BMC Pediatrics

RESEARCH

Open Access

Efficient administration of a combination of nifedipine and sildenafil citrate versus only nifedipine on clinical outcomes in women with threatened preterm labor: a systematic review and meta-analysis

Elham Manouchehri[1,2], Somayeh Makvandi[3], Mahdieh Razi[4], Maryam Sahebari[1] and Mona Larki[5,6*]

Abstract

Background Preterm labor (PTL) is a common and serious pregnancy disorder that can cause long-term neurological issues in the infant. There are conflicting studies concerning whether sildenafil citrate (SC) reduces preterm labor complications. Therefore, the meta-analysis aimed to examine the clinical outcomes in women with threatened PTL who received nifedipine plus SC therapy versus only nifedipine.

Methods For the original articles, six databases were searched using relevant keywords without restriction on time or language until January 13, 2024. The Cochrane risk-of-bias tool for randomized trials (RoB) and the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS) were both used to assess the risk of bias in randomized and non-randomized studies, and GRADE determined the quality of our evidence. Meta-analysis of all data was carried out using Review Manager (RevMan) version 5.1.

Results Seven studies with mixed quality were included in the meta-analysis. The study found that combining nifedipine and SC resulted in more prolongation of pregnancy (MD = 6.99, 95% CI: 5.32, 8.65, $p < 0.00001$), a lower rate of delivery in the 1st to 3rd days after hospitalization (RR = 0.62, 95% CI: 0.50, 0.76, $p < 0.00001$), a higher birth weight (252.48 g vs. nifedipine alone, $p = 0.02$), and the risk ratio of admission to the neonatal intensive care unit (NICU) was significantly lower (RR = 0.62, 95% CI: 0.50, 0.76, $p < 0.00001$) compared to nifidepine alone. The evidence was high for prolongation of pregnancy, delivery rate 24–72 h after admission, and NICU admission, but low for newborn birth weight.

Conclusions Given the effectiveness of SC plus nifedipine in increased prolongation of pregnancy and birth weight, lower delivery in the 1st to 3rd days after hospitalization, and NICU admission, Gynecologists and obstetricians are suggested to consider this strategy for PTL management, although additional article rigor is required to improve the quality of the evidence.

Keywords Nifedipine, Sildenafil citrate, Preterm labor, Systematic review, Meta-analysis

*Correspondence:
Mona Larki
mona.larki66@gmail.com
Full list of author information is available at the end of the article

Introduction

Approximately 13.4 million preterm births were born globally in 2023. 15% of preterm deliveries globally occurred before 32 weeks of gestation between 2010 and 2020, requiring additional medical care [1]. Preterm labor (PTL) is a common and serious pregnancy condition that can cause long-term neurological issues in the infant [2]. Therefore, to reduce its effects on families and the healthcare system, PTL must be prevented [3]. Tocolytic therapy postpones childbirth for 24–48 h to administer corticosteroids. This reduces the occurrence and severity of respiratory complications and facilitates the transfer of the fetus to a hospital with a suitable neonatal critical care unit (NICU) [4, 5]. As per the guidelines of the Royal College of Obstetricians and Gynecologists, nifedipine is the recommended medicine choice for tocolytics [6]. According to updated World Health Organization (2022) antenatal corticosteroids recommendations, the Lancet recently reported an important point on tocolytic therapy in PTL. The guideline panel emphasized that tocolytic therapy should only be given when the potential advantages outweigh the risks for mother and fetus and safety requirements were also ensured [7, 8]. The hypothesis suggests that Sildenafil citrate (SC) can promote uterine quietness in patients at risk of premature birth by causing smooth muscle relaxation using the release of nitric oxide (NO) [9]. The increasing utilization of SC in the management of vascular or contractile diseases during pregnancy was just introduced [10, 11]. Currently, the advantages of utilizing the drug in managing preeclampsia [12, 13], in addition to the verified presence of growth restriction conditions [14, 15].

A 2020 Iranian study proposed that the addition of SC to nifedipine treatment for threatened PTL resulted in several positive outcomes. The positive outcomes seen were a longer delay in delivery in cases of PTL, a decreased risk for respiratory distress syndrome (RDS), a reduction in NICU admissions, and an increase in neonatal birth weight [16]. An additional study was done in Egypt in 2023 in which two groups were given nifedipine alone or in combination with SC, and it was found that there was no statistically significant difference between the two groups in terms of the number of neonatal infections or the outcome of the fetus. However, a significant difference was found between the two groups under investigation concerning newborn respiratory distress, with an increased incidence of this disease in the group receiving nifedipine alone ($P=0.02$) [17].

To efficiently allocate resources towards managing the risk of PTL and providing evidence-based quality care, it is crucial to have strong and well-supported evidence for prioritizing investments. This is particularly important considering the mixed clinical outcomes of administering SC treatment in combination with a first-line drug in PTL in various research studies. The meta-analysis aimed to examine the clinical outcomes in women with threatened PTL who received nifedipine plus SC therapy versus only nifedipine.

Materials and methods

This systematic review and meta-analysis follows the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) standards.

Search strategy

For original publications about "Efficacy of a combination of nifedipine and SC versus nifedipine in clinical outcomes in PTL," a search was conducted until January 13, 2024. The search process was conducted for MEDLINE through the PubMed interface, Scopus, Web-of-Science, Science Direct, the Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar. The search terms included MESH, entrance terms, and keyword selections by experts. They comprised: sildenafil citrate, Viagra, Revatio, Nifedipine, Adalat, Acetildenafil, Preterm labor, Premature birth (Table 1).

Inclusion and exclusion criteria

Articles were included that met the following criteria: (a) Type of study: randomized clinical trials (RCTs) and quasi-experimental studies in which the effect of nifedipine versus a combination of nifedipine and SC on clinical outcomes of PTL; (b) Type of intervention: administration of nifedipine combined with SC with any dose; length of time in women with threatened PTL was considered; (C) Outcomes: weight of birth, admission to the NICU, and latency in childbirth were considered. Exclusion criteria included (a) studies conducted on animals; (b) lack of access to full text; (C) letters to the editor; commentary; articles presented at conferences; preprint articles; and retracted articles. We imposed no language and no time restrictions.

Data abstraction

The primary output of the search procedure was examined in terms of title and abstract by two different researchers after duplicate articles had been removed and unrelated items had been discarded. The remaining articles' full texts were then read. Unrelated articles were eliminated, and only those that met the eligibility criteria remained. To arrive at a final joint opinion in cases where there was a difference of opinion between reviewers, the two appraisers' differences were resolved through discussion, and in cases where there was still disagreement, the third person would enter into the discussion.

