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Meta - analysis

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Vaginal misoprostol (Prostin®) for intrauterine insemination: A meta - analysis of randomized trials

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Abstract

Introduction: The seminal fluid contains prostaglandins which seem to be important during the fertilization process. However, these are cleaved during semen preparation for intrauterine insemination (IUI). The purpose of the present meta - analysis is to investigate if vaginal application of prostaglandin E (PGE) improves the pregnancy rates among women undergoing IUI.

Materials and methods: We systematically searched Pubmed (1966 - 2015), Scopus (2004 - 2015), ClinicalTrials.gov (2008 - 2015), Cochrane Central Register (CENTRAL) and Google Scholar (2004 - 2015) for published randomized controlled trials (RCTs). Statistical meta-analysis was performed using the RevMan 5.1 software.

Results: Six RCTs were included in the present meta-analysis which enrolled 1,403 women. PGE placement in the posterior vaginal fornix immediately after the IUI did not improve the pregnancy rates per cycle (1,734 cycles, OR= 1.16, 95% CI: 0.80 - 1.67). The most frequent adverse effects were abdominal cramping and vaginal spotting.

Conclusion: Routine use of PGE is not justified among women undergoing IUI because it does not seem to improve the pregnancy rates and it is associated with adverse effects. However, further studies are needed in the field because our meta-analysis is restricted by the low number of included RCTs.

Keywords: intrauterine insemination; prostaglandin E; misoprostol; sperm; infertility

Assisted reproductive technology has become the standard of care for infertile couples during the last 2 decades. Intrauterine insemination (IUI) is the first technique doctors recommend to treat couples with mild male infertility (oligospermia, asthenospermia) and cervical factor infertility. In a recent study Goldman et al reported that the live births after IUI ranged between 8.8 and 11.8%[1]. Several factors seem to influence the success of IUI including age, the duration of infertility, the presence of endometriosis, the endometrial thickness, the luteal phase progesterone, the sperm preparation time and others[2-4].

