CANCELLATIONS OF PROGRESS OF IN VITRO FERTILIZATION TREATMENT CYCLES DATA OF OUR CLINIC AND CLASSIFICATION

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SUMMARY

Introduction: *A major problem of practitioners of assisted reproductive techniques (ART) is fertile aging, which is defined by the desire to have children in later years of life as a result of most women take an active role in the modern way of life and business life. One of the critical titles of infertility treatment is controlled ovarian hyperstimulation cycle cancellations are related with poor response to gonadortopins, patient incompliance, choosing wrong treatment technique, ovarian hyperstimulation syndrome, embryo transfer procedure problems. This issue also causes money, motivation and time lose for both patients and physicians.*

Aim: *To analyze the clinical and biochemical data of patients for various reasons of canceled IVF cycle in our clinic and to ensure standardization in this regard is to develop a classification.*

Material and methods: *Between the years 2002 and 2009 in our infertility clinic, patients whom are enrolled to IVF treatment and cancelled during KOH, ovum pick-up (OPU) or embryo transfer process were seperated in three main groups by creating a database. The selected datas were; patient age and infertility etiology and during interval as demographic datas, selected gonadotropin regimen and total dose administrated. The main criteria was obtained as the indication of cancellation and timing of the cancellation. Mean, highest and lowest values were shown in the created tables.*

Outcome: *Most of the 175 patients whom were failed to reach the embryo transfer stage were in the group of KOH process (69,7 %). In this particular group the most common indication was poor response to gonadotropins (60 %). In 12 cases (6,8 %) OPU cancellation was done, 8 of the male couple suffered from aspermia. Embryo transfer failure was observed in 23,5 % of patients, in this subgrup the main problem was fertilization failure. The routine implementation of classification system of IVF cycle cancellation which we propose will help evaluating ART failure and the standardization will be provided.*

Key words: *classification of cycle cancellations, IVF cycle cancellation*

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İN VİTRO FERTİLİZASYON SÜRECİNDE GERÇEKLEŞEN SİKLUS İPTALLERİ KLİNİĞİMİZE AİT VERİLER VE SINIFLAMA

ÖZET

Giriş: *Modern hayat tarzı ve kadınların iş hayatında etkin olarak rol almalarının sonucu; fertil yaşlılık olarak tanımlanan geç çocuk sahibi olma isteği yardımcı üreme teknikleri uygulayıcılarının önemli bir sorunudur. Gonadotropinlere zayıf yanıt alınan olgular, ayrıca kontrollü ovaryan hiperstimülasyon (KOH) sürecinde hasta uyumsuzluğu veya yanlış tedavi seçimleri, ovaryan hiperstimülasyon sendromu (OHSS) gelişmesi ya da embriyo transferi ile ilgili sorunların ortaya çıkması halinde hekim ve hasta için zaman, moral ve ekonomik kayıplara yol açan siklus iptalleri infertilitenin kritik başlıklarından biridir.*

Amaç: *Kliniğimizde çeşitli nedenlerle IVF siklusu iptal edilen olgulara ait klinik ve biyokimyasal verileri analiz etmek, bu konuda standardizasyon sağlamak üzere bir sınıflama geliştirmektir.*

Gereç ve yöntemler: *2002-2009 yıllarında kliniğimizde IVF planlanan çeşitli nedenlerle KOH, ovum pick-up (OPU) ve embriyo transfer iptalleri yapılan olgular üç ana gruba ayrılıp veritabanı oluşturularak kaydedildi. Bu olgulara ait veriler demografik veriler; yaş, infertilite süresi ve türü, siklus öncesi menses 3.gün FSH, E2 ve antral folikül düzeyleri, IVF sürecine ait veriler; uygulanan protokol, gonadotropin türü ve toplam dozu, antagonist protokollerde antagonist uygulama süre ve dozu alt başlıklarında analiz edildi. Değerlendirmenin ana kriteri iptal endikasyonu ve zamanlaması olarak belirlendi. Ortalama, üst ve alt değerler sunuldu. Kıyaslamalı tablolar oluşturuldu.*

