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Does the route of administration matter? Systematic review and meta-analysis of randomized clinical trials between vaginal *versus* intramuscular progesterone administration in the prevention of preterm birth

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ABSTRACT

Objective. To determine the effectiveness of intramuscular progesterone compared to vaginal application in the prevention of asymptomatic preterm birth (PTB) in randomized clinical trials.
Materials and Methods. A systematic search of electronic databases (Embase, PubMed and Scopus) was performed. Randomized clinical trials comparing vaginal and Intramuscular progesterone (17-OHPC) in pregnant women at high risk of PTB. Additionally, bias and certainty assessment were performed.
Results. Six clinical trials with a total of 1,408 randomized patients were included. The reported incidence of PTB < 37 weeks ranged from 10.9% to 43.9% for vaginal progesterone, and 14.0% to 38% for 17-OHPC. At the time of meta-analysis, patients receiving 17-OHPC was associated with a lower incidence of PTB < 28 weeks than vaginal use (Risk Difference 0.14; CI 0.01-0.29; $I^2 = 83.9\%$; $T^2 = 0.02$) with no significant difference in differences in PTB < 37 and < 34 weeks. Additionally, on neonatal outcomes, the most common was admission to the neonatal ICU independent of the method of administration (6.1% and 7.7%), followed by APGAR < 7 (4.1% and 5.2%), with no significant differences in neonatal outcomes.
Conclusions. Both the use of vaginal progesterone and 17-OHPC in the prevention of PTB in singleton high-risk gestations are reasonable options, with similar incidence of PTB and no additional impact on short-term neonatal complications. Thus, costs, resource availability and patient preferences should be considered when choosing a route of administration.

INTRODUCTION

Preterm birth (PTB) is one of the most complex and important challenges in obstetrics, since it constitutes three quarters of perinatal mortality and more than half of long-term neonatal morbidity [1, 2]. Meanwhile, in Peru, preterm births have an increasing trend according to the Peruvian Ministry of Health, with 27,383 between January and October 2022, resulting in an incidence of 6.79% of all live births [3]. A history of spontaneous PTB increases the risk of developing a new spontaneous PTB by 18-54% [4, 5].
In singleton pregnancies with risk of spontaneous preterm delivery, there are multiple possible pharmacological and non-pharmacological therapies, including cervical pessary, cerclage, progesterone, among others [6]. In singleton gestations with a history of PTB, the use of 17-alpha hydroxyprogesterone caproate (17-OHPC) is recommended from

16-20 weeks to 36 weeks [7, 8]. However, the use of progesterone vaginally has been shown to be a viable therapeutic option in reducing the incidence of PTB in high-risk gestations [9].
The aim of the present systematic review is to compare the effectiveness in randomized clinical trials conducted to date between the use of vaginal and intramuscular progesterone (17-OHPC) in the prevention of asymptomatic PTB in singleton high-risk pregnancies.

METHODS

Selection criteria

This review was based on the Cochrane Manual for Systematic Reviews of Interventions [10]. A systematic search was carried out in electronic databases (Embase, PubMed, Scopus), exporting the references found in the Rayyan information manager [11]. A search engine was performed with the terms "High-Risk pregnancy", "progesterone", "17-OPHC", "Cervical length", "progestogens", "Singleton", "17-alpha-hydroxyprogesterone caproate", "vagina;" and "Intramuscular". Data were obtained on each basis through January 2023. No language or geographic location restrictions were applied.

Study selection

We included randomized clinical trials that considered the direct comparison between two well-defined treatment schedules: vaginal progesterone (control group) or intramuscular progesterone (intervention group), which have as main outcome the incidence of PTB, and are available in the mentioned electronic databases. We did not include quasi-randomized clinical trials. Trials that considered multiple gestations as part of the study population were not included.
In addition, the following types of articles were excluded: case reports, conference abstracts, duplicate publications, case series, cross-sectional or retrospective investigations, scoping reviews, or systematic reviews.