Prostaglandins (PGs) seem to be important dur-

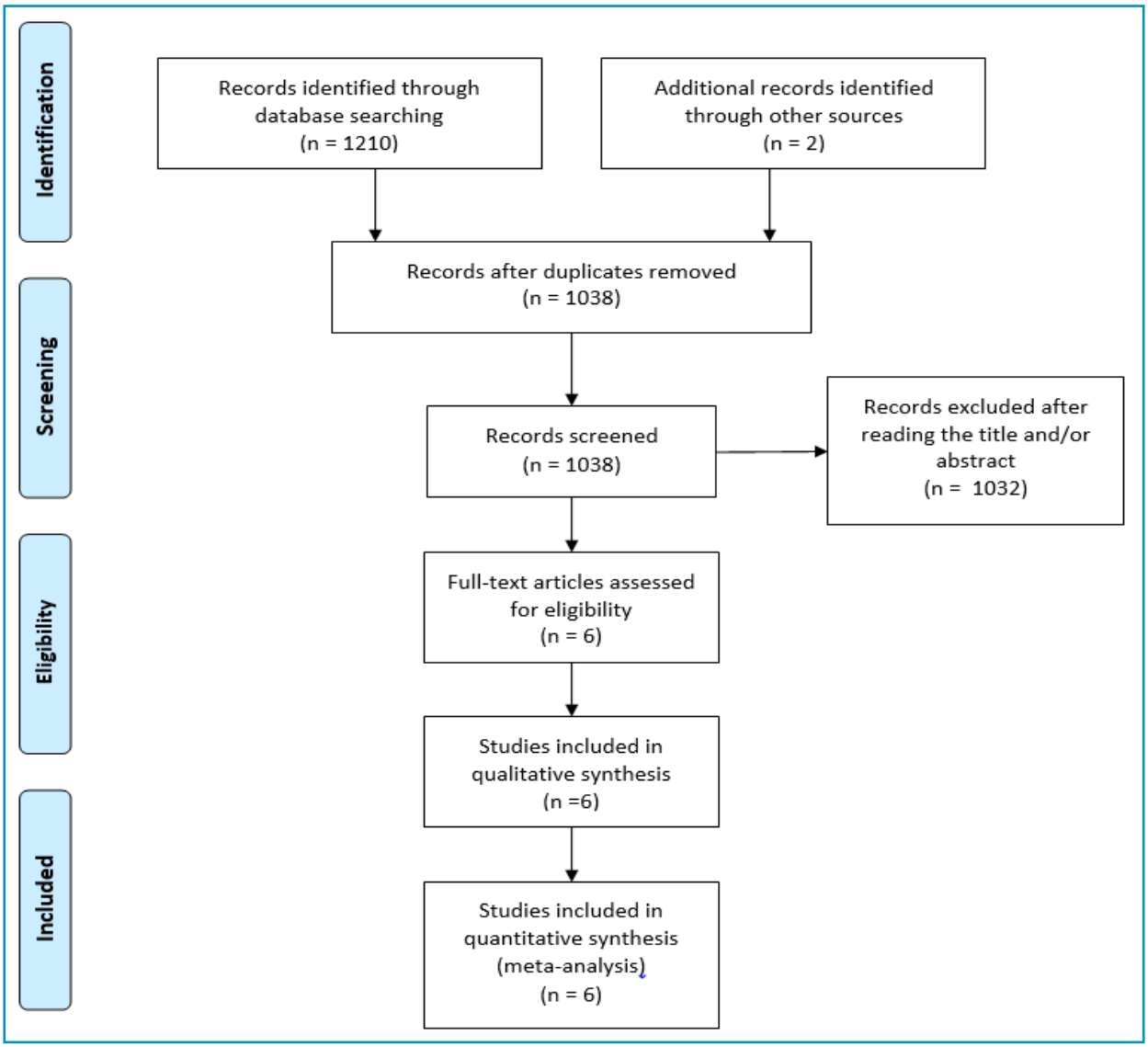

Figure 1. Search flow diagram

ing the fertilization process because they improve the endometrial receptivity[5]. During this process, prostaglandin E (PGE), which is abundant in human semen in its 19 - hydroxy form, promotes the expression of interleukin - 8 which serves as chemotactic agent and inhibits secretory leucocyte protease inhibitor[6]. In 1970, Bygdeman et al reported a relation between PGE of seminal fluid and fertility[7]. Later, Bendvold et al reported a decrease in the concentration of PGE, prostaglandin F (PGF), 19 - hydroxy - PGE, and 19 - hydroxy - PGF in the seminal fluid of men who were treated with naproxen (a non - steroidal anti - inflammatory drug - NSAID which which inhibits the production of PGs)[8]. However, they did not observe any decrease on sperm density or motility. Billiet et al also speculated that PGs might be beneficial during the IUI process because they enhance the uterine muscle contractility, and thus, possibly the transfer of semen and gametes through the uterine horn[9]. Woods et al were the first to infuse PGE2 prior to IUI in mares and observed that this effect signifi-

	2001; Barroso	2001; Brown	2008; Billiet	2009; Moslemizadeh	2013; Chikkagowdra	2015; Zahiri Sorouri
Was the study described as random?	+	+	+	+	+	+
Was the randomization scheme described and appropriate?	+	−	−	−	+	−
Was the study described as double - blind?	+	+	+	+	−	+
Was the method of double blinding appropriate?	−	+	+	+	−	+
Was the a description of dropouts and withdrawals?	−	−	+	+	+	+

