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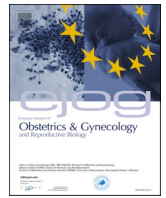
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Review article



Prospective multicenter observational real-world study to assess the use, efficacy and safety profile of follitropin delta during IVF/ICSI procedures (DELTA Study)

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ABSTRACT

Objective: To describe the use, efficacy and safety profile of follitropin delta in women undergoing IVF/ICSI in routine clinical practice after one treatment cycle.

Study design: This was a French multicenter, prospective, observational study conducted in 14 fertility centers between June 2020 and June 2021. During this period, 248 women undergoing IVF or ICSI were treated with follitropin delta for the first time. Women were followed up to 10–11 weeks after the first fresh or frozen embryo transfer. The main outcomes were use of dosing algorithm, follitropin delta dosing patterns, ovarian response, pregnancy, and adverse drug reactions in routine clinical practice.

Results: The analyzable population consisted of 223 patients with mean \pm SD age of 33.0 ± 4.4 years, body weight of 65.7 ± 11.8 kg, and the median (IQR) AMH level was 2.6 (1.5–4.0) ng/mL. For 193 patients (86.5 %) it was the first IVF/ICSI cycle and for 30 (13.5 %) the second. The algorithm was used for the calculation of the starting dose for 88.3 % of the patients. The mean daily starting dose of follitropin delta was 11.4 ± 4.1 mcg for the whole analyzable population and 14.4 ± 5.2 mcg for the sub-group of 26 patients dosed without the algorithm. The mean duration of stimulation with follitropin delta was 10.8 ± 5.2 days. The mean total dose of follitropin delta administered was 122.2 ± 80.0 mcg. An antagonist protocol was used in 90.3 % of patients. The mean \pm SD number of oocytes retrieved among patients that started stimulation was 11.3 ± 6.8 and 46.1 % of patients achieved the targeted response of the algorithm of 8–14 oocytes retrieved. A fresh transfer was performed for 77.6 % of patients; the mean \pm SD number of embryos transferred was 1.3 ± 0.5 . The implantation rate was 36.0 %. Per started cycle, clinical pregnancy was reported in 35.0 % of the patients and ongoing pregnancy in 29.6 %. In total, 5 patients (2.2 %) reported an event of OHSS.

Conclusion: Clinical results as collected in routine clinical practice are promising, showing a favorable effectiveness-safety profile of follitropin delta for a very varied patient population (including anovulatory PCOS,

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very poor responders, or non-IVF naïve patients). These real-world data complement results from clinical trials and provide useful information for usual clinical practice within a heterogeneous population group.

Introduction

Controlled ovarian stimulation (COS) aims to obtain an adequate number of competent oocytes to be used for assisted reproductive technologies such as *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI), with minimum risks for the woman [1].

Although ovarian response is influenced by the dose of gonadotropin, there is a large variability in response across women for the same dose of gonadotropin [2]. Excessive response increases the risk of complications such as ovarian hyperstimulation syndrome (OHSS) [3].

Individualizing COS regimens is therefore crucial to ensure appropriate dosing from the start of stimulation, in order to reduce the risk of cycle cancellation due to poor or suboptimal response and minimize the risks due to an excessive response [4]. Follitropin delta is a human cell line-derived recombinant FSH with a dosing algorithm that individualizes the dose based on patient characteristics to provide a predictable ovarian response that optimizes safety and efficacy [5]. It is based on two parameters; the weight, which standardizes ovarian gonadotrophin exposure [2,5], and the AMH, which is the best parameter for predicting maximal response to follitropin delta [5].

The efficacy and safety of algorithmic dosing of follitropin delta has been evaluated and compared with conventionally-dosed follitropin alfa and beta across several phase III trials but always in the first IVF cycle and with restrictive inclusion criteria, such as the exclusion of the anovulatory PCOS patients. The algorithmic dosing of follitropin delta was found to be non-inferior to conventionally-dosed follitropin alfa with regards to ongoing pregnancy [6,7] and to conventionally-dosed follitropin beta with regards to number of oocytes retrieved [8]. Additionally, more women achieved the target ovarian response of 8–14 oocytes and had less need of OHSS preventive measures in these trials [6–8].

