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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

1 **Abstract**

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

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

10 **Results:** SC significantly required a lower number of monitoring visits compared to mNC
11 (3.6 ± 0.9 vs. 4.4 ± 1.1 , respectively, $P<0.0001$), a lower number of blood tests (2.7 ± 0.8 vs.
12 3.5 ± 1.0 , respectively, $P<0.0001$), and a lower number of ultrasounds (1.2 ± 0.4 vs. 1.5 ± 0.6 ,
13 respectively, $P=0.0039$). FET during “non-opening” hours (22.6% vs. 27.5% , respectively,
14 $P=0.32$) and cancellation rates (8.6% vs. 12.3% , respectively, $P=0.52$) were comparable
15 between the SC and mNC groups. No difference concerning HCG-positive rates ($P=0.47$) nor
16 live birth rates was observed ($P=0.69$). Quality of life as defined by the FertiQol score was not
17 different ($P>0.05$ for each item).

18 **Conclusion:** Altogether, our findings can be used for everyday clinical practice to better
19 inform patients when deciding on the protocol to use for FET. Our results suggest that mNC is
20 a good option for patients reluctant to have injections, but requires increased monitoring. SC
21 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

22 **Introduction**

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

33

34 Insuring the best conditions prior to frozen embryo transfer is of utmost importance. FET
35 should be performed at a time when the endometrium is receptive, defined as "implantation
36 window" (Casper and Yanushpolsky, 2016; Mackens et al., 2017). Endometrial preparation
37 for frozen embryo transfer can be performed by hormone replacement therapy (HRT),
38 stimulated cycle (SC), or close monitoring of a natural cycle (NC). So far, no consensus exists
39 on which protocol leads to the best pregnancy rates and clinical outcomes (6–11). Hence, the
40 choice of which protocol to use to prepare the endometrium for FET should rely on other
41 criteria, such as convenience for patients. Indeed, since medically assisted reproduction
42 (MAR) treatments, regular follow-ups, and repeated tests are psychologically and physically
43 burdensome for patients, optimizing quality of life for patients is essential. A large number of
44 couples abandon during the process, and up to 26% after failure of a first IVF cycle (de La
45 Rochebrochard et al., 2009; Troude et al., 2014). Although endometrial preparation using
46 natural cycle may appear more physiological and less invasive since it does not require

47 injections, it might also be less convenient for patients by engendering more monitoring, as
48 well as less convenient for centers by reducing flexibility (Mackens et al., 2017; Montagut et
49 al., 2016). To date, no study has compared the convenience of stimulated cycle versus
50 modified natural cycle (mNC) for FET.

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

54

55

56 **Materials and Methods**

57 **Patients and study design**

58 Our prospective open-labeled randomized controlled study was led in the public Medically
59 Assisted Reproduction Center of Creteil Intercommunal Hospital (France). Patients eligible
60 included women aged between 20-38 years old, covered by the general plan of the French
61 social security system with 100% coverage for infertility, having regular menstrual cycles of
62 26-35 days, undergoing intra-conjugal IVF/ICSI, with at least 2 embryos frozen at Day 2 or
63 Day 3, and for whom it was the first or second FET performed.

64 Non-inclusion criteria were: (i) IVF/ICSI with sperm donor; (ii) women with irregular cycles
65 and/or polycystic ovary syndrome; (iii) Day 1 or Day 5/Day 6 frozen embryos, transfers of
66 embryos at different moments during the same cycle, or transfers of 3 embryos
67 simultaneously; (iv) patients for whom more than 3 FETs or more than 3 oocyte retrievals had
68 already been performed, or for whom more than 6 embryos had already been replaced without
69 subsequent pregnancy; (v) patients with a uterine malformation; (vi) presence of a
70 hydrosalpinx.

