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ARTICLE

Comparison of stimulated versus modified natural cycles for endometrial preparation prior to frozen embryo transfer: a randomized controlled trial

BIOGRAPHY

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KEY MESSAGE

In everyday clinical practice, patients should be informed that modified natural cycle for endometrial preparation before frozen embryo transfer is a good option for those reluctant to have injections, but requires increased monitoring.

ABSTRACT

Research question: To compare stimulated cycle (STC) versus modified natural cycle (MNC) for endometrial preparation prior to frozen embryo transfer (FET) in terms of convenience and efficacy.

Design: Prospective, open-label, randomized controlled study including 119 patients aged 20–38 years, undergoing intra-conjugal IVF/intracytoplasmic sperm injection, having regular cycles, at least two day 2 or day 3 frozen embryos, for whom it was the first or second FET performed, randomized to either MNC (n = 59) or STC (n = 60). Monitoring consisted of ultrasound and hormonal measurements. The number of monitoring visits required was compared between the two groups.

Results: STC required a significantly lower number of monitoring visits compared with MNC (3.6 ± 0.9 versus 4.4 ± 1.1, respectively, $P < 0.0001$), a lower number of blood tests (2.7 ± 0.8 versus 3.5 ± 1.0, respectively, $P < 0.0001$) and of ultrasounds (1.2 ± 0.4 versus 1.5 ± 0.6, respectively, $P = 0.0039$). FET during 'non-opening' hours (22.6% versus 27.5%, respectively, $P = 0.32$) and cancellation rates (11.7% versus 11.9%, respectively, $P = 0.97$) were comparable between the STC and MNC groups. No difference concerning HCG-positive rates (34.0% versus 23.1%, respectively, $P = 0.22$) nor live birth rates (24.5% for STC versus 23.1% for MNC, respectively, $P = 0.86$) was observed. Quality of life as defined by the FertiQol score was no different ($P > 0.05$ for each item).

Conclusion: Taken together, these findings can be used for everyday clinical practice to better inform patients when deciding on the protocol to use for FET. The results suggest that MNC is a good option for patients reluctant to have injections, but requires increased monitoring. STC may offer more flexibility for patients and IVF centres.

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KEYWORDS

Endometrial preparation
FertiQol
Frozen embryo transfer
Modified natural cycle
Stimulated cycle

INTRODUCTION

The number of frozen embryo transfers (FET) carried out has been continuously increasing in the past few years (*De Geyter et al., 2018*). The practice of FET has been enhanced by significant improvements in the field of cryopreservation (vitrification) and by the favourable pregnancy and neonatal outcomes reported (*Wong et al., 2017*). FET is performed in cases of supernumerary embryos after fresh embryo transfer, where there is a freeze-all strategy after gonadotrophin-releasing hormone (GnRH) agonist trigger in antagonist protocols for patients at risk of ovarian hyperstimulation syndrome (OHSS), in preimplantation genetic diagnosis/screening, for late-follicular progesterone elevation, and in cases of embryo–endometrial asynchrony (*Roque et al., 2015*). The increasing number of elective single embryo transfers is also resulting in more frozen embryos being available for subsequent FET cycles.

Ensuring the best conditions prior to FET is of utmost importance. FET should be performed at a time when the endometrium is receptive, defined as the 'implantation window' (*Casper and Yanushpolsky, 2016*; *Mackens et al., 2017*). Endometrial preparation for FET can be performed by hormone replacement therapy, stimulated cycle (STC) or close monitoring of a natural cycle. So far, there is no consensus on which protocol leads to the best pregnancy rates and clinical outcomes (*Cerrillo et al., 2017*; *Ghobara et al., 2017*; *Groenewoud et al., 2013*, *2016*; *Peeraer et al., 2015*; *Yu et al., 2015*). Hence, the choice of which protocol to use to prepare the endometrium for FET should rely on other criteria, such as convenience for patients. Indeed, because medically assisted reproduction (MAR) treatments, regular follow-ups and repeated tests are psychologically and physically burdensome for patients, optimizing quality of life for patients is essential. Many couples abandon their attempts during the process, and up to 26% after failure of a first IVF cycle (*de la Rochebrochard et al., 2009*; *Troude et al., 2014*). Although endometrial preparation using natural cycle may appear more physiological and less invasive because it does not require injections, it might also be less convenient for patients because of the need for more monitoring, as well as being less convenient for centres due to reduced flexibility (*Mackens et al., 2017*; *Montagut et al., 2016*). To date, no study has compared the convenience of stimulated cycle versus modified natural cycle (MNC) for FET.