Figure 2. Jadad score

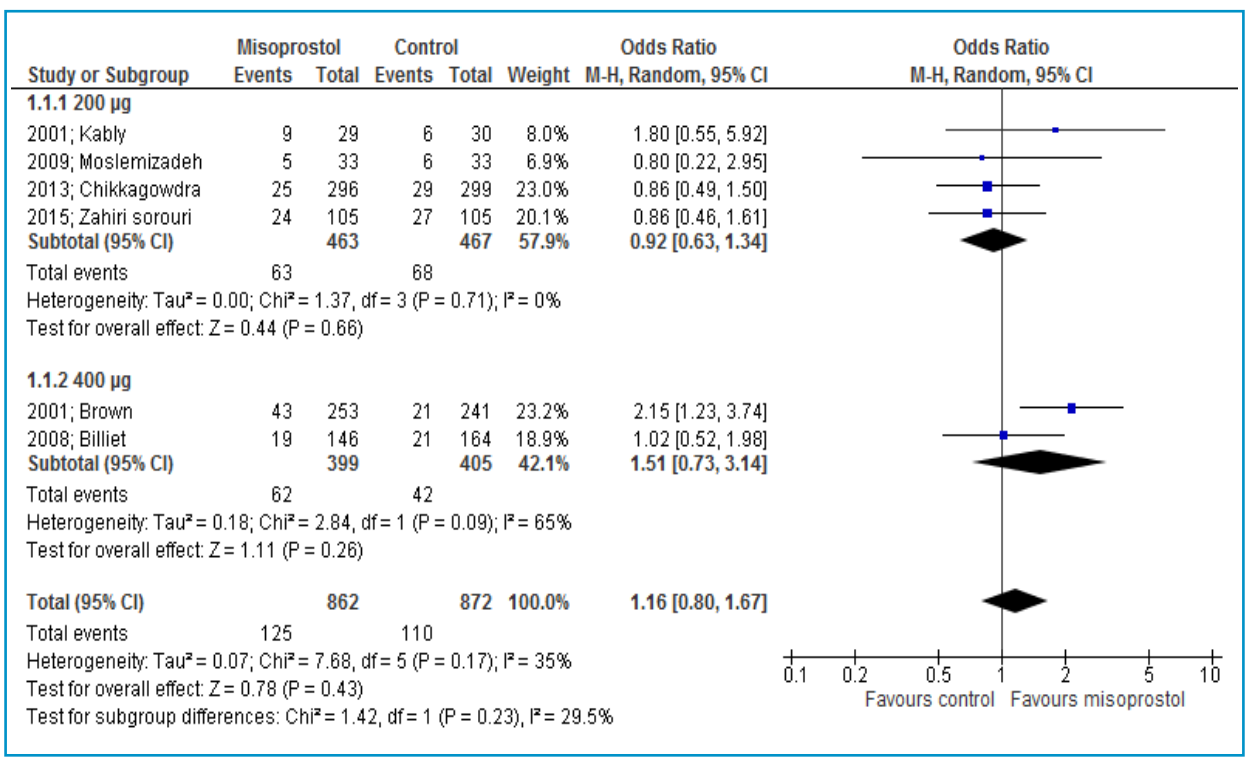

Figure 3. OR for pregnancy rates among groups. The overall effect was not statistically significant (p= 0.43). (Vertical line= "no difference" point between the two regimens, squares= mean differences, diamonds= pooled mean differences for all studies, horizontal lines= 95% CI)

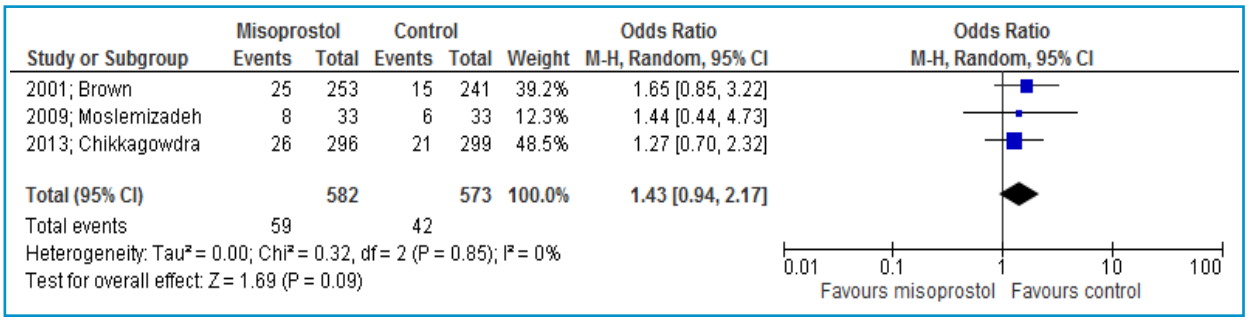

Figure 4. OR for vaginal spotting rates among groups. The overall effect was not statistically significant (p= 0.09). (Vertical line= "no difference" point between the two regimens, squares= mean differences, diamonds= pooled mean differences for all studies, horizontal lines= 95% CI)

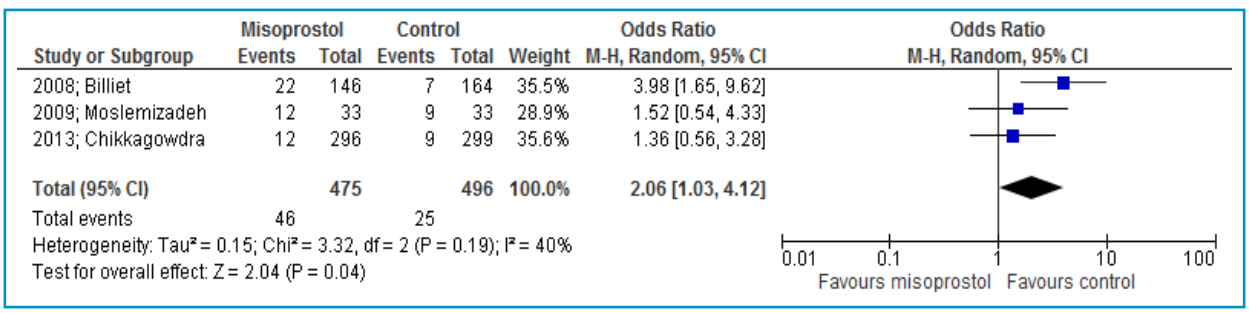

Figure 5. OR for abdominal pain among groups. The overall effect was statistically significant (p= 0.04). (Vertical line= "no difference" point between the two regimens, squares= mean differences, diamonds= pooled mean differences for all studies, horizontal lines= 95% CI)

cantly improved the fertility rates when the semen quality was good[10].

