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Progestin-primed ovarian stimulation for oocyte cryopreservation in patients with nonmedical indications: a case–control study

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Abstract

Background The PPOS (Progestin Primed Ovarian Stimulation) protocol has been evaluated and has proved its effectiveness in preventing the LH (luteinizing hormone) surge. This protocol is often used for cryopreservation for social reasons because it is simpler and more cost-effective. The objective of our study was to evaluate the efficacy and the convenience of the PPOS protocol in the context of oocyte cryopreservation for social reasons.

Methods In this bicentric matched case–control study, all PPOS cycles performed for nonmedical reasons between January 2021 and June 2023 were included. Each PPOS cycle was matched with 2 control cycles performed with the antagonist protocol on the basis of the antral follicle count (+/- 5), BMI (+/- 2 kg/cm^2) and starting gonadotropin dose (+/- 75 UI). The primary endpoint was the number of mature oocytes. The secondary endpoints were other parameters and outcomes of COS. We evaluated the convenience of PPOS by analysing the frequency of monitoring sessions. Univariate analysis was performed via univariate conditional logistic regression. Multivariate analysis was performed via conditional multivariate logistic regression for significant parameters in the univariate analysis ($p < 0.2$).

Results The patient characteristics were comparable, except the median age, which was lower in the antagonist group (35.5 vs. 34.6 years, $p < 0.001$). Multivariate analysis revealed no statistically significant difference in the number of metaphase II (MII) oocytes between the groups ($p = 0.91$) or in the total number of COCs retrieved (0.94). There was no statistically significant difference between the groups in terms of the maturation rate or the OSI ($p = 0.38$ and $p = 0.16$). The number of monitoring sessions was significantly lower in the PPOS protocol group ($p < 0.001$).

Conclusion The response to ovarian stimulation with the PPOS protocol for oocyte cryopreservation in patients with nonmedical indications does not differ statistically from that with the antagonist protocol in terms of the number of MII oocytes. This protocol offers the advantages of a more patient-friendly approach through oral administration, a

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significantly lower number of monitoring sessions with the same efficacy as the antagonist protocol and could be offered as a first line treatment.

Clinical trial number NA.

Trial registration date NA.

Keywords Social freezing, Fertility preservation, Dydrogesterone, Progestin-stimulated ovarian stimulation, Ovarian stimulation index

Background

Improvements in cryopreservation techniques, particularly the development of vitrification, have revolutionized oocyte freezing, leading to a dramatic increase of female fertility preservation programs [1, 2]. Initially authorized in France for medical purposes (such as cancer and endometriosis), oocyte cryopreservation has been subsequently extended for individuals with nonmedical indications—in other words, for social reasons—in 2021 after the revision of French bioethics law. Consequently, any woman in France aged 29 to 36 years, without medical contraindications, can opt to undergo oocyte self-preservation. Although fertility declines with aging, the average age at first birth in France increased to 30.9 years in 2011, which is four years greater than that reported in 1981 [3]. This discrepancy has resulted in a significant surge in the demand for fertility preservation, with 11,500 requests recorded within one year of the law's implementation in France.

This process requires controlled ovarian stimulation (COS) before oocyte retrieval [4] combining simultaneous follicle stimulation with gonadotropin and the prevention of a premature luteinizing hormone (LH) surge to avoid spontaneous ovulation [5, 6]. For numerous years, the traditional COS protocol has relied on gonadotropin-releasing hormone (GnRH) agonists to prevent premature LH surges [7]. Since then, GnRH antagonist protocols have been preferred over GnRH agonist protocols because of their lower risk of ovarian hyperstimulation syndrome (OHSS) [8–10]. Nevertheless, GnRH antagonist protocols remain costly and necessitate additional daily injections [7, 11].

