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ARTICLE

Oocyte retrieval of few follicles does not require analgesia: a large-scale multicentre pain analysis

BIOGRAPHY

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KEY MESSAGE

The median pain intensity is mild (3/10) if one or few follicles are aspirated without anaesthesia and analgesia. The intensity does not increase with repetitive aspirations, and the complication rate is low. Therefore, repetitive oocyte retrievals can be easily carried out without anaesthesia and analgesia to reduce time and costs.

ABSTRACT

Research question: What is the pain intensity of oocyte retrieval (OCR) without anaesthesia and analgesia in women with a low or medium number of follicles?

Design: Multicentre observational study analysing IVF cycles without anaesthesia and analgesia in seven IVF centres in Germany and Switzerland between January 2022 and March 2023. In total, 2290 cycles of natural cycle IVF or minimal stimulation IVF from 1039 patients were recorded. Pain score was assessed using a VAS graded 0 to 10. A descriptive analysis was conducted, followed by a statistical evaluation using a linear mixed model to analyse the effect on the pain score of the number of oocytes retrieved and the number of repeated IVF cycles.

Results: The number of oocytes retrieved varied from 0 to 16 (IQR 1–2). Pain score varied from 0 to 10, with a median pain score of 3.0 (IQR 2–4), defined as 'mild' pain. Compared with a reference value of aspirations with one oocyte, the pain score increased slightly by 0.5 points if no oocyte was retrieved, by 0.42 points if two to five oocytes were retrieved and by 1.14 points if six or more oocytes were retrieved, all with little clinical relevance. Pain decreased slightly with repeated aspirations (−0.05 points per cycle) ($P = 0.028$). The complication rate requiring hospitalization per aspiration was less than 0.1%.

Conclusion: Pain intensity during OCR of one or few follicles is mild. Therefore, OCR can be offered without anaesthesia and analgesia to reduce aspiration time and cost.

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KEYWORDS

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Oocyte retrieval
Pain

INTRODUCTION

The gold standard for oocyte retrieval (OCR) in human IVF is ultrasound-guided transvaginal follicle aspiration (*D'Angelo et al., 2019*; *Greenberger et al., 2020*). As the procedure can be painful, it is usually carried out under anaesthesia and analgesia (*Ng et al., 2001*). Procedural sedation, an intravenous conscious sedation analgesia, is commonly used (*Trout et al., 1998*; *Kwan et al., 2018*; *Thanikachalam and Govindan, 2023*). It is considered safe and effective, with minimal effect on oocyte quality and embryo development (*Tobias and Leder, 2011*). Other analgesic strategies are also available, but no one technique or specific medication is better than another for effectively managing pain during OCR (*Kwan et al., 2018*).

Some patients are concerned about anaesthesia, as OCR with anaesthesia requires more treatment time and is more expensive. Furthermore, some patients may even have contraindications to anaesthesia. Therefore, it is clinically relevant to know under what conditions anaesthesia and analgesia are not required.

The main factors that influence the intensity of pain are the size of the aspiration needle and the number of follicles, which is related to the duration of the procedure (*Ng et al., 2001*).

Oocyte retrieval in natural cycle IVF (NC-IVF) is usually undertaken without anaesthesia and, in many cases, without analgesia. The volume of the aspiration needles is only 19G to 20G (*Von Wolff, 2022*), and the procedure takes less than 30 s (*Schwartz et al., 2020*). In contrast, in polyfollicular fully stimulated conventional IVF treatments, the volume of the aspiration needles is often larger and the procedure takes longer owing to the high number of follicles.

Several studies have already shown that pain intensity increases with needle volume (*Aziz et al., 1993*; *Awonuga et al., 1996*; *Wikland et al., 2011*; *Nakagawa et al., 2015*; *Iduna Antigoni Buisman et al., 2021*). *Wikland et al. (2011)* also found higher complication rates in women aspirated with 17 gauge (G) versus 20G needles, but no difference in aspiration time, oocyte yield, fertilization, cleavage rate, number of good quality embryos and pregnancy rate.