Since then certain researchers have investigated the impact of misoprostol, an artificial PGE analogue, in women undergoing IUI cycles. However, their results seem to be conflicting. The purpose of the present meta - analysis is to accumulate the current evidence in the field and investigate whether PGE improves the pregnancy rates among these women.

Materials and methods

Our study was designed according to the PRISMA guidelines[11]. Eligibility criteria were predetermined by the authors. Maximos Frountzas and Anastasia Prodromidou independently searched the literature. No language or date restrictions were applied during the literature search. All randomized and quasi - randomized controlled studies which investigated the impact of vaginal PGE on IUI outcomes were included in the present systematic review. Case reports, reviews and animal studies were excluded from tabulation. All discrepancies during the data collection, synthesis and analysis were resolved by the consensus of all authors.

The literature was systematically searched using the Medline (by using Pubmed) (1966 - 2015), Scopus (2004 - 2015), ClinicalTrials.gov (2008-2015), Cochrane Central Register (CENTRAL) and Google Scholar (2004 - 2015) databases along with the reference list of all articles which were retrieved in full text. Our search strategy included the words "misoprostol, prostaglandin, intrauterine insemination, assisted reproductive" and is presented in Figure 1.

The methodological quality of included randomized trials was evaluated with the modified Jadad scale using the following criteria: description

Table 1. Methodological characteristics of included studies

Date; Author	Type of study	Inclusion criteria	Misoprostol treatment
2001; Barroso	RCT	Patients aged between 25 and 35 years old. Normal sperm morphology and tube patency. Normal basal FSH, LH and E2 on day 3 and normal male factor. No signs of asthma, renal, hepatic or cardiac failure, systemic hypertension or allergic reactions in PGs. No history of radiation, or surgical treatment of the ovaries, tubes or uterus.	200μg
2001; Brown	DB-RCT	No history of allergic response or sensitivity to misoprostol or PG, or any known history of kidney or liver disorders. Infertility due to male factor, minimal or mild endometriosis, polycystic ovarian syndrome (PCOS), oligo-ovulation or anovulatory cycles, tubal disease, uterine disease, decreased ovarian reserve and unexplained infertility	400μg
2008; Billiet	DB-qRCT	Women between the age of 20 and 36 years with bilateral tubal patency. Total motile fraction of the semen sample >1.1 million after preparation. No history of previously failed IUI, severe comorbidity (endometriosis, fibroma) or previous allergic reactions to misoprostol	400μg
2009; Moslemizadeh	DB-RCT	Mild male factor infertility, PCOS or unexplained	200 μg
2013; Chikkagowdra	RCT	All infertile women	200μg
2015; Zahiri Sorouri	DB-RCT	Male factor infertility, idiopathic factors, and lack of pregnancy as a result of anovulation, and other etiologies such as marital relationship problems	200μg

of the studies as randomized along with details of randomization, description of the studies as double blind, details of double blinding procedure, information on withdrawals, and allocation concealment (Figure 2)[12].

Statistical meta-analysis was performed using the RevMan 5.1 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Confidence intervals (CI) were set at 95%. Odds ratios (OR) and 95% CI for all primary and secondary outcomes were calculated using the DerSimonian-Laird random effect model (REM) due to significant heterogeneity which was present among studies (Table 1)[13]. The cut - off for statistical significance was set to $p \leq 0.05$. Publication bias was not tested due to significant heterogeneity of included studies, a significant confounder, which may influence the methodological integrity of these tests[14].

The placement of misoprostol in the posterior vaginal fornix was performed immediately after the removal of the intrauterine catheter which was placed for the insemination protocol. Barroso et al did not administer placebo or any other treatment in their control group[15]. All other studies used placebo tablets as control[9,16-18].