Follitropin delta is the most recent gonadotrophin to receive marketing authorization approval in European countries. It is the first recombinant FSH to be derived from a human cell line, and it is also the only one to be administered with a dosing algorithm and dosed in micrograms. For the first time in France, a study has been set up to provide a detailed overview of the use of this newest gonadotropin, and this is crucial for post-marketing authorization surveillance. The aim of the study was to describe the use, the efficacy and the safety of follitropin delta in routine clinical practice, and therefore in a more diverse population than the previous randomized controlled trials.

Materials and methods

Study design

This was a French, multicenter, prospective, observational study conducted between June 2020 and June 2021. The study was performed in compliance with the Declaration of Helsinki and current regulations, including local institutional review board ethics approval. Women were treated according to routine clinical practice and enrolled after the decision to treat with follitropin delta had been made. No aspect of this study interfered with the routine medical procedures and/or medications received. The physician collected the non-objection to data collection in each patient's medical record. The [ClinicalTrials.gov](https://clinicaltrials.gov) identifier is NCT0450370.

Study population

Women ≥ 18 years, who were either treatment naïve or had undergone one previous IVF/ICSI treatment cycle and were prescribed

follitropin delta for the first time were consecutively included in this study.

Women participating in an interventional clinical trial, requiring mandatory treatment or follow-up, or with a contraindication for follitropin delta treatment were excluded from this study, as well as oocyte donors or women undergoing ovarian stimulation for fertility preservation.

Data collection

The investigators collected data for one stimulation cycle with follitropin delta. Women were followed-up until ongoing pregnancy (10–11 weeks) after the first fresh or frozen transfer.

Baseline data included socio-demographic data: age, body weight, height, reproductive history, reasons of infertility, antral follicle count, most recent AMH test result, and laboratory measurements: FSH, LH, estradiol, progesterone, as available.

Data collected at follow-up visits were: treatment protocol used; preventive measures for OHSS; ovarian response; number of oocytes retrieved and fertilized; number of embryos transferred; pregnancy outcome: positive β hCG, clinical pregnancy (defined as at least one gestational sac 5–6 weeks after transfer) and ongoing pregnancy (defined as at least one intrauterine viable fetus 10–11 weeks after transfer); pregnancy loss; cycle cancelled and reason for cancellation; serious and non-serious adverse drug reactions (SADRs and ADRs).

Study outcomes

The primary endpoint was follitropin delta real-life treatment patterns, including use of the dosing algorithm, dosing regimen (daily and total dose of follitropin delta administered, duration of treatment), type of GnRH protocol used and triggering of follicle maturation. The secondary endpoints included the ovarian response (number of oocytes retrieved), number of embryos, cycle cancellation, implantation rate, pregnancy loss, clinical and ongoing pregnancy. Safety endpoints included OHSS occurrence, preventive interventions for early OHSS and all ADRs.

Statistics

The sample size was calculated to ensure meaningful data was obtained for the description of follitropin delta use patterns, effectiveness, and safety at the first follitropin delta cycle.

As the statistical analyses were purely descriptive, the sample size calculation was based on the precision of the confidence intervals (CIs) for observed frequencies. A planned sample size of 190 to 250 women was considered sufficient to address the objectives of this study.

The analyzable population contained all enrolled women who met the inclusion/exclusion criteria and received at least one dose of follitropin delta.

The safety population contained all enrolled women who received at least one dose of follitropin delta.

Continuous/quantitative variables were described using the number of women with data to be summarized (n), mean \pm standard deviation (SD), median (Interquartile Range (IQR)), and the number of missing data. Categorical/qualitative variables were presented using frequency counts and percentage of each response. The total number of women (without missing data) was used as the denominator for percentage calculations, unless otherwise specified. Only frequency counts were displayed for missing values. 95 % CIs of the mean and percentages were provided, if relevant.

Results

Baseline characteristics

248 women were included in 14 sites. The analyzable population consisted of 223 women (89.9 %), 25 women were excluded, either because they did not meet the selection criteria (N = 4), or the start date of follitropin delta was missing (N = 21). The analyzable population presented a mean age of 33.0 ± 4.4 years, a body weight of 65.7 ± 11.8 kg, and a BMI of 24.0 ± 4.0 kg/m². The median AMH level was 2.6 (1.5–4.0) ng/mL. The mean duration of infertility was 3.4 ± 2.2 years. The majority of women had primary infertility (N = 161; 72.2 %) (Table 1).

