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Variations of the relative parasympathetic tone assessed by ANI during Oocyte Retrieval under Local Anaesthesia with Virtual Reality : A Randomized, Controlled, Monocentric, Open Study

Florent Malard ^a, Ludovic Moy ^b, Vincent Denoual ^c, Helene Beloeil ^d, Emilie Leblong ^e

Authors' affiliations

a CHU Rennes, Anesthesia and Intensive Care Department, F-35000 Rennes, France.

b Clinique Mutualiste La Sagesse Rennes, Medically Assisted Procreation Department, F-35000, Rennes, France.

c Clinique Mutualiste La Sagesse Rennes, Anesthesia and Intensive care Department, F-35000, Rennes, France.

d Univ Rennes, CHU Rennes, Inserm, CIC-1414, COSS 1242, Anesthesia and Intensive Care Department, F-35000 Rennes, France.

e MD MSc, Rehabilitation Center, Pole Saint Helier, Department of Clinical Research, Rennes, France

Corresponding author: Helene Beloeil, Pole Anesthésie-Réanimation Medecine Interne Geriatrie, CHU Rennes, 2 avenue Henri Le Guillou, 35033 Rennes Cedex, France.

Telephone : +033(0)299282422

Email: helene.beloeil@chu-rennes.fr

Abstract

Background: Transvaginal oocyte retrieval is an outpatient procedure performed under local anaesthesia. Hypno-analgesia could be effective in managing comfort during this procedure. This study aimed to assess the effectiveness of a virtual reality headset as an adjunct to local anaesthesia in managing nociception during oocyte retrieval.

Methods: This was a prospective, randomized single-centre study including patients undergoing oocyte retrieval under local anaesthesia. Patients were randomly assigned to the intervention group (virtual reality headset + local anaesthesia) or the control group (local anaesthesia). The primary outcome was the efficacy on the ANI®, which reflects the relative parasympathetic tone. Secondary outcomes included pain, anxiety, conversion to general anaesthesia rate, procedural duration, patient's and gynaecologist's satisfaction and virtual reality headset tolerance.

Results: ANI was significantly lower in the virtual reality group during the whole procedure (*mean ANI* : 79.95 CI [77; 81] vs 74.95 CI [72; 76]; $p < 0.001$; *effect size Cohen's d* -0.53 [-0.83, -0.23]), and during the two most painful moments : infiltration (mean ANI : 81 +/-11 vs 74 +/- 13; $p < 0.001$; *effect size Cohen's d* -0.54[-0.85, -0.24]) and oocytes retrieval (*mean ANI* : 78 +/- 11 vs 74.40 +/- 11 ; $p = 0.020$; *effect size Cohen's d* -0.37 [-0.67, -0.07]). There was no significant difference in pain measured by VAS. No serious adverse events related were reported.

Conclusion: The integration of virtual reality as an hypnotic tool during oocyte retrieval under local anaesthesia in assisted reproductive techniques could improve patient's comfort and experience.

Keywords: perioperative pain ; virtual reality ; hypnotic tool

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1. Introduction

The prevalence of transvaginal oocyte retrieval procedures has increased steadily in recent years due to advances in medical assisted reproduction (MAR). This outpatient procedure can be carried out under local or general anaesthesia. Indeed, the procedure is painful due to the puncturing of the vaginal skin, the ovarian capsule and the manipulation of the ovaries. The main factors influencing the choice in the type of anaesthesia are medical, including the accessibility of the ovaries, the number of follicles and a history of endometriosis. However, studies have shown that anaesthetic drugs can penetrate the follicular fluid and adversely affect oocyte fertilization and embryo growth [1–3]. In addition, general anaesthesia requires a longer postoperative recovery. In this context, local anaesthesia seems to be the best choice for oocyte retrieval. However, this technical procedure can still be uncomfortable and can be a source of anxiety [4].