Table 1 Search strategy of databases

PUBMED			
("sildenafil"[Title/Abstract] OR "Viagra"[Title/Abstract] OR "Homosildenafil"[Title/Abstract] OR "Revatio"[Title/Abstract] OR "Acetildenafil"[Title/Abstract]) AND ("Nifedipine"[Title/Abstract] OR "Adalat"[Title/Abstract] OR "Fenigidin"[Title/Abstract] OR "Procardia"[Title/Abstract] OR "cordipin*"[Title/Abstract]) AND ("preterm"[Title/Abstract] OR "premature"[Title/Abstract]) AND 1985/01/01:2024/12/31[Date—Publication]			7 results
Web of Science			
# Web of Science Search Strategy (v0.1) # Database: Web of Science Core Collection # Entitlements: - WOS.SCI: 1945 to 2024 - WOS.AHCI: 1975 to 2024 - WOS.ESCI: 2019 to 2024 - WOS.SSCI: 1956 to 2024 # Searches: 1: ((((TS = (sildenafil)) OR TS = (Viagra)) OR TS = (Homosildenafil)) OR TS = (Revatio)) OR TS = (Acetildenafil) Date Run: Sat Jan 13 2024 09:14:14 GMT + 0330 (Iran Standard Time) Results: 13468 2: ((((TS = (nifedipine)) OR TS = (adalat)) OR TS = (Fenigidin)) OR TS = (Procardia)) OR TS = (cordipin*) Date Run: Sat Jan 13 2024 09:16:17 GMT + 0330 (Iran Standard Time) Results: 22095 3: (TS = (preterm)) OR TS = (premature) Date Run: Sat Jan 13 2024 09:17:04 GMT + 0330 (Iran Standard Time) Results: 252524 4: #1 AND #2 AND #3 Date Run: Sat Jan 13 2024 09:17:42 GMT + 0330 (Iran Standard Time) Results: 7			7 results
Scopus			
#1 TITLE-ABS-KEY (sildenafil) OR TITLE-ABS-KEY (viagra) OR TITLE-ABS-KEY (homosildenafil) OR TITLE-ABS-KEY (revatio): 23,225 document results #2 TITLE-ABS-KEY (nifedipine) OR TITLE-ABS-KEY (adalat) OR TITLE-ABS-KEY (fenigidin) OR TITLE-ABS-KEY (procardia): 55,195 document results #3 TITLE-ABS-KEY (preterm) OR TITLE-ABS-KEY (premature): 355,668 document results #4 #1 AND #2 AND #3: 35 document results			35 results
ScienceDirect			
("sildenafil citrate" OR viagra) AND (nifedipine OR adalat) AND (preterm OR premature)			114 results
Cochrane library			
Date Run:		13/01/2024 09:02:44	2 results
ID	Search	Hits	
#1	MeSH descriptor: [Sildenafil Citrate] explode all trees	1098	
#2	MeSH descriptor: [Nifedipine] explode all trees	2245	
#3	MeSH descriptor: [Premature Birth] explode all trees	2180	
#4	preterm	17,810	
#5	#3 OR #4	18,263	
#6	#1 AND #2 AND #5	2	

Data extraction

The research team initially constructed a data extraction tool, and the data was extracted based on the items. This was done to extract the data from the articles in an integrated manner. The first author's name, the publication year, the country, the type of study, the sample size, sample characteristics, the intervention, the comparison, the tools used to collect the data, the quality assessment, and the outcomes were all listed. Using independent pairwise evaluations, two researchers (EM and ML) conducted the assessment. Disagreements were once again settled through debate or, in cases where it was not feasible, by requesting the participation of the independent third author. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) was used to rate the quality of the studies that were included. GRADE is a well-known way to figure out how certain evidence is by looking at its risk of bias, imprecision, inconsistency, indirectness, and publication bias [18].

Risk of bias

Two authors conducted separate evaluations to determine the quality of the research studies that were included. The risk of bias for randomized and non-randomized trials was evaluated by version 2 of the risk-of-bias tool for

randomized trials (RoB2) in the Cochrane Handbook [19] and the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS) tool, respectively [20].

The ROB2 tool has five domains through which bias might be introduced into the result including [1] randomization process, [2] deviations from the intended interventions, [3] missing outcome data, [4] measurement of the outcome, and [5] selection of the reported result. Each domain assessed and each study overall is shown to have either a low risk of bias, some concerns relating to the risk of bias, or a high risk of bias.

All sources of bias currently considered to have an impact on the results of nonrandomized studies of interventions are covered by the domains contained in the RoBANS tool. It includes 6 domains that assess bias in participant selection, confounding variables, exposure measurement, outcome assessment blinding, incomplete outcome data, and selective outcome reporting. In both instruments, each domain was rated as "yes," "no," or "unclear" Then, each study was classified into 1 of 3 categories: "poor" (high risk of bias), "good" (low risk of bias), or "unclear." Any disagreement between the researchers was resolved through discussion.

Ethical considerations

Mashhad University of Medical Sciences in Mashhad, Iran, has acknowledged the systematic review and meta-analysis (code number 4021715). We diligently adhered to all research ethics requirements in the current study. The authors attempted to prevent plagiarism and refrain from manipulating the data for their advantage. The research team thoroughly addressed all ethical concerns in the stages of identification, screening, extraction, and data analysis.

Statistical analyses

Meta-analyses of all data were performed using Review Manager (RevMan) version 5.1. For the same outcome that had a mean and standard deviation, if the same assessment scale was used between studies, the mean difference (MD) was used to estimate the effect size, with 95% confidence intervals (CI) to express the confidence level. In one of the studies, quantitative data were given as median (range), which were converted into mean and standard deviation [21]. We used the risk ratio (RR) with a 95% CI to express dichotomous data. Heterogeneity between studies was assessed using Chi^2 and I-squared, and I-squared > 50% was considered to be significantly heterogeneous. If there was no significant statistical heterogeneity, the fixed effects estimate was typically used as the summary measure. In a single picture, the forest plots were used to provide an overview of the data from separate research, provide a visual representation of the degree of study heterogeneity, and display the estimated common impact. Publication bias was not evaluated due to the limited number of research studies considered in each forest plot. Moreover, subgroup analyses were set up to explore whether the results of the effect values were the same under different conditions, and sensitivity analysis was used to verify the reliability of the meta-analysis results and reduce heterogeneity.

Results

Characteristics of the included studies

After the electronic search, out of 364 retrieved studies, 41 studies were evaluated after the initial screening process and 7 studies were included in the meta-analysis (Fig. 1). The publication date of the articles was between 2019 and 2023, and 4 articles (57%) were published in [17, 22–24], which indicates that a combination of nifedipine and SC has recently been considered in PTL management. The characteristics of the articles included in the meta-analysis are shown in Table 2. The included articles were conducted in Iran (28.5%) [16, 23], Pakistan (28.5%) [22, 25], Egypt (28.5%) [17, 26], and India (14.5%) [24]. The sample size in the articles varied from 60 [24] to 292 [25] per study. The study design in 6 studies (85.5%) was a randomized control trial (RCT) and one study (14.5%) was quasi-experimental [24].

The number of participants in the included articles was 1105, of which 554 were in the Nif + Sil (case) group and 551 were in the Nif (control) group. Out of 6 RCTs, the" block randomization method" was used in two studies [16, 23], and the "computerized random number table generator" was used in four studies [17, 22, 25, 26]. In all of the included studies, nifedipine was started with 20 mg followed by 10 mg every 6–8 h. Only in the study of Mohammadi et al. the starting dose was 10 mg [16].

In the inclusion criteria of the participants, the gestational age varied between 24 and 37 weeks. In 5 studies, the maximum gestational age was considered to be 34 weeks [16, 17, 22, 23, 26]. Also, in three studies, the minimum gestational age was 24 weeks [23, 25, 26].

