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Consequences of Asynchronous Follicle Growth during Controlled Ovarian Stimulation: Management Strategy

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Abstract

GnRH antagonists protocol for controlled ovarian stimulation (COS) in IVF can cause an asynchronous ovarian growth that may interfere with cycle outcome. In this retrospective study, 313 antagonist cycles with a leading follicle ≥ 16 mm detected on first control were compared to 247 controls. If an asynchronous follicle and E2 less than 600 pg/ml were detected, antagonist was delayed. Main objective of this study was to verify if asynchronous cycle management strategy was able to overcome possible adverse cycles outcomes compared to synchronic cycles. Both groups were comparable in terms of age, antral follicle count, starting dose, OC pill use or male factor. In the asynchronous group, a higher number of cystic follicles were seen but no significant differences were found in stimulation length, final follicle number, E2 level, number and mature ovocytes or embryo number and quality. Fecundation rate was higher with lower implantation and cancellation rate. No differences were found in pregnancy rate, miscarriage rate, multiple pregnancy rate or live birth rate.

Our strategy allowed us to reach similar stimulation length with lower cancellation rate and no differences on final follicle number and E2. No impairment in ovocyte quality was detected as no differences appeared in ovocytes or embryos parameters fecundation rate was higher. Nevertheless, implantation rate was significantly lower in the asynchronous group pointing at a deleterious effect in endometrial receptivity.

Keywords: Ovarian stimulation; IVF; Synchronic follicular growth

Introduction

Cycles of controlled ovarian stimulation (COS) with GnRH antagonists for *in vitro* fertilization (IVF) have become the most commonly used protocol in IVF centres. Since first studies [1] found worst IVF outcome compared to long protocols with GnRH agonists, later publications [2,3] have proved similar results in terms of clinical pregnancy rates and live birth rates. Current use of antagonist protocol is preferred because it requires less stimulation time, lower gonadotropin doses and consequently a lower cost [4]. Another important fact is that by using antagonist protocol, trigger can be done with GNRH analogues reducing significantly hyperstimulation risk [5,6].

Nevertheless, antagonist cycles tend to cause an asynchronous ovarian growth with an early dominant follicle leading and heterogeneous size follicle cohort [4]. During COS, antral follicles are required to grow co-ordinately in response to exogenous gonadotropins to accomplish simultaneous functional and morphological maturation. Marked follicular size discrepancies are related to differences in follicles sensitivity to FSH and un-satisfactory maturation. This phenomenon potentially reduces the number of viable oocytes and embryos and the probability of conception [7,8]. This asynchrony may constitute a plausible explanation for the putative poorer IVF-embryo transfer (ET) outcome with GnRH antagonist detected in firsts RCT when experience with antagonists protocols was more limited [1]. Management of asynchronous cycles can be problematic since early antagonist introduction may reduce smaller follicle growth and too late antagonist initiation can cause a premature LH surge, interfere with ovocyte maturation and quality or with endocrinal milieu and endometrial receptivity. We propose a strategy in which if a leading follicle of 16 mm was detected, antagonist was delayed until E2 reached 600 pg/ml or until another follicle reached 14 mm. By ignoring the early growing follicle, we pretend to get more follicles from the cohort and to prolong the cycle and consequently to get more mature oocytes. Main objective of this study was to check whether our strategy with asynchronous cycle management was able to correct possible adverse impact of asynchrony. For that purpose, we compared those cycles to ovarian stimulation cycles were follicular growth was synchronous.

Materials and Methods

We underwent a retrospective case control study including 560 antagonist stimulation cycles in Human Reproduction Unit, Hospital 12 de Octubre in 2013. Cases were 313 antagonist cycles with a leading follicle ≥ 16 mm detected on first control,

between forth or sixth stimulation days were compared with 247 controls. Controls were patients with no follicle of more than 15 mm on first control (S4-S6). First stimulation control was fixed between forth or sixth stimulation days depending of internal organisation.

