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Optimization of Ovarian Stimulation After Preparation with Oral Hormonal Contraceptives

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Abstract: Introduction: Ovarian stimulation can be performed in early follicular phase or after pretreatment with OCPs. The aim of this study is to know if OCPs prior to ovarian stimulation improve the results in an IVF cycle. Material and methods: Retrospective case-control study. We included 132 patients (aged 18-40 years) undergoing two consecutive IVF-ICSI cycles (264 cycles). One cycle was initiated without pretreatment and the other after pretreatment with dienogest 2 mg/etinylestradiol 0.03 mg. The dose and type of gonadotropins used was adjusted according to age, body mass index and antral follicle count. During ovarian stimulation, serial ultrasound and analytical controls were performed until the day of ovulation induction and puncture programming. Results: There were statistically significant differences in gestation rates with a higher number of pregnancies in the OCPs group (37.18% vs. 13.95%, p=0.005). The live newborn rate was higher in the group of patients prepared with OCPs (30.77% vs. 5.81%, p=0.005). Total days of stimulation was lower in the OCPs group (8.50 vs. 9.13, p=0.000). There were no statistically significant differences in the total number of oocytes retrieved, metaphase II oocytes or embryo quality. Conclusions: the use of OCPs can be considered as a pre-treatment in an IVF cycle since it allows us to plan ovarian stimulation without worsening the live birth rate.

Keywords: Oral Contraceptive Pill, Live Birth Rate, Controlled Ovarian Stimulation, IVF, ICSI

1. Introduction

Assisted Reproductive Techniques (ART) such as In Vitro Fertilization (IVF) and Intracytoplasmic Injection (ICSI) are the options with the highest success rates for achieving a live newborn in the infertile population [1]. The use of GnRH antagonist protocols has increased significantly in the last 20 years because it achieves similar live birth rates with lower rates of ovarian hyperstimulation syndrome with respect to the classical GnRH agonist protocol [2-4]. Classically, ovarian stimulation begins in the early follicular phase. However, it has been shown that follicular recruitment can occur at any time during the menstrual cycle. From close observation of regular ovarian cycles, completely different follicular dynamics have been described. Different theories speak of continuous recruitment throughout a cycle and others of the production of up to four waves of follicular recruitment with subsequent follicular atresia [5-6].

In addition, human reproductive specialists, motivated to improve the results in patients with poorer reproductive prognosis and with the added benefit of being able to plan treatments, have studied strategies such as the use of oral

hormonal contraceptives (OCP) as pre-treatment in an IVF cycle.

Oral hormonal contraceptives are widely used by women, and at different ages, to prevent pregnancy. Contraceptives consist of estrogens and gestagens that reduce endogenous FSH and LH production by negative feedback on the pituitary gland [7]. Thus, it causes ovarian suppression and, in the absence of an LH peak, ovulation does not occur. In addition, gestagens have the ability to decrease the normal hypothalamic GnRH pulse, resulting in a dual system of pituitary inhibition. The use of combined contraceptives as pre-treatment in an IVF cycle favors the synchronization of follicular development and prevents a spontaneous LH surge [8]. Furthermore, if we consider the management and coordination of a Human Reproduction Unit, the use of oral hormonal contraceptives has been shown to be effective in treatment planning, avoiding day-to-day work overload and, even more so, during weekends and holidays, especially useful in a public health system or private centers with less available resources [9-11]. However, the published evidence regarding efficacy is controversial, with no consensus on the real effect of the advantages of contraception to the detriment of the effect on live birth rates [12, 13].

Considering the debate generated by the multiple publications, we have designed a matched case-control study with the aim of finding out whether contraceptives as a pretreatment for ovarian stimulation improve the results of an IVF cycle in the same infertile woman.

2. Material and Methods

This is a retrospective matched case-control study conducted at the Human Reproduction Unit of the third level public hospital Complejo Hospitalario Universitario Insular Materno Infantil (Las Palmas, Spain) between January 2019 and December 2020. We included 132 patients aged between 18 and 41 years undergoing two consecutive IVF-ICSI cycles. One of the cycles was classically initiated in early follicular phase and the other after pre-treatment with an oral hormonal contraceptive (dienogest 2 mg/ethinylestradiol 0.03 mg), this not being the order of the treatments in all cases.

On the one hand, in those cycles that began in the early follicular phase, an ultrasound control was performed between the first and third day of menstruation with the aim of assessing the endometrium and follicular non-dominance in order to begin the administration of gonadotropins. On the other hand, the cycles that we started after pre-treatment with OCPs, the patients began taking a daily tablet on the first day of menstruation and were scheduled for an ultrasound check-up around tablet 14-16. After confirming ovarian rest, termination of OCP and initiation of gonadotropins was indicated after 5 days of washout. The dose and type of gonadotropins used was adjusted according to age, body mass index and antral follicle count.