The aim of the present study was to compare the convenience and efficacy of stimulated cycle versus modified natural cycle for endometrial preparation prior to FET in a prospective cohort of patients.

MATERIALS AND METHODS

Patients and study design

This prospective, open-label, randomized controlled study was led by the public Medically Assisted Reproduction Centre of the Centre Hospitalier Intercommunal de Créteil in Paris. Eligible patients included women aged 20–38 years old, covered by the general plan of the French social security system with 100% coverage for infertility, having regular menstrual cycles of 26–35 days, undergoing intra-conjugal IVF/intracytoplasmic sperm injection (ICSI), with at least two embryos frozen at day 2 or day 3, and for whom it was the first or second FET performed.

Non-inclusion criteria were: (i) IVF/ICSI with sperm donor; (ii) women with irregular cycles and/or polycystic ovary syndrome; (iii) day 1 or day 5/day 6 frozen embryos, transfers of embryos at different times during the same cycle, or transfers of three embryos simultaneously; (iv) patients for whom more than three FET or more than three oocyte retrievals had already been performed, or for whom more than six embryos had already been transferred without subsequent pregnancy; (v) patients with a uterine malformation; (vi) presence of a hydrosalpinx.

Information on the study protocol was given to patients satisfying inclusion and non-inclusion criteria during a dedicated consultation. After a reflection period, patients willing to participate in the study were required to sign a consent form prior to enrolment. After inclusion, patients were randomized by the use of sealed envelopes (computer-generated randomization) between the MNC and STC groups.

The study was conducted according to institutional and ethical rules concerning research on patients. Patients could withdraw their consent at any time. Other cases of withdrawal from the study included absence of progesterone rise >2 ng/ml, lysis of all frozen embryos, absence of transfer, and patients lost to follow-up. The study was authorized by the French Medicinal Products Agency on 10 February 2015 (ANSM, no. 15014B-62) and approved by an ethical committee on 21 April 2015 (Comité de Protection des Personnes, Paris Ile de France 3, approval no. 3249). No specific risk was associated with the study because it involved routine treatment protocols. The study was registered at ClinicalTrials.gov (NCT02834117).

Treatment protocol

The treatment protocol is described in Supplementary Figure 1. Patients in the STC group were treated with 75 IU of recombinant FSH (Gonal F®, Merck) from day 6 to day 11 and ovulation was triggered with recombinant human chorionic gonadotrophin (HCG) (Ovitrelle® 250 µg, Merck) when the leading follicle was >17 mm. Patients in the MNC group received no gonadotrophin treatment. In both groups, hormonal and ultrasound monitoring were started at day 12 of the cycle. Hormonal monitoring consisted of the measurement of oestradiol, LH and progesterone levels. Ultrasound monitoring consisted of measuring endometrial thickness and size and count of follicles in each ovary. There was no ultrasound monitoring of follicle rupture. Endometrial thickness was measured in both groups. Endometrial thickness ≥7 mm was considered mandatory for proceeding with embryo transfer.

Due to the variability of the LH surge and the lack of precise data on its use to detect ovulation, the occurrence of ovulation was based on the rise of progesterone levels. As serum progesterone levels >1.5 ng/ml have previously been associated with the onset of ovulation (*Weissman et al., 2011*), and levels >5 ng/ml to the mid-luteal phase (*Leiva et al., 2015*), the day progesterone reached 2 ng/ml was considered to be the day of oocyte retrieval for synchronization purposes. When a leading follicle was detected, the monitoring was then limited to hormonal monitoring until progesterone reached the threshold of 2 ng/ml.

FET was programmed 2 days later for day 2/3 embryos. If FET day fell on a Sunday

or during holidays, the transfer was performed 1 day earlier in the case of day 2 embryos, and 1 day later in the case of day 3 embryos. Intravaginal progesterone (Progestan® 200 mg twice a day, Besins) was started in both groups when plasma progesterone was ≥2 ng/ml, and was continued until 4 weeks of gestation in case of pregnancy. The pregnancy test was performed 14 days starting from the day of progesterone rise >2 ng/ml. HCG measurements were repeated every 48 h until HCG >1000 IU/l. An ultrasound to detect cardiac activity was performed at 6 weeks of amenorrhoea (4 weeks of gestation).

