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.

who did not receive the medication (316) had a median pain score of 5 (P=.005) (Fig. 1).

Those patients who achieved pregnancy, regardless of the treatments they received, were younger (32.6 ± 3.7 vs. 33.8 ± 3.5, P=.0007). The BMI and stimulation protocol had no effect on the pregnancy outcome data.

DISCUSSION

Despite theoretical concerns, our study suggests that ketorolac does not negatively impact implantation rates or pregnancy rates when used at the time of oocyte retrieval. In addition, the use of ketorolac improved pain scores in the postoperative period after oocyte retrieval.

Postoperative pain control is an important aspect of patient care that can be overshadowed during an IVF cycle in the attempt to achieve the patient's primary goal of pregnancy. Ketorolac and other NSAIDs have proven benefit at the time of gynecologic surgery (11, 12) but have been avoided after oocyte retrieval (13). In a study of British fertility centers, 57% of those surveyed avoided NSAID use after oocyte retrieval, and only one center used the NSAID ketorolac (14). Limited data are available on the actual use of ketorolac, or NSAIDs as a broader group, after oocyte retrieval.

Prostaglandin synthesis, a key component to implantation, is a product of arachidonic acid (AA) and is mediated by the rate limiting cyclooxygenase enzymes COX-1 and COX-2 (1). Both COX-1 and COX-2 convert the AA to prostaglandin H2 (PGH2), which can then be converted into a wide range of other prostaglandins. Although COX-1 and COX-2 are isoforms that share similar structural and kinetic properties, they are encoded by separate genes, and each has separate cell-specific properties. COX-1, a constitutive enzyme found in the cell membrane, functions primarily in cellular "housekeeping" roles; COX-2, an inducible enzyme found in the nuclear envelope, is primarily responsible for the increase of prostaglandins during the inflammatory response (2, 3). This separation of function is illustrated during decidualization and implantation. In response to peaks in midcycle estradiol and progesterone concentrations, COX-1 production decreases, but there is a local increase of COX-2, which is thought to be driven by an inflammatory reaction surrounding the blastocyst. Unlike COX-1, the increase in COX-2 is not affected by steroid hormones (4).

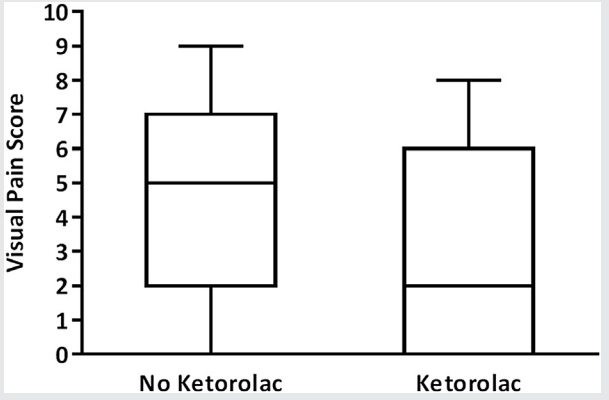
The prostaglandin-rich environment, most specifically prostaglandin E2 and I2, surrounding the blastocyst at the site of implantation plays an important role in the implantation process. A release of prostaglandins from the blastocyst in both animal models and humans has been reported (5). An interruption of implantation can be induced in the animal model if indomethacin, a NSAID, is administered (6–8). Furthermore, it has been shown that an infusion of prostaglandins can induce decidualization of the endometrium in rats (9). In a knockout model, mice deficient in COX-2 have multiple reproductive impairments, including errors in decidualization of the endometrium (10).

Ketorolac inhibits COX-1 and COX-2 and thus there is concern that the medication could prevent the cascade of cytokines important to implantation. As described by Chakraborty et al. (2) and Das et al. (3), the expression of the two COX enzymes is both cycle dependent and influenced by the presence or absence of the blastocyst. Although Lim et al. (10, 15) have shown that COX-2 is essential for implantation, and others have illustrated that inhibition of the COX system in the animal model with NSAIDs leads to failed decidualization and implantation (6, 16, 17), a single dose of ketorolac at the time of oocyte retrieval does not seem to negatively affect implantation.

A possible explanation for the discrepancy between the effects of ketorolac on implantation seen in laboratory studies and the results of this analysis of IVF cycles at our institution can be found in the timing of administration of ketorolac and its pharmacokinetic properties. The half-life of ketorolac is 4 to 7 hours, and 98% is excreted in the first 24 hours after administration (18). During the window of implantation, approximately 6 to 8 days after the oocyte retrieval, there is no longer biologically active ketorolac available to alter the inflammatory response thought to be necessary for implantation. Fortunately, the COX system does not appear to play an important role in the late proliferative phase at the time of oocyte aspiration (2).

The findings of our study are consistent with the findings of Kailasam et al. (19), who studied the impact of diclofenac sodium, a NSAID suppository, during assisted reproduction in a randomized double-blind study. In that study, 381 patients were randomized to receive either diclofenac sodium or placebo immediately after oocyte retrieval; no difference in implantation or pregnancy rates was seen (diclofenac sodium: 25.3% and 38.9%, respectively, vs. placebo: 21.6% and 32.6%, respectively). The patients who received diclofenac sodium also had statistically significantly lower pain scores (19). A second, smaller study of diclofenac sodium suppositories also showed a reduction in visual pain scores when used after oocyte retrieval (20).

FIGURE 1



Box and whisker plot comparing the effect of IV ketorolac on patient comfort when used immediately after oocyte retrieval. (*Bars* represent the median, *boxes* extend from the 25th to 75th percentiles, and *whiskers* represent the 10th and 90th percentiles.) Differences between the two groups were calculated using a Mann-Whitney test (P=.005).

Mesen. Ketorolac and IVF outcome. Fertil Steril 2013.

Our study is limited by its retrospective design and the size of the cohort studied. It is conceivable, although unlikely given the current data, that a small, statically significant, but not biologically important difference could be detected with a larger number of subjects. In addition, there were no instances of treatment with the "flare" protocol in patients who received ketorolac, so we cannot rule out the possibility of a negative effect of ketorolac in patients receiving that treatment.

This is the first study to date investigating the impact of ketorolac on pregnancy rates when used at the time of follicular aspiration in an IVF cycle. The results of this study and a review of the literature suggest that the theoretical concerns surrounding the use of ketorolac at the time of follicular aspiration are unfounded. These results support the use of ketorolac for patient pain alleviation without concern for adversely affecting implantation or pregnancy rates.

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