Returning to the Simplest Way: Clinical Results of Patients Undergoing Ivf in Natural Vs Modified Natural Cycles

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Abstract

Background

In recent years, natural cycle IVF has been undergoing a revival, gaining recognition as a safer, cheaper, and more comfortable option for patients. we define natural cycle 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 modified natural 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 modified 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 in the number of oocytes obtained after oocyte retrieval was (1.03 vs 1.63, $p < 0.001$), number of mature oocytes (0.9 vs 1.3, $p < 0.01$), fertilization rate (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 find significant differences in terms of pregnancy rate (26,3% vs 19,6%, $p = 0.251$) or live birth rate (16.3% vs 14,3%, $p = 0.7806$)

Conclusions

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

Plain English Summary

Our aim was 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. We retrospectively analysed all natural cycle IVF and modified – natural cycle IVF (adding oral medication such as letrozole or clomiphene citrate) treatments that took place in our clinic during the studied period. 401 patients had

a total of 1,285 cycles. Of these, 812 (63.2%) were natural cycle-IVF and 473 (36.8%) were modified natural cycle-IVF.

We found significant differences in the number of oocytes obtained after oocyte retrieval was (1.03 vs 1.63, $p < 0.001$), number of mature oocytes (0.9 vs 1.3, $p < 0.01$), fertilization rate (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 find significant differences in terms of pregnancy rate (26.3% vs 19.6%, $p = 0.251$) or live birth rate (16.3% vs 14.3%, $p = 0.7806$), so adding oral medication to natural cycle IVF does not seem to have an impact on the clinical results of the cycle.

Background

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-releasing 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).

According to the terminology proposed by *ISMAAR* (The International Society for Mild Approaches in Assisted Reproduction), we define natural cycle 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 modified natural cycle 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 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 modified natural cycles with pure natural cycles (cycles in which medication is only used for final oocyte maturation) from clinical and laboratory results obtained in 1,285 IVF cycles (812 pure natural cycles vs 473 modified natural cycles) performed on 401 patients since our centre opened in 2016.

Materials And Methods

We retrospectively analysed all natural or modified 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) and on the experiences with previous cycles (if any)

In the natural cycle-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 modified natural cycle-IVF group from the third day of the cycle until ovulation induction.

In both groups, ovulation induction was performed with a gonadotropin-releasing hormone (GnRH) agonist (triptorelin, 0.2 mg subcutaneous). Oocyte retrieval was performed thirty-six hours after triggering.

Anaesthesia was not administrated for oocyte retrieval, and the absence of follicles as 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 natural cycle-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 embryo transfer.

In all cases, intracytoplasmic sperm injection (ICSI) was performed.

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.

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.

Results

During the study period, 401 patients had a total of 1,285 cycles. Of these, 812 (63.2%) were natural cycle-IVF and 473 (36.8%) were modified natural cycle-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.

Table 1
Patient characteristics.

	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

The most common cause of an infertility diagnosis was advanced maternal age (42.1%), followed by mixed causes (21.7%), and low ovarian reserves (5.8%). Furthermore, 62.4% were patients with primary sterility.

In the modified natural cycle-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 natural cycle-IVF group and 1.63 from the modified natural cycle-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, $p < 0.01$), fertilization rate (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.

Table 2
Clinical results.

	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

Regarding cancellations, 61.6% of the natural cycle-IVF and 62.5% of the modified natural cycle-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 natural cycle-IVF vs 25% in modified natural cycle-IVF) and premature ovulation (12% in natural cycles vs. 7% in modified natural cycles).

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

In total, cancellation rate for natural cycle-IVF was 75.6% and 72.4% for modified natural cycle-IVF; no differences were found.

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

Regarding the day of embryo development (when the transfer was performed), we did not find differences between the two groups, with 47.4% of cases being on day 3, followed by day 5 (35.2%), day 2 (10.5%), and day 4 (7%).

The pregnancy rate was 26.3% for natural cycle-IVF and 19.6% for modified natural cycle-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 natural cycle-IVF and 14.3% for modified natural cycle-IVF ($p = 0.7806$).

Discussion

Natural cycle 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 orl modified natural cycle-IVF for 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 beneficial 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 natural cycle-IVF and modified natural cycle-IVF, demonstrating their comparability in terms of sucessful pregnancy with stimulated IVF cycles(16, 17).

Studies have already been performed using this stricter definition of the modified natural cycle. Abe et al. (6) reported pregnancy rates of 22.3% after a single modified natural cycle-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 modified natural cycle-IVF could be a preferred option than natural

cycles to natural cycles, due to their lower cancellation rate (at least one oocyte was obtained in 86% of the cases), as well as 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 natural cycle-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 modified natural cycle-IVF. This may be due to the effect that clomiphene citrate has on the endometrium, which has been reflected in numerous studies(20).

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 modified natural cycles should be started with oral drugs only, following with gonadotropins treatment 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 “pure” 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 natural cycle group and 14.29% for the modified natural cycle 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 modified natural cycles along with oral medication 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 modified natural 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

COX cyclooxygenase

LBR live birth rate

FSH follicle stimulating hormone

Declarations

- Ethics approval and consent to participate

The research ethics committee of the University Hospital Puerta de Hierro in Madrid has approved this study.

- Consent for publication

Not applicable

- Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

- Competing interests

The authors declare that they have no competing interests

- Funding

No fundings were needed to the realization of this study

- Authors' contributions

AB, NG, BC and EG contributed to the data collection

EG analyzed and interpreted the patient data

AB and EG were major contributors in writing the manuscript.

All authors read and approved the final manuscript

- Acknowledgements

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Figures

Figure 1

Results comparison.

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