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Évaluation de la douleur au cours du parcours de Fécondation In Vitro : l'étude ENDALGOFIV 2

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List of abbreviations

AMH: Anti Mullerian Hormone

APC: Antral Follicular Count

ART: Assisted Reproductive Technology

BMI: Body Mass Index

DN4: Neuropathic Pain Diagnostic 4

EQ-5D: EuroQol 5D

E2: Estradiol

FSH: Follicle Stimulating Hormone

GnRH: Gonadotropin-Releasing Hormone

HAD: Hospital Anxiety and Depression

hCG: human Chorionic Gonadotropin

ICSI: Intracytoplasmic Sperm Injection

IVF: In Vitro Fertilization

NPRS: Numeric Pain Rating Scale

PCS: Pain Catastrophism Scale

QDSA: Saint Antoine pain Questionnaire

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Abstract

Introduction:

The ENDALGOFIV 1 study was performed to evaluate the typology and impact of pain between patients with or without endometriosis undergoing an In Vitro Fertilization (IVF) process. This initial study showed a stable pain level in patients with endometriosis and an increase in the average pain level for patients without endometriosis during the IVF attempt. The objective of our study was to compare the pain levels in patients undergoing an IVF process before and after a new pain management protocol.

Materials and methods :

A prospective, monocentric, observational cohort study called ENDALGOFIV 2 with a historical control group (ENDALGOFIV 1) was conducted in the Lille University Hospital Assisted Reproductive Technology (ART) department from January 2023 to March 2024**.** Pain assessment questionnaires using validated scales were completed at key points in the IVF course: before starting treatments, at the end of stimulation and on the day of oocyte retrieval.

Results :

The data from 278 patients included in ENDALGOFIV 1 (73 with endometriosis) and 207 patients in ENDALGOFIV 2 (51 with endometriosis) was analyzed. The average pain scores were similar between the two groups at the patients' baseline apart from a higher level of catastrophizing in patients from ENDALGOFIV 2. In both groups, patients with endometriosis had a higher average pain level, neuropathic pain level and depression rates. After oocyte retrieval, pain levels were higher with the new protocol for patients without endometriosis (numeric pain rating score 3.80 versus 3.11 $p = 0.0145$) but no significant difference was found for patients with endometriosis.

During the stimulation period, more patients took the treatment prescribed according to the new protocol if they had endometriosis (34.6 versus 15.4 p = 0.030). Only half of the patients took the treatment after oocyte retrieval whether they had endometriosis or not.

Conclusion :

Pain management during an IVF attempt remains complex for patients with and without endometriosis. Pain levels were higher in ENDALGOFIV 2 after oocyte retrieval compared to ENDALGOFIV 1 especially for patients without endometriosis, highlighting the need for further studies in order to better adapt pain treatments to patients' needs.

Key words: pain, endometriosis, in vitro fertilization, infertility, reproduction

Introduction

Infertility is defined as the inability to conceive after at least 12 months of regular unprotected intercourse. According to the World Health Organization, infertility affects 8 to 10% of couples worldwide (1). Due to the rise in infertility diagnoses, more and more patients are receiving reproductive treatment. According to the International Committee for Monitoring Assisted Reproductive Technology (ART), more than 8 million babies have been born in the last 40 years thanks to In Vitro Fertilization (IVF) (2). The French Agency of Biomedicine reported that 147 730 ART procedures were performed nationwide in 2016.

More and more IVF procedures are performed every year especially for patients with endometriosis, an illness associated with infertility which has a large impact on the quality of life for these patients (3). Studies estimate that 25 to 50% of patients with endometriosis suffer from infertility (4–7). However, few studies have looked into pain management for patients undergoing IVF despite pain representing one of the main symptoms for patients with endometriosis.

A prospective observational study was performed in the Lille University Hospital ART department from November 2019 to June 2021 in order to assess the level of pain, the type of pain and its impact in patients with or without endometriosis at key moments in their IVF cycle (ENDALGOFIV) (8). This study found that at the start of the IVF process, patients with endometriosis had higher pain scores than disease-free women (mean numerical scale score 3.47 versus 1.12 $p < 0.0001$) and 17.81% of patients with endometriosis had neuropathic pain. No increase in pain was observed during IVF for these patients. During IVF, for patients without endometriosis, pain increased significantly between the baseline, the end of stimulation and on the day of retrieval ($p = 0.05$). These results highlighted the need for better pain management during IVF.

Therefore, a new pain management protocol was put in place in the ART department aimed at all patients being treated whether they suffered from endometriosis or not. A key part of this new protocol was the possibility of a consultation with a pain management specialist for all patients with endometriosis. Patients were also given a specific pain medication prescription to be used during the stimulation period that included paracetamol, an antispasmodic (phloroglucinol), an anti-inflammatory (ketoprofene) and lamaline (paracetamol opium codeine) and another one for after the oocyte retrieval that included paracetamol, phloroglucinol and lamaline. Additionally, a standardized analgesia protocol was put into place during the oocyte retrieval, the details of which can be found in the appendix.

We performed a second study (ENDALGOFIV 2) in the department in order to evaluate the efficiency of this new protocol by comparing the pain levels in patients from ENDALGOFIV 1 and the current levels of pain in patients undergoing the process of IVF.

Materials and methods

We performed a prospective, single-centre, observational, non-interventional, cohort study called ENDALGOFIV 2 with a historical control group (ENDALGOFIV 1) inside the Department of ART and Fertility Preservation of the Lille University Hospital (France) from January 2023 to March 2024.

The primary objective of our study was to evaluate the impact of the new pain management protocol in all patients undergoing an IVF process by comparing their pain levels to those from our previous study ENDALGOFIV 1.

The secondary objective was to compare the evolution of their pain levels over the course of the whole process, specifically the difference at the beginning of the process, at the end of the stimulation period and after oocyte retrieval and to compare this evolution with the data from ENDALGOFIV 1.

IVF process

The key components of the IVF process are ovarian stimulation, oocyte retrieval, fertilization and embryo transfer. There are two main protocols for ovarian stimulation: the agonist and the antagonist protocols. In the agonist protocol, GnRH is used to suppress natural hormone production by overstimulating the pituitary gland before injecting gonadotropin hormones. For the antagonist protocol, gonadotropin hormones are injected from the start before using a GnRH antagonist to prevent premature ovulation. Each protocol is chosen based on the patient's medical history and hormone levels. Patients are then followed closely via ultrasounds and blood tests to monitor the number of follicles before a trigger product (hCG, GnRH agonist or double trigger) is used. An oocyte retrieval is then performed 36 hours later.

The next step is fertilization which can be done via classic IVF or Intracytoplasmic Sperm Injection (ICSI) which allows us to obtain embryos. These embryos can be either transferred to the patient's uterus or frozen via vitrification (freeze all technique).

Study population

All patients starting an IVF cycle in the ART department of Lille University Hospital (France) (first attempt or not) were eligible for our study. We excluded patients who had already participated in the study, refused to participate, were a minor or over 43 years old, had a Body Mass Index (BMI) > 35 kg/m^2, were unable to understand the information about the study, were under a guardianship or trusteeship, had no health coverage, or were undergoing IVF with egg donation or egg preservation.

Conduct of the study

We used the same pain assessment questionnaires as those used in ENDALGOFIV 1. The Numeric Pain Rating Scale (NPRS) allowed us to analyze the pain level, the Saint Antoine pain Questionnaire (QDSA) (9) for the emotional and sensory dimensions of the pain, the Neuropathic Pain Diagnostic 4 (DN4) (10) questionnaire to diagnose neuropathic pain in patients, the Pain Catastrophism Scale (PCS) (11) questionnaire for the level of catastrophizing in patients, the Hospital Anxiety and Depression questionnaire (HAD) (12) for depression and anxiety levels and the EuroQol 5D (EQ-5D) (13) scale for quality of life.

The ENDALGOFIV 2 study was presented in person to patients during their IVF consultation. If the patient orally expressed an interest in participating in the study, they were given a letter of information, a non-opposition form and a prescription for pain medication to be taken during the stimulation period.

All patients were given the prescription even if they didn't later on participate in the study since this prescription was part of the new pain management protocol. Patients with endometriosis were also offered the option of a consultation with a pain management specialist. If a patient wanted this consultation, one was organized in the following month. After seeing the specialist, patients were prescribed, if necessary, different pain medication which generally included gabapentin in order to better treat neuropathic pain (14). Participation in our study did not impact on the choice of treatment for IVF (agonist or antagonist protocol) or require any other additional appointments.

The questionnaires were distributed using WEPI software (EPICONCEPT, a certified health data hosting company), an IT platform designed for the creation and management of online questionnaires for healthcare professionals. As a result, patients filled out the questionnaires on their own at home whereas for ENDALGOFIV 1, they filled out a printed questionnaire that they had to hand in during different appointments.

The link to the first questionnaire was sent to the patient after registering for IVF. This contained NPRS, QDSA, DN4, PCS, HAD and EQ-5D and allowed us to know the baseline status of the patient before any treatment.

The second questionnaire was sent to patients following an agonist protocol and included NPRS, QDSA and DN4.

The third questionnaire (NPRS, QDSA, DN4) was to be filled out at the end of the stimulation period before induction of ovulation.

The fourth questionnaire (NPRS, QDSA, DN4) was sent the day of oocyte retrieval.

The fifth questionnaire (NPRS, QDSA, DN4, PCS, HAD, EQ-5D) was sent to patients who underwent an embryo transfer fifteen days later, after they had received the results of their blood test (HCG).

The last questionnaire (NPRS, QDSA, DN4, PCS, HAD, EQ-5D) was sent six weeks after oocyte retrieval to all patients.

The overview of the different questionnaires during the IVF process can be found in the appendix.

The remaining data required for our study, including the patient's clinical and paraclinical information (medical history, anthropometric data, type of infertility, endometriosis stage…), was retrieved from the patient's medical file located on JFIV®, an electronic health record software (version 1.8; RD S Services, Langlade, France). We used the REDCAP software to create a database combining all the different information.

Statistical analysis

The number of inclusions for ENDALGOFIV 2 was based on the study ENDALGOFIV 1 with a control group of 278 patients. The average pain level as shown by the QDSA score was found to be at 7.16 (standard deviation = 8.06). We estimated that the new pain management protocol would lower the pain level by 30% thus the average pain level would be 5.012. Considering a risk of 5%, a power of 80% and the control group, 185 patients would have to be recruited to show a difference. Considering 10% of non-analyzable data, the objective was to recruit 207 subjects for the study.

Categorical variables were expressed as a frequency (percentage). Quantitative variables were expressed as a mean ± standard deviation (SD) or a median [interquartile range (IQR)] in cases of non-normal distribution. Normal data distributions were checked graphically and by applying the Shapiro–Wilk test. Baseline characteristics were compared between the two groups using Student's t-test or Mann-Whitney U test (depending on the data distribution) for quantitative variables and using a chi-squared test (or Fisher's exact test in case of expected value <5) for categorical variables.

The evolution of pain questionnaires (QDSA) from baseline to oocyte retrieval was compared between the two groups by using a covariance analysis (ANCOVA) adjusted on the baseline value. Additional analysis was performed adjusted on age, medical history, smoking, BMI, infertility characteristics (duration of infertility, type of infertility, IVF rank and primary IVF indications), and biological (AMH, FSH, E2) and ultrasound (AFC) characteristics. Mean difference and its 95% confidence interval (CI) were expressed as effect size.

Missing values on confounding factors were handled (except for variables with missing values rate greater than 50%) by multiple imputation procedures. The missing data was imputed under the missing at random assumption using a regression switching approach (chained equation with m = 10 imputations) with predictive mean matching method for continuous variables and logistic regression (binary, ordinal, or polynomial) for qualitative factors.. The imputation procedures were performed using demographics, clinical parameters, predefined confounding factors and study groups, and estimates obtained in the different imputed data sets were combined using the Rubin's rules.

The evolution of the QDSA score (total score and sub-scores), pain intensity (NPRS) and neuropathic pain (DN4) were compared between the two groups using a linear mixed regression model (covariance pattern model using a compute symmetry covariance matrix to account for a correlation between repeated measures within patients) including group, time (first visit (T1), after GnRH treatment (T2), after stimulation (T3), after oocyte retrieval (T4), 15 days after transfer (T5) and 1 month after transfer (T6)), and an interaction term between group*time as fixed effect. Subgroup analysis was performed according to if the patient had endometriosis or not.

The evolution of EQ5D, HAD score and PCS measured at T1, T5 and T6 was compared between the two groups using the same method described previously for the evolution of the QDSA score.

The evolution of neuropathic pain and catastrophizing was compared between the two groups using a generalized linear mixed regression model (binomial distribution with a logit link function), including patients as random effect and group as fixed effect. Odds ratios (OR) were reported as effect sizes with their 95% CI.

In the ENDALGOFIV 2 group, all the previous analyses were also performed to compare patients with endometriosis to patients without endometriosis using the same methods as described above for the comparisons between ENDALGOFIV1 and ENDALGOFIV2.

Statistical testing was conducted at the two-tailed *P* value of 0.05. The data was analyzed using the SAS software version 9.4 (SAS Institute, USA).

Ethical approval

This study received approval from the South East III Committee on the Protection of Persons of Bron Hospital, France (2022-A01468-35).

