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Higher live birth rate with stimulated rather than artificial cycle for frozen-thawed embryo transfer

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ABSTRACT

Objective: To study which endometrial preparation allows a better ongoing pregnancy rates (OPR) and live birth rate (LBR) after frozen-thawed embryo transfer (FET) between mild gonadotropin ovarian stimulation (OS) and artificial cycles (AC).
Study design: Retrospective follow-up study including all FET performed in one fertility center from 2013 to 2016. In the OS group, gonadotropins were followed by r-hCG triggering. Vaginal micronized progesterone (200 mg/day) was given systematically. In the AC group, estradiol (E2) was started on Day 1. Vaginal micronized progesterone (600 mg/d) was added to E2 for 12 weeks. Data were analyzed using a multiple regression model.
Results: Among 1021 FETs, 35% underwent OS preparation, 65% had an AC. As expected, patients in the AC group suffered more from endometriosis (18.5% *vs.* 12.9%; $p = .021$) and polycystic ovarian syndrome (21.7% *vs.* 10.9%; $p < .0001$) than patients in the OS group. There was no difference between groups with respect to endometrial thickness, number of embryos transferred, development stage at FET, cryopreservation technique. Despite a similar clinical pregnancy rate (CPR) (24.4% *vs.* 20.8%; $p = .189$), the OPR was significantly higher in the OS than in the AC group (17.9% *vs.* 11%; $p = .002$), leading to an increased LBR (17.1% *vs.* 9.8%; $p < .001$). After adjusting for parameters usually linked to early pregnancy losses or potential bias (patient age at freezing, smoking status, PCOS, endometriosis, rank of transfer and previous miscarriages), the results remained significant.
Conclusion: Despite a similar CPR, LBR was significantly higher with mild OS than with the AC preparation, even after adjusting for potential confounders. In light of these results, the first-line endometrial preparation could be OS instead of an AC. In an AC, a potential defect of the luteal phase may exist, treatment could be optimized to avoid pregnancy losses. A randomized controlled trial should be undertaken to assess the role of OS and ACs in FET.

Introduction

Over the last decade, the use of frozen-thawed embryo transfer (FET) in assisted reproductive techniques has increased, mainly due to elective single-embryo transfer and "freeze-all" policies to avoid ovarian hyperstimulation syndrome or the detrimental effects of ovarian stimulation on endometrial receptivity. For example, in Europe the number of FETs increased from 129,693 in 2011 to 154,712 in 2013 [1,2]. Improvements in cryopreservation techniques with vitrification, supported this recourse to embryo freezing.

In addition to embryo survival and quality, successful FET also depends on endometrial receptivity at the time of transfer. Different protocols can be used to prepare the endometrium for FET. The most common protocols are (a) the natural cycle (NC) (modified with hCG triggering (mNC) or not), (b) the artificial cycle (AC) and (c) the mild ovarian stimulation (OS) cycle. The choice of

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the best protocol adapted to each patient is still a matter of debate. For a long time, the AC protocol has been preferred as the first-line protocol for endometrial preparation before FET for better patient comfort avoiding injections, easier FET scheduling, and presumption of better results. However, some patients may prefer a few days of subcutaneous injections compared to three months of vaginal high-dose hormonal support associated with the risks of estrogen supplementation (*i.e.*, thrombosis) [3]. Also, the use of a GnRH antagonist allows enough regulation of FETs with OS for endometrial preparation.

Concerning the presumption of better results with an AC, recent reviews and meta-analysis [4–6] have concluded that the different methods of endometrial preparation (mNC, NC or AC) appeared to be equally successful in terms of pregnancy rate (PR), ongoing pregnancy rate (OPR) and live birth rate (LBR) in women with regular cycles. However, these reviews were based on very few randomized controlled trials and different populations. In addition, the AC protocols were very different in each study (route of administration of estrogen and progesterone, dosage, duration, *etc.*). Since these publications, several studies were performed comparing NC (or mNC) with AC with contradictory results identifying equivalence between the two protocols [7–11], or a higher CPR with NC [12,13] or AC [14]. However, few of these studies focused on results in terms of OPR and LBR. The first studies focusing on AC described a higher PR in AC than in NC, but no significant difference in LBR was observed owing to a higher rate of pregnancy loss in AC [15,16]. Tomàs et al. retrospectively compared more than 4000 FET cycles and described an increased miscarriage rate in AC compared to that in NC or OS protocols [15]. A higher number of patients with polycystic ovary syndrome (PCOS) in the AC group and a lack of compliance due to the long duration treatment was supposed to be an explanation for the higher pregnancy loss rate.