In 5 studies, the participants had received corticosteroids for fetal lung maturation, in 4 studies dexamethasone [17, 22, 25, 26], and in one study betamethasone was prescribed [22]. However, in the study of Singh et al. [24] and Mohammadi et al. [16] there was no mention of corticosteroid administration.

In 3 studies cervical assessment by transvaginal ultrasound was also performed as a screening tool to determine the likelihood of birth within 48 h of admission [17, 24, 26].

Risk of bias assessment

In the assessment of the methodological quality of the included RCTs using the ROB2 tool, five studies were at high risk of bias [17, 22, 23, 25, 26] and one trial was rated as having some concerns [16] (Table 3). Also, a methodological quality assessment of

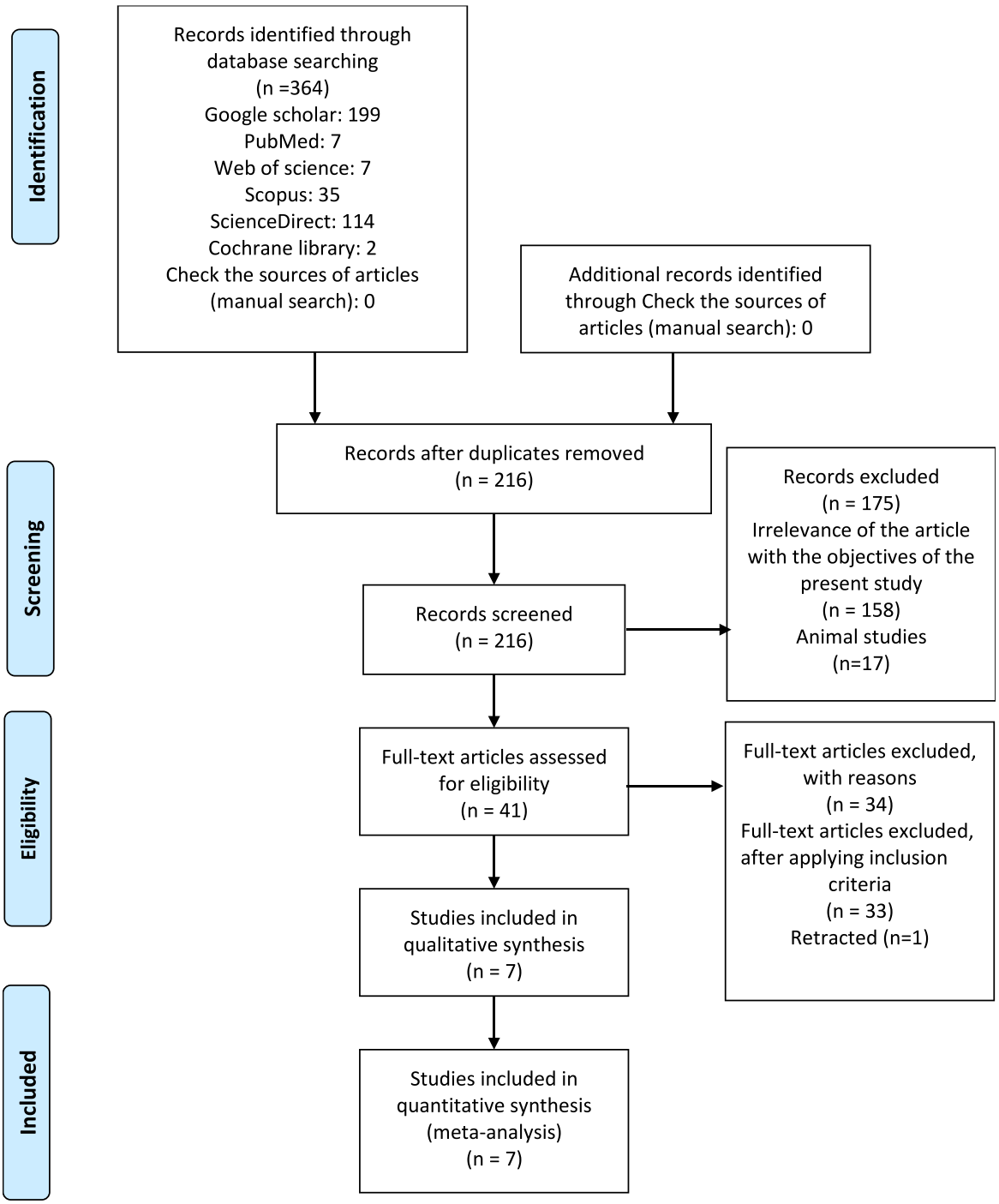

Fig. 1 Flowchart of the process of selecting articles based on PRISMA

one non-randomized study was performed using the RoBANS tool, which was reported as high risk of bias [24]. The biggest weakness in the qualitative evaluation of the studies was 'deviations from intended interventions' [17, 24, 25].

All of the studies had a low risk of bias on "missing outcome data" and "selective reporting " items (Table 3).

Table 2 Characteristics of the articles included in the meta-analysis

First author/ Publication year	Country	Study type	Randomization Method	Sample size	Sample characteristics	Intervention	Comparison	outcome	Quality assessment
Hassan A. (2023) [22]	Pakistan	RCT	computer-generated random number table (balloting method)	160 (80 + 80)	"singleton gestation presenting at gestational age 30 weeks to 34 weeks with PTL and cervical dilatation of ≤ 3 cm"	"nifedipine 20 mg orally, followed by 10 mg orally every eight hours for 48 h and vaginal administration of sildenafil citrate, 25 mg at eight-hour intervals, for 48 h"	"nifedipine 20 mg orally, followed by 10 mg orally every 8 h for 48 h."	sildenafil citrate plus nifedipine showed a significant effect in the management of PTL and prolongation in mean gestational age at delivery	high
Nasrolahei Sh. (2023) [23]	Iran	RCT	block randomization method	126 (63 + 63)	"PTL at the age of 15–45 yr, cases of threatened PTL (uterine contractions > 4 in 20 min with cervical dilatation and effacement), between 24–34 weeks gestation, intact fetal membranes, cervical dilatation less than 4 cm, does not have any significant chronic medical conditions, has no medical restrictions for Nif and SC therapy, and has not experienced PTL in the past"	Nif 20 mg orally (single dose), then 10 mg every 6-h, and at the same time vaginal SC 25 mg every 8 h (Nif + SC)	Nif 20 mg orally (single dose), then 10 mg every 6-h	Nif with SC is superior to Nif alone in women at risk of PTL due to increasing gestational age and better neonatal outcomes	high
Mohammadi E. (2021) [16]	Iran	RCT	block randomization method	132 (66 + 66)	pregnant women with a gestational age of 26–34 weeks with singleton pregnancy and diagnosis of preterm delivery	nifedipine (10 mg every 6 to 8 h, orally) plus sildenafil (25 mg every 8 h, vaginally)	nifedipine (10 mg every 6 to 8 h, orally)	In PTL instances, using SC in addition to nifedipine results in a longer delivery time, a decreased risk of respiratory distress syndrome (RDS), fewer admissions to the NICU, and preservation of neonatal birth weight	high

Table 2 (continued)