Stimulation protocol and follitropin delta dosing

Of 223 women, 193 women (86.5 %) were naïve (first IVF/ICSI cycle) and 30 (13.5 %) were non-naïve (second IVF/ICSI cycle). The follitropin delta dosing algorithm was used to calculate the starting dose for 197 women (88.3 %) and 183 (82.1 %) women maintained this dose during stimulation. The calculation tools (dosing app or website) were used for 162 women (72.6 %). In the treatment-naïve subgroup, 170

Table 1
Baseline patient characteristics.

Characteristics	Analyzable population (N = 223)
Age (years)	
All women	33.0 ± 4.4
< 35	144 (64.6)
[35;37]	35 (15.7)
[38;40]	37 (16.6)
> 40	7 (3.1)
Body weight (kg)	
All women	65.7 ± 11.8
≤ 55	42 (18.8)
[56;63]	79 (35.4)
[64;80]	77 (34.5)
> 80	25 (11.2)
BMI (kg/m ²)	24.0 ± 4.0
Infertility history	
Duration of infertility (years)	3.4 ± 2.2
Primary infertility	161 (72.2)
Reason of infertility*	
Unexplained infertility	41 (18.4)
Tubal infertility	42 (18.8)
Male factor	110 (49.3)
Anovulatory Infertility WHO Group I	3 (1.3)
Anovulatory Infertility WHO Group II	40 (17.9)
Endometriosis	42 (18.8)
Uterine abnormality	6 (2.7)
Other	14 (6.3)
AFC	18.0 (13.0–30.0)
AMH (ng/mL) [#]	
All women	2.6 (1.5–4.0)
< 1	31 (14.0)
[1;2]	58 (26.1)
[2.1;4.9]	96 (43.2)
> 4.9	37 (16.7)
Laboratory measurements at baseline ^{&}	
FSH (IU/L)	6.7 (5.4–8.0)
LH (IU/L)	5.3 (3.8–7.2)
Progesterone (nmol/L)	0.8 (0.6–1.6)
Estradiol (pg/mL)	43.0 (32.0–59.5)

Note: Values are mean \pm SD, median (interquartile range), or number (percentage), unless stated otherwise.

*Women could present more than one reason of infertility.

[#] The subgroups have been defined with a cut off of 2.1 ng/mL, as this is the dosing algorithm threshold, above which all women receive 12 mcg of follitropin delta. For 73.5 % of patients, an automatized AMH dosage was reported (66.8 % was dosed with ELECSYS AMH Assay). The AMH assay was missing for 20.6 % of the patients.

[&] 93.1% of dosages were realized between day 2–5 of the menstrual cycle.

women (88.1 %) versus 27 (90 %) in the non-naïve subgroup were dosed according to the follitropin delta dosing algorithm (Table 2 and Supplementary Table 1).

For 14 women (7.1 %), the calculated starting dose was modified prior to the first dose. The main reason for this was targeting a higher number of follicles. For 40 women (17.9 %), the daily dosage was adjusted during stimulation. The two main reasons were ovarian hypo-response and ovarian hyper-response.

The mean starting dose of follitropin delta was 11.4 ± 4.1 mcg. For the 197 women who received follitropin delta based on the algorithm, the mean starting dose was 11.0 ± 3.8 mcg and for women who received follitropin delta not based on the algorithm, it was 14.4 ± 5.2 mcg (Table S2, Supplementary Materials).

The mean total dose of follitropin delta administered was 122.2 ± 80.0 mcg over 10.8 ± 5.2 days. A GnRH antagonist protocol was used in 90.3 % of women (Table 2).

Table 2
Stimulation protocol and follitropin delta use.