The effects of hypno-analgesia on perioperative anxiety and pain are well documented. Numerous studies have evaluated the cerebral changes (functional MRI) and clinical benefits of hypnotic trance as an anaesthetic method [5–7]. In addition, some teams have suggested that the use of hypnosis in medically assisted reproduction, particularly during embryo transfer, could improve implantation rates and patient acceptance of the treatment process [8]. Hypnosis is therefore an interesting alternative during oocyte retrieval to reduce perioperative pain and anxiety while minimizing the risks of medication and anaesthesia. Three basic conditions are necessary to achieve a hypnotic trance: patient motivation, cooperation, and trust in the therapist. The introduction and use of hypnosis in the operating room is limited by several factors, including the availability of health professionals trained in hypnosis, the time and effort required by health professionals practicing hypnosis, and the cognitive availability of patients who may vary in their susceptibility to hypnosis [9,10]. The development of new technologies such as virtual reality (VR) may facilitate hypnotic induction through three-dimensional visual immersion. Studies have already demonstrated the potential of VR for stress management. Immersion in VR has been shown to alleviate anxiety, focus attention and concentrate on the scenario [11–13].

HypnoVR® combines three-dimensional visual immersion through VR with conversational hypnosis using a headset. This combination allows for the cumulative benefits of both techniques to be exploited. Conversational hypnosis guides and accompanies the patient in synchrony with the visual immersion. The rapid development of VR is associated with its use in many different situations in anaesthesia [14–19].

Therefore, before implementing the systematic use of VR during oocyte retrieval in our institution, we designed a study hypothesizing that the use of a virtual reality headset (VRH) would reduce perioperative nociception.

2 . Methods

2.1 Study design

This prospective, randomized single-centre study with a two-arm parallel-group design was conducted at the Mutualist Clinic La Sagesse in Rennes, France. Patients scheduled for oocyte retrieval under local anaesthesia were enrolled starting October 2022. After inclusion and written informed consent, patients were randomized in two groups: control or VR group. Patients were followed up until discharge from the outpatient department. Investigators, participants, and care providers were not blinded to the treatment allocation.

2.2 Patients

Adult patients over 18 years of age scheduled to undergo oocyte retrieval under local anaesthesia as part of an assisted reproductive technology procedure were included. Non-inclusion criteria were: oocyte retrieval performed as part of oocyte donation; uncontrolled epilepsy; auditory and/or visual impairment contraindicating the use of VRH; poor understanding of the French language; medical indication to perform oocyte retrieval under general anaesthesia; drug allergy or hypersensitivity to paracetamol, ibuprofen, or nefopam prescribed during premedication; patient under legal protection; and refusal to use the virtual reality headset.

2.3 VRH material

VR was performed using a virtual reality headset (PICO; CE mark) and an audio headset (Bose Quiet Comfort 35; CE mark) connected to a digital tablet (*Figure 1*). The software used was HypnoVR V1.9.X, developed by HypnoVR (HypnoVR®, Strasbourg, France). It provides a classical medical hypnosis session (induction, suggestion and return), and integrates sequences of controlled breathing, cardiac coherence and hypnotic suggestions.

2.4 Study protocol

Participants were screened, approached and recruited by study staff who assessed patient eligibility, obtained informed consent, and enrolled the participants. Patients were randomized in a 1:1 ratio to either in the control group or in the VR group. Randomization was centralized and computer-generated, and each patient received a unique randomization number by opening an envelope on arrival in the operating room. In line with our usual management of oocyte retrieval, all enrolled patients received an oral analgesic premedication (paracetamol 1g, ibuprofen 400mg and nefopam 20mg) and were required to complete the Beck anxiety scale prior to surgery. All patients then received a local anaesthesia with infiltration of 40 to 80 ml of 0.5% non-adrenalized-lidocaine into the vaginal wall at the vaginal fundus under ultrasound guidance, respecting the toxic dose of 5 mg/kg. If patients were randomized to the VR group, they also received a session of VR. In the control group, patients only received the usual procedure. In both groups, the patients were accompanied by the same study nurse to ensure their comfort. At the beginning of the VR session patients could choose their visual universe (undergrowth, diving, tropical beach, astral travel, snowy landscape) and the voice (male or female) (*Figure 2*). The session could be interrupted at any time for medical reasons or at the patient's request.

2.5 Study outcomes

The primary outcome was the difference in nociception measured with ANI during oocyte retrieval in the VR group compared to local anaesthesia alone. The ANI reflects the patient's relative parasympathetic tone, with 100 indicating the absence of stress. The ANI calculation is based on the

influence of the respiratory cycle on the RR interval of the electrocardiogram [20]. The ANI data (ANI monitor V2, Metrodoloris Medical systems SAS®) were collected directly from the monitor by automatic recording to a USB drive.

