

## Original Research Articles

# Should a waiting period between consecutive IVF cycles be advised for normal or low responders?

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The purpose of this study is to examine the impact of the time elapsed between repeated oocyte retrievals, on the number of oocytes retrieved, according to the ovarian response of the patient.

This retrospective cohort study, found no correlation between the time interval between consecutive oocyte retrievals of 30 up to 180 days and the number of oocytes or mature (MII) oocytes retrieved, neither in patients with low response with up to 4 oocytes retrieved nor those with 5 oocytes or more.

## INTRODUCTION

As most patients fail to achieve a pregnancy in their first IVF -ET treatment cycle, the question regarding the optimal time frame to induce a subsequent IVF is raised frequently, and many patients request advise whether or not a waiting period is advisable before the consecutive treatment cycle. The number of retrieved oocytes in an IVF cycle represents a major parameter which has been shown to correlate directly with the chances to achieve livebirth.<sup>1</sup> The challenge in treating patients with low ovarian reserve to maximize their ovarian response in each treatment cycle is even more acute. In daily practice the decision to use a specific ovarian stimulation protocol is individualized as presently no omnipotent COH exists that would work for each patient. Although the ovarian response may be affected by the interval between each COH and OPU, the literature examining the outcome of repeated OPU according to the time interval between them is scarce and controversial. As presented in [table 1](#), some studies reported no correlation between the interval of the first and subsequent IVF cycle, others reported advantage of short interval, especially in patients with low ovarian reserve.

The aim of our study was to examine the impact of the time elapsed between repeated oocyte retrievals after COH for IVF, on the number of oocytes retrieved, according to the ovarian response of the patient.

## MATERIALS AND METHODS

A retrospective cohort study was conducted including all patients that underwent consecutive IVF-ET at different time intervals in the IVF unit of Barzilai University Medical Center during the period between January 2016 to December 2019. Demographic data as well parameters of ovarian response to the COH and number of oocytes and mature oocytes retrieved was recorded for each treatment cycle.

Two types of comparisons were made. First, the women in the sample were divided into four groups according to the time intervals between treatments: (A) up to 30 days (B) 30 to 60 days (C) 60 to 90 days (D) 90 to 120 days. Second, patients were divided according to time intervals between treatments and according to the number of oocytes retrieved (A) ≤4; (B) > 4 oocytes. Statistical significance was considered lower than 5%.

All patients underwent a GnRH-antagonist protocol for COH, using Gonal-F or Pergoveris (Merck, Germany) and GnRH-antagonist (Cetrotide 0.25mg/day, Serono international SR, Geneva, Switzerland or Orgalutan 0.25 mg/day, NV Organon, Oss, The Netherlands) administered when the leading follicle reached 12-14 mm or serum estradiol reached 400 pg/ml. Final oocyte maturation was induced using dual triggering (Ovitrelle 250 mg/ml (Merck, Germany) and 0.2 mg Decapeptyl (Lapidot, Natania, Israel).

Data were processed in SPSS software version 27. Descriptive statistics were produced using means, standard deviations, and ranges for the continuous variables, and

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**Table 1. Studies on the outcome of consecutive IVF cycles.**

Authors	COH protocol	reported time interval between the first and consecutive IVF cycle	number of oocytes retrieved in the consecutive cycle
Reichman et al. <sup>2</sup>	GnRH-antagonist	35-55 days vs 56-140 days	Similar (164 vs 557 patients)
Pailis et al. <sup>3</sup>	GnRH-antagonist	<45 days vs 45-180 days	Increased (632 low responders)
Bayoglu Tekin et al. <sup>4</sup>	GnRH-antagonist	6 months	Similar (227 normo-responders)
Eppsteiner et al. <sup>5</sup>	Variable	12 months	Increased in patients with normal ovarian reserve (AFC >10) (n=248). Similar in 44 patients with lower ovarian reserve (AFC ≤10).
Hoveyda et al. <sup>6</sup>	long GnRH-a protocol	4 years	Similar (190 normo-responders)
Doldi ei al. <sup>7</sup>	long GnRH-a protocol	5 years	Similar (1350 cycles)

frequencies and percentages for the categorical variables. Comparison between patients in the demographic and clinical variables by time between treatments were assessed using Kruskal Wallis analyzes for the continuous variables (e.g., age), and chi-square tests for the categorical variables (e.g., diagnosis). Demographic parameters, parameters of ovarian response to the COH and number of oocytes and mature oocytes retrieved were compared between the groups.