	Analyzable population (N = 223)		
Rank of the attempt distribution			
Naïve patient	193 (86.5)		
Non-Naïve patient	30 (13.5)		
Type of GnRH protocol used			
Antagonist	196 (90.3)		
Agonist	21 (9.7)		
Women with dose prescribed based on the algorithm	197 (88.3)		
Starting daily dose maintained or modified compared to the algorithm*			
Maintained	183 (92.9)		
Increased	6 (3.0)		
Decreased	8 (4.1)		
Reason for initial dose modification			
Targeting a higher number of follicles	9 (75.0)		
Based on physician's perception	2 (16.7)		
Based on previous treatment experience from non-naïve Patient	2 (16.7)		
Other	1 (8.3)		
Women with Dosing App or Website used	162 (72.6)		
Starting dose of follitropin delta prescribed (mcg)	11.4 ± 4.1		
Mean daily dose of follitropin delta (mcg)	11.5 ± 4.1		
Duration of ovarian stimulation with follitropin delta (days)	10.8 ± 5.2		
Total dose of follitropin delta administered (mcg)	122.2 ± 80.0		
Women with a dose adjusted during the ovarian stimulation	40 (17.9)		
Reasons for dose adjustments			
Ovarian hypo-response	24 (60.0)		
Ovarian hyper-response	13 (32.5)		
Women who developed OHSS or became at risk of OHSS	2 (5.0)		
Other	1 (2.5)		
Preventive interventions for early OHSS	33 (14.8)		
GnRH agonist triggering and freeze all hCG triggering and freeze all	24 (72.7)		
Coasting	4 (22.6)		
Cycle cancellation	1 (12.1)		
GnRH agonist triggering and fresh embryo/blastocyst transfer	3 (3.0)		
Total hCG triggering	1 (3.0)		
Total GnRH agonist triggering	182 (81.3)		
	41 (18.3)		

Note: Values are mean \pm SD, median (interquartile range), or number (percentage), unless stated otherwise.

*Percent calculated based on women with dose prescribed based on the algorithm (N = 197).

Oocyte retrieval and embryo transfer

Among the overall study population, a total of 206 women (93.2 %) had an oocyte pick-up with a mean number of 11.3 ± 6.8 oocytes retrieved. The algorithm targeted response (8–14 oocytes) was observed in 95 women (46.1 %); 65 women (31.6 %) had an ovarian response below the target (<8 oocytes) and 46 women (22.3 %) above target (≥ 15 oocytes). 78.2 % obtained an ovarian response of 4–19 oocytes (Table 3). Specifically, in the 40 women who received a starting dose of follitropin delta not based on the algorithm, the mean number of oocytes retrieved was 12.6 ± 8.4 and 9 women (22.5 %) had < 8 oocytes retrieved.

A total of 170 women (76.9 %) had an embryo transfer, with a mean number of 1.3 ± 0.5 embryos transferred. 132 women (77.6 %) had a fresh transfer and 38 women (22.4 %) a frozen transfer after a freeze-all strategy.

Twelve (5.4 %) cycles were cancelled before oocyte pickup. The reasons were poor ovarian response (N = 6), medical reasons (N = 5) and excessive ovarian response (N = 1). Also 27 cancellations (12.2 %) occurred after oocyte pickup, the main reasons being absence of collected oocytes (N = 3), fertilization failure (N = 4), abnormal fertilization (N = 1), no embryo development (N = 6), abnormal embryo development (N = 3), apparition of OHSS (N = 3) and other medical reasons (N = 7).

Pregnancy rate

Per started cycle, 92 women (41.2 %) had a positive β hCG test, clinical and ongoing pregnancy were reported for 78 (35.0 %) and 66

Table 3
Oocyte retrieval, embryology, and pregnancy outcomes.

	Analyzable population (N = 223)
Women with an oocyte retrieval	206 (93.2)
Total number of oocytes retrieved	11.3 ± 6.8
Ovarian response by categories*	
< 4 oocytes	18 (8.7)
4–7 oocytes	47 (22.8)
8–14 oocytes (algorithm target)	95 (46.1)
15–19 oocytes	19 (9.2)
≥ 20 oocytes	27 (13.1)
Number of oocyte retrieval by GnRH protocol	
Agonist	8.5 ± 3.4
Antagonist	11.4 ± 6.9
Number of oocyte retrieval by AMH level	
< 1 ng/mL	6.2 ± 4.4
[1;2] ng/mL	9.5 ± 3.9
[2.1;4.9] ng/mL	12.6 ± 7.1
> 4.9 ng/mL	14.7 ± 8.1
Number of oocytes fertilized	7.7 ± 5.8
Number of embryos D2-D3	6.2 ± 4.5
Number of blastocysts D5-D6	2.9 ± 3.4
Woman with embryo transfer	170 (76.9)
Type of transfer	
Fresh transfer	132 (77.6)
Frozen transfer	38 (22.4)
Number of embryos transferred	1.3 ± 0.5
Women with cancellation before oocyte pickup	12 (5.4)
Women with cancellation after oocyte pickup	27 (12.2)
Implantation rate* [#] , %	36.0
Positive β hCG per initiated cycle	92 (41.2)
Clinical pregnancy per initiated cycle	78 (35.0)
Ongoing pregnancy* per initiated cycle	66 (29.6)
Pregnancy loss	24 (10.7)