In recent years, research interest has shifted towards replacing GnRH agonists with progestins to control LH surges, leading to the development of a new protocol known as the progestin-primed ovarian stimulation (PPOS) protocol [12, 13]. This protocol was discovered in an oncological context when fertility preservation had to be carried out urgently in the luteal phase [14]. During these types of stimulation, the endogenous secretion of progesterone can prevent the LH increase and further spontaneous ovulation [15]. Indeed, progesterone reduces GnRH pulsatility from the hypothalamus, thus inhibiting the estradiol-induced LH release [16]. Therefore, a new strategy for COS, i.e., the PPOS protocol, has been increasingly investigated. Kuang et al. first used medroxyprogesterone acetate (MPA) for LH suppression in patients undergoing COS, which resulted in outcomes similar to those of the short agonist protocol [17]. Owing to its economic and clinical convenience, the PPOS protocol has gained considerable popularity. Several investigations on the use of the PPOS protocol in patients with different ovarian reserves have been reported [18–21]. A large meta-analysis was carried out by Guan et al., who compared the PPOS protocol to the antagonist protocol or short agonist protocol [19]. The study population included women with normal, decreased or increased ovarian reserves, depending on the study, who underwent stimulation in the context of infertility. Clinical and ongoing pregnancy as well as live birth rates following PPOS protocol were not different from those of the control group. Compared with GnRH agonists or GnRH antagonists, the use of progestin for LH suppression is associated with promising advantages, such as oral administration, convenience for users, and lower costs [22]. The main disadvantage of using the PPOS protocol in infertile patients is the requirement of the cycle segmentation. Indeed, since the endometrium becomes out of phase as a result of early progestin exposure, a fresh embryo transfer cannot be considered. This makes the PPOS protocol the protocol of choice in cycles where a freezeall strategy is adopted, such as in COS cycles performed for oocyte cryopreservation or egg donation [22, 23].

A variety of progestins are currently available, with varying antigonadotropic effects. As mentioned before, MPA was the first progestin to be evaluated [17]. Subsequent studies have examined the risk of LH elevation with dydrogesterone, desogestrel and even the levonorgestrel intrauterine device, which offers patients the advantage of maintaining their contraception [19, 24, 25]. Other studies have evaluated the PPOS protocol using dienogest as a progestin in the context of fertility preservation for patients with endometriosis [26].

In response to the significant demand for fertility preservation, assisted reproductive technology (ART) services have been overwhelmed. To meet this demand, our clinic has chosen to utilize the PPOS protocol as the first-line method for fertility preservation, given its more practical approach.

The aim of our study was to evaluate the efficacy and convenience of the PPOS protocol with dydrogesterone in the management of patients undergoing oocyte cryopreservation after COS for nonmedical indications compared with an antagonist protocol.

Methods

Study design

We conducted a retrospective observational case–control study from January 2021 to June 2023 at two French centres of reproductive medicine (Jean Verdier Hospital, Bondy and Antoine Beclere Hospital, Clamart). Data were extracted from the "Medifirst" software of the two centres in August 2023.

Selection of cases and controls

A case was defined as follows: a patient aged between 29 and 37 years who was undergoing COS for oocyte cryopreservation for a nonmedical indication (social reasons) via the PPOS protocol with dydrogesterone. Patient age and date of inclusion were defined according to French law for nonmedical fertility preservation for women.

A COS cycle was excluded if COS was performed with a protocol other than the PPOS protocol, if a progestin other than dydrogesterone was used, if the antral follicle count (AFC) was less than 7 or if the oocyte pick-up was cancelled.

The inclusion criterion for the control group was a COS cycle in which the patient was between 29 and 37 years of age, an antagonist protocol was used for COS, and the indications for COS were oocyte cryopreservation or intracytoplasmic sperm injection (ICSI) or egg donations. Controls were excluded if they had ovarian cysts or endometriomas, in case of past history of cancer or ovarian surgery or an AFC less than 7.

Each case was matched to 2 controls from the same ART centre on the basis of BMI (± 2 kg/m$^{2)}$, the AFC (±- 5) and the FSH starting dose (± 75 IU).

