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ARTÍCULO

AÑADIR MEDICACIÓN ORAL A LOS CICLOS DE FIV EN CICLO NATURAL NO APORTA BENEFICIO A LOS RESULTADOS CLÍNICOS.

ADDING ORAL MEDICATION DOES NOT HAVE ANY BENEFIT ON NATURAL-CYCLE IVF RESULTS.

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Conflicto de intereses
Los autores declaran que no existe conflicto de intereses.

Declarations

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RESUMEN

Introducción: En los últimos años, los tratamientos de FIV en ciclo natural y la FIV con estimulación ovárica "suave" están resurgiendo como una opción más segura, económica y cómoda para las pacientes. Definimos FIV en ciclo natural como el tratamiento en el que los ovocitos son obtenidos de un ciclo ovulatorio espontáneo. Cuando añadimos fármacos orales (citrato de clomifeno o letrozol), hablamos de estimulación "mínima". El objetivo de este estudio es clarificar si la introducción de esta medicación es beneficiosa para las pacientes.

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Materials y métodos: Analizamos retrospectivamente los tratamientos de FIV en ciclo natural o con estimulación mínima llevados realizados en nuestro centro de enero 2016 a diciembre 2020.

Resultados: Encontramos diferencias significativas entre los dos protocolos en el número de ovocitos obtenidos después de la punción folicular (1.03 vs 1.63, p<0.001), número de ovocitos maduros (0.9 vs 1.3, p < 0.01), ovocitos fecundados (0.7 vs 1.1, p < 0.01), y número de embriones disponibles para transferencia (0.5 vs 0.7, p < 0.01). Sin embargo, no encontramos diferencias en la tasa de embarazo (26,3% vs 19,6%, p=0.251) ni en la tasa de recién nacido vivo (16.3% vs 14,3%, p=0.7806).

Discusión: Añadir medicación oral a la FIV en ciclo natural no parece tener ningún impacto sobre los resultados clínicos del ciclo. Son necesarios más estudios, pero podríamos reconsiderar la necesidad de añadir esta medicación, ya que supone un mayor coste para los pacientes.

Palabras clave:
FIV con estimulación mínima, FIV ciclo natural, FIV de bajo coste, Medicación oral para FIV.

ABSTRACT

Introduction: In recent years, natural cycle IVF and minimal ovarian stimulation IVF had been undergoing a revival, gaining recognition as safer, cheaper, and more comfortable options for patients. We define natural cicle IVF as the treatment in which oocytes are obtained from a spontaneous ovulatory cycle. When oral drugs are used (usually clomiphene citrate or letrozole), the process is referred to as minimal ovarian stimulation cycle IVF. The aim of this study is to clarify whether the introduction of oral medication is beneficial for patients.

Methods: We retrospectively analysed all natural or minimal ovarian stimulation IVF treatments that took place in our clinic during the studied period (January 2016 - December 2020). Descriptive variables were analysed with a t-test, and a chi-square test was performed on result variables.

Results: We found significant differences, between both protocols, in the number of oocytes obtained after oocyte retrieval (1.03 vs 1.63, p<0.001), number of mature oocytes (0.9 vs 1.3, p < 0.01), fertilized oocytes (0.7 vs 1.1, p < 0.01), and number of embryos available for transfer (0.5 vs 0.7, p < 0.01).However, we did not found signficant differences in terms of pregnancy rate (26,3% vs 19,6%, p=0.251) or live birth rate (16.3% vs 14,3%, p=0.7806).

Discusion: Adding oral medication to natural cycle IVF does not seem to have an impact on the clinical

results of the cycle. More studies are necessary, but we could reconsider the need to add oral medication since they suppose a higher cost for the patient.

Keywords:
Minimal stimulation cycle IVF, Natural cycle IVF, Low cost IFV, Oral medication for IVF.

