The effect of ketorolac on pregnancy rates when used immediately after oocyte retrieval

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Objective: To study the effect of ketorolac, a potent anti-inflammatory medication, on in vitro fertilization (IVF) pregnancy outcomes when used at the time of oocyte retrieval.
Design: Retrospective review of 454 patients from 2003–2009.
Setting: Tertiary hospital-affiliated fertility center.
Patient(s): Consecutive subfertile women undergoing their first IVF cycle.
Intervention(s): Ketorolac administration immediately after oocyte retrieval.
Main Outcome Measure(s): Pregnancy, implantation, live-birth, and miscarriage rates, and postsurgical visual analog pain score.
Result(s): Of the 454 patients undergoing their first IVF cycle for all indications, 103 received intravenous ketorolac immediately after oocyte retrieval, based on anesthesiologist preference. Patient and procedural characteristics were similar between both groups. The use of ketorolac had no effect on the rates of implantation, miscarriage, pregnancy, live birth, or multiple pregnancy. The patients receiving ketorolac experienced statistically significantly less pain.
Conclusion(s): This study suggests ketorolac has no apparent detrimental effect on IVF pregnancy outcomes when administered immediately after oocyte retrieval. Ketorolac appears to be a safe and effective analgesic to use at the time of oocyte retrieval. (Fertil Steril® 2013;100:725–8. ©2013 by American Society for Reproductive Medicine.)
Key Words: Implantation, in vitro fertilization, ketorolac, nonsteroidal anti-inflammatory agents

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Ketorolac tromethamine is a potent nonsteroidal anti-inflammatory drug (NSAID) that is often used to control postoperative pain. However, some fertility specialists avoid administering this medication immediately after oocyte retrieval because of theoretical concerns that NSAIDs may negatively impact embryo implantation due to their cyclooxygenase (COX) inhibitory effects. This concern for administration of NSAIDs is appropriate, as 20 years of literature support the hypothesis that prostaglandins and the COX system play a crucial role in decidualization and implantation (1–10). We investigated whether the use of ketorolac, a potent COX-1 and COX-2 inhibitor, negatively impacts IVF implantation and pregnancy rates when it is given to alleviate pain immediately after oocyte retrieval.

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MATERIALS AND METHODS

All patients undergoing their first IVF cycle who met inclusion criteria between January 1, 2003, and July 1, 2009 (454 patients), at a single-site fertility center in North Carolina comprised the study cohort for this retrospective review. The protocol was approved by the Carolinas HealthCare System institutional review board. Inclusion criteria limited the study population to women younger than 40 years of age who were undergoing their first cycle of oocyte retrieval with subsequent in vitro fertilization–intracytoplasmic sperm injection (IVF-ICSI) during our time frame, regardless of infertility diagnosis.

Before an IVF cycle was initiated, the patients were medically optimized.

The hemoglobin level was checked on all patients, and any anemia was corrected before moving forward with the fertility treatment. In brief, we used standard gonadotropin-releasing hormone (GnRH) agonist (leuprolide acetate), GnRH antagonist (ganirelix acetate), and "flare" down-regulation (leuprolide acetate) protocols in all patients. Gonadotropin stimulation was achieved with commercially available gonadotropins with either purified or recombinant follicle-stimulating hormone (FSH) or human menopausal gonadotropin (hMG). We administered 250–500 μg of recombinant human chorionic gonadotropin (hCG; Ovidrel) or 5,000 to 10,000 IU of hCG when two follicles of 18 mm or greater were identified with transvaginal ultrasound monitoring. Approximately 36 hours after hCG administration, patients underwent oocyte retrieval with propofol sedation.

Hospital, clinic, and anesthesia documentation was reviewed to determine patient demographics, cycle information, retrieval data, and IVF outcome data in a retrospective manner. The use of 30 mg of intravenous ketorolac tromethamine immediately after oocyte retrieval was anesthesiologist dependent and was recorded in the anesthesia record. Once the patient left the operating room, the administration of ketorolac or other NSAIDs by the nursing staff was prohibited. In addition, patients were given verbal and written instructions to avoid all NSAIDs during fertility treatments before they were discharged from the postoperative care unit. During the postoperative period, a visual analog scale from 0–10 was used to determine the level of postoperative pain at the first nursing assessment.

