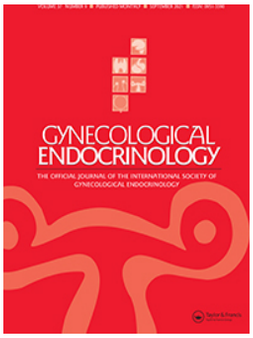

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SYSTEMATIC REVIEW
ASSISTED REPRODUCTION

Effect of piroxicam administration in infertile women undergoing assisted reproductive technologies: A systematic review and meta-analysis

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ABSTRACT

Objective: To evaluate piroxicam effect on different pregnancy outcomes among infertile women undergoing assisted reproductive technologies (ART).

Methods: We searched for the available randomized clinical trials (RCTs) in four different databases during January 2021 that compared piroxicam (intervention group) to placebo/no treatment (control group) in infertile women performing ART. We extracted the available data from included studies and pooled them in a meta-analysis model using RevMan software. We pooled the dichotomous data as risk ratios (RR) with the corresponding 95% confidence intervals (CI) using RevMan software. Our outcomes were rates of clinical pregnancy, ongoing pregnancy, miscarriage, and any adverse events.

Results: Seven RCTs met our inclusion criteria with a total number of 1226 patients. Piroxicam was linked to a significant increase in clinical pregnancy rate compared to control group (RR = 1.30, 95% CI [1.09, 1.55], $p = .003$). However, we did not report any significant difference between both groups in ongoing pregnancy rate (RR = 1.27, 95% CI [0.72, 2.24], $p = .41$). In addition, the rates of miscarriage and adverse events were not different among both groups.

Conclusions: Piroxicam administration increases the clinical pregnancy rate among infertile women. However, piroxicam does not affect miscarriage and ongoing pregnancy rates.

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KEYWORDS
Piroxicam; pregnancy; assisted reproductive technologies; ART

Introduction

Infertility is failure of conception after unprotected regular sexual intercourse for one year [1]. It seems to affect one out of six couples in their reproductive lives [2,3]. The assisted reproductive technologies (ART) have gained a great reputation in recent years due to their increased request among infertile or subfertile couples and the great progress in reproductive sciences [4,5].

Different ART procedures sometimes cause pain as a result of the inflammatory reaction producing excess inflammatory cytokines. This inflammatory reaction may cause excess uterine contractions and decline in uterine receptivity [6]. Uterine contractility is considered an important prognostic factor in predicting the endometrial receptivity and ART success [7]. Moreover, extra-uterine particles (bacteria, detritus, and cervical mucus) introduction during procedure in addition to exogenous manipulation may be also responsible for a pro inflammatory status resulting in ART failure [8].

Prostaglandins play a crucial role in excess uterine contractions induction during ART procedures, thus, nonsteroidal anti-inflammatory drugs (NSAIDs) administration during ART performance may result in decline in uterine contractility and improvement in procedure success [9]. Piroxicam is considered one of the most common NSAIDs used by the studies in order to assess the benefits of NSAIDs in ART.

The published trials have shown a great controversy during their assessment of piroxicam in improving the pregnancy rates. A recent study has concluded no benefits from piroxicam administration before frozen embryo transfer (ET) in improving pregnancy rates [10]. In contrary, another study found a great improvement in implantation and pregnancy rates with piroxicam utilization in frozen and fresh ET cycles [11].

Thus, we aimed to conduct a meta-analysis for evaluation of the effect of piroxicam on different pregnancy outcomes among infertile women undergoing to perform ART.

Materials and methods

We performed this systematic review and meta-analysis following the Cochrane Handbook for Systematic Reviews of Interventions [12]. We followed the PRISMA (Preferred Reporting Items for Systematic reviews and meta-analysis) statement guidelines during review preparation [13].

Literature search

We searched for the available clinical trials in Cochrane Library, PubMed, ISI web of science, and Scopus using the following search strategy; (Piroxicam OR Non-steroidal anti-inflammatory

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drugs) AND (IVF OR *In vitro* fertilization OR ICSI OR Intracytoplasmic sperm injection OR Embryo transfer OR ART OR Assisted reproduction techniques OR IUI OR Intrauterine Insemination) during January 2021. Two authors performed the search strategy without any restrictions by publication year or language.