The ClinicalTrials.gov identifier is NCT05591521.

Results

The data of 278 patients who underwent oocyte retrieval for IVF/ICSI in our department from 18 November 2019 to 30 June 2021 was analyzed for the first study ENDALGOFIV 1 and the data of 207 patients, with planned oocyte retrieval for IVF/ICSI from 16 January 2023 to 13 March 2024, was analyzed for ENDALGOFIV 2. Out of the 207 patients included in the second study, 181 of them benefitted from a retrieval and 26 attempts were cancelled.

Out of the 207 patients included in ENDALGOFIV 2, 17% of patients filled out the second questionnaire, 67% of patients for the third questionnaire, 73% of patients for the fourth questionnaire, 26% of patients for the fifth questionnaire and 51% of patients for the sixth and final questionnaire.

All dropouts and exclusions were noted, and partial results were collated.

When offered a consultation with a pain specialist, 21 patients with endometriosis (41%) accepted and 30 patients (59%) did not want one.

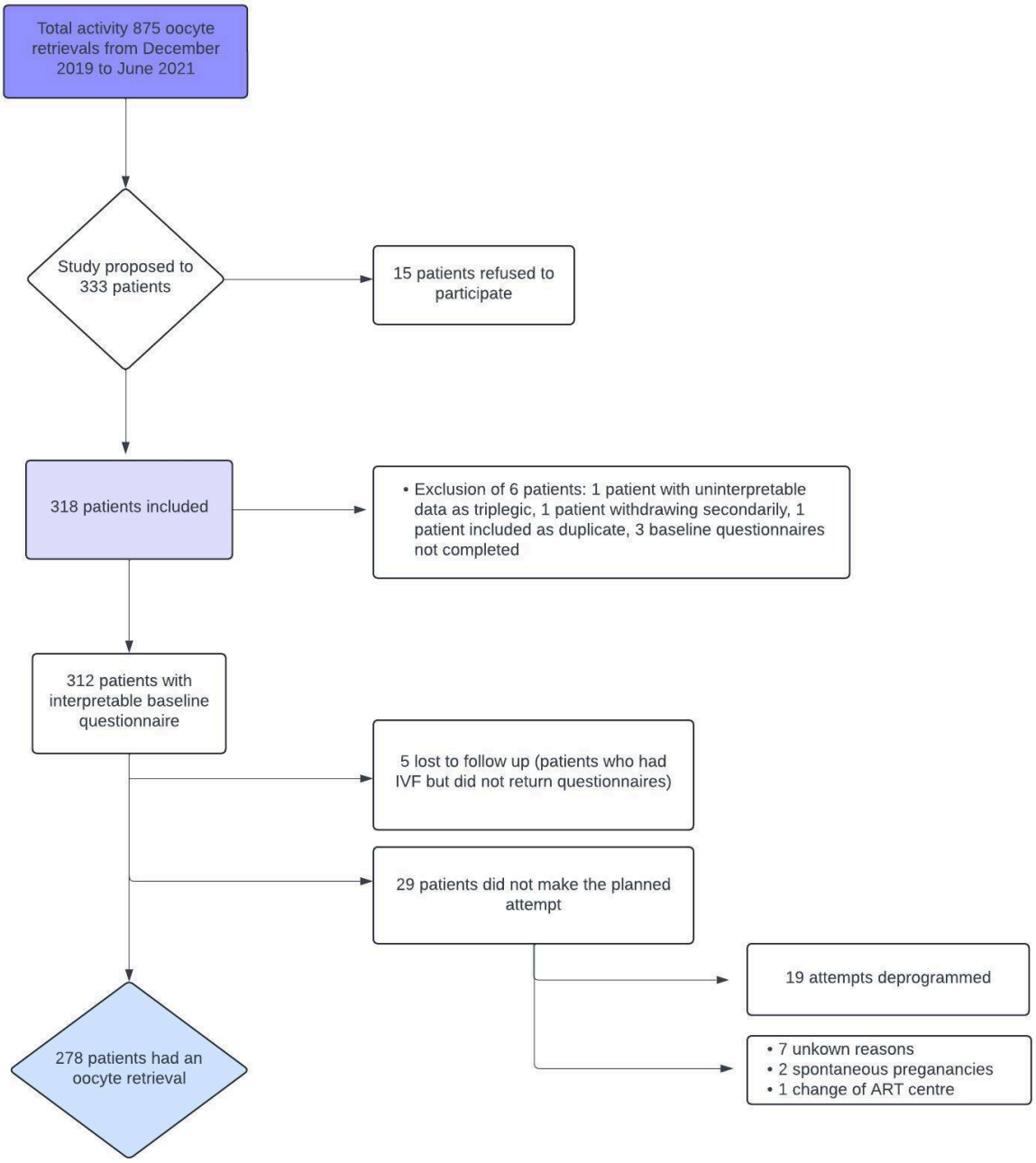


Figure I: Flow chart ENDALGOFIV 1

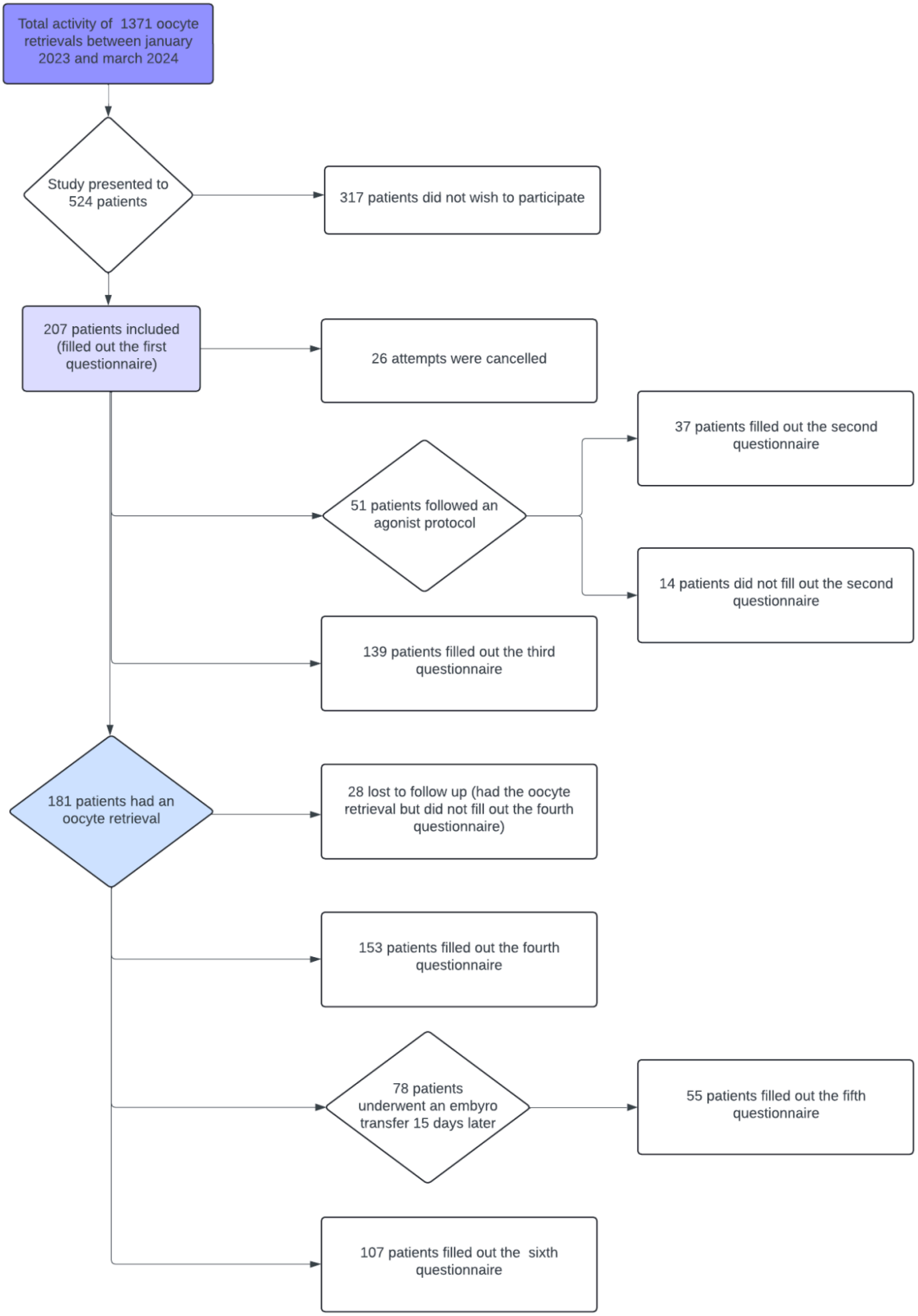


Figure II: Flow chart ENDALGOFIV 2

Analysis between patients from ENDALGOFIV 1 and ENDALGOFIV 2

The main characteristics of patients in both groups are shown in **Table 1**. Out of the 278 patients included in ENDALGOFIV 1, 73 of them had endometriosis (26.3%). A similar rate was found for the patients included in ENDALGOFIV 2 since 51 patients out of 207 (24.8%) suffered from endometriosis. No differences were found between the two groups in terms of average age, BMI or active smoking. The main infertility type was primary in both groups but the rate was higher in patients from ENDALGOFIV 2 (92.7% versus 86.6% [P = 0.004]). The rest of the patient characteristics (primary and secondary indications for IVF procedures, IVF rank, duration of infertility AMH, FSH, E2 and AFC) were similar between the two groups.

Table 1: Patient characteristics			
total n (number of patients who completed Q1) = 485			
	ENDALGOFIV 1 n = 278	ENDALGOFIV 2 n = 207	p value
Age (years) (mean ± SD)	33.6 ± 4.4	33.3 ± 4.8	0.57
BMI (mean ± SD)	24.4 ± 4.4	25.1 ± 5.3	0.14
Active smoking (n (%))	36 (12.9)	38 (18.9)	0.075
Patient with endometriosis (n (%))	73 (26.2)	51 (24.8)	0.64
Infertility type (n (%))			0.004
primary	241 (86.6)	193 (92.7)	
secondary	37 (13.4)	15 (7.3)	
Duration of infertility (months) (mean ± SD)	54.8 ± 35.1	50.5 ± 29.5	0.14
Primary indication (n (%))			NA
isolated tubal	36 (12.9)	18 (9.0)	
tubal and male infertility	16 (5.8)	8 (4.0)	
idiopathic	25 (9.0)	41 (20.5)	
endometriosis	53 (19.1)	34 (17.0)	
male infertility ICSI	119 (42.8)	80 (40.0)	
ovulatory	19 (6.8)	15 (7.5)	
other	10 (3.6)	4 (2.0)	
Secondary indication (n (%))			NA
none	203 (73)	170 (82)	
isolated tubal	3 (0.7)	2 (0.9)	
endometriosis	17 (4.4)	5 (2.4)	
male infertility ICSI	6 (1.5)	6 (2.9)	
diminished ovarian reserves	38 (10)	14 (6.7)	
other	11 (2.9)	10 (4.8)	
IVF rank (n (%))			NA
1	191 (68.7)	131 (67.9)	
2	49 (17.6)	46 (23.8)	
3	24 (8.6)	12 (6.2)	
4	13 (4.7)	3 (1.6)	
5	1 (0.4)	1 (0.5)	
AMH (pmol/L) (median [Q1;Q3])	16.3 (9.4 ; 31.2)	18.0 (10.3 ; 32.6)	0.45
FSH (IU/L) (median [Q1;Q3])	6.8 (5.7 ; 8.2)	6.3 (5.4 ; 7.8)	0.21
E2 (pg/mL) (median [Q1;Q3])	37.0 (30.0 ; 49.0)	37.0 (28.0 ; 56.0)	0.78
AFC (mean ± SD)	24.0 ± 15.6	25.4 ± 16.0	0.30

NA: no test due to high number of variables
SD=standard deviation, BMI=body mass index, n=number of cases, , ICSI = intracytoplasmic sperm injection, AMH=anti Mullerian hormone, FSH=follicle-stimulating hormone, E2=oestradiol, AFC=antral follicular count

The characteristics of the IVF attempts are detailed in **Table 2**. There were no significant differences between the two groups for the stimulation protocol and the total dose of gonadotropins.

HCG was found as the most common trigger product in both groups but more so for ENDALGOFIV 1 (92.8% versus 56.6% $p < 0.0001$). The use of a double trigger was more frequent for ENDALGOFIV 2 (29.1% versus 0.4% $p < 0.0001$). More oocytes were retrieved and fertilized in ENDALGOFIV 2 (10.4 ± 6.6 versus 7.5 ± 4.7 $P < 0.0001$ and 10.0 ± 6.7 versus 6.4 ± 4.5 $p < 0.0001$). The average number of embryos obtained was higher in ENDALGOFIV 2 but there was no significant difference between the two groups. We found a higher number of embryos transferred in ENDALGOFIV 1 (0.8 ± 0.8 versus 0.5 ± 0.5 $p < 0.0001$) with a higher number of fresh transfers (62.1% versus 43.1% $p < 0.0001$). The number of frozen embryos was higher in ENDALGOFIV 2 (2.3 ± 3.1 versus 1.2 ± 1.7 $p < 0.0001$). The number of clinical pregnancies after fresh transfer was similar between the two groups (15.6 % for ENDALGOFIV 1 vs 17.9% for ENDALGOFIV 2).