Bias and certainty assessment

Bias assessment was performed based on the Cochrane Handbook for Systematic Reviews of Interventions [10]. Possible biases were divided into the following categories: 1) random generation of sequences (selection bias), 2) allocation concealment (selection bias), 3) blinding of participants and personnel (performance bias), 4) blinding of outcome assessment (detection bias), 5) incomplete outcome data (attrition bias), 5) selective information (information bias), and 6) other biases. According to the authors' criteria, each category was divided into "Low risk of bias", "High risk of bias," or "Unclear risk of bias" (**Figure 1**).
Similarly, the included clinical trials were evaluated by grading the certainty of the tests, taking into consideration the risk of bias, inconsistency, indirect evidence, imprecision and other consid-

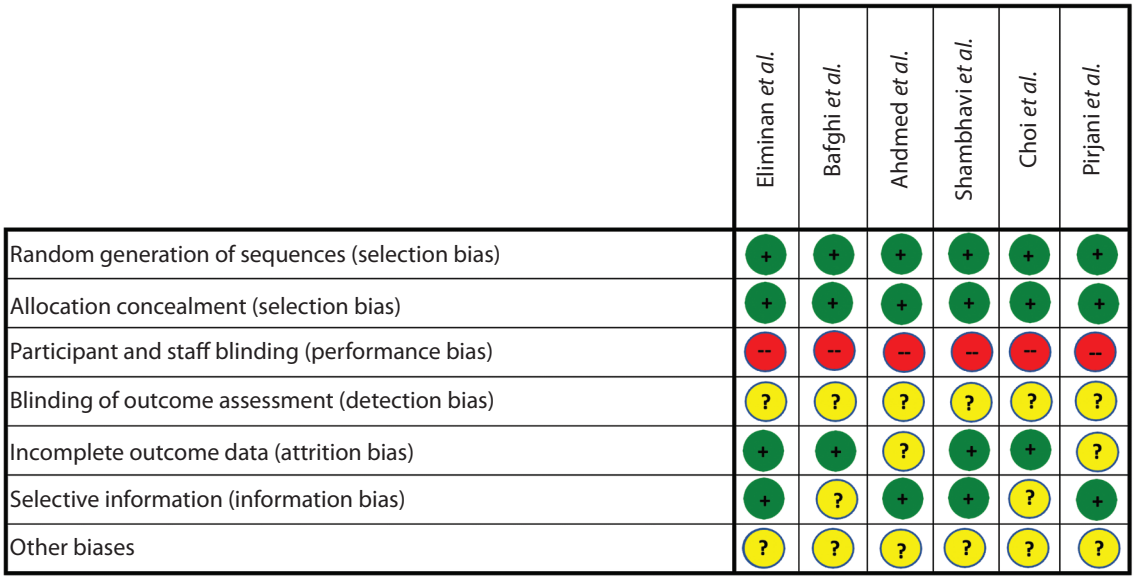

Figure 1. *Assessment of bias.*
Plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias.

erations, according to the Cochrane Handbook for Systematic Reviews of Interventions [10].

Data extraction

Clinical trial participants were evaluated according to the treatment group to which they were randomly assigned in the trials included in this review. The incidence of PTB < 34 weeks was considered as the primary outcome. Additionally, according to the included trials, the incidence of PTB was evaluated according to gestational week (< 37 weeks, < 34 weeks and < 28 weeks). Additionally, according to each study, peri-neonatal outcomes and reported adverse effects were evaluated.

The titles and abstracts resulting from the literature search were exported to the Endnote 20 reference management software, eliminating duplicates. Subsequently, when exported to the "Rayyan" program, they were analysed independently by authors. Once the potential literature to be included had been determined, the complete text was evaluated by two authors. Subsequently, by applying inclusion and exclusion criteria, they were included in the review. In case of disagreement on the inclusion or exclusion of a trial, it was discussed among all authors until a consensus was reached. The study selection process is represented in the PRISMA flowchart (**Figure 2**).