Secondary outcomes included the assessment of the efficacy of VR on perioperative anxiety using the Beck Anxiety Inventory scale on admission to the hospital and on return to the ward one hour after oocyte retrieval [21]; assessment of clinical tolerability of VR using the SSQ self-report questionnaire (negligible: < 5, minimal: 5 – 10, significant: 10 – 15, and concerning: 15 – 20) [22]; the assessment of the patient's perceived pain during the procedure assessed by the Visual Analogue scale (VAS) given to the patient on return to the outpatient department; the need for postoperative analgesic treatment (molecule and dosage); the rate of unplanned conversion from local anaesthesia to general anaesthesia at the discretion of the anaesthetist or the surgeon; assessment of the impact of VR on the total duration of the surgical procedure by recording the total time (in minutes) between entering and leaving the operating room; gynaecologist and patient satisfaction using a numerical scale from 1 to 10 (0 being 'not satisfied').

2.6 Sample

For the sampling calculation, we collected data on the changes and variability of the ANI from Abdullayev's study [23]. The standard error of measurement (SEM) ranged from 1.13 to 2.99, and the minimum detectable change (MDC) ranged from 3.2 to 8.13. We chose an MDC of 5 points with a standard deviation of 13.2 for the sampling calculation. With an alpha risk of 5%, a power of 80%, and an estimated low loss to follow-up of 5%, the total number of subjects to be included was 182.

2.7 Statistical analysis

Randomization was performed using a balanced randomization list with Rstudio [24]. Descriptive statistics such as mean, median, standard deviation, quartiles, and interquartile range for continuous variables and absolute and relative frequencies for categorical variables were calculated. Outliers were tested using "outliers" [25]. Data were assessed for normality using the Shapiro–Wilk test. Comparisons

between groups were assessed using mean \pm standard deviation of t-tests (when applicable) or Wilcoxon sum rank test for continuous variables, whereas comparisons for categorical variables were made using chi-squared tests. Correlation analysis was used to examine the correlation coefficients between ANI data and other continuous variables. For all tests, a p-value < 0.05 was considered statistically significant. Data were analysed using RStudio [24]. Graphs were generated using “ggpubr” [26].

3. Results

3.1 Patient:

Between October 2022 and May 2023, 182 patients were randomized. Data from 168 patients could be analysed (Figure 3). Demographics were similar between the two groups (Table 1). In the VR group 89% of the patients completed the virtual reality session to the end of the procedure. Reasons for not completing the full session were the need to convert to general anaesthesia, anxiety or severe pain. The mean duration of the procedure was 16 \pm 5 minutes. 18.4% of the patients had incomplete premedication and 2.2% of them had a non-compliant premedication.

3.2 Primary outcome:

Nociception assessed by ANI was significantly lower in the VR group during the whole procedure (mean ANI : 79.95 CI [77; 81] vs 74.95 CI [72; 76]; $p < 0.001$; effect size Cohen's d -0.53 [-0.83, -0.23]), and during the two most painful moments : infiltration (mean ANI : 81 \pm 11 vs 74 \pm 13; $p < 0.001$; effect size Cohen's d -0.54 [-0.85, -0.24]) and oocytes retrieval (mean ANI : 78 \pm 11 vs 74.40 \pm 11;; $p = 0.020$; effect size Cohen's d -0.37 [-0.67, -0.07])(Figure 4).

3.3 Secondary outcomes:

Pain experienced during the procedure, as measured by VAS on return to the outpatient department, was similar in both groups ($p = 0.164$). There was no significant reduction in postoperative anxiety compared to preoperative anxiety on the Beck Anxiety Scale in either group ($p = 0.732$). The conversion rate to general anaesthesia was not different in the VR group ($n = 2$) than in the control group ($n = 5$) ($p = 0.3046$). One case in the control group required additional sedation. There was no statistically significant

difference between the groups in terms of the duration (*16 +/- 5 min in the control group vs 16 +/- 5 min in the VR group, $p=0.410$*), patient satisfaction (*$p=0.072$*) and gynaecologist satisfaction (*$p=0.29$*) (Table 2).

