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Systematic Review

Therapeutic Strategies in the Treatment and Prevention of Preterm Labor: A Systematic Review

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ABSTRACT

Introduction: Prematurity remains the leading cause of prenatal and newborn mortality and morbidity worldwide. Numerous trials with varying degrees of efficacy have been carried out to identify therapies to prevent premature birth. Therefore, the purpose of this study is to analyze the efficacy of medications with different dosages that have been previously studied in terms of their ability to delay premature labor.

Material and Methods: The authors searched for randomized-controlled trials (RCTs) that addressed the use of therapy to prevent or treat preterm birth in pregnant patients who were either diagnosed with or at risk for preterm birth. The PRISMA approach was used to conduct the search using electronic databases, including Embase, ProQuest, PubMed, and Cochrane.

Results: We obtained 34 RCTs that met the inclusion criteria. We discovered that 400 mg of progesterone administered intravaginally consistently had a substantial effect in postponing preterm birth. Other kinds of aspirin, such as 60 mg and 81 mg, are effective in postponing premature birth. In addition, taking supplements of docosahexaenoic acid (omega-3 fatty acid) throughout pregnancy considerably delays premature birth. Preterm labor is also markedly delayed in pregnant women with HIV when selenium supplements are taken.

Conclusion: Intravaginal progesterone, oral low-dose aspirin, and docosahexaenoic acid supplementation have the potential to be therapies to prevent preterm labor.

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INTRODUCTION

The four classifications of preterm birth (PTB) are extremely preterm (less than 28 weeks), very preterm (between 28 and 32 weeks), early moderate preterm (between 32 and 34 weeks), and late moderate preterm (between 34 and 37 weeks) [1]. PTB occurs before 37 weeks of gestation. Globally, PTB is a leading cause of neonatal and perinatal mortality and morbidity. It is estimated that PTB affects about 15 million pregnancies annually and results in morbidity in one million children. PTB is still quite common in Indonesia, where it is believed to affect 10–15% of births, or 600,000 instances annually [2]. PTB is responsible for 36% of all neonatal deaths in Indonesia. Asphyxia (25%), sepsis (11%), and premature birth and its complications (45%) accounted for 60,000 of the recorded newborn fatalities in Indonesia in 2019 [3].

The effectiveness of therapy in treating PTB and preterm labor has been the subject of numerous studies. Among the medications known as tocolytics, which can postpone premature labor, are betamimetics, COX inhibitors, calcium-channel blockers, magnesium sulfate, oxytocin receptor antagonists, and nitric oxide donors. Beta receptor agonists are commonly used betamimetics, which reduce uterine contractions by simulating the effects of noradrenaline and adrenaline in the heart, lungs, and smooth muscle tissue. Betamimetics can be administered orally, subcutaneously, intramuscularly, or intravenously [4]. COX inhibitors increase intracellular calcium levels and promote the establishment of myometrial gap junctions, which limit the conversion of arachidonic acid into

prostaglandins, hormone-like substances that are crucial to the labor process [4]. In most cases, COX inhibitors are used orally and intrarectally. Calcium-channel blockers (nifedipine/nicardipine), which are frequently used to treat pregnancy-related hypertension, have a tocolytic effect by preventing calcium from passing through cell membranes and lowering the tone of vascular smooth muscle. A tocolytic medication, magnesium sulfate, is frequently used to prevent and treat eclampsia because it lowers the frequency of smooth muscle depolarization, which prevents uterine contractions [4].

Magnesium sulfate can be administered intramuscularly or intravenously. A free radical called nitric oxide causes vasodilation, cervical ripening, and smooth muscle relaxation. Nitric oxide can be applied sublingually, transdermally, or intravenously [4]. In addition, several studies were conducted using food and hormone supplements to delay PTB both in preclinical and clinical trial stages [5]. Clinical investigations employed a variety of substances, including n−3 long-chain polyunsaturated fatty acids [6,7] and Docosahexaenoic acid [8–10]. Each drug has different effectiveness in delaying premature birth. Therefore, the purpose of this study is to analyze the efficacy of medications with different dosages that have been previously studied in terms of their ability to delay premature labor.

MATERIAL AND METHODS

Study Design and Search Strategy

The search for this systematic review was carried out using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. From 2018 to 2023, the author collected data from all studies that compared the usage of particular drugs and substances in preterm births. The following databases were searched in accordance with the inclusion criteria: Embase, ProQuest, PubMed, and Cochrane.

Meanwhile, the studies collected had two groups, namely the "intervention" and "control" groups. Keywords used to search for articles, namely (“preterm” OR “preterm birth” OR “preterm labor” OR “preterm labor” OR “PTB”) AND (“therapy” OR “drug” OR “medicine” OR “tocolytic agents ” OR “tocolytic” OR “nicorandil” OR “isosorbide dinitrate” OR “nicardipine” OR “celecoxib” OR “oxytocin receptor antagonist” OR “retosiban” OR “barosiban” OR “17-OH-Progesterone” OR “PGF2-a receptor” OR “dehydrogesterone” OR “indomethacin” OR “aspirin” OR “Omega-3 fatty acid” OR “selenium”) AND (“drug development” OR “clinical trial” OR “randomized-controlled trial” OR “RCT” OR “interventional studies”). Additionally, the author compiled all pertinent publications using Google Scholar and references from previously acquired materials.

Study Selection

The following are requirements for inclusion (1) RCT studies, (2) patient age >18 years, (3) patients in pregnancy who are either at risk or not at risk of premature birth who are given certain drugs to prevent premature birth, (4) there are results related to delaying premature birth or gestational age at birth. The exclusion criteria include (1) duplication, (2) not speaking English, (3) non-specific drug name, and (4) not reporting the desired result. The acquired studies were evaluated for inclusion in the systematic review by the authors through discussion.