Once the articles to be included in the review were available, data were extracted from each article. The information was collected using a data collection form. The following data were extracted: title, authors, years, country, institutions, randomization process, inclusion and exclusion criteria, main outcome (PTB), secondary outcomes (adverse effects, peri-neonatal outcomes), application protocols/dose of vaginal and intramuscular progesterone, gestational age, detailed explanation of each intervention, conflict of interest and funding sources.

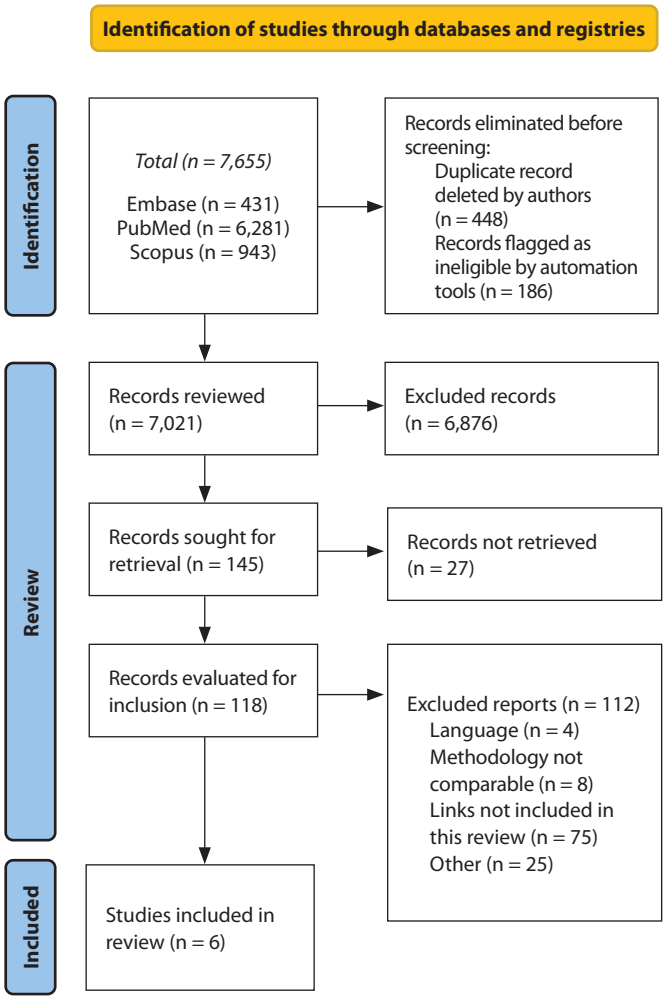

Figure 2. *PRISMA flowchart.*

Data analysis

Data analysis was exported to STATA statistical software. Complete analyses were compared, while any differences were resolved by data review and independent analysis. The forms of measurement were reported as relative risk (RR) or mean difference (MD), with 95% confidence interval (CI). A random-effects model using the DerSimonian-Laird model was used for quantitative synthesis and meta-analysis, and study heterogeneity was assessed using I^2. Tau^2 was also used to measure between-study variance. Publication bias was assessed using the Begg and Egger test. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Out of the total number of studies reviewed in the literature search (7,655), 6 clinical trials were included (**Figure 2**) with a total of 1,408 participants. Of the total, 677 were randomized to receive treatment with vaginal progesterone and 673 with intramuscular progesterone. In all clinical trials, singleton pregnancies with a history of one or more PTB was considered as an inclusion criterion. Additionally, the Choi *et al*. and Pirjani

et al. trial included pregnant women with short cervix (< 25 mm) [12].

