

Received: December 2023 Accepted: January 2024

DOI: <https://doi.org/10.58262/ks.v12i2.094>

Comparison between the Effects of Two Analgesic Drugs on Ivf Regarding Oocytes Quality and Pregnancy Outcomes

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Abstract

Background: Numerous human and experimental investigations have shown that anesthetic substances exist in follicular fluid, potentially having effects on hormone concentration, embryo quality, and the success of following fertilization and implantation rates. *Objective:* Aim to evaluate the impact of medications used for general anesthesia (remifentanyl vs. fentanyl) on the results of ICSI, the concentration of hormones in follicular fluid, and oocyte retrieval. *Patients and methods:* The current prospective comparative study was approved by the ethics committee of the Faculty of Science at Mansoura University in Egypt. It was carried out at the infertility center of the "High Institute of Infertility Diagnosis and Assisted Reproductive Technologies/ Reproductive Physiology/ Al-Nahrain University/ Baghdad/ Iraq." Sixty infertile women who were undergoing intracytoplasmic sperm injections (ICSI) for various infertility-related problems participated in the trial. The women ranged in age from twenty to forty-five. The study's original September 2022 deadline was pushed out to September 2023. Those persons were divided into two groups based on the anesthetic routine used for the retrieval of oocytes during general anesthesia. While remifentanyl, midazolam, and propofol were given to the second group, fentanyl, midazolam, and propofol were given to the first group. *Results:* The current study's findings demonstrated that remifentanyl increased the rate of fertilization (52.40) than fentanyl (47.87); comparing the hormonal levels in The follicular fluid showed significantly higher FSH levels in the remifentanyl group ($p = 0.046$); on the other hand, there were no significant differences between the fentanyl and remifentanyl groups regarding follicular fluid LH and prolactin levels, with p values equal to 0.632 and 0.320. According to the results, the fentanyl group showed insignificantly higher total oocyte counts ($p = 0.973$) and metaphase II oocytes ($p = 0.495$). On the contrary, there were insignificantly fewer abnormal oocytes ($p = 0.919$), germinal vesicles ($p = 0.259$), and ruptured oocytes ($p = 0.406$) in the fentanyl group. There were also no significant differences between the studied groups regarding total transferred embryos ($p = 1.00$) or grade I embryos ($p = 0.739$). *Conclusion:* Because of remifentanyl's quicker recovery period and substantial association with specific IVF and ICSI characteristics, it is preferable to fentanyl when used under general anesthesia for ova collection operations.

Keywords: ICSI, general anesthesia, oocyte retrieval, fentanyl, remifentanyl, Follicular Fluid.

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1. Introduction

When a woman's fertility either declines or is completely absent. A diagnosis of infertility is made. In other words, it doesn't mean the lady can't get pregnant; it just means she might want some sort of support or therapy to do so. The term "infertility" is frequently used when a couple hasn't conceived after 12 months of regular, unprotected sexual contact or after six months for women over 35 (1). A 10% to 15% prevalence of infertility is estimated for the entire world (2). Female factors, male factors, ovarian dysfunction, tubal factors, endometriosis, uterine causes, or other reasons are some of the etiological causes of infertility. While the etiology is complex in some couples, it is referred to as unexplained infertility in others (3). Assisted reproductive technologies (ARTs), medical and/or surgical therapy of the underlying cause, fertility drugs, and fertility counseling are all included in infertility management (4).

All procedures that include treating human oocytes, sperm, or embryos in vitro for reproductive purposes are collectively referred to as assisted reproductive technologies (ARTs). This includes assisted hatching, gamete intrafallopian transfer, zygote intrafallopian transfer, in vitro fertilization (IVF), embryo transfer (ET), intracytoplasmic sperm injection (ICSI), embryo biopsy, preimplantation genetic diagnosis (PGD), assisted conception, gamete and embryo cryopreservation, semen, oocyte and embryo donation, and gestational carrier (5).

IVF is defined as "a system of operations that includes extracorporeal fertilization of gametes. ICSI and traditional in vitro fertilization are included. (6). A series of IVF phases, including controlled ovarian stimulation (COS), ovum pick-up (OPU), fertilization, embryo transfer (ET), and implantation, are required for IVF to be successful. Because the quality of the oocyte influences fertilization, embryo quality, and implantation, the OPU procedure is crucial (7). IVF is one of the most painful and stressful procedures; thus, it needs sedation, analgesia, and anesthesia (8). A greater pregnancy rate, an effective surgical anesthetic with few side effects, and quick recovery are all requirements for the optimum anesthesia approach (9).