These findings prompted the assessment of pain levels in women with monofollicular or oligofollicular ovarian responses undergoing NC-IVF and minimally stimulated IVF. A multicentre study was conducted involving centres with experience of aspiration without anaesthesia and analgesia, to obtain a realistic picture of pain levels in NC-IVF and minimal stimulation IVF. To allow comparisons between centres, IVF treatments were carried out in centres that were part of a network of NC-IVF and minimally stimulated IVF centres working in a similar way (*Helmer et al., 2022*; *Magaton et al., 2022*; *2023*). Centres, however, also follow their own centre-specific OCR policies regarding the type of aspiration needle, aspiration pressure and follicle flushing, which allowed real-world data to be generated on the pain intensity of OCR without anaesthesia and analgesia in women with low follicle numbers, moderate follicle numbers, or both. The aim of the present study was to evaluate the pain score of OCR without anaesthesia and analgesia in NC-IVF and minimal stimulation IVF, and to calculate the complication rates.

MATERIALS AND METHODS

Study design and setting

A multicentre observational study was conducted between January 2022 and March 2023. Four outpatient centres in Germany and three outpatient centres in Switzerland participated in the study. The participating centres were part of the 'IVF-Naturelle' network (www.IVF-Naturelle.com), a group of IVF centres specializing in natural cycle and minimal stimulation IVF (Appendix).

The lead centre was the Division of Gynaecological Endocrinology and Reproductive Medicine, University Women's Hospital, Inselspital, Bern, Switzerland, which organized the study, set up the database, conducted the statistical analysis in collaboration with the Department of clinical Research of the University of Bern, and prepared the manuscript. The 'Strengthening the reporting of observational studies in epidemiology' statement was followed to report this work (*von Elm et al., 2007*). The study was registered at ClinicalTrial.Gov, study number NCT05125497.

Study participants

All patients treated at the participating centres were offered the opportunity to participate in the study and were enrolled within the time period specified above. A total of 2290 cycles in 1039 patients were included.

Patients were eligible for the study if they fulfilled the following criteria: provided informed consent; and were undergoing IVF cycles (NC-IVF, minimal stimulation IVF, or both) with intention to fresh transfer. The exclusion criteria were as follows: frozen–thawed IVF cycle; medical or social freezing cycle; and pre-implantation genetic testing cycle.

The primary end point was the pain score without anaesthesia and analgesia. The secondary end point was the rate of complications.

Analysis of pain, the primary end point

Pain was assessed by self-report using a visual analogue scale (VAS) consisting of a coloured (green to red) 10-cm horizontal line ranging from 0 to 10, anchored by a verbal descriptor (*McCormack et al., 1988*; *Williamson and Hoggart, 2005*). The score 0 was described as no pain, 1–3 as mild pain, 4–6 as moderate to severe pain, 7–9 as very severe and 10 as worst pain possible. Immediately after each OCR and, if possible, before the patient was told the number of oocytes retrieved, she was asked to mark the intensity of the pain caused by the aspiration.

Complications, the secondary end point

The following OCR complications were recorded: none, significant vaginal or abdominal bleeding requiring major intervention, bowel injury, bladder injury, peritonitis, hospitalization and any surgical treatment. In the present study, vaginal bleeding was defined as significant bleeding that required some local compression.

Exposures

Natural cycle IVF

Natural cycle IVF was defined as IVF treatment without gonadotrophin stimulation. Only gonadotrophin-releasing hormone antagonist injections were given, for example, to avoid premature LH surges before weekends. Ovulation was induced with HCG.

Minimal stimulation IVF

Minimal stimulation IVF was defined as IVF treatments with 100 IU or less of human menopausal gonadotrophin (HMG) or recombinant human FSH (rFSH) per day, oral agents, such as 50 mg or less of clomiphene citrate, or 5 mg or less of aromatase inhibitors (AI) per day.

Protocols were standardised between centres to allow comparison. The following minimal stimulation protocols were used (*Von Wolff, 2022*):

Minimal stimulation IVF with CC. 25 mg of CC was started around day 4 of the cycle until the day of the ovulation trigger (Protocol "CC"). The aim of this protocol was to increase oocyte number and avoid premature LH surge (*Von Wolff et al., 2014*).

Minimal stimulation IVF with CC and hMG or rFSH. The "CC" protocol was used and 75-100 IU/day of hMG of rFSH was added from around day 4 of the cycle until the day before the ovulation trigger was given (Protocol "CC plus gonadotropins"). The purpose of the gonadotropins was to increase the number of oocytes.

Minimal stimulation IVF with hMG or rFSH. 75-100 IU of hMG or rFSH daily was started around day 4 of the cycle until the day before the ovulation trigger was given (Protocol "gonadotropins"). The aim of this protocol was to increase the number of oocytes without the risk of endometrial thinning due to CC.