The collection of data for this study was approved by the Institutional Review Board (no. 0102-20-BRZ)

## RESULTS

From a total of 790 patients included in the study, 254 underwent a consecutive OPU within 30 days (group A), 202 within 30-60 days (group B), 178 within 60-90 days (group C), and 156 within 90-120 days (group D). The ratio of patients with ≤4 oocytes retrieved was 54.3, 52.9, 54.5 and 48.0, in the four groups, accordingly.

The demographic parameters of all patients included in this study, according to the time interval groups is presented in [Table 2](#). Comparing demographic parameters, the average age in group A, was significantly higher than group D. No differences were found in number of pregnancies/deliveries in the past, BMI, ovarian reserve according to AFC and prevalence of baseline FSH less than 10 IU between the groups. The main indication for IVF was male factor.

The comparison of parameters of the age, BMI, COH and ovarian response, between the first and consecutive treatment, according to the four groups of time interval between the oocyte retrievals, is presented in [Table 3](#).

In the group of patients with a consecutive cycle within 30 days, in their consecutive cycle the dose of gonadotropin administered was lower and the number of oocytes retrieved was lower, but the number of mature oocytes retrieved was similar.

In the group of patients with a consecutive cycle within 30-60 days, in their consecutive cycle the dose of go-

nadotropin administered was higher and the number of follicles was higher, but the number of oocytes and mature oocytes retrieved was similar.

In the group of patients with a consecutive cycle within 60-90 days, none of the parameters examined differed in their consecutive cycle.

In the group of patients with a consecutive cycle within 90-180 days, none of the parameters examined differed in their consecutive cycle.

The comparison of parameters of the age, BMI, COH and ovarian response, between the first and consecutive treatment, according to the time interval between the treatments and according to the number of oocytes retrieved (≤4 or ≥5) is presented in [table 4](#).

In the group of patients with a consecutive cycle within 30 days, in their consecutive cycle the dose of gonadotropin administered was lower in both groups of patients with up to 4 oocytes or more. However, the number of oocytes and mature oocytes retrieved was similar in both groups of patients with up to 4 oocytes or more.

In the group of patients with a consecutive cycle within 30-60 days, in their consecutive cycle the dose of gonadotropin administered was higher in both groups of patients with up to 4 oocytes or more. However, the number of oocytes and mature oocytes retrieved was similar in both groups of patients with up to 4 oocytes or more.

In the group of patients with a consecutive cycle within 60-90 days, in both groups of patients with up to 4 oocytes or more, none of the parameters examined differed in their consecutive cycle.

In the group of patients with a consecutive cycle within 90-180 days, in both groups of patients with up to 4 oocytes or more, none of the parameters examined differed in their consecutive cycle.

## DISCUSSION

Among the parameters that may impact ovarian response is the interval between each COH and OPU, but there is

**Table 2. Demographic parameters, according to the time interval groups.**

	Consecutive cycle Within 30 days (n=254)	Consecutive cycle Within 30-60 days (n=202)	Consecutive cycle Within 60-90 days (n=178)	Consecutive cycle Within 90-180 days (n=156)	P
Age	37.10 (5.08)	35.19 (5.96)	35.74 (5.37)	32.64 (6.00)	<.01
# of pregnancies	0.88 (0.89)	1.04 (1.35)	0.90 (1.35)	1.16 (1.36)	.71
# of deliveries	0.37 (0.62)	0.54 (0.85)	0.46 (0.65)	0.43 (0.65)	.43
BMI	27.15 (5.63)	26.58 (5.62)	26.79 (6.26)	26.31 (6.24)	.70
AFC	10.44 (4.95)	10.37 (3.58)	11.37 (6.41)	12.48 (4.77)	.89
FSH					
< 10 IU/L	72%	68%	69%	62%	
>10 IU/L	28%	32%	31%	38%	
Main indication for IVF					
Male	64.2%	65.3%	50.0%	60.6%	
Anovulation/PCO	15.8%	0	7.0%	11.9%	
Unexplained	20.0%	15.1%	23.2%	13.5%	
Mechanical	0	10.2%	13.5%	10.5%	
Endometriosis	0	9.4%	6.3%	3.5%	

no consensus regarding the optimal time frame to induce a subsequent IVF cycle when the first one was unsuccessful.

