European Journal of Obstetrics & Gynecology and Reproductive Biology 150 (2010) 66–71

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Effect of alfentanil dosage during oocyte retrieval on fertilization and embryo quality

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ARTICLE INFO

Article history:
Received 26 August 2009
Received in revised form 26 November 2009
Accepted 25 January 2010

Keywords:
Alfentanil
Fertilization
Good quality embryo
Oocyte retrieval
Pain relief

ABSTRACT

Objective: A possible negative effect of pain-relieving analgesics used during oocyte retrieval on fertilization and embryo development has been discussed. This study examines whether alfentanil dosage adversely affects fertilization and/or embryo quality.
Study design: In a retrospective observational study the effect of different doses of alfentanil on two primary endpoints, fertilization rate and good quality embryo (GQE) rate, were compared in 663 women.
Results: In group A ($\leq$0.5 mg alfentanil) and group B (>0.5 mg alfentanil) mean fertilization rate was 0.6 ± 0.3 versus 0.6 ± 0.2 ($P = 0.678$, adjusted $P = 0.937$, 95% CI for the difference −0.041; 0.044) and mean GQE rate was 0.6 ± 0.3 versus 0.5 ± 0.3 ($P = 0.207$, adjusted $P = 0.179$, 95% CI for the difference −0.015; 0.078), respectively. A paired comparison of 65 women who underwent repeated IVF cycles found that, compared with $\leq$0.5 mg alfentanil, doses of >0.5 mg alfentanil had no adverse effects on fertilization rate (mean difference 0.05 ± 0.3, $P = 0.231$, 95% CI −0.02; 0.12) or GQE rate (mean difference -0.02 ± 0.4, $P = 0.970$, 95% CI −0.12; 0.09).
Conclusion: The amount of alfentanil is not associated with adverse effects on fertilization rate, embryo development, or clinical pregnancy rate, which is reassuring and indicates that women can be offered adequate pain relief.

1. Introduction

Oocyte retrieval should be performed with a high degree of safety and efficacy to secure optimal surgical and reproductive outcome. Whether analgesic agents used for pain relief during oocyte retrieval during in vitro fertilization (IVF) harmfully affect fertilization and/or embryo development has been discussed [1–6]. Since some women require high doses of sedatives and analgesics to obtain adequate pain relief while others do not, various pain-relieving methods are in use and a wide variation in doses can be assumed. To date, evidence for which analgesic methods are superior to others is insufficient [5,7].

Exposure of mouse oocytes to propofol produced toxic effects on oocyte maturation and fertilization [8–10]. Human studies report conflicting results concerning adverse effects of analgesic agents on fertilization and embryo development. Early studies found that nitrous oxide, especially in combination with general anesthesia, impairs pregnancy rate [11,12]. Currently, fast-acting opiates, alone or in combination with local analgesia, are commonly used for conscious sedation during oocyte retrieval. Soussis et al. [6] compared follicular fluid and plasma concentrations of midazolam, fentanyl and alfentanil in 45 patients. Low follicular fluid concentrations of all agents were detected. No differences in fertilization rate or pregnancy rate between groups were found. In a later study, Wilhelm et al. compared general anesthesia with remifentanil in a retrospective study on 251 women and found a significantly lower pregnancy rate in the general anesthesia group, 17.9% versus 30.6% ($P < 0.05$).

Lidocaine's influence on pain relief, fertilization, and embryo development has been studied concerning application technique and dosage [1,13,14]. No negative effects on any parameter were reported.

Patient convenience and safety aspects are important issues in assisted reproduction techniques. The aim of the present study was to investigate potential adverse effects of varied doses of an analgesic drug commonly used during oocyte retrieval – alfentanil – on fertilization rate and embryo development. Further, potential adverse effects of benzodiazepine and nitrous oxide were investigated.

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doi:10.1016/j.ejogrb.2010.01.007

2. Patients and methods

2.1. Study design

This study, a retrospective, observational study, was carried out at Reproductive Medicine, Sahlgrenska University Hospital, Sweden. Data were collected from the IVF database at Reproductive Medicine and from patients' records. The Regional Ethical Review Board in Göteborg, Sweden approved the study.

2.2. Study population

Consecutive women treated with IVF or intracytoplasmic sperm injection (ICSI) between August 2005 and June 2006 were selected. Exclusion criteria were (i) women treated with oocyte donation, (ii) women with a cancer diagnosis (who stored frozen oocytes or embryos for a future embryo transfer), and (iii) women undergoing IVF due to preimplantation genetic diagnosis (PGD). All other women who underwent oocyte retrieval, where oocytes were retrieved, during this period were included.