Results

Six randomized controlled trials (RCTs) were included in the present systematic review which enrolled 1,403 women[9,15-19]. These women undergone 862 cycles with misoprostol and 872 cycles with placebo. The methodological characteristics of included studies were summarized in Table 1. In Table 2 we present the baseline characteristics of en-

Table 2. Maternal characteristics and clinical outcomes. The pregnancy rates were based on total pregnancies / total cycles per group

Date; Author	Number of patients	Age	Body Mass Index (BMI)	Number of cycles	Pregnancy rates	Spotting	Abdominal pain	Vaginal bleeding
2001; Barroso	29 vs 30	30.5 ± 3.7 vs 30.2 ± 3.3	N/A	29 vs 30	9/29 vs 6/30	N/A	N/A	N/A
2001; Brown	274	33.6 ± 0.29 vs 33.9± 0.30	27.3 ± 0.47 vs 26.5 ± 0.43	253 vs 241	43/253 vs 21 /241	23/253 vs 15/241	N/A	N/A
2008; Billiet	99 vs 100	N/A	N/A	146 vs 164	19/146 vs 21/164	N/A	22/146 vs 7/164	18/146 vs 3/164
2009; Moslemizadeh	33 vs 33	26.27 ± 4.9 vs 26.13 ± 4.3	26.20 ± 3.1 vs 26.03 ± 3.3	33 vs 33	5/33 vs 6/33	8/33 vs 6/33	12/33 vs 9/33	2/33 vs 0/33
2013; Chikkagowdra	296 vs 299	28.62 ± 6.1 vs 28.32 ± 5.45	27.3 ± 0.47 vs 26.5 ± 0.43	296 vs 299	25/296 vs 29/299	26/296 vs 21/299	12/296 vs 9/299	N/A
2015; Zahiri Sorouri	105 vs 105	31.01 ± 5.43 vs 29.59 ± 5.41	28.11 ± 6.33 vs 28.02 ± 7.56	105 vs 105	24/105 vs 27/105	N/A	N/A	N/A

rolled women and the outcomes of interest.

PGE2 treatment did not affect the pregnancy rates per cycle (OR= 1.16, 95% CI: 0.80 - 1.67, Figure 3). This effect remained unaffected by the dose of PGE2. There was an inclination towards higher rates of vaginal spotting among women who were treated with PGE2; however, this did not reach statistical significance (OR= 1.43, 95% CI: 0.94 - 2.17 Figure 4). Abdominal pain was significantly more prevalent among women receiving PGE2 (OR= 2.06, 95% CI: 1.03 - 4.12 Figure 5).

Discussion

Our meta - analysis suggests that vaginal PGE application does not enhance the pregnancy rates of women undergoing IUI. Furthermore, it seems to be accompanied by significant side effects which include spotting, vaginal bleeding and abdominal pain/cramping (Table 2). Billiet et al characteristically stated that they were forced to stop their study after randomization of 200 patients due to the high frequency of severe adverse reactions[9].

Prostaglandins have been previously reported to improve the fertility rates of women undergoing embryo transfer who had a thin endometrium[20]. A potential explanation for this observation was suggested by Achache et al who reported that women with recurrent implantation failure had extremely low levels of cytosolic lipase A2, which is a key regulator of PGs synthesis[21].The same authors concluded that the disrupted PGs synthesis can ultimately lead to altered endometrial receptivity. On the other hand studies investigating the effects of NSAIDs (which are potent inhibitors of PGs synthesis) have suggested that their consumption is related to defective angiogenesis and impaired cell adhesion which could, consecutively, alter the embryo attachment to the human endometrium[22,23]. Nevertheless, these associations remain until today indirect because there is an absence of published studies in this field.

Given the findings of our study, misoprostol administration during IUI cycles should be limited to women participating in clinical trials. It is our belief that misoprostol should be restricted to 200μg

among these studies to avoid the potential undesirable side effects which arise from the higher dose. Despite the fact that there seem to be evidence to support the potential benefit of PGs on semen quality, endometrial receptivity and uterine contractility these are relatively old and certainly need re - evaluation. Our understanding on the beneficial mode of action of PGs during the fertilization process is not clear and further investigation, both clinical and experimental, is mandated in the field.

Our study presents thorough information on the quality of included studies (Jadad score) and summarizes their limitations and their methodological heterogeneity (Table 1). The randomized and double blinded nature of the majority of included studies precludes selection bias. The main weakness of our study relies in the low number of included studies and their methodological heterogeneity.

Conclusion

Current evidence does not justify the administration of PGE among women undergoing IUI. Its use does not improve the pregnancy rates and seems to be accompanied by significant adverse effects. Further studies are needed in the field to corroborate our findings because they are restricted by the low number of included studies.

Conflict of interest

All authors declare no conflict of interest.

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