Interestingly, the literature examining the outcome of repeated OPU according to the time interval between them is controversial and lacks uniform methodology and time frames. Reviewing the relevant literature, we noted that some studies reported no correlation between the interval of the first and subsequent IVF cycle and the number of oocytes retrieved, others reported advantage or no advantage of a short interval, either for normal responders or in patients with low ovarian reserve. As presented in [Table 1](#), the reported time interval between the first and consecutive IVF cycle in the various studies was variable, ranging from 35-55 days vs 56-140 days; <45 days vs 45-180 days; 6 months; 12 months; 4 years; 5 years. The number of oocytes retrieved in normal responders as well as in low responders was comparable or increased in the various reports, leaving no possibility for deduction of clear conclusions.

In a study by Reichman et al.,<sup>2</sup> including 164 normal responders when consecutive cycle was performed within 35-55 days (representing one full menstrual cycle), the number of oocytes retrieved was similar compared to 557 women with a consecutive retrieval within 56-140 days. In all patients similar GnRH-antagonist protocol was used. In a study by Eppsteiner et al.<sup>5</sup> including 292 women, when a consecutive cycle was performed within 12 months, the number of oocytes retrieved increased in patients with normal ovarian reserve (AFC >10) (n=248). Variable COH protocols were used. The increase in the number of oocytes was

small but significant (mean difference +1.8 oocytes, range -18 to +25) and mature oocytes (+1.8 oocytes, range -16 to +18). The only independent factor related to this effect was found to be the gonadotropin dose administered. However, for 44 patients with lower ovarian reserve (AFC ≤10), this effect was not observed. In a study by Hoveyda et al.<sup>6</sup> including 190 normal responders treated by long GnRH-agonist protocol, when three consecutive cycle was performed within 4 years, the number of oocytes retrieved was similar compared to that in their first cycle. Doldi et al.<sup>7</sup> reported a study including 400 women treated by a long protocol of GnRH-agonist who underwent three consecutive IVF cycles: during a period of 5 years. A fourth cycle was performed in only 150 patients. A total of 1350 cycles was analyzed to evaluate the ovarian performance in women of different ages in consecutive cycles. Comparing subsequent cycles versus the first treatment cycle they found no significant differences in serum estradiol levels, number of follicles produced, or oocytes retrieved. They observed a statistically increased number of ampules of recFSH needed to reach follicle maturation (p= 0.05) but higher doses of gonadotropin in consecutive cycles in each age group did not result in differences in number and quality of oocytes. The exact time interval between the first and the consecutive cycles was not presented or analyzed. Bayoglu Tekin et al.<sup>4</sup> in a study including 227 normo-responder women, treated by GnRH-antagonist protocol, reported comparable number of oocytes and mature oocytes retrieved in the first or the consecutive cycle, performed within an interval period of up to 6 months. In a study by Pailis et al.<sup>3</sup> including 632 low

**Table 3. Comparison of parameters of the age, BMI, COH and ovarian response, between the first and consecutive treatment, according to the time interval between the oocyte retrievals.**