During ovarian stimulation, the patients attended ultrasound and analytical controls for the determination of serum estradiol by electrochemiluminescence immunoassay (Cobas by Roche Diagnostics, Basel, Switzerland, European Union). These controls were serialized until the day of ovulation induction and programming of the puncture with subsequent fresh or delayed transfer by elective vitrification of the embryos (risk of ovarian hyperstimulation, endometrial pathology, elevation of serum progesterone). Micronized progesterone 200 mg every 8 hours vaginally from the evening of the day of the puncture was used to support the luteal phase and was maintained until week 12 of gestation with a decreasing pattern from week 10. The b-HCG test was performed 14 days after transfer.

Data analysis was performed using the IBM SPSS statistical package for social sciences version 25 for Mac. A description of the main variables included in the study was made. For qualitative variables, absolute and relative frequencies and percentages were determined. A bivariate statistical analysis was performed to determine the possible associations between the different variables considered; for the association of two qualitative variables, McNemar's test for paired samples was used. For the analysis of differences between quantitative variables, the Student's test for paired samples was used. Statistical significance was established for a $p < 0.05$.

As this was a retrospective study, it was not necessary to fill out an informed consent form on the part of the patients.

3. Results

The data corresponding to 132 patients with a total of 264 cycles initiated in the study period were analyzed. The mean age was 35.34 years for the OCPs stimulation group and 34.75 years for the group initiated in early follicular phase ($p = 0.000$). There were no changes with respect to weight or body mass index between the two stimulations. Likewise, there were no statistically significant differences with respect to the mean antral follicle count at the beginning of each cycle, being 12.04 in the OCPs group (in the ultrasound performed on pill 14-16) and 12.42 in the non-OCP group (in the ultrasound performed between the first and third day of menstruation), with a p value of 0.423 (Table 1).

Table 1. *Patient characteristics at the beginning of the cycle. Data are means (minimum-maximum).*

	non-OCP	OCP	P value
Age (years)	34,75 (22-41)	35,34 (24-41)	0,000 (IC 95% 0,429-0,753)
Weight (kg)	67,08 (46-99)	67,61 (47-105)	0,083 (IC 95% -0,070-1,134)
BMI (kg/m^2)	25,09 (18,73-32,41)	24,91 (18,44-32,41)	0,096 (IC 95% -0,034 – 0,404)
AFR (n)[a]	12,42 (3-42)	12,04 (4-40)	0,423 (IC 95% -1,322-0,558)

a. AFR: antral follicle count.

Regarding the dose of gonadotropins used there were no statistically significant differences, although the total number of days of stimulation was lower in the OCPs group with 8.50 days vs. 9.13 days (p=0.000). Serum estradiol levels on trigger day were similar in both groups (2512.86 pg/ml vs 2540.89 pg/ml, p=0.824), detecting differences with respect to progesterone levels, which were higher in the group that had a previous preparation with OCPs (1.4027 ng/ml vs 1.1641 ng/ml with a p value of 0.005). There were no statistically significant differences with respect to the total number of oocytes retrieved, number of oocytes in metaphase II, number of embryos transferred fresh or number of embryos vitrified (Table 2).

Table 2. *Data corresponding to ovarian stimulation during the IVF-ICSI cycle. Data are means (minimum-maximum).*

	non-OCP	OCP	P value
Total FSH dose (IU)	1956,59 (108-3600)	1867,17 (100-3300)	0,135 (IC 95% -207,115-28,280)
Total dose HMG (IU)	800,90 (262-2725)	687,86 (225-3300)	0,085 (IC 95% -242,144-16,060)
Total days of stimulation (days)	9,13 (6-15)	8,50 (5-13)	0,000 (IC 95% -0,958-(-0,300))
Estradiol (pg/ml)	2540,89 (645-9637)	2512,86 (837-6563)	0,824 (IC 95% -277,202-221,153)
Progesterone (ng/ml)	1,1641 (0,30-8,37)	1,4027 (0,24-4,53)	0,005 (IC 95% 0,0747-0,402)
Rescued oocytes	7,19 (1-28)	7,50 (0-24)	0,497 (IC 95%-0,576-1,181)
MII oocytes	6,05 (0-20)	6,32 (0-24)	0,520 (IC 95% -0,566-1,111)
Embryos transferred in fresh	1,12 (0-2)	1,03 (0-2)	0,370 (IC 95% -0,298-0,112)
Embryos vitrified	0,76 (0-7)	0,93 (0-8)	0,323 (IC 95% -0,164-0,495)

In the group of patients inhibited with OCPs, there was no fresh transfer in 54 of them (40.9%), 16 dues to non-recovery of oocytes during the puncture and 38 dues to elective vitrification. In the group that started stimulation in the early follicular phase, no oocytes were retrieved in 9 patients and there was elective vitrification in 37, so that there was no fresh transfer in 46 patients (34.8%). When embryo quality was studied, no differences were detected between the two groups, 14 patients had good quality embryos in both cycles, 27 only in the cycle preceded by OCPs and 26 only in the group initiated in early follicular phase (p=1.000). With respect to the gestation rate, excluding biochemical gestations, there were statistically significant differences, with a higher number of pregnancies in the group inhibited with OCPs (29 of 78 transfers vs. 12 of 86 transfers, p=0.005). The live birth rate was higher in the group of patients prepared with OCPs with 30.77% vs. 5.81% in the group stimulated in the early follicular phase (p=0.005) (Table 3).