Procedures

In the PPOS group, all patients were planned to receive pretreatment with oestrogen-progestin pills for 15 to 60 days, except if women presented with medical contraindications for this treatment. After a wash-out period of 5 to 7 days, the patients concomitantly started daily gonadotropin injections (one injection per day) and 20 mg dydrogesterone (one 10 mg oral pill, twice per day) without monitoring. Dydrogesterone was chosen for the PPOS protocol because it is not measurable in the blood, thus avoiding any interference with progesterone level measurement during stimulation.

In the control group, pretreatment with an oestrogen-progestin pill or oestrogen was prescribed. For oestrogen-progestin pill pretreatment, ultrasound and blood samples were monitored before the initiation of injections after a wash-out period of 5 to 7 days. For oestrogen pretreatment, the pretreatment began in the luteal phase; a monitoring evaluation was performed during menstruation, and exogenous gonadotropin administration was started the day after monitoring, without a washout period.

The GnRH antagonist was initiated at 0.25 mg daily starting on day 6 of the stimulation cycle.

In both groups, the starting gonadotropin dose was chosen at the discretion of each clinician according to the patient's age, ovarian reserve parameters (AFC or anti-Müllerian hormone (AMH) level) and BMI. After 6 or 8 days, the patients undergoing COS were monitored every 48–72 h via transvaginal ultrasonography (assessing the number of follicles and median follicle size) and hormone measurements (serum LH, oestradiol and progesterone levels).

When at least 3 follicles measuring more than 16 mm in diameter on average were measured, ovulation triggering was performed by either human chorionic gonadotrophin (hCG) (Ovitrelle® 250 mg, CS), or GnRH agonist (Triptorelin 0.2 mg, CS), or both. Oocytes were retrieved transvaginally 36 h after triggering. All follicles with diameters > 10 mm were aspirated via a 17- or 19-gauge needle guided by transvaginal ultrasonography. The search for cumulus-oocyte complexes (COCs), assessment of oocyte maturity and preparation of oocytes were performed as previously described [27].

Collected data

We collected information regarding patient characteristics (age, BMI, smoking habits, menstrual cycle regularity, AFC, AMH level) and COS characteristics (pretreatment method, type of gonadotropin used, starting dose of gonadotropin, total dose of gonadotropin, duration of stimulation, triggering method, number of follicles with a diameter ≥ 16 mm the trigger day; if no ultrasound was performed on the trigger day, we collected information on the number of follicles with a diameter > 14 mm the day before the trigger day or > 12 mm two days before the trigger day).

Data concerning the COS outcomes (the number of COCs retrieved and the number of mature oocytes (MII oocytes) were also collected.

The oocyte maturity rate (number of MII oocytes/number of COCs retrieved)*100 and ovarian sensitivity index (OSI) (number of oocytes retrieved divided by the total dose of gonadotropins multiplied by 1000) were calculated.

Objectives

The primary objective was to evaluate the efficacy of the PPOS protocol compared with that of an antagonist

protocol, and the primary endpoint was the number of mature oocytes. The secondary endpoints were other parameters and COS outcomes: the duration of stimulation, total dose of gonadotropins used, number of follicles with a diameter above 16 mm on the trigger day, oocyte maturity rate and OSI. Finally, we intended to evaluate the convenience of the PPOS protocol by analysing the frequency of monitoring sessions.

Subject approval

According to French law, our study did not require specific patient approval since the study was completely anonymous and noninterventional (observational). The present study was approved by the local ethics committee (Comité local d'éthique d'Avicenne: CLEA-2023-n°334) in accordance with the Declaration of Helsinki. A non-opposition agreement to the research was signed by the patients at the time of their initial treatment.

Statistical analysis

For the description of patients' characteristics, we used the medians and interquartile ranges (IQRs: 25th -75th). A comparison of initial characteristics between the PPOS group and the matched control group (1:2) was conducted via univariate conditional logistic regression. As the qualitative data did not follow a normal distribution, they were transformed into classes either by using commonly accepted thresholds (such as the BMI or gonadotropin starting dose) or by creating tertiles.