Consecutive cycle Within 30 days (n=254)	1st cycle	Consecutive cycle	P=
Age	37.10 (5.08)	37.22 (4.92)	.782
BMI	27.15 (5.63)	27.59 (4.92)	.851
Parameters of COH			
Length of treatment (days)	10.50 (0.70)	11.13 (0.93)	.067
Total dose of GN (IU)	3600 (1908)	3132.5 (1189)	.028
Parameters of ovarian response			
Peak Estradiol	2434 (907)	2462 (924)	ns
Progesterone	1.30 (0.70)	1.32 (0.75)	ns
Endometrial thickness	10.33 (2.19)	11.33 (2.19)	ns
# of follicles	7.00 (2.82)	7.16 (0.75)	.682
# of ova	15.55 (0.92)	13.67 (1.13)	.037
# of mature ova	7.23 (1.34)	7.65 (1.54)	.187
Consecutive cycle Within 30-60 days (n=202)	1st cycle	Consecutive cycle	P=
Age	35.19 (5.96)	35.32 (6.21)	.923
BMI	26.58 (5.62)	27.10 (7.22)	.684
Parameters of COH			
Length of treatment (days)	10.88 (3.03)	11.13 (0.93)	.201
Total dose of GN (IU)	2766 (1662)	3172.5 (1188.9)	.002
Parameters of ovarian response			
Peak Estradiol	1593 (917)	1593 (917)	ns
Progesterone	0.70 (0.40)	0.70 (0.40)	ns
Endometrial thickness	10.33 (2.19)	10.13 (1.65)	ns
# of follicles	5.00 (2.12)	5.87 (2.32)	.021
# of ova	10.50 (0.70)	9.36 (0.85)	.172
# of mature ova	4.50 (0.78)	4.30 (0.48)	.797
Consecutive cycle Within 60-90 days (n=178)	1st cycle	Consecutive cycle	P=
Age	35.74 (5.37)	35.93 (5.38)	.887
BMI	26.79 (6.26)	27.10 (7.82)	.691
Parameters of COH			
Length of treatment (days)	9.60 (1.26)	9.42 (1.03)	.301
Total dose of GN (IU)	1680.75 (617.25)	1684.5 (342.75)	.893
Parameters of ovarian response			
Peak Estradiol	2250 (1688)	2352 (1338)	ns
Progesterone	1.22 (0.59)	1.32 (0.56)	ns
Endometrial thickness	10.15 (2.02)	9.84 (2.02)	ns
# of follicles	5.60 (4.16)	5.86 (4.36)	.102
# of ova	10.33 (6.80)	9.33 (5.71)	.067
# of mature ova	4.67 (2.10)	4.31 (3.45)	.891
Consecutive cycle Within 90-180 days (n=156)	1st cycle	Consecutive cycle	P=

Consecutive cycle Within 30 days (n=254)	1st cycle	Consecutive cycle	P=
Age	32.64 (6.00)	33.23 (7.10)	.208
BMI	26.31 (6.24)	27.99 (7.12)	.392
Parameters of COH			
Length of treatment (days)	10.54 (1.89)	9.87 (1.82)	.533
Total dose of GN (IU)	2115 (1167)	2088.75 (1077)	.182
Parameters of ovarian response			
Peak Estradiol	1710 (799)	1780 (812)	ns
Progesterone	1.09 (0.88)	1.13 (0.88)	ns
Endometrial thickness	10.04 (3.21)	9.87 (2.89)	ns
# of follicles	5.31 (3.14)	5.21 (2.46)	.298
# of ova	10.17 (2.85)	9.82 (2.85)	.091
# of mature ova	4.33 (2.06)	4.54 (2.06)	.578

responders, when a consecutive cycle was performed within <45 days, the number of oocytes retrieved and the number of available embryos was increased ( $p=0.03$  and  $0.023$ , accordingly) compared to those with a consecutive retrieval within 45-180 days. The rate of ongoing pregnancy and live birth was similar.

Moreover, a relatively new concept of COH for low responders was introduced, named DuoStim, including two consecutive ovarian stimulations performed within the same ovarian cycle.<sup>8-11</sup> That is, the interval between the first OPU and the start of the consecutive COH is several days. Comparing the number of oocytes retrieved, several studies reported an increase of the number of oocytes retrieved in the second cycle.

Our study cannot be directly compared to studies on DuoStim, as the consecutive treatment was not initiated in the same menstrual cycle. There is a possibility that ovarian stimulation in the first attempt may influence follicles that will reach maturation during the second wave of stimulation. Our results show that the number of mature oocytes retrieved are not correlated with the duration of the interval between consequent COH for IVF, corroborating previous reports<sup>2,4,6,7</sup> for normo-responders, as well as low responders.<sup>5</sup> Our observation in patients with low response do not corroborate the results presented by Pailis et al.<sup>3</sup>

Our study has some limitations. The study was conducted retrospectively, which inherently may carry a risk of selection bias and confounding variables. The lack of randomization and control over the treatment groups could influence the validity of the results. Also, the study's retrospective design might not capture the potential long-term effects of different time intervals on patients' overall fertility and health.