Data Extraction and Study Quality Assessment

Researchers used inclusion and exclusion criteria to filter literature in order to perform the data extraction method. (1) Name of study or first author, (2) year of publication, (3) research design and country, (4) participant criteria, (5) participant age, (6) participant number, (7) drug type, (8) length of drug usage, and (9) study results are among the extracted data. The Modified Jadad Scale [11] was then used by the author to evaluate the study's quality.

This scale includes eight components: randomization, blinding, withdrawal, dropout, inclusion/exclusion criteria, side effects, and statistical analysis. The sum of the ratings assigned to each item determines the overall score for each article, which ranges from 0 to 8. The literature search yielded 115.661 publications published over several years, with studies with scores between 0 and 3 being categorized as low quality and those with values between 4 and 8 as good quality. Some papers (n = 3.293) were excluded due to study duplication. 2.330 publications were disqualified because they contained ineligible data, such as books and review articles, or because they were inaccessible owing to subscription requirements. Then, several papers (n = 2) do not adhere to the inclusion criteria and study design. Fig.1 shows the PRISMA flowchart. 34 papers were included in the systematic review as a result.

RESULTS

Study Selection

The PRISMA flow diagram [Fig.1] was used as a guide for database searches to find study selection information. The research was carried out using data from 2018–2023. Embase, ProQuest, PubMed, and Cochrane identified 5661 potentially relevant

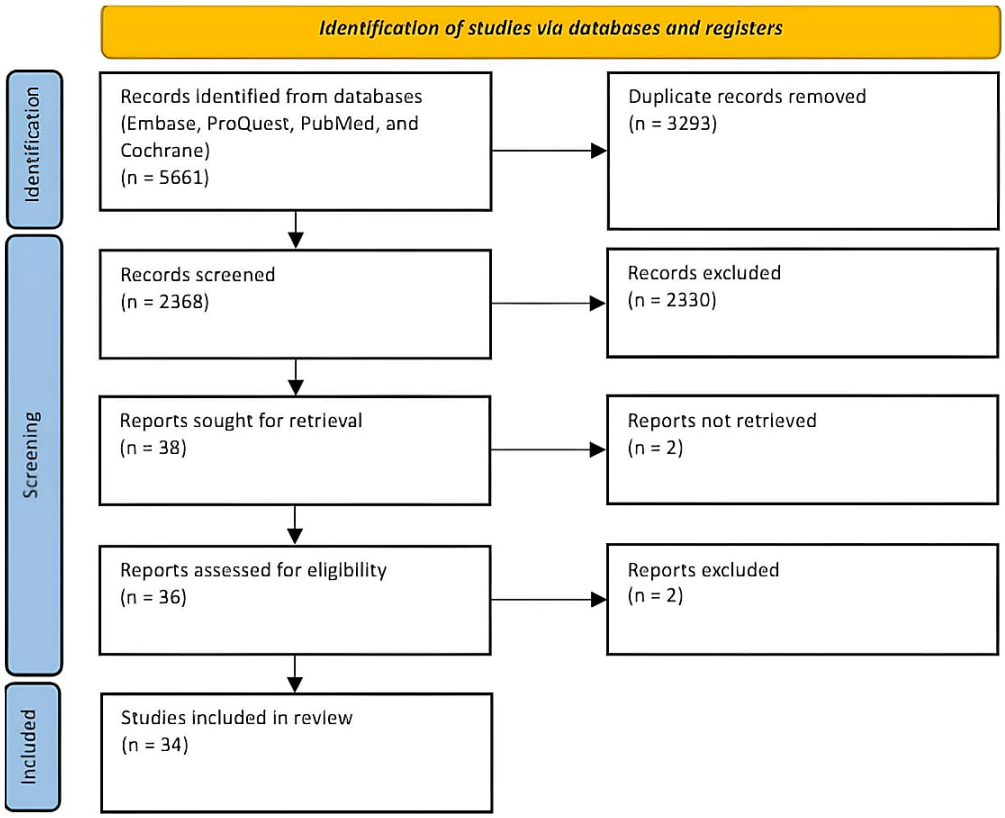


Fig.1. PRISMA Flow Diagram of the Study Selection Process

publications. Then, there were 3293 duplicate articles and articles unrelated to the topic discussed based on their titles, which were removed. Based on the abstract and full text, we excluded 2330 articles that were not RCTs, secondary or repeat studies, and pharmacodynamic/ pharmacokinetic studies. Of the 38 articles obtained, 2 articles were not taken because the results did not meet the expected criteria. We assessed 36 complete articles for inclusion in the study. Following that, two articles were disqualified due to their failure to satisfy the selection criteria. Finally, 34 articles were chosen for systematic evaluation.

Study Characteristics and Results

Of the 34 studies obtained, there were several types of therapy used to prevent or treat premature birth. Meanwhile, all studies were RCTs, some of which were carried out in multicenter and some were carried out double-blind. The author found 11 studies using the Progesterone group [12-22], 3 studies comparing Cox inhibitors with placebo [23- 25], 1 study compared Cox inhibitors and Calcium-channel blockers [26], 2 studies compared Calcium-channel blockers with placebo [27,28], 4 studies compared Calcium- channel blockers and Nitric oxide donors [29-32], 1 study compared Magnesium sulfate with placebo [33], 2 studies compared Magnesium sulfate and Calcium-channel blockers [34,35], as well as other drugs such as Docosahexaenoic acid [8,9], Esomeprazole [36], Metformin [37], Selenium [38], n−3 long-chain polyunsaturated fatty acids [6,7], Ulinastatin [39], Oxytocin receptor antagonists (Retosiban and Atosiban) [40], and betamimetics (Betamethasone) [41]. Meanwhile, the basic characteristics of each study can be seen in Table 1.