Minimal stimulation IVF with AI. 5 mg of letrozole was started around day 4 of the cycle for 5 days (Protocol "AI"). The aim of this protocol was to increase the number of oocytes and avoid premature LH surge.

Minimal stimulation IVF with AI and hMG or rFSH. The "AI" protocol was used and 75-100 IU/day of hMG of rFSH was added from around day 4 of the cycle until the day before ovulation was induced (Protocol "AI plus gonadotropins"). The purpose of the gonadotropins was to increase the number of oocytes and to reduce the risk of premature LH surge.

Couples were allowed to choose a protocol based primarily on their personal preferences.

Ovarian response was monitored by transvaginal ultrasound and assessment of serum LH and oestradiol concentrations analysed by electrochemiluminescence. When the diameter of the first follicle(s) reached 18 mm, 5000 IU of HCG was administered (*Helmer et al., 2022*). Oocyte retrieval was carried out 36 h after HCG injection. Transvaginal OCR was carried out using the following aspiration needles and needle volumes: 17G (Ovum Aspiration Needle Single Lumen) Cook (Bloomington IN, USA), 19G (Small Gage Ova-Stiff™ Ovum Aspiration Needle Single Lumen) (Cook Medical, IN, USA); Single Lumen (Kitasato, Shizuoka, Japan); Sense double Lumen (Vitrolife, Gothenburg, Sweden) or 20G (Sense Single Lumen) (Vitrolife, Gothenburg, Sweden). Vitrolife® Sense double Lumen has a 16G body and a 19G needle tip. Vitrolife® Sense single Lumen has a 17G body and a 20G needle tip. In the TABLE 3 and in the discussion, the reference of the needle volume is the tip of the needle. Aspiration pressure varied among centres from −130 to −220 mmHg. In most cases, follicles were flushed three to five times (*Schwartz et al., 2020*). As anaesthesia and analgesia were not administered, an empty stomach was not required. All treating doctors had been performing OCRs without anaesthesia for many years. The fertilization technique used was either standard IVF or intracytoplasmic sperm injection (ICSI). Embryo transfer was carried out on day 2, 3 or 5, depending on the clinic's protocol.

Statistical analysis

Baseline patient and cycle characteristics of the study population were stratified by study centre and overall, without any formal statistical test. Categorical variables are summarized as numbers and percentages, continuous variables as range, i.e. minimum and maximum, medians with interquartile ranges (IQR) or means with SD, as appropriate. For cycle characteristics, information on the pain score and the number of retrieved oocytes are provided.

The statistical analysis of the study consisted of two parts. First, a descriptive analysis was undertaken. Namely, boxplots were used to illustrate the variation of pain scores in relation to the number of collected oocytes (0, 1, 2 to 5, ≥6) and in relation to the number of repeated IVF cycles (1 to 10 cycles). Each box indicates the range in which 50% of all values lie. The lower end of the box is the first quartile and the upper end is the third quartile.

Second, the effect of repeated IVF cycles, number of collected oocytes and needle size on the pain score using a linear mixed model were analysed. The model includes the pain score (dependent variable), the fixed effects of the IVF cycle number (numeric), the number of collected oocytes (categorical: 0, 1, 2–5, ≥6), the needle size (categorical: 17, 19, 20G), and was adjusted for the patient's age, body mass index (BMI) (continuous variable) and for the IVF protocol (categorical, NC-IVF or minimal stimulation IVF protocols). A random intercept for the site (categorical, site 1 to 7) and patient (nested with site) were included to consider the structure of the dataset.

Ethical approval

Ethical approval was given by the cantonal ethics committee of Bern, for Switzerland (04.10.2021, KEK 2021-01689) and by the four regional ethics committee of Germany (Baden-Württemberg (ID F-2024-068, 22.08.2024), Fertility Centres Ulm and Neckarsulm, Niedersachsen (ID Grae/080/2024, 30.08.2024), Fertility Centre Hildesheim, Bavaria (ID mb24043, 12.09.2024), Fertility Centre kïz, Munich and Nordrhein-Westfalen (ID 2024194, 30.10.2024), Fertility Centre Bonner-Bogen, Bonn). Written informed consent was provided from participants.