For the comparison of COS outcomes, qualitative transformation was performed in the same manner. Both medians and IQRs and percentages for each class group are presented. Univariate analysis was performed via univariate conditional logistic regression. Multivariate analysis was performed via conditional multivariate logistic regression for significant parameters in univariate analysis ($p < 0.2$). Adjustments for age, pretreatment method, and gonadotropin type were applied for the total dose of gonadotropin, duration of stimulation, number of follicles with a diameter above 16 mm and number of monitoring sessions. Adjustments for age, pretreatment method, gonadotropin type, and triggering method were applied for the OSI, maturity rate, number of COCs retrieved and number of MII oocytes. All the statistical tests were 2-sided, and a p value < 0.05 was considered to indicate statistical significance. All the statistical analyses were performed via NCSS statistical software (2021).

Results

Flow chart

During the study period, a total of 976 cycles of COS for oocyte cryopreservation were performed (Fig. 1). Among these cycles, 527 were performed using the PPOS protocol, including 262 cycles for elective oocyte freezing. A total of 29 cycles were cancelled, 20 cycles could not be matched, and 10 cycles could not be included because of missing data on matching parameters. A total of 203 cycles were thus included in the case group, and 406 were used as controls.

The 30 cycles that could not be included in the case group due to missing data or a lack of matching were compared with those included in the case group. No significant differences were found in terms of patient characteristics (age, AFC, AMH level, BMI, etc.) (data not shown).

Patient and initial controlled ovarian stimulation characteristics

The characteristics of the two populations are described in Table 1. The two groups were not significantly different in terms of menstrual cycle regularity ($p = 0.95$), AMH level ($p = 0.64$) or smoking habits ($p = 0.31$). Median ages in the PPOS and antagonist groups were 35.5 (34.4–36.6) years and 34.6 (32.1–35.8) years, respectively ($p < 0.001$). With respect to COS characteristics, more patients were pretreated with oestrogen-progestin pills in the PPOS group than in the antagonist group (96.0% vs. 38.7%; $p < 0.001$). The type of gonadotropin varied significantly between the groups ($p < 0.001$), with follicle-stimulating hormone (FSH) activity alone being the predominant type in the PPOS group (81.3% vs. 62.3%). Finally, the triggering mode was also significantly different between the groups, as more cycles were triggered with GnRHa in the PPOS group (53.7% vs. 46.6%, $p < 0.001$).

Controlled ovarian stimulation outcomes

COS outcomes are presented in Table 2. Univariate analysis revealed no significant differences in the total dose of gonadotropins used, the number of oocytes with a diameter above 16 mm on the trigger day, the number of COCs retrieved, or the number of MII oocytes between the groups. The stimulation duration significantly differed, with more cycles lasting less than 8 days in the PPOS group ($p < 0.001$).

After adjustment for potential confounding variables such as age, type of gonadotropin used, and pretreatment method, there was no statistically significant difference in the duration of stimulation between the groups ($p = 0.34$). The number of monitoring sessions remained significantly lower in the PPOS group, with more than 75% of patients requiring fewer than three monitoring sessions, compared with 36.9% of patients in the antagonist group ($p < 0.001$).

The OSI showed statistical significance in the univariate analysis ($p = 0.02$), but this significance was not maintained in the multivariate analysis ($p = 0.16$). There was no statistically significant difference in the maturation rate