Controlled ovarian stimulation cycle with GnRH antagonist protocol started on second or third day of cycle. In all patients a transvaginal ultrasound was done to check there were no follicles of more than 10 mm before starting stimulation. Gonadotropin dose was chosen according to BMI, ovarian antral follicle count, day 3 FSH; patient age or previous cycle response. We used recombinant FSH and additional LH effect (recombinant LH or HMG) was reserved for patient with suspected impaired ovarian reserve. Follicle growth was monitored every 48 or 72 h by transvaginal ultrasound; oestradiol measurement was done at each control visit.

If an asynchronous follicle was detected, antagonist was delayed until E2 reached 600 pg/ml. In control group, antagonist was introduced when main follicles got to 14 mm and E2 was above 400 pg/ml. In control group, with synchronic follicle growth, antagonist started when leading follicles were at 14 mm and E2 was above 400 pg/ml or when E2 was higher than 600 pg/ml even thaw follicles were still small.

First outcome was live birth rate and secondary ones were number of mature oocytes, fertilization rates, number of embryos; number of good quality embryos; implantation rates; cancellation rates, pregnancy rates. Variables concerning patient's characteristics and cycle evolution were also reported.

Descriptive statistics for categorical variables were expressed as the percentage (%), whereas continuous variables were expressed as mean ± standard deviations. The Chi- square (χ^2) test was used to compare categorical variables. The Student t test was used to compare continuous variables. Normality of continuous variables was verified with Shapiro-Wilk test. Variance equality was tested with levene test. A p value of less than 1.5 was considered to be statistically significant. All the statistical analyses were performed using the programme Stata 13.0 (STATA Corporation, College Station, Texas). No specific ethic approval was necessary as the study was a retrospective review design based on electronic patient's chart review and intervention was proposed (Orden 730/2004, de 30 de junio, del Consejero de Sanidad y Consumo de la Comunidad de Madrid) . Before IVF treatment informed concerned was signed allowing medical data to be used for medical investigation.

Results and Discussion

Incidence

In our clinic, 55.89% of antagonist cycles had an early growing leading follicle measuring more than 15 mm before S6. No statistical differences were found when comparing case and control group in terms of patient's age, day 3 FSH; antral follicle count or associated male factor. Use of hormonal contraception in previous cycle was not significantly different in the two groups **(Table 1)**.

Table 1 Patients characteristics.

	No Follicle<15 mm at Stimulation day 4-5	Follicle>15 mm at Stimulation day 4-5	P value
Age (mean ± SD)	34.56 ± 3.74	34.79 ± 3.71	0.48
Antral follicular count (mean ± SD)	11,65 ± 7.01	11.17 ± 6.51	0.32
Day 3 FSH (mean ± SD)	8,67 ± 7,3	7.85 ± 6.08	0.24
REM (mean ± SD)	11.54 ± 13.7	12.30 ± 15.01	0.56
Previous oral contraceptive (%)	29.7	27.79	0.57
Initial FSH dosage (IU) (mean ± SD)	335.35 ± 106.06	331.20 ± 106.45	0.65
Initial LH dosage (IU) (mean ± SD)	172.63 ± 123.82	163.98 ± 106.86	0.39

Cycle characteristics

Stimulation was longer in synchronic group (9.39 vs. 9.10 days) but no statistical significance could be detected in sense. In first control, from day 4 to day 6 stimulation day, the number of follicles over 14 mm (14-15 mm) was higher in cycles with an early dominant follicle ($p<0.05$). Oestradiol level in first control was logically higher in asynchronous group ($p<0.05$). At the end of stimulation, they were similar number of follicles of 16 mm or more, potentially having mature oocytes in both groups but cystic follicles over 22 mm were more when there had been an early dominant follicle ($p<0.05$). No differences were found in final E2 level **(Table 2)**.

Table 2 Cycle characteristics.