A recent systematic review and meta-analysis [17] concluded again that outcomes were similar between NC *versus* AC but that mild OS may be promising. Indeed, in this meta-analysis, an increased PR and LBR with OS compared to AC was described, but with limited data and various OS protocols. In the literature, few articles focus on mild OS with gonadotropins for FET preparation, and there are contradictory results [13,18–21].

The main objective of this retrospective study was to compare the LBR between mild OS with gonadotropins (*i.e.* with a functional corpus luteum) and an AC for FET in daily clinical practice. In addition, the other objectives were to compare the OPR and CPR between these two groups.

Material and methods

This study included all 1021 autologous FET in one French academic fertility center from January 2013 to December 2016. The embryos were derived either from conventional *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) cycles.

The Ethical committee gave its unrestricted approval for the study and all patients had previously given their informed consent for the use of their data (Comité de l'évaluation de l'ethique des recherches biomédicales Paris Nord », IRB 00006467: ID 2018-013). All the data were collected from the Medifirst® software, which meets recognized medical and ethical specifications according to the French information protection commission (ID 2068638).

Endometrial preparation protocols

The 2 protocols used before the FET were the following:

1 OS cycle: gonadotropin stimulation was initiated between Day 2 and Day 8 (initial dose 25 to 75UI per day). A GnRH antagonist could be used to program the timing of the FET. The initial dose of gonadotropin ranked from 25 to 112,5 UI per day. A first ultrasound and hormonal (estradiol, progesterone and LH) testing was performed by Day 8 to 11 and repeated if needed according to the ovarian follicular response. Once the dominant follicle reached 16–20 mm, a bolus of 6500 IU r-hCG (Ovitrelle®, Merck, Darmstadt, Germany) was administered to induce ovulation. Luteal phase support with vaginally administered progesterone 100 mg twice a day was begun two days after ovulation induction. FET was performed 5 days after hCG injection for cleaved embryos and 7 days after hCG injection for blastocysts. In case of a positive pregnancy test, the patients continued the progesterone until the 6th week of gestation (WG).
2 AC: Endometrial preparation started with estradiol (E2) administered orally (2 mg x 2 or 3/day) or transdermally (200 μg/3 days) from the first cycle day. The initial dose of E2 was 4 mg/day in most case. If the endometrial thickness was below 7 mm after 14 days of E2 treatment, the dose of E2 was raised to 6 mg/day. An initial dose of 6 mg/day was prescribed if the increased E2 dose was needed in a previous cycle. A first ultrasound and hormonal (estradiol, progesterone and LH) testing was performed by Day 12 to 14 and repeated if needed. When the thickness of the endometrium reached at least 7 mm and the serum progesterone level was below 1 ng/ml, progesterone supplementation was started with vaginal progesterone 600 mg daily starting three days before the FET for cleaved embryos or 5 days before the FET for blastocysts. The supplementation continued until a pregnancy test was performed. In case of a positive test, the patients were instructed to continue treatment until the 12th WG since no gestational corpus luteum could maintain the progesterone level until there was enough placental progesterone production.

Embryos

Embryos were frozen according to the slow freezing protocol (Embryo Freezing/Thawing, Origio, Versailles, France) before 2014 and vitrified (VitKit®, Irvine Scientific, Santa-Ana, USA) after 2014. Embryos were mainly frozen at the cleavage stage until April 2016 and then at the blastocyst stage afterwards. They were transferred on the same day as thawing for D3 embryos or blastocysts and thawed the day before transfer for D2 embryos.

Pregnancies

Pregnancy was defined as a positive pregnancy test performed 10–12 days after FET (according to embryo stage at transfer). A vaginal ultrasound was performed 4–5 weeks after a positive pregnancy test to confirm a clinical pregnancy (gestational sac) and at the 12th WG to confirm an ongoing pregnancy (heartbeat). An early pregnancy loss was defined as the spontaneous cessation of a clinical pregnancy before the 12th WG. Recurrent pregnancy losses were defined as $\geq$ 3 previous miscarriages.