RESULTS

In total, 2290 cycles from 1039 patients were included. Patients characteristics are presented in TABLE 1. The age of the included patients ranged from 23–46 years, with an overall mean (SD) age of 36.6 (4.1) years. The median (IQR) anti-Mullerian hormone level was 1.7 (0.7–3.1) ng/ml, ranging from 0.0 to 21.0 ng/ml. The mean (SD) BMI was 23.4 (4.4) kg/m^2. Indications for IVF treatment were male infertility (n = 300 [29%]), female infertility (n = 280 [27%]), female and male infertility (n = 222 [21%]), idiopathic infertility (n = 207 [20%]) and homosexuality (n = 30 [2.9%]). A median of two cycles, ranging from one to 10, were carried out in patients.

The main results and the characteristics of the cycles are presented in TABLE 2. The median (IQR) pain score per aspiration was 3 (2–4), with a range of 0 to 10. A pain score of 2 or 3 on the visual analogue score (VAS) was described as mild, and a score of 4 as moderate (*McCormack et al., 1988*; *Williamson and Hoggart, 2005*).

TABLE 1 BASELINE CHARACTERISTICS OF OVERALL PATIENT POPULATION ACCORDING TO STUDY CENTRE

Characteristics[a]	Overall	Centre						
		1	2	3	4	5	6	7
Patients, *n*	1039	365	151	142	133	123	99	26
IVF cycles per patient, *n*								
Median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–4.0)	1.0 (1.0–2.0)	2.0 (1.0–3.0)	1.0 (1.0–2.0)	2.0 (1.0–2.5)	2.0 (1.0–2.0)	1.0 (1.0–2.0)
Range (minimum, maximum)	(1.0, 10.0)	(1.0, 10.0)	(1.0, 7.0)	(1.0, 8.0)	(1.0, 6.0)	(1.0, 10.0)	(1.0, 8.0)	(1.0, 3.0)
Female age at first oocyte retrieval oocyte retrieval, years								
Mean (SD)	36.6 (4.1)	36.4 (3.8)	37.6 (3.7)	36.8 (5.0)	37.0 (4.5)	36.0 (4.1)	35.4 (3.7)	36.3 (3.9)
Range (minimum, maximum)	(23.0, 46.0)	(23.0, 45.0)	(27.0, 45.0)	(24.0, 45.0)	(24.0, 46.0)	(24.0, 46.0)	(27.0, 44.0)	(28.0, 42.0)
Body mass index, kg/m^2								
Mean (SD)	23.4 (4.4)	22.9 (4.1)	24.1 (4.4)	23.9 (4.9)	23.8 (5.1)	23.0 (4.1)	23.6 (4.0)	23.4 (4.6)
Range (minimum, maximum)	(15.4, 44.2)	(16.6, 44.2)	(16.8, 42.7)	(16.6, 38.2)	(16.3, 40.8)	(15.4, 39.2)	(15.8, 40.6)	(18.6, 34.4)
Duration of infertility, years								
Median (IQR)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–5.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)
Range (minimum, maximum)	(1.0, 15.0)	(1.0, 12.0)	(1.0, 13.0)	(1.0, 15.0)	(1.0, 13.0)	(1.0, 15.0)	(1.0, 10.0)	(1.0, 9.0)
Causes of infertility, *n* (%)								
Male factor, *n* (%)	300 (29)	95 (26)	35 (23)	50 (35)	42 (32)	41 (33)	33 (33)	4 (15)
Female factor, *n* (%)	280 (27)	114 (31)	52 (34)	26 (18)	23 (17)	38 (31)	16 (16)	11 (42)
Male and female, *n* (%)	222 (21)	58 (16)	30 (20)	42 (30)	36 (27)	22 (18)	28 (28)	6 (23)
Idiopathic, *n* (%)	207 (20)	89 (24)	19 (13)	24 (17)	26 (20)	22 (18)	22 (22)	5 (19)
Homosexuality, *n* (%)	30 (2.9)	9 (2.5)	15 (9.9)	0.0 (0)	6 (4.5)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Anti-Müllerian hormone level, ng/ml								
Median (IQR)	1.7 (0.7–3.1)	1.9 (0.8–3.2)	1.3 (0.6–2.2)	1.5 (0.4–3.0)	1.8 (0.6–3.6)	1.5 (0.6–3.2)	2.0 (1.0–3.7)	0.8 (0.2–2.0)
Range (minimum, maximum)	(0.0, 21.0)	(0.0, 13.5)	(0.0, 9.5)	(0.0, 16.8)	(0.0, 15.0)	(0.0, 21.0)	(0.0, 15.0)	(0.0, 4.7)
Missing	9	0	0	1	1	0	3	4

[a] Statistics have been calculated using data collected at the time of the first IVF cycle.

