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Comparison Of Some Cycle Characteristics Between Poor Responder Women With And Without Oocyte Retrieval Following Transvaginal Follicle Aspiration

Transvajinal Folikül Aspirasyonunu Takiben Oosit Toplanabilen ve Toplanamayan Kötü Yanıtlı Hastaların Siklus Karakteristiklerinin Karşılaştırılması

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ÖZ

Giriş: Bu çalışmanın amacı, zayıf yanıtlı hastalarda transvajinal folikül aspirasyonu sonrası oosit elde edilen ve edilmeyen grupların siklus özelliklerini belirlemektir.

Gereç ve Yöntem: Zayıf yanıtlı olup folikül aspirasyonu sonrası hiç oosit çıkmayan 68 hasta ile en az bir oosit çıkan 60 hastalanın bazı siklus özellikleri karşılaştırıldı. Tüm hastalarda bazal FSH, estradiol ve AMH değerlerine göre karar verilen düşük over rezervi mevcuttu. Düşük over rezervi, FSH değeri > 10 IU/L, antral folikül sayısı < 6 veya AMH < 1.1 ng/ml veya daha önceden zayıf cevap olarak tanımlandı.

Sonuçlar: İki grup arasında, infertilite süresi, bazal östradiol süresi ve 14 mm nin üzerindeki folikül sayısı ve tetikleme günü pik estradiol düzeyleri (397 versus 1301 pg/ml) bakımından anlamlı fark mevcuttu. Çok değişkenli regresyon analizinde, infertilite süresi ve pik estradiol süresi oosit toplama prosedürü sonrası hiç oosit çıkmaması ile ilişkili saptanmıştır. Pik östradiol düzeyi (AUC=0.888, P < 0.001) ve infertilite süresi (AUC=0.776, P < 0.001) hiç oosit çıkmamasını anlamlı öngörmekteydi. Pik östradiol için optimal eşik değer 412 pg/ml (88% sensitivite, 70% spesifisite %), infertilite süresi için ise 4.75 yıl (72 % sensitivite, 75% spesifisite) olarak saptandı.

Tartışma: Tetikleme günü bakılan pik östradiol düzeyi zayıf cevaplı hastalarda transvajinal oosit aspirasyon işlemi sonrası hiç oosit elde edilmemesini öngörmek üzere kullanılabilir.

Anahtar Kelimeler: boş folikül sendromu, granuloza hücre apoptozu düşük over rezervi

ABSTRACT

Aim: The aim of this study was to figure out the differences in the cycle characteristics differences between poor responder women with and without oocyte retrieval with transvaginal follicle aspiration.

Material and Method: Some cycle characteristics of sixty-eight women with no oocyte retrieval were compared with sixty women with at least one oocyte retrieval following transvaginal follicle aspiration. All women had poor ovarian reserve determined by basal FSH, estradiol, AMH levels and antral follicle count. Diminished ovarian reserve was defined according to the basal FSH value >10 IU/L, antral follicle count <6 or AMH <1.1 ng/ml and/or a previous poor ovarian response.

Results: There were significant differences between groups with regard to duration of infertility, basal estradiol level and number of follicles > 14 mm and peak estradiol on the trigger day (397 versus 1301 pg/ml). In multivariate regression analysis, duration of infertility and peak estradiol level were significantly associated with no oocyte retrieval following oocyte pick up procedure. Peak estradiol (AUC=0.888, P < 0.001) and duration of infertility (AUC=0.776, P < 0.001) were significant predictors for no oocyte yield. Optimal cut off value was 412 pg/ml (88% sensitivity, 70% specificity % specificity) for peak estradiol level and 4.75 years (72 % sensitivity, 75% specificity) years for duration of infertility.

Conclusions: Estradiol level at trigger day may be utilized to predict no oocyte yields following transvaginal follicle aspiration in women with poor ovarian reserve.