First author/ Publication year	Country	Study type	Randomization Method	Sample size	Sample characteristics	Intervention	Comparison	outcome	Quality assessment
Qurat-ul-Ain (2021) [25]	Pakistan	RCT	random number table	292(146 + 146)	threatened PTL with a singleton pregnancy between 24 and 36 + 6 weeks of gestation	nifedipine 20 mg orally (stat dose), followed by 10 mg orally every 8 h and at the same time oral administration of SC (25 mg at 8-hourly intervals)	nifedipine 20 mg orally (stat dose), followed by 10 mg orally every 8 h	Oral SC combined with nifedipine is an effective option for tocolytic therapy for threatened PTL	high
El-Sayed Y. (2023) [17]	Egypt	RCT	computerized random number table	96 (48 + 48)	Pregnancy with a single fetus between 28 and 34 weeks, with no rupture of the membranes	"Oral nifedipine 20 mg (stat dosage), then 10 mg every 6 h concurrently with oral SC 20 mg given at 8 h"	nifedipine 20 mg orally (stat dose), followed by 10 mg orally every 6 h	A statistically significant difference was observed between the two groups under study in delivery 24,48 and 72 h after admission, with fewer early deliveries among the nifedipine with sildenafil group. Vaginal SC plus with nifedipine is most effective tocolytic medication in threatened PTL	high
Maher M. (2019) [26]	Egypt	RCT	computerized random number table generator	239 (121 + 118)	Pregnancies with singleton fetuses between 24 and 34 weeks' gestation are threatened by PTL	" The nifedipine and SC groups received the same dosage as the nifedipine-only group, with the additional dose given by 25 mg of SC every 8 h vaginally."	"nifedipine only group (20 mg nifedipine orally followed by 10 mg orally every 6 to 8 h)"	The combination of SC administration and nifedipine is a highly successful choice for tocolytic therapy in cases of PTL	high
Singh Sh. (2023) [24]	India	Quasi-experimental	no (convenient sampling)	60 (30 + 30)	Singleton pregnancy with 28–37 gestational age and without vaginal discharge	"Nifedipine 20 mg orally stat dose followed by 10 mg orally every 6–8 h at the same time as vaginal administration of sildenafil citrate 25 mg at 8th hourly interval every 6-8 h."	"Administer a single oral dose of Nifedipine at 20 mg and a maintenance dose of 10 mg orally every 6–8 h."	SC plus nifedipine is more effective than nifedipine alone in avoiding PTL	high

Table 3 Risk of bias of included studies

Cochrane Risk of Bias Assessment Tool for Randomized Studies 2 (RoB 2)							
Studies	**Randomization Process**	**deviations from intended interventions**	**missing outcome data**	**measurement of the outcome**	**selection of the reported result**		**Overall risk of bias**
Hassan A. (2023) [22]	Low	High	Low	Low	Low		High
Nasrolahei Sh. (2023) [23]	Low	High	Low	Low	Low		High
Mohammadi E. (2021) [16]	Some concerns	Low	Low	Low	Low		Some concerns
Qurat-ul-Ain (2021)	High	High	Low	High	Low		High
El-Sayed Y. (2023) [17]	Some concerns	High	Low	High	Low		High
Maher M. (2019) [26]	Low	High	Low	High	Low	High	
The Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS)							
Studies	**Selection of participants**	**Confounding variables**	**Measurement of exposure**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective outcome reporting**	**Overall**
Singh Sh. (2023) [24]	unclear	unclear	low	unclear	low	low	high

Meta-analysis findings

Effect of the intervention on the prolongation of pregnancy

Common effect size Figure 2 shows the forest plot of the intervention on the prolongation of pregnancy. The pooled analysis showed that the combination of nifedipine and sildenafil citrate was associated with more prolongation of pregnancy compared to nifedipine alone (MD = 6.99, 95% CI: 5.32, 8.65, $p < 0.00001$). The heterogeneity among the studies was moderate (I-squared = 45%). Due to the limited number of articles, the publication bias could not be evaluated.

Sensitivity analysis Due to the moderate heterogeneity, it was necessary to perform a sensitivity analysis to check the reliability of the results. After excluding the study with the highest body weight [16], the pooled effect size favored the combination therapy group (MD = 7.86, 95% CI: 5.02,10.69, $p < 0.00001$). Additionally, when excluding the study with the largest sample [26], the pooled effect size was better for the combination therapy group (MD = 6.39, 95% CI: 5.29, 7.50, $p < 0.00001$).

Even if the trial with the smallest sample was excluded [24], the pooled effect size still showed greater pregnancy prolongation in the combination therapy group (MD = 7.71, 95% CI: 4.82–10.59, $p < 0.00001$). Therefore, the reanalysis performed on heterogeneity did not yield different results from the primary analysis.

Effect of the intervention on the delivery rate in the 24–72 h after admission

Common effect size The forest plot of the combination therapy effect on the delivery rate in the 24–72 h after admission is presented in Fig. 3. Based on the findings of this plot, the use of SC along with Nifdipin compared to Nifdipin alone was associated with a lower rate of delivery in the 1st to 3rd days after hospitalization, which was statistically significant (RR = 0.62, 95% CI: 0.50, 0.76, $p < 0.00001$). Due to the lack of significant heterogeneity (I-squared = 0%, $p = 1.0$), the fixed effect model was used. The publication bias was not measured due to the small number of articles.

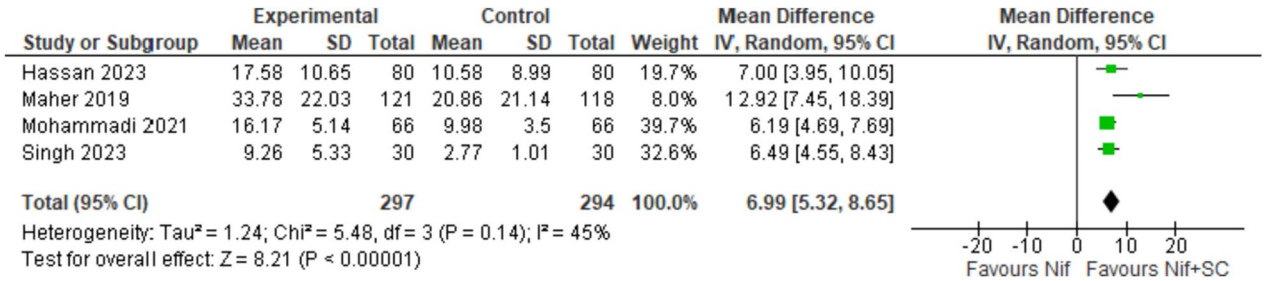

Fig. 2 Forest plot of the effect of Sildenafil citrate along with Nifedipine compared to Nifedipine alone on the prolongation of pregnancy (days)