Table 2 : Characteristics of IVF attempts			
number of patients who underwent IVF n= 485			
	ENDALGOFIV 1 n = 278	ENDALGOFIV 2 n = 207	p value
Adverse events during the attempt (n (%))	25 (9.0)	2 (1.1)	< 0.001
Stimulation protocol (n (%))			NA
programmed GnRH antagonist	118 (42.4)	87 (45.3)	
non programmed GnRH antagonist	23 (8.3)	51 (26.6)	
long GnRH agonist	134 (48.2)	51 (26.6)	
short GnRH agonist	3 (1.1)	3 (1.6)	
Total dose of gonadotropins (IU) (mean ± SD)	2863 ± 1649	2815 ± 1589	0.90
Trigger product (n (%))			< 0.001
hCG	258 (92.8)	103 (56.6)	
GnRH agonist	19 (6.8)	26 (14.3)	
double trigger	1 (0.4)	53 (29.1)	
Number of follicles (mean ± SD)	8.5 ± 4.2	8.8 ± 4.6	0.34
Total number of oocytes retrieved (mean ± SD)	7.5 ± 4.7	10.4 ± 6.6	< 0.001
Number of oocytes fertilized (mean ± SD)	6.4 ± 4.5	10.0 ± 6.7	< 0.001
Number of embryos obtained (mean ± SD)	4.2 ± 3.4	5.4 ± 4.5	0.009
Number of embryos transferred (mean ± SD)	0.8 ± 0.8	0.5 ± 0.5	<0.001
Number of frozen embryos (mean ± SD)	1.2 ± 1.7	2.3 ± 3.1	<0.001
Fresh transfer realized (n (%))	172 (62.1)	78 (43.1)	<0.001
Cancellation (n (%))	32 (11.5)	26 (12.9)	0.65
Clinical pregnancy* (n (%))	27 (15.6)	14 (17.9)	NA

NA: no test due to high number of variables , SD=standard deviation, n=number of cases, GnRH=Gonadotropin-releasing hormone, hCG= human chorionic gonadotropin
***only fresh transfer**

The baseline status of patients of both groups based on their answers to the first questionnaire are shown in **Table 3**. The average pain level (QDSA score) of patients was similar between the two groups. There was also no significant difference in terms of pain intensity, neuropathic pain, depression, anxiety, affective and sensory dimensions of the pain and quality of life as shown by the EQ5D score. The level of catastrophizing was different between the two groups with a higher rate in ENDALGOFIV 2 (24% versus 13% p = 0.001). The same trend was found also for the impotence score (5.8 ± 6.0 versus 3.6 ± 5.2 p < 0.001), the amplification score (2.6 ± 2.8 versus 1.9 ± 2.6 p = 0.001) and the rumination score (5.3 ± 4.7 versus 2.8 ± 4.0 p < 0.001).

Table 3 : Baseline status (questionnaire 1)			
total n (number of patients who completed Q1) = 485			
	ENDALGOFIV 1 n = 278	ENDALGOFIV 2 n = 207	p value
NPRS (mean ± SD)	1.7 ± 2.4	2.0 ± 2.7	0.59
Pain intensity (n (%))			
mild	215 (77)	151 (72)	
moderate	51 (18)	47 (22)	
severe	11 (3.9)	8 (3.8)	
Sensory QDSA (mean ± SD)	3.2 ± 4.7	3.4 ± 5.3	0.59
Affective QDSA (mean ± SD)	3.1 ± 5.5	3.7 ± 5.8	0.16
Neuropathic pain DN4 (mean ± SD)	0.6 ± 1.2	0.7 ± 1.4	0.87
Neuropathic pain DN4 (n (%))	24 (8.6)	22 (10)	-
Depression (mean ± SD)	3.6 ± 3.2	3.7 ± 3.1	0.63
absent (n (%))	245 (88)	183 (88)	
suspected (n (%))	20 (7)	17 (8)	
proven (n (%))	13 (4)	6 (2.9)	
Anxiety (mean ± SD)	7.6 ± 3.9	7.8 ± 3.9	0.44
absent (n (%))	152 (54)	107 (51)	
suspected (n (%))	61 (21)	49 (23)	
proven (n (%))	65 (23)	50 (24)	
Presence of catastrophizing (n (%))	36 (13)	50 (24)	0.001
impotence score (mean ± SD)	3.6 ± 5.2	5.8 ± 6.0	< 0.001
amplification score (mean ± SD)	1.9 ± 2.6	2.6 ± 2.8	0.001
rumination score (mean ± SD)	2.8 ± 4.0	5.3 ± 4.7	< 0.001
EQ5D (mean ± SD)	0.9 ± 0.2	0.9 ± 0.2	0.57

NA: no test due to low number of participants
NPRS = numerical pain rating scale, QDSA=Saint Antoine pain questionnaire, DN4=Neuropathic Pain 4 questionnaire,, EQ5D=EuroQol 5D, n=number of cases, SD=standard deviation

The baseline status of patients with and without endometriosis inside of each group is shown in **Table 4**. The average pain scores (NPRS, QDSA) were higher in patients with endometriosis compared to patients without endometriosis in both groups. More neuropathic pain, depression and catastrophizing was also found in patients with endometriosis as opposed to patients without endometriosis.

Table 4 : Baseline status (questionnaire 1)					
total n (number of patients who completed Q1) = 485					
	ENDALGOFIV 1 n = 278		ENDALGOFIV 2 n = 207		
	patients with endometriosis n = 73	patients without endometriosis n =205	patients with endometriosis n = 51	patients without endometriosis n = 156	p value
NPRS (mean ± SD)	3.47 ± 2.66	1.12 ± 2.01	4.3 ± 2.8	1.2 ± 2.2	< 0.001
Pain intensity (n (%))					< 0.001
mild	36 (49.32)	179 (87.75)	20 (39.2)	131 (84.5)	
moderate	1 (42.47)	20 (9.80)	24 (47.1)	23 (14.8)	
severe	6 (8.22)	5 (2.45)	7 (13.7)	1 (0.6)	
Sensory QDSA (mean ± SD)	6.78 ± 6.30	1.87 ± 3.16	7.1 ± 6.3	2.1 ± 4.2	< 0.001
Affective QDSA (mean ± SD)	6.77 ± 7.38	1.8 ± 3.87	7.1 ± 7.6	2.5 ± 4.7	< 0.001
Presence of neuropathic pain DN4 (n (%))	13 (17.81)	11 (5.37)	9 (17.6)	13 (8.4)	0.003
Depression					0.011
absent (n (%))	57 (78.08)	188 (91.71)	42 (82.4)	141 (91.0)	
suspected (n (%))	9 (12.33)	11 (5.37)	5 (9.8)	12 (7.7)	
proven (n (%))	7 (9.59)	6 (2.93)	4 (7.8)	2 (1.3)	
Anxiety					0.13
absent (n (%))	33 (45.21)	119 (58.08)	23 (45.1)	84 (54.2)	
suspected (n (%))	16 (21.92)	45 (21.95)	10 (19.6)	39 (25.2)	
proven (n (%))	24 (32.88)	41 (20)	18 (35.3)	32 (20.6)	
Presence of catastrophizing (n (%))	21 (28.77)	15 (7.32)	21 (41.2)	29 (18.7)	< 0.001
impotence score (mean ± SD)	6.71 ± 6.57	2.47 ±4.05	9.0 ± 6.8	4.7 ± 5.3	< 0.001
amplification score (mean ± SD)	3.37 ± 3.07	1.44 ± 2.28	3.5 ± 2.8	2.3 ± 2.8	< 0.001
Rumination score (mean ± SD)	4.49 ± 4.89	2.24 ± 3.45	7.1 ± 5.1	4.8 ± 4.4	< 0.001
EQ5D (mean ± SD)	0.78 ± 0.22	0.91 ± 0.11	0.8 ± 0.2	0.9 ± 0.2	0.57

NA: no test due to low number of participants
NPRS = numerical pain rating scale, QDSA=Saint Antoine pain questionnaire, DN4=Neuropathic Pain 4 questionnaire,, EQ5D=EuroQol 5D, n=number of cases, SD=standard deviation

The pain scores at the end of stimulation before induction of ovulation (questionnaire 3) are shown in **Table 5**. No significant difference was found for the NPRS or for the presence of neuropathic pain (DN4 score). The QDSA score was significantly higher in ENDALGOFIV 2 for patients with endometriosis (14.72 vs 10.02 p = 0.01) and for patients without endometriosis (9.9304 vs 5.8672 p < 0.0001).

Table 5 : Evolution after stimulation (questionnaire 3)

number of patients who completed the questionnaire 3 n= 417						
	Patients with endometriosis n = 100			Patients without endometriosis n = 317		
	ENDALGOFIV 1 n = 73	ENDALGOFIV 2 n = 27	p value	ENDALOGFIV 1 n = 205	ENDALGOFIV 2 n = 112	p value
NPRS (mean)	3.05	3.34	0.55	2.29	2.76	0.05
Total QDSA (mean)	10.02	14.72	0.01	5.86	9.93	<.0001
Sensory QDSA (mean)	6.12	8.29	0.03	4.13	5.45	0.0063
Affective QDSA (mean)	3.97	6.42	0.01	2.01	4.45	<.0001
Presence of neuropathic pain DN4 (n (%))	7 (9.72)	3 (11.11)	0.77	15 (7.73)	9 (8.03)	0.55

NPRS = numerical pain rating scale, QDSA=Saint Antoine pain questionnaire, DN4=Neuropathic Pain 4 questionnaire, , n=number of cases, SD=standard deviation

The pain scores after oocyte retrieval (questionnaire 4) are shown in **Table 6**. The average pain level (QDSA score and NPRS) was higher in ENDALGOFIV 2 than ENDALGOFIV 1 (QDSA 11.8 versus 7.16 p < .0001; NPRS 3.77 versus 3.12 p = 0.0110) specifically the affective dimension of pain (4.70 versus 2.09 p < .0001). There was no difference between the two groups in terms of neuropathic pain.

Table 6 : Pain scores for Questionnaire 4

number of patients who completed the questionnaire 4 n= 431			
	ENDALGOFIV 1 n = 278	ENDALGOFIV 2 n = 153	p value
NPRS (mean ± SD)	3.12 ± 2.54	3.77 ± 2.61	0.0110
Total QDSA (mean ± SD)	7.16 ± 8.04	11.80 ± 11.78	<.0001
Sensory QDSA (mean ± SD)	5.06 ± 5.18	7.09 ± 7.40	0.0007
Affective QDSA (mean ± SD)	2.09 ± 3.82	4.70 ± 5.66	<.0001
Neuropathic pain score (mean ± SD)	0.65 ± 1.10	0.99 ± 3.71	0.1794

NPRS = numerical pain rating scale, QDSA=Saint Antoine pain questionnaire, DN4=Neuropathic Pain 4 questionnaire, , n=number of cases, SD=standard deviation

The different scores between patients with and without endometriosis inside each group is shown in **Table 6 bis**. The NPRS was significantly increased in ENDALGOFIV 2 compared to ENDALGOFIV 1 for patients without endometriosis (3.80 vs 3.11 p = 0.01) but not for patients with endometriosis (3.70 vs 3.11 p = 0.50). The higher level of affective pain in ENDALGOFIV 2 compared to ENDALGOFIV 1 was significant for patients with endometriosis (2.67 versus 5.45 p = 0.009) and for patients without (1.88 versus 4.47 p < 0.0001).

Table 6 bis : Pain scores for Questionnaire 4						
number of patients who completed the questionnaire 4 n= 426						
	Patients with endometriosis n = 108			Patients without endometriosis n = 318		
	ENDALGOFIV 1 n = 73	ENDALGOFIV 2 n = 35	p value	ENDALOGFIV 1 n = 205	ENDALGOFIV 2 n = 113	p value
NPRS (mean ± SD)	3.16 ± 5.05	3.70 ± 2.94	0.50	3.11 ± 5.63	3.80 ± 2.91	0.01
Total QDSA (mean ± SD)	8.47 ± 16.56	13.09 ± 24.96	0.01	6.68 ± 9.12	11.41 ± 13.25	< .0001
Sensory QDSA (mean ± SD)	5.79 ± 10.41	7.63 ± 14.90	0.11	4.80 ± 5.95	6.93 ± 8.12	0.002
Affective QDSA (mean ± SD)	2.67 ± 7.57	5.45 ± 12.45	0.009	1.88 ± 4.41	4.47 ± 6.38	< .0001
Presence of neuropathic pain DN4 (n (%))	9 (12.34)	7 (20)	0.48	9 (4.48)	8 (7.07)	0.20

NPRS = numerical pain rating scale, QDSA=Saint Antoine pain questionnaire, DN4=Neuropathic Pain 4 questionnaire, , n=number of cases, SD=standard deviation

During the IVF attempt, the evolution of the NPRS score is shown in **Table 7**. The average level of pain after oocyte retrieval was higher in patients included in ENDALGOFIV 2 than patients included in ENDALGOFIV 1 (3.77 versus 3.12 p = 0.01).