Keywords: empty follicle syndrome, granulosa cell apoptosis, poor ovarian reserve

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Introduction

Empty follicle syndrome (EFS) is defined to be failure of oocyte retrieval from mature follicles following an appropriate ovarian hyperstimulation and ovulation induction. It is not known whether if the follicle is empty or the oocyte is failed to be retrieved due to concerns about oocyte pick-up procedure (1-4). Two types have been defined up to date based on the human chorionic gonadotropin (hCG) level at the time of oocyte retrieval (5). If the hCG level on the follicle rupture is optimal, this condition was defined to be genuine type of empty follicle syndrome (EFS). The exact underlying mechanism is still a debate (2,6). Early oocyte atresia has been proposed to be an underlying abnormality by some authors (7). Some other authors pointed the necessity of longer exposure to human chorionic gonadotropin for the release of oocyte cumulus complex from the follicular wall (8). On the other hand, in the literature it is believed that ovarian aging lead to the malfunction of granulosa cells that result in EFS (9). Genetic factors, a drop in estradiol before trigger and human error are some other factors that lead to this unwanted outcome (10, 11).

Luteal phase stimulation following oocyte pick up procedure was proposed for an approach for the cases with no oocyte retrieved in the same conventional IVF to save time to obtain mature oocyte (12).

The aim of this study was to figure out some cycle characteristic differences between poor responder women with and without oocyte retrieval with oocyte pick up procedure.

Materials and Methods

This retrospective study was conducted from between July 2016 and December 2016 in the IVF/ICSI unit of Zeynep Kamil Women and Children's Health Training and Research Hospital. A total of 128 women with (n=60) and without (n=68) oocyte harvest following transvaginal follicle aspiration were retrospectively screened from the hospital database and cycles with and without oocyte yield were compared in terms of some cycle characteristics. Women were included in the study if they had, regular menstrual cycles, normal serum prolactin levels and had not had hormone treatment in 3 months, ages ranged from 34 to 42. Exclusion criteria were; women with previous cycle with empty follicle syndrome and technical difficulty during oocyte pick up procedure in the current cycle and other infertility causes including tubal factor, male factor, and endometriosis. All patients had assisted reproductive technology treatment because of their previous poor response and/or poor ovarian reserves. Diminished ovarian reserve was defined according to the basal FSH value >10 IU/L, antral follicle counts <6 or AMH <1.1 ng/ml and/or a previous poor ovarian response (13). Antagonist protocol was used in all cases for both cycles. On the second day of the menstrual cycle, depending on the patient's response, rFSH 300 IU were administered and follicular growth was monitored using transvaginal sonography. The dosage of rFSH was adjusted starting from Day 5 of stimulation according to the ovarian response. Follicle monitorization was performed by two-dimensional measurements of growing follicles and the calculation of mean value at each visit.

Antagonist (Cetrorelix, Merk-Sereno, Geneva, Switzerland) 0.25 mg/day was administered when the follicular size was 12-14 mm. After the follicular size reached 18 mm, Beta rhCG 250 μg was administered, and follicular puncture was performed after 34–36 hours by 17-gauge double-lumen needle (Cook Ireland Ltd., Limerick, Ireland). Each aspirated follicle was flushed up to four times using a manually pressed syringe with 5 ml of culture media warmed to 37□C. All retrievals were performed by one of two physicians in a single center to minimize surgical variability. Age, duration of infertility, serum FSH, estradiol, total gonadotropin dose, # of follicles > 14 mm, peak estradiol level were compared between groups.

Sample Collection

In the morning, 8:00 a.m. to 10:00 a.m., on the 3rd day of ovarian stimulation and the day of ovulation trigger between 8:00 a.m. and 10:00 a.m, 3∼5 ml venous blood sample was taken to be assayed. Concentrations of estradiol and progesterone were measured.

Hormone Assay

Serum samples were analyzed using Immulite 2000 reproductive hormone assays (Diagnostic Product Corporation, Siemens, Los Angeles, CA). The sensitivity was 0.1 mlu/ml for FSH; 15 pg/ml for estradiol.