71 Information on the study protocol was given to patients satisfying inclusion and non-inclusion
72 criteria during a dedicated consultation. After a reflection period, patients willing to
73 participate in the study were required to sign a consent form prior to enrolment. After
74 inclusion, patients were randomized by the use of sealed envelopes (computer generated
75 randomization) between the modified natural cycle (mNC) and stimulated cycle (SC) groups.
76 The study was conducted according to institutional and ethical rules concerning research on
77 patients. Patients could withdraw their consent at any time. Other cases of withdrawal from
78 the study included absence of progesterone rise >2 ng/ml, lysis of all frozen embryos, absence
79 of transfer, and patients lost to follow-up. The study was authorized by the French Medicinal
80 Products Agency (ANSM, n° 15014B-62) and approved by an ethical committee (Comité de
81 Protection des Personnes, Paris Ile de France 3, Approval n° 3249). No specific risk was
82 associated to the study since it involved routine treatment protocols. The study was registered
83 on ClinicalTrials (NCT02834117).

84

85 **Treatment protocol**

86 Treatment protocol is described in Supplementary Figure 1 (detailed version in
87 Supplementary Figure 2). Patients in the SC group were treated by 75 IU of recombinant FSH
88 (Gonal F®, Merck) from Day 6 to Day 11 and ovulation was triggered with recombinant
89 HCG (Ovitrelle® 250µg, Merck) when the leading follicle was >17 mm. Patients in the mNC
90 group received no gonadotropin treatment. In both groups, hormonal and ultrasound
91 monitoring were started at Day 12 of the cycle. Hormonal monitoring consisted in the
92 measurement of estradiol, LH, and progesterone levels. Ultrasound monitoring consisted in
93 the measurement of endometrial thickness and size and count of follicles in each ovary. There
94 was no ultrasound monitoring of follicular rupture. Endometrial thickness was measured in

95 both groups. Endometrial thickness ≥ 7 mm was considered mandatory for proceeding with
96 embryo transfer.

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

104 FET was programmed 2 days later for Day 2/3 embryos. If FET day fell on a Sunday or
105 during holidays, the transfer was performed 1 day earlier in case of Day 2 embryos, and 1 day
106 later in case of Day 3 embryos. Intravaginal progesterone (Progestan® 200mg twice a day,
107 Besins) was started in both groups when plasmatic progesterone was ≥ 2 ng/ml, and was
108 continued until 4 weeks of gestation in case of pregnancy. The pregnancy test was performed
109 14 days starting from the day of progesterone rise > 2 ng/ml. HCG measurements were
110 repeated every 48h until HCG > 1000 . An ultrasound to detect cardiac activity was performed
111 at 6 weeks of amenorrhea (4 weeks of gestation).

112

113 **Study endpoints and definitions**

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

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

120 cancelation rate per cycle, whatever the cause (premature ovulation, organizational problems);
121 (iii) number of transfers performed on weekends and holidays; (iv) pregnancy rate per
122 transfer, defined by HCG >100 IU/L; (v) clinical pregnancy rate per transfer, defined by
123 ultrasound detection of fetal cardiac activity; (vi) live birth rate per transfer, defined by the
124 birth of at least one live baby; (vii) percentage of multiple pregnancies; (viii) implantation
125 rate; (ix) early pregnancy loss rate (occurring before 12 weeks of gestation).

126 *The FertiQol tool* (Boivin et al., 2011) was validated by the European Society of Reproductive
127 Medicine and Embryology. FertiQol is composed of 36 items that assess general quality of
128 life (Core FertiQol: 24 items divided into “emotional”, “relational”, “mind/body” and “social”
129 subscales) and treatment-related quality of life (optional FertiQol: 10 items, divided into
130 “environment” and “tolerability” subscales), as well as overall life and physical health (2
131 items). Each question is associated to five levels of graded response. A score of 0 corresponds
132 to the lowest level of satisfaction/well-being, whereas a score of 4 corresponds to the highest
133 level. Scores attributed to each item are then added. The higher the final score is, the better
134 the quality of life. The FertiQol survey was completed in electronic format on a computer
135 made available in the transfer room before embryo transfer.

136

137

138 **Statistical analysis**

139 In our center, the mean number of visits required before FET using stimulated cycle is
140 2.6 ± 1.5 standard deviation (SD). We calculated that 48 patients per group were required to
141 demonstrate a decrease of 1 visit using stimulated cycle compared to modified natural cycle
142 (two-sided alpha-error of 0.05 and 90% power). The number of patients was increased by
143 30% to consider patients lost to follow-up and cycle cancellations. Hence, 62 patients in each
144 group, i.e. a total of 124 patients, were required in our study.