Table 7 : Evolution of the difference of NPRS between the two groups during the IVF attempt			
total number of patients included in the two studies n = 485			
	ENDALGOFIV 1 n = 278	ENDALGOFIV 2 n = 207	p value
Questionnaire 1 (mean ±SD)	1.7 ± 2.4	2.0 ± 2.7	0.59
Questionnaire 2 (mean ±SD) (1)	1.84 ± 0.17	1.68 ± 0.32	0.66
Questionnaire 3 (mean ±SD) (2)	2.49 ± 0.12	2.92 ± 0.18	0.05
Questionnaire 4 (mean ±SD) (3)	3.12 ± 2.54	3.77 ± 2.61	0.01
Questionnaire 5 (mean ±SD) (4)	2.75 ± 0.17	2.67 ± 0.27	0.82
Questionnaire 6 (mean ±SD) (5)	2.92 ± 0.14	3.55 ± 0.19	0.01

NPRS = numerical pain rating scale, n=number of cases, SD=standard deviation
(1) 37/51 responded to Q2 in ENDALGOFIV 2 (data missing from 14 patients); (2) 139 patients filled out Q3 for ENDALGOFIV 2; (3) 153 patients filled out Q4 for ENDALGOFIV 2; (4) 55/78 responded to Q5 for ENDALGOFIV 2; (6) 107 patients filled out Q6 for ENDALGOFIV 2

After taking into account whether the patient had endometriosis or not (**Table 7 bis**), the difference in pain levels after oocyte retrieval was significant for patients without endometriosis (3.80 versus 3.11 p = 0.01). No significant difference was found in patients with endometriosis. Six weeks after transfer, only patients without endometriosis had a significantly higher score in ENDALGOFIV 2 compared to ENDALGOFIV 1 (3.38 versus 2.65 p = 0.01).

Table 7 bis : Evolution of the difference of NPRS between the two groups during the IVF attempt						
total number of patients included in the two studies n = 485						
	Patients with endometriosis n = 124			Patients without endometriosis n = 361		
	ENDALGOFIV 1 n = 73	ENDALGOFIV 2 n =51	p value	ENDALGOFIV 1 n = 205	ENDALGOFIV 2 n = 156	p value
Questionnaire 1 (mean)	3.47	4.3	-	1.12	1.2	-
Questionnaire 2 (mean) (1)	2.82	1.85	0.20	1.49	1.60	0.80
Questionnaire 3 (mean) (2)	3.05	3.34	0.55	2.29	2.76	0.05
Questionnaire 4 (mean) (3)	3.16	3.70	0.50	3.11	3.80	0.01
Questionnaire 5 (mean) (4)	3.93	2.67	0.07	2.32	2.65	0.36
Questionnaire 6 (mean) (5)	3.66	4.00	0.52	2.65	3.38	0.01

NPRS = numerical pain rating scale, n=number of cases, SD=standard deviation
(1) 37/51 responded to Q2 in ENDALGOFIV 2 (data missing from 14 patients); (2) 139 patients filled out Q3 for ENDALGOFIV 2; (3) 153 patients filled out Q4 for ENDALGOFIV 2; (4) 55/78 responded to Q5 for ENDALGOFIV 2; (6) 107 patients filled out Q6 for ENDALGOFIV 2

The evolution of the NPRS score for patients with endometriosis between the two groups is shown in **Figure 1** and the evolution for patients without endometriosis is shown in **Figure 2.** In both groups patients with endometriosis seemed to have a more stable pain score level whereas patients without endometriosis had a lower pain level at their baseline which then increased up until the oocyte retrieval.

Figure 1: Evolution of the difference of NPRS between the two groups for patients with endometriosis

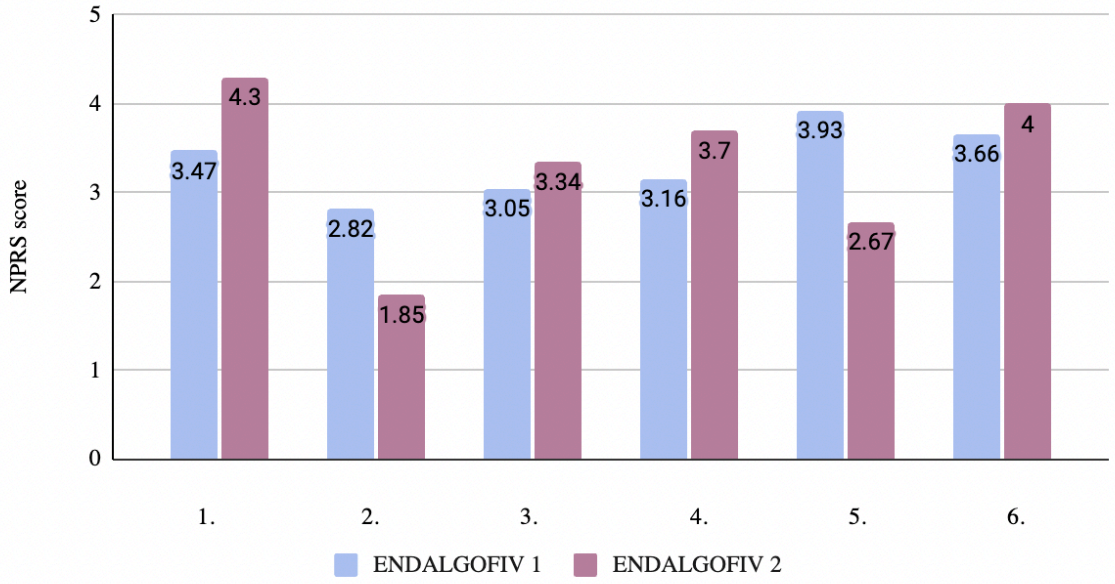
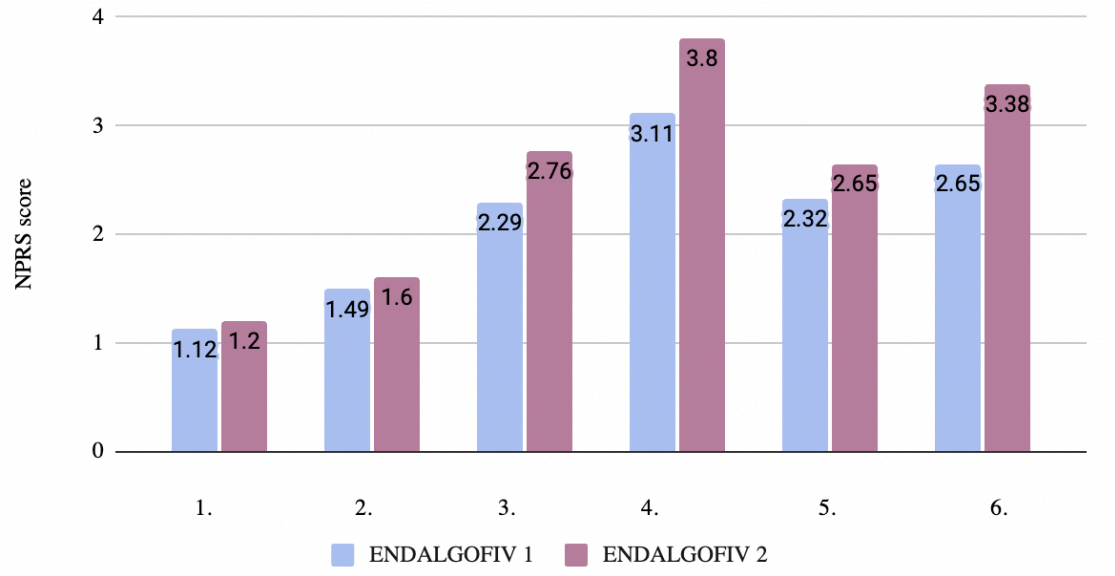


Figure 2: Evolution of the difference of NPRS between the two groups for patients without endometriosis



During the IVF attempt, the evolution of the DN4 score is shown in **Table 8**. The evolution was similar between the two groups.

Table 8: Evolution of the difference of DN4 between the two groups during the IVF attempt			
total number of patients included in the two studies n = 485			
	ENDALGOFIV 1 n = 278	ENDALGOFIV 2 n = 207	p value
Questionnaire 1 (mean ±SD)	0.6 ± 1.2	0.7 ± 1.4	0.87
Questionnaire 2 (mean ±SD) (1)	0.53 ± 0.13	0.51 ± 0.24	0.96
Questionnaire 3 (mean ±SD) (2)	0.73 ± 0.09	0.81 ± 0.13	0.62
Questionnaire 4 (mean ±SD) (3)	0.65 ± 1.10	0.99 ± 3.71	0.17
Questionnaire 5 (mean ±SD) (4)	0.71 ± 0.13	0.52 ± 0.20	0.43
Questionnaire 6 (mean ±SD) (5)	0.55 ± 0.10	0.65 ± 0.14	0.54

DN4=Neuropathic Pain 4 questionnaire, , n=number of cases, SD=standard deviation
(1) 37/51 responded to Q2 in ENDALGOFIV 2 (data missing from 14 patients); (2) 139 patients filled out Q3 for ENDALGOFIV 2; (3) 153 patients filled out Q4 for ENDALGOFIV 2; (4) 55/78 responded to Q5 for ENDALGOFIV 2; (6) 107 patients filled out Q6 for ENDALGOFIV 2

The evolution of the presence of neuropathic pain between patients with and without endometriosis inside each group is shown in **Table 8 bis**.

Table 8 bis : Evolution of the difference of the presence of neuropathic pain between the two groups during the IVF attempt				
total number of patients included in the two studies n = 485				
	ENDALGOFIV 1 n = 278		ENDALGOFIV 2 n = 207	
	patients with endometriosis n = 73	patients without endometriosis n =205	patients with endometriosis n = 51	patients without endometriosis n = 156
Questionnaire 1 (n(%))	13 (17.81)	11 (5.37)	9 (17.6)	13 (8.4)
Questionnaire 2 (n(%))	4 (9.52)	2 (2.53)	0 (0)	1 (3.84)
Questionnaire 3 (n(%))	7 (9.72)	15 (7.73)	3 (11.11)	9 (8.03)
Questionnaire 4 (n(%))	9 (12.34)	9 (4.48)	7 (20)	8 (7.07)
Questionnaire 5 (n(%))	6 (18.75)	7 (7.77)	1 (8.33)	0 (0)
Questionnaire 6 (n(%))	6 (10.9)	4 (2.68)	4 (18.18)	6 (7.05)

DN4=Neuropathic Pain 4 questionnaire, , n=number of cases
(1) 37/51 responded to Q2 in ENDALGOFIV 2 (data missing from 14 patients); (2) 139 patients filled out Q3 for ENDALGOFIV 2; (3) 153 patients filled out Q4 for ENDALGOFIV 2; (4) 55/78 responded to Q5 for ENDALGOFIV 2; (6) 107 patients filled out Q6 for ENDALGOFIV 2

During the IVF attempt, the evolution of the QDSA score is shown in **Table 9**. The level of pain was higher in ENDALGOFIV 2 after stimulation (questionnaire 3) (11.19 versus 6.94 p < .001), after oocyte retrieval (11.80 versus 7.16 p < .001) and six weeks after the retrieval (questionnaire 6) (8.73 versus 5.80 p = 0.0004).

Table 9 : Evolution of the difference of QDSA between the two groups during the IVF attempt			
total number of patients included in the two studies n = 485			
	ENDALGOFIV 1 n = 278	ENDALGOFIV 2 n = 207	p value
Questionnaire 1 (mean ±SD)	6.3 ± 9.6	7.0 ± 10.5	0.72
Questionnaire 2 (mean ±SD) (1)	5.20 ± 0.62	7.94 ± 1.13	0.03
Questionnaire 3 (mean ±SD) (2)	6.94 ± 0.42	11.19 ± 0.63	< .0001
Questionnaire 4 (mean ±SD) (3)	7.16 ± 8.04	11.80 ± 11.78	< .0001
Questionnaire 5 (mean ±SD) (4)	9.83 ± 0.61	9.42 ± 0.94	0.71
Questionnaire 6 (mean ±SD) (5)	5.80 ± 0.48	8.73 ± 0.66	0.0004

QDSA=Saint Antoine pain questionnaire,, n=number of cases, SD=standard deviation
(1) 37/51 responded to Q2 in ENDALGOFIV 2 (data missing from 14 patients); (2) 139 patients filled out Q3 for ENDALGOFIV 2; (3) 153 patients filled out Q4 for ENDALGOFIV 2; (4) 55/78 responded to Q5 for ENDALGOFIV 2; (6) 107 patients filled out Q6 for ENDALGOFIV 2

The evolution of the QDSA score between patients with and without endometriosis inside each group is shown in **Table 9 bis**.

