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

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Convenience and efficacy of stimulated cycle versus natural cycle for endometrial preparation prior to frozen embryo transfer: a randomized controlled trial

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Running title:
Convenience of mNC vs. SC for FET: an RCT

Abstract

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

Design: Prospective, open-labeled, randomized, controlled study. 119 patients aged 20-38yo, undergoing intra-conjugal IVF/ICSI, having regular cycles, at least two Day 2 or Day 3 frozen embryos, for whom it was the first or second FET performed were randomized to either mNC (n=59) or SC (n=60). Monitoring consisted in ultrasound and hormonal measurements. The number of monitoring visits required was compared between the two groups.

Results: SC significantly required a lower number of monitoring visits compared to mNC (3.6±0.9 *vs.* 4.4±1.1, respectively, $P<0.0001$), a lower number of blood tests (2.7±0.8 vs. 3.5±1.0, respectively, $P<0.0001$), and a lower number of ultrasounds (1.2±0.4 vs. 1.5±0.6, respectively, $P=0.0039$). FET during "non-opening" hours (22.6% vs. 27.5%, respectively, $P=0.32$) and cancellation rates (8.6% vs. 12.3%, respectively, $P=0.52$) were comparable between the SC and mNC groups. No difference concerning HCG-positive rates ($P=0.47$) nor life birth rates was observed ($P=0.69$). Quality of life as defined by the FertiQol score was not different ($P>0.05$ for each item).

Conclusion: Altogether, our findings can be used for everyday clinical practice to better inform patients when deciding on the protocol to use for FET. Our results suggest that mNC is a good option for patients reluctant to have injections, but requires increased monitoring. SC may offer more flexibility for patients and IVF centers.

Keywords:

frozen embryo transfer
endometrial preparation
stimulated cycle
modified natural cycle
fertiqol

Trial registration number: Clinicaltrial NCT02834117

Introduction

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

Insuring the best conditions prior to frozen embryo transfer is of utmost importance. FET should be performed at a time when the endometrium is receptive, defined as "implantation window" (Casper and Yanushpolsky, 2016; Mackens et al., 2017). Endometrial preparation for frozen embryo transfer can be performed by hormone replacement therapy (HRT), stimulated cycle (SC), or close monitoring of a natural cycle (NC). So far, no consensus exists on which protocol leads to the best pregnancy rates and clinical outcomes (6–11). 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, since 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. A large number of couples abandon 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 since it does not require

injections, it might also be less convenient for patients by engendering more monitoring, as well as less convenient for centers by reducing 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

Our prospective open-labeled randomized controlled study was led in the public Medically Assisted Reproduction Center of Creteil Intercommunal Hospital (France). Patients eligible included women aged between 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/ICSI, with at least 2 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 moments during the same cycle, or transfers of 3 embryos simultaneously; (iv) patients for whom more than 3 FETs or more than 3 oocyte retrievals had already been performed, or for whom more than 6 embryos had already been replaced 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 modified natural cycle (mNC) and stimulated cycle (SC) 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 (ANSM, n° 15014B-62) and approved by an ethical committee (Comité de Protection des Personnes, Paris Ile de France 3, Approval n° 3249). No specific risk was associated to the study since it involved routine treatment protocols. The study was registered on ClinicalTrials (NCT02834117).

Treatment protocol

Treatment protocol is described in Supplementary Figure 1 (detailed version in Supplementary Figure 2). Patients in the SC group were treated by 75 IU of recombinant FSH (Gonal F®, Merck) from Day 6 to Day 11 and ovulation was triggered with recombinant HCG (Ovitrelle® 250µg, Merck) when the leading follicle was >17 mm. Patients in the mNC group received no gonadotropin treatment. In both groups, hormonal and ultrasound monitoring were started at Day 12 of the cycle. Hormonal monitoring consisted in the measurement of estradiol, LH, and progesterone levels. Ultrasound monitoring consisted in the measurement of endometrial thickness and size and count of follicles in each ovary. There was no ultrasound monitoring of follicular 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 > 1.5ng/mL have previously been associated to the onset of ovulation (Weissman et al., 2011), and levels > 5ng/mL to the mid-luteal phase (Leiva et al., 2015), we considered the day progesterone reached 2 ng/ml as 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 case of Day 2 embryos, and 1 day later in case of Day 3 embryos. Intravaginal progesterone (Progestan® 200mg twice a day, Besins) was started in both groups when plasmatic progesterone was $\geq$ 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 48h until HCG >1000. An ultrasound to detect cardiac activity was performed at 6 weeks of amenorrhea (4 weeks of gestation).

Study endpoints and definitions

Our primary objective was to compare stimulated cycle versus modified natural cycle in terms of number of visits required per patient to prepare FET. A visit was defined as a travel to the MAR center for a hormonal assessment and/or ultrasound and embryo transfer, and/or as a travel to the medical laboratory for hormonal assessment in outpatient practice.