Note: Values are mean \pm SD, or number (percentage), unless stated otherwise.

*The percentages are calculated on the total number with an oocyte retrieval (N = 206).

[#] Implantation rate, defined as number of intrauterine viable fetus after transfer divided by the number of embryos transferred.

[&] Two data points are missing.

women (29.6 %), respectively. 24 women (10.7 %) reported pregnancy loss (Table 3).

The ongoing pregnancy rate per transfer according to the type of transfer, age, AMH level, and weight are shown in Table 4.

Safety outcomes

Overall, of the 226 women included in the safety population, five women reported one adverse drug reaction, all were OHSS, four were mild cases and one was severe. Only one woman was hospitalized for OHSS with a duration of 2 days.

A total of 33 women (14.8 %) had preventive intervention(s) for early OHSS, (interventions detailed in Table 2).

Discussion

The current study describes the use, effectiveness, and safety profile of follitropin delta after one treatment cycle in women undergoing IVF/ICSI in real-world conditions in France. Notably, it is one of the very few prospective real-world studies with follitropin delta to include non-naïve women alongside IVF/ICSI treatment-naïve women. Women with one previous cycle and treated with a different gonadotropin were included to understand real-world treatment with follitropin delta in women who had a history of COS treatment.

The innovative dosing algorithm using patient characteristics to provide an individualized starting dose of follitropin delta was used for 88.3 % of women, and the dosing calculation tools was used for 72.6 % of women, representing good use of follitropin delta dosage calculation tools in clinical practice. The use of the dosing algorithm was similar between the IVF/ICSI treatment-naïve women (88.1 %) and the non-naïve women (90 %).

The mean total dose of follitropin delta was higher than in the phase III ESTHER-1 trial (122.2 ± 80.0 mcg versus 90.0 ± 25.3 mcg) despite the current study population having a slightly higher mean AMH level (2.6 ng/mL versus 2.3 ng/mL). This could be explained both by the fact that there were women in this real-world study who received follitropin delta without the algorithm (mean starting daily dose: 14.4 ± 5.2 mcg [range: 5.0 to 24.0 mcg] versus 11.4 ± 4.1 mcg for the overall study population), and that the mean duration of stimulation in this study was 2 days longer than in the ESTHER-1 trial (10.8 ± 5.2 versus 8.9 ± 1.9 days) [6].

In the subgroup of women for whom the algorithm was not used, AMH levels were lower (1.8 ± 1.3 ng/mL) compared to the subgroup

Table 4
Ongoing pregnancy rate by transfer according to type of transfer, age, AMH level, and weight (Base: women with transfer N = 170).

	Ongoing pregnancy rate* (%)
Transfer type	
Fresh transfer (N = 132)	38.6
Frozen transfer (N = 38)	34.2
Age (years)	
< 35 (N = 113)	41.6
≥ 35 (N = 57)	29.8
AMH Level (ng/mL)	
< 1 (N = 22)	31.8
[1; 2] (N = 47)	34.0
[2.1; 4.9] (N = 74)	46.0
> 4.9 (N = 26)	26.9
Weight [#] (kg)	
≤ 55 (N = 34)	44.1
[56;63] (N = 58)	32.8
[64;80] (N = 58)	39.7
> 80 (N = 20)	35.0

*Ongoing pregnancy rate was calculated based in women with a transfer in each subgroup.