Table 9 bis : Evolution of the difference of QDSA between the two groups during the IVF attempt				
total number of patients included in the two studies n = 485				
	ENDALGOFIV 1 n = 278		ENDALGOFIV 2 n = 207	
	patients with endometriosis n = 73	patients without endometriosis n =205	patients with endometriosis n = 51	patients without endometriosis n = 156
Questionnaire 1 (mean)	13.4	3.7	14.1	4.7
Questionnaire 2 (mean) (1)	9.81	3.39	10.33	7.04
Questionnaire 3 (mean) (2)	10.01	5.86	14.72	9.93
Questionnaire 4 (mean) (3)	8.47	6.68	13.09	11.41
Questionnaire 5 (mean) (4)	14.05	8.37	13.27	7.90
Questionnaire 6 (mean) (5)	9.77	4.33	15.73	6.59

QDSA=Saint Antoine pain questionnaire,, n=number of cases
(1) 37/51 responded to Q2 in ENDALGOFIV 2 (data missing from 14 patients); (2) 139 patients filled out Q3 for ENDALGOFIV 2; (3) 153 patients filled out Q4 for ENDALGOFIV 2; (4) 55/78 responded to Q5 for ENDALGOFIV 2; (6) 107 patients filled out Q6 for ENDALGOFIV 2

The evolution of the quality of life shown by the EQ5D score is shown in **Table 10.** There were no significant differences between the two groups during the IVF attempt.

Table 10 : Evolution of the difference of EQ5D between the two groups at T1, T5 and T6			
total number of patients included in the two studies n = 485			
	ENDALGOFIV 1 n = 278	ENDALGOFIV 2 n = 207	p value
Questionnaire 1 (mean ±SD)	0.9 ± 0.2	0.9 ± 0.2	0.57
Questionnaire 5 (mean ±SD) (1)	0.81 ± 0.009	0.78 ± 0.014	0.17
Questionnaire 6 (mean ±SD) (2)	0.85 ± 0.007	0.86 ± 0.010	0.94

EQ5D=EuroQol 5D, n=number of cases, SD=standard deviation
(1) 55/78 responded to Q5 for ENDALGOFIV 2; (2) 107 patients filled out Q6 for ENDALGOFIV 2

The evolution of the EQ5D score between patients with and without endometriosis inside each group is shown in **Table 10 bis**.

Table 10 bis : Evolution of the difference of EQ5D between the two groups during the IVF attempt				
total number of patients included in the two studies n = 485				
	ENDALGOFIV 1 n = 278		ENDALGOFIV 2 n = 207	
	patients with endometriosis n = 73	patients without endometriosis n =205	patients with endometriosis n = 51	patients without endometriosis n = 156
Questionnaire 1 (mean)	0.78	0.91	0.8	0.9
Questionnaire 5 (mean) (1)	0.83	0.75	0.66	0.82
Questionnaire 6 (mean) (2)	0.89	0.78	0.71	0.89

EQ5D=EuroQol 5D, n=number of cases, (1) 55/78 responded to Q5 for ENDALGOFIV 2; (2) 107 patients filled out Q6 for ENDALGOFIV 2

The evolution of the HAD score during the IVF attempt is shown in **Table 11**. The two groups are similar in terms of depression and anxiety.

Table 11 : Evolution of the difference of HAD between the two groups at T1, T5 and T6			
total number of patients included in the two studies n = 485			
	ENDALGOFIV 1 n = 278	ENDALGOFIV 2 n = 207	p value
HAD depression			
Questionnaire 1 (mean ±SD)	3.6 ± 3.2	3.7 ± 3.1	0.63
Questionnaire 5 (mean ±SD) (1)	4.67 ± 0.20	4.39 ± 0.31	0.44
Questionnaire 6 (mean ±SD) (2)	4.06 ± 0.15	4.10 ± 0.21	0.87
HAD anxiety			
Questionnaire 1 (mean ±SD)	7.6 ± 3.9	7.8 ± 3.9	0.44
Questionnaire 5 (mean ±SD) (1)	7.87 ± 0.18	7.92 ± 0.29	0.88
Questionnaire 6 (mean ±SD) (2)	7.06 ± .014	6.73 ± 0.20	0.18

HAD: hospital anxiety and depression, n=number of cases, SD=standard deviation, (1) 55/78 responded to Q5 for ENDALGOFIV 2; (2) 107 patients filled out Q6 for ENDALGOFIV 2

The evolution of the HAD score during the IVF attempt between patients with and without endometriosis inside each group is shown in **Table 11bis**.

Table 11 bis : Evolution of the difference of HAD between the two groups at T1, T5 and T6				
total number of patients included in the two studies n = 485				
	ENDALGOFIV 1 n = 278		ENDALGOFIV 2 n = 207	
	patients with endometriosis n = 73	patients without endometriosis n =205	patients with endometriosis n = 51	patients without endometriosis n = 156
HAD depression				
Questionnaire 1 (mean)	4.58	3.25	4.8	3.3
Questionnaire 5 (mean) (1)	4.68	4.66	4.54	4.28
Questionnaire 6 (mean) (2)	4.44	3.95	5.46	3.72
HAD anxiety				
Questionnaire 1 (mean)	8.55	7.20	8.5	7.5
Questionnaire 5 (mean) (1)	8.08	7.79	9.34	7.46
Questionnaire 6 (mean) (2)	8.18	6.67	7.80	6.40

HAD: hospital anxiety and depression, n=number of cases
(1) 55/78 responded to Q5 for ENDALGOFIV 2; (2) 107 patients filled out Q6 for ENDALGOFIV 2

During the IVF attempt, the evolution of the level of catastrophizing is shown in **Table 12**. The level is similar between both groups apart from the level of rumination six weeks after transfer (questionnaire 6) where the level was higher for patients in ENDALGOFIV 2 (3.94 versus 2.67 $p < .0001$).

Table 12 : Evolution of the difference of PCS between the two groups at T1, T5 and T6			
total number of patients included in the two studies n = 485			
	ENDALGOFIV 1 n = 278	ENDALGOFIV 2 n = 207	p value
PCS total			
Questionnaire 1 (mean ±SD)	8.4 ± 11.1	13.7 ± 12.5	< 0.001
Questionnaire 5 (mean ±SD) (1)	9.42 ± 0.53	8.19 ± 0.82	0.21
Questionnaire 6 (mean ±SD) (2)	7.45 ± 0.41	8.80 ± 0.57	0.05
PCS impotence			
Questionnaire 1 (mean ±SD)	3.6 ± 5.2	5.8 ± 6.0	< 0.001
Questionnaire 5 (mean ±SD) (1)	3.76 ± 0.25	3.15 ± 0.39	0.19
Questionnaire 6 (mean ±SD) (2)	3.07 ± 0.19	3.54 ± 0.27	0.16
PCS amplification			
Questionnaire 1 (mean ±SD)	1.9 ± 2.6	2.6 ± 2.8	0.001
Questionnaire 5 (mean ±SD) (1)	2.19 ± 0.13	2.08 ± .21	0.67
Questionnaire 6 (mean ±SD) (2)	1.70 ± 0.09	1.97 ± 0.14	0.13
PCS rumination			
Questionnaire 1 (mean ±SD)	2.8 ± 4.0	5.3 ± 4.7	< 0.001
Questionnaire 5 (mean ±SD) (1)	3.25 ± 0.21	3.12 ± 0.34	0.76
Questionnaire 6 (mean ±SD) (2)	2.67 ± 0.17	3.94 ± 0.23	< .0001

PCS: pain catastrophizing scale, n=number of cases, SD=standard deviation
(1) 55/78 responded to Q5 for ENDALGOFIV 2; (2) 107 patients filled out Q6 for ENDALGOFIV 2

The evolution of the PCS score between patients with and without endometriosis inside each group is shown in **Table 12 bis**.

Table 12 bis : Evolution of the difference of PCS between the two groups at T1, T5 and T6				
total number of patients included in the two studies n = 485				
	ENDALGOFIV 1 n = 278		ENDALGOFIV 2 n = 207	
	patients with endometriosis n = 73	patients without endometriosis n =205	patients with endometriosis n = 51	patients without endometriosis n = 156
PCS total				
Questionnaire 1 (mean)	14.37	6.17	20.12	11.66
Questionnaire 5 (mean) (1)	15.55	6.93	14.37	6.51
Questionnaire 6 (mean) (2)	13.28	5.10	15.98	7.01
Presence of catastrophizing				
Questionnaire 1 (n (%))	21 (28.77)	15 (7.32)	21 (41.2)	29 (18.7)
Questionnaire 5 (n (%))	10 (13.89)	8 (3.98)	5 (41.67)	3 (7.69)
Questionnaire 6 (n (%))	11 (15.07)	4 (1.99)	8 (36.36)	10 (11.76)
PCS impotence				
Questionnaire 1 (mean)	6.71	2.47	9.0	4.7
Questionnaire 5 (mean) (1)	6.57	2.64	6.37	2.28
Questionnaire 6 (mean) (2)	5.73	2.03	6.89	2.65
PCS amplification				
Questionnaire 1 (mean)	3.37	1.44	3.5	2.3
Questionnaire 5 (mean) (1)	3.54	1.63	3.36	1.73
Questionnaire 6 (mean) (2)	2.77	1.26	3.90	1.49
PCS rumination				
Questionnaire 1 (mean)	4.49	2.24	7.1	4.8
Questionnaire 5 (mean) (1)	5.37	2.40	4.93	2.65
Questionnaire 6 (mean) (2)	4.76	1.82	6.40	3.34

PCS: pain catastrophizing scale, n=number of cases
1) 55/78 from ENDALGOFIV 2 responded to Q5; (2) 107 patients filled out Q6

Analysis between patients with and without endometriosis treated with the new protocol (ENDALGOFIV 2)

The baseline status of patients included in ENDALGOFIV 2 is shown in **Table 13**. Patients with endometriosis had a significantly higher NPRS score (4.3 vs 1.1 $p < 0.001$), QDSA score on all aspects, neuropathic pain level (1.2 vs 0.6 $p < 0.001$), PCS score and depression level. There were no significant differences in anxiety levels or quality of life (EQ5D score).

Table 13 : Baseline status (questionnaire 1)			
patients included in ENDALGOFIV 2 n = 207			
	patients with endometriosis n = 51	patients without endometriosis n = 156	p value
NPRS (mean ± SD)	4.3 ± 2.8	1.2 ± 2.2	< 0.001
Total QDSA (mean ± SD)	14.1 ± 13.0	4.7 ± 8.4	< 0.001
Sensory QDSA (mean ± SD)	7.1 ± 6.3	2.1 ± 4.2	< 0.001
Affective QDSA (mean ± SD)	7.1 ± 7.6	2.5 ± 4.7	< 0.001
Neuropathic pain DN4 (mean ± SD)	1.2 ± 1.5	0.6 ± 1.4	< 0.001
Neuropathic pain DN4 (n (%))	9 (17.6)	13 (8.4)	0.003
Depression (mean ± SD)	4.8 ± 3.2	3.3 ± 3.0	0.002
absent (n (%))	42 (82.4)	141 (91.0)	0.011
suspected (n (%))	5 (9.8)	12 (7.7)	
proven (n (%))	4 (7.8)	2 (1.3)	
Anxiety (mean ± SD)	8.5 ± 4.1	7.5 ± 3.8	0.23
absent (n (%))	23 (45.1)	84 (54.2)	0.13
suspected (n (%))	10 (19.6)	39 (25.2)	
proven (n (%))	18 (35.3)	32 (20.6)	
Presence of catastrophizing (n (%))	21 (41.2)	29 (18.7)	< 0.001
impotence score (mean ± SD)	9.0 ± 6.8	4.7 ± 5.3	< 0.001
amplification score (mean ± SD)	3.5 ± 2.8	2.3 ± 2.8	0.001
rumination score (mean ± SD)	7.1 ± 5.1	4.8 ± 4.4	0.003
EQ5D (mean ± SD)	0.8 ± 0.2	0.9 ± 0.2	0.57

NA: no test due to low number of participants
NPRS = numerical pain rating scale, QDSA=Saint Antoine pain questionnaire, DN4=Neuropathic Pain 4 questionnaire,, EQ5D=EuroQol 5D, n=number of cases, SD=standard deviation

The baseline status of patients with endometriosis is shown in **Table 14.** Higher pain levels (NPRS, QDSA, DN4) were found in patients that requested a pain consultation as well as higher depression and anxiety levels. However, catastrophizing was more frequent in patients that did not want a pain consultation (53 % versus 28 %).

Table 14 : Baseline status (questionnaire 1)		
patients with endometriosis n = 51		
	patients requesting pain consultation n = 21	patients denying a pain consultation n = 30
NPRS (mean)	5	3.97
Total QDSA (mean)	18.4	13.12
Sensory QDSA (mean)	8.2	6.72
Affective QDSA (mean)	10.2	6.4
Neuropathic pain DN4 (n (%))	6 (28)	3 (10)
Depression (mean)	6.2	4.6
Anxiety (mean)	9.1	8.6
Presence of catastrophizing (n (%))	6 (28)	16 (53)
EQ5D (mean)	0.82	0.80

NA: no test due to low number of participants
NPRS = numerical pain rating scale, QDSA=Saint Antoine pain questionnaire, DN4=Neuropathic Pain 4 questionnaire,, EQ5D=EuroQol 5D, n=number of cases

The evolution of the NPRS score is detailed in **Table 15**. Patients with endometriosis seemed to have a higher level of pain at the beginning of the IVF attempt (questionnaires 1 and 2) whereas after stimulation, the NPRS score was higher in patients without endometriosis, with a significant difference after oocyte retrieval but not for the other keys points of IVF.