Study endpoints and definitions

The primary objective was to compare STC versus MNC in terms of number of visits required per patient to prepare FET. A visit was defined as travel to the MAR centre for a hormonal assessment and/or ultrasound and embryo transfer, and/or as travel to the medical laboratory for hormonal assessment in outpatient practice.

Secondary objectives included comparison between STC and MNC in terms of: (i) quality of life (assessed by the FertiQol score) (*Boivin et al., 2011*); (ii) cancellation rate per cycle, whatever the cause (premature ovulation, organizational problems); (iii) number of transfers performed on weekends and holidays; (iv) pregnancy rate per transfer, defined by HCG >100 IU/l; (v) clinical pregnancy rate per transfer, defined by ultrasound detection of fetal cardiac activity; (vi) live birth rate per transfer, defined by the birth of at least one live baby; (vii) percentage of multiple pregnancies; (viii) implantation rate, defined as the number of gestational sacs/number of embryos transferred expressed as a percentage; (ix) early pregnancy loss rate (occurring before 12 weeks of gestation).

The FertiQol tool (*Boivin et al., 2011*) was validated by the European Society of Reproductive Medicine and Embryology. FertiQol is composed of 36 items that assess general quality of life (Core FertiQol: 24 items divided into 'emotional', 'relational', 'mind/body' and 'social' subscales) and treatment-related quality of life (optional FertiQol: 10 items, divided into 'environment' and 'tolerability' subscales), as well as overall life and physical health (two items). Each question is associated with five levels of graded response. A score of 0 corresponds to the lowest level of satisfaction/well-being, whereas a score of 4 corresponds to the highest level. Scores attributed to each item are then added. The higher the final score is, the better the quality of life. The FertiQol survey was completed in electronic format on a computer made available in the transfer room before embryo transfer.

Statistical analysis

In the study centre, the mean (± SD) number of visits required before FET using STC was 2.6 ± 1.5. It was calculated that 48 patients per group were required to demonstrate a decrease of one visit using STC compared with MNC (two-sided alpha error of 0.05 and 90% power). The number of patients was increased by 30% to consider patients lost to follow-up and cycle cancellations. Hence, 62 patients in each group, i.e. a total of 124 patients, were required in this study.

Data were expressed in terms of frequencies and percentages, or by mean values ± SD. Depending on their distribution, Student or Mann–Whitney tests were used to analyse continuous variables. Discrete variables were compared with chi-squared tests. $P < 0.05$ was considered to be statistically significant. Analyses were performed with STATA 13/SE (StataCorp LP, College Station, TX, USA).

RESULTS

Patients were recruited from May 2015 to October 2017. Among the 124 patients selected, three did not meet inclusion criteria, and two were excluded because of invalid consent forms. Hence, 119 patients were randomized between the two groups (MNC: $n = 59$; STC: $n = 60$). Seven patients in each group withdrew from the study. In total, the number of embryo transfers performed was 52 in the MNC group, and 53 in the STC group (FIGURE 1).