Sonuç: *Kliniğimizde embriyo transferi aşamasına ulaşamayan 175 siklusun en çok KOH sırasında iptal edildiğini (%69.7) , bu grupta en büyük dilimi %60 ile düşük over yanıtlı hastaların oluşturduğunu görmekteyiz. OPU iptalleri 12 olguda (%6.8) görülmüş olup, bu grupta ilk sırada %4.5 ile testiküler sperm ekstraksiyonunda (TESE) sperm bulunamaması yer almıştır. Embriyo transfer iptali %23.5 oranında olup bu bölümde en önemli oranı %16.5 ile fertilizasyonun gerçekleşmemesi ile sonuçlanan grup oluşturmuştur. IVF siklus ipallerinde önerdiğimiz sınıflamanın rutin uygulanması ile IVF siklus başarısızlıklarının değerlendirilmesi ve istatistiksel analizinde standardizasyon sağlanabilecektir.*

Anahtar sözcükler: *IVF siklus iptali, siklus iptallerinin sınıflması*

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INTRODUCTION

Rapid development of assisted reproductive techniques created a stir over infertile couples and doctors. Succesful outcomes of cases which have no possibility for pregnancy 30 years-ago leads to bigger targets for future.As the modern life style grows up; active roles of women in working-life have made them delay pregnancy plans and resulted in confidence to assisted reproductive techniques,redundantly. In consideration to tuboperitoneal factor related to increase in incidence of sexually transmitted diseases, endometriozis and increasing rates in male factor, possibilty of the IVF failure emerges, regardless of age. IVF processes as a long, expensive and anxious duration may be cancelled before progress to embryo transfer step, thus rsulting in loss of money,time and hope. Cycle cancellation could be encountered in IVF procedure because of some reasons. And this is a significant factor in IVF failure. Although we use the term of cycle cancellation, there is a uncertainity in terminology. Principally, cancellation of IVF cycle includes a description. Suggested classification of IVF cycle is shown in Table I. Although cancellation rates change dependig on the demographic data in various clinics, ovarian response comes into prominence if the male factor is excluded [1]. Based on this study and literature information we give etiologic spectrum of cycle cancellation which is one of the important handicap in infertility treatment and detailed analysis of cases.

Table I: *Classification of the IVF cycle cancellation.*

1. COH[1] cancellation	İncludes cycle cancellation before HCG day
2. OPU[2] cancellation	Failure of the ovum aspiration after HCG day
3. ET[3] cancellation	Failure of the embrio transfer

[1]: controlled ovarian hyperstimulation, [2]: Ovum pick-up, [3]: Embrio transfer

MATERIALS AND METHODS

1848 IVF cycles applied in our clinics between years 2002-2009 were screened retrospectively. 175 cycles of which 163 could not reach embryo transfer step were selected. Cases those stopped in stimulation step were described as cycle cancellation, however cases which could not reach embryo transfer although stimulation is completed and oocyte aspiration is performed are described as IVF progress. Data were collected in demographic and IVF progress maintopics. So that, age,length and etiology of infertility, stimulation protocole in IVF progress data, gonadotropin agent and total given doses, duration of stimulation ad time of cycle cancellation were recorded as demographic data. Final results were determined as cancellation indication and screened data were analyzed in the maingroups of cylce cancellation and stopped IVF progress and also subgroups of these indications. According to these data, subgroups of cycle cancellation were determined as low ovarian response, patient incompliance, anatomic reasons, the onset on OHSS; however, subgroups ofstopped IVF progress were determined as fertilization failure and male factor. Criteria described by Garcia at all were used for low ovarian response (pls look discussion)[2,3]. Because the subgroup of low ovarian response compose a great part of the group, data related to this subgroup were summarized on its own tables.

Thus COH cancellations are low ovarian response, patient incompliance, OHSS,OPU cancellations, absence of sperm in TESE, improper HCG administration, failure to get and transfer embryo due to oocyte factor or techniqual causes.

OUTCOMES

In our clinics between years 2002-2009 175 cycles of 1848 (9,4%) were cancelled and embryo transfer could not be perfromed. In 122 cases (69,7%) cycle was cancelled in COH stimulation step. In 105 ofthese (60%) low ovarian response was detected. Other indications were patient incompliance 7 (4%), uterine pathologies (endometrial polyp,gross myomas) 7 (4% and OHSS 3(1,7%), respectively, In 12 (8,5%) of the patients OPU cancellation weere seen, because testicular sperm could not be obtained via TESE or micro TESE (male factor) from 8 (4.5%) of them and remaining 4 were incompatible patients-3 of them did not come to take HCG, one did not come back to control. In 41 case (23%) whose embryo transfer could not ocur; 31 (17.7%) were not fertilized, 8 had blighted ovum, 1 (0.5%) had servikal stenosis ane 1 had 7cm myoma distroting cavity passage. Mean age of all the case was 34.25(20-44) and mean age of the group with fertilization failure was 35.7 (25-44) and mean age of the others was 32.1 (20-38).