Table 15: Evolution of NPRS for patients treated with the new protocol			
patients included in ENDALGOFIV 2 n = 207			
	with endometriosis n = 51	without endometriosis n = 156	p value
Questionnaire 1 (mean ±SD)	4.3 ± 2.8	1.2 ± 2.2	< 0.001
Questionnaire 2 (mean ±SD) (1)	2.06 ± 0.70	1.43 ± 0.39	0.46
Questionnaire 3 (mean ±SD) (2)	2.50 ± 0.41	3.12 ± 0.20	0.21
Questionnaire 4 (mean ±SD) (3)	3.70 ± 2.94	3.80 ± 2.91	0.003
Questionnaire 5 (mean ±SD) (4)	2.59 ± 0.60	2.85 ± 0.30	0.71
Questionnaire 6 (mean ±SD) (5)	3.33 ± 0.44	3.67 ± 0.21	0.51

NA: no test due to low number of participants
NPRS = numerical pain rating scale, n=number of cases, SD=standard deviation
1) 37/51 responded to Q2 (data missing from 14 patients); (2) 139 patients filled out Q3; (3) 153 patients filled out Q4; (4) 55/78 responded to Q5; (6) 107 patients filled out Q6

The evolution of neuropathic pain is detailed in **Table 16**. Patients with endometriosis tended to have a higher level of neuropathic pain during the IVF attempt apart from after the oocyte retrieval, where the score was higher for patients without endometriosis. However, there were no significant differences between the two groups apart from the baseline.

Table 16: Evolution of DN4 for patients treated with the new protocol			
patients included in ENDALGOFIV 2 n = 207			
	with endometriosis n = 51	without endometriosis n = 156	p value
Questionnaire 1 (mean ±SD)	1.2 ± 1.5	0.6 ± 1.4	< 0.001
Questionnaire 2 (mean ±SD) (1)	0.57 ± 0.71	0.46 ± 0.42	0.89
Questionnaire 3 (mean ±SD) (2)	1.07 ± 0.42	0.75 ± 0.23	0.51
Questionnaire 4 (mean ±SD) (3)	0.91 ± 2.90	1.02 ± 4.88	0.56
Questionnaire 5 (mean ±SD) (4)	0.87 ± 0.62	0.38 ± 0.34	0.48
Questionnaire 6 (mean ±SD) (5)	1.50 ± 0.47	0.47 ± 0.23	0.05

NA: no test due to low number of participants
DN4=Neuropathic Pain 4 questionnaire, n=number of cases, SD=standard deviation
1) 37/51 responded to Q2 (data missing from 14 patients); (2) 139 patients filled out Q3; (3) 153 patients filled out Q4; (4) 55/78 responded to Q5; (6) 107 patients filled out Q6

The evolution of the pain level shown by the QDSA score is shown in **Table 17**. There were no significant differences between the two groups but the score was higher for patients without endometriosis after GnRH treatment, end of stimulation and day of stimulation (questionnaires 2, 3 and 4) but lower afterwards (questionnaires 5 and 6).

Table 17: Evolution of QDSA for patients treated with the new protocol			
patients included in ENDALGOFIV 2 n = 207			
	with endometriosis n = 51	without endometriosis n = 156	p value
Questionnaire 1 (mean)	14.1	4.7	< 0.001
Questionnaire 2 (mean) (1)	10.33	7.04	0.52
Questionnaire 3 (mean) (2)	14.72	9.93	0.18
Questionnaire 4 (mean) (3)	13.09	11.41	0.02
Questionnaire 5 (mean) (4)	13.27	7.90	0.80
Questionnaire 6 (mean) (5)	15.73	6.59	0.18

NA: no test due to low number of participants, QDSA=Saint Antoine pain questionnaire, n=number of cases, SD=standard deviation
1) 37/51 responded to Q2 (data missing from 14 patients); (2) 139 patients filled out Q3; (3) 153 patients filled out Q4; (4) 55/78 responded to Q5; (6) 107 patients filled out Q6

The evolution of the EQ5D score is shown in **Table 18**. The score was higher for patients without endometriosis after the IVF attempt which shows a lower quality of life.

Table 18: Evolution of EQ5D for patients treated with the new protocol at T1, T5 and T6			
patients included in ENDALGOFIV 2 n = 207			
	with endometriosis n = 51	without endometriosis n = 156	p value
Questionnaire 1 (mean ±SD)	0.8 ± 0.2	0.9 ± 0.2	0.57
Questionnaire 5 (mean ±SD) (1)	0.70 ± .03	0.81 ± 0.01	0.003
Questionnaire 6 (mean ±SD) (2)	0.73 ± .02	0.88 ± 0.01	< .0001

NA: no test due to low number of participants, EQ5D=EuroQol 5D, n=number of cases, SD=standard deviation
1) 55/78 responded to Q5; (2) 107 patients filled out Q6

The evolution of depression and anxiety during the IVF attempt is shown in **Table 19**. The evolution of both groups was similar.

Table 19: Evolution of HAD for patients treated with the new protocol at T1, T5 and T6			
patients included in ENDALGOFIV 2 n = 207			
	with endometriosis n = 51	without endometriosis n = 156	p value
HAD depression			
Questionnaire 1 (mean ±SD)	3.59 ± 0.30	3.28 ± 0.17	0.011
Questionnaire 5 (mean ±SD) (1)	4.00 ± 0.61	4.50 ± 0.33	0.48
Questionnaire 6 (mean ±SD) (2)	4.79 ± 0.46	3.91 ± 0.23	0.09
HAD anxiety			
Questionnaire 1 (mean ±SD)	7.72 ± 0.27	7.44 ± 0.15	0.13
Questionnaire 5 (mean ±SD) (1)	8.67 ± 0.55	7.68 ± 0.31	0.12
Questionnaire 6 (mean ±SD) (2)	7.08 ± 0.41	6.66 ± .20	0.36

NA: no test due to low number of participants, HAD: hospital anxiety and depression, n=number of cases, SD=standard deviation
1) 55/78 responded to Q5; (2) 107 patients filled out Q6

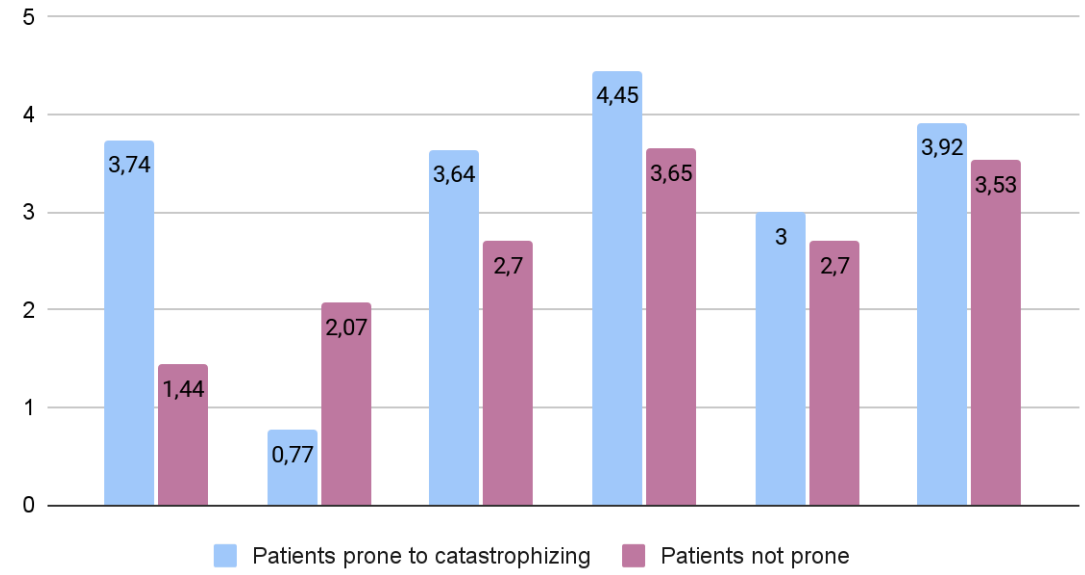
The evolution of catastrophizing is detailed in **Table 20**. Catastrophizing was significantly higher in patients with endometriosis six weeks after oocyte retrieval (questionnaire 6) on all scales (impotence, amplification and rumination).

Table 20: Evolution of PCS for patients treated with the new protocol at T1, T5 and T6			
patients included in ENDALGOFIV 2 n = 207			
	with endometriosis n = 51	without endometriosis n = 156	p value
PCS total			
Questionnaire 1 (mean ±SD)	20.12 ± 0.82	11.66 ± 0.46	NA
Questionnaire 5 (mean ±SD) (1)	12.19 ± 1.73	9.73 ± 0.91	0.22
Questionnaire 6 (mean ±SD) (2)	14.43 ± 1.27	9.68 ± 0.62	0.001
PCS impotence			
Questionnaire 1 (mean ±SD)	9.0 ± 0.37	4.72 ± 0.20	NA
Questionnaire 5 (mean ±SD) (1)	5.21 ± 0.80	3.55 ± 0.41	0.07
Questionnaire 6 (mean ±SD) (2)	6.07 ± 0.58	3.77 ± 0.28	0.0007
PCS amplification			
Questionnaire 1 (mean ±SD)	3.5 ± 0.20	2.3 ± 0.11	NA
Questionnaire 5 (mean ±SD) (1)	2.82 ± 0.43	2.16 ± 0.23	0.18
Questionnaire 6 (mean ±SD) (2)	3.39 ± 0.31	1.85 ± 0.15	< .0001
PCS rumination			
Questionnaire 1 (mean ±SD)	7.1 ± 0.37	4.8± 0.21	NA
Questionnaire 5 (mean ±SD) (1)	4.57 ± 0.77	3.92 ± 0.42	0.47
Questionnaire 6 (mean ±SD) (2)	6.17 ± 0.57	4.50 ± 0.28	0.01

NA: no test due to low number of participants, PCS: pain catastrophizing scale n=number of cases, SD=standard deviation, n=number of cases
1) 55/78 responded to Q5; (2) 107 patients filled out Q6

The evolution of NPRS for patients with and without a tendency towards catastrophizing is shown in **Figure 3**. We can see that patients prone to catastrophizing have higher pain scores at every questionnaire apart from after GnRH treatment. The gap between the two groups is most evident for the first questionnaire.

Figure 3: Evolution of NPRS between patients prone or not to catastrophizing included in ENDALGOFIV 2



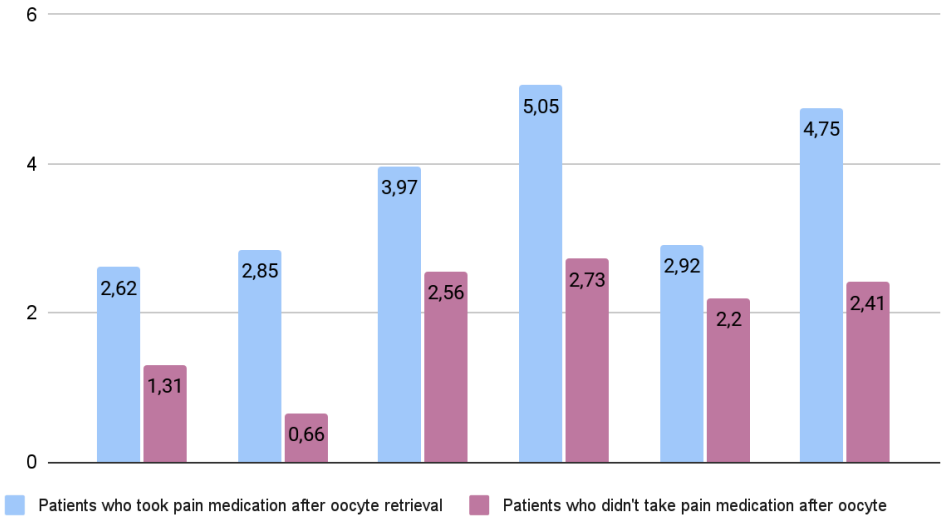
The last questionnaire included binary questions where the answers are shown in **Table 21**. A higher proportion of patients with endometriosis took the treatment prescribed during stimulation than patients without (34.6 versus 15.4 p = 0.030). However, there was no difference for treatment taken after oocyte retrieval where around half of patients took the treatment whether they had endometriosis or not. The rate of clinical pregnancies in case of fresh transfer was not significantly different but we did find a higher rate in patients with endometriosis (62.5% of patients with endometriosis vs 32.5% of patients without p = 0.13).

Table 21: Answers to binary questions in questionnaire 6			
patients included in ENDALGOFIV 2 who replied to questionnaire 6 n = 107			
	with endometriosis n = 26	without endometriosis n = 91	p value
Pain consultation (n(%))	5 (19.2)	-	-
Treatment taken during stimulation (n(%))	9 (34.6)	14 (15.4)	0.030
Treatment taken after oocyte retrieval (n(%))	12 (54.5)	44 (51.8)	0.82
Clinical pregnancy* (n (%))	5 (62.5)	13 (32.5)	0.13

n=number of cases, *fresh transfer only (8/26 patients with endometriosis who replied to the last questionnaire had a fresh transfer and 40/91 patients without endometriosis)

The evolution of NPRS for patients with endometriosis based on if they took the pain medication or not during the stimulation period is shown in **Figure 4**. Patients who took the medication prescribed had a higher pain score at each questionnaire. Patients who did not take the treatment had a relatively stable pain level during the process.