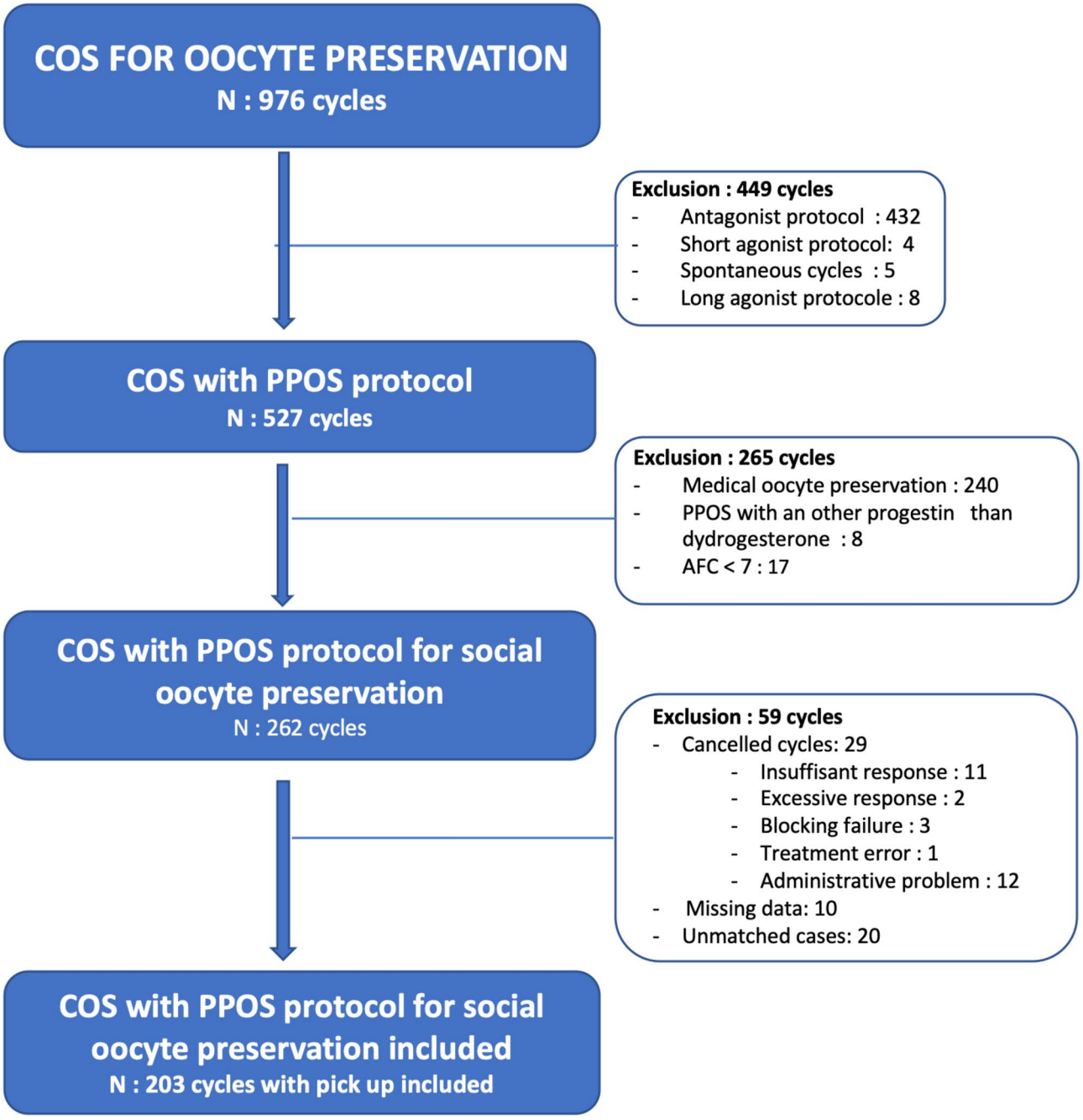

Fig. 1 Flow chart of the selection of cases
COS: controlled ovarian stimulation, PPOP: progestin-primed ovarian stimulation, AFC: antral follicle count

between the groups according to the univariate and multivariate analyses (p = 0.05 and p = 0.38, respectively).

Discussion

Our case–control study aimed to evaluate the efficacy and convenience of the PPOS protocol with dydrogesterone in the context of COS for oocyte cryopreservation for nonmedical indications (i.e., social reasons). We found that the ovarian response to COS with the PPOS protocol did not significantly differ from that of the antagonist protocol in terms of the number of mature oocytes obtained, number of COCs retrieved, maturation rate and OSI, with a significantly lower number of monitoring sessions performed.

