradiol concentration is predictive of in vitro fertilization outcome. Hum Reprod 11:2777–2782
4. Hung EYN, Yeung WSB, Lau EYL, So WWK, Ho PC (2000) High serum oestradiol concentrations in fresh IVF cycles do not impair implantation and pregnancy rates in subsequent frozen-thawed embryo transfer cycles. Hum Reprod 15:250–255
5. Simon C, Coro F, Valbuena D, Remohi J, Pellicer A (1995) Clinical evidence for a detrimental effect on uterine receptivity of high serum oestradiol concentrations in high and normal responder patients. Hum Reprod 10:2432–2437
6. Inge GB, Brinsden PR, Elder KT (2005) Oocyte number per live birth in IVF: were Steptoe and Edwards less wasteful? Hum Reprod 20:588–592
7. Simon C, Garcia Velasco JI, Valbuena D, Peinado JA, Moreno C et al (1998) Increasing uterine receptivityby decreasing oestradiol levels during the preimplantation period in high responders with the use of a follicle stimulating hormone step-down regimen. Fertil Steril 70:234–239
8. Pellicer A, Valbuena D, Cono F, Remohi J, Simon C (1996) Lower implantation rates in high-responders: evidence for an altered endocrine milieu during the preimplantation period. Fertil Steril 65:1190–1195
9. Pellicer A, Simon C, Castellui RM, Colatayud C, Ruiz A, Ruiz M et al (1989) Is the retrieval of high numbers of oocytes desirable

in patients treated with gonadotrophin-releasing hormone analogues and gonadotrophins? Hum Reprod 4:536–540
10. Valbuena D, Martin J, de Pablo JL, Remohi J, Pellicer A, Simon C (2001) Increasing levels of E2 are deleterious to embryonic implantation because they directly affect the embryo. Fertil Steril 76:962–968
11. Bianco K, Mahutte NG, Arici A, Sakkas D, Taylor HS (2009) Effect of estradiol on oocyte development. Int J Gynaecol Obstet 104(3):230–232
12. Toner JP, Brzyski RG, Oehninger S, Veeck LL, Simonetti S, Muasher SJ (1991) Combined impact of the number of preovulatory oocytes and cryopreservation on IVF outcome. Hum Reprod 6:284–289
13. Sharara FI, McClamrock HD (1999) High oestradiol levels and high oocyte yield are not detrimental to in vitro fertilization outcome. Fertil Steril 72(3):401–405
14. Gidley-Baired AA, O' Neill C, Sinosich MJ, Porter RN, Pike IL, Sounders DM (1986) Failure of implantation in human in vitro fertilization and embryo transfer patients: the effects of altered progesterone/estrogen ratios in humans and mice. Fertil Steril 45:69–74
15. Testart J, Belaisch-Allart J, Frydman R (1986) Relationship between embryo transfer results and ovarian response and in vitro fertilization rates: analysis of 186 human pregnancies. Fertil Steril 45:237–243
16. Tarin JJ, Sampaio MC, Colatayud C, Castellui RM, Bonilla-Musoles F, Pellicer A (1992) Relativity of the concept "high responder to gonadotrophins". Human Reprod 7:19–22
17. Forman R, Fries N, Testart J, Belaisch-Allart J, Hazout A, Frydman R (1988) Evidence for an adverse effect of elevated serum estradiol concentrations on embryo implantation. Fertil Steril 49:118–122
18. Makkar G, Ng EHY, Tang OS, Yeung WSB, Ho PC (2006) Reduced expression of Interleukin-11 and Interleukin-6 in the peri-implantation endometrium of excessive ovarian responders during in vitro fertilization treatment. J Clin Endocrinol Metab 91:3181–3188
19. Chen Q-J, Sun X–X, Li L, Gao X-H, Wu Y, Gemzell-Danielsson K, Cheng L-N (2007) Effects of ovarian high response on implantation and pregnancy outcome during controlled ovarian hyperstimulation (with GnRH agonist and rFSH). Acta Obstetricia et Gynecologica 86:849–854
20. Var T, Tonguc E, Dogan M, Mollamahmutoğlu L (2010) Relationship between the oestradiol/oocyte ratio and the outcome of assisted reproductive technology cycles with gonadotropin releasing hormone agonist. Gynecol Endocrinol July 20 (Epub ahead of print)
21. Ernest Hung Yu Ng (2000) What is the threshold value for serum estradiol levels associated with adverse IVF outcomes? [letter]. Fertil Steril 73:1071
22. Wu C-H, Kuo T-C, Wu H-H, Yeh G-P, Tsai H-D (2007) High serum estradiol levels are not detrimental to in vitro fertilization outcome. Taiwan J Obstet Gynecol 46(1):54–59
23. Friedler S, Zimerman AL, Schachter M, Raziel A, Strassburger D, Ron El R (2002) The impact of peak follicular estradiol (E2) levels and its dramatic mid-luteal decline on the outcome of IVF-ET. Fertil Steril 78(1):52
24. Friedler S, Zimerman A, Schachter M, Raziel A, Strassburger D, Ron El R (2005) The midluteal decline in serum estradiol levels is drastic but not deleterious for implantation after in vitro fertilization and embryo transfer in patients with normal or high responses. Fertil Steril 83(1):54–60
25. Joo BS, Park SH, An BM, Kim KS, Moon SE, Moon HS (2010) Serum estradiol levels during controlled ovarian hyperstimulation influence the pregnancy outcome of in vitro fertilization in a concentration-dependent manner. Fertil Steril 93(2):442