Because of their quick-acting time (8–10 minutes), quick onset, rapid elimination and clearance rate without drug accumulation, quick recovery time, and improved fertility outcome in association with OPU, fentanyl, and remifentanyl have inspired several authors (9, 10, 11, 12). Itchy skin, nausea, vomiting, hypotension, bradycardia, and respiratory damage are some of the side effects (13). To the best of our knowledge, no information compares the effects of fentanyl and remifentanyl on fertility in a single study during oocyte retrieval.

2-Patients and Memethods

The present prospective comparative study was approved by the ethical committee of the Faculty of Science at Mansoura University in Egypt and was conducted at the infertility center of the "High Institute of Infertility Diagnosis and Assisted Reproductive Technologies/Reproductive Physiology/Al-Nahrain University/Baghdad/Iraq." The trial included 60 infertile women receiving intracytoplasmic sperm injections (ICSI) for a range of infertility-related conditions. The women ranged in age from twenty to forty-five. The study's original September 2022 deadline was pushed out to September 2023. Based on the anesthetic regimen used during general anesthesia for oocyte retrieval, those patients were divided into two groups. Midazolam, propofol, and fentanyl were given to the first group, and remifentanyl, midazolam, and propofol were given to the second.

All participants completed the standard ICSI procedure, which entails clinical evaluation (history, examination, and investigation), controlled ovarian stimulation, triggering of

ovulation, oocyte harvesting under general anesthesia, and other steps. Also, follicular fluid sample collection was done after anesthesia to assess the concentration of hormones (prolactin, follicular stimulating hormone (FSH), luteal hormone (LH), oocyte denudation, oocyte maturation evaluation, intracytoplasmic sperm injection of mature (MII) oocytes, evaluation of fertilization and cleavage and embryo grading, embryo selection and embryo transfer, and beta hCG determination (to document biochemical pregnancy). Oocyte denudation has been followed by sperm processing. The quality of oocytes and embryos was evaluated based on microscopical morphological standards. In a private laboratory, follicular fluid was obtained using an enzyme-linked.

3-Results

The Follicular fluid hormone concentrations of infertile women enrolled in this study are shown in (table 1), (figure 1, and Figure 2). The follicular fluid showed significantly higher FSH levels in the remifentanyl group (59.53 ± 15.66 vs. 52.83 ± 8.89 ; $p = 0.046$); on the other hand, there were no significant differences between the fentanyl and remifentanyl groups regarding follicular fluid LH and prolactin levels, with p values equal to 0.632 and 0.320 respectively. However, The comparison of oocytes and embryo characteristics between fentanyl and remifentanyl groups were illustrated in (Table), (figure 3, and Figure 4). According to the results fentanyl group showed insignificantly higher total oocyte counts (10.50 ± 7.51 vs. 10.43 ± 7.93 ; $p = 0.973$), metaphase II oocytes (8.10 ± 6.13 vs. 7.07 ± 5.51 ; $p = 0.495$).

On the contrary, there were insignificantly lower abnormal oocytes (0.93 ± 0.25 vs. 0.97 ± 0.21 ; $p = 0.919$), germinal vesicles (0.93 ± 0.22 vs. 1.60 ± 0.54 ; $p = 0.259$) in the fentanyl group. There were also no significant differences between the studied groups regarding total transferred embryos (2.07 ± 0.83 vs. 2.07 ± 0.74 ; $p = 1.00$).

Table 1: Comparison of Follicular Fluids Lh, Fsh, and Prolactin Levels Between Fentanyl and Remifentanyl Groups.

Parameters	Fentanyl group n=30 (Mean \pm SD)	Remifentanyl group n=30 (Mean \pm SD)	p value
LH (mIU/ml)	76.33 ± 2.26	74.63 ± 2.71	0.632 T NS
FSH (mIU/ml)	52.83 ± 8.89	59.53 ± 15.66	0.046 T S
Prolactin (ng/ml)	1542 ± 93	1656 ± 66	0.320 T NS

LH: Luteinizing hormone; FSH: Follicle stimulating hormone; NS: Not significant ($p > 0.05$); S: Significant ($p \leq 0.05$); T: Independent sample t test

Table 2: Comparison of ICSI Outcome Between Fentanyl and Remifentanyl Groups.