INTRODUCTION

Although the first successful in vitro fertilizations (IVF)were achieved following the spontaneous ovulation of patients, the natural cycle IVF was gradually relegated by: (a) the use of ovarian stimulation (with clomiphene, gonadotropins, etc.), to obtain a greater number of oocytes; and (b) the introduction of drugs that reduced the risk of spontaneous ovulation (such as gonadotropin-realising hormone agonists and antagonists), in order to reduce cancellation rates and improve cycle profitability(1).

In recent years, natural cycle IVF has been undergoing a revival, gaining recognition as a safer, cheaper, and more comfortable option for patients(2). Due to this recognition, some fertility centers that focus their activity on minimal stimulation or natural cycle in vitro fertilization treatments have emerged, such as the Kato clinics or our own centre(3,4).

In our centre, we attend in our daily practice a population of poor prognosis for fertility treatments: advance maternal age (mean age over 39 years old), history of previous IVF treatments without success (usually from 2 to 3 previous cycles) and low ovarian reserve (mean values of FSH over 10 mUI / mL). In Xthese circumstances, natural cycle IVF could be a good option as the last oportunity with patient's own eggs before considering to move to egg donation. Frequently, clomiphene citrate or letrozole are added during the cycle looking for a high number of retrieved oocytes.

According to the terminology proposed by ISMAAR (The International Society for Mild Approaches in Assisted Reproduction), we define natural cicle IVF (NC-IVF) as the treatment in which oocytes are obtained from a spontaneous ovulatory cycle. When oral drugs are used (usually clomiphene citrate or letrozole), the process is referred to as minimal ovarian stimulation cycle IVF (MS-IVF) (5). This medication is added during the natural cycle of ovulation in an effort to counteract the high cancellation rates that are inevitably associated to natural cycle IVF. However, not all studies that compare both protocols have found an improvement in cycle profitability(6).

The aim of this study is to clarify whether the introduction of oral medication, in order to further support natural cycle IVF treatments, is beneficial to pregnancy and prevents cancellation rates. To do this, we compared ther results from 1285 IVF cycles

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METHODS

We retrospectively analysed all NC-IVF or MS-IVF treatments that took place in our clinic during the studied period (January 2016 - December 2020). The decision whether to use oral medication or not was based on the usual practice of each gynecologist in the clinic, normally based on the preferences of each patient (their desire to avoid medication at all or not), on the experiences with previous cycles (if any) and the antral follicle count obtained in the basal ultrasound on the first 3 days of the cycle.

In the NC-IVF group, ultrasound controls were performed from the beginning of the menstrual cycle until the view of at least one follicle >15 mm. Clomiphene citrate (50-100 mg/day, Omifin) or letrozole (5 mg/day, Femara©) were administered in the MS-IVF group from the third day of the cycle until ovulation induction. Keeping clomiphene citrate or letrozole beyond the usual five days we seek to avoid the selection of only one dominant follicle. Furthermore, daily use of clomiphene citrate until day of triggering block spontaneus LH surge in most of patients, reducing spontaneos ovulation previous to oocyte retrieval (18,19).

In both groups, ovulation triggering was performed with a gonadotropin-releasing hormone (GnRH) agonist (triptorelin, 0.2 mg subcutaneous) when the leading follicle reach more than 15mm. Oocyte retrieval was performed thirty-six hours after triggering.

Anaesthesia was not administrated for oocyte retrieval, and the absence of follicles (observed by ultrasound monitoring) before oocyte retrieval was considered premature ovulation. Non-selective cyclooxygenase (COX) inhibitors, such as ibuprofen, have been shown to substantially inhibit ovulation(7). As some studies show that COX inhibitors do not appear to have negative effects on NC-IVF(8), oral ibuprofen (600 mg /8 h) was administered from ovulation triggering to oocyte retrieval.

The study was carried out in an assisted reproduction clinic specialized in low stimulation or natural cycle-IVF and lower cost therapies. In order for the clinic to run smoothly and to reduce the cost of the treatments, no punctures or embryo transfers were carried out during the weekend, which sometimes forced us to adapt the initial plan on the day selected for the embrio transfer.