Statistics

All analyses were performed using Stata for Windows (version 14; StataCorp). The patients' age at freezing, smoking status, PCOS status, endometriosis history, rank of transfer and history of recurrent pregnancy losses were included in the multiple regression model as potential confounders.

Results

From January 2013 to December 2016, 1021 FETs were performed, and all were included in this retrospective analysis.

A total of 357 (35%) patients received mild OS, and 664 (65%) underwent an AC before FET. Baseline characteristics are presented in Table 1.

They were issued from 1313 initiated cycles. No difference in cycle cancellation rate was observed between the mild OS and AC groups before thawing (18.7% *vs.* 15.3%, respectively; p = .13) or after thawing (5.8%; *vs.* 7.4% p = .33).

Groups with FET (N = 1021) were comparable with respect to age at transfer and at freezing, BMI, history of recurrent pregnancy losses, viral status and smoking habits (Table 1). As expected, patients in the AC group suffered from endometriosis (18.5% *vs.* 12.9%) (p = .021) and PCOS (21.7% v 10.9%) (p < .0001) more frequently than patients in the mild OS group since PCOS and endometriosis are classical indications for an AC endometrial preparation for FET. In contrast, for patients undergoing the mild OS preparation, the indication of ART was more frequently male factor infertility (49.3% *vs.* 41.1%; p = .012). The rank of transfer was statistically lower in AC *versus* OS. No significant difference was

Table 1
Baseline characteristics.

Total number of FET	Mild ovarian stimulation (OS) N = 357		Artificial Cycle (AC) N = 664		
	Mean (SD)	n (%)	Mean (SD)	n (%)	*p* value
Age (y) at transfer	34.9 (4.10)		34.8 (4.51)		.67
Age(y) at freezing	33.8 (4.21)		33.8 (4.61)		.87
BMI (kg/m2)	23.1 (7.75)		23.3 (7.56)		.66
Ongoing smoking women		37 (10.4%)		60 (9.0%)	.77
Primary infertility		134 (37.5%)		246 (37.0%)	.88
Viral status					
Woman with HIV		34 (9.5%)		61 (9.2%)	.86
Woman with HBV		27 (7.6%)		66 (9.9%)	.21
Woman with HCV		4 (1.1%)		5 (0.8%)	.55
Previous miscarriages ≥3		26 (7.3%)		47 (7.1%)	.90
Diagnoses					
Endometriosis		46 (12.9%)		123 (18.5%)	**.021**
Male infertility		176 (49.3%)		273 (41.1%)	**.012**
Tubal infertility		139 (36.1%)		231 (34.8%)	.67
PCOS		39 (10.9%)		144 (21.7%)	<**.0001**
Hormonal parameters on day 3					
FSH (IU/L)	6.65 (2.20)		6.42 (2.13)		.15
E2 (pg/mL)	45.95 (27.0)		42.94 (26.9)		.13
AMH (ng/mL)	3.55 (2.69)		4.88 (4.40)		<**.0001**
TSH (mIU/ml)	1.81 (1.10)		1.68 (1.05)		.14
Total dose of gonadotropin (IU)	372.29 (217.6)			–	
Per os E2 treatment	–			87.0%	
GnRH agonist co-treatment	–			12.7%	
Initial ART					.064
ICSI		261 (73.1%)		448 (67.5%)	
IVF		96 (26.9%)		216 (32.5%)	
Last endometrial thickness *(mm)					.35
< 6 mm		14 (3.9%)		17 (2.6%)	
6-14mm		334 (93.6%)		635 (95.6%)	
> 14mm		9 (2.5%)		12 (1.8%)	
Rank of transfer					0.34
1		205 (57.4%)		434 (65.4%)	
2		102 (28.6%)		166 (25.0%)	
3		37 (10.4%)		51 (7.7%)	
4 or more		13 (3.6%)		13 (1.9%)	
Embryos transferred					.36
1		188 (52.7%)		366 (55.1%)	
2		168 (47.1%)		292 (44.0%)	
3		1 (0.3%)		6 (0.9%)	
Developmental stage at FET					.66
Cleavage stage (D2 or D3)		305 (85.4%)		574 (86.4%)	
Blastocyst stage (D5 or D6)		52 (14.6%)		90 (13.6%)	
Cryopreservation technique					.52
Vitrification		218 (61.1%)		392 (59.0%)	
Slow freezing		139 (38.9%)		272 (41.0%)	
Duration of cryopreservation (days)					.92
<90		104 (29.1%)		199 (30.0%)	
90–365		150 (42.0%)		287 (43.2%)	
>365–1095		65 (18.2%)		113 (17.0%)	
>1095		38 (10.6%)		65 (9.8%)	
Intact blastomeres post thawing (cleavage stage embryos) (%)					.318
100		315 (88.2%)		570 (85.9%)	
50–90		42 (11.8%)		94 (14.1%)	
Embryo's survival (%)	92.3 (18.7)		92.4 (18.6)		.914