Parameter	Fentanyl group (Mean \pm SD)	Remifentanyl group (Mean \pm SD)	p-value
Total oocytes count	10.50 ± 7.51	10.43 ± 7.93	0.973 T NS
Metaphase II oocytes	8.10 ± 6.13	7.07 ± 5.51	0.495 T NS
Abnormal oocytes	0.93 ± 0.25	0.97 ± 0.21	0.919 T NS
GV oocytes	0.93 ± 0.22	1.60 ± 0.54	0.259 T NS
Rupture oocytes	0.53 ± 0.22	0.80 ± 0.23	0.406 T NS
Fertilization rate %	47.87 ± 20.28	52.40 ± 16.55	0.257 T NS
Transferred embryos	2.07 ± 0.83	2.07 ± 0.74	1.00 T NS
Grade I embryos	2.00 ± 0.80	2.07 ± 0.77	0.739 T NS
Grade II embryos	3.00 ± 0.0	$2.00 \pm ---$	-----

GV: Germinal Vesicles; NS: not Significant ($P > 0.05$); T: Independent Sample T Test.

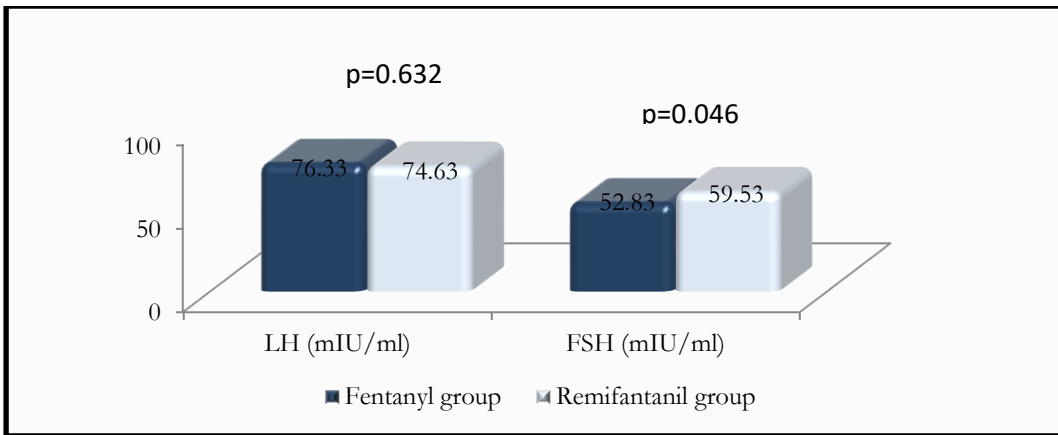


Figure 1: Comparison of Follicular Fluids Lh and Fsh Levels between Fentanyl and Remifentanyl Groups.

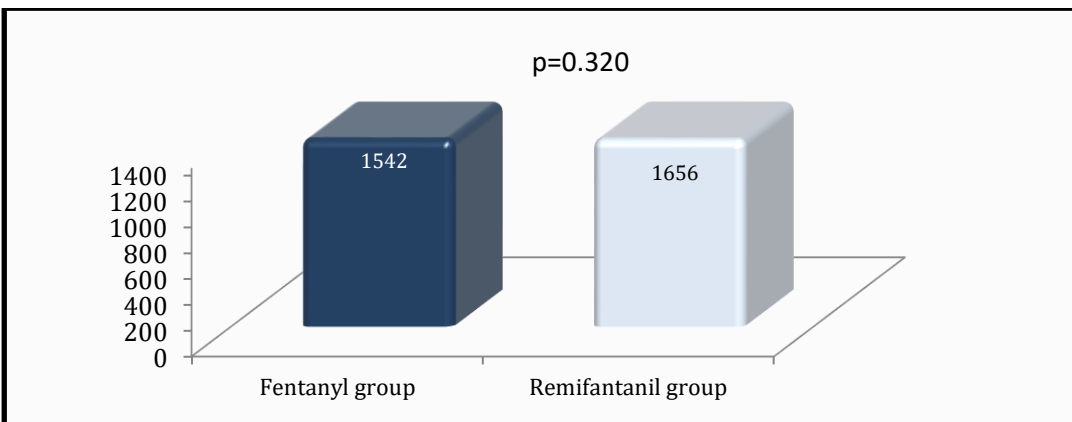


Figure 2: Comparison of Follicular Fluids Prolactin Levels between Fentanyl and Remifentanyl Groups.