145 Data were expressed in terms of frequencies and percentages, or by mean values +/- standard
146 deviations. Depending on their distribution, Student or Mann-Whitney tests were used to
147 analyze continuous variables. Discrete variables were compared with Chi² tests. *P*<0.05 was
148 considered as statistically significant. Analyzes were performed with STATA 13/SE,
149 StataCorp, USA.

150

151

152 **Results**

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

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

162 Patient characteristics are detailed Table 1. Mean age of patients was 32.9 (\pm 3.7) years old.

163 Both groups were comparable on demographics and basal hormonal measurements. Most
164 patients were treated for primary infertility (56.8%). A majority of patients (78.4%) had been
165 stimulated with an antagonist protocol. 60.7% of patients had IVF, and 39.3% ICSI. It was the
166 first oocyte retrieval for 76.9% of patients. In average, 14 oocytes were retrieved, 7 embryos
167 obtained, and 5 embryos were frozen. 22% patients had a freeze-all strategy. Endometrial
168 thickness before performing embryo transfer was similar in both groups (8.9mm (\pm 1.8SD)
169 for NC vs. 8.5mm (\pm 1.5SD) for SC, respectively).

170
171 The number of visits required for endometrial preparation prior to FET was significantly
172 lower in the SC group compared to the mNC group (3.6 ± 0.9 vs. 4.4 ± 1.1 , respectively,
173 $P<0.0001$). The SC group was significantly associated to a lower number of blood tests
174 (2.7 ± 0.8 vs. 3.5 ± 1.0 , respectively, $P<0.0001$), and to a lower number of ultrasounds
175 performed (1.2 ± 0.4 vs. 1.5 ± 0.6 , respectively, $P=0.0039$). Both the number of FET during
176 “non-opening” hours (22.6% vs. 27.5%, respectively, $P=0.32$) and cancellation rates (8.6%
177 vs. 12.3%, respectively, $P=0.52$) were comparable between patients in the SC and mNC
178 groups.

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

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

185

186

187 **Discussion**

188 Our study demonstrates that stimulated cycle for endometrial preparation prior to FET
189 requires one monitoring visit less than modified natural cycle, without impairing quality of
190 life nor pregnancy outcomes. Stimulated cycle was significantly associated to both a lower
191 number of blood tests and a lower number of ultrasounds required.

192

193 So far, studies have failed to identify the best protocol to prepare the endometrium before
194 FET. Although our study was underpowered to detect differences in pregnancy outcomes, we

195 did not observe a significant difference between mNC and SC in terms of pregnancy nor live
196 birth rates. Consistently, a 2017 Cochrane Collaboration review of 18 randomized controlled
197 trials comparing different cycle regimens for FET in 3815 women concluded that there was
198 insufficient evidence to support the use of one protocol over another with regard to live birth
199 and clinical pregnancy rates(Ghobara et al., 2017). Groenewoud *et al.*'s (Groenewoud et al.,
200 2013) meta-analysis observed no difference between NC, mNC (ovulation triggered by HCG),
201 and artificial cycles (AC) in terms of pregnancy outcomes, and subsequent RCTs comparing
202 AC and mNC led to similar results (Greco et al., 2016a; Groenewoud et al., 2016).
203 Concerning endometrial preparation by stimulated cycle, although SC was significantly
204 associated to higher live birth rates and to lower early pregnancy loss rates compared to AC
205 ($P<0.0001$) in a recent retrospective study (Hatoum et al., 2018), Wright *et al.*'s (Wright et
206 al., 2006) prospective randomized trial reported similar implantation rates (8.5 for AC vs.
207 7.3% for SC, respectively), pregnancy rates (16% for AC vs. 13% for SC, respectively) and
208 cancellation rates (23% for both) between the two protocols. Moreover, data on early
209 pregnancy loss remain to be clarified, as some studies have reported an association between
210 AC and preclinical and clinical pregnancy loss rates (Tomás et al., 2012). Hence, in view of
211 the lack of a clear benefit between one protocol or another in terms of pregnancy outcomes,
212 other factors should be considered in the choice of the protocol to prepare the endometrium
213 prior to FET.