Correlation analysis to identify potential pain determinants (age, body mass index, number of previous oocytes retrieval, Apfel score, anxiety on the Beck Scale) showed that only the level of preoperative anxiety measured on the Beck Scale had a significant effect on pain at the time of infiltration (*$p=0.023$*). A post-hoc analysis was performed but no significant difference was found in favour of the VR group in terms of number of oocytes retrieved (*$p=0.334$*), number of viable embryos (*$p=0.06$ ~~0.058~~*) and number of clinical pregnancies (*$p=0.73$*).

3.4 Security outcomes:

Tolerance to virtual reality was assessed using the SSQ scale. The mean tolerance was 4.41 (+/-4.6) with no significant difference between the two groups (*$p=0.67$*). An SSQ score of less than 5 is considered to be negligible cybersickness. Two serious adverse events were reported as a result of the surgical procedure: haemoperitoneum and severe abdominal pain requiring re-hospitalization. No serious adverse events related to the VR session were reported. Other reported adverse events included vaginal bleeding (n=7), nausea (n=2), vomiting due to nefopam (n=1).

4. Discussion

In this randomized controlled trial, VR as an adjunct to local anaesthesia for oocytes retrieval, reduced the procedure-related parasympathetic tone ~~reception~~ as measured by ANI during MAR. In addition, this non-pharmacological tool appeared to be a safe with no risk of major adverse effects.

No previous study has demonstrated the benefit of VR on perioperative pain during oocyte retrieval. However, studies have reported the benefit of VR on pain or anxiety in different situations using various measurement tools. In randomised trials, authors have reported a reduction in pain in patients undergoing colonoscopy without anaesthesia using a VAS pain scale [27] and in awake patients undergoing hand surgery with local anaesthesia and no tourniquet using a 10-point Likert scale [28]. *Faruki et al.* indirectly demonstrated a reduction in pain by assessing the reduction in intraoperative propofol doses administered during hand surgery under regional anaesthesia [29]. In an observational study, *Lachkar et al.* showed a reduction in anxiety levels during bronchoscopy using a numerical scale ranging from 0 to 10 [18]. *Ganry et al.* reported a reduction in perioperative anxiety in maxillofacial surgery using VAS [30].

It is interesting to note that the significant reduction in ANI was not reflected in patient self-reported pain rating using VAS in the VR group. Indeed, patient self-reported pain is subjective and strongly influenced by the context. In this study, the reassuring presence of our nurse may have reduced the pain reported by patients in the control group. Patients were also asked to rate the pain they experienced during the procedure after it was over. With the distance from the oocyte retrieval and the relief that it was over, this could have led to recall errors. In the present study, we chose to use the ANI because it is a simple, non-invasive way of assessing parasympathetic tone, which is suggested to reflect nociception. It provides a qualitative and quantitative measure of heart rate variability, modulated by the autonomic nervous system. *Boselli et al.* have shown that ANI measurement in the awake patient in the immediate postoperative period is significantly correlated with pain intensity [31]. It can be hypothesized that the significant result on the ANI and not the patient-reported VAS suggests that the effect we observed on physiological variables was not clinically significant in terms of pain experienced by the patient. Even

within the control group, the median pain scores on the VAS were remarkably low, making it difficult to demonstrate a reduction in pain on the VAS during this study. Moreover, as ANI represents the relative parasympathetic tone, which is related to patient comfort, in particular during hypnosis, an evaluation of global patient comfort on a 0-10 NRS would have maybe shown a difference. The benefit of the VR headset might be more on comfort than on pain *per se*.

As previously described by *Frederiksen et al.*, we reported increased pain in patients with high anxiety scores [32]. This relationship between anxiety and pain has also been observed in patients undergoing a hysterectomy, where high levels of preoperative anxiety were associated with increased postoperative pain [33]. VRH has previously been shown to reduce anxiety [18,30]. However, it was not the case in our study. It should be noted that in our study the average level of preoperative anxiety was low in both groups according to the Beck Inventory.