In the progesterone group, use of Dydrogesterone dose of 10 mg may have a positive effect on delaying preterm labor through prolonging the latent period [12] and preventing recurrent uterine contractions [22], and can have an impact on the APGAR score, especially at 1 minute [14]. In contrast to oral usage, intravaginal use of progesterone, only two studies with a dose of 400 mg revealed a significant effect on gestational age at delivery, decreased premature birth rates, and favorable neonatal outcomes [13,21]. Meanwhile, another study used a dose of 300 mg twice a day [17], and 200 mg once daily [18,20] did not show significant results. In 17-OHPC, only one study showed a significant effect in preventing labor before 37 weeks of gestation at a dose

of 250 mg intramuscularly, included the PROLONG research, which did not yield meaningful effects on the incidence of premature labor [16,19].

In the COX inhibitor group, some studies utilized aspirin, while others used indomethacin. Oral doses of aspirin at 60 mg [23] and 81 mg [25] were shown to significantly reduce the rate of delivery before 34 weeks in women with hypertensive pregnancy disorders, as well as decrease the risks of preterm birth, perinatal death, and fetal loss. For the indomethacin group, research has shown that administering 100 mg of indomethacin rectally along with 20 mg of oral nifedipine over a 48-hour period is effective in preventing early labor, delaying its onset, and prolonging pregnancy [26].

In the Calcium-channel blocker group, it becomes interesting where 2 studies comparing a placebo had different results. At the same dose, namely 20 mg Nifedipine orally at the initial dose, at 48 hours, it does not show a significant effect in delaying labor <37 weeks, labor <48 hours [27]. However, subsequent studies showed cessation of contractions within 90 minutes and successful treatment in the Nifedipine group [28]. In comparison with Nitroglycerin and Magnesium sulfate, the results shown were inconsistent. Some studies show that Nifedipine is better at delaying preterm labor either [31,35], but on the contrary, there are more studies that state the opposite, where Nitroglycerin [29,30] or Magnesium sulfate (34) is better than Nifedipine. However, the results of the MAGENTA study [33] showed that it had no discernible impact on the final result.

Several investigations using different medication classes and compounds revealed that a 200 mg oral dose of docosahexaenoic acid was effective in lowering the incidence of early preterm birth [8]. Subsequent research revealed that good compliance with 200 mg and 800 mg had better outcomes than low dosages or poor compliance [9]. In the ORIP research, the next compound is 500 mg fish oil capsules (900 mg n−3 long-chain polyunsaturated fatty acids), which include 800 mg docosahexaenoic acid and 100 mg eicosapentaenoic acid. The findings, however, did not indicate any discernible impact on either intervention for post-term birth or lowering the frequency of early preterm delivery [6]. However, additional research that excluded repeated pregnancies revealed a positive impact on lowering the risk of early preterm delivery, particularly in women with low omega-3 levels [7]. Preterm labor was then decreased in studies involving the administration of selenium supplements to HIV patients [38].

In medicine, taking a PPI (esomeprazole 40 mg) orally has a positive effect on lowering the risk of placental abruption but does not significantly extend the pregnancy [36]. The use of 6 mg of short-acting betamethasone phosphate combined with 6 mg of long-acting betamethasone acetate positively influences gestational age at birth between 28 and 34 weeks and reduces the likelihood of respiratory distress syndrome. The subsequent medication, Metformin extended-release 3 grams taken orally, did not effectively lengthen the duration of pregnancy [37]. The time of preterm birth was not significantly impacted by group oxytocin receptor antagonists (Retosiban and Atosiban) or ulinastatin [39,40].

Evaluation of the Quality of Study Methods

Using the modified Jadad scale, 34 studies were evaluated. Based on this evaluation, 19 studies (55.88%) were obtained with a score of 8 [13–18,22–28,33,36–40], 5 studies (14.70%) with a value of 7 [6–9,19], 2 studies (5.88%) with a value of 6.5 [31,32], 5 studies (14.70%) with a value of 6 [20,21,30,35,41], 2 studies (5.88%) with a score of 5 [12,29], and 1 study (2.94%) with a value of 4 [34]. The final modified Jadad scale score for each study can be seen in Table 2.

DISCUSSION

This systematic review includes 34 RCT trials from 2018–2023 that address treatments for preterm birth. One of the most dangerous and common complications is still premature birth. Premature birth is typically caused by four mechanisms: infection/inflammation (40%), premature activation of the mother's or fetus's hypothalamic-pituitary-adrenal axis owing to stressors (30%), decidual abruption/bleeding (20%), and mechanical stretching. 10% is the uterus. Premature birth also increases the risk of newborn morbidity and mortality, which can reach 70–75% and result in neurological developmental abnormalities [42].

In the 1960s, betamimetics were used to identify a way to cure premature birth. Terbutaline was one of the treatments that was once utilized, but it was later taken off the market after the Federal medicine Administration (FDA) made a contentious declaration in 2011, classifying it as a Category C medicine (drugs linked to negative results in animal studies) [5]. The next medication is an analog of progesterone (P4). This is due to progesterone's ability to sustain a pregnancy. One method is by inhibiting the myometrium's expression of procontractile genes, particularly Connexin-43, which reduces uterine contractions [43].

Due to its positive benefits between 16 and 36 weeks of pregnancy, progesterone use has been suggested in a number of guidelines in recent years [44]. Progesterone comes in a variety of forms, including injectable 17-OHPC, intravaginal progesterone, and oral Dydrogesterone. Following the FDA's discontinuation of Makena®, a medicine that includes 17-OHPC, due to

an RCT study that found 17-OHPC had no effect on preventing spontaneous preterm delivery, progesterone-related research has emerged in recent years [45]. PROLONG was one of the studies that was considered; the findings of this systematic review showed that 17-OHPC had no influence on mother and baby outcomes or the reduction of premature deliveries [16]. While the study by Shadab et al. [19] demonstrated that 17-OHPC can delay preterm delivery in women with a prior history of preterm birth, other trials using 17-OHPC had comparable results [15,20]. In individuals with a sonographically estimated cervix of less than 25 mm, progesterone given intravaginally has been demonstrated to prevent premature labor [17]. This aligns with the findings of Rehal et al., who reported that intravaginal progesterone reduces the risk of spontaneous preterm birth before 32 weeks in women with a cervical length under 30 mm [17]. In another trial, 400 mg of intravaginal progesterone was found to be useful in preventing preterm labor and extending the latent period [13,21]. The effectiveness of oral preparations in lowering premature labor has been mixed [12,14,22].