Eligibility criteria

We included the studies according to the following inclusion criteria: (I) Population: Infertile women undergoing ART; (ii) Intervention: Piroxicam; (iii) Comparator: placebo or no treatment; (IV) Study outcomes: Clinical pregnancy, ongoing pregnancy, miscarriage rates, and any reported adverse events; and (V) Study design: RCTs. Screening was conducted in a two stepwise manner (title and abstract screening then full-text screening) by two authors. Differences were discussed, and a consensus was reached after discussion. We excluded studies for the following reasons: (1) non-randomized studies, (2) irrelevant studies, and (3) review articles.

Data extraction

We extracted the available data from included studies on an Excel sheet. The following data were collected: list of authors, sample size, year of publication, and summary of the included studies. Also, we extracted our main outcomes for analysis. Our outcomes were clinical pregnancy, ongoing pregnancy, miscarriage rates, and any reported adverse events. Reevaluation of women with positive pregnancy beta-human chorionic gonadotropin (β-HCG) test (more than 25 mIU/mL) was done by the included studies at sixth week using ultrasonography in order to confirm clinical pregnancy when fetal heart beat was reported. Continuation of pregnancy more than 20 weeks of gestation is called ongoing pregnancy. Moreover, spontaneous fetal loss before 20 weeks of gestation is called miscarriage.

Risk of bias assessment

Two authors evaluated the included studies quality and risk of bias using the Cochrane risk of bias assessment tool [14]. The Cochrane risk of bias assessment tool includes the following domains: random sequence generation, allocation concealment, performance bias (blinding of participant and personnel), detection bias (blinding of outcome assessment), attrition bias, reporting bias, and other sources of bias. The authors' judgment is categorized as 'Low risk,' 'High risk,' and 'Unclear risk' of bias.

Data synthesis

The data analysis was completed independently by two authors, then the results were compared, and any difference was solved by discussion. We pooled dichotomous data as risk ratio (RR) with the corresponding 95% confidence intervals using the Mantel-Haenszel. All statistical analyses were performed using the Revman software. When no heterogeneity was observed among the studies, we used fixed-effect model. The random-effect model was used when heterogeneity was found among the studies.

The statistical heterogeneity was assessed between studies by using I-squared (I^2) statistics and values of $\geq$ 50% indicated a substantial heterogeneity [15]. The substantual heterogeneity if reported was solved by sensitivity analysis where we excluded one study at a time and evaluated its impact on the summary results and between-study heterogeneity.

Publication bias

Publication bias assessment using funnel plot method and Egger's test was unreliable for fewer than ten included studies according to Egger and colleagues. Therefore, we could not assess for the publication bias due to our inclusion of only 7 randomized studies [16,17].

Results

Results of the literature search

After searching in different databases, we found 353 studies. After title and abstract screening, 23 articles were reliable for entering the full-text screening. Then, we excluded 16 articles, and finally, seven studies met our inclusion criteria in our meta-analysis. The PRISMA flow diagram of study selection is shown in Figure 1.

Characteristics of included studies

Seven RCTs [10,11,18–22] met our inclusion criteria with a total number of 1226 patients in which 613 were in piroxicam group and 613 were in control group. Four studies performed IVF with fresh embryo transfer [18,19,21,22]. One study reported their findings on IVF with frozen embryo transfer only [10]. One study used IVF with fresh and frozen embryo transfer in their trial [11]. One study assessed piroxicam effectiveness among women undergoing intrauterine insemination (IUI) [20]. The included studies used either GnRH agonist or antagonist protocol for controlled ovarian stimulation. The summary of the included studies including the main findings is shown in Table 1.

Risk of bias assessment

The quality of included RCTs was done based on the Cochrane risk of bias assessment tool. The summary of the risk of bias assessment of RCTs is shown in Figure 2.