Descriptive statistics including means and standard deviations or counts and percentages were calculated. For data measured on the interval scale, a Student's *t* test was used. If the data were ordinal or not normally distributed, the Wilcoxon rank sum test was employed. For nominal data we employed a chi-square analysis. SAS version 9.2 was used for all analyses. A two-tailed $P<.05$ was considered statistically significant.

RESULTS

For this retrospective study, 454 met the inclusion criteria. The patient demographics were similar between all groups. The average age of the cohort was 33.2 ± 3.65 years. The average body mass index (BMI) in the cohort was 25.3 ± 5.91. The majority (n = 393, 86.6%) of patients used a leuprolide down-regulation protocol, 38 (8.4%) patients used a GnRH antagonist protocol, and 21(4.6%) patients used a flare protocol (Table 1). Of these patients, 241 (53.1%) achieved pregnancy.

TABLE 1

Demographics and cycle characteristics for patients who did or did not receive ketorolac.

Characteristic	Ketorolac (n = 103)	No ketorolac (n = 351)	*P* value
Age	33.0 ± 3.2	33.2 ± 3.8	.69
BMI	25.8 ± 6.1	25.1 ± 5.8	.31
Embryo transferred	2.3 ± 0.65	2.2 ± 0.65	.66
Operating time	58.6 ± 16.2	61.5 ± 17.0	.08
Stimulation protocol[a]			.04
Agonist	93 (90.3)	302 (86.0)	
Antagonist	10 (9.7)	28 (8.0)	
Flare	0 (0)	21 (6.0)	

Note: Values are mean (standard deviation) unless otherwise indicated.
[a] Value is given as number (percentage).

Mesen. Ketorolac and IVF outcome. Fertil Steril 2013.

Of the 454 women in our sample, at the time of oocyte retrieval, 103 (22.7%) received intravenous ketorolac, and 351 (77.3%) did not. When comparing these patients, we found no differences in age, procedure time, BMI, number of oocytes retrieved, fertilization rate, or the number of embryos transferred (see Table 1). No patient experienced excessive bleeding during or after the egg retrieval. There was a difference between the two groups in the type of stimulation protocol used ($P=.04$), but on secondary analysis the stimulation type did not affect the pregnancy outcome (data not shown).

The use of ketorolac had no effect on pregnancy outcomes. The pregnancy rate in women who received ketorolac (54.4%) compared with those not receiving the medication (52.7%) was not statistically significant ($P=.77$), nor was the live-birth rate (48.5% vs. 46.7%, respectively; $P=.77$). The implantation rate was also similar between the two groups (30.1% vs. 30.2%, respectively; $P=.83$). There was no statistically significant difference in miscarriage rate, defined as the loss of pregnancy after established fetal heart rate on transvaginal ultrasound (10.7% vs. 11.4%, respectively; $P=.89$). There was no statistically significant difference in the number of twins or triplets between the two groups (40.0% vs. 39.6%, respectively; $P=.96$) (Table 2).

Visual analog pain scores were available for 419 of the 454 patients. The patients who received ketorolac (103) experienced less pain with a median pain score of 2, and those

TABLE 2

In vitro fertilization outcomes for patients who did or did not receive ketorolac.

Outcome	Ketorolac (n = 103)	No ketorolac (n = 351)	*P* value	Odds ratio (95% confidence interval)
Pregnancy rate	56/103 (54.4%)	185/351 (52.7%)	.77	1.1 (0.69–1.70)
Live-birth rate	50/103 (48.5%)	164/351 (46.7%)	.74	1.2 (0.78–1.90)
Implantation rate	72/233 (30.1%)	236/782 (30.2%)	.83	1.0 (0.82–1.28)
Miscarriage rate	6/56 (10.7%)	21/185 (11.4%)	.89	0.94 (0.36–2.50)
Multiple pregnancy rate	20/50 (40.0%)	65/164 (39.6%)	.96	0.99 (0.52–1.90)

Note: Pregnancy rate is defined as a positive serum β-hCG concentration.

Mesen. Ketorolac and IVF outcome. Fertil Steril 2013.