Etiologies of the infertilites were ranked as unexplained infertility 74 (42%), male factor 67 (38%), tubal factor 18 (10%), ovulatory factor 13 (7.4%), mixed 3 (1.7%), respectively. This classification was made depending on pre-cycle 3rd day hormone profile as the primary

Table II: *the percentage distrubation according to causes of IVF process cancellation.*

Cycle cancellation in COH duration			**OPU** cancellation**			**Cancellation of Embrio transfer**		
Low ovarian response	105	% 60	Absence of sperm of TESE	8	%4.5	Failure of fertilization	31	%17.7
Patient incompliance	7	% 4	Patient incompliance	4	%2.3	Empty follicule	8	%4.5
Uterin patologies	7	% 4				Cervical stenosis	1	%0.5
OHSS	3	% 1.7				Uterin patologies	1	%0.5
Total	122	% 69.7		12	%6.8		41	%23.5

**controlled ovarian hyperstimulation, **ovum pick-up*

Table III: *Summary of the demographic and IVF process data in the most extended subgroup cases.*

Causes*	median[1] age	İnf[2] etiology	Time of İnf	Stm[3] protokcole			Stm duration	Mean st dose	Mean. cancellation day[4]
				Ant%	Kısa %	Uzun%			
Low ovarian response	35.7	Unexplained (%47)	8.6	64	6.6	28.5	11.2	4200	13.5
Failure of fertilization	36	Unexplained (%39)	7.5	66	8	26	9.1	3683	-
Patient incompliance	31	Unexplained	2.3	68	6	26	8.6	2355	9.8
OHSS	32	Ovulatuar(%66)	4.1	33	-	66	7.0	2053	7.6
Other	33.5	Male (%72)	6.8	61	10	29	9.4	3024	11.1

**:endication of cycle cancellation, 1: median, 2: infertility, 3: standart, 4: mean cancellation day*

evaluation, sperm analysis, andrology consultation, transvaginal USG and hysterosalphingography. Mean infetility duration of the cases were 8,6 years (1-20) and 24 (13%) of them had pelvic surgery and 16 (9.1%9 had hysteroscopy anamnesis.It was found that 19 (79%) patients who had pelvic surgery was in the low ovarian response group.

During IVF progress, in 116 (66%) cycles antagonist, in 47 cycles (26%) long agonist and 12 cylces (6.8%) short agonist stimulation protocole was applied. It was seen that in low ovarian response cases with similar rates, 68 (64.4%), antagonist 30 (28.5%) long agonist, 7 (6.6%) short agonist protocole was applied. Mean induction duration 9,06 days(3-18), mean stimulation dose was 3100 IU(650-6750) in 3100 cases using recombinant FSH(rFSH), 2760 IU (900-4700) in 54 cases using human menouposal gonadotropin (HMG), 2000 IUrFSH (800-3100) and 1800IU (600-2100) HMG in 20 cases using combined agents. Mean cycle cancellation duration was detected 11 days(3-18). Oocytes were found grade 2 or below in 29 (93%) of 31 cases with fertilizaition failure and mean age of these cases was 36(28-43). The most routinely used tests to predict the ovarian response were 3rd day estradiol and FSH levels, number of antral follicles and aspirated oocytes.

And these parameter were compared in two subgroups as low ovarian response and others, on Table IV. From the cases reported as patient incompliance, 3 of them did not take HCG, 3 did not take her anatagonist, 4 had gonadotropin in one session and lastly one did not come back to control on time resulting in spontenous ovulation.