Figure 4: Evolution of NPRS for patients with endometriosis



Discussion

Our study found a higher level of pain for patients included in ENDALGOFIV 2 than ENDALGOFIV 1, as shown by the NPRS and QDSA score after oocyte retrieval. For the QDSA score, the emotional dimension of pain was significantly higher than the sensory. Patients treated with the new protocol seemed to be more affected by how the pain made them feel (tired, suffocated, worried…) rather than the physical aspect of pain. However, there were no significant differences after oocyte retrieval in terms of neuropathic pain, quality of life, depression and anxiety levels.

It is important to remember that our baseline status between the two groups differed in terms of catastrophizing, with a higher level to begin with in patients treated by the new protocol. Patients with a higher score for catastrophizing tend to fixate on the worst possible outcome from situations and any negative thoughts or feelings are exaggerated beyond the patients' control (15). It is possible that this could in part explain the higher level of affective pain.

We also noted some differences in the IVF attempts between the two groups. More oocytes were retrieved during the procedure in ENDALGOFIV 2 with a higher number of oocytes fertilized and embryos obtained. We should therefore consider that the higher levels of pain after oocyte retrieval could be linked to the higher number of oocytes recovered which would extend the duration of the procedure. This can be explained in part by the fact that a double trigger was used for around a third of patients included in ENDALGOFIV 2 whereas it was only used for one patient in ENDALGOFIV 1. The study Haas et al. 2020 (16) found a higher number of oocytes retrieved after use of a double trigger compared to hCG alone. However, the difference in pain between the two groups was not evaluated. No study seems to have studied the different pain levels in patients depending on the trigger used during IVF. The difference in number of oocytes retrieved can also be explained by the fact that the stimulation tended to be weaker during the COVID-19 pandemic (ENDALGOFIV 1) to lower

the risk of ovarian hyperstimulation syndrome and thus reduce the number of hospitalizations during this period. This change in stimulation protocol could be to a certain extent responsible for the difference in pain levels between the two groups. We also found that more embryos tended to be frozen than transferred for ENDALGOFIV 2 compared to ENDALGOFIV 1. This shows a recent change of strategy inside the ART department with a higher number of freeze all (17).

Our study also compared the different pain components during the IVF attempt with the new protocol between patients with and without endometriosis. Unlike the initial study (Cathelain et al., 2023) (8), the average pain level was higher in patients without endometriosis after oocyte retrieval shown by the NPRS and QDSA score. There was also no significant difference in terms of neuropathic pain between the two groups, which is known to be more present in patients with endometriosis. Even if no difference was found, this study demonstrated that the level of neuropathic pain tended to be higher for patients with endometriosis throughout the procedure apart from after the oocyte retrieval. This suggests that the new protocol had a greater impact on pain management for neuropathic pain during oocyte retrieval for patients with endometriosis than those without. When studying the quality of life of patients with the EQ5D score, we found a rise in the score for patients without endometriosis during the IVF attempt but a decrease in the score for patients with endometriosis. Patients with endometriosis even seemed to have an improvement in quality of life during the process. It is possible that by undergoing IVF with a new focus on pain management, patients with endometriosis benefited from new or different treatments compared to before the procedure. It is interesting to note that even though the pain levels were higher during the attempt compared to the patients' baseline, this did not impact their quality of life, since it in fact improved. Other studies have found that for patients with endometriosis, their pain levels did not increase during ART (18–21).

Even though no significant difference was identified, we found that depression and anxiety levels were higher for patients with endometriosis, which was also one of the results of the study by Ceran in 2020 (Ceran et al., 2020) (22). Finally, we studied the level of catastrophizing between the two groups of patients. Catastrophizing was more present, and actually increased in patients with endometriosis, compared to a decrease in patients without endometriosis. This concurs with the study performed in 2022 by Evans et al., which found a higher pain catastrophizing in patients with endometriosis (23).

The final questionnaire, sent six weeks after the oocyte retrieval, included binary questions to find out if the patients had taken the treatments prescribed. We found that patients with endometriosis were more likely to take the treatment during the stimulation period, although the rate remained low among the patients who answered the final questionnaire (34.6% for patients with endometriosis, 15.4% for patients without endometriosis). More patients took the treatment after the oocyte retrieval but the average rate was around 50% in both groups. The low number of patients without endometriosis who took the treatment shows a certain reluctance in patients to take medication which is prescribed even with relatively high pain scores. Another explanation could be that patients with endometriosis are probably more used to taking different pain medicine therefore they are more willing to do so from the beginning of the IVF attempt, but further research is needed on this subject.

One of the main limitations of our study is the low response level to the last questionnaires and a smaller study population for ENDALGOFIV 2 at certain moments of the attempt compared to ENDALGOFIV 1. The loss to follow up can in part be explained by the online nature of the questionnaires. Patients seemed more willing to fill out the questionnaires by hand and give them back to their doctor during the different consultations than to filling them out online despite receiving reminders. Adopting an alternate method to complete the questionnaires between the two studies could also impact the difference in patients' answers.

For example, in ENDALGOFIV 1 patients filled out the fourth questionnaire before leaving the hospital after their oocyte retrieval whereas for ENDALGOFIV 2 they could fill it out anytime including once they were back home and the different pain medications they were given had worn off, which could lead to higher pain scores. Some patients also stated that they felt that filling out six questionnaires as well as following the IVF protocol seemed like too many obligations at once and they preferred to focus only on the IVF itself. This reaction once again echoes back to the higher level of catastrophizing found in the second group. Moreover, it is important to remember that the initial study happened during the COVID-19 pandemic which could impact patients' replies to the different questionnaires. With a higher risk of cancellation, it is possible to imagine some patient's relief in being able to undergo IVF treatment, which could lower their pain scores.

Another limitation of our study is the possibility of undiagnosed endometriosis especially for patients with idiopathic infertility which represents 20.5% of patients included in ENDALGOFIV 2. Patients' medical history would need to be further examined to see whether they had an imaging or surgery which ruled out endometriosis.

This study highlights the complexity of pain management for patients undergoing IVF, whether they have endometriosis or not, and the need for further steps to be taken. With the evolution of techniques in IVF, the way pain is managed in these patients needs to also constantly evolve. This goes hand in hand with the changes the population faces in terms of mental health (for example the higher level of pain catastrophizing in our more recent study). It can be concluded that every patient's baseline status needs to be evaluated in order to offer them a treatment best suited to them. Pain is closely linked to the patient's mental health status, which emphasizes the importance in offering a psychological consultation as well as a consultation with a pain specialist at the beginning of an IVF attempt.

This study also shows the importance of evaluating new protocols. Higher pain scores in the group ENDALGOFIV 2 were found, demonstrating that results of these evaluations can be unexpected. Our findings could be linked to the smaller population in the group treated with the new protocol. It is also possible that by sending out multiple questionnaires, the patients most motivated to answer all of them are those with higher pain scores. Another area to explore in further research is, if by opening up the discussion around pain for patients in IVF, we have made them more aware of any potential pain which they may not have focused on beforehand. This could explain the higher pain scores at the beginning (questionnaire 1) for ENDALGOFIV 2.

Conclusion

Pain management for patients in IVF is complex for both patients with and without endometriosis. The way we treat pain in these patients must evolve with the changes in population but also with changes in IVF strategies. Patients from the more recent study had an increased pain rating before beginning IVF as well as a greater tendency to catastrophizing. Higher pain levels were also found after oocyte retrieval in our ART department following the implementation of a new pain management protocol, more so for patients without endometriosis. Patients however showed a certain reluctance to take the treatment prescribed despite these pain scores, especially if they didn't have endometriosis.

These results highlight the need for further studies on how to encourage patients to take treatments during IVF and how to adapt these treatments to their specific needs in terms of medical history or mental health.

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List of appendices

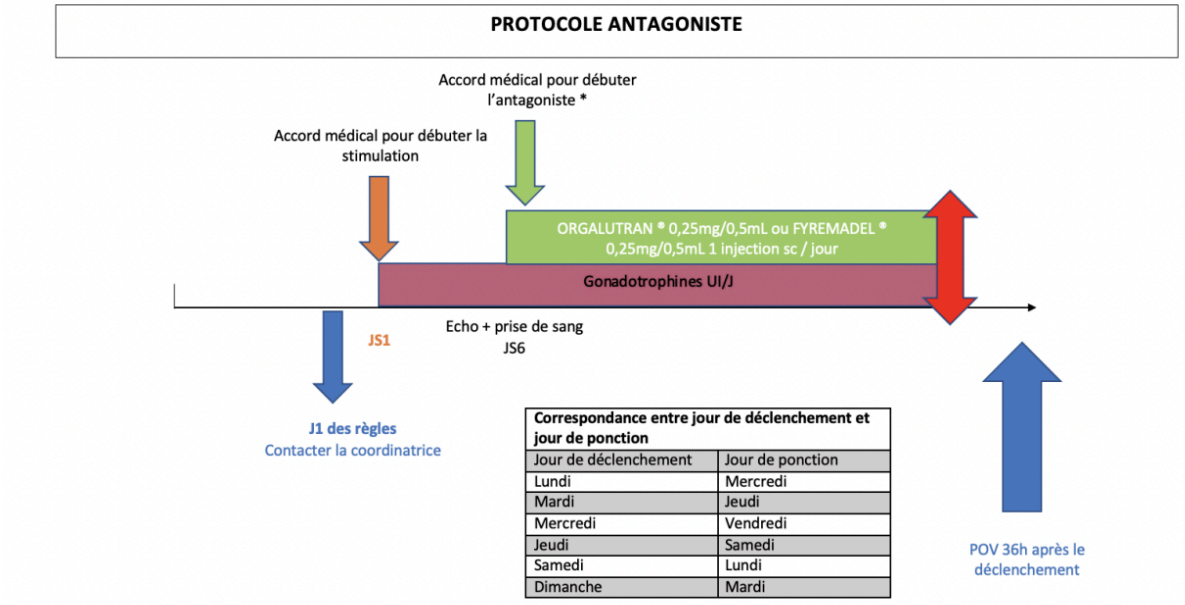
Description of the different pain assessment questionnaires :

- **NPRS (Numerical Pain Rating scale)**: an auto evaluation where the patient rates their current pain between 0 and 10. The pain is rated mild between 0 and 3, moderate between 4 and 7 and intense between 8 and 10.
- **QDSA (Questionnaire Douleur de Saint-Antoine)**: a French pain assessment questionnaire that evaluates the intensity and characteristics of chronic pain in patients. There are 16 items with the first nine items focusing on the sensory dimension of pain (e.g., sharp, burning) and the last seven focusing on the emotional dimension (e.g., distressing, exhausting). Patients are asked to rate the intensity of their pain for each selected item, typically using a scale (e.g., 0 to 4), where 0 means "no pain" and 4 means "extreme pain". The total of the ratings gives an overall score out of 64.
- **DN4**: a questionnaire evaluating the presence of neuropathic pain. It consists of two parts: an interview with the patient asking them about seven specific pain sensations (e.g., burning, electric shocks) and a clinical examination assessing pain responses to light touch, pinprick, and brushing. There are a total of 10 items and each item is scored as either "yes" or "no," with a total score of 4 or more indicating a high likelihood of neuropathic pain. When only the interview is performed like in our study, a total score of 3 or more indicates a high probability of neuropathic pain.
- **HAD (Hospital Anxiety and Depression)**: a questionnaire assessing anxiety and depression levels in patients with 7 items focusing on symptoms of anxiety (e.g., restlessness, tension, and worry) and another 7 focusing on symptoms of depression (e.g., sadness, anhedonia, and low energy). Each item is scored on a scale from 0 to 3, resulting in separate scores for anxiety and depression. Scores are then categorized to indicate normal (0 to 7), suspected (8 to 10), or proven (11 and over) levels of anxiety

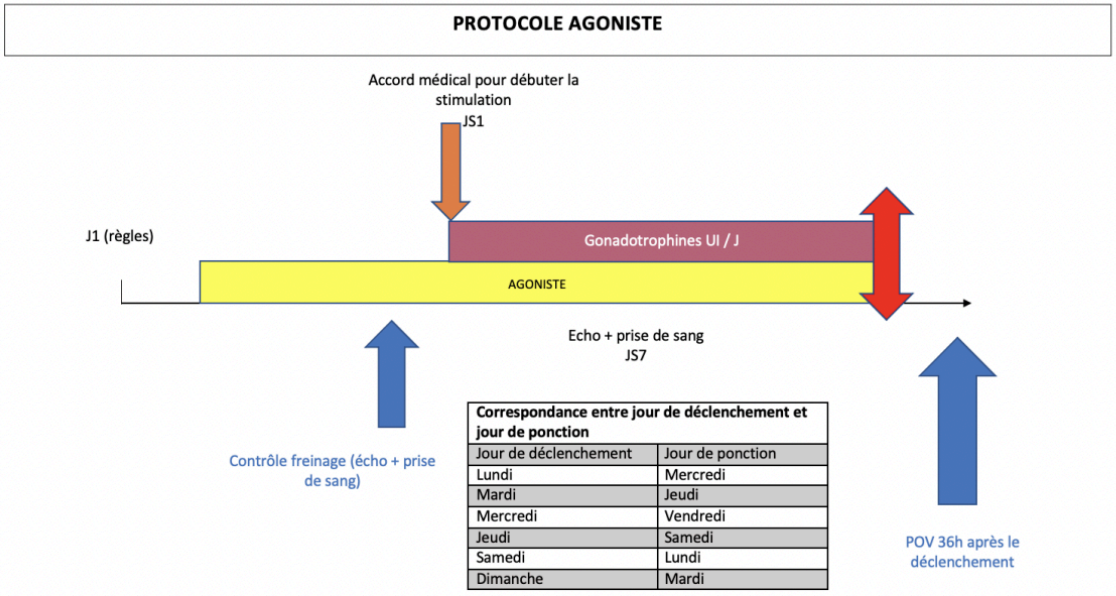
and depression.