COX inhibitors are the next group of medications. Prostaglandins contribute to the pathophysiology of preterm labor by causing membrane rupture, cervical ripening and dilatation, and myometrial contraction [46]. PGF2α and prostaglandin E2 (PGE2), which are involved in uterine contractions, are produced by the prostaglandin pathway, which is regulated by cyclooxygenase (COX). Furthermore, there was an upregulation of connexin-43, oxytocin receptor (OTR), and COX-2 [46], and the activity of NF-κB, mitogen-activated protein kinases (MAPK), phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), and calcineurin/nuclear factor of activated T-cells (NFAT) will all increase as PGF2α rises. Consequently, there is potential for the development of oxytocin receptor antagonists and COX inhibitors as treatments for delaying preterm labor. However, because oxytocin receptor antagonists like Atosiban and Retosiban have been linked to neonatal deaths, their usage was not approved by the FDA [5]. Additionally, it was discovered that atosiban increased maternal glucose levels [5]. Furthermore, the findings of the Saade et al. investigation showed that neither Atosiban nor Retosiban could delay premature birth [40].

Aspirin is a COX inhibitor that is widely used to prevent premature birth, especially with risk factors for preeclampsia. Aspirin alone has been shown to be useful in delaying preterm births that occur before 34 weeks [5]. This is consistent with the findings of this trial, which showed that aspirin at doses of 60 and 81 mg was useful in delaying preterm birth [23–25]. In addition to its ability to delay preterm birth, aspirin has fewer adverse effects on mothers than other Cox inhibitors, such as Indometachin [5]. Because Ca2+ influx aids in intracellular calcium mobilization and affects the production of Ca2+-dependent transcription factors like NF-κB and NFAT, Cox is also relevant to calcium channels [46]. Consequently, research by Kashanian et al. indicates that the combination of nifedipine and indomethacin is more effective than either medication used alone [26]. However, the use of Indomethacin is contraindicated in chronic kidney or liver disease, peptic ulcer disease, and coagulation disorders [5].

Numerous studies have demonstrated the effectiveness of calcium-channel blockers in delaying preterm delivery. By lowering intracellular calcium levels, calcium-channel blockers indirectly decrease myosin light-chain kinase activity, which in turn lessens contractions [46]. According to one study, nifedipine can lessen contractions for less than 90 minutes [28]. One study [34] found that magnesium sulfate (MgSO4) had a positive effect on acute tocolysis, whereas another study [35] found that nifedipine was more effective at delaying premature birth. Naturally, more investigation is needed to determine whether the effects of MgSO4 over a placebo are statistically insignificant [33]. Magnesium sulfate ($MgSO_4$) reduces uterine contractions by inhibiting calcium entry into smooth muscle cells and/or preventing its binding to storage sites, thereby decreasing the rate of smooth muscle depolarization [34]. In contrast to nitric oxide donors, the findings of two trials [29,30] indicated that nitroglycerin was superior in extending pregnancy by less than 48 and more than 48 hours, while one study [31] found that nifedipine was superior. Given that it may be a nitric oxide donor that causes smooth muscle relaxation, cervical ripening, and vasodilation, this should also be a concern for future research [4].

Other medications, like PPIs and Metformin, are ineffective at extending pregnancy or delaying a premature delivery, aside from the primary categories mentioned above [36,37]. Nonetheless, betamethasone lowers the risk of respiratory distress syndrome and has a positive effect on gestational age at birth, which is between 28 and 34 weeks [41]. Steroids are useful for lung maturation, but it's important to keep in mind that they are only administered if an early birth is predicted to happen within seven days, based on the woman's symptoms or reliable predictive testing [44].

Omega-3 or docosahexaenoic acid (DHA) is a compound other than medications that has been shown to be useful in lowering early preterm birth, particularly in singleton pregnancies [6–9]. This is because polyunsaturated fatty acids play a crucial role in immune system modulation. Inflammatory dysregulation may result from poor polyunsaturated fatty acid transport after preterm delivery. As a result, DHA supplementation can assist in meeting the immune system and inflammatory regulation demands of

newborns [47–49]. The last supplement is selenium, which lowers the risk of premature labor in HIV patients [38]. The activity of the enzyme glutathione peroxidase (GPX), which defends against ROS, depends on selenium, an antioxidant that helps shield the body from the harmful effects of free radicals (50). Selenium supplementation is crucial in HIV to avoid morbidity and death for both maternals and neonates, as selenium deficiency is linked to disease progression and mortality [38].

The limitations of this systematic review include limited sample sizes for several studies; therefore, the conclusions cannot be extended to the general population. Then, in some studies, there may be bias, especially in single-center studies where the role of race can be influential. Furthermore, some studies do not differentiate between single and multiple pregnancies, which also means there may be differences in the effectiveness of therapy. The author suggests conducting a prospective RCT study on a larger scale. Basic characteristics must be well defined to minimize the occurrence of bias or error. Of course, in future developments, it is very possible to develop other therapies that are not discussed in this research.

CONCLUSION

Intravaginal progesterone, oral low-dose aspirin, and docosahexaenoic acid supplementation consistently significantly delayed preterm labor with minimal side effects. Thus, these drugs have the potential to prevent premature birth.

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CONFLICT OF INTEREST

In the interest of transparency, the authors disclaim any conflicts of interest pertaining to the publication of this work.

Availability of Data and Materials

The data corpora created and/or evaluated during this inquiry are listed in the accompanying reference list.

Ethics Approval and Consent to Participate

The study's methodological framework excluded the use of either human or animal participants in any way. Therefore, neither obtaining institutional review board ethical approval nor obtaining participants' informed consent was necessary.