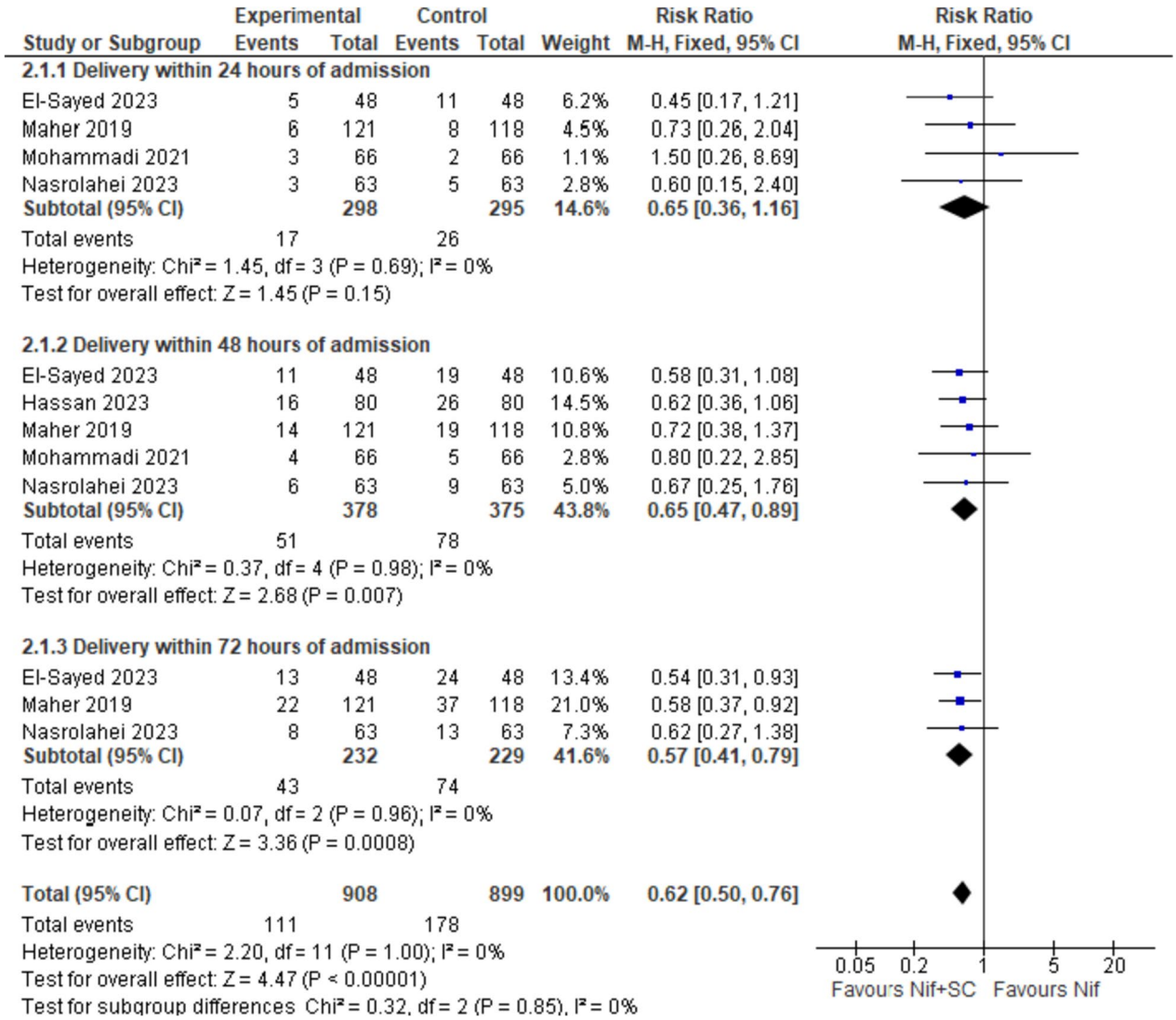

Fig.3 Forest plot of the effect of Sildenafil citrate along with Nifedipine compared to Nifedipine alone on the delivery rate in the 24–72 h after admission

Subgroup analysis Analysis of subgroups showed that in the first 24 h after the intervention, the risk ratio of delivery was not significantly different in the two studied groups (RR = 0.65, 95% CI: 0.36, 1.16, $p = 0.15$). but, at 48 h (RR = 0.65, 95% CI: 0.47, 0.89, $p = 0.007$) and 72 h (RR = 0.57, 95% CI: 0.41, 0.79, $p = 0.0008$) after the intervention, the risk ratio of delivery rate was significantly lower in the SC and nifedipine group compared to the nifedipine group alone.

Effect of the intervention on neonatal birth weight

Common effect size Figure 4 shows the forest plot of the effect of nifedipine and SC treatment regimen compared to nifedipine alone on the birth weight of neonates. The results of the meta-analysis showed that according to the random effect model, the birth weight of neonates in the combination therapy group was 252.48 g more than the nifedipine group alone, which was statistically significant ($p = 0.02$). Publication bias was not assessed because the number of studies was insufficient.

Sensitivity analysis Due to high heterogeneity between studies (I-squred = 93%, $p < 0.00001$), sensitivity analysis was performed. The findings showed that by excluding the study with the largest weight [16], the birth weight in the combination therapy group was significantly higher than the comparison group (MD = 167.72, 95% CI: 99.16, 236.28, $p < 0.00001$). Also, by excluding the study with the largest sample size [26], the findings were still in favor of the combination therapy group (MD = 301.82, 95% CI: 72.22, 512.65, $p = 0.01$). However, with the withdrawal of the study with the smallest sample size [24], although the birth weight of neonates was still higher in the combination therapy group compared to the nifedipine group, the *P*-value increased to 0.5 and therefore this difference was out of significance (MD = 242.90, 95% CI: -3.47, 489.45, $p = 0.05$).

Effect of the intervention on the NICU admission

Figure 5 shows the forest plot of the pooled risk ratio of the intervention effect on the rate of NICU admission. According to the findings of the meta-analysis, in the group using the combination of nifedipine and SC, the risk ratio of admission to the NICU was significantly lower than in the group using Nifedipine alone (RR = 0.62, 95% CI: 0.50, 0.76, $p < 0.00001$). A fixed effect model was used due to low heterogeneity (I-squared = 0%, $p = 0.83$). Publication bias was not evaluated due to the small number of studies.

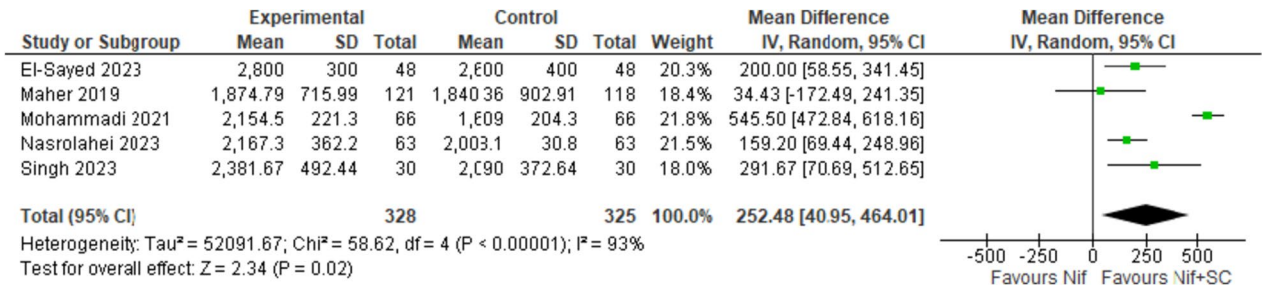

Fig. 4 Forest plot of the effect of Sildenafil citrate along with Nifedipine compared to Nifedipine alone on neonatal birth weight (grams)