In all cases, intracytoplasmic sperm injection (ICSI) was performed, as it is standard protocol in our clinic.

Luteal phase supplementation was administered with intravaginal progesterone 400 mg/day (Utrogestan) until week 10 of gestation or a negative pregnancy test.

The embryo transfer day was decided according to the conditions of standard clinical practice and it was in line with the preferences of the doctors, embryologists, and patients' medical history backgrounds.

Fresh embryo transfer was performed in all cases, except when endometrial thickness was less than 7 mm or progesterone levels ≥ 1.5 ng/ml. In such cases, we cancelled fresh embryo transfer and cryopreserved all embryos. Subsequently, we performed cryopreserved embryo transfer during the next cycle to improve the clinical pregnancy rate.

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Pregnancy tests were performed 10-14 days after embryo transfer, and we considered results of beta-human chorionic gonadotropin (bHCG) > 10 U/L a positive result. Furthermore, we followed up with all patients until after delivery.

Data analysis

All analyses were conducted using R software, version 3.6.2. Descriptive variables were analysed with a t-test, and a chi-square test was performed on result variables.

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RESULTS

During the study period, 401 patients had a total of 1,285 cycles. Of these, 812 (63.2%) were NC-IVF and 473 (36.8%) were MS-IVF; patient characteristics are provided in Table 1. We did not find statistically significant differences between the two groups in terms of any of the variables.

In the MS-IVF group, 289 (62%), the oral medication clomiphene citrate (50-100 mg /24h) was used. In the remaining 177 (38%), letrozole (5 mg/24h) was used.

The average oocyte number obtained after oocyte retrieval was 1.03 (95% CI: 0.96-1.09) from the NC-IVF group and 1.63 from the MS-IVF group (95% CI: 1.5 -1.76), with significant differences between both groups ($p < 0.001$).

We also found significant differences between both groups in terms of the number of mature oocytes (0.9 vs 1.3, $p < 0.01$), fertilized oocytes (0.7 vs 1.1, $p < 0.01$), and number of embryos available for transfer (0.5 vs 0.7, $p < 0.01$). The results are provided in Table 2.

Regarding cancellations, 61.6% of the NC-IVF and 62.5% of the MS-IVF reached oocyte retrieval. No significant differences between both groups were found ($p < 0.78$). The leading causes of cancellation before oocyte retrieval were lack of response (21.2% in NC-IVF vs 25% in MS-IVF) and premature ovulation (12% NC-IVF vs. 7% in MS-IVF).

After oocyte retrieval, the main cause of cancellation in both groups was the absence of an oocyte (23.9% in NC-IVF vs 21.5% in MS-IVF) and the absence of embryos for transfer (13.2% in NC-IVF vs 16% in MS-IVF). No significant differences were found regarding the causes of cancellation.

In total, cancelation rate for NC-IVF was 75.6% and 72.4% for MS-IVF; no differences were found.

We performed fresh embryo transfer on 89.4% of the patients in the NC-IVF group and 70.1% in the MS-IVF group; we found significant differences in this item ($p < 0.001$).

Embryo transfer was performed on day 3 of embryo development in the 47.4%, followed by day 5 (35.2%), day 2 (10.5 %), and day 4 (7%). We did not find differences in the distribution between the two groups.

The pregnancy rate was 26.3% for NC-IVF and 19.6% for MS-IVF. We did not find significant differences between the two groups ($p = 0.251$), nor did we find differences in the live birth rate (LBR) which was 16.3% for NC-IVF and 14.3% for MS-IVF ($p = 0.7806$).