Statistical Analyses

Data were analysed using SPSS 15.0 for Windows. Multivariate regression analyses were used to assess the adjusted associations. ROC analyses were used to assess the predictive value of the test and to calculate sensitivity and specificity. P value < 0.05 was accepted to be statistically significant.

Results

There were significant differences between groups with regarding duration of infertility, basal estradiol level and number of follicles > 14 mm and peak estradiol on the trigger day (397 versus 1301 pg/ml) (Table 1).

Table 1 : Comparison of some demographic and clinical characteristics between groups with and without oocyte yield with transvaginal follicle aspiration

	Groups		
	Study (n=68)	Control (n=60)	
	Mean ± SD	Mean ± SD	
Age (Years)	36.2 ± 5.04	35.9 ±3.3	NS
Duration of infertility (Years)	3.86 ± 3.979	7.96 ± 5.002	< 0.001
FSH (mIU/ml)	13.8 ±6.7	10.9 ±1.1	NS
Estradiol (pg/ml)	39.9 ±21.3	52.9 ±35.9	< 0.05
Total gonadotropin Dose (U)	3650 ±1.560.1	3751.2 ± 832.6	NS
# of follicles > 14 mm	1.5 ±1.08	3.8 ± 2.7	< 0.001
Estradiol at trigger day (pg/ml)	397.1 ±305.7	1301.8 ±717.1	< 0.001

FSH:Follicle stimulating hormone, #: Number

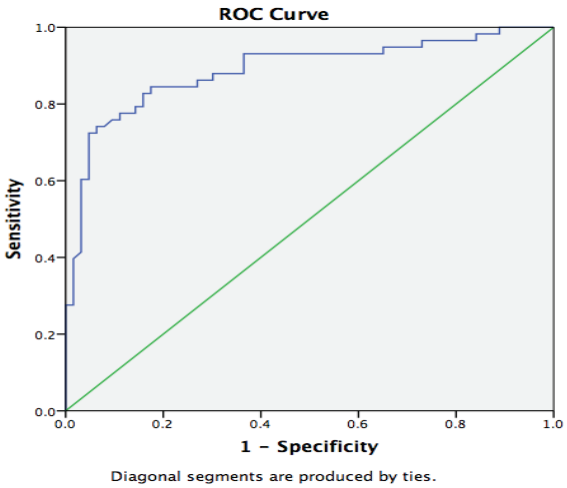
In multivariate regression analysis, duration of infertility and peak estradiol level were significantly associated with no oocyte retrieval (Table 2).

Table 2 : Summary of multivariate analysis showing significant association between duration of infertility and the peak estradiol level with no oocyte yield with transvaginal follicle aspiration

Model	Standardized Coefficients	t	P
	Beta		
(Constant)		15.026	.000
Day 3 estradiol (pg/ml)	-.072	-1.085	.280
Estradiol at trigger day (pg/ml)	-.576	-8.619	.000
Duration of infertility (Years)	-.286	-4.243	.000

Peak estradiol (AUC=0.888, P < 0.001) and duration of infertility (AUC=0.776, P < 0.001) were significant predictors for no oocyte harvest (Figure 1).

Figure 1: ROC curve of peak estradiol to predict no oocyte yield with transvaginal follicle aspiration



Optimal cut off value was 412 pg/ml (88 % sensitivity, 70 % specificity) for peak estradiol level and 4.75 (72 % sensitivity, 75 % specificity) years for duration of infertility.

Discussion

In this study, we tried to assess the predictors of no oocyte yield following ovarian hyperstimulation and transvaginal follicle aspiration in women with poor ovarian reserve. Duration of infertility was longer, basal estradiol level, number of follicles > 14 mm and peak estradiol at trigger day were lower in group with no oocyte retrieval following transvaginal follicle aspiration. In multivariate regression analysis, duration of infertility and peak estradiol level were significantly associated with no oocyte retrieval following transvaginal follicle aspiration.