Side effects were rare and benign, as previously reported [34]. We decided to propose the SSQ questionnaire to both study groups to compare whether the VRH group reported more symptoms related to cybersickness. No significant difference was observed. In this study, the SSQ score in both groups was less than 5, which corresponds to negligible symptoms, the results of this questionnaire being negligible: < 5, minimal: 5 - 10, significant: 10 - 15, and concerning: 15 - 20. The use of the VR seems to be well tolerated in routine practice.

Our study has several limitations. First it is a monocentric study with six surgeons, who are trained and accustomed to performing oocyte punctures under local anaesthesia alone. Second, because of the nature of the technique, neither the patients nor the surgeons were blinded to the treatment. Nurses and surgeons routinely use the relaxation technique and this may minimize the positive results of the study. Thirdly, there were minor deviations from the protocol related to incomplete or non-compliant premedication due to missed prescriptions or treatment not taken by the patient. These deviations were detected in the middle of the study and subsequently corrected by excluding patients with incorrect premedication. It is clear that this may affect the primary endpoint.

Furthermore, at our centre, patients can watch the live ultrasound image of their oocyte puncture on a screen in front of them. For some, this provides reassurance and allows them to validate an additional step in their MAR process. With the VR headset, it is not possible to see the puncture screen, which can be a barrier for some patients who want to be actively involved in their care. The inability to explain and discuss the procedure with the patient as it progresses is also a barrier to the use of VR for some gynaecologists. Finally, it was found that anxiety levels were significantly higher in patients who refused local anaesthesia and opted for general anaesthesia. Therefore, some of the most anxious patients, who might be sensitive to the VR hypnosis tool were not included.

During the MAR process, *Levitas et al.* showed that hypnosis could increase implantation and clinical pregnancy rates, especially during embryo transfer [8]. We did not find these results in the post-hoc analysis. Indeed, it seems that the efficacy of VR could have a positive effect not during the puncture itself, but rather during the embryo transfer. Further studies are needed on this topic.

Installation of the VR headset was quick and easy, and required no special training. It was found that there was no impact on procedure times, as they were not longer in the VR group. Moreover, patient demand for the use of this tool was high. 42% of eligible patients were included, although a significant proportion were not enrolled to organizational issues.

5. Conclusion

The integration of virtual reality as an hypnotic tool during oocyte retrieval under local anaesthesia could improve patient's comfort and experience. The potential of this tool remains to be explored and could benefit patients undergoing other types of procedures under local anaesthesia, in the MAR process as well as in other medical fields. Another advantage of VR is that hypnosis is delivered by a software that is always available, unlike traditional hypnosis, which requires a trained operator. This makes VR easier to implement than traditional hypnosis. In addition, ongoing technological developments in the world

of virtual reality, particularly in terms of graphics, are likely to enable us to offer patients a more immersive experience.

Ethical Approval

The study was approved by the ethics committee (Comité de Protection des Personnes, France, n°22.00441.000079) according to French law and registered at National Agency for the Safety of Medicines and Health Products (ANSM, France). Written informed consent was obtained from all patients. The trial was registered prior to patient enrolment at clinicaltrials.gov (NCT05567315). The institution or the investigators did not have any financial link with HypnoVR.

Authors' contributions

HB had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. HB, FM, VD, LM contributed to the conception and design of the study. FM, VD, LM contributed to the acquisition, analysis and interpretation of the data. FM wrote the first draft of the manuscript. HB and VD critically revised the manuscript. EL was responsible for the statistical analysis. All authors approved the final version of the manuscript.

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Legends of the figures and tables

Figure 1: Photo of virtual reality equipment installation. Image supplied by HYPNOVR®.

Figure 2: Different visual universes available to patients supplied by HYPNOVR®. A: Tropical beach, B: Diving, C: Undergrowth, D: Snowy landscape, E: Autumn landscape, F: Astral travel.

Figure 3: Flow-chart. VR: virtual reality, ANI: analgesia nociception index.

Figure 4: Histogram kernel density curve and mean difference for main judgment criterion. A= ANI overall, Standardized Mean Difference (SMD): -0.53, 95% CI[-0.83, -0.23] ; B= ANI infiltration SMD: -0.54, 95% CI[-0.85, -0.24]; C=ANI oocyte retrieval SMD: -0.3. Blue: control group, Yellow: VR group. VR: virtual reality.