The study was conducted at a single IVF unit in Israel. This may limit the generalizability of the findings, as different patient populations, protocols, and laboratory conditions at other centers could yield different results.

The study includes 790 patients, which might be considered a relatively small group, especially when divided into

subgroups based on ovarian response. A larger sample size could enhance the statistical power and reliability of the results.

The study categorizes the interval durations into specific groups (30-60 days, 61-90 days, etc.), based on the average of 30 days interval between menstruation cycles. Theoretically, different interval durations within these groups could lead to different outcomes.

As the COH protocols used were individualized and not fixed, changes in protocols across cycles and patients could affect ovarian response independently of the time interval. However, as presented in [table 3](#), the total dose of gonadotropins administered did not influence the number of mature oocytes retrieved. In the patients who underwent a consecutive cycle within 30 days, the mean total dose of gonadotropins administered was lower, resulting in less oocytes retrieved, but with similar number of usable, mature oocytes. In the patients who underwent a consecutive cycle within 30-60 days, the mean total dose of gonadotropins administered was higher, with no clinical effect on the mean number of oocytes/mature oocytes retrieved. In our study patients with lower response in their first cycle (up to 4 oocytes retrieved) had similar mean number of oocytes retrieved in their consecutive cycle, irrespective of the interval.

The study primarily focuses on the number of retrieved oocytes as the main outcome measure. As our study was not empowered to examine pregnancy rates, clinical outcomes regarding implantation rate and pregnancies were not presented. Still, the correlation between the number of oocytes retrieved and the live-birth rate is well established in the literature.

In our study, the mean age of patients with the longest interval was lower compared to those with the shortest interval. This might be explained due to less feeling of pressure by the time passing without a consecutive cycle or because of having cryopreserved embryos, which delayed the need for a consecutive OPU. The mean BMI and ovarian reserve markers (AFC, baseline FSH) were similar among the

**Table 4. Comparison of parameters of the age, BMI, COH and ovarian response, between the first and consecutive treatment, according to the time interval between the treatments and according to the number of oocytes retrieved ( $\leq 4$  or  $\geq 5$ )**

		# of ova retrieved $\leq 5$ (n=116)			# of ova retrieved $\geq 4$ (n=138)	Consecutive cycle Within 30 days (n=254)
P=	Consecutive cycle	1st cycle	P=	Consecutive cycle	1st cycle	
.310	7.18 (1.36)	7.02 (1.10)	.542	7.03 (0.75)	6.98 (1.31)	# of follicles
.332	10.02 (1.30)	10.21 (1.01)	.215	2.57 (1.02)	2.85 (1.12)	# of ova
.201	7.56 (1.02)	7.37 (1.32)	.187	1.99 (1.54)	2.10 (1.54)	# of mature ova
.899	37.29 (2.10)	37.32 (3.20)	.782	37.11 (3.22)	36.90 (4.18)	Age
.772	27.69 (2.11)	27.33 (3.41)	.851	27.12 (3.42)	27.02 (4.12)	BMI
.102	11.19 (0.72)	10.76 (1.31)	.127	11.02 (0.83)	10.42 (1.10)	Length of treatment (days)
.039	3198 (1440.75)	3593.25 (1367.25)	.028	3157.5 (1338.75)	3586.5 (1443)	Total dose of GN (IU)
		# of ova retrieved $\leq 5$ (n=95)			# of ova retrieved $\geq 4$ (n=107)	Consecutive cycle Within 30-60 days (n=202)
P=	Consecutive cycle	1st cycle	P=	Consecutive cycle	1st cycle	
.102	5.59 (1.39)	5.12 (2.98)	.074	5.98 (1.12)	4.90 (3.32)	# of follicles
.110	9.10 (0.98)	10.32 (0.98)	.123	3.25 (0.95)	2.82 (0.87)	# of ova
.529	4.21 (0.78)	4.65 (1.01)	.451	1.57 (0.88)	.37 (0.98)1	# of mature ova
.792	35.28 (5.11)	35.01 (2.30)	.863	35.41 (6.21)	35.29 (4.93)	Age
.512	27.19(3.32)	26.45 (3.52)	.484	27.02 (7.22)	26.88 (5.62)	BMI
.340	11.02 (1.93)	10.35 (2.62)	.201	11.33 (0.93)	10.91 (3.03)	Length of treatment (days)
.003	3199.5 (1488.75)	2773.5 (1369.5)	.002	3157.5 (1059.75)	2753.25 (1737)	Total dose of GN (IU)
		# of ova retrieved $\leq 5$ (n=81)			# of ova retrieved $\geq 4$ (n=97)	Consecutive cycle Within 60-90 days (n=178)
P=	Consecutive cycle	1st cycle	P=	Consecutive cycle	1st cycle	
.203	5.56 (5.36)	5.96 (3.46)	.202	5.91 (4.13)	5.42 (3.26)	# of follicles
.102	9.10 (4.35)	10.54 (4.50)	.391	3.13 (6.71)	2.92 (5.53)	# of ova
.656	4.62 (3.45)	4.37 (2.10)	.488	2.16 (3.45)	1.86 (0.98)	# of mature ova
.767	35.73 (5.38)	35.62 (4.52)	.415	36.10 (4.54)	35.94 (5.37)	Age
.586	27.60 (5.82)	26.96 (5.34)	.392	26.82 (5.42)	26.62 (5.44)	BMI
.492	9.42 (2.03)	9.35 (3.26)	.533	9.13 (2.33)	9.87 (3.36)	Length of treatment (days)