FET: frozen-thawed embryo transfer; BMI: body mass index; HIV: human immunodeficiency virus; HBV: hepatitis B virus; HCV: hepatitis C virus; PCOS: polycystic ovarian syndrome; FSH: folliculo stimulating hormone; E2: estradiol; AMH: anti-müllerian hormone; TSH: thyroid stimulating hormone; GnRH: gonadotropin-releasing hormone; ART: assisted reproductive techniques; IVF: *in vitro* fertilization; ICSI: intra-cytoplasmic sperm injection *last endometrial thickness recorded by ultrasound (0–4 days before triggering (in OS cycles) or beginning of progesterone supplementation (in AC cycles)).

Table 2
Outcomes per FET according to endometrial preparation.

Outcomes per cycle with embryo transfer	Mild ovarian stimulation (OS) N (%)	Artificial cycle (AC) N (%)	p value	adjusted[a] p value
Number of cycles with FET	N = 357	N = 664		
Implantation rate (%)	18.90 %	16.30 %	.247	.145
Positive pregnancy test	100 (28%)	156 (23.5%)	.113	.075
Clinical pregnancy	87 (24.4%)	138 (20.8%)	.188	.105
Early pregnancy loss	21 (5.9%)	60 (9.0%)	.078	.097
Ectopic pregnancy	2 (0.56%)	5 (0.75%)	.723	.672
Ongoing pregnancy after 12 W G (OP)	64 (17.9%)	73 (11.0%)	**.002**	**.001**
Medical interruption of pregnancy (after 12 W G)	2 (0.56%)	5 (0.75%)	.723	.637
Late pregnancy loss (after 12 W G)	0	3 (0.45%)	NA	NA
In Utero fetal death	1 (0.28%)	0	NA	NA
Live birth	61 (17.1%)	65 (9.8%)	<**.001**	<**.0001**
Multiple pregnancy (% of OP)	9 (14.1%)	9 (12.2%)	.741	.896

FET: frozen-thawed embryo transfer; WG: weeks of gestation; PCOS: Polycystic Ovarian Syndrome.
[a] Adjusted on age at freezing, woman smoking status, PCOS, endometriosis, previous history of recurrent pregnancy loss, and rank of transfer.

Table 3
Outcomes per clinical pregnancy and per ongoing pregnancy according to endometrial preparation.

	Mild ovarian stimulation (OS) N (%)	Artificial cycle (AC) N (%)	p value	adjusted[a] p value
Outcomes per Clinical Pregnancy	N = 87	N = 138		
Early pregnancy loss	21 (24.1%)	60 (43.5%)	**.004**	**.002**
Ectopic pregnancy	2 (2.3%)	5 (3.6%)	.581	.512
Medical interruption of pregnancy after 12 W G	2 (2.3%)	5 (3.6%)	.581	.468
Late pregnancy loss after 12 W G before 22 WG	0	3 (2.2%)	NA	NA
In utero fetal death	1 (1.1%)	0	NA	NA
Live Birth	61 (70.1%)	65 (47.1%)	**.001**	<**.0001**
Outcomes per Ongoing Pregnancy after 12 W G	N = 64	N = 73		
Medical interruption of pregnancy after 12 W G	2 (0.03%)	5 (6.8%)		
Late pregnancy loss after 12 W G before 22 WG	0	3 (4.1%)	NA	NA
In utero fetal death	1 (1.2%)	0	NA	NA
Live Birth	61 (95.3%)	65 (89.0%)	.190	.089