	No Follicle<15 mm at Stimulation day 4-5	Follicle>15 mm at Stimulation day 4-5	P Value
Stimulation length (d) (mean ± SD)	9.39 ± 1.43	9.10 ± 2.18	0.07
N° of follicles between 14 and 15 mm in S4-6 (mean ±SD)	0.98 ± 1.47	1.34 ± 1.78	0.009
N° of follicles>16 mm (mean ± SD)	0	2.32 ± 2.97	0.0001
E2 in S4-6 (mean ± SD)	89.60 ± 52.91	713.44 ± 489.57	0.0001
N° of follicles>15 mm day of HCG (mean ± SD)	6.13 ± 4.16	6.55 ± 3.89	0.22
N° of follicles>22 mm día de HCG (mean ± SD)	0.63 ± 1.13	0.96 ± 1.34	0.002
E2 (pg/ml) day of HCG (mean ± SD)	1943.86 ±1209.32	1962.68 ± 1106.34	0.85

Cycle outcome

No differences were found in oocytes number, mature oocyte rate or atresic oocytes rate. Nevertheless, a higher number of immature oocyte was observed in the control group. Fertilization rate was significantly higher in patients with an early dominant follicle (62.9% vs. 59.5%; p<0.05). Number of obtained embryos and good quality embryos, or even good quality embryo rate, were more favourable in case group but differences didn't reach significance. An important difference was observed in implantation rate: 16.39% in control group vs. 9.47% in cases (p<0.05). Pregnancy rate, multiple pregnancy rates, miscarriage rate and live birth rate appeared to be similar in both group.

Cancelation rate was defined, as cycles where no transfer was possible: cancelled oocyte pick-up, no available embryos or cancelled embryo transfer because of hyperstimulation risk. Cancelation rate was significantly lower in asynchronous cycles: 22.98% vs. 7.96% **(Table 3)**.

Table 3 Cycle outcome.

	No Follicle<15 mm at Stimulation day 4-5	Follicle>15 mm at Stimulation day 4-5	P Value
N° of oocytes (mean ± SD)	7.85 ± 6.19	7.16 ± 5.55	0.28
N° of MII oocytes (mean ± SD)	4.63 ± 3.65	4.83 ± 3.51	0.55
N° of Immature oocytes (mean ± SD)	1.34 ± 1.62	1.01 ± 1.26	0.019
Ratio: MII/immature oocytes (%)	3.36	3.31	0.9
N° of atresic oocytes (mean ± SD)	1.19 ± 0.11	1.03 ± 1.48	0.25
Ratio: MII/atresic oocytes (%)	2.99	3.35	0.52
Fecundation rate (%)	59.5	62.9	0.03
N° good quality embryos (mean ± SD)	0.85 ± 1.28	1.01 ± 1.34	0.18
N° of embryos (mean ± SD)	3.34 ± 2.68	3.4 ± 2.62	0.81
Ratio: good quality embryos/available embryos (%)	0.07	0.14	0.22
Nº embryos transferred (mean ± SD)	1.85 ± 0.59	1.84 ± 0.56	0.84
Implantation rate (%)	16.39	9.47	0.006
Pregnancy rate (%)	21.25	24.19	0.57
Multiple pregnancy rate (%)	13.64	15	0.84
Miscarriage rate (%)	4.18	6.99	0.97
Live birth rate (%)	17.7	16.56	0.82
Cancelation rate (%)	22.98	7.96	0.0001

Discussion

Incidence

Incidence of asynchronous and fast ovarian growth was as high as 55.89% in our antagonist cycle series. Asynchrony has already been described when using antagonist stimulation protocols in which there is no endogenous down-regulation like in long agonist protocol [4]. Accelerated follicle growth has been associated to lower ovarian reserve [9] and it is important to note that in our centre 53% of our patients were classified as low ovarian reserve. Nevertheless, no difference could be found between patient's age, antral follicular count, day 3 FSH or gonadotropin starting dose for ovarian stimulation.