Patients between 14 and 22 weeks of gestation were included. The majority of trials [12-15, 17] considered between 16 and 20-24 weeks, while the trial of Ahmed *et al*. included pregnant women between 14 and 18 weeks [16]. Regarding the type of treatment received, all trial participants received 250 mg intramuscular 17-OHPC every week, applied by trained health personnel. In contrast, the vaginal dose of progesterone did vary. In two trials [12, 15] they received 200 mg

Table 1. *Summary of clinical trials included in this systematic review.*

Study	Place	Sample		Vaginal progesterone	Intramuscular progesterone	Inclusion criteria	Main outcome	Gestiacional age
		Group 1 (Vaginal)	Group 2 (Intramuscular)					
Eliminan *et al*. [13]	United States (2016)	79	66	100 mg of progesterone daily (Self-applied)	250 mg IM weekly of 17-alpha-hydroxyprogesterone caproate	Women with singleton delivery and history of previous preterm labor followed by premature rupture of membranes between 20.0 and 36.6 weeks	Incidence of delivery before 37 weeks	16.0-20.6
Bafghi *et al*. [14]	Iran (2015)	39	39	300 mg of progesterone daily (Self-applied)	250 mg IM weekly of 17-alpha-hydroxyprogesterone caproate	Singleton gestation, viable fetus and the presence of risk factors for preterm delivery (preterm delivery with normal cervix length or cervix length < 25 mm*)	Incidence of preterm birth and gestational age at the time of delivery	16-20
Maher *et al*. [16]	Saudi Arabia (2012)	262	256	90 mg of progesterone daily in gel presentation (Applied by health personnel)	250 mg IM weekly of 17-alpha-hydroxyprogesterone caproate	Singleton gestation and a history of one or more preterm births	Incidence of delivery before 34 weeks	14-18
Pirjani *et al*. [17]	Iran (2016)	152	152	400 mg of progesterone daily (Self-applied)	250 mg IM weekly of 17-alpha-hydroxyprogesterone caproate	Singleton gestation, cervix length < 25 m	Incidence of delivery before 34 weeks	16-24
Shambhavi *et al*. [15]	India (2018)	50	48	200 mg progesterone daily (Self-applied)	250 mg IM weekly of 17-alpha-hydroxyprogesterone caproate	History of previous mid-trimester miscarriage or with preterm delivery of a single fetus (>16 and < 37 weeks) due to spontaneous preterm labor or premature rupture of membranes (PPROM)	Incidence of preterm birth and gestational age at the time of delivery	16-24
Choi *et al*. [12]	South Korea (2020)	95	112	200 mg of progesterone daily (Self-applied)	250 mg IM weekly of 17-alpha-hydroxyprogesterone caproate	Pregnant women older than 20 years, with a history of spontaneous preterm labor or cervical length <25mm between 15 - 22 weeks of gestation	incidence of delivery before 37 weeks	16-22

*If both risk factors were present, they were excluded.

daily, in one [13] 100 mg, in one [17] 400 mg and in another [14] 300 mg. Regardless of the dosage form, treatment was continued until 37 weeks or until development of the primary outcome (PTB) (**Table 1**).

The incidence of PTB according to treatment is shown in **Table 2**: significant differences were found in the clinical trial of Maher *et al*. [16], finding that pregnant women treated with vaginal progesterone had a lower incidence of PTB between 28 and 32 weeks (5.1% *vs* 10.4%) but a higher incidence between 34 and 37 weeks (16.6% *vs* 9.6%) than intramuscular progesterone.

The higher the gestational age, the higher the incidence of PTB. The highest incidence was reported in Eliminan *et al*. [13], both in pregnant women treated with vaginal (43.9%) and intramuscular (38.0%) progesterone.

Similarly, this trial found that the highest incidence of PTB in < 34 weeks (19.7% *vs* 17.7%) and in < 28 weeks (10.6% *vs* 10.1%). Detailed percentages of PTB by gestational age are shown in **Table 2**.