Although the empty follicle syndrome is not frequently encountered with an incidence of 0.6–7.0%, it has some significant consequences for the patients in terms of cost and emotional frustration (14).

Some authors suggested the genuine type empty follicle syndrome as a variant of low ovarian reserve (14,15). Additionally, poor ovarian reserve and response were proposed to be one of the underlying mechanism of EFS (16). In another report by Bustillo (17), ovarian dysfunction lead to impaired follicular maturation and ovulation and result in EFS. This argument was confirmed by Zreik et al (14).

In a recent study by Madani et al, empty follicle syndrome was shown to be more frequent in cycles with miniflare protocol and the authors pointed that this protocol is preferred in cases with poor ovarian reserve, as a result study indicated poor ovarian reserve to be the main underlying etiology for EFS (18). Altered granulosa cell function and metabolism were shown to result in significantly lower estradiol concentrations on the day of hCG in women with EFS (14). An ongoing granulosa cell apoptosis has been shown in previous studies and it was also stated that the neither gonadotropins nor the IGF-1 is effective to prevent this ongoing process (19). Additionally, study indicated the importance of neighbouring theca cells and local factors in the regulation and apoptosis of follicular cells (19). This data was confirmed in another study indicating increase in the percentage of cells undergoing apoptosis in women undergoing IVF with day 3 serum FSH > or = 10 mIU/mL compared to women with day 3 serum FSH < or = 6 mIU/mL (20). Furthermore, higher rate of granulosa cell apoptosis was shown in women aged > 37 with poor ovarian reserve (21). A significant impact of duration of infertility on intrauterine insemination cycles was shown in a recent study, authors concluded that, by increase in the duration of infertility the outcome of assisted reproductive techniques -IUI will be decreased markedly (22). In contrast to this finding we found a positive correlation between duration of infertility and at least one oocyte yield following oocyte pick-up procedure.

Our data showed that, despite the presence of mature follicles visualized at transvaginal sonography, presumed increased granulosa cell apoptosis secondary to age and/or poor ovarian reserve lead to decreased peak estradiol level which has significant predictive value for failure of oocyte harvest with transvaginal follicle aspiration. Therefore these cases may be candidates for luteal phase stimulation following oocyte pick up procedure as the recent review indicated double stimulation to be associated with shorter time for retrieving mature oocytes especially in cases with no oocytes were retrieved in the same conventional IVF (12), so the cut off for peak estradiol suggested in our study may be utilized to determine candidates to inform and prepare for double stimulation. The main disadvantage of this study was lack data regarding the rate of granulosa cell apoptosis in cases with no oocyte yield.

In conclusion, cut off value for the peak estradiol level proposed in this study may be used to determine candidates for double stimulation.

References

1. Kim JH, Jee BC. Empty follicle syndrome. Clin Exp Reprod Med. 2012 Dec;39(4):132-7.
2. Uygur D, Alkan RN, Batuoğlu S. Recurrent empty follicle syndrome. J Assist Reprod Genet. 2003 Sep;20(9):390-2.
3. Reichman DE, Greenwood E, Meyer L, Kligman I, Rosenwaks Z. Can in vitro fertilization cycles be salvaged by repeat administration of intramuscular human chorionic gonadotropin the day after failed injection? Fertil Steril. 2012 Sep;98(3):671-4.
4. Zegers-Hochschild F, Fernández E, Mackenna A, Fabres C, Altieri E, Lopez T. The empty follicle syndrome: a pharmaceutical industry syndrome. Hum Reprod. 1995 Sep;10(9):2262-5.
5. Stevenson TL, Lashen H. Empty follicle syndrome: the reality of a controversial syndrome, a systematic review. Fertil Steril. 2008 Sep;90(3):691-8.
6. Hourvitz A, Maman E, Brengauz M, Machtinger R, Dor J. In vitro maturation for patients with repeated in vitro fertilization failure due to "oocyte maturation abnormalities". Fertil Steril. 2010 Jul;94(2):496-501.
7. Tsuiki A, Rose BI, Hung TT. Steroid profiles of follicular fluids from a patient with the empty follicle syndrome. Fertil Steril 1988 Jan;49(1):104-107.
8. MeniruGI,CraftIL. Evidencefromasalvagedtreatmentcycle supports an aetiology for the empty follicle syndrome that is related to terminal follicular developmental events. Hum Reprod 1997 Nov;12(11):2385-2387.