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Table 1. Study Characteristics and Results

No	Study, Year	Design	Subject	Mean of ages (years)		Total of subjects		Intervention	Control	Outcome
				Intervention	Control	Intervention	Control			
						Progesterone				
1	Alizadeh et al., 2022 [12]	Prospective, multicenter, unblinded RCT in Iran	Women with singleton pregnancies of 28-34 weeks of gestation	28.60 ± 4.04/26.53 ± 4.55	28.71 ± 3.98	55	55	10 mg Dydrogesterone orally, three times daily/ 250 mg 17-OHPC intramuscularly weekly	Without intervention	There were significant differences in prolongation of the latent period, gestational age at delivery, birth weight, and better APGAR scores in the progesterone group.
2	Hyett et al., 2022 [13]	Prospective, single-center, double-blind, RCT in Iran	Women with a gestational age of 24-34 weeks with symptoms of threatened preterm labor	27.6 ± 7.6	27 ± 4.8	45	40	400 mg Progesterone intravaginally daily until 34 weeks of gestation	Placebo	There were significant differences in prolongation of the latent period, gestational age at delivery, cervical length after 1 week, birth weight, and the need for a better NICU in the progesterone group, but not significant in neonatal death, RDS, and the need for mechanical ventilation.
3	Keshtmandi et al., 2023 [14]	Prospective, single-center, double-blind, RCT in Iran	Women with singleton pregnancies of 24-34 weeks of gestation who experience preterm labor pain and intact membranes	29.2 ± 4,0	28 ± 3.5	55	55	10 mg Dydrogesterone orally three times daily after meals until delivery or 37 weeks	Placebo	There were no significant differences in recurrent uterine contractions, incidence of preterm labor, gestational age at delivery, latent period, cervical dilation, effacement, 5-minute Apgar score <7, and drug side effects, but there was a significant difference in the percentage of neonates with a 1-minute Apgar score <7 higher in the Placebo group.
4	Langen et al., 2018 [15]	Prospective, two-center, double-blind, RCT in United States	Women with a singleton pregnancy of 24-32 weeks' gestation, with a clinical diagnosis of PPROM without evidence of active infection or major fetal malformation	31.7 ± 1.9	31.7 ± 2.0	10	11	Intramuscular 17-OHPC up to 34 weeks of gestation	Placebo	There were no significant differences in attainment of 34 weeks' gestation, latency period, and maternal or neonatal outcomes.
5	PROLONG, 2020 [16]	Prospective, multicenter, double-blind, RCT	Women with a gestational age of 16-20 weeks with a history of a previous single spontaneous preterm birth	30.0 ± 5.2	29.9 ± 5.2	1130	578	250 mg 17-OHPC intramuscularly weekly until delivery or 36 weeks of gestation	Placebo	There were no significant differences in the frequency of preterm birth <35 weeks, neonatal morbidity index, frequency of fetal/early infant death, or maternal outcomes (need for cerclage placement, tocolysis, antenatal corticosteroid therapy, gestational diabetes, preeclampsia, chorioamnionitis, and abruptio placentae).
6	Rehal et al., 2021[17]	Prospective, multicenter, double-blind, RCT	Women with twin pregnancies	34.1 (Range, 30.3-37.7)	34.0 (Range, 30.0-37.6)	582	587	300 mg intravaginal progesterone twice daily until 34 weeks of gestation	Placebo	There was no significant difference in reducing the incidence of spontaneous birth at 24-33 weeks of gestation, maternal adverse events, or neonatal death, neonatal complications, neonatal therapy, and poor fetal growth, but it may reduce the risk of spontaneous birth before 32 weeks of gestation in women with a cervical length <30 mm and increase the risk in women with a cervical length ≥30 mm.
7	Salim et al., 2019 [18]	Prospective, two-center, double-blind, RCT in Israel	Women with gestational age 13-26 weeks with vaginal bleeding	28.7 ± 4.8	29.8 ± 6.0	60	49	200 mg intravaginal micronized progesterone once daily until delivery or 36 weeks' gestation	Placebo	There were no significant differences in spontaneous deliveries <37 weeks, proportion of births <34 weeks, survival curves, and neonatal morbidity.
8	Shadab et al., 2018 [19]	Prospective, single-center, double-blind, RCT in Pakistan	Women with <20 weeks of gestation and with a past history of premature birth	26.75 ± 3.76	27.99 ± 1.43	66	66	250 mg 17-OHPC intramuscularly up to 37 weeks of gestation	Placebo	There was a significant difference in preventing delivery before 37 weeks of gestation in the 17-OHPC group.
9	Shambhavi et al., 2018 [20]	Prospective, single-center,	Women with a singleton pregnancy with a gestational age of 16-24 weeks and ≥ 1	28.00 ± 4.13	26.94 ± 4.02	50	48	200 mg intravaginal tablet of micronized effervescent progesterone daily until	250 mg 17-OHPC intramuscularly weekly	There were no significant differences in spontaneous preterm delivery <37 weeks, <34 weeks or <28 weeks, neonatal outcomes, and maternal adverse events.