Regarding neonatal outcomes (**Table 3**), the most reported outcome was admission to the neonatal ICU, both in the use of vaginal and intramuscular progesterone (68 (6.1%) and 87 (7.7%) cases, respectively), followed by APGAR < 7 at 5 minutes (42 (4.1%) and 53 (5.2%)). In the included trials, Choi *et al*. [12] reported significant differences in lower APGAR < 4 in pregnant women treated with intramuscular progesterone and Maher *et al*. [16] reported higher neonatal ICU admission in the same. The other comparisons were not significant.

A meta-analysis (**Figure 3**) found that the use of 17-OPHC is associated with a lower incidence of PTB < 24 weeks than vaginal use (Risk Difference 0.14; CI 0.01-0.29; $I^2 = 83.9\%$; $T^2 = 0.02$). On the other hand, a non-significant trend of lower incidence of PTB < 37 weeks was found with patients treated with 17-OPHC (CI -0.05 to -0.04; I^2

Table 2. *Incidence of preterm delivery according to gestational age reported in included clinical trials.*

	Preterm Delivery by gestational age	Vaginal Progesterone		Intramuscular Progesterone		P-value	
		n	%	n	%		
Shambhavi *et al*. [15]	< 37 weeks	10	20.0	10	20.8	0.92	NS
	< 34 weeks	2	4.0	4	8.3	0.32	NS
	< 28 weeks			1	2.1	0.49	NS
Maher *et al*. [16]	≥ 34 a < 37 weeks	42	16.6	24	9.6	0.03	S
	≥ 32 a < 34 weeks	21	8.3	29	11.6	0.27	NS
	≥ 28 a < 32 weeks	13	5.1	26	10.4	0.04	S
	≥ 24 a < 28 weeks	5	2.0	6	2.5	0.97	NS
	< 24 weeks	3	1.2	3	1.2	0.70	NS
Bafghi *et al*.* [14]		37.0 ± 2.23		36.81 ± 2.8		0.77	NS
Ellminan *et al*. [13]	< 37 weeks	29	43.9	30	38.0	0.58	NS
	< 34 weeks	13	19.7	14	17.7	0.50	NS
	< 28 weeks	7	10.6	8	10.1	0.83	NS
Pirjani *et al*. [17]	< 37 weeks	21	10.9	23	14.0	0.72	NS
	34-36 weeks	9	6.1	14	9.3	0.59	NS
	< 34 weeks	7	4.8	7	4.8	0.64	NS
Choi *et al*. [12]	< 37 weeks	22	22.7	33	25.8	0.57	NS
	< 34 weeks	16	13.4	11	8.6	0.22	NS
	< 28 weeks	8	6.7	4	3.1	0.19	NS

Table 3. *Short-term neonatal outcomes reported in included clinical trials.*

	Trials	Sample	Vaginal Progesterone		Intramuscular Progesterone	
			n	%	n	%
APGAR < 7	12,13,15,16	1026	42	4.1	53	5.2
Neonatal sepsis	13,15,16	819	7	0.9	9	1.1
Neonatal Respiratory Distress Syndrome	13,16	721	28	3.9	31	4.3
Use of supplemental oxygen	13	174	3	1.7	1	0.6
Mechanical ventilation	13,16	721	19	2.6	25	3.5
Bronchopulmonary dysplasia	16	547	3	0.5	4	0.7
Necrotizing enterocolitis	13,15,16	819	4	0.5	4	0.5
Retinopathy of prematurity	13,15	272	0	0.0	3	1.1
Intraventricular haemorrhage	13,15,16	819	6	0.7	9	1.1
Neonatal seizure	16	547	21	3.8	29	5.3
Admission to neonatal ICU	15,15,16,17	1123	68	6.1	87	7.7
Neonatal mortality	13,15,16	819	11	1.3	18	2.2

= 0%; $T^2 = 0$) and lower incidence of PTB < 34 weeks in pregnant women treated with vaginal progesterone (CI -0.07 - 0.04; $I^2 = 58.9\%$; $T^2 = 0.0$). At the time of evaluating the certainty, the outcome of PTB < 37 and < 34 weeks had a moderate level of evidence, while the outcome of PTB < 28 weeks had a low level of evidence (**Table 4**).