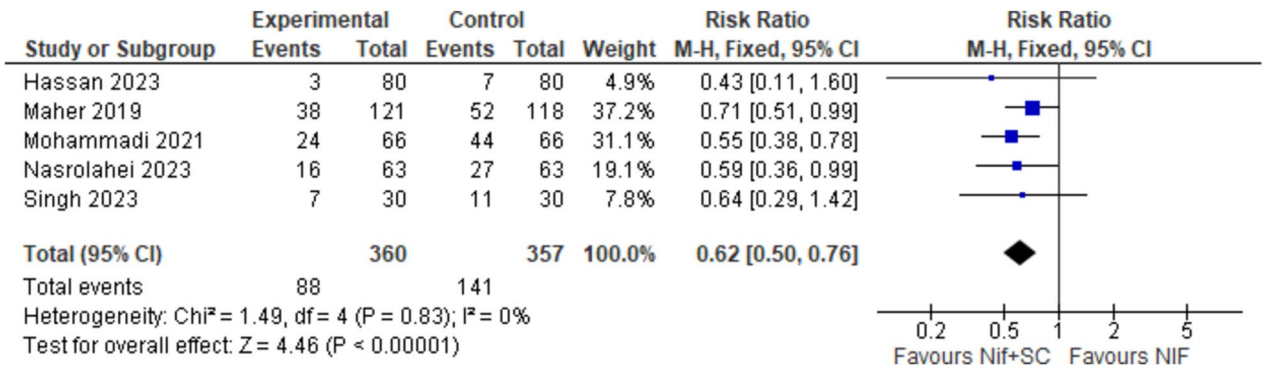

Fig. 5 Forest plot of the effect of Sildenafil citrate along with Nifedipine compared to Nifedipine on the rate of NICU admission

Table 4 GRADE evidence profiles for outcomes among the studies included in the meta-analysis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nifedipine and Sildenafil**	**Nifedipine alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Prolongation of pregnancy												
4	randomised trials	very serious[a]	not serious	not serious	not serious	very strong association	297	294	-	MD 6.99 higher (5.32 higher to 8.65 higher)	⨁⨁⨁⨁ High	CRITICAL
Delivery rate in the 24–72 h after admission												
5	randomised trials	very serious[a]	not serious	not serious	not serious	very strong association	111/908 (12.2%)	178/899 (19.8%)	RR 0.62 (0.50 to 0.76)	75 fewer per 1,000 (from 99 to 48 fewer)	⨁⨁⨁⨁ High	CRITICAL
Neonatal birth weight												
5	randomised trials	very serious[a]	serious[b]	not serious	not serious	strong association	328	325	-	MD 252.48 higher (40.95 higher to 494.01 higher)	⨁⨁◯◯ Low	IMPORTANT
NICU admission												
5	randomised trials	very serious[a]	not serious	not serious	not serious	very strong association	88/360 (24.4%)	141/357 (39.5%)	RR 0.62 (0.50 to 0.76)	150 fewer per 1,000 (from 197 to 95 fewer)	⨁⨁⨁⨁ High	IMPORTANT

CI Confidence interval, *MD* Mean difference, *RR* Risk ratio

Explanations

[a] The overall bias for most of the studies is high risk

[b] The magnitude of the results in the individual studies vary and high heterogeneity exists

Quality of evidence We used GRADEpro GDT (Guideline Development Tool) to assess the quality of evidence for outcomes, and the results are shown in Table 4. The quality of evidence was high for prolongation of pregnancy, delivery rate in the 24–72 h after admission, and NICU admission. They were given two downgrades by the risk of bias and two upgrades by very large effect size. The quality of evidence was low for neonatal birth weight. It was given three downgrades by inconsistency and risk of bias and one upgrade by large effect size.

Discussion

This systematic review and meta-analysis was conducted to compare a combination of nifedipine and SC versus only nifedipine in terms of clinical outcomes in women with threatened PTL. In the current systematic review and meta-analysis, we examined 6 RCTs and 1 quasi-experimental study involving women with threatened PTL. The pooled analysis showed that the combination of nifedipine and SC was associated with significantly more prolongation of pregnancy, a lower rate of delivery in the 1st to 3rd days after hospitalization, higher birth weight of neonates, and lower admission to the NICU compared to nifedipine alone.

We believe this meta-analysis is the first to directly assess the efficacy of a combination of nifedipine and SC with only nifedipine in preterm pregnancy, and no meta-analysis has examined the effects of sildenafil on PTL.

Numerous Cochrane systematic studies on the impact of various tocolytics on the outcomes of mothers and newborns have been performed [27–29]. The Cochrane reviews investigated only randomized trials and often concluded that there is insufficient evidence addressing the benefits and possible disadvantages of tocolysis in particular groups of women. This conclusion highlights the crucial matter of exploring alternative pharmaceuticals to achieve optimal results in cases of PTL.

In a 2022 meta-analysis, Cochrane compared tocolytics for premature birth prolongation. Betamimetics, calcium channel blockers, magnesium sulfate, oxytocin receptor antagonists, and nitric oxide donors may have helped to delay early birth for up to seven days and 48 h compared to a placebo or no drug treatment. But tocolytics induce several side effects, from mild to severe. The three most efficacious tocolytics, including nifedipine, oxytocin receptor antagonists, and nitric oxide donors, demonstrated the most beneficial balance between advantages and risks. Nifedipine has the potential to diminish the incidence of respiratory complications, neurodevelopmental disorders, and low birth weight [30].

The current meta-analysis showed significantly higher pregnancy prolongation and a lower birth rate in the first to third days following hospitalization. The prolongation of pregnancy variable was investigated in four studies [16, 22, 24, 26]. Postponing premature birth can provide an opportunity for crucial, internationally approved measures to enhance the health of newborns, such as the prescription of prenatal corticosteroids or a shift to a more advanced level of medical care [31]. One potential mechanism for the impact of SC on PTL is the inhibition of the enzyme phosphodiesterase type 5 by SC. This inhibition results in an elevation of C-guanosine monophosphate levels in smooth muscle in the arteries, which increases the expansion of smooth muscle [23].

Meta-analysis results showed a combination of nifedipine and SC leads to a significantly higher birth weight in neonates; it was investigated in five studies [16, 17, 23, 24, 26]. It is absolutely obvious that with pregnancy prolongation, the weight of the fetus will increase. Evidence suggests that newborns with very low birth weights (VLBW) are frequently the most seriously ill and most at risk for future morbidity and death. They also contribute significantly to the number of hospital days overall and take up a significant amount of the time, energy, and financial resources of NICU staff [32]. As a result, reducing LBW has been declared to be an important health goal, and the international community established a global objective of 30% fewer newborns born with LBW between 2010 and 2025 [33]. It is important to find strategies that lead to a reduction in NICU hospitalization, given the imposed burden. Recent research revealed that the out-of-pocket expenses of families and the utilization of long-lasting medical equipment were linked to heightened financial distress [34, 35].

In a study conducted by Abdulhameed et al. (2021), the use of sildenafil citrate along with routine tocolytics (case group) was compared with the routine tocolytics group (control group). According to the results of this study, in the case group, the mean gestational age and the mean weight of the neonate were higher than the control group. On the other hand, fetal anomaly and fetal growth restriction were more in the control group than in the case group. The live birth rate was also higher in the case group, but none of the above outcomes were statistically significant [6].The results of this study are consistent with the present meta-analysis in terms of higher gestational age and birth weight.