IQR, interquartile range.

The overall median (IQR) number of oocytes retrieved per cycle per patient was 1 (1–2), ranging from 0 to 16. The median (IQR) number of oocytes retrieved by each participating centre was 1 (1–5). The pain score (0 to 10) per OCR according to the number of oocytes retrieved is presented in FIGURE 1. The pain score (0 to 10) according to the number of repeated IVF cycles with retrieval (1 to 10) is presented in FIGURE 2.

The main results of the linear mixed model are presented in TABLE 3. The model shows a statistically significant influence of the number of oocytes collected on the pain score ($P < 0.001$). Compared with the reference situation in which only one oocyte was retrieved, the pain score increased by 0.5 points (95% CI 0.25 to 0.75) when no oocyte was retrieved and by 0.42 (95% CI 0.23 to 0.62) points when two to five oocytes were retrieved. When six or more oocytes were retrieved, the pain score increased by 1.1 points (95% CI 0.60 to 1.70).

Results of the mixed linear model also showed a statistically significant effect of the number of repeated IVF cycles on the pain score ($P = 0.028$). Namely, the pain score decreased by 0.05 (95% CI −0.10 to −0.01) points with each new aspiration, showing an inverse relationship between pain score and number of IVF cycles performed. Needle size (17, 19 or 20G) had no significant effect on the pain score ($P = 0.12$). The same was true for BMI ($P = 0.5$) and for IVF protocol (NC-IVF and minimal stimulation IVF protocols, $P = 0.7$).

The women's age had a significant effect on the pain score ($P = 0.041$). For each additional year of age, the pain score decreased by 0.02 points (95% CI −0.05 to 0.00). The characteristics of the aspiration method in each study centre are presented in Supplementary Table 1. The complication rates in the overall

TABLE 2 CYCLE CHARACTERISTICS FOR OVERALL POPULATION AND ACCORDING TO STUDY CENTRE

Characteristics	Overall	Centre						
		1	2	3	4	5	6	7
Patients, *n*	1039	365	151	142	133	123	99	26
IVF cycles, *n*	2290	1069	208	292	226	260	197	38
Retrieved oocytes, *n*								
Median (IQR)	1 (1–2)	1 (1–1)	3 (2–5)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–1)
Range (minimum, maximum)	(0, 16)	(0, 16)	(0, 12)	(0, 6)	(0, 8)	(0, 16)	(0, 7)	(0, 2)
Pain score per oocyte retrieval								
Median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–5)	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)
Range (minimum, maximum)	(0, 10)	(0, 10)	(0, 8)	(0, 10)	(0, 8)	(0, 10)	(0, 9)	(0, 7)

IQR, interquartile range.

population are presented in Supplementary Table 2. Fifteen cases of vaginal bleeding (0.7%), two cases of abdominal bleeding (<0.1%) and two hospitalizations (<0.1%) were documented.

DISCUSSION

The present study showed that the level of pain caused by OCR of one or few follicles without analgesia and anaesthesia is only mild, with a median score of 3 on a VAS scale of 0 to 10. The present study also revealed that the complication rate of such OCRs is low. To the best of our knowledge, the present study is the first multicentre study to show that OCR can be carried

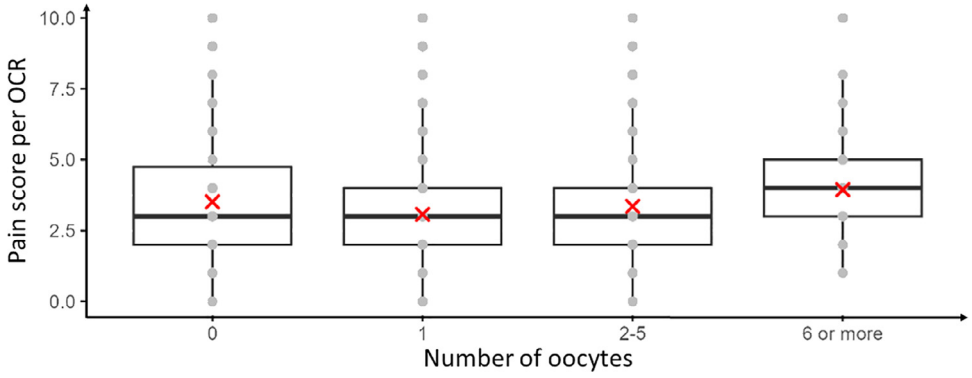

FIGURE 1 Box and whisker plots depicting pain score per oocyte retrieval (OCR) according to oocyte number retrieved. Interquartile range, maximum and minimum values and outliers (grey points) are shown. Median, solid line in the box; mean, red cross.