Secondary objectives included comparison between stimulated cycle and modified natural cycle in terms of: (i) quality of life (assessed by the FertiQol score) (Boivin et al., 2011); (ii)

cancelation 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 pregnanaturaies; (viii) implantation rate; (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 (2 items). Each question is associated to 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 our center, the mean number of visits required before FET using stimulated cycle is 2.6±1.5 standard deviation (SD). We calculated that 48 patients per group were required to demonstrate a decrease of 1 visit using stimulated cycle compared to modified natural cycle (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 our study.

Data were expressed in terms of frequencies and percentages, or by mean values +/- standard deviations. Depending on their distribution, Student or Mann-Whitney tests were used to analyze continuous variables. Discrete variables were compared with Chi^2 tests. $P<0.05$ was considered as statistically significant. Analyzes were performed with STATA 13/SE, StataCorp, USA.

Results

Patients were recruited from May 2015 to October 2017. Among the 124 patients selected, 3 finally did not meet inclusion criteria, and 2 were excluded because of invalid consent forms. Hence, 119 patients were randomized between the two groups (mNC: n=59; SC: n=60). 7 patients in each group withdrew from the study. In total, the number of embryo transfers performed was of 52 in the mNC group, and 53 in the SC group (Figure1).

Out of the 30 pregnancies obtained (defined by HCG >100), 2 corresponded to ectopic pregnancies, and 3 to spontaneous miscarriages. The 25 pregnancies with cardiac activity detected by ultrasound developed favorably, and lead to 25 deliveries and 27 live births (1 multiple pregnancy with triplets; Figure 1).

Patient characteristics are detailed Table 1. Mean age of patients was 32.9 (±3.7) years old. 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 76.9% of patients. In average, 14 oocytes were retrieved, 7 embryos obtained, and 5 embryos were frozen. 22% patients had a freeze-all strategy. Endometrial thickness before performing embryo transfer was similar in both groups (8.9mm (+/-1.8SD) for NC *vs*. 8.5mm (+/-1.5SD) for SC, respectively).

The number of visits required for endometrial preparation prior to FET was significantly lower in the SC group compared to the mNC group (3.6±0.9 vs. 4.4±1.1, respectively, P<0.0001). The SC group was significantly associated to a lower number of blood tests (2.7±0.8 vs. 3.5±1.0, respectively, P<0.0001), and to a lower number of ultrasounds performed (1.2±0.4 vs. 1.5±0.6, respectively, P=0.0039). Both the number of FET during "non-opening" hours (22.6% vs. 27.5%, respectively, P=0.32) and cancellation rates (8.6% vs. 12.3%, respectively, P=0.52) were comparable between patients in the SC and mNC groups.

Quality of life as defined by the FertiQol score was not different between the two groups (*P*>0.05 for every item; Table 2).

Concerning pregnancies, HCG-positive rates were not significantly different in SC compared to mNC patients (29.1% vs. 23.1%, respectively, P=0.47). No difference concerning implantation rates (P=0.44) nor life birth rates was observed between the two groups (20.0% for SC vs. 23.1% for mNC, respectively, P=0.69).

Discussion

Our study demonstrates that stimulated cycle for endometrial preparation prior to FET requires one monitoring visit less than modified natural cycle, without impairing quality of life nor pregnancy outcomes. Stimulated cycle was significantly associated to 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 our study was underpowered to detect differences in pregnancy outcomes, we

did not observe a significant difference between mNC and SC in terms of pregnancy nor 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). Groenewoud *et al.'s* (Groenewoud et al., 2013) meta-analysis observed no difference between NC, mNC (ovulation triggered by HCG), and artificial cycles (AC) in terms of pregnancy outcomes, and subsequent RCTs comparing AC and mNC led to similar results (Greco et al., 2016a; Groenewoud et al., 2016). Concerning endometrial preparation by stimulated cycle, although SC was significantly associated to higher live birth rates and to lower early pregnancy loss rates compared to AC (P<0.0001) in a recent retrospective study (Hatoum et al., 2018), Wright *et al.*'s (Wright et al., 2006) prospective randomized trial reported similar implantation rates (8.5 for AC *vs.* 7.3% for SC, respectively), pregnancy rates (16% for AC *vs.* 13% for SC, 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 AC and preclinical and clinical pregnancy loss rates (Tomás et al., 2012). Hence, in view of the lack of a clear benefit between one protocol or another in terms of pregnancy outcomes, other factors should be considered in the choice of the protocol to prepare the endometrium prior to FET.