Ashraf Ali et al. (2018) investigated seven randomized controlled trials of atosiban versus nifedipine to conclude which one was better at inhibiting PTL. They found that atosiban had fewer adverse effects on mothers than nifedipine, but both drugs made pregnancy last the same amount of time. In terms of safety, nifedipine caused greater maternal adverse effects than atosiban, including headaches and tachycardia [36]. It was also stated that nifedipine's oral method, low cost, and potential to

reduce newborn morbidity, especially RDS, support its usage, although it can cause maternal side effects.

According to a meta-analysis conducted in 2023, prophylactic SC use in infants at risk of bronchopulmonary dysplasia (BPD) did not appear to have any positive effects on mortality, BPD, or other outcomes; it also did not appear to have any increased side effects [37]. With only three trials and a limited sample size of 162 newborns, this study could not achieve an ideal information size for all outcomes evaluated.

In the current meta-analysis, there was variability in some factors. Nevertheless, we did not conduct subgroup analyses to examine the potential factors contributing to this variability, such as the precise dosage of SC, the gestational age at which it was administered, or the particular method employed. This was because the assessed research lacked adequate, comprehensive data regarding their methods of inquiry. Hence, a crucial objective would be to determine the most suitable dosing schedules for SC treatments to avoid any adverse effects and maximize their efficacy. Furthermore, the administration of tocolytic medicines should be tailored to each individual and based on the potential for negative side effects and the overall health of the mother.

In the articles included in the present study, side effects following the use of SC were not reported. The maternal tolerance generally in pregnancy was analyzed by Dunn et al. [38] and Ferreira et al. [39], considering that using SC during pregnancy did not cause any serious side effects in the mother and that the available information supports the medication's safety and potential for use as a treatment for specific diseases affecting the mother and fetus. On the other hand, the Dutch STRIDER experiment revealed that newborns exposed to SC had a higher chance of developing neonatal pulmonary hypertension [40]. The study sample consisted of pregnancies at high risk with fetal growth restrictions. However, there is a lack of research examining the safety of SC in pregnancies with normal risk. The controversy and extensive media coverage surrounding the STRIDER trials have raised public awareness of the risks associated with using this drug class in pregnant populations. This view presents significant obstacles for subsequent studies in this particular field. No long-term research followed infants, so we couldn't determine the medicine's childhood impacts. Due to its safety during pregnancy and lack of teratogenic effects, SC may be a potential premature delivery medicine.

Given that there is no universally accepted method for evaluating the certainty of the effect estimates produced by the meta-analysis, we followed the GRADE Working Group's advice and applied the rigorous method for assessing the reliability of network evidence. In general, the quality of the evidence ranged greatly, and our level of confidence in the estimations varied from low for neonatal birth weight to high for prolongation of pregnancy, delivery rate in the 24–72 h after admission, and NICU admission certainty. Of course, despite all the above interpretations, due to the overall risk of bias in the articles included in the present study, we suggest conducting randomized studies with high power regarding the effect of SC on PTL, especially with special attention to the domain of deviations from intended interventions.

This review's advantages include following the Cochrane Handbook to identify and reduce all biases. This review includes trials identified through a comprehensive, language-free search. At least two review authors independently screened, extracted, and assessed bias. We have many review weaknesses. Most RCTs we examined had poor methodology, affecting study reliability. It is important to realize that the trials in the study recruited women with different clinical features when interpreting the outcomes. Not all trials recorded adverse effects; therefore, these analyses were underpowered. To consolidate neonatal birth weight evidence, more high-quality, big trials are needed. Finally, publication bias may result from the small number of studies. More research will concentrate on maternal SC treatment's long-term consequences. Although randomized trials with these women are challenging, well-conducted retrospective observational studies may assist global clinical decision-making. An economic evaluation must be done to consider benefits, risks, supply costs, and resource needs when assessing SC and nifedipine.

Conclusion

The combination of nifedipine and sildenafil citrate was associated with more prolongation of pregnancy, a lower rate of delivery in the 1st to 3rd days after hospitalization, a high birth weight of neonates, and lower admission to the NICU compared to nifedipine alone. Further high-quality, large trials are required to improve the certainty of the evidence about the neonatal birth weight variable. The results of this study can be useful for policymakers and experts in the field of obstetrics and gynecology to consider different options when providing health services with fewer complications to women at risk of premature birth.

Acknowledgements
Not applicable.

Authors' contributions
M.L, E.M, and S.M conducted title and full-text screening. E.M and M.R extracted data. M.S and S.M performed a risk of bias assessment and GRADE. S.M, M.R and M.L performed the ROB and RoBANS assessment and publication bias assessment, formulated the final tables, and drafted the first version of the manuscript. M.L conceived the study, provided methodologic and content

expertise, and supervised all steps of the study. All authors reviewed the article and approved its content.

Funding
The present meta-analysis study was conducted with the financial support of the Mashhad University of Medical Sciences, Mashhad, Iran.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Rheumatic Diseases Research Center, Mashhad University of Medical Sciences, Mashhad, Iran. [2]Department of Midwifery, Faculty of Nursing and Midwifery, Mashhad Medical Sciences, Islamic Azad University, Mashhad, Iran. [3]Menopause Andropause Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. [4]Department of Pediatrics, School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran. [5]Nursing and Midwifery Care Research Center, Mashhad University of Medical Sciences, Mashhad, Iran. [6]Department of Midwifery, School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran.

Received: 2 January 2024 Accepted: 23 January 2024
Published online: 10 February 2024