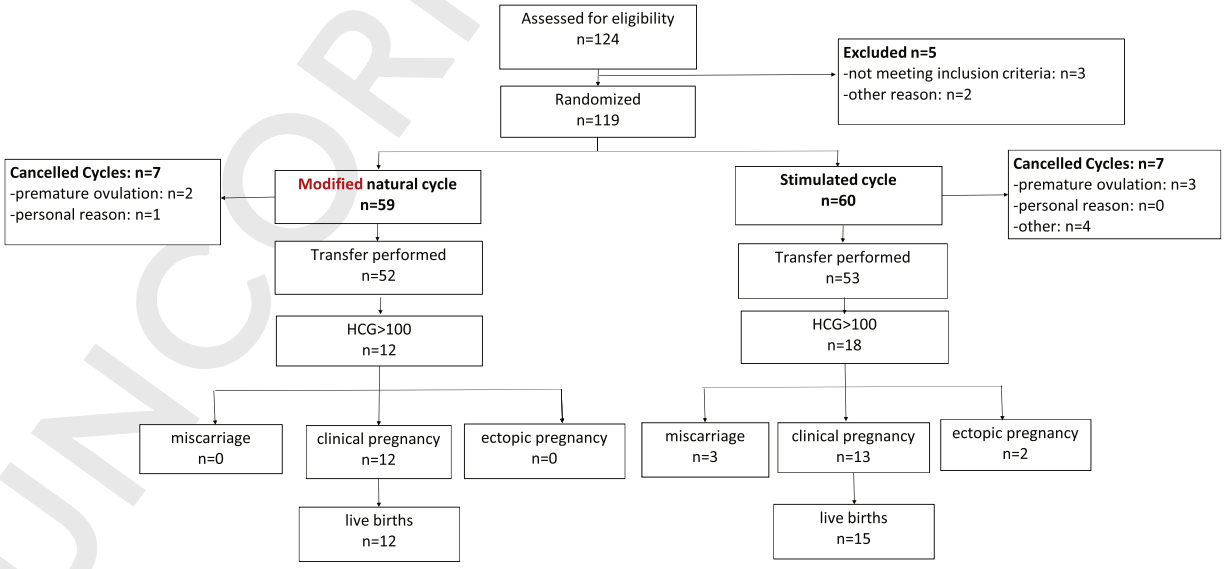

FIGURE 1 Flow chart of patients included in the study and treatment outcomes. One clinical pregnancy in the stimulated cycle group resulted in the birth of triplets.

Out of the 30 pregnancies obtained (defined by HCG >100 IU/l), two corresponded to ectopic pregnancies, and three to spontaneous miscarriages. The 25 pregnancies with cardiac activity detected by ultrasound developed favourably, and led to 25 deliveries and 27 live births (one multiple pregnancy with monozygotic triplets with transfer of one day 3 embryo; FIGURE 1).

Patient characteristics are detailed in TABLE 1. Mean age of patients was 32.9 (±3.7) years. Both groups were comparable on demographics and basal hormonal measurements. Most patients were treated for primary infertility (56.8%). A majority of patients (78.4%) had been stimulated with an antagonist protocol; 60.7% of patients had IVF, and 39.3% ICSI. It was the first oocyte retrieval for 78.0% of patients in the MNC group, and for 73.3% of patients in the STC group, respectively ($P = 0.56$). In mean values, 14 oocytes were retrieved, 7 embryos obtained and 5 embryos were frozen; 19.5% of patients had a freeze-all strategy. Endometrial thickness before performing embryo transfer was similar in both groups (8.9 ± 1.8 mm for MNC versus 8.5 ± 1.5 mm for STC, respectively).

TABLE 1 PATIENT CHARACTERISTICS FOR MNC AND STC GROUPS

Parameters	MNC ($n = 59$)	STC ($n = 60$)	*P*-value
Age (years)	33.3 ± 3.3	32.0 ± 3.9	0.052
BMI (kg/m^2)	23.4 ± 3.2	23.8 ± 4.0	0.55
Infertility status			0.69
Primary	34 (58.6)	33 (55.0)	
Secondary	24 (41.4)	27 (45.0)	
Cause of infertility			0.41
Male	20 (34.5)	15 (26.3)	
Endometriosis	6 (10.3)	7 (12.3)	
Mixed	10 (17.2)	5 (8.8)	
Idiopathic	13 (22.4)	13 (22.8)	
Tubal	8 (13.8)	14 (24.6)	
Ovulatory	1 (1.7)	1 (1.8)	
Other	0 (0.0)	2 (3.5)	
Duration of infertility (years)	4.0 ± 2.0	3.9 ± 2.5	0.81
History of conception	34 (57.6)	33 (55.0)	0.69
Smoking	9.0 (15.3)	11 (18.3)	0.65
Antral follicular count	17.4 ± 8.6	18.8 ± 11.9	0.46
AMH (ng/ml)	3.4 ± 2.1	3.6 ± 2.8	0.66
FSH (UI/l)	6.6 ± 1.7	6.8 ± 2.2	0.58
Initial treatment			0.76
IVF	36 (62.1)	35.0 (59.3)	
ICSI	22 (37.9)	24.0 (40.7)	
Protocol			0.50
Antagonist	47 (81.0)	44 (75.9)	
Other	11 (19.0)	14 (24.1)	
Total dose of FSH	1950.2 ± 785.5	2089.0 ± 975.5	0.39
Oocytes retrieved	13.1 ± 5.6	14.1 ± 5.3	0.32
Total number of embryos	6.3 ± 3.3	6.8 ± 3.3	0.41
Number of frozen embryos	4.8 ± 2.9	5.0 ± 2.8	0.70
Freeze-all	11.0 (18.6)	12.0 (20.3)	0.85

Data are presented as mean ± SD or *n* (%).