- **PCS (Pain Catastrophizing Scale)**: an assessment questionnaire measuring the extent of catastrophic thinking related to pain. It consists of 13 items that evaluate three key dimensions (rumination, amplification and impotence) and thoughts associated with them. Rumination involves persistent thoughts about pain and an inability to distract oneself from it. Amplification reflects the tendency to exaggerate the threat or seriousness of the pain. Impotence represents feelings of being unable to manage or control the pain. Patients rate how frequently they experience these thoughts from 0 ("not at all") to 4 ("all the time"). A total score over 23 shows a high risk of catastrophizing.
- **EQ5D (EuroQol 5D)**: a questionnaire measuring health related quality of life. It included 5 items: mobility, self-care, daily activities, pain/discomfort and anxiety/depression. Each item is rated 0 (no problem) to 5 (extreme problem). The patient's answer forms a 5 - digit code which represents a health state and is converted to a single utility index score.

Stimulation protocols for IVF:



Correspondance entre jour de déclenchement et jour de ponction	
Jour de déclenchement	Jour de ponction
Lundi	Mercredi
Mardi	Jeudi
Mercredi	Vendredi
Jeudi	Samedi
Samedi	Lundi
Dimanche	Mardi

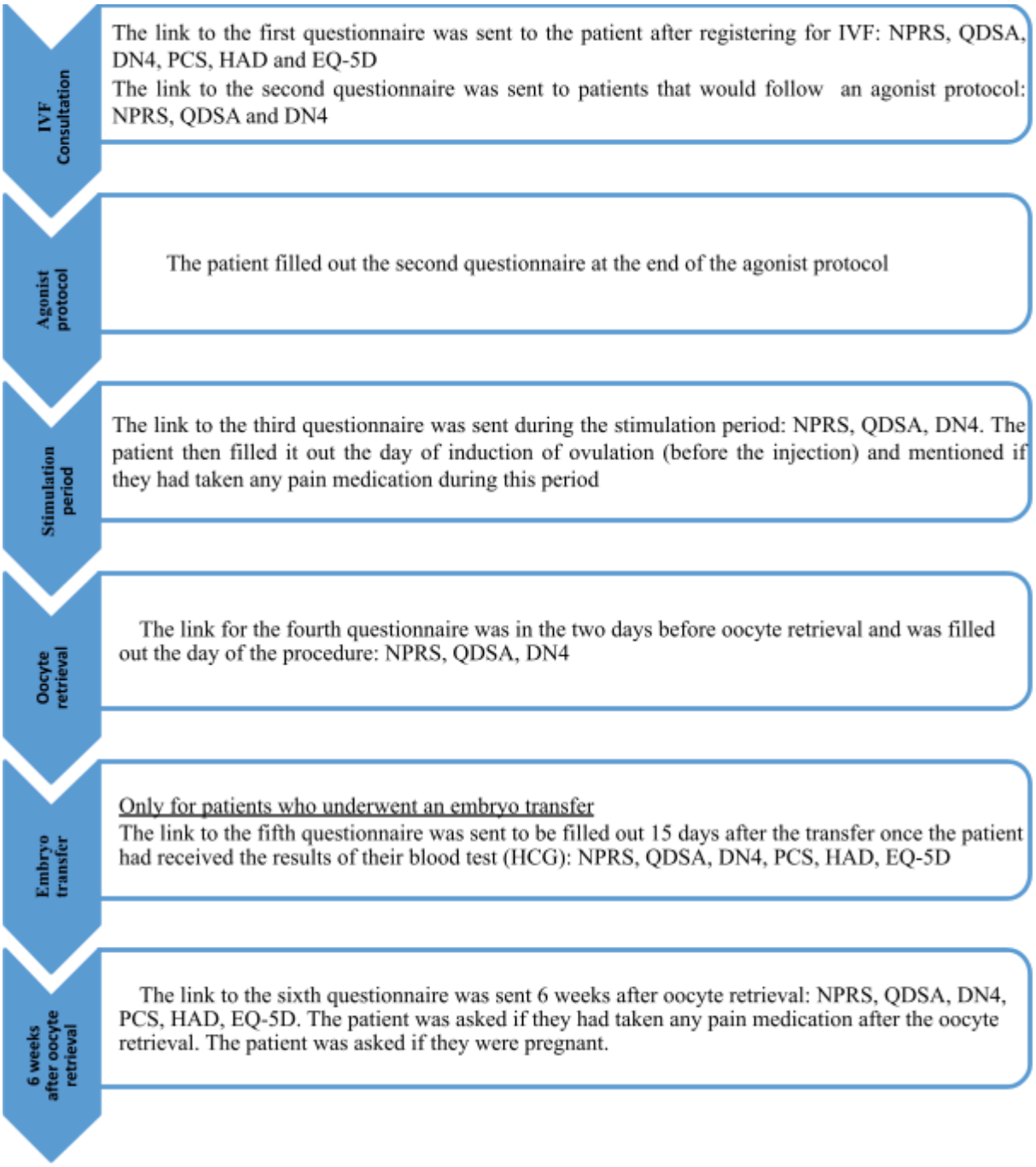


Correspondance entre jour de déclenchement et jour de ponction	
Jour de déclenchement	Jour de ponction
Lundi	Mercredi
Mardi	Jeudi
Mercredi	Vendredi
Jeudi	Samedi
Samedi	Lundi
Dimanche	Mardi

Overview of each different pain assessment questionnaire during the IVF attempt:

	Initial consultation	After agonist protocol	At the end of the stimulation period before induction of ovulation	After oocyte retrieval	15 days after embryo transfer	6 weeks after oocyte retrieval
Personal information (name, date of birth)	X	X	X	X	X	X
Endometriosis yes/no	X					
HCG result					X	
Ultrasound (only if transfer)						X
NPRS	X	X	X	X	X	X
QDSA	X	X	X	X	X	X
DN4	X	X	X	X	X	X
HAD	X				X	X
PCS	X				X	X
EQ-5D	X				X	X
Binary questions yes/no			X			X

Study design:



ENDALGOFIV 2 protocol during oocyte retrieval:

CHU LILLE *Pôle Anesthésie-Réanimation* *Hôpital Jeanne de FLANDRES*	**Protocole ENDALGOFIV 2** **PRISE EN CHARGE ANESTHÉSIQUE**	Code du document : [P_TYPE] / [P_UNIT] / [P_REF] Date d'application : [P_APPLICATION_DATE] Version : [P_REVISION] Page 1 sur 3

Rédaction	Validation
Nom / Prénom : MAHIET Félicien **Fonction :** PHARc	**Nom / Prénom : RICHART Pierre** **Fonction :** PHAR

Périmètre d'application :

A l'arrivée dans le service de PMA, vérification par la sage-femme des éléments de la Check-list HAS.
Pose d'une VVP et perfusion de KETOPROFENE 100mg IVL sur 15 minutes, en l'absence de contre-indication.

Rappel des contres indications aux AINS :

- Antécédent d'allergie ou d'asthme provoqué par la prise de médicaments de la même famille ou de la famille de l'aspirine
- Antécédent de saignement ou de perforation digestifs lié à la prise d'AINS
- Ulcère de l'estomac ou du duodénum
- Maladie grave du foie
- Insuffisance cardiaque ou insuffisance rénale grave
- Grossesse en cours

Dès l'arrivée de la patiente en salle d'intervention

Vérification de la Check-List HAS

1. Scope ECG, Saturation, PNI
2. Installation de la patiente en position gynécologique
   Repérage échographique
   Badigeon
   Réassurance, anxiolyse verbale
   Oxygénation par O2 lunettes 3L/min
3. SUFENTANIL IVD 0,1 à 0,3µg/kg
4. Au moins 3 minutes après l'injection du SUFENTANIL et après information de la patiente, PROPOFOL en titration en quantité suffisante pour obtenir le confort de la patiente.

5. Débuter rapidement les antalgiques post opératoires
   PARACETAMOL IVL
   < 50kg : 500mg
   > 50kg : 1000mg
   SPASFON 80mg (2 ampoules) IVL

6. Rédaction de l'ordonnance post opératoire par l'équipe de PMA pour les 48 heures post opératoires
   - PARACETAMOL Per Os
     60mg/kg/J en 3 ou 4 prises, 6 heures minimum entre les prises, systématique pendant 48 heures.

   - KETOPROFENE Per Os, systématique pendant 48 heures.
     100mg LP Matin et soir
     Contres indications : cf supra

   - LANSOPRAZOLE 15mg, associé à la prise des AINS seulement si antécédents d'ulcère gastroduodénal, ou traitement par antiagrégant plaquettaire ou corticoïde associé.

   - LAMALINE (PARACETAMOL 300mg/OPIUM 10mg/CAFEINE 30mg)
     Poids < 50kg : 1 comprimés fois 3 par jour, 6 heures entre les prises.
     Poids > 50kg : 2 comprimés fois 3 par jour, 6 heures entre les prises.
     En remplacement du PARACETAMOL si persistance des douleurs malgré PARACETAMOL et KETOPROFENE à posologie maximale.
     NE PAS ASSOCIER PARACETAMOL ET LAMALINE.

AUTEURE : Nom : HILL **Prénom :** Emma

Date de soutenance : 18 octobre 2024

Titre de la thèse : Évaluation de la douleur au cours du parcours de Fécondation In Vitro : l'étude ENDALGOFIV 2

Thèse - Médecine - Lille 2024

Cadre de classement : *Gynécologie - médecine de la reproduction*

DES + FST/option : *Gynécologie obstétrique*

Mots-clés : douleur, endométriose, Fécondation In Vitro, infertilité

Résumé :

Introduction: L'évaluation de la douleur en procréation médicalement assistée (PMA) est très peu étudiée. L'étude ENDALGOFIV 1 d'évaluation de la douleur au cours du parcours de FIV du CHU de Lille, menée de novembre 2018 à juillet 2020 a montré que les patientes endométriosiques ont des douleurs intenses, notamment à caractère neuropathique avant même de débuter leur parcours de FIV comparativement aux patientes indemnes d'endométriose, mais sans majoration des scores de douleurs au cours de celui-ci. Suite à cette étude, un nouveau protocole de prise en charge de la douleur a été mis en place pour toutes les patientes suivies en vue d'une FIV.

L'objectif de l'étude ENDALGOFIV 2 était d'évaluer et comparer les niveaux de douleur à travers des questionnaires d'évaluation de la douleur à des périodes clés de leur parcours FIV entre les patientes traitées par le nouveau protocole et les patientes d'ENDALGOFIV 1.

Méthode: Il s'agit d'une étude prospective, comparative, contrôlée avec un groupe contrôle historique menée entre janvier 2023 et mars 2024. Des questionnaires d'évaluation de la douleur à l'aide d'échelles validées ont été envoyés aux patientes aux moments clés du parcours de FIV : avant de débuter les traitements, en fin de freinage, en fin de stimulation, le jour de la ponction ovocytaire, 15 jours après le transfert d'embryon et 6 semaines après la ponction.

Résultats: 278 patientes ont été incluses en ENDALGOFIV 1 dont 73 avec de l'endométriose et 207 patientes en ENDALGOFIV 2 dont 51 avec de l'endométriose. Les scores de douleur étaient similaires entre les deux groupes avant de débuter leur parcours FIV à part un taux de catastrophisme plus élevé dans ENDALGOFIV 2. Dans les deux groupes, les patientes avec de l'endométriose avaient des douleurs plus importantes dont une douleur neuropathique et des niveaux de dépression plus importants par rapport aux patientes sans endométriose. Après ponction ovocytaire, les patientes ayant bénéficié du nouveau protocole ont signalé une douleur plus importante quand elles n'avaient pas d'endométriose (EN 3.80 versus 3.11 p = 0.0145) sans différence significative pour les patientes avec de l'endométriose. Pendant la période de stimulation, les patientes avec de l'endométriose avaient plus tendance à prendre le traitement prescrit (34.6 versus 15.4 p=0.030). Environ la moitié des patientes incluses en ENDALGOFIV 2 ont pris le traitement après la ponction ovocytaire.

Conclusion: La prise en charge de la douleur des patientes en parcours de FIV reste complexe que les patientes aient de l'endométriose ou pas. Les taux de douleur plus élevés des patientes incluses en ENDALGOFIV 2 après ponction ovocytaire soulèvent la nécessité d'études supplémentaires pour adapter les traitements aux besoins des patientes.

<u>Composition du Jury</u> :

Président : Madame le Professeur Sophie CATTEAU - JONARD

Assesseurs :

- **Madame le Docteur Alice CATHELAIN DELAOUSTRE**
- **Monsieur le Docteur Félicien MAHIET**
- **Madame le Docteur Pauline PLOUVIER**

Directeur de thèse : Madame le Professeur Chrystèle RUBOD DIT GUILLET

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