References

1. Ohuma EO, Moller A-B, Bradley E, Chakwera S, Hussain-Alkhateeb L, Lewin A, et al. National, regional, and global estimates of preterm birth in 2020, with trends from 2010: a systematic analysis. Lancet. 2023;402(10409):1261–71.
2. Giouleka S, Tsakiridis I, Kostakis N, Koutsouki G, Kalogiannidis I, Mamopoulos A, et al. Preterm labor: a comprehensive review of guidelines on diagnosis, management, prediction and prevention. Obstet Gynecol Surv. 2022;77(5):302–17.
3. Boobpamala S, Jindapaisan S, Wanniyom N, Thessawadwong R. Effectiveness of the Preterm Labor Prevention Program for High-Risk Pregnant Women: A Randomized Controlled Trial. Pacific Rim Intl Journal of Nursing Research. 2024;28(1):71–87.
4. Harrison MS, Goldenberg RL. Global burden of prematurity. Semin Fetal Neonatal Med. 2016;21(2):74–9.
5. Catov JM, Scifres CM, Caritis SN, Bertolet M, Larkin J, Parks WT. Neonatal outcomes following preterm birth classified according to placental features. Am J Obstet Gynecol. 2017;216(4):411. e1-.e14.
6. Abdulhameed WA, Abbood MS, Jwad MA. Comparison between the effect of sildenafil citrate and routine tocolytic agents in a prevention of preterm labor. NVEO NAT VOLATILES ESSENTIAL OILS J . 2021:4590–602.
7. Organization WH. WHO recommendations on antenatal corticosteroids for improving preterm birth outcomes. In: WHO recommendations on antenatal corticosteroids for improving preterm birth outcomes. 2022. p. 40.
8. Vogel JP, Ramson J, Darmstadt GL, Qureshi ZP, Chou D, Bahl R, Oladapo OT. Updated WHO recommendations on antenatal corticosteroids and tocolytic therapy for improving preterm birth outcomes. Lancet Glob Health. 2022;10(12):e1707–8.
9. Khan RN, Hamoud H, Warren A, Wong LF, Arulkumaran S. Relaxant action of sildenafil citrate (Viagra) on human myometrium of pregnancy. Am J Obstet Gynecol. 2004;191(1):315–21.
10. Reynolds LP, Caton JS, Redmer DA, Grazul-Bilska AT, Vonnahme KA, Borowicz PP, et al. Evidence for altered placental blood flow and vascularity in compromised pregnancies. J Physiol. 2006;572(1):51–8.
11. Sun X, Wang K, Wang W, Li B. Clinical study on sildenafil in treatment of pregnant women with pulmonary arterial hypertension. Zhonghua Fu Chan Ke Za Zhi. 2014;49(6):414–8.
12. Brownfoot FC, Tong S, Hannan NJ, Cannon P, Nguyen V, Tu'uhevaha J. Effect of sildenafil citrate on circulating levels of sFlt-1 in preeclampsia. Pregn Hypertens. 2018;13:1–6.
13. Trapani A Jr, Gonçalves LF, Trapani TF, Vieira S, Pires M, de Souza Pires MM. Perinatal and hemodynamic evaluation of sildenafil citrate for preeclampsia treatment: a randomized controlled trial. Obstet Gynecol. 2016;128(2):253–9.
14. Shehata NA, Ali HA, Fahim AS, Katta MA, Hussein GK. Addition of sildenafil citrate for treatment of severe intrauterine growth restriction: a double blind randomized placebo controlled trial. J Matern Fetal Neonatal Med. 2020;33(10):1631–7.
15. Trapani A Jr, Gonçalves L, Trapani T, Franco M, Galluzzo R, Pires M. Comparison between transdermal nitroglycerin and sildenafil citrate in intrauterine growth restriction: effects on uterine, umbilical and fetal middle cerebral artery pulsatility indices. Ultrasound Obstet Gynecol. 2016;48(1):61–5.
16. Mohammadi E, Teymoordash SN, Norouzi AR, Norouzi F, Norouzi HR. Comparison of the effect of nifedipine alone and the combination of nifedipine and sildenafil in delaying preterm labor: a randomized clinical trial. J Fam Reprod Health. 2021;15(2):112.
17. El- Sayed Y, Hamed R, Aboelwan Y, Abdel-Salam WA, Hamed BM. Comparative study between nifedipine alone versus nifedipine combined with sildenafil citrate for cases with threatened preterm labour. Zagazig Univ Med J. 2023;29(1.1):1–8.
18. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–6.
19. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, Thomas J. Updated guidance for trusted systematic reviews: a new edition of the cochrane handbook for systematic reviews of interventions. Cochrane Database Syst Rev. 2019;10(10):ED000142.
20. Kim SY, Park JE, Lee YJ, Seo H-J, Sheen S-S, Hahn S, et al. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. J Clin Epidemiol. 2013;66(4):408–14.
21. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5(1):1–10.
22. Hassan A, Waseem H, AlDardeir N, Nasief H, Khadawardi K, Alwazzan AB, et al. A Comparison of Nifedipine Versus a Combination of Nifedipine and Sildenafil Citrate in the Management of Preterm Labour. Cureus. 2023;15(7):e42422.
23. Nasrolahei S, Hoseini SA, Hosseini SA, Hosseini SNK, Hosseini SS, Lotfi PM. Effect of nifedipine with and without sildenafil citrate for the management of preterm labor in pregnant women: A randomized clinical trial. Int J Reprod Biomed. 2023;21(5):379.
24. Singh SHSS. Effect of oral nifedipine or combined with sildenafil citrate for management of threatened preterm labour randomized trial. Indian Journal of Obstetrics and Gynecology Research. 2023;10(3):313–9.
25. Qurat-ul-ain FS, Fariha, Akmal N, Malik KK, Rashid M. Comparison between sildenafil citrate & nifedipine with nifedipine alone for the treatment of threatened preterm Labour. Pak J Med Health Sci. 2020;14(2):433–6.
26. Maher M, Sayyed T, El-Khadry S. Retracted: nifedipine alone or combined with sildenafil citrate for management of threatened preterm labour: a randomised trial. BJOG. 2019;126(6):729–35.
27. Flenady V, Reinebrant HE, Liley HG, Tambimuttu EG, Papatsonis DN. Oxytocin receptor antagonists for inhibiting preterm labour. Cochrane Database Syst Rev. 2014;6(6):CD004452.
28. Flenady V, Wojcieszek AM, Papatsonis DN, Stock OM, Murray L, Jardine LA, Carbonne B. Calcium channel blockers for inhibiting preterm labour and birth. Cochrane Database Syst Rev. 2014;5(6):CD002255.
29. Neilson JP, West HM, Dowswell T. Betamimetics for inhibiting preterm labour. Cochrane Database Syst Rev. 2014;5(2):CD004352.

30. Wilson A, Hodgetts-Morton VA, Marson EJ, Markland AD, Larkai E, Papadopoulou A, et al. Tocolytics for delaying preterm birth: a network meta-analysis (0924). Cochrane Database Syst Rev. 2022;8(8):CD014978.
31. Organization WH. WHO recommendations on interventions to improve preterm birth outcomes. 2015.
32. Eichenwald EC, Stark AR. Management and outcomes of very low birth weight. N Engl J Med. 2008;358(16):1700–11.
33. McGuire S. World Health Organization. Comprehensive implementation plan on maternal, infant, and young child nutrition. Geneva, Switzerland, 2014. Adv Nutr. 2015;6(1):134–5.
34. Lakshmanan A, Song AY, Belfort MB, Yieh L, Dukhovny D, Friedlich PS, Gong CL. The financial burden experienced by families of preterm infants after NICU discharge. J Perinatol. 2022;42(2):223–30.
35. Lambiase CV, Mansi G, Salomè S. et al. The financial burden experienced by families during NICU hospitalization and after discharge: A single center, survey-based study. Eur J Pediatr. 2023. https://doi.org/10.1007/s00431-023-05352-y.
36. Ali AA, Sayed AK, El Sherif L, Loutfi GO, Ahmed AMM, Mohamed HB, et al. Systematic review and meta-analysis of randomized controlled trials of atosiban versus nifedipine for inhibition of preterm labor. Int J Gynecol Obstet. 2019;145(2):139–48.
37. Hirata K, Nakahari A, Takeoka M, Watanabe M, Nishimura Y, Katayama Y, et al. Prophylactic sildenafil in preterm infants at risk of bronchopulmonary dysplasia: A systematic review and meta-analysis. Authorea Preprints. 2023.
38. Dunn L, Greer R, Flenady V, Kumar S. Sildenafil in pregnancy: a systematic review of maternal tolerance and obstetric and perinatal outcomes. Fetal Diagn Ther. 2017;41(2):81–8.
39. Ferreira RDdS, Negrini R, Bernardo WM, Simoes R, Piato S. The effects of sildenafil in maternal and fetal outcomes in pregnancy: a systematic review and meta-analysis. PloS one. 2019;14(7):732.
40. Pels A, Derks J, Elvan-Taspinar A, van Drongelen J, de Boer M, Duvekot H, et al. Maternal sildenafil vs placebo in pregnant women with severe early-onset fetal growth restriction: a randomized clinical trial. JAMA Netw Open. 2020;3(6):e205323.

Publisher's Note