Table IV: *Group 1, low ovarian response cases. Group 2, failure of fertilization other etiologic subgroups*

	E2	FSH	AFS	AOI
Group1	53,63pg/dl	11.836mlU/ml	1.6	0.8
Group 2	45,27pg/dl	9.47mlU/ml	4.1	9

DISCUSSION

In literature we could not reach similar reported data related to global cancellation rate in IVF cycles. In this retrospective trial, characteristic features of cancelled IVF cycles in our clinics were examined. It is reported that low ovarian response between 9%-24% in related trials(3). The basic factor of rate variation is that there is no concensus in definiton of low ovarian response. It is first described by Garcia at all in 1983 as peak E2 concentration <300pg/ml in response to standart stimulation regimen of 150IU/day HMG administration, low amount of follicle growth, insufficient oocyte obtainment. Today, although different definitions have been made by various criteria; basic criteria are number of growing follicles or number of obtained oocytes. Some authors characterized low ovarian response as < 5 aspired oocytes(4,5), some did <5 aspired follicules(6-8).

The most expressed factors in etiology was high maternal age supported by literature data in our trials (Table I). In a performed IVF cycle, no response to stimulation shows low ovarian response, however some cases may respond normally up to the note of % 64 in another cycle(11). Considering this situation, ıt is impossible to establish a standard approach to low ovarian response, neverthless it is so important to

predict these cases and to develop a appropriate strategies in order to prevent problems mentioned before. For this purpose, lots of ovarian reserve prediction tests were established. Recently, bioactivity and production of GnSAF from moleculer analyses[12] and IGF 1[13] come into prominence as predictive value. Beyond all of these, USG - as a simple and noninvasive method - has a better predictive value in term sensitivity and specifity among of the predictive testes.

Considering retrospectively, in 1997 measurement of ovarian volume[14], ın 1998 account of antral follicules [15] and in 1999 blood flow doppler analyses[16] were the suggested techniques. From this point, ovarian reserve testes aims to measure ovarian response according to her own age in ovarian group and this state is the first step to define the chronologic age in ovarian reserve[17,18]. All these detailed tests help to product that in young woman ovarianresponse may be low, however in a old woman ıt can be high unexpectedly.

Another issue is the situmulates protocoles to perform to these patients. Our clinic tend to administer antagonist protocole in % 64 rate in low ovarian response cases. The aim of this protocole to prevent premature LH peak and to eliminate suppressor effect of GNRH analogs[19] over ovarian receptors via adjusting follicules to gonadotrophine. Two studies were published supporting to flare up agonist protocoles. One of them was prospective randomized[20] trial showing advanced pregnancy outcomes and the other was retrospective case control trial[21].

This protocole results in less cycle cancellation, more amount of oocyte obtainment, but no marked change in pregnancy results. In our study, our clinics prefers antogonist protocole in approach to low ovarian response cases, although there is no control group of normal ovarian response. When compared to other cases these could not completed for some reasons. It is realized that IVF process in low ovarian response cases total induction dose, median patient age and excess of inductive duration are in concordant to literature data.

When we looked cycle cancelled cases because of OHSS it is seen that we have 32 moderate and severe OHSS cases hospitalized; these of which were cycle cancelled. Characteristic of OHSS cases were analyzed in another assay, but in here we see that appropriate cases should be selected and cycle may proceed via costing effect.

We have mentioned before that IVF process is lond and challenging duration. Patient have active roles in IVF process so that they are needed to informed in detail by nurses, doctors and all other medical person. We think that in our clinics nurses, doctors and assistant doctors fullfill their mission. However, we believe that it should be taken care to the patient communication because of patient incompliance related % 6 cycle cancellation rate. Another important point was that endometriums of three cases whose cycle were cancelled because of endometrial polyp were natural infact. It was though that these polyps generated or realized durind situmulation from this point, we should make outpatient hysterescopic evaluation before IVF in order to prevent cycle cancellation and IVF failure, especially for irregular cavities.

In our clinics, instructors manage IVF cases in rotation and ther is no consensus in approach to myomas in infertility treatment so that in five cases other instructors prefered cycle cancellation whereas other started the cycle. In one case, embrio transfer couldnot be performed for cervical stenosis.

The most important reason of the fertilization failure is accepted as ovarian aging related to decrease of the oocyte quality expressed in literature and laboratuary mistakes are not found meaningfull.

In conclusion, becuse of poor oocyte quality infertilized 29 cases and 113 low ovarian responded IVF cases compose of % 81 of the 175 disturbed cases in transfer step of IVF process and it is important to develop alternative treatment as long as pregnancy is delayed older ages.

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