DISCUSSION

Progesterone has an integral role in human gestation, from early forms with its production in the corpus lunate such as maintaining uterine quiescence during the second half of pregnancy, inhibiting contraction-associated progesterone genes in the myometrium [18, 19], inhibition of foetal membrane apoptosis, decidual anti-inflammatory and inhibition of cervical remodelling [20-22].

A review by Cochrane concluded that the use of progesterone significantly decreases the risk of preterm delivery [23, 24], a finding similar to that reported in different clinical trials [25-27]. However, both the dose and route of administration is controversial. Despite literature concluding the benefits of vaginal progesterone [9, 28], a recent systematic review reported that the use of vaginal progesterone does not decrease the risk of PTB in singleton high-risk gestations with adequate cervical length [29], findings similar to clinical trials conducted in Brazil and England where it did not generate long-term benefits and did not decrease neonatal mortality and morbidity [30, 31]. Contrary to the above, another clinical trial did find that progesterone supplementation was associated with less frequent uterine contractions and PTB compared to placebo [32]. Of note, this trial included high-risk pregnant women.

The use of intramuscular progesterone has been commonly associated with better outcomes in pregnant women with a history of PTB in previous pregnancies, having similar efficacy to cerclage [33]. However, a retrospective cohort study in the United States did not find an effect on PTB < 35 weeks in women indicated for cervical cerclage [34].

In our results we found that the incidence of PTB is similar in both routes of administration evaluated, with Maher *et al*. [16] reporting significant differences in favour of both vaginal (PTB between ≥ 34 to < 37 weeks) and intramuscular (PTB between ≥ 28 to < 32 weeks) progesterone use. The incidence of PTB < 28 weeks ranged from 0% [15] to 10.6% [12] for pregnant women treated with vaginal progesterone and from 1.2% [16] to 10.1% [13] for intramuscular progesterone. This, along with the results of the meta-analysis, where despite finding significant differences in the vaginal progesterone factor, the difference in risk is minimal, may indicate that both routes of administration are acceptable strategies for PTB in singleton pregnancies.

The most frequently reported neonatal complication was the need for hospitalization in neonatal critical units, with significant differences in one trial [16], in favour of vaginal progesterone. Other fre-