Outcomes

Clinical pregnancy rate

Piroxicam was linked to a significant increase in clinical pregnancy rate compared to control group (RR = 1.30, 95% CI [1.09, 1.55], $p = .003$) as shown in Figure 3. The pooled studies did not show a substantial heterogeneity ($p = .08$, $I^2 = 47\%$).

Ongoing pregnancy rate

There was no significant difference between both groups in ongoing pregnancy rate (RR = 1.27, 95% CI [0.72, 2.24], $p = .41$) as shown in Figure 4. The pooled studies were heterogeneous ($p = .04$, $I^2 = 68\%$). We reduced the reported heterogeneity by removing one study [21] ($p = .68$, $I^2 = 0\%$) showing no difference in ongoing pregnancy rate among both groups (RR = 0.96, 95% CI [0.69, 1.33], $p = .79$).

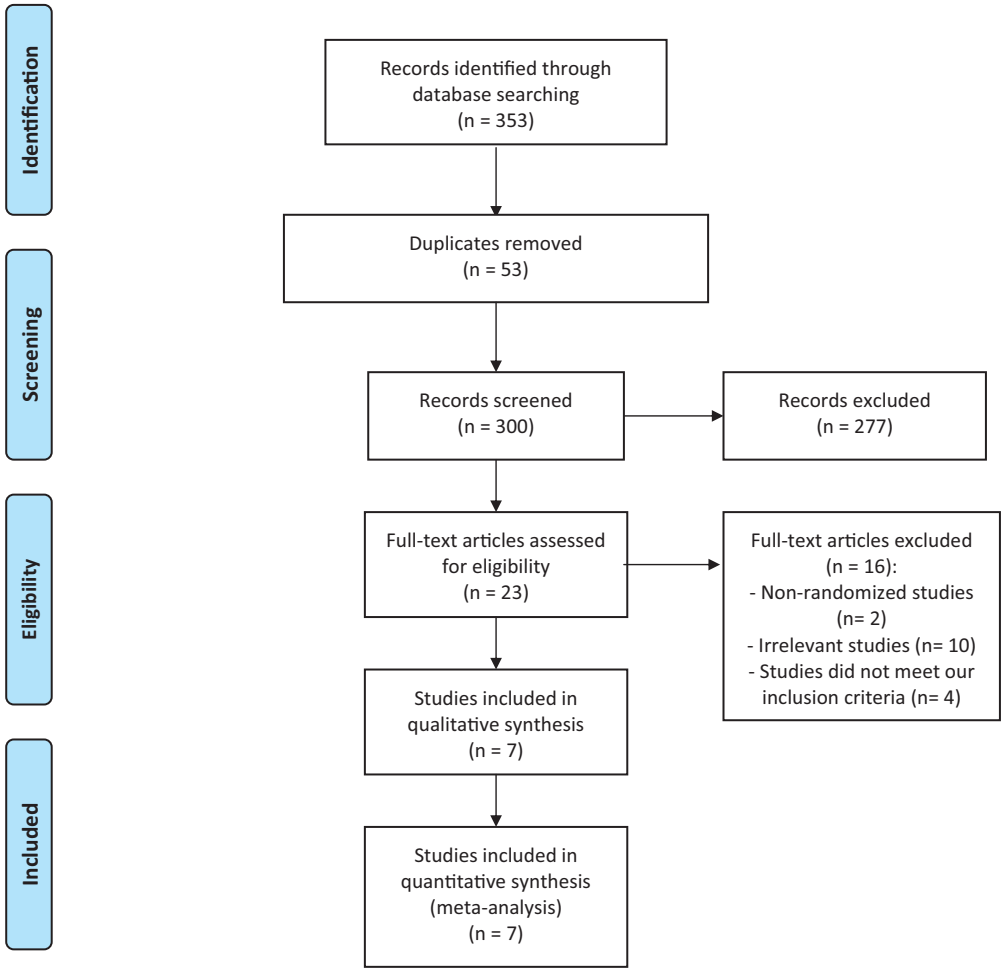

Figure 1. PRISMA flow diagram.