No	Study, Year	Design	Subject	Mean of ages (years)		Total of subjects		Intervention	Control	Outcome
				Intervention	Control	Intervention	Control			
		unblinded RCT in India	previous spontaneous preterm delivery					delivery or 37 weeks of gestation	until delivery or 37 weeks of gestation	
10	Sirisangwon and Phupong, 2021[21]	Prospective, single-center, unblinded RCT in Thailand	Women with preterm labor at 24-34 weeks of gestation	29.5 ± 6.9	30.0 ± 5.9	44	46	400 mg intravaginal micronized progesterone daily until delivery or 36 weeks of gestation	Without intervention	There were significant differences in prolongation of latency, high gestational age at delivery, decreased preterm birth <34 weeks, low birth weight, RDS, and NICU admission in the Progesterone group.
11	Thongchan and Phupong, 2021[22]	Prospective, single-center, double-blind, RCT in Thailand	Women at risk of preterm birth at 24-34 weeks of gestation	29.9 ± 5.7	29.2 ± 7.6	24	24	10 mg Dydrogesterone orally three times per day	Placebo	There was a significant difference in the prolongation of uterine contraction recurrence time in the Dydrogesterone group but not significant in gestational age at delivery, percentage of preterm delivery <34 weeks and <37 weeks, pregnancy outcome, neonatal outcome, and other side effects.
						COX Inhibitor				
12	Andrikopoulou et al., 2018 [23]	Prospective, multicenter, double-blind, RCT in United States of America	Women with a singleton pregnancy with a previous termination of pregnancy but no previous spontaneous pregnancy loss <20 weeks	19 (Range, 17-23)	19 (Range, 17-23)	1262	1281	60 mg Aspirin orally until labor occurs	Placebo	There was a significant difference in the rate of spontaneous preterm birth <34 weeks which was lower in the Aspirin group, but not significant in the rate of overall preterm birth and spontaneous preterm birth <37 weeks
13	APRIL, 2022 [25]	Prospective, multicenter, double-blind, RCT in Netherlands	Women with singleton pregnancies with a gestational age of 22-37 weeks with a history of spontaneous preterm birth	32.8 ± 3.9	32.3 ± 3.6	204	202	80 mg aspirin orally daily until 36 weeks of gestation or delivery	Placebo	There were no significant differences in preterm birth <37 weeks, poor neonatal outcomes, and serious adverse events.
14	ASPIRIN, 2020 [25]	Prospective, multicenter, double-blind, RCT	Women with nulliparous pregnancies with a gestational age of 6-13 weeks	<20 years: 38.6%; 20-29 years: 59.3%; >29 years: 2.2%	<20 years: 39.4%; >20-29 years: 58.4%; >29 years: 2.2%	5787	5771	81 mg Aspirin orally daily until gestational age <37 weeks or delivery	Placebo	There were significant differences in the reduction of preterm births <37 weeks, reduction of perinatal mortality, fetal loss, and the incidence of women delivering <34 weeks with hypertensive pregnancy disorders, but not significant in other maternal and neonatal outcomes.
						COX Inhibitor and Calcium-channel blocker				
15	Kashanian et al., 2019 [26]	Prospective, single-center, double-blind, RCT in Iran	Women with a gestational age of 26-34 weeks of pregnancy with premature labor	Ind: 26.19 ± 6.29, Nif: 27.11 ± 5.99	Com: 28.27 ± 6.55	Ind: 36, Nif: 36	Com: 41	100 mg Indomethacin per rectal with a maximum dose of 200 mg/day or 20 mg Nifedipine orally with a maximum dose of 180 mg/day for 48 hours	Combination of rectal Indomethacin and oral Nifedipine	There were significant differences in the inhibition of preterm labor, delay of labor, and prolongation of gestational duration in the combination group.
						Calcium-channel blocker				
16	Hawkins et al., 2021[27]	Prospective, single-center, double-blind, RCT in Texas	Women with a single pregnancy with a gestational age of 28-33 weeks with uterine activity, intact membranes, and cervical dilation of 2-4 cm	25.5 ± 5.8	26.7 ± 6.7	46	42	20 mg Nifedipine orally, then another 20 mg after 90 minutes if contractions persist, continue every 4 hours after the first dose for 48 hours	Placebo	There were no significant differences in delivery before 37 weeks' gestation, delivery <48 hours, or neonatal outcomes.
17	Songthamwat et al., 2018 [28]	Prospective, single-center, double-blind, RCT in Thailand	Women with threatened preterm labor (regular uterine contractions occurring at least once every 10 minutes and lasting for more than 30 minutes before completing 37 weeks of	27.1 ± 5.73	25.6 ± 5.85	103	103	20 mg Nifedipine orally every 30 minutes with a maximum total of 3 doses until the contractions stop then the maintenance dose using Nifedipine 20 mg orally every 8 hours	Placebo	There were significant differences in cessation of contractions within 90 minutes and successful treatment in the Nifedipine group, but not significant in maternal complications, gestational age at delivery, proportion of deliveries <48 hours, proportion of deliveries <37 weeks, and neonatal outcomes.