Few data exist on the cost-effectiveness of these treatments. Evaluating cost-benefit is particularly challenging since it greatly differs by country and by center, 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 to monitoring (blood samples, ultrasound scans, time and work load for centers), and costs supported by patients (transportation, absences from work). Groenewoud *et al.*(Groenewoud et al., 2016) concluded

that costs associated to NC were comparable to those of AC (€617.50 per cycle for NC *vs.* €625.73 per cycle for AC, 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.*(Greco et al., 2016b) observed no difference between AC and mNC despite the use of different pharmaceuticals (64.0 ± 1.6 and 59.88 ± 0.0 euros, 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 to SC in our 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 gonadotropin therapy have to be considered in the decision on which protocol to use. Indeed, in addition to increased costs, gonadotropin stimulation can induce undesirable side effects for patients such as the risk of abdominal discomfort, cyst formation, ovarian hyperstimulation syndrome, 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 of particular importance 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). We found that mNC required 4.5 +/- 1.0 visits, which is consistent with literature (Fatemi et al., 2010; Weissman et al., 2009). Larger effectives are needed to confirm an advantage of SC versus mNC on cancellation rates and transfers performed during "non-opening" hours, as both were comparable for patients treated by SC compared to mNC. Moreover, FETs on Sundays were not feasible in our center due to our relatively small medical staff. In centers

where FET could be performed on Sundays, it is a valuable information to know if SC could reduce the number of FET performed on a non optimal day, compared to 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; Weissman et al., 2011). Comparing a protocol of mNC using ovulation triggering by HCG and SC would be particularly interesting to evaluate a potential impact of ovulation trigger by HCG on the number of monitoring visits required for FET compared to SC. Planning FET with mNC also carries the risk of unexpected ovulation, and thus of cancelled cycles, which is a particularly distressing event. An uncertain planning can be bothersome for patients, as well as a source of organizational problems for centers (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 centers.

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

Author contributions

Wrote the paper: Labrosse, Massin, Jung
Proofreading English text: Labrosse
Conceived and designed the experiments: Massin, Loberzstajn, Jung
Collected the data: Labrosse, Loberzstajn, Brussieux, Piétin-Vialle, Dessapt, Bry-Gauillard, Pasquier, Massin
Analyzed the data: Labrosse, Jung, Brussieux, Massin
Contributed to materials/analysis tools: Loberzstajn, Piétin-Vialle, Dessapt, Bry-Gauillard, Pasquier, Massin

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Data availability

All data are available on reasonable request.

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Figure legends

Figure 1: Flow chart

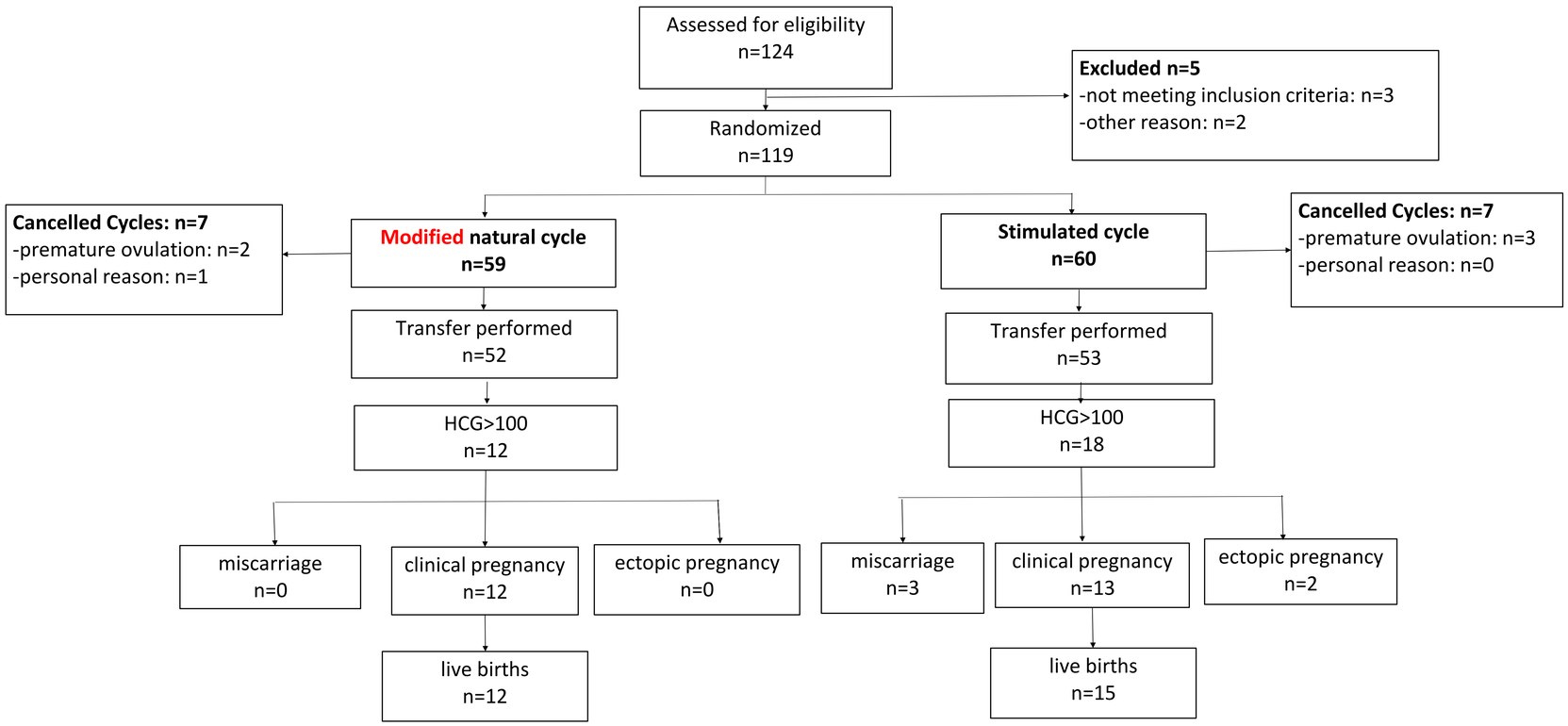
Assessed for eligibility
n=124
Excluded n=5
-not meeting inclusion criteria: n=3
-other reason: n=2
Randomized
n=119
Cancelled Cycles: n=7
-premature ovulation: n=2
-personal reason: n=1
Modified natural cycle
n=59
Stimulated cycle
n=60
Cancelled Cycles: n=7
-premature ovulation: n=3
-personal reason: n=0
Transfer performed
n=52
Transfer performed
n=53
HCG>100
n=12
HCG>100
n=18
miscarriage
n=0
clinical pregnancy
n=12
ectopic pregnancy
n=0
miscarriage
n=3
clinical pregnancy
n=13
ectopic pregnancy
n=2
live births
n=12
live births
n=15