Miscarriage rate

There was no significant difference between both groups in miscarriage rate (RR = 0.80, 95% CI [0.49, 1.31], $p = .38$) as shown in Figure 5. The pooled studies were homogeneous ($p = .19$, $I^2 = 34\%$).

Adverse events

There were no significant differences between both groups in adverse events (RR = 0.90, 95% CI [0.37, 2.17], $p = .81$) as shown in Figure 6. The pooled studies were homogeneous ($p = .27$, $I^2 = 24\%$). One study reported one ectopic pregnancy in piroxicam group versus two in control group [18]. Two studies reported multiple pregnancies in their trials [19,20]. One study reported four patients suffering from abdominal cramps among control group with no cases reported in piroxicam group [22].

Discussion

In this meta-analysis, we found a significant improvement in clinical pregnancy rate with piroxicam administration. Rates of ongoing pregnancy, miscarriage, and adverse events were not significantly different among piroxicam and control groups.

Many studies have examined piroxicam effectiveness in improving pregnancy rate among infertile women undergoing ART and found conflicting results. Moon et al. [11] found piroxicam was linked to a significant increase in implantation and pregnancy rates in both frozen and fresh ET cycles. Moreover, Firouzabadi et al. [19] performed a randomized study in which they randomly allocated 180 fresh IVF-ET cycles into piroxicam and control groups for pregnancy rate assessment. They found a significant improvement in implantation and clinical pregnancy rates with piroxicam administration one to two hours prior to the procedure [19]. In addition, they reported a significant decline in miscarriage rate with piroxicam administration with no difference in adverse events between intervention and control groups [19].

Zarei et al. [10] included 178 patients in their randomized double blinded trial for assessment of piroxicam benefit in pregnancy rate among infertile women undergoing IVF and frozen ET cycles. They reported single dose of piroxicam administration one to two hours prior to the procedure had no benefits in clinical and biochemical pregnancy rates with no reported adverse events. Furthermore, Kumbasar et al. [21] reported no significant differences in clinical pregnancy, ongoing pregnancy, and miscarriage rates between piroxicam and control groups. Another study found more increase in clinical pregnancy rate among piroxicam group with no effect on ongoing pregnancy and miscarriage rates among infertile women undergoing artificial insemination [20]. Sohrabvand et al. [22] did not find any difference between piroxicam and control groups regarding clinical pregnancy rate with more increase in adverse events reported among control group.

Table 1. Summary of the included studies.

Study ID	Study arms	Sample size	Country	Maternal age (years)	Infertility duration (years)	Endometrial thickness	No. of retrieved oocytes	No. of transferred embryos	Main findings
Zarei et al. 2021	Piroxicam group	89	Iran	33.20 ± 5.43	7.26 ± 4.89	8.40 ± 1.17	NA	2.52 ± 0.82	Piroxicam administration before ET has no beneficial effects on pregnancy rate among women undergoing IVF and frozen–thawed ET.
	Control group	89		32.09 ± 4.50	6.97 ± 4.26	8.18 ± 0.86	NA	2.42 ± 0.70	
Zarei et al. 2016	Piroxicam group	130	Iran	28.8 ± 4.7	NA	NA	NA	NA	Administration of piroxicam is associated with increased pregnancy rate and pregnancy rate per cycle in IUI cycles. However, piroxicam does not have any effect on abortion, multiple pregnancy and ongoing pregnancy rates.
	Control group	130		28.9 ± 5.3	NA	NA	NA	NA	
Sohrabvand et al. 2014	Piroxicam group	25	Iran	28.65 ± 4.32	6.70 ± 3.94	NA	NA	NA	Piroxicam administration 30 minutes prior to embryo transfer cannot increase pregnancy rates, but can prevent or reduce uterine cramps after the procedure.
	Control group	25		27.68 ± 4.58	6.18 ± 3.37	NA	NA	NA	
Moon et al. 2004	Piroxicam group	94	Korea	33.2 ± 4.7	NA	NA	10.9 ± 6.2	4.0 ± 2.1	Piroxicam increases IR and PR after IVF–ET in both fresh and frozen–thawed ET cycles.
	Control group	94		32.7 ± 4.3	NA	NA	11.3 ± 6.4	4.0 ± 2.0	
Kumbasar et al. 2017	Piroxicam group	85	Turkey	32.04 ± 5.43	7.8 ± 4.4	10.8 ± 1.6	9.16 ± 5.20	3.082 ± 1.27	Piroxicam before ET has no additional effect on pregnancy outcome in patients undergoing in vitro fertilization.
	Control group	85		31.67 ± 5.68	7.2 ± 3.9	10.3 ± 1.5	10.53 ± 5.68	3 ± 1.21	
Firouzabadi et al. 2007	Piroxicam group	90	Iran	28.5 ± 4.8	NA	NA	NA	NA	Treatment with piroxicam before ET could prepare a suitable uterus for embryo implantation.
	Control group	90		28.7 ± 5.1	NA	NA	NA	NA	
Dal Prato et al. 2009	Piroxicam group	100	Italy	35.7 ± 3.7	3.1 ± 2.3	NA	13.4 ± 6.1	2.5 ± 0.6	Piroxicam before embryo transfer has no additional effect on pregnancy outcome after IVF and ICSI.
	Control group	100		35.8 ± 3.4	2.7 ± 1.8	NA	12.7 ± 5.1	2.6 ± 0.6	