No	Study, Year	Design	Subject	Mean of ages (years)		Total of subjects		Intervention	Control	Outcome
				Intervention	Control	Intervention	Control			
			pregnancy without cervical dilation)							
Calcium-channel blockers and nitric oxide donors										
18	Goyal et al., 2023 [29]	Prospective, single-center, RCT in India	Women with preterm labor pain at 28-37 weeks gestation	24.94 ± 3.7	24.4 ± 3.3	65	65	10 mg Nitroglycerin transdermal patch every 24 hours with a maximum dose of 20 mg/24 hours until contractions end for a maximum of 7 days	30 mg Nifedipine orally once, followed by 20 mg after 90 minutes, then 20 mg Nifedipine every 8 hours for a maximum of 7 days	There was a significant difference in pregnancy prolongation <48 hours in the Nitroglycerin group but higher in pregnancy prolongation >21 days, mean gestation, and treatment success in the Nifedipine group.
19	Jamil et al., 2020 [30]	Prospective, single-center, RCT in Pakistan	Women with premature labor	30.43 ± 5.76	26.07 ± 4.39	50	50	5 mg Nitroglycerin transdermal patch for 12 hours with a maximum of 10 mg	10 mg Nifedipine orally once, then 10 mg Nifedipine every 8 hours for 48 hours	There was a significant difference in prolongation of pregnancy >48 hours in the Nitroglycerin group, but not significant in prolongation of pregnancy, in the Nifedipine group it was significant in acute tocolysis failure, headache, but there was no difference in neonatal outcomes (birth weight, low birth weight and very low birth weight babies, need and duration of NICU care)
20	Kaur et al., 2021[31]	Prospective, single-center, single-blind, RCT in India	Women with singleton pregnancies with gestational age of 28-34 weeks with preterm labor	24.52 (Range, 20-24)	24.26 (Range, 25-29)	50	50	Nitrogliserin patch transdermal	20 mg Nifedipine orally and a maintenance dose of 10 mg three times daily	There were significant differences in prolongation of pregnancy and lower headaches in the Nifedipine group but not significant in tachycardia, hypotension, palpitations, and birth weight of the baby.
21	Sharma et al., 2019 [32]	Prospective, single-center, single-blind, RCT in India	Women with singleton pregnancies with gestational age of 28-34 weeks with preterm labor	24.4 ± 3.8	24.1 ± 2.8	51	49	20 mg Nifedipine orally, additional 10 mg if contractions continue, maintenance dose 10 mg every 6 hours for up to 48 hours	20 mg Nitroglycerin transdermal patch every 24 hours	There was no significant difference in the percentage of women who delivered > 48 hours, tocolysis failure, however headaches were significantly higher in the Nitroglycerin group and maternal tachycardia was more common in the Nifedipine group.
Magnesium sulfate										
22	MAGENTA, 2023 [33]	Prospective, multicenter, double-blind, RCT in Australian and New Zealand	Women at risk of premature birth at 30-34 weeks of gestation	30.5 ± 6.2	30.6 ± 6.9	691	674	4 grams of magnesium sulfate intravenously over 30 minutes	Placebo	There were no significant differences in gestational age at birth, Cerebral Palsy-free survival at 2 years of age, and other outcomes.
Magnesium sulfate and calcium-channel blockers										
23	Aziz et al., 2018 [34]	Prospective, single-center, RCT in Pakistan	Women with singleton pregnancies with gestational age of 28-36 weeks with preterm labor	24.66 ± 4.35	23.98 ± 4.05	91	91	4 gr magnesium sulfate initial dose intravenously >15 minutes followed by a maintenance dose of 2-3 gr/hour	30 mg Nifedipine orally, then 30 mg twice daily for up to 5 days	There was a significant difference in higher efficacy for acute tocolysis of preterm labor in the Magnesium sulfate group.
24	Faisal et al., 2020 [35]	Prospective, single-center, RCT in Pakistan	Women with premature labor complaining of labor pain at 24-36 weeks of gestation	27 ± 5.8	27 ± 3.9	30	30	4 grams of magnesium sulfate initial dose intravenously >20 minutes followed by a maintenance dose of 1 gram/hour until contractions stop or a maximum of 48 hours	20 mg Nifedipine orally, then 10 mg after half an hour followed by 20 mg for 48 hours	There was a significant difference in delay of labor and fewer side effects in the Nifedipine group.
Other groups										
25	Carlson et al., 2018 [8]	Prospective, multicenter, double-blind, RCT in Missouri	Women with a gestational age of 12-20 weeks	25.6 ± 4.7	25.6 ± 4.7	169	176	200 mg Docosahexaenoic acid capsules orally, three times daily until the end of pregnancy	Placebo	There was a significant difference in the reduction in the incidence of early preterm birth, very low birth weight, and low birth weight in the Docosahexaenoic acid group.

No	Study, Year	Design	Subject	Mean of ages (years)		Total of subjects		Intervention	Control	Outcome
				Intervention	Control	Intervention	Control			
26	Carlson et al., 2023 [9]	Prospective, multicenter, double-blind, RCT in Missouri	Women with a single pregnancy before 20 weeks of gestation	27.6 ± 5.6 / 31.3 ± 5.5	30.1 ± 5.6	124 / 416	492	200 mg Docosahexaenoic acid capsule orally + 800 mg Docosahexaenoic acid capsule orally with adherence <5.5%/≥5.5%	200 mg Docosahexaenoic acid kapsul orally + Placebo	There was a significant difference in the reduction of early preterm birth and preterm birth in the group that adhered to high-dose docosahexaenoic acid, and the greatest effect of adherence in reducing early preterm birth was in women with low baseline docosahexaenoic acid levels.
27	Cluver et al., 2018 [36]	Prospective, single-center, double-blind, RCT in South Africa	Women with premature preeclampsia with gestational age 26-31 weeks)	Median, 24 (Range, 21-31)	Median, 30 (Range, 25-34)	59	60	40 mg Esomeprazole orally daily	Placebo	There was a significant difference in placental abruption, but not significant in prolongation of gestational age, maternal and neonatal outcomes.
28	Cluver et al., 2021[37]	Prospective, single-center, double-blind, RCT in South Africa	Women with premature preeclampsia with gestational age 26-31 weeks)	Median, 29 (Range, 25-33)	Median, 27 (Range, 23-34)	90	90	3 g Metformin extended-release orally (1 g three times a day)	Placebo	There were no significant differences in gestational age prolongation and maternal and neonatal outcomes.
29	Okunade et al., 2022 [38]	Prospective, single-center, double-blind, RCT in Nigeria	Women with singleton pregnancies at 14-27 weeks of gestation who are HIV seropositive	29.3 ± 6.3	30.1 ± 5.8	78	80	200 µg elemental selenium	Placebo	There was a significant difference in reducing preterm birth, but not significant in reducing the risk of full-term birth with low birth weight, the risk of perinatal death, and drug side effects.
30	ORIP, 2019 [6]	Prospective, multicenter, double-blind, RCT in Australia	Women with single or multiple pregnancies	Median, 30 (Range, 26-34)	Median, 30 (Range 27-33)	2734	2752	500 mg fish oil capsules (900 mg n−3 long-chain polyunsaturated fatty acids) orally three times daily until 34 weeks of gestation or delivery	500 mg vegetable oil capsules (trace n−3 long-chain polyunsaturated fatty acids)	There were no significant differences in early preterm delivery, incidence of post-term delivery, adverse events, or neonatal outcomes, except that the percentage of very large for gestational age infants was higher, and minor gastrointestinal disturbances were more common in the n−3 long-chain polyunsaturated fatty acids group.
31	Otsuki et al., 2018 [39]	Prospective, multicenter, double-blind, RCT	Women with a gestational age of 16-26 weeks with a short cervical length <25 mm and diagnosed with genital infection	32.6 ± 5.5	34.1 ± 4.7	35	35	Ulinastatin intravaginal	Placebo	There was no significant difference in the incidence of preterm delivery before 28, 30, 32, 34 and 37 weeks of gestation and in perinatal outcomes.
32	Saade et al., 2021 [40]	Prospective, multicenter, double-blind, RCT in New Zealand	Women with preterm birth in singleton pregnancies with gestational age of 24-33 weeks	30.8 ± 2.63 36.3 ± 2.84	30.5 ± 2.49 36.3 ± 2.74	10 47	13 50	6 mg Retosiban intravenously >5 minutes followed by Retosiban infusion 6 mg/hour	Placebo 6.75 mg Atosiban intravenously >1 minute followed by Atosiban infusion 18 mg/hour for 3 hours, then reduced to 6 mg/hour	There were no significant differences in time to delivery/treatment failure, side effects, or neonatal outcomes.
33	Walters et al., 2023 [41]	Prospective, single-center, double-blind, RCT in New Zealand	Women at risk of preterm birth with gestational age 24-<37 weeks	25.2 + 5.8	26.0 + 5.9	560	582	6 mg Betamethasone phosphate, short-acting, and 6 mg Betamethasone acetate, long-acting, intramuscularly	Placebo	There was a significant difference in the risk of RDS reduction with better efficacy in male infants and gestational age at birth of 28-34 weeks in the Betamethasone group, but not significant in fetal or neonatal death, neonatal or maternal infection, neonatal hypoglycemia, cesarean delivery, and lactation status.
34	Yelland et al., 2023 [7]	Prospective, multicenter, double-blind, RCT in Australia	Women with single or multiple pregnancies	Median, 30 (Range, 26-34)	Median, 30 (Range 27-33)	2654	2674	500 mg fish oil capsules (900 mg omega−3 long-chain polyunsaturated fatty acids) orally three times daily until 34 weeks of gestation or delivery	500 mg vegetable oil capsules	There was a significant difference in the reduction of early preterm births (<34 weeks) in the omega−3 long-chain polyunsaturated fatty acids group and a reduction in preterm births (<37 weeks) in multiparous women in the omega−3 long-chain polyunsaturated fatty acids group.