9. Aktas M, Beckers NG, van Inzen WG, Verhoeff A, de Jong D. Oocytes in the empty follicle: a controversial syndrome. Fertil Steril 2005 Dec;84(6):1643-1648.

10. Baum M, Machtinger R, Yerushalmi GM, Maman E, Seidman DS, Dor J, et al. Recurrence of empty follicle syndrome with stimulated IVF cycles. Gynecol Endocrinol 2012 Apr;28(4):293-295.

11. Castillo JC, Garcia-Velasco J, Humaidan P. Empty follicle syndrome after GnRHa triggering versus hCG triggering in COS. J Assist Reprod Genet 2012 Mar;29(3):249-253.

12. Zhang J. Luteal phase ovarian stimulation following oocyte retrieval: is it helpful for poor responders?. Reprod Biol Endocrinol. 2015 Jul 25;13:76.

13. Cohen J, Chabbert-Buffet N, Darai E. Diminished ovarian reserve, premature ovarian failure, poor ovarian responder--a plea for universal definitions. J Assist Reprod Genet. 2015 Dec;32(12):1709-12.

14. Zreik TG, Garcia-Velasco JA, Vergara TM, Arici A, Olive D, Jones EE. Empty follicle syndrome: evidence for recurrence. Hum Reprod 2000 May;15(5):999-1002.

15. Younis JS, Skournik A, Radin O, Haddad S, Bar-Ami S, Ben- Ami M. Poor oocyte retrieval is a manifestation of low ovarian reserve. Fertil Steril 2005 Feb;83(2):504-507.

16. Beck-Fruchter R, Weiss A, Lavee M, Geslevich Y, Shalev E. Empty follicle syndrome: successful treatment in a recurrent case and review of the literature. Hum Reprod 2012 May;27(5):1357-1367.

17. Bustillo M. Unsuccessful oocyte retrieval: technical artefact or genuine 'empty follicle syndrome'? Reprod Biomed Online 2004 Jan;8(1):59-67.

18. Madani T, Jahangiri N. Empty Follicle Syndrome: The Possible Cause of Occurrence. Oman Med J. 2015 Nov;30(6):417-20.

19. Billig H, Chun SY, Eisenhauer K, Hsueh AJ. Gonadal cell apoptosis: hormone-regulated cell demise. Hum Reprod Update. 1996 Mar-Apr;2(2):103-17.

20. Greenseid K, Jindal S, Zapantis A, Nihsen M, Hurwitz J, Pal L. Declining ovarian reserve adversely influences granulosa cell viability. Fertil Steril. 2009 Jun;91(6):2611-5.

21. Y. Fan, L. Wei, Y. Shi, J. Chen, X. Liang. Apoptosis of granulosa cells and clinical outcomes between normal and poor ovarian reserve patients undergoing IVF/ICSI. P-43 Tuesday, October 18, 2016

22. Ahmed K. Allow, Sadek S. M. Abdulmogny A2, Bracamonte Maryam3, Khilood Naji Ghafouri Al- Ani4, Muhammed-Baqir Fakhrildin4 and Wael Muhamad. The Relationship between Duration of Infertility and Intrauterine Insemination: A Multi-Centers Study. Journal of Clinical Developmental Biology 2016; 1(3):1-7