NA: Not available.

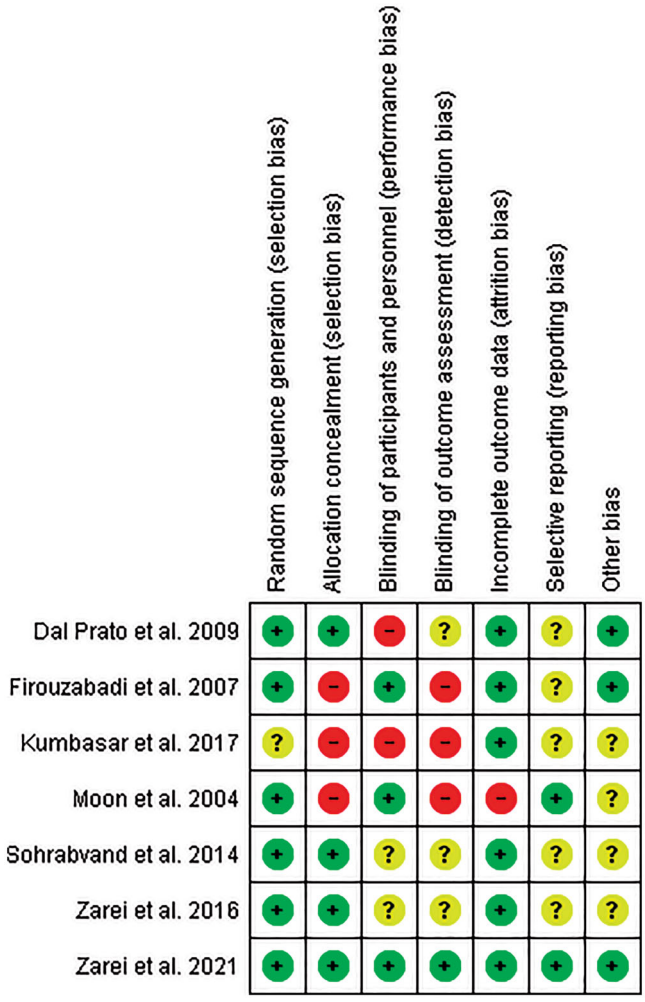

Figure 2. Risk of bias summary.

A recent Cochrane review was conducted to evaluate the benefits of different NSAIDs among women undergoing ART [23]. They concluded an uncertainty about the effect of different NSAIDs in women suffering from infertility undergoing to perform assisted reproduction in different pregnancy outcomes [23]. They found no effect from different NSAIDs administration in improving clinical pregnancy rates when compared to control group (RR = 1.23, 95% CI [1.00–1.52]) [23]. Moreover, they reported no benefit from piroxicam administration in improving ongoing pregnancy rates and reducing rates of miscarriage [23].