A plausible mechanism for irregular follicle growth, involves the premature, gradient FSH elevation that occurs during the late luteal phase in the menstrual cycle [10]. During the luteal-follicular transition, FSH preserves early antral follicles from atresia and ensures their subsequent growth [11]. Previous oral contraception would have avoided small luteal phase FSH elevation than could determine initial growth of most sensitive follicles. Nevertheless, in our study, previous contraception treatment didn't seem to have any effect on early follicular growth incidence.

Beside all those finding, as all patients had an ultrasound to check there was no follicle oversized (>10 mm) before COS, asynchronous follicle growth would rather correspond to an abnormal dynamic of natural folliculogenesis in our population even though we couldn't correlate it with low ovarian reserve. Experimental studies have demonstrated a shortened follicular phase in ovulatory older women caused by a shortening in early follicular phase related to an advanced selection of dominant follicle [9].

Cycle Characteristics

Criteria for triggering are the same in all cases (more than 3 follicles of more than 18 mm), that will justify the fact that no differences were found in the number of follicles of more, 15 mm and the final E2 level and the length of stimulation. In the first control, in patients with a follicle of more 16 mm or more, it appeared more likely to find more follicles of 14-15 mm pointing at a specially accelerated folliculogenesis in that kind of patients.

Cycle outcome

Even if a slight (although not significant) shortening in cycle was observed when a big follicle was detected on first control, no differences were found in oocytes maturity or atresic rate neither in total oocyte number or metaphase II oocyte number. This could be a justified by a correct folliculogenesis in terms of oocyte maturation besides initial speed and besides the fact than a higher number of cystic follicles were detected at the end of stimulation. Maintaining the same criteria for ovulation induction should have contributed to reach similar maturity rates. Larger studies would help to confirm those findings.

The finding of higher fertilization rates in patients with an early dominant follicle (62.9% vs. 59.5%, $p<0.05$) may reflect a better quality oocyte but embryo quality didn't confirm it. No significant differences were found when analysing the number of obtained embryos and good quality embryos, or good quality embryo rate. Whether a larger sample size would clarify a possible effect on oocyte and embryo quality remains to be elucidated.

Implantation impairment observed in control group could be explained by a lower endometrial receptivity as no effect on embryo quality could be observed. Previous studies found a negative correlation between progesterone levels on HCG day [12-16] and even to a chronic exposure to progesterone during follicular phase. Final follicular phase progesterone measure is related to oestradiol level [17]. A fast follicle growth could be related to higher progesterone levels since earlier in follicle phase as oestradiol appeared to be higher in first control [18,19]. This hypothesis couldn't be confirmed, as routine progesterone was not measured in our clinical practice.

In our protocol, a very fast follicle growth was not a criterion for cancelation. This allowed us to avoid many early cancelations for mono or oligo-follicular growth, by waiting for the follicle cohort. As only 1.17 % of the cycles reaching oocyte pick-up, were cancelled because of hyperstimulation risk, we can conclude that most of the avoid cancelations are due to an insufficient ovarian response. Delaying antagonist until another follicle had reached 14 mm or E2 above 600 pg/ml, allowed us to collect oocytes with no apparent quality impairment but this strategy could have a detrimental effect on endometrial receptivity.

Conclusion

In GnRH antagonists an asynchronous follicle growth is often observed since first stimulation days with early dominant follicle over 15 mm. In such cases, we propose an expectant management for antagonist initiation in order to allow the rest of the follicle cohort to reach 14 mm or oestradiol level to be above 600 pg/ml. This strategy avoids cancelations for low response and didn't show any impairment in oocyte and embryo quality parameters even though fertility rate was significantly better in asynchronous group. The major inconvenience was a reduction in implantation rate that could be justified by a lower endometrial receptivity. No adverse effect was observed in clinical pregnancy rates or in live birth rates. Further studies with larger series and sequential measure of progesterone levels would be needed to confirm these results. A correct management asynchronous cycle is essential to avoid cancellations and to control a possible negative effect in endometrium receptivity.

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Declaration of Interests

No conflicts of interests were to declare.

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