Table 1: Demographics. No statistical difference was observed. Age (years), BMI (kg/m²): body mass index, VR: virtual reality.

Table 2: Secondary outcomes. VR: Virtual Reality, VAS: Visual Analogue Scale, SSQ: Simulator Sickness Questionnaire.



Figure 1: Photo of virtual reality equipment installation. Image supplied by HYPNOVR®.

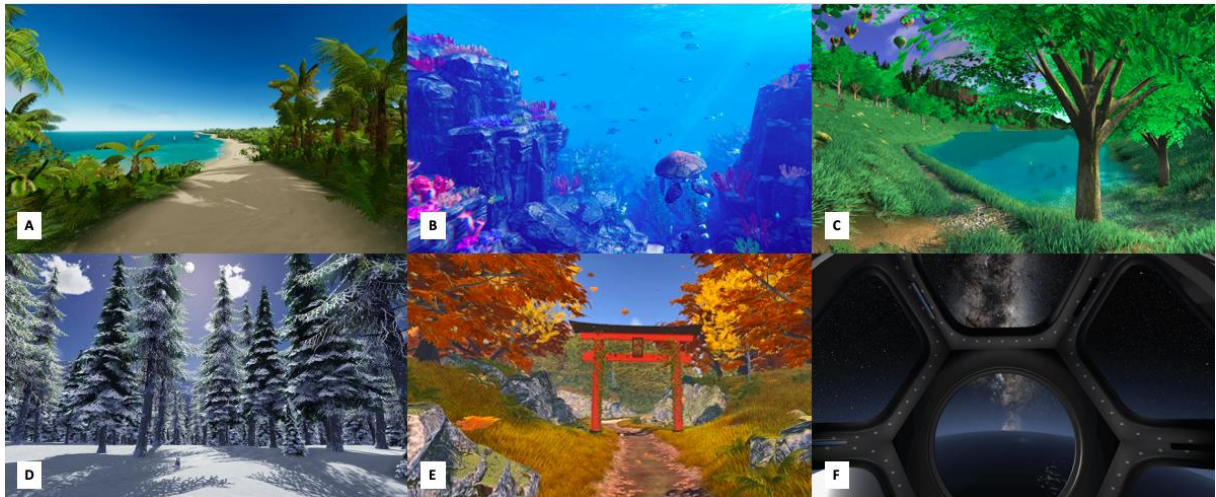


Figure 2: Different visual universes available to patients supplied by HYPNOVR®. A: Tropical beach, B: Diving, C: Undergrowth, D: Snowy landscape, E: Autumn landscape, F: Astral travel.