[#] Subgroups established to be clinically relevant and have the best distribution, as 63 kg is the median weight in this study.

treated according to the algorithm (3.2 ± 2.6 ng/mL) (Table S2, Supplementary Materials), suggesting that for women with a lower ovarian reserve, physicians considered that 12 mcg was not sufficient to obtain an adequate ovarian response.

Although this study was not designed to compare the use and the efficacy of follitropin delta with or without use of the dosing algorithm, the mean starting dose of follitropin delta seemed to be higher when the dosing was not calculated according to the algorithm (14.4 ± 5.2 mcg while it was 11.4 ± 4.1 mcg for the overall population studied). We could hypothesize, that in real-world practice the algorithm may be perceived as being too cautious for use in specific patients, and additional studies are needed to confirm this assumption. Furthermore, in certain patients the target ovarian response is over 14 oocytes, whereby the algorithmic approach would not apply.

In the overall population of our study, the mean number of oocytes retrieved was 11.3 ± 6.8 , and the target ovarian response (8–14 oocytes retrieved) was achieved by 46.1 %. In line with these results, the ESTHER-1 trial reported that 43.3 % of women treated with follitropin delta and 38.4 % of women treated with follitropin alfa achieved the target ovarian response [6].

A similar ongoing pregnancy rate per started cycle was reported in our study versus ESTHER-1 (29.6 % versus 30.7 %) [6].

We reported encouraging results in very low responder patients ([AMH] < 1 ng/mL), with an OPR per transfer of 31.8 %. The OPR per transfer in our non-naïve IVF/ICSI patients was also encouraging, at 40.7 %.

The incidence of OHSS was low ($n = 5$) (2.2 %), four incidents were mild, and one was severe. All OHSS occurred in women who were on GnRH antagonist protocol and received a starting dose based on the follitropin delta dosing algorithm. In our study, 33 women (14.8 %) had preventive interventions for early OHSS. No SADR leading to treatment withdrawal or death were reported in this study. The safety profile was comparable to the profile described in the phase III trials and the SmPC of follitropin delta [6–9]. Considering the inclusion of the quite heterogeneous population in this study, the results are reassuring.

The current study's strengths include its large sample size, with over 223 women prospectively recruited. As a descriptive, real-world study, our work presents results for a broader population than the phase III study ESTHER-1, with a higher dispersion for the age, weight, BMI, and menstrual cycle duration. Also, contrary to the phase III trial, our study included anovulatory PCOS patients and non-naïve patients, reflecting the real-world usage of follitropin delta. Finally, this prospective study with primary data collection reduced the risk of missing data compared to retrospective studies.

We acknowledge that this study has some limitations, namely a lack of a control group and a lack of adjustment for unmeasured confounding. Results have not been stratified according to IVF/ICSI treatment-naïve women and those women on their second IVF/ICSI cycle due to a small number of patients in the second IVF/ICSI cycle subgroup. In some analyses, the relatively small number of women and events in subgroups requires caution in the interpretation of these results.

Conclusion

For the first time, our study has collected clinical results of follitropin delta in routine clinical practice in France. It shows a usage mainly based on the algorithm. A favorable effectiveness-safety profile is demonstrated even considering the inclusion of non-IVF/ICSI naïve women, very low responders, anovulatory PCOS patients and for women who received follitropin delta without the algorithm. These real-world data consolidate results from clinical trials and provide useful information for clinical practice.

CRedit authorship contribution statement

Géraldine Porcu-Buisson: Conceptualization, Data curation,

Formal analysis, Investigation, Validation, Writing – review & editing. **Chloé Maignien:** Investigation, Writing – review & editing. **Nelly Swierkowski-Blanchard:** Investigation, Writing – review & editing. **Catherine Rongières:** Investigation, Writing – review & editing. **Noémie Ranisavljevic:** Investigation, Writing – review & editing. **Pierre Oger:** Investigation, Writing – review & editing. **Christine Decanter:** Investigation, Writing – review & editing. **Claude Hocké:** Investigation, Writing – review & editing. **Hélène Bry-Gauillard:** Investigation, Writing – review & editing. **Michaël Grynberg:** Investigation, Writing – review & editing. **Paul Barrière:** Investigation, Writing – review & editing. **Mathilde Bernot:** Conceptualization, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Anne Guivarc'h-Levéque:** Investigation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Conflict of Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejogrb.2023.12.011>.

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