WG: weeks of gestation; PCOS: Polycystic Ovarian Syndrome.
[a] Adjusted on age at freezing, woman smoking status, PCOS, endometriosis, previous history of recurrent pregnancy loss and rank of transfer.

found in embryos characteristics or final endometrial thickness between groups (Table 1). Total gonadotropin dose in the mild OS group was low (372.29 UI (+/- 217.6)). The maximum dose of daily gonadotropin was 112,5 UI at the end of stimulation, but for the majority of patients it was 50 UI per day or less. The mean stimulation duration was 6 days (1 to 26 days). For 187 patients gonadotropin stimulation was used only for less than 6 days, in addition to GnRH antagonist to allow a better scheduling of the hCG trigger and of the embryo transfer.

Pregnancy outcomes per FET are shown in Tables 2 and 3 and Fig. 1. Despite a similar CPR (24.4% *vs.* 20.8%; p = .189), the OPR per FET at 12 W G was significantly increased in the mild OS group (11% *vs.* 17.9%; p = .002) leading to an increased LBR in this group (9.8% *vs.* 17.1%; p=<.001) compared to that in the AC group (Table 2, Fig. 1). After adjusting for parameters usually linked to early pregnancy losses and potential bias (patient age at freezing, smoking status, PCOS status, endometriosis history, an history of recurrent pregnancy losses and rank of transfer), the results remained significant (Table 2). Additional adjustments for BMI and male factor infertility did not affect the results.

A lower rate of early pregnancy loss in the mild OS group was found that did not reach significance per FET cycle (p = .070) (Table 2, Fig. 1) but was significant per CP (24.1% *vs.* 43.5%; p < .001) (Table 3). This result remained significant after adjustment (Table 3).

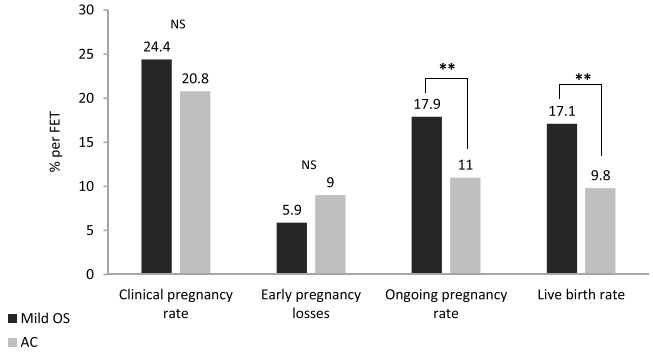

Fig. 1. Outcomes per frozen-thawed embryo transfer (FET) according to endometrial preparation. FET: frozen-thawed embryo transfer; OS: gonadotropin ovarian stimulation; AC: artificial cycle; NS: non-significant; **: p < 0.001.

Comment

This retrospective analysis of more than a thousand FETs revealed that the OPR and the LBR were significantly higher with mild OS than with AC despite a similar CPR. The results were confirmed even after adjusting for PCOS status, age at freezing, endometriosis history, BMI, male factor infertility, smoking status, history of recurrent pregnancy loss and rank of transfer. Therefore, mild OS (*i.e.* with a functional corpus luteum) is associated with better outcomes after FET than an AC.

This study has numerous strengths. The sample is composed of a large exhaustive series including all FETs performed over a 4-year period. This cohort is made up of a population mirroring daily clinical practice. There is an agreement in the significant results both with and without adjustment. The monocentric nature of this

study guarantees homogeneity of the protocols and consequently better comparability. However, the study has some limitations due to its retrospective nature and the lack of power to analyze certain subgroups (*e.g.* different embryo freezing protocols and embryo stages at the time of freezing). Nevertheless, no difference was found between groups for these parameters.