Tabla 3. *Pregnancy outcomes.*

	non-OCP	OCP	P value
Clinical PR (fresh cycle)	13,95% (12/86)	37,18% (29/78)	0,005
LBR (fresh cicle)	5,81% (5/86)	30,77% (24/78)	0,005
Embryos vitrified	17,69% (23/130)	13,17% (17/129)	0,323

4. Discussion

Nowadays, the age of onset of first pregnancy is increasingly older, which means that assisted reproductive techniques are needed more frequently. There are many protocols designed and used for ovarian stimulation during an IVF cycle, with the short protocol with an antagonist being the most widely used today [2-4]. Equally as important as ovarian stimulation with gonadotrophins is prior oocyte preparation, whether with oestrogens, gestagens or oral hormonal contraceptives. With regard to the latter, their high availability and ease of use with few side effects, and the fact that they have an inhibitory effect on the hypothalamic-pituitary axis, has led to an increase in their use in oocyte preparation in recent years.

The studies published so far are very controversial, and this is the first paired case-control study published so far. According to our results, pre-treatment of an IVF cycle with OCPs improves the clinical gestation rate and live birth rate, although there are no differences in the number of oocytes retrieved, number of metaphase II oocytes or embryo quality.

The use of OCPs prior to the initiation of gonadotrophins favors the synchronization of follicular recruitment as well as facilitating the planning of laboratory activity [11]. Early published studies were encouraging about the beneficial effect of OCPs in assisted reproductive techniques [14, 15]. However, a systematic review and meta-analysis published by Griesinger in 2008 [16] showed no statistically significant difference in clinical pregnancy rates between patients receiving OCPs followed by a stimulation protocol with GnRH antagonists and gonadotrophins. In addition, this same author published another meta-analysis in 2010 in which, after analyzing six studies, he concluded that the use of OCPs not only decreases the rate of live gonadotrophins (relative risk: 0.80, 95% confidence interval: 0.66 to 0.97; rate difference: -5%, 95% CI: -10% to -1%), but also increases the duration of stimulation and the use of gonadotrophins [13]. These results have to be considered but with caution, as the six studies included both normo- and poor responders, half of the studies included 30 or fewer patients per arm, different types of OCP were used, different duration of administration (14-28 days) and, most relevantly, different pill-free intervals of 2-5 days. In synchrony with these results, another Cochrane review published later demonstrates a lower live birth and clinical gestation rate in the group prepared with OCPs, without finding clear evidence of a difference between groups with respect to miscarriage rate [17].

Our data are not in agreement with these publications. We observed that there were no differences in the dose of

gonadotrophins used, but there were differences in the number of days, with a lower number of days of stimulation in the group that received OCPs (8.53 vs. 9.13 with a p-value of 0.000). This may lead us to believe that we are more aggressive in the dose used in a patient with OCPs, despite not obtaining statistically significant differences in the antral follicle count. In addition, we did find differences in favour of the OCP group with a higher pregnancy rate (37.18% vs 13.95%) and live birth rate (30.77% vs 5.81%) despite a higher age of women in this group (35.34 vs 34.75 years, p=0.000). In a randomised clinical trial comparing a group of patients who received OCP prior to a short course with antagonists versus another group in which the classical protocol was carried out, when patients received a pill only for 12-16 days, and had a 5-day washout period, no difference in live birth rates was found between the groups [12]. Another randomized controlled trial compared cycle outcome in women who planned their cycles with the pill versus estrogen-only cycle planning, as described above [18, 19]. Again, no difference in live birth rates was found [20].

It is true that the results of the different studies are inconsistent and the comparison between studies is complicated mainly due to the difference in sample sizes, type of OCP used, duration of OCPs and lack of consensus on the washing time prior to the use of gonadotrophins. One of the limitations of our study that may interfere with the results is that the cumulative gestation rate after cryotransfer of vitrified embryos was not analyzed. In addition, the dose of gonadotrophins used during ovarian stimulation was not pre-specified. However, the strength of the study is that the same sample of patients underwent two consecutive protocols.

5. Conclusions

Considering the above, the use of OCP can be considered as pre-treatment in an IVF cycle regardless of the ovarian reserve and the age of the patient. The use of contraceptives allows us to plan ovarian stimulation and, consequently, the activity of the IVF laboratory, saving days of stimulation and all this without worsening the live birth rate. It would be convenient to carry out cost-effectiveness studies in order to demonstrate the hypothesis that the use of OCP as a pre-treatment to the use of gonadotropins in ovarian stimulation improves the efficiency of an IVF cycle.

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