214 Few data exist on the cost-effectiveness of these treatments. Evaluating cost-benefit is
215 particularly challenging since it greatly differs by country and by center, and should be
216 individually assessed. Costs engendered do not only include the price of medications used
217 (injections, drugs). Cost-analysis also needs to assess costs associated to monitoring (blood
218 samples, ultrasound scans, time and work load for centers), and costs supported by patients
219 (transportation, absences from work). Groenewoud *et al.*(Groenewoud et al., 2016) concluded

220 that costs associated to NC were comparable to those of AC (€617.50 per cycle for NC vs.
221 €625.73 per cycle for AC, respectively, $P=0.54$). Data directly related to treatments had been
222 obtained from healthcare insurances, and the number of visits, transport mode, distance
223 travelled during treatment, as well as number of days taking a leave of absence or sick leave
224 had been collected using a web-based survey completed by patients. Similarly, considering
225 only drug costs, Greco *et al.* (Greco et al., 2016b) observed no difference between AC and
226 mNC despite the use of different pharmaceuticals (64.0 ± 1.6 and 59.88 ± 0.0 euros,
227 respectively, $P=0.44$). These data suggest that although mNC has the advantage of sparing
228 the cost of injections, the effect might be reversed by the cost of more monitoring required.
229 Altogether, the fact that mNC required one supplementary monitoring visit compared to SC in
230 our study can be used for everyday clinical practice to better inform patients when deciding
231 on the protocol for endometrial preparation prior to FET. The drawbacks of gonadotropin
232 therapy have to be considered in the decision on which protocol to use. Indeed, in addition to
233 increased costs, gonadotropin stimulation can induce undesirable side effects for patients such
234 as the risk of abdominal discomfort, cyst formation, ovarian hyperstimulation syndrome, and
235 multiple pregnancies in case of exaggerated response to stimulation and/or intercourse
236 concomitant with ovulation. However, although one monitoring visit less might be negligible
237 for clinicians, it can be of particular importance for patients. Given that regular follow-ups
238 and repeated tests are particularly tiring and stressful, it appears essential to minimize the
239 impact of treatment on patients' personal, professional, and social lives (Brandes et al., 2009).
240 We found that mNC required 4.5 ± 1.0 visits, which is consistent with literature (Fatemi et
241 al., 2010; Weissman et al., 2009). Larger effectives are needed to confirm an advantage of SC
242 versus mNC on cancellation rates and transfers performed during "non-opening" hours, as
243 both were comparable for patients treated by SC compared to mNC. Moreover, FETs on
244 Sundays were not feasible in our center due to our relatively small medical staff. In centers

245 where FET could be performed on Sundays, it is a valuable information to know if SC could
246 reduce the number of FET performed on a non optimal day, compared to mNC.

247

248 Although mNC has the advantage of requiring no treatment, ensuring timely thawing and
249 transfer of embryos using mNC implies awaiting the LH surge, which varies between cycles
250 and between patients. Thereby, previous studies have reported that using HCG to trigger
251 ovulation in mNC could significantly reduce the number of monitoring visits required,
252 without any adverse effect on reproductive outcome (Weissman et al., 2009; Weissman et al.,
253 2011). Comparing a protocol of mNC using ovulation triggering by HCG and SC would be
254 particularly interesting to evaluate a potential impact of ovulation trigger by HCG on the
255 number of monitoring visits required for FET compared to SC. Planning FET with mNC also
256 carries the risk of unexpected ovulation, and thus of cancelled cycles, which is a particularly
257 distressing event. An uncertain planning can be bothersome for patients, as well as a source of
258 organizational problems for centers (Gameiro et al., 2012). Saving one visit might enable
259 simplification of the treatment process, less time-consuming tests (ultrasounds and hormonal
260 assays), and reduction of workload for MAR centers.