Several recent studies and meta-analyses concluded that all current methods of endometrial preparation appear to be equally successful in terms of OPR, and some of these studies extend the results to LBR, but very different populations and treatment protocols were used [4–7,17,22]. Due to easier FET scheduling and presumption of patient better comfort and less cost avoiding injections, the AC protocol has been preferred as the first-line protocol for endometrial preparation before FET. However, in our work we demonstrated that in mild OS protocols the total gonadotropin dose is very low and allow good FET scheduling with GnRH antagonist use.

Few studies specifically focused on endometrial preparation with OS *versus* AC. Three studies identified no difference in PR between these two protocols [19,20,23] in small unselected populations. In PCOS patients, Yu et al. concluded that these two protocols led to the same PR [21]. Based on these few data, the meta-analysis of Yarali et al. in 2016 described an increased CPR and LBR when employing OS *versus* an AC, but this analysis included OS with either gonadotropin or letrozole [17]. Recently, a retrospective French study described a higher rate of pregnancy loss with an AC *versus* OS leading to a lower LBR in the AC group, but there was neither description of the population nor adjustment [18]. In particular, the parameters usually linked to early pregnancy losses were not described and/or adjusted (*i.e.*, PCOS status, history of recurrent pregnancy losses, *etc.*). A higher pregnancy loss rate was also described in the AC group in Tomàs et al.'s [15] work, but it was linked to the higher prevalence of PCOS patients in that group. In our study, even after adjusting for PCOS status, the OPR was lower in the AC group compared to the OS group despite similar implantation and CPR.

A deficient luteal phase in the AC group could be the cause of the decreased OPR with an asynchronized window of implantation. Indeed, implantation besides the normal "window of implantation" is associated with early pregnancy losses [24]. Moreover, an optimal progesterone level seems to be needed in ACs for the evolution of pregnancy. Yovich et al. [25] described an optimal level between 15 and 30 ng/ml 3–4 days after blastocyst, and Kofinas et al. [26] indicated a level between 10 and 20 ng/ml on day of blastocyst transfer. A level of progesterone over 20 ng/ml is associated with a decreased OPR [26]. A recent study on the optimal duration of progesterone administration before FET with an AC protocol confirmed a higher early pregnancy loss rate when the period of progesterone supplementation is too short [27]. When the duration of progesterone supplementation is adequate, a suboptimal progesterone level in AC endometrial preparation could be due to a lack of adherence or defective absorption [28]. Better absorbance and adherence should be observed with injectable administration, leading to better pregnancy outcomes. This result was suggested by three studies, including one recent randomized controlled trial [29], all concluding that intramuscular administration was superior to vaginal administration [29–31], whereas many studies have reported similar pregnancy outcomes [6,32–35]. Adaptation of AC treatment according to progesterone levels was suggested as a way to improve OPR [25,36,37] and decrease pregnancy losses [38]. However, the administration route and dose also need to be taken into account when performing serum progesterone monitoring since the pharmacokinetics of each progesterone treatment are different and may also lead to a desynchronization of the implantation window [39,40].

During OS, a corpus luteum is active, secreting progesterone progressively until stabilization, leading to a more constant progesterone level [39]. Moreover, ovulation triggering is performed with hCG which provide a luteotropic effect in the early luteal phase [21]. Finally, other factors are also secreted by the corpus luteum, leading to different (possibly more natural) endometrial protein secretion profiles than with an AC [39].

In women with PCOS, AC is often chosen because of oligo-anovulation. In the literature, PCOS is a known risk factor for pregnancy loss, and the choice of the best endometrial preparation protocol is even more challenging. Only one study focused specifically on women with PCOS, and that study concluded that OS was not superior to an AC in terms of PR in this specific population [21]. In our study, we controlled for PCOS status. It could be interesting to explore whether patients with PCOS could potentially benefit even more from a mild OS for FET.

In our daily practice population, we found that, despite a same CPR, the OPR and LBR were higher with mild OS than with an AC, even after adjusting for numerous potential sources of bias (*e.g.*, PCOS, history of recurrent pregnancy losses, *etc.*). In an AC, a potential defect in the luteal phase may exist, and treatment could be optimized to avoid pregnancy losses. In the light of the OPR and LBR results, we think the first-line endometrial preparation for FET should be OS instead of an AC even for patients with PCOS or endometriosis. Nevertheless, randomized controlled trials should be undertaken to assess these preliminary results.

Declaration of Competing Interest

None.

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