		# of ova retrieved 5≤ (n=116)			# of ova retrieved ≥ 4 (n=138)	Consecutive cycle Within 30 days (n=254)
.759	1661.25 (275.25)	1668.75 (617.25)	.312	1705.5 (342.75)	1698 (334.5)	Total dose of GN (IU)
		# of ova retrieved 5≤ (n=81)			# of ova retrieved ≥ 4 (n=75)	Consecutive cycle Within 90-180 days (n=156)
P=	Consecutive cycle	1st cycle	P=	Consecutive cycle	1st cycle	
.389	5.02 (3.66)	5.57 (4.54)	.102	5.51 (3.46)	5.09 (4.63)	# of follicles
.298	9.41 (3.85)	10.02 (3.44)	.188	3.10 (3.44)	2.86 (2.85)	# of ova
.491	4.83 (2.16)	4.03 (3.44)	.752	1.34 (2.06)	1.63 (2.06)	# of mature ova
.390	33.02 (5.82)	32.54 (4.12)	.887	33.45 (6.55)	32.87 (5.31)	Age
.495	28.19 (5.31)	26.56 (5.24)	.691	27.59 (7.12)	26.11 (3.24)	BMI
.877	9.68 (2.82)	10.83 (1.10)	.462	9.92 (1.82)	10.14 (2.89)	Length of treatment (days)
.289	2078.25 (1152)	2126.75 (947)	.893	2098.5 (1077)	2107.5 (1160)	Total dose of GN (IU)

groups. AMH was not recorded as in our country this test is not yet covered by all the health insurance organizations.

One may note that Ratna et al<sup>12</sup> presenting a prediction model based on the Human Fertilisation and Embryology Authority (HFEA) database in UK, aiming to estimate individualized chances of cumulative live birth over three additional complete cycles of IVF, stated that the 'time interval of egg retrieval between the first and second complete cycle' was not shown to be statistically significant predictor of live birth. (11 vs 4 months, 0.95 (0.93 to 1.00), although comparison of the number of oocytes retrieved in consecutive cycles was not reported.

## CONCLUSIONS

In this retrospective cohort study, the time interval between consecutive oocyte retrievals within 30 and up to 180 days, had no correlation with the number of oocytes or mature (MII) oocytes retrieved, neither in patients with up to 4 oocytes retrieved (low responders) nor those with 5 oocytes or more retrieved. Examining our results and those published previously one may deduce that among the various factors determining the specific ovarian response and the number of collectable mature oocytes, the interval between ovarian stimulations does not play a significant role.

As the time interval between consecutive IVF cycles does not represent a significant factor impacting the oocyte yield, a waiting period between treatments has no advantage nor for normal responders neither for low responders.

## STATEMENTS AND DECLARATIONS

- The authors have no relevant financial or non-financial interests to disclose.
- The authors have no competing interests to declare that are relevant to the content of this article.
- All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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