*17-OHPC: *17α-hydroxyprogesterone caproate*, RDS: *respiratory distress syndrome*, APGAR: *appearance, pulse, grimace, activity, and respiration*, Com: *Combination of* Indometachin dan Nifedipine, Ind: Indometachin, NICU: *neonatal intensive care unit*, Nif: Nifedipine, PPROM: *preterm premature rupture of the membranes*, RCT: *randomized-controlled trial*.

Table 2. Modified Jadad Score Study

ID	Included studies	Was the research described as randomized? #	Was the approach of randomization appropriate? *	Was the research described as blinding? #	Is the approach of blinding appropriate? *	Was there a presentation of withdrawals and dropouts? #	Was there a presentation of the inclusion/exclusion criteria? #	Was the approach used to assess adverse effects described? #	Was the approach of statistical analysis described? #	Total
1	Alizadeh et al., 2022	1	1	0	0	1	1	0	1	5
2	Hyett et al., 2022	1	1	1	1	1	1	1	1	8
3	Keshtmandi et al., 2023	1	1	1	1	1	1	1	1	8
4	Langen et al., 2018	1	1	1	1	1	1	1	1	8
5	PROLONG, 2020	1	1	1	1	1	1	1	1	8
6	Rehal et al., 2021	1	1	1	1	1	1	1	1	8
7	Salim et al., 2019	1	1	1	1	1	1	1	1	8
8	Shadab et al., 2018	1	1	1	1	0	1	1	1	7
9	Shambhavi et al., 2018	1	1	0	0	1	1	1	1	6
10	Sirisangwon and Phupong, 2021	1	1	0	0	1	1	1	1	6
11	Thongchan and Phupong, 2021	1	1	1	1	1	1	1	1	8
12	Andrikopoulou et al., 2018	1	1	1	1	1	1	1	1	8
13	APRIL, 2022	1	1	1	1	1	1	1	1	8
14	ASPIRIN, 2020	1	1	1	1	1	1	1	1	8
15	Kashanian et al., 2019	1	1	1	1	1	1	1	1	8
16	Hawkins et al., 20211	1	1	1	1	1	1	1	1	8
17	Songthamwat et al., 2018	1	1	1	1	1	1	1	1	8
18	Goyal et al., 2023	1	1	0	0	0	1	1	1	5
19	Jamil et al., 2020	1	1	0	0	0	1	1	1	6
20	Kaur et al., 2021	1	1	0.5	0	1	1	1	1	6.5
21	Sharma et al., 2019	1	1	0.5	0	1	1	1	1	6.5
22	MAGENTA, 2023	1	1	1	1	1	1	1	1	8
23	Aziz et al., 2018	1	1	0	0	0	0	1	1	4
24	Faisal et al., 2020	1	1	0	0	0	1	1	1	6
25	Carlson et al., 2018	1	1	1	1	0	1	1	1	7
26	Carlson et al., 2023	1	1	1	1	0	1	1	1	7
27	Cluver et al., 2018	1	1	1	1	1	1	1	1	8
28	Cluver et al., 2021	1	1	1	1	1	1	1	1	8
29	Okunade et al., 2022	1	1	1	1	1	1	1	1	8
30	ORIP, 2019	1	1	1	1	1	1	0	1	7
31	Otsuki et al., 2018	1	1	1	1	1	1	1	1	8
32	Saade et al., 2021	1	1	1	1	1	1	1	1	8
33	Walters et al., 2023	1	1	1	1	0	1	0	1	6
34	Yelland et al., 2023	1	1	1	1	1	1	1	0	7

Note: [a]: double-blind got 1 score, single-blind got 0.5 score.
#: "1" means "Yes", "0" means "No";
*: "1" means "Yes", "0" means "Not described"