In total, 891 oocyte retrievals occurred during the study period. Fifty cycles were excluded: 45 due to oocyte donation, of embryos in cancer patients, or PGD, 1 due to general anesthesia and 4 due to missing documentation on alfentanil dosage. The remaining 841 IVF cycles occurred in 663 women. The main analysis comprised in total 663 cycles: one cycle (the woman's first oocyte retrieval during the study period) per woman. Women were placed in one of two groups according to the alfentanil dose they received: group A $\leq$ 0.5 mg alfentanil (n = 370) or group B $>$ 0.5 mg alfentanil (n = 293). A secondary analysis comprised 65 cycles: the second IVF cycle of 65 women undergoing repeated oocyte retrieval that used a different alfentanil dose compared to the first cycle.

2.3. Ovarian stimulation

The women had undergone a stimulation protocol which included down-regulation with a gonadotropin-releasing hormone agonist (Suprecur™ Hoechst, Frankfurt, Germany) that began in the follicular *or* in the luteal phase. After down-regulation, stimulation was performed with recombinant follicle-stimulating hormone (Gonal-F™, MerckSerono, Geneva Switzerland; Puregon™, Organon, Oss, The Netherlands) or urinary-derived hormone (Menopur™, Ferring, Denmark). Monitoring was performed via vaginal ultrasound scans and serum estradiol measurements. When adequate stimulation was achieved, human chorionic gonadotrophin (hCG, Ovitrelle, MerckSerono or Pregnyl, Organon) was administered, and oocytes were retrieved with a single lumen aspiration needle (Swemed Lab International AB, Billdal, Sweden). Fertilization was performed by conventional IVF or ICSI using standard techniques. One or two embryos were transferred 2 or 3 days after oocyte retrieval. Luteal phase support (progesterone) was administered daily. A pregnancy test was done on day 19 after embryo transfer. Clinical pregnancy was defined as an ultrasound-verified pregnancy, with fetal heartbeat, 5 weeks after embryo transfer.

Table 1
Patient characteristics.

Characteristics	Alfentanil dose $\leq$0.5 mg (0.25–0.5 mg) (n = 370)	Alfentanil dose $>$0.5 mg (0.75–1.5 mg) (n = 293)	P-value
Age (years)			
Mean ± SD (min–max)	32.5 ± 3.9 (21.0–41.0)	31.7 ± 4.0 (20.0–39.0)	0.017[a]
BMI (kg/m^2)			
Mean ± SD (min–max)	24.0 ± 4.1 (17.0–38.0)	24.5 ± 4.1 (17.0–33.0)	0.077[a]
Fertilization method, n (%)			
IVF	210 (56.8)	156 (53.2)	
ICSI	148 (40.0)	124 (42.3)	
Combined IVF/ICSI	12 (3.2)	13 (4.4)	0.549[b]
Smoker, n (%)			
Yes	60 (16.3)	49 (16.8)	1.936[c]
Completed IVF cycles, n (%)			
1	269 (72.7)	196 (67.1)	
2	52 (14.1)	62 (21.2)	
3	35 (9.4)	28 (9.6)	
4	11 (3.0)	5 (1.7)	
5	3 (0.8)	1 (0.3)	0.779[b]
Previously pregnancies			
Mean ± SD	0.6 ± 1.1	0.6 ± 1.1	0.464[a]
Previously miscarriages			
Mean ± SD	0.3 ± 0.8	0.3 ± 0.7	0.118[a]
Previously deliveries, n (%)			
0	334 (90.5)	271 (92.5)	
1	27 (7.3)	14 (4.8)	
2	6 (1.6)	6 (2.0)	
3	2 (0.5)	2 (0.7)	0.698[b]
Reason for infertility, n (%)			
Tubal factor	44 (11.9)	46 (15.7)	
Endometriosis	31 (8.4)	11 (3.8)	
Hormonal factor	42 (11.4)	36 (12.3)	
Male factor	149 (40.3)	123 (42.0)	
Unexplained	104 (28.0)	77 (26.3)	0.077[b]

IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection; BMI = body mass index.
[a] Mann–Whitney U-test.
[b] Mantel–Haenszel chi-square test.
[c] Fisher's exact test.