In MNC group data on infertility status, cause of infertility, initial treatment and protocol are reported for 58 patients (one missing value). In STC group there were three missing values for cause of infertility ($n = 57$), one missing value for initial treatment ($n = 59$), two missing values for protocol ($n = 58$) and one missing value for freeze-all ($n = 59$).

AMH = anti-Müllerian hormone; BMI = body mass index; ICSI = intracytoplasmic sperm injection; MNC = modified natural cycle; STC = stimulated cycle.

The number of visits required for endometrial preparation prior to FET was significantly lower in the STC group compared with the MNC group (3.6 ± 0.9 versus 4.4 ± 1.1, respectively, $P < 0.0001$). The STC group was significantly associated with a lower number of blood tests (2.7 ± 0.8 versus 3.5 ± 1.0, respectively, $P < 0.0001$), and with a lower number of ultrasounds performed (1.2 ± 0.4 versus 1.5 ± 0.6, respectively, $P = 0.0039$). Both the number of FET during 'non-opening' hours (22.6% versus 27.5%, respectively, $P = 0.32$) and cancellation rates (11.7% versus 11.9%, respectively, $P = 0.97$) were comparable between patients in the STC and MNC groups.

Quality of life as defined by the FertiQol score was no different between the two groups ($P > 0.05$ for each item; TABLE 2).

Concerning pregnancies, HCG-positive rates per transfer were not significantly different in STC compared with MNC patients (34.0% versus 23.1%, respectively, $P = 0.22$). No difference concerning implantation rates (for STC: 16/74 = 21.6%; for MNC: 12/73 = 16.4%; $P = 0.42$), clinical pregnancy rate (for STC: 13/53 = 24.5%; for MNC: 12/52 = 23.1%; $P = 0.86$), multiple pregnancy rate (for STC: 1/53 = 1.9%; for MNC: 0/52 = 0%; $P = 0.32$), early pregnancy loss rate (for STC: 3/16 = 18.8%; for MNC: 0/12 = 0%; $P = 0.11$), or live birth rates per transfer was observed between the two groups (24.5% for STC versus 23.1% for MNC, respectively, $P = 0.86$).

DISCUSSION

This study demonstrates that STC for endometrial preparation prior to FET requires one monitoring visit less than MNC, without impairing quality of life or pregnancy outcomes. STC was significantly associated with both a lower number of blood tests and a lower number of ultrasounds required.

So far, studies have failed to identify the best protocol to prepare the endometrium before FET. Although

TABLE 2 TOTAL FERTIQOL SCORE AND FERTIQOL SUBSCALES FOR MNC AND STC GROUPS

Scale	MMNC	STC	*P*-value
Total FertiQol/144	67 ± 15	69 ± 12	0.60
Core FertiQol	68 ± 16	69 ± 13	0.56
Treatment FertiQol	68 ± 17	68 ± 14	0.98
Core FertiQol subscales			
Emotional	58 ± 20	61 ± 19	0.56
Relational	74 ± 19	78 ± 12	0.16
Mind/body	66 ± 20	69 ± 20	0.55
Social	72 ± 21	69 ± 16	0.59
Treatment FertiQol subscales			
Environment	69 ± 17	73 ± 18	0.30
Treatment tolerability	67 ± 26	61 ± 22	0.28

Data are presented as mean ± SD.

Higher scores indicate more favourable quality of life.

MNC = modified natural cycle; STC = stimulated cycle.

this study was underpowered to detect differences in pregnancy outcomes, no significant difference between MNC and STC was observed in terms of pregnancy or live birth rates. Consistently, a 2017 Cochrane Collaboration review of 18 randomized controlled trials comparing different cycle regimens for FET in 3815 women concluded that there was insufficient evidence to support the use of one protocol over another with regard to live birth and clinical pregnancy rates (*Ghobara et al., 2017*). A meta-analysis by *Groenewoud et al. (2013)* observed no difference between natural cycle, MNC (ovulation triggered by HCG) and artificial cycles in terms of pregnancy outcomes, and subsequent RCT comparing artificial cycles and MNC led to similar results (*Greco et al., 2016a*; *Groenewoud et al., 2016*). Concerning endometrial preparation by stimulated cycle, although STC was significantly associated with higher live birth rates and to lower early pregnancy loss rates compared with artificial cycles ($P < 0.0001$) in a recent retrospective study (*Hatoum et al., 2018*), a prospective randomized trial by *Wright et al. (2006)* reported similar implantation rates (8.5% for artificial cycles versus 7.3% for STC, respectively), pregnancy rates (16% for artificial cycles versus 13% for STC, respectively) and cancellation rates (23% for both) between the two protocols. Moreover, data on early pregnancy loss remain to be clarified, as some studies have reported an association between artificial cycles and preclinical and clinical pregnancy loss rates (*Tomás et al., 2012*). Hence, in view of the lack of a clear benefit between one protocol and another in terms of pregnancy outcomes, other factors should be considered in the choice of protocol to prepare the endometrium prior to FET.