Other studies evaluating the PPOS protocol in other contexts have reported similar results in terms of the number of mature oocyte retrieved [26, 28–31] or even better results with the PPOS protocol [32]. In 2020,

Table 1 Patient profiles and initial cycle characteristics

		PPOS ***n*** **= 203** ***n*** **(%) or Med (25th-75th)**	**Antagonist protocol** ***n*** **= 406** ***n*** **(%) or Med (25th-75th)**	***P***
Age (year)		35.5 (34.4–36.6)	34.6 (32.1–35.8)	**< 0.001**
BMI (kg/m^2) *		21.8 (20.0–23.4)	21.7 (20.2–23.69)	NA
Smoking habits (yes)		29 (14.3%)	46/404 (11.4%)	0.31
Regular menstrual cycle (yes)		184 (90.6%)	362/404 (89.6%)	0.94
AFC (n) *		18 (13.0–23.0)	17 (12.0–23.0)	NA
AMH (ng/mL) (*n* = 195 and 384)		2.1 (1.37–3.60)	2.1 (1.35–3.37)	0.65
COS Indication	Social reason	203 (100%)	134 (33%)	**< 0.001**
	Oocyte donation		5 (1.2%)	
	ICSI for masculine indication		131 (32.3%)	
	ICSI with sperm donation		10 (2.5%)	
	ICSI for IVF failure		32 (7.8%)	
	ICSI for Preimplantation genetic testing		94 (23.1%)	
Pretreatment method	Oestroprogestative pill	194 (96%)	157 (38.7%)	**< 0.001**
Type of gonadotropin	FSH alone	165 (81.3%)	253 (62.3%)	**< 0.001**
	FSH + LH activity	38 (18.7%)	153 (37.7%)	
Initial dose of gonadotropin (UI)*		300 (225–375)	300 (200–400)	NA
Triggering mode				**< 0.001**
hCG		55 (27%)	172 (42.4%)	
GnRHa		109 (53.7%)	189 (46.6%)	
hCG + GnRHa		39 (19.2%)	45 (11%)	

* matched variables

Rashidi et al. conducted a comparative analysis of the PPOS protocol with dydrogesterone and an antagonist protocol in the context of IVF/ICSI [32]. Their study reported a greater yield of MII oocytes in the PPOS group than in the antagonist group (7.90 ± 3.62 vs. 6.26 ± 3.64, p < 0.01), consistent with the study by Vidal et al. [33]. In 2022, Khurana et al. investigated the use of the PPOS protocol with MPA in donor cycles, a context that can be easily extrapolated to nonmedical fertility preservation [22]. Similar to our study, their study did not reveal a significant difference in the number of MII oocytes retrieved when comparing the PPOS protocol with the antagonist protocol (10.41 ± 4.04 with the antagonist protocol and 10.25 ± 3.23 with the PPOS protocol, P = 0.964).

Regarding the characteristics of the stimulation, after adjustment, no statistically significant difference was found in the duration of stimulation between the groups in our study. Several studies reported nonsignificant differences in stimulation duration, corroborating our findings [22, 30, 33].

Furthermore, the number of monitoring sessions was significantly lower in the PPOS group. We attribute this difference to two factors. First, in the antagonist protocol, a monitoring session typically occurs between day 4 and 6 of stimulation to assess the timing of antagonist introduction, which is not needed in the PPOS protocol. Second, in cases of pretreatment with estroprogestin pills, we opted not to perform monitoring before the initiation of stimulation, as this pretreatment is known to be highly anti gonadotropic and simplifies patient management. On the basis of our results, this decision did not affect the number of MII oocytes frozen. In a context of less anti gonadotropic pre-treatment with estradiol or progestin only instead of estroprogestin pills, a monitoring before gonadotropin stimulation may be useful to assess the follicular homogeneity to improve ovarian stimulation outcome.

While our study did not directly assess cost-effectiveness, previous research suggests that the PPOS protocol offers economic advantages due to factors such as lower medication costs and decreased monitoring requirements [18, 22, 26].