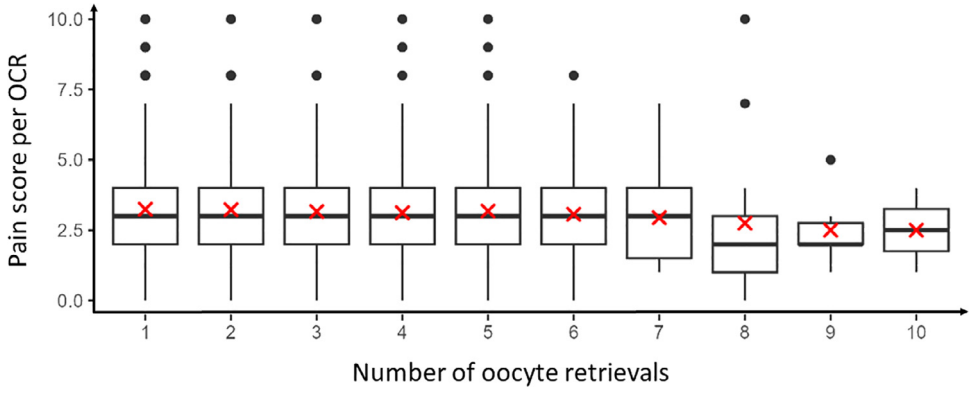

FIGURE 2 Box and whisker plots illustrating pain score according to repeated IVF cycle number with oocyte retrieval (OCR). Interquartile range, maximum and minimum values and outliers (black circles) are shown. Median, solid line in the box; mean, red cross.

TABLE 3 ASSOCIATIONS BETWEEN THE PAIN SCORE, AND PROCEDURAL AND DEMOGRAPHIC CHARACTERISTICS, ANALYSED USING A LINEAR MIXED MODEL

Characteristics	Estimate	95% CI	*P*-value
Oocytes, *n*			<0.001
0	0.50	0.25 to 0.75	
1[a]	–	–	
2–5	0.42	0.23 to 0.62	
≥6	1.10	0.59 to 1.70	
IVF cycles, n	−0.05	−0.10 to −0.01	0.028
NC-IVF and minimal stimulation IVF, protocols			0.7
NC-IVF	–	–	
Protocol clomiphene citrate	0.01	−0.27 to 0.29	
Protocol clomiphene + HMG or FSH	0.15	−0.22 to 0.52	
Protocol HMG or FSH	0.14	−0.20 to 0.47	
Protocol letrozole	−0.07	−0.44 to 0.31	
Protocol letrozole + HMG or FSH	0.23	−0.15 to 0.61	
Aspiration needle (gauge)			0.12
17	–	–	
19	−0.03	−0.68 to 0.62	
20	−0.65	−1.50 to 0.26	
BMI, kg/m^2	0.01	−0.01 to 0.03	0.5
Woman's age, years	−0.02	−0.05 to 0.00	0.041

–, no values; BMI, body mass index; HMG, human menopausal gonadotrophin; NC-IVF, natural-cycle-IVF.
[a] Reference value.

out without analgesia and anaesthesia in women with few follicles, thus reducing treatment costs and treatment time.

The strength of the study is its multicentre design and the use of different needle sizes and aspiration pressures. Therefore, the study results are not limited to one specialized centre, but provide a real-word evidence based on many centres and different aspiration conditions. Furthermore, as 78% of the patients in the present study had not undergone previous embryo transfer before inclusion, they can be expected to be new to all types of follicle aspiration, which allows transfer of our findings to most women without any aspiration experience.

The limitation is that a selected group of patients was included in the study. The present study only included patients who had been accepted by the physician to be aspirated without analgesia and anaesthesia and who had consented. Therefore, the study results cannot be generalized to the whole IVF population. In addition, our study was neither based on the number of follicles punctured and needle insertion attempts, but on the number of oocytes retrieved. This may have led to some overestimation of the pain score, as the number of follicles is usually higher than the number of oocytes retrieved.