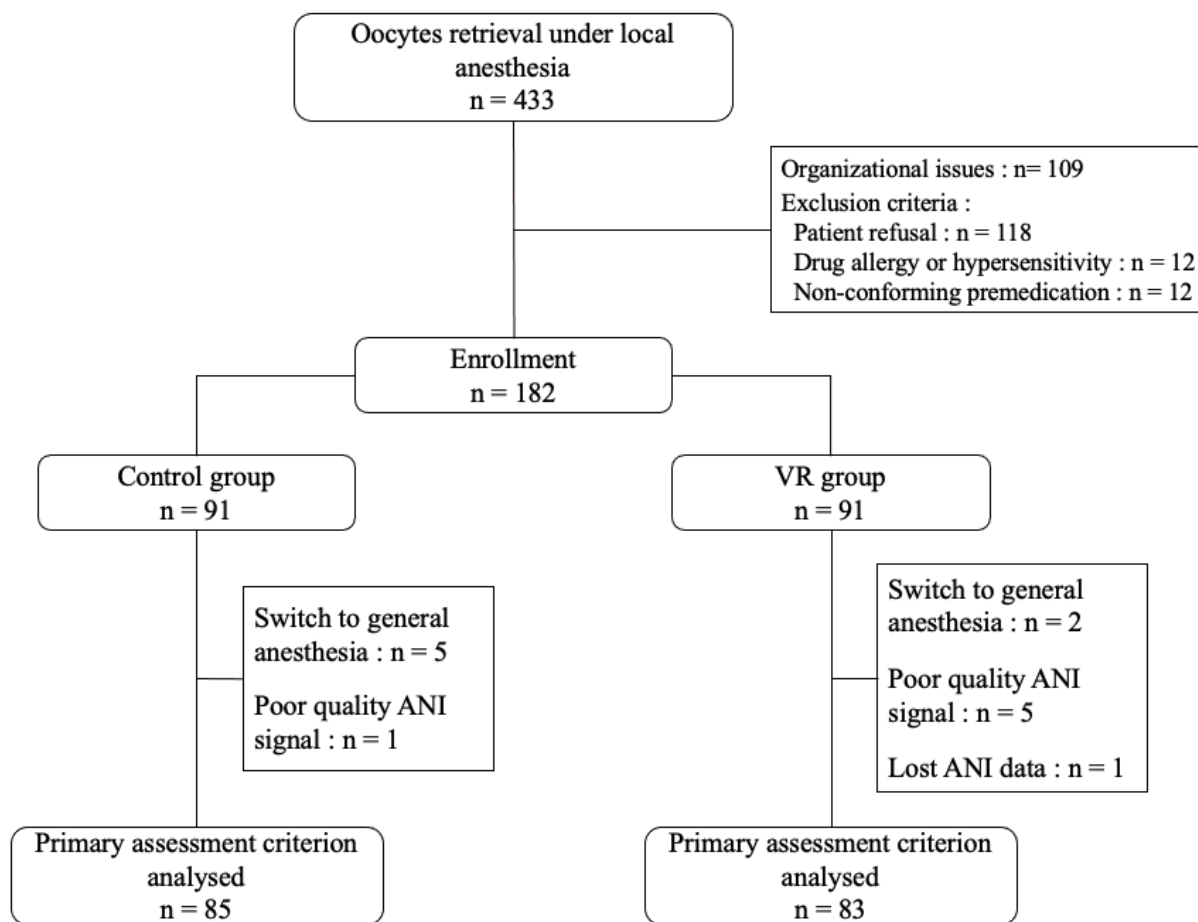


Figure 3 : Flow-chart. VR: virtual reality, ANI: analgesia nociception index.