As oocyte preservation was recently authorized in France, we were unable to assess the reuse of frozen oocytes or their fertilization and live birth potential. However, several studies have examined the reutilization of oocytes obtained via the PPOS protocol, yielding highly reassuring results as described below. With respect to euploidy rates, all studies agree that there is no significant difference between the PPOS and antagonist protocols, regardless of the progestin used [28, 30, 33]. For example, Wang et al. conducted a retrospective cohort study involving 608 preimplantation genetic testing for aneuploidy (PGT-A) cycles, including 146 women in the PPOS group, 160 women in the GnRH agonist group, and 302 women in the GnRH antagonist group. They reported that the euploid blastocyst rate per injected MII oocyte was similar among the three groups (14.60% vs. 14.09%

Table 2 Controlled ovarian stimulation outcomes

	PPOS Protocol ***n*** **= 203** ***n*** **(%) or med (25th -75th)**	**Antagonist Protocol** ***n*** **= 406** ***n*** **(%) med (25th -75th)**	***P***	***P**/***
Total dose of gonadotropin (UI)	**2700 (2100–3850)**	**2763 (2025–4050)**		
≤ 2275	68 (33.5%)	136 (33.5%)	0.38	0.78*
2275–3000	72(35.5%)	131(32.3%)		
> 3000	63(31%)	(34.2%)		
Duration of stimulation (days)	**10.0 (8.0–11.0)**	**10.5 (10.0–12.0)**		
≤ 8	52 (25.6)	46 (11.3)	< 0.001	0.34*
9	27 (13.3)	50 (12.3)		
10	55 (27.0)	107 (26.3)		
11	29 (14.3)	93 (22.9)		
> 11	40 (19.7)	110 (27.0)		
Number of follicles with a diameter ≥ 16 mm on the trigger day	**7.0 (4.0–10.0)**	**7.0 (5.0–10.0)**		
≤ 5	73 (36.1%)	129 (32.3%)	0.21	0.29*
6–9	71 (35.1%)	171 (42.9%)		
> 9	58 (28.7%)	99 (24.8%)		
Number of monitoring sessions during stimulation	**3 (2–3)**	**5 (4–5)**		
≤ 3	159 (78.3%)	82 (20.6%)	< 0.001	< 0.001*
4	43 (21.2%)	260 (65.3%)		
> 5	1 (0.5%)	56 (14.0%)		
Number of cumulus-oocyte complexes retrieved	**9.0 (7.0–13.0)**	**10.0 (7.0–14.0)**		
≤ 8	81 (39.9%)	150(36.9%)	0.22	0.91**
9–12	65 (32.0%)	115(28.3%)		
> 12	57 (28.0%)	141(34.7%)		
Number of MII Oocytes retrieved	**8.0 (6.0–12.0)**	**8.0 (5.0–12.0)**		
≤ 7	81(39.9%)	159 (39.2%)	0.90	0.94**
9–10	57(28.0%)	110 (27.1%)		
> 10	65(32.0%)	137 (33.7%)		
Oocyte maturation rate (%)	**88.9 (76.9–100.0)**	**88.9 (72.7–100)**		
≤ 75	47 (23.2%)	124 (30.6%)	0.05	0.38**
> 75	156 (76.8%)	281 (69.4%)		
OSI	**3.6 (1.7–5.8)**	**3.6 (1.7–6.7)**		

Table 2 (continued)

	PPOS Protocol *n* = 203 *n* (%) or med (25th -75th)	Antagonist Protocol *n* = 406 *n* (%) med (25th -75th)	*P*	*P**/**
≤ 2.24	69 (34.0%)	134 (33.0%)	0.02	0.16**
2.25–5.24	78 (38.4%)	126 (31.0%)		
> 5.24	56 (27.6%)	146 (35.9%)		

OSi: Ovarian sensitivity index = number of oocytes retrieved divided by the total dose of gonadotropins multiplied by 1000