It would also have been of clinical interest if the pain score had been related to the experience of the physicians, but as all physicians were experienced, this could not be analysed.

Finally, regarding the assumption that OCR without anaesthesia and analgesia saves costs and time, it should be noted that analgesics are cheap and do not affect treatment time.

In NC-IVF and minimal stimulation IVF, treatments are carried out monthly. Anaesthesia should, therefore, be avoided. Furthermore, low complication rates and the lowest possible costs and treatment times are required.

In conventional IVF with high-dose gonadotrophin stimulation, requirements are different. In the case of polyfollicular response, large-lumen aspiration needles are preferred to reduce OCR time. The increased pain associated with such needles is not relevant, as anaesthesia is used. The higher costs and longer OCR times are also less relevant owing to the expected high number of aspirated oocytes and the lower number of IVF cycles required until the desired pregnancy is achieved.

Several studies have analysed the pain experienced during follicle aspiration (*Aziz et al., 1993*; *Awonuga et al., 1996*; *Wikland et al., 2011*; *Nakagawa et al., 2015*; *Iduna Antigoni Buisman et al., 2021*). All these studies showed lower pain scores with thinner needles. As they all used analgesics or even anaesthesia, the results cannot be compared with our study and cannot be extrapolated to an analgesia- and anaesthesia-free setting.

The only study without analgesia and anaesthesia was conducted by *Nakagawa et al. (2015)*. Seventy-five women undergoing monofollicular IVF were included. The women were randomized to OCR with either 20G or 19G needles. Overall pain was rated by the patients immediately after the OCR using a VAS score between 0 and 10. Pain was significantly lower in those aspirated with 20G needles compared with 19G needles (mean VAS score ± SD: 3.2 ± 2.0 versus 4.9 ± 2.2, $P < 0.01$).

The investigators described a pain score in patients aspirated with 20G needles, which is similar to the present study. We described a mean VAS score across all centres of three points in women with one oocyte, which increased by 0.42 points when two to five oocytes were retrieved and by 1.1 points when six or more oocytes were retrieved. In contrast to the study mentioned above, however, in which pain scores were significantly higher in women aspirated with 19G needles, all but one centre in our study used 19G or even 17G needles (Supplementary Table 1) and still reported a low pain score. Furthermore, in the present study, needle size had no significant effect on the pain score. Accordingly, the overall experienced pain in our study was lower than in the study by *Nakagawa et al. (2015)*. The reason for this difference is difficult to explain. It is possible that the difference is due to different populations: *Nakagawa et al. (2015)* included Japanese participants; the present study included German and Swiss participants; or differences in aspiration setting and needle handling, but this remains speculative.

Both studies also analysed the proportion of patients with vaginal bleeding. In the study by *Nakagawa* et al. *(2015)*, vaginal bleeding, defined as persistent signs of bleeding even after 30 s of direct compression, occurred in 26.3% of patients aspirated with 20G needles compared with 48.6% aspirated with 19G needles. In the present study, vaginal bleeding occurred in only 0.7% of all patients (15 cases), even though some centres in the present study carried out OCR with needles even larger than 19G. As vaginal bleeding in our study was defined as significant bleeding requiring compression, however, the results of the two studies are not fully comparable. Overall, the rate of major complications in the present study was low, with only two patients (0.09%) hospitalized for intra-abdominal bleeding.

One of the most striking results of the present study was the pain score in relation to the number of retrieved oocytes. The pain score increased by only 0.42 points in cases in which two to five oocytes were retrieved. This small increase was statistically significant but clinically insignificant.

This finding is of great clinical importance as it opens up the concept of analgesia-free OCR to a wide range of women with a poor ovarian response. The reason for the minimal increase in aspiration pain is that penetration of the vaginal skin is most painful, whereas aspiration of additional follicles with minimal manipulation of the needle causes little more pain.

Our results raise the question of the extent to which the intensity of pain experienced is influenced by the outcome of the OCR, as the pain score increased by 0.5 points in women with no oocytes retrieved. Therefore, it can be speculated that a negative result, such as an OCR with no oocytes, may lead to a more intense pain experience, whereas a high number of retrieved oocytes may lead to the opposite, i.e. a less intense pain experience.