Piroxicam which is from the family of NSAIDs is considered an oxicam derivative with analgesic, antipyrertic, and anti-inflammatory properties. Its main effect is through inhibition of prostaglandin synthesis like other NSAIDs. It is absorbed orally and reaches its peak plasma concentration within three to five hours after oral intake [24]. Furthermore, it has long elimination half-life causing stable plasma concentrations during the day if used as a single daily dose. Based on the classification of the food and drug administration (FDA), most of NSAIDs including piroxicam are graded as a C category drugs during pregnancy and their administration did not increase the hazard of low birth weight, preterm labor congenital anomalies, and different complications [25].

Our inclusion of RCTs with adequate sample size (1226 patients), the comprehensive eligibility criteria and search methodology, and the strict adherence to the steps reported in the Cochrane handbook of systematic review for interventions are the main strengths of our systematic review and meta-analysis.

Our study limitations include; non-blinding of some of the included trials, different demographic characteristics among the studies, differences in drug doses and time of their administration among the included studies, and the limited number of the studies that met our inclusion criteria.

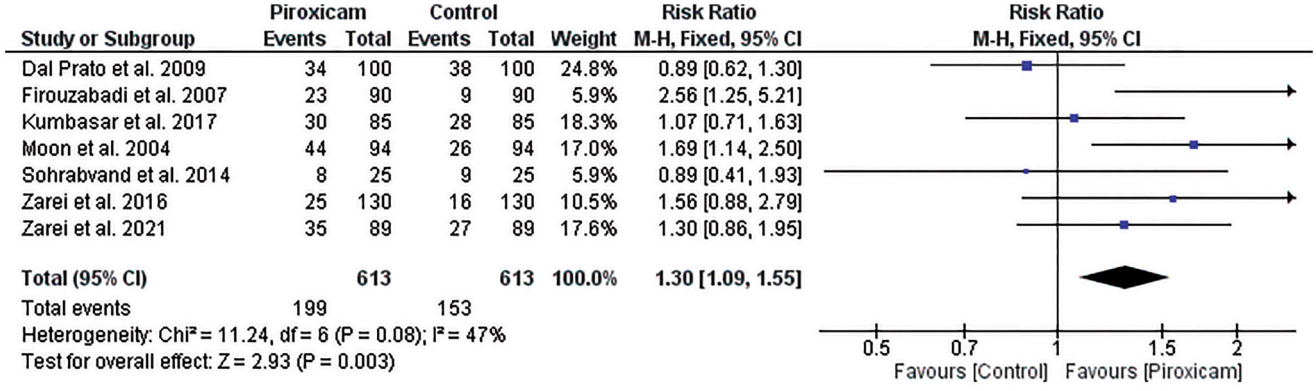

Figure 3. Clinical pregnancy rate.

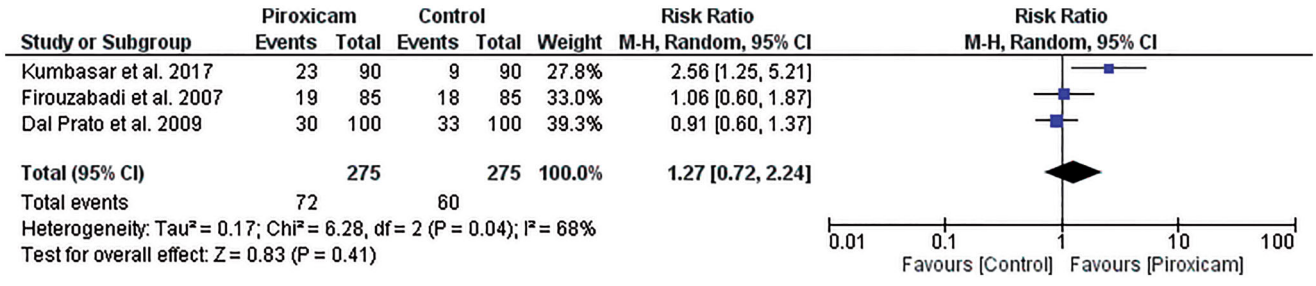

Figure 4. Ongoing pregnancy rate.