*Adjustment for age, pretreatment method, and gonadotropin type

**Adjustment for age, pretreatment method, gonadotropin type, and triggering method

vs. 13.94%, respectively; p > 0.05) [28]. Zhou et al. conducted a retrospective study comparing fertilization and blastulation rates between the PPOS protocol with MPA and the antagonist protocol in patients with diminished ovarian reserve, normal ovarian reserve, or PCOS [30]. In the normal ovarian reserve group, no significant differences were found in the fertilization or blastulation rates (p = 0.67, p = 0.17, respectively). However, the number and ratio of good-quality blastocysts were significantly lower in the PPOS group than in the GnRH antagonist group (2.82 ± 2.83 vs. 3.20 ± 2.79, P = 0.032 and 63.9% vs. 68.5%, P = 0.021) [30]. Another study by Devesa et al. assessed fertilization and blastulation rates in the context of oocyte donation and reported no significant differences between the protocols (p = 0.233 and p = 0.221, respectively) [24].

The literature is more conflicting regarding the live birth rate (LBR). Zhou et al. reported that the cumulative LBR (cLBR) for the PPOS protocol was significantly lower than that for the GnRH antagonist protocol in patients with a normal ovarian reserve (28.4% vs. 40.7%, P = 0.004). The results were maintained in the multivariate analysis after adjusting for potential confounders (adjusted OR = 0.556; 95% CI, 0.377–0.822) [30]. However, Ye et al. reported no significant difference in the cLBR between the protocols in a population of infertile women with a normal ovarian reserve (p = 0.199) [31], as did Devesa et al. [24].

In terms of neonatal outcomes, a systematic review and meta-analysis conducted in 2020 included 4,510 newborns born to women who received the PPOS protocol and 4,774 born to women who received a GnRH agonist protocol [34]. The risks of congenital malformations, low birth weight and premature birth were similar between the PPOS and GnRH agonist groups (OR = 0.92 95% CI [0.63–1.34] P = 0,65; OR 1.06 95% CI [0.95–1.18] P = 0.29; OR 0.90, 95% CI [0.80–1,02] P = 0,10; respectively).

Overall, the present study has several strengths. It has a robust design, with a large population of selected cases and matched controls. For all cycles, we accounted for various potential confounders in the multivariate analysis, such as patient age, pretreatment method, type of gonadotropin used, and triggering method. Furthermore, the results of our study are consistent with findings reported in the literature. However, to our knowledge, no study has investigated the PPOS protocol in the context of nonmedical fertility preservation. Our investigation aimed to fill this gap.

Our study is limited by its retrospective design, which introduces certain biases and limitations compared with prospective studies. There were notable differences between the case and control groups. Only 33% of the stimulations in the control group were conducted for patients with social fertility preservation indication,

whereas the remaining cases were treated for other indications without ovarian pathology, such as male factor infertility or tubal factor infertility. Additionally, there were differences in the pretreatment, type of gonadotropin and triggering method between the case and control groups. These discrepancies could introduce confounding variables and affect the comparability of the two groups even if they were included in the multivariate analysis.

Conclusion

Our case–control study aimed to compare the PPOS protocol with dydrogesterone to an antagonist protocol for COS in patients with nonmedical indications (i.e., social reasons) for oocyte cryopreservation. We found that the PPOS protocol is a convenient treatment allowing for a lower number of monitoring sessions and oral treatments with no significant difference in the number of mature oocytes retrieved or any other studied markers of the ovarian response to COS (the number of COCs retrieved, maturation rate and OSI).

However, further prospective randomized studies are needed to confirm our findings and explore pregnancy outcomes after the use of cryopreserved oocytes, allowing clinicians to safely recommend the PPOS protocol as the first-line treatment in freeze-all cycles.

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Author contributions
made conception and design of the work: MP, CS, MG, OSmade the acquisition of data: OS, LCA, CV, CB, MM, VP, CS, FE, LH, AM, ICDmade analysis and interpretation of data: CS, ICD, MG, MP, OS, LCAhave drafted the work: OS, MP, CSsubstantively revised the work: ICD, MG, VPAll authors reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
According to French law, our study did not require specific patient approval since the study was completely anonymous and noninterventional (observational). The present study was approved by the local ethics committee (CLEA-2023-n°334) in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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