	Natural cycle	Modified natural cycle	P-value
Age (years)	40.48 (95% CI: 40.17-40.79)	40.48 (95% CI: 40.06-40.9)	0.9946
BMI (kg/m^2)	22.32 (95% CI: 21.85-22.79)	22.75 (95% CI: 22.09-23.41)	0.2918
FSHb (mIU/ml)	18.16 (95% CI: 15-21.32)	18.20 (95% CI: 14.54-21.87)	0.986
No. previous IVFs	2.38 (95% CI: 2.12-2.63)	2.56 (95% CI: 2.2-2.93)	0.4133

Tabla 1.- Patient characteristics

	Natural cycle	Modified natural cycle	P-value
No. oocytes	1.03 (95% CI: 0.96, 1.09)	1.63 (95% CI: 1.5, 1.76)	<0.001
MII No.	0.85 (95% CI: 0.79, 0.92)	1.3 (95% CI: 1.18, 1.42)	<0.001
No. P2N2	0.66 (95% CI: 0.6, 0.72)	1.05 (95% CI: 0.94, 1.17)	<0.001
No. embryos	0.47 (95% CI: 0.41, 0.52)	0.68 (95% CI: 0.59, 0.78)	<0.001
% patients reaching oocyte retrieval	61.6%	62.5%	0.78
Cancellation rate	75.6%	72.4%	0.261
Fresh embryo transfer	89.4%	70.1%	<0.001
Pregnancy rate	26.3%	19.6%	0.251
LBR	16.3%	14.3%	0.7806

Tabla 2.- Clinical results

DISCUSSION

We have studied if adding oral drugs for ovarian stimulation could have any impact on NC-IVF carried out on poor prognosis patients. No significant differences have been found in terms of laboratory or clinical results. This could be expected taking into account that a similar number of embryo (next to 1) have been transfered in both groups.

NC-IVF has become more popular as a treatment alternative, especially for: (a) patients who reject stimulation due to fears concerning its possible side effects, needle phobia, etc.,; (b) patients for whom it is contraindicated, e.g., those with hormone-dependent cancer; and (c) patients with very low ovarian reserves, who rarely generate more than 1-3 oocytes with high doses of gonadotropins(9).

But before discussing the benefits that natural or minimal ovarian stimulation cycle-IVF could have for patients, we must first look at the drawbacks of IVF treatments with conventional ovarian stimulation. These treatments (based on the administration of gonadotropins) can cause physical and emotional stress, which makes many couples abandon treatments prematurely, thus reducing the chances of success…."(10). Some factors that must be also considered are the use of daily injections, the discomfort that may result from the sides effects of drugs, the costs and complications of treatments, and the ethical dilemmas that some couples may face regarding the selection and cryopreservation of embryos(11).

Natural cycle treatments can be benefitial form patients because the costs are lower, injections are not needed, and embryo cryopreservation generally is not necessary. However, up to three times more cycles are considered necessary to achieve pregnancy(12). Häemmerli et al. compared the treatment-associated psychological stress of couples under fertility therapies, concluding that patients who underwent natural cycle-IVF treatments experienced lower stress levels during treatment and lower levels of depression, even after three cycles, when compared with those couples who underwent a conventional gonadotropin-stimulated IVF(13).

As early as 2007, Heijnet et al. demonstrated that IVF treatments via soft stimulation presented similar success rates than treatments via conventional gonadotropin-stimulated IVF(14). Since then, interest in this type of treatment has increased. Indeed, Silber et al.(15) showed that the intrinsic fertility per oocyte in natural cycle-IVF was higher than that reported in gonadotropin-stimulated IVF cycles, with an up to 26% differences.This is particularly significant for patients over 34 years old.

In addition, several studies have analysed the results in both NC-IVF and MS-IVF, demonstrating their comparability in terms of sucessful pregnancy with stimulated IVF cycles(16,17).

Studies have already been performed using just oral medicantion for MS-IVF. Abe et al.(6) reported pregnancy rates of 22.3% after a single MS-IVF using only clomiphene citrate, with pregnancy rates of 39.2% after three cycles. It is important to emphasize that the average age of patients in this study was 38.4 years old. As expected, LBR was also highly influenced by maternal age. The authors also concluded that MS-IVF could be a preferred option than natural cycles due to their lower cancellation rate (at least one oocyte was obtained in 86% of the cases), and the higher number of oocytes obtained (1.5).