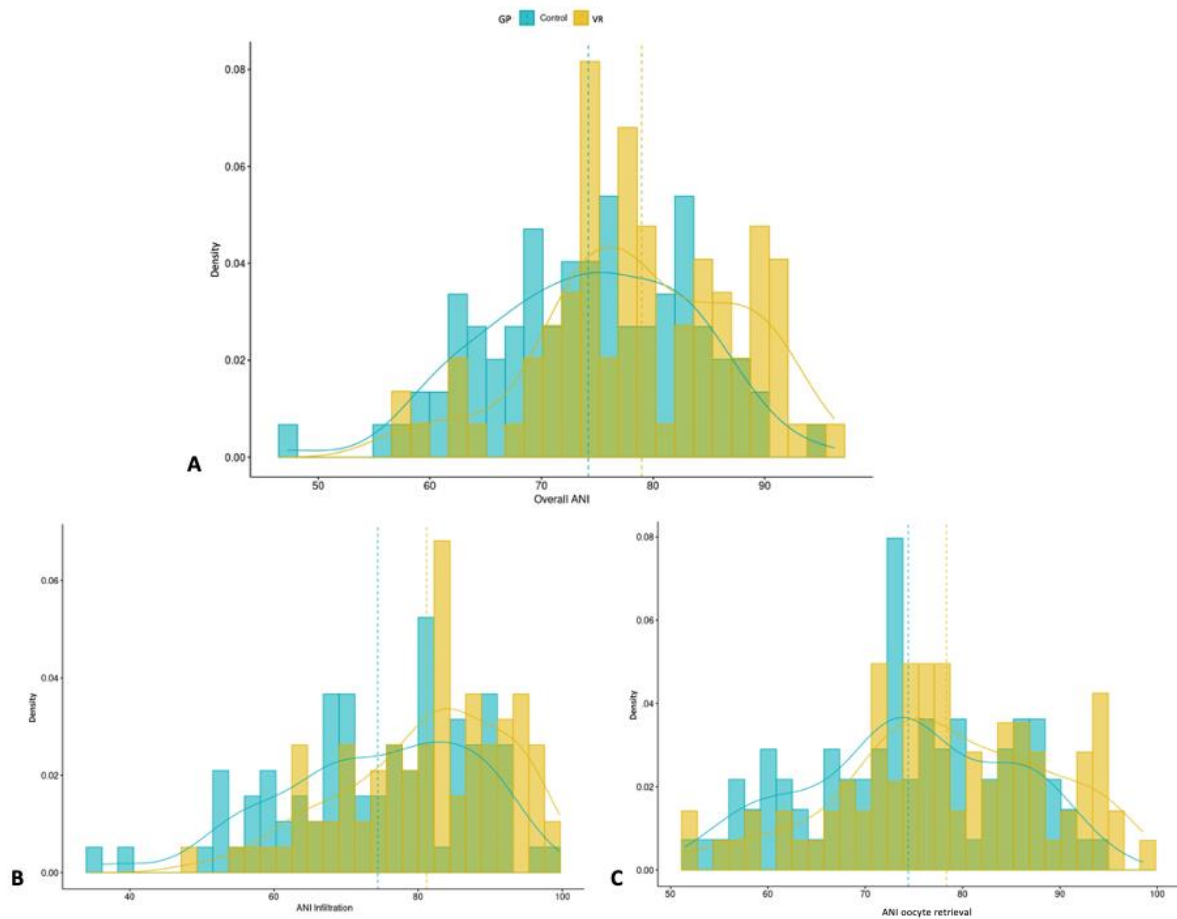


Figure 4 : Histogram kernel density curve and mean difference for main judgment criterion. The solid line represents the kernel density curve and the vertical dotted lines represent the means. A= ANI overall, Standardized Mean Difference (SMD): -0.53, 95% CI[-0.83, -0.23] ; B= ANI infiltration SMD: -0.54, 95% CI[-0.85, -0.24]; C=ANI oocyte retrieval SMD: -0.3. Blue: control group, Yellow: VR group. VR: virtual reality. ANI: analgesia/nociception index.

Variable Count	Control group 91	VR group 91	Total 182	p.value Wilcoxon rank-sum
Age				0.34
Mean (SD)	33 (4.3)	34 (4.0)	33 (4.2)	
BMI				0.12
Mean (SD)	23 (3.8)	25 (5.6)	24 (4.8)	
APFEL score				0.9
Mean (SD)	2 (0.7)	2 (0.7)	2 (0.7)	
BECK score				0.45
Mean (SD)	6 (6.6)	7 (6.5)	7 (6.5)	
Number of prior oocyte retrievals				chi square 0.29
N (%)				
0	56 (62%)	57 (63%)	113 (62%)	
1	17 (19%)	24 (26%)	41 (22%)	
2	11 (12%)	5 (6%)	16 (9%)	
3	2 (2%)	3 (3%)	5 (3%)	
≥ 4	5 (5%)	2 (2%)	7 (4%)	

Table 1: Demographics. No statistical difference was observed. Age (years), BMI (kg/m²): body mass index, VR: virtual reality.

Variable	Control group	VR group	Pvalue (Wilcox)
VAS (cm)			p = 0.16
Median (IQR)	3 (3.4)	3 (4.4)	
Min / Max	0 / 8.5	0 / 10	
Missing	1	1	
Gain on Beck's score (difference between pre and postoperative score)			p = 0.73
Mean (SD)	0.5 (6.9)	0.8 (5.3)	
Missing	2	0	
Gynaecologist satisfaction			p = 0.29
Median (IQR)	10 (2)	9 (2)	
Missing	0	1	
Patient satisfaction			p = 0.07
Median (IQR)	10 (1)	10 (2)	
Missing	1	0	
Duration of procedure (min)			p = 0.41
Mean (SD)	16 (5)	16 (5)	
Missing	1	3	
Conversion to general anaesthesia			p (χ^2) = 0.3
N (%)	5 (5.5%)	2 (2.2%)	
SSQ score			p = 0.67
Mean (SD)	5 (5.5)	4 (3.4)	
Missing	1	0	

Table 2: Secondary outcomes. VR: Virtual Reality, VAS: Visual Analogue Scale, SSQ: Simulator Sickness Questionnaire.