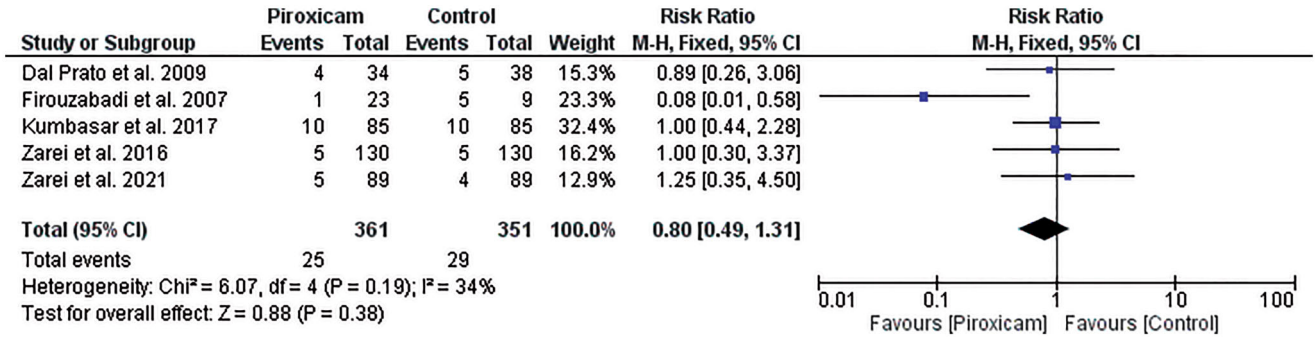

Figure 5. Miscarriage rate.

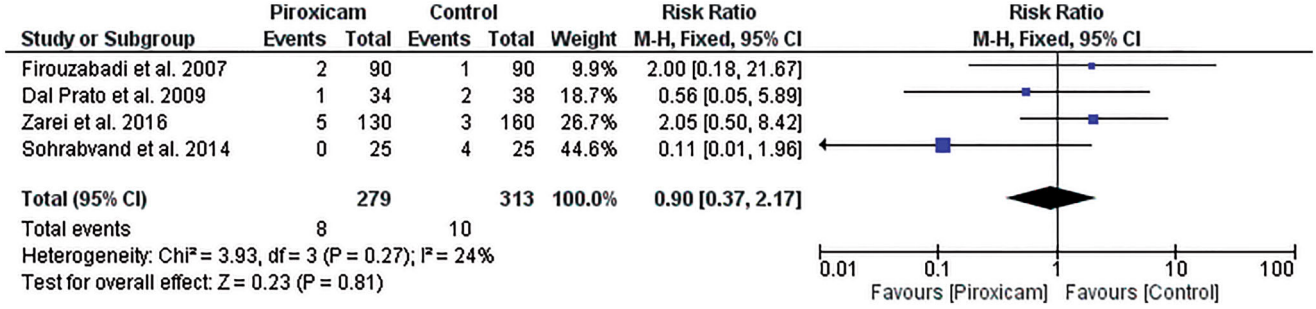

Figure 6. Adverse events.

Further multicenter RCTs with a larger sample size and longer follow-up until live birth are required to confirm our findings. The future trials should be performed on the frozen ET cycles as they become the desired choice among infertile patients undergoing ART. The rates of ongoing pregnancy, live birth, and miscarriage should be the primary outcomes of the future studies with reporting of any side effects. More accurate confirmation of the blinding, allocation concealment, and randomization in the future trials in methods section is preferable in order to eliminate any risk of bias.

Conclusion

Piroxicam administration increases the clinical pregnancy rate among infertile women undergoing ART. However, piroxicam does not affect miscarriage and ongoing pregnancy rates.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Sources of financial support for the research

None.

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