In addition to increasing follicle stimulating hormone (FSH) secretion, clomiphene citrate has the effect of delaying luteinizing hormone (LH) peak(18), which would decrease cancellation rates due to spontaneous ovulation. In clinical trials, von Wolff observed that the administration of clomiphene citrate in patients undergoing NC-IVF reduced the rate of premature ovulation from 27.8% (absence of using clomiphene citrate) to 6.8%(19). This effect was observed in our study too.
However, we found that the fresh embryo transfer rate was lower in patients who underwent MS-IVF. This may be due to the effect that clomiphene citrate has on the endometrium, which has been reflected in numerous studies(20). This impact on endometrium thickness implies an increase in cycle costs (embryo vitrification, higher number of visits to the clinic, deferred embryo transfer), so using of oral drugs, in the absence of a positive impact on clinical outcomes, must be analyzed and discussed with patients, who should be informed of this possibility.

Karakida et al.(21) measured the usefulness of adding gonadotropins in modified natural cycles, comparing it with the only addition of oral drugs (in this case, clomiphene citrate). After studying both groups, they discovered that although the number of oocytes per cycle obtained was greater for cycles with gonadotropins therapy, the cumulative LBR were comparable. They concluded that all cycles with minimal stimulation should be started with oral drugs only, following with gonadotropins treatement only if insufficient endogenous gonadotropins secretion levels are observed during the late follicular phase. In our case, we only analysed cycles in which gonadotropins were not used at any stage.

In our study, we saw that although the numbers of oocytes and embryos available were higher in the group that used oral medication (which is similar to that obtained in previous studies), we did not find any differences in success rates in terms of pregnancy or LBR. This may be due to the same principle that is demonstrated in 2017 by Silber et al.(15), which shows a higher LBR per oocyte in natural cycle-IVF than in oocytes from conventional gonadotropin-stimulated cycles. For this reason, we question whether adding oral medication provides an advantage in terms of success rates compared to natural cycles. However, more research is needed in order to confirm this.

Despite the high cancellation rates, we found global LBR rates per transfer of 16.27% for the NC-IVF group and 14.29% for the MS-IVF group. It is necessary to carry out an analysis stratified by age, but the data is in agreement with the data presented by other groups(6).

Due to this, we believe that natural cycles or minimal stimulation cycles along with oral medication only may be a good alternative to conventional gonadotropin-stimulated IVF, with acceptable successful pregnancy rates; especially in patients with poor prognosis who reject oocyte donation or who are looking for a more comfortable and affordable treatment. Looking at the patients' characteristics (average age of 40.48 years old, bFSH of 18.18 mIU/ml, number of previous IVF of 2.44) we can see that these patients have a very poor prognosis.

For patients that have a low chance of success, it is especially important to have more comfortable treatments with fewer side effects that do not cause as much physical and emotional stress.

It is important to point out that this is a retrospective study, carried out under current conditions of routine clinical practice. Under these conditions, it is especially important to be aware of the type of patients that are opting for this kind of treatment, and of the results they are obtaining.

CONCLUSIONS

Both natural cycle and minimal stimulation cycle-IVF with oral medication may be a suitable alternative to conventional gonadotropin-stimulated IVF cycles, with acceptable success rates, especially for patients with poor prognosis who reject oocyte donation or who are looking for more comfortable and affordable treatment.

Adding oral medication to natural cycle IVF, although reducing cancellation rates, does not seem to have an impact on the clinical results of the cycle. Therefore, patients should be informed of this before they decide if this policy, which is associated with an increase in the cost of medication and cycle, is the best option for them.

Furthermore, the increased need to perform cryopreserved embryo transfers (due to the effect that clomiphene citrate has on the endometrium) increases both the costs and the time required for the transfer, which may be another reason for patients to opt for a pure natural cycle.

List of abbreviations

IVF in vitro fertilization
NC-IVF Natural cycle- IVF
MS-IVF Minimal stimulation - IVF
COX cycoloxygenase
LBR live birth rate
FSH follicle stimulating hormone

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