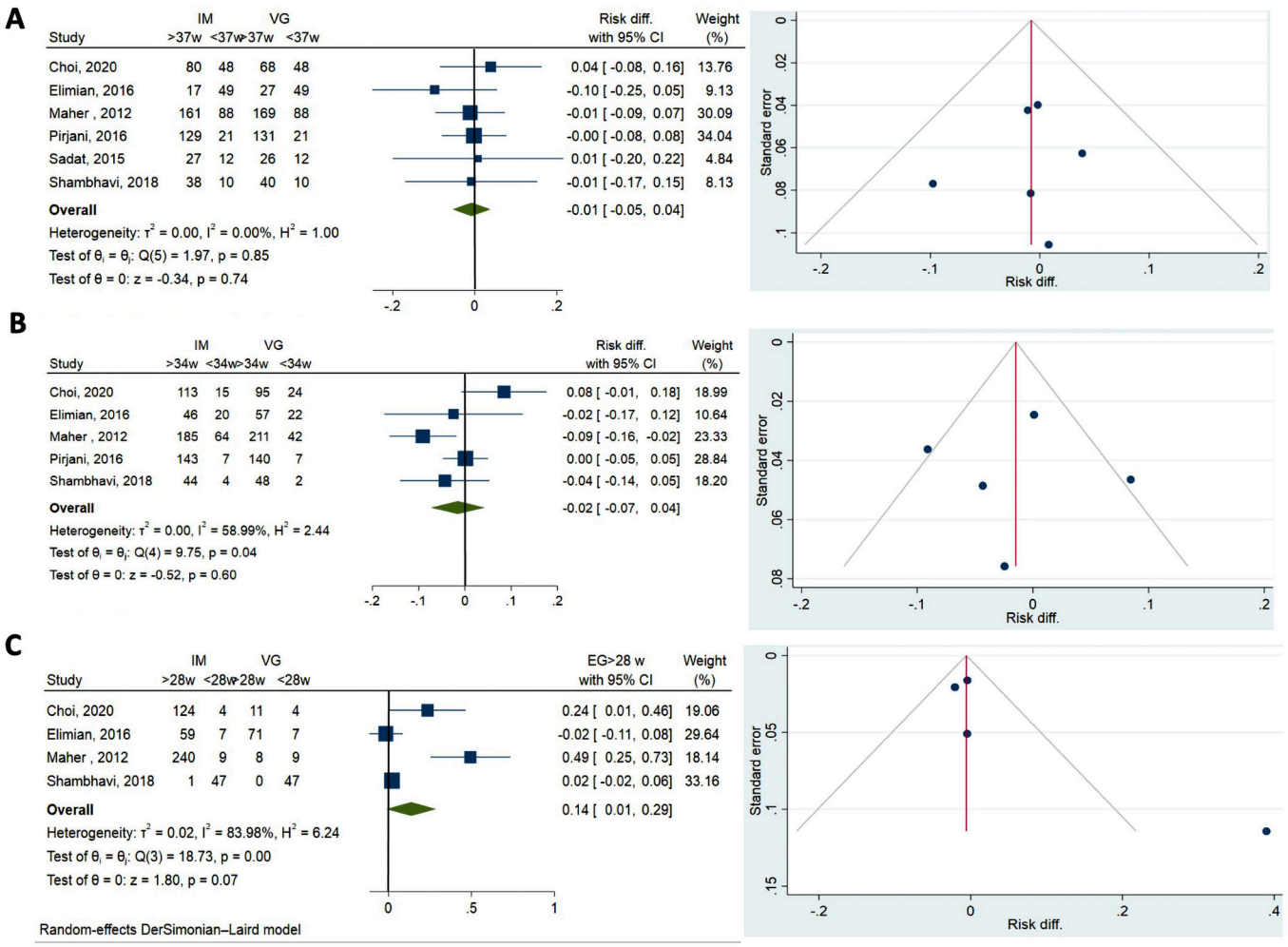

Figure 3. *Meta-analysis and publication bias between vaginal and intramuscular progesterone in the reduction of spontaneous preterm delivery.*
***(A)** < 37 weeks; **(B)** < 34 weeks; **(C)** < 28 weeks.*

quent complications were low APGAR levels and neonatal respiratory distress syndrome. However, in the other complications reported in **Table 3**, no differences were found according to the route of administration, while total neonatal mortality was less than 3%. Thus, the use of progesterone, regardless of the route of administration, is safe and does not represent a detrimental effect on short-term neonatal outcomes, since no outcome was reported in more than 10% of neonates, which coincides with the literature reviewed [31].

The interpretation of our results should also be put into the current context. There are factors associated with preterm delivery, including infectious or inflammatory processes, such as periodontal infectious [35], limnologically mediated processes [36], uterine overdistension or stress [37]. Among infections we found COVID-19 infection. Although previous studies show that pregnant patients do not usually present severe forms of COVID-19 infection [38, 39], patients with symptomatic COVID-19 infection at the time of delivery have a higher percentage of preterm delivery than asymptomatic pregnant women [40]. However, obstetric and neonatal outcomes appear to improve with vaccination [38].