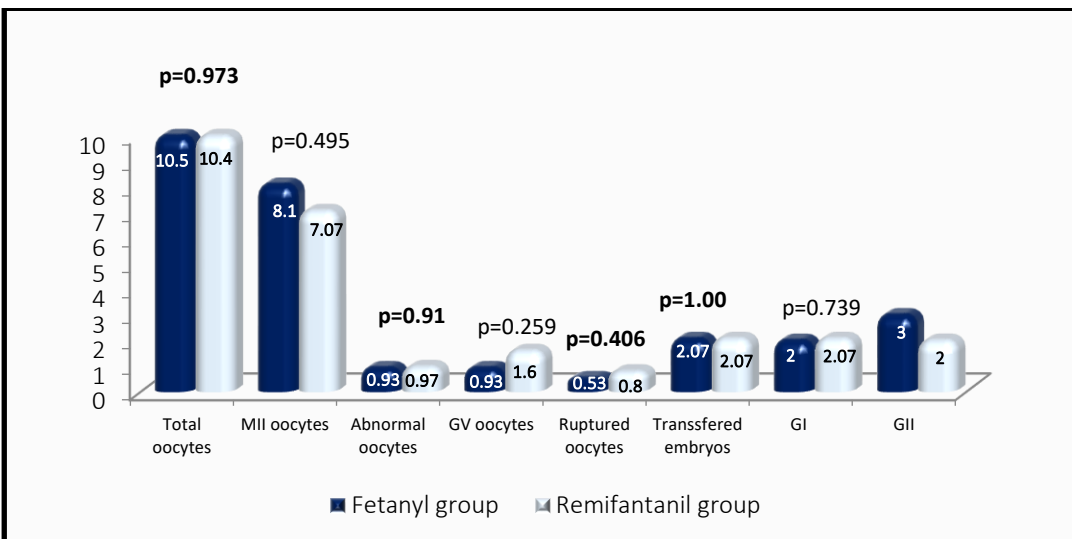


Figure 3: Comparison of ICSI Outcomes between Fentanyl and Remifentanyl.

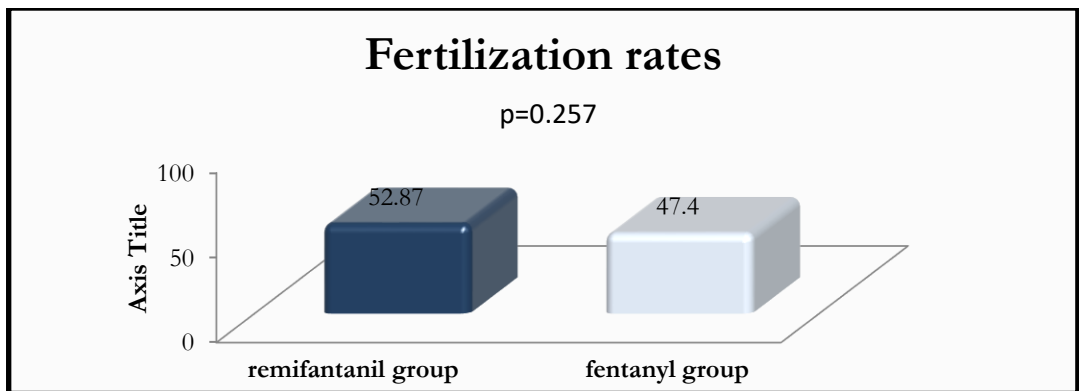


Figure 4: Comparison of Fertilization Rates between Fentanyl and Remifentanyl Groups

4-Discussion

In this study, 60 infertile women were randomly selected and divided into two groups: 30 received fentanyl, and 30 received remifentanyl during general anesthesia for oocyte retrieval. The purpose of this was to compare the results of the intracytoplasmic sperm injection (ICSI) cycle, specifically oocyte characteristics and embryonic characteristics. In the current study, the FF concentration of FSH, LH, and PRL hormones in the fentanyl and remifentanyl groups showed significantly higher FSH levels in the remifentanyl group ($p = 0.046$). In the past, only a small number of researchers examined the FF concentration of anesthetic drugs without measuring any hormone concentration in FF, and some of them used a small sample size; therefore, more studies are necessary to get a safe conclusion (14).