261

262 In conclusion, considering treatment burden and patient preference are major factors in the
263 choice of the protocol to be used to prepare the endometrium before FET. In everyday clinical
264 practice, patients should be informed that modified natural cycle is a good option for those
265 reluctant to have injections, but requires increased monitoring. Stimulated cycle may reduce
266 unnecessary anxiety and operational costs, and offer more flexibility for patients and IVF
267 centers. Studies on larger effectiveness, as well as an economic evaluation of the costs involved,
268 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

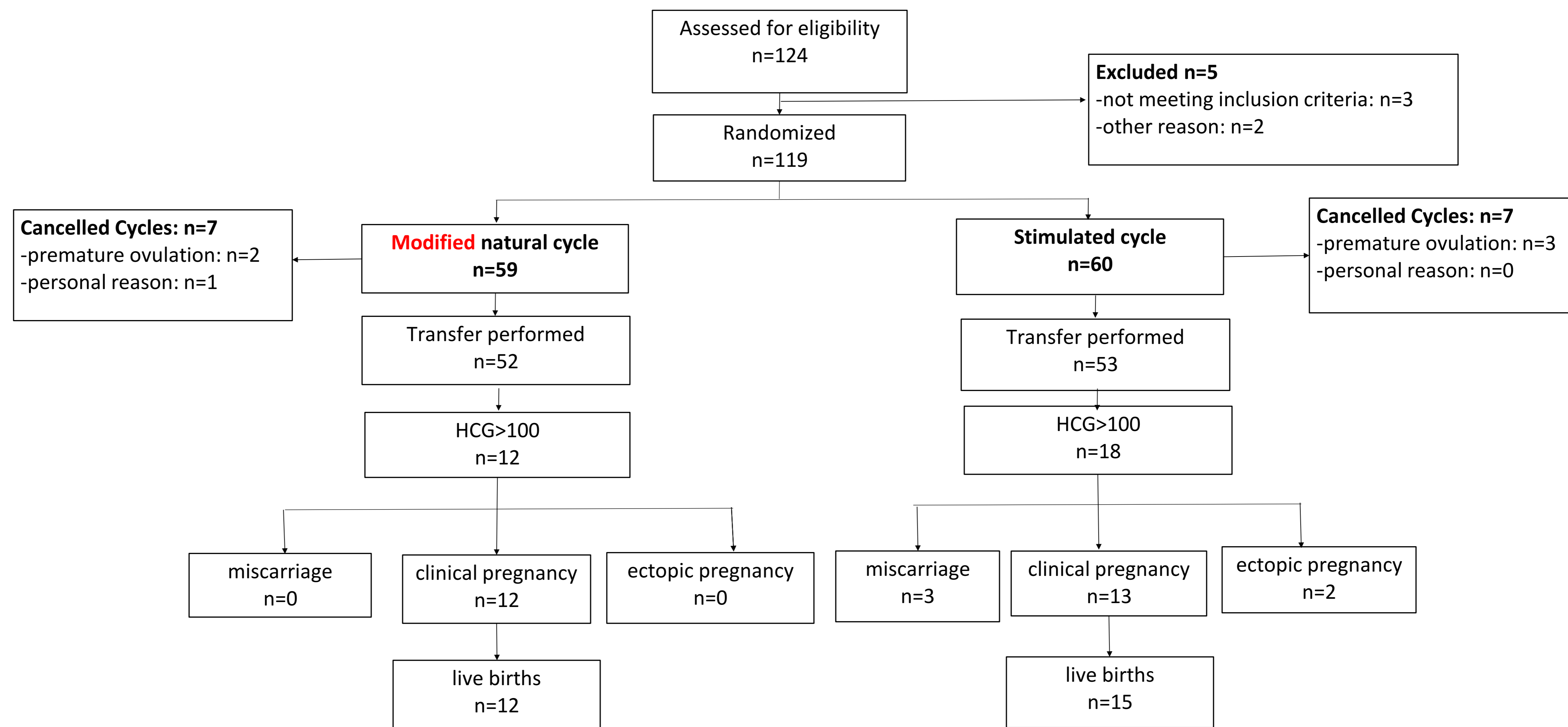


Table 1: Patient characteristics for modified natural cycle and stimulated cycle groups

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