Another important factor to consider is adverse effects of the treatment. The vaginal route, as opposed to the oral and intramuscular routes, avoids metabolism steps and has more bioavailability at the uterine level with low progesterone levels in blood, as opposed to optimal progesterone values in blood by the intramuscular route [41]. Maher *et al*. [16] reported that the most common adverse effects of intramuscular progesterone were headache, pain and swelling at the puncture site, reported in 14.1%, while vaginal progesterone was more associated with nausea, pain and vaginal bleeding in 7.5% (p = 0.017), which can be explained by the longer half-life of intramuscular progesterone. Similarly, Sham-

Table 4. *Certainty assessment for the preterm birth < 37 weeks, < 34 weeks and < 28 weeks.*

Certainty assessment							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirect Evidence	Imprecision	Other Considerations	Intramuscular Progesterone	Vaginal Progesterone	Relative (95% CI)	Absolut (95% CI)	
Preterm Birth < 37 weeks (evaluated with: births < 37 weeks/total of births)											
6	Randomized Clinical Trials	Serious	Non serious	Non serious	Non serious	None	228/680 (33.5%)	226/687 (32.9%)	RR -0.01 (-0.05 to 0.04)	332 less per 1000 (From 345 minus to 316 minus)	⊕⊕⊕◯ Medium
Preterm Birth < 34 weeks (evaluated with: births < 34 weeks/total of births)											
5	Randomized Clinical Trials	Serious	Non serious	Non serious	Non serious	None	110/641 (17.2%)	97/648 (15.0%)	RR -0.02 (-0.07 to 0.04)	153 less per 1000 (From 160 minus to 144 minus)	⊕⊕⊕◯ Medium
Preterm Birth < 28 weeks (evaluated with: births < 28 weeks/ total of births)											
4	Randomized Clinical Trials	Serious	Non serious	Non serious	Non serious	Publication bias is strongly suspected	21/491 (4.3%)	24/401 (6.0%)	RR 0.170 (-0.048 to 0.081)	50 less per 1000 (From 63 minus to 55 minus)	⊕⊕◯◯ Low

bhavi *et al*. [15] found that 20% of pregnant women treated with vaginal progesterone reported adverse effects (mainly mild vaginal discharge), less than 29.2% of pregnant women treated with intramuscular progesterone (mainly pain at the puncture site). These results coincide with existing literature [42].

Despite these adverse effects, Bafghi *et al*. [14] and Choi *et al.* [12] used the Likert Scale (Very Low-Very High) to measure participants' perception of the treatment, and both reported high values of satisfaction with progesterone supplementation, independent of the route of administration.

Due to the importance of PTB prevention, there are multiple pharmacological and non-pharmacological therapeutic options. For example, one clinical trial found that the use of adjuvant vaginal progesterone following McDonald-type cervical cerclage decreased second-trimester losses and improved perinatal outcomes [43]. However, the evidence for the combination of these therapeutic options (tocolytics, antibiotics, pessaries, *etc*.) is not sufficient at this time [44, 45] and represents an opportunity for future research to reduce perinatal morbidity and mortality.

This study represents, to our knowledge, the first systematic review that evaluates the vaginal and intramuscular use of progesterone in the prevention of preterm labour, also assessing certainty assessment and evaluation of bias. Our results allow us to establish, based on evidence, an adequate treatment of pregnant patients at high risk of preterm delivery.

CONCLUSIONS

According to our results, the use of vaginal or intramuscular progesterone are two viable options in the reduction of PTB in singleton pregnancies with high risk, having also a low incidence of neonatal complications in the short term. In addition, although adverse effects are more associated with intramuscular use, both routes of administration are well accepted in the studied population. Several factors should be considered when choosing a treatment, including costs and patient preferences.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

M.G.B.: Conceptualization, data curation, investigation, validation, visualization. A.O.L.: Formal analysis, methodology, software. M.N.C.: Supervision, writing – review & editing. All authors: writing – original draft.

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Study registration

PROSPERO International Prospective Register for Systematic Reviews ID CRD42023401123.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

N/A.

Informed consent

N/A.

Data sharing

Since no database was created for this review, no data sharing is necessary. This is because this systematic review and meta-analysis was based on previously published clinical trials.

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