Few data exist on the cost-effectiveness of these treatments. Evaluating cost–benefit is particularly challenging because it differs greatly by country and by centre, and should be individually assessed. Costs engendered do not only include the price of medications used (injections, drugs), cost analysis also needs to assess costs associated with monitoring (blood samples, ultrasound scans, time and workload for centres), and costs supported by patients (transportation, absences from work). *Groenewoud et al. (2016)* concluded that costs associated with natural cycles were comparable to those of artificial cycles (€617.50 per cycle for natural cycles versus €625.73 per cycle for artificial cycles, respectively, $P = 0.54$). Data directly related to treatments had been obtained from healthcare insurances, and the number of visits, transport mode, distance travelled during treatment, as well as number of days taking a leave of absence or sick leave had been collected using a web-based survey completed by patients. Similarly, considering only drug costs, *Greco et al. (2016b)* observed no difference between artificial cycles and MNC despite the use of different pharmaceuticals (€64.0 ± 1.6 and €59.88 ± 0.0, respectively, $P = 0.44$). These data suggest that although MNC has the advantage of sparing the cost of injections, the effect might be reversed by the cost of more monitoring required.

Altogether, the fact that MNC required one supplementary monitoring visit compared with STC in this study can be used for everyday clinical practice to better inform patients when deciding on the protocol for endometrial preparation prior to FET. The drawbacks of gonadotrophin therapy have to be considered in the decision about which protocol to use. Indeed, in addition to the cost of injections, gonadotrophin stimulation can induce undesirable side effects for patients, such as the risk of abdominal discomfort, cyst formation, OHSS and multiple pregnancies in case of exaggerated response to stimulation and/or intercourse concomitant with ovulation. However, although one monitoring visit less might be negligible for clinicians, it can be particularly important for patients. Given that regular follow-ups and repeated tests are particularly tiring and stressful, it appears essential to minimize the impact of treatment on patients' personal, professional and social lives (*Brandes et al., 2009*). It was found that MNC required 4.5 ± 1.0 visits, which is consistent with the literature (*Fatemi et al., 2010*; *Weissman et al., 2009*). Larger studies are needed to confirm an advantage of STC versus MNC on cancellation rates and transfers performed during 'non-opening' hours, as both were comparable for patients treated by STC compared with MNC. Moreover, FET on Sundays were not feasible in the study centre due to the relatively small medical staff. In centres where FET could be performed on Sundays, it is valuable information to know whether STC could reduce the number of FET performed on a non-optimal day, compared with MNC.

Although MNC has the advantage of requiring no treatment, ensuring timely thawing and transfer of embryos using MNC implies awaiting the LH surge, which varies between cycles and between patients. Thereby, previous studies have reported that using HCG to trigger ovulation in MNC could significantly reduce the number of monitoring visits required, without any adverse effect on reproductive outcome (*Weissman et al., 2009*, *2011*). Comparing a protocol of MNC using ovulation triggering by HCG and STC would be particularly interesting

to evaluate a potential impact of ovulation trigger by HCG on the number of monitoring visits required for FET compared with STC. Planning FET with MNC also carries the risk of unexpected ovulation, and thus of cancelled cycles, which is a particularly distressing event. Uncertain planning can be bothersome for patients, as well as a source of organizational problems for centres (*Gameiro et al., 2012*). Saving one visit might enable simplification of the treatment process, less time-consuming tests (ultrasounds and hormonal assays), and reduction of workload for MAR centres.

In conclusion, considering treatment burden and patient preference are major factors in the choice of protocol to be used to prepare the endometrium before FET. In everyday clinical practice, patients should be informed that MNC is a good option for those reluctant to have injections, but requires increased monitoring. STC may reduce unnecessary anxiety and operational costs, and offer more flexibility for patients and IVF centres. Larger studies, as well as an economic evaluation of the costs involved, are warranted to confirm the present data.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rbmo.2020.01.007.

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