The second striking result of the present study was the effect of repeated IVF cycles with OCR on pain intensity, which has also not been studied previously. We found that the pain score decreased by 0.05 points with each new aspiration. Although the decrease is minimal, it clearly shows that repeated aspirations are not associated with a more intense pain experience. This is particularly striking, as repeated IVF cycles could be associated with increased frustration owing to treatment failures. It cannot, however, be excluded that the lower pain score is a result of bias, as those patients who documented a higher pain score might have dropped out after a few OCRs and decided to undergo conventional IVF treatments with OCR under anaesthesia and analgesia.

The present results also raise the question of whether OCR without anaesthesia and analgesia could be carried out in selected normal or even high responders, as the pain score reported in our study was only 1.1 points higher in women with six or more oocytes compared with those with one oocyte.

Two studies on OCRs in conventionally stimulated IVF treatments without analgesia and anaesthesia have been published (*Greenberger et al., 2020*; *Gilboa et al., 2021*).

Greenberger et al. *(2020)* analysed patient satisfaction with OCR performed without anaesthesia and analgesia using 20G needles and with a mean (± SD) aspiration of four ± three oocytes. Fifty patients undergoing their first OCR without anaesthesia and analgesia were included. The results showed a high level of satisfaction with the performance of OCR, with a mean (± SD) score of 8.7 ± 1.8 (on a VAS of 1 to 10). In addition, 90% of the women would recommend OCR using this method to their friends. Interestingly, the expectation of pain before the procedure was similar to the actual pain experienced (mean ± SD expected pain, 5.5 ± 1.7; actual pain experienced, 5.1 ± 2.3) (*Greenberger et al., 2020*).

Similar results regarding satisfaction with OCR without anaesthesia and analgesia were found in the study by *Gilboa* et al. *(2021)*. The primary aim of the study was to understand the reasons why patients decide to have the procedure without anaesthesia and analgesia. Fifty out of 100 women opted for OCR without anaesthesia and analgesia using a 20G tip aspiration needle. The other group of 50 women carried out OCR with anaesthesia and analgesia. Seventy-six per cent of patients who underwent OCR without anaesthesia and analgesia reported a pain score less than 6 and 24% of 6 or above on a VAS of 0–10. Patients were also asked whether they regretted undergoing the procedure without anaesthesia and analgesia. A total of 98% of patients who underwent OCR without anaesthesia and analgesia said they did not regret the decision. Furthermore, the results showed that the most important determinants supporting the decision to undergo the procedure without anaesthesia and analgesia were the expected low number of oocytes and the fear of anaesthesia (*Gilboa et al., 2021*).

All these studies show that OCR without anaesthesia and analgesia is a feasible option. The studies, however, also show that this is probably only the case in selected patients, as only those patients who agreed to be aspirated without analgesia and anaesthesia were included in the studies. It can be assumed that patients who are sensitive to pain, such as women with symptomatic endometriosis, may have opted for aspiration with anaesthesia and analgesia.

In conclusion, OCR can be easily carried out in selected patients without anaesthesia and analgesia in women with only one or few follicles, provided that thin needles are used and sufficient experience with this type of OCR is available. This saves costs and treatment time, and may also reduce anxiety in patients who are afraid of anaesthesia.

DATA AVAILABILITY

Data will be made available on request.

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AUTHORS' ROLES

IM and MVW: Substantial contributions to conception and design of the study, data acquisition, analysis and interpretation; drafting and revising the article; and final approval of the version to be submitted; MR: substantial contribution to analysis

and interpretation of data; revising the article for important intellectual content; and final approval of the version to be submitted; RMP, EB, SE, CH-Z, MN, IS and J-SL: substantial contribution to acquisition of data; revising the article for important intellectual content; final approval of the version to be submitted.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.rbmo.2024.104696.

APPENDIX. PARTICIPATING CENTRES

- Centre number 1: Fertility centre kïz in Munich, Germany
- Centre number 2: Fertility clinic Bonner Bogen in Bonn, Germany
- Centre number 3: Fertility clinic Frauenärzte in Neckarsulm, Germany
- Centre number 4: Fertility clinic Villa Kinderwunsch in Ulm, Germany
- Centre number 5: Division of Gynaecological Endocrinology and Reproductive Medicine, University Women's Hospital, Inselspital, Bern, Switzerland
- Centre number 6: Fertility clinic Kinderwunschzentrum Baden, Switzerland
- Centre number 7: Institute for Gynaecological Endocrinology and Reproductive Medicine Fiore Praxis AG in St. Gallen, Switzerland

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