Some studies (15) and (16) measured the concentration of a variety of anesthetic agents (thiopental, thiamylal, lidocaine, midazolam, fentanyl, alfentanil, and propofol) in FF; however, data about hormone concentration in FF are lacking. It is noteworthy to notice that the FF assessment for hormone concentration was first included in the current investigation. Furthermore, no prior research has compared the effects of the FF hormone concentrations of remifentanyl and fentanyl on the features of the oocyte and embryo in women undergoing oocyte retrieval for IVF/ICSI programs. The results showed that there are no significant differences in ICSI outcome (total oocyte count, metaphase II oocytes, abnormal oocytes, GV oocytes, rupture oocytes, transferred embryos, Grade I embryos, and Grade II embryos) between the remifentanyl group and the fentanyl group ($p > 0.05$).

When comparing anesthetic techniques using propofol and fentanyl versus midazolam and remifentanyl associated with paracervical block with lidocaine, or comparing GA (atropine, remifentanyl, and propofol) versus paracervical block or analgesia with remifentanyl versus anesthesia with propofol and alfentanil, it has been found that remifentanyl has no negative effect on the quality of retrieved oocytes (9). (12). (17). Remifentanyl also has an advantage over local anesthetics in that, when administered as a continuous intravenous infusion, the total oocyte count is much higher (18). Or administered as part of GA (remifentanyl combined with isoflurane or propofol) and contrasted with sedation (midazolam, diazepam, or propofol) (19). Comparing the effects of fentanyl, thiopental, and propofol for sedation during oocyte retrieval, some writers observed no discernible detrimental effect of fentanyl on oocyte quality (20). Comparing fentanyl to propofol, ketamine, propofol, or isoflurane, other investigations found no discernible detrimental effects on oocyte quality or quantity (21).

Thus far, the debate above suggests two things. Firstly, there hasn't been a study that compares fentanyl and remifentanyl. The second is that there is ongoing debate on the impact of both medications on the quantity and quality of oocytes, necessitating more study. Remifentanyl did not significantly alter the quality of the embryos when compared to alfentanil/propofol, local anesthetic, or pethidine/midazolam, according to certain research (18). (22). On the other hand, additional research revealed that remifentanyl outperforms fentanyl in terms of embryo scoring (11). The effects of fentanyl and remifentanyl on the quality of embryos in women undergoing oocyte retrieval for IVF/ICSI programs have not been compared in any prior research. However, as far as is known, this study is the first to compare the effects of remifentanyl and fentanyl on embryo quality, and it has demonstrated that remifentanyl is better than fentanyl since low-quality embryos were only included in the group that received fentanyl treatment. Remifentanyl's brief duration of action and quick excretion from the systemic circulation without drug buildup may help to explain this (9).

This could result in reduced anesthetic exposure with less predictable effects on the oocyte and later the embryo. Remifentanyl's quick metabolism by tissue and plasma non-specific esterase, primarily to carboxylic acid (a non-active byproduct), accounts for its quick clearance and elimination (23). Remifentanyl was compared to propofol-alfentanil for transvaginal oocyte retrieval in a randomized clinical trial conducted by Matsota et al. in 2012, but not fentanyl. Fertilization and cleavage rates did not significantly differ between the two drugs (17). Additionally, remifentanyl has been reported to have no discernible negative effects on the rate of fertilization when compared to fentanyl, propofol, alfentanil, nitrous oxide, and local anesthetics. However, several publications have shown that women who get fentanyl have a much lower rate of fertilization than women who receive thiopental and propofol (7), (24), and (25). This study is the first to compare the effects of remifentanyl and fentanyl on oocyte retrieval, fertilization, and cleavage rates. The results strongly suggest that remifentanyl should be used instead of fentanyl, as the rate of fertilization was significantly higher in women who received remifentanyl than in those who received fentanyl.

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