Table 1: Patient characteristics for modified natural cycle and stimulated cycle groups

Parameters	mNC (n= 59)	SC (n= 60)
Age (years, mean +/- SD)	33.3 (+/-3.3)	32.0 (+/-3.9)
Body Mass Index (kg/m^2, mean +/- SD)	23.4 (+/-3.2)	23.8 (+/-4.0)
Infertility status		
Primary	34.0 (58.6%)	33.0 (55.0%)
Secondary	24.0 (41.4%)	27.0 (45%)
Cause of infertility		
Male	20.0 (34.5%)	15.0 (26.3%)
Endometriosis	6.0 (10.3%)	7.0 (12.3%)
Mixed	10.0 (17.2%)	5.0 (8.8%)
Idiopathic	13.0 (22.4%)	13.0 (22.8%)
Tubal	8.0 (13.8%)	14.0 (24.6%)
Ovulatory	1.0 (1.7%)	1.0 (1.8%)
Other	0.0 (0.0%)	2.0 (3.5%)
Duration of infertility (years, mean+/- SD)	4.0 (+/- 2.0)	3.9 (+/- 2.5)
Conception history	34.0 (57.6%)	33.0 (55.0%)
Smoking	9.0 (15.3%)	11.0 (18.3%)
Antral follicular count (mean+/- SD)	17.4 (+/-8.6)	18.8 (+/-11.9)
AMH (ng/mL, mean+/- SD)	3.4 (+/-2.1)	3.6 (+/-2.8)
FSH (UI/l, mean+/- SD)	6.6 (+/-1.7)	6.8 (+/-2.2)
Initial treatment		
IVF	36.0 (62.1%)	35.0 (59.3%)
ICSI	22.0 (37.9%)	24.0 (40.7%)
Protocol		
Antagonist	47.0 (81.0%)	44.0 (75.9%)
Other	11.0 (19.0%)	14.0 (24.1%)
Total dose of FSH (mean+/- SD)	1950.2 (+/-785.5)	2089.0 (+/-975.5)
Oocytes retrieved (mean+/- SD)	13.1 (+/-5.6)	14.1 (+/-5.3)
Total number of embryos (mean+/- SD)	6.3 (+/-3.3)	6.8 (+/-3.3)
Number of frozen embryos (mean+/- SD)	4.8 (+/-2.9)	5.0 (+/-2.8)
Freeze-all	11.0 (18.6%)	12.0 (20.3%)

Table 2: Total FertiQol score and FertiQol subscales for modified natural cycle and stimulated cycle groups

Scale	**mNC (mean±SD)**	**SC (mean±SD)**	*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	**mNC (mean±SD)**	**SC (mean±SD)**	*p*-value
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	**mNC (mean±SD)**	**SC (mean±SD)**	*p*-value
Environment	69±17	73±18	0.30
Treatment tolerability	67±26	61±22	0.28

*Higher scores indicate more favorable quality of life