

## Literature Review

**Nifedipine, Calcium Channel Blocker (Antihypertensive), as a Tocolytic to inhibit Premature Birth in Reducing the Risk of Neonatal Death in Childbirth: Meta-Analysis and Systematic Review of Large Clinical Trial*****Nifedipine, Penghambat Kanal Kalsium (Antihipertensi), sebagai Tokolitik dalam Menghambat Kelahiran Prematur dalam Menurunkan Risiko Kematian Neonatus pada Persalinan: Meta-Analisis dan Telaah Sistematis dari Studi Besar Uji Klinis***

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Jakarta***Abstract****Objective:** To evaluate the role of nifedipine as a tocolytic agent.**Methods:** Literature searches use medical search engines for example Pubmed, Google Scholar and Medical scientific journals, as like the American kind of Journal that is Learning Obstetrics and also learn about Gynecology. The literature used were published from 1986 to 2020. The main data extraction was in the form of an extended gestation period, divided into 48 hours, 7 days, and 37 weeks with data analysis using the RevMan 5.4 application.**Result:** Twenty-four clinical trials were analyzed with total amount shown of 2,889 study subjects. The purpose of using kind of nifedipine to be such a tocolytic indicates no significant difference, within 48 hours or (RR 1.06; 95% CI, 0.99 - 1.13; p shown = 0.12), 7 days (RR 1.02; 95% CI, 0.95 - 1.09; p = 0.57), and up to 37 weeks (RR 1.22; 95% then CI, 0.96 - 1.54; p = 0.10) at the time it is compared with the group of control.**Conclusion:** Administration of nifedipine as a tocolytic did not have a statistically significant difference, both in prolonging pregnancy and side effects for pregnant women and neonates compared to the control group.**Keywords:** meta-analysis, nifedipine, preterm delivery, prolongation pregnancy, tocolytic.**Abstrak****Tujuan:** Untuk mengevaluasi peran nifedipin sebagai tokolitik.**Metode:** Pencarian literatur menggunakan mesin pencari medis seperti Pubmed, Google Scholar dan jurnal ilmiah medis, seperti American Journal of Obstetrics and Gynecology. Literatur yang digunakan dalam rentang tahun 1986 - 2020. Kata kunci adalah ("pregnant woman" OR pregnancy) AND ("preterm birth" OR "preterm labor") AND nifedipine. Ekstraksi data utama berupa perpanjangan masa kehamilan, dibagi menjadi 48 jam, 7 hari, dan 37 minggu dengan analisis data menggunakan aplikasi RevMan 5.4**Hasil:** Dua puluh empat uji klinis yang dianalisa dengan total 2,889 subjek penelitian. Penggunaan nifedipin sebagai tokolitik menunjukkan tidak ada sesuatu yang berbeda secara signifikan, dalam 48 jam (RR 1.06; 95% then CI, 0.99 - 1.13; p results = 0.12), 7 hari (RR shown 1.02; 95% then CI, 0.95 - 1.09; p = 0.57), dan sampai 37 minggu (RR 1.22; 95% CI, 0.96 - 1.54; p shown = 0.10) apabila dibandingkan dengan kelompok kontrol. Begitu pun dengan efek samping pada ibu hamil (RR 0.99; 95% CI, 0.74 - 1.31; p = 0.92) dan neonatus (RR 0.93; 95% of CI, 0.83 - 1.04; p shown = 0.21), ditemukan adanya kesamaan yang serupa pada grup atau golongan dalam kendali.**Kesimpulan:** Pemberian nifedipin sebagai tokolitik tidak memiliki perbedaan yang signifikan secara statistik, baik dalam memperpanjang masa kehamilan maupun efek samping kepada ibu hamil dan neonatus dibandingkan dengan kelompok kontrol.**Kata kunci:** kehamilan memanjang, kelahiran prematur, meta-analysis, nifedipin, tokolitik.**Correspondence author.** Axel J. Olda. Department of Obstetrics and Gynecology  
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## INTRODUCTION

Preterm birth is an issue of healthcare and social awareness which were claimed as the reason led of mortality rate in neonates around the world. They make it collected into upper rates kind of being neurodevelopmental in morbidity, then comes to sensorineural of impairments and also complications else.<sup>1</sup> Preterm of labor claimed it parturition which happens at the time in 20 0/7 of weeks from gestation then 36 6/7 of weeks. It also get categorized becoming an early and also late of preterm. The meaning of early preterm claimed as the time that the baby get brought to the world in previous 33 weeks, then the late preterm happened the time a baby get brought to the world in 34 and also 36 weeks.<sup>2,3</sup>

Preterm birth interferes with normal maturation development of the organ systems, causing severe and prolonged side effects. It was found that it is easier and earlier for preterm-born to get high blood pressure, cardiac dysfunction, obstructive lung disease, elevation in blood glucose and mental state issues then those of the in-term population. Adverse health conditions can significantly effect on the welfare of individuals who were born prematurely from their childhood to adulthood.

Initiation of at the meaning given is complicated and incomprehensible. Felt Spontaneous onset of preterm labor coming from the rupture of membranes and or contractions definite explanation hasn't been founded, especially regarding the sequence and timing of events. There's still limited proof of the advantage of antenatal intervention, but using well-known risky categories of spontaneous from preterm delivery to elect between pregnant woman for getting more thorough interventions which should be targeted individually most matter compared to the perspective given from medical and also caregiving.<sup>4,5</sup> Indonesia was known to be registered some of countries which has the biggest preterm of giving birth in the year 2010.<sup>6</sup>

The condition defined the preterm of giving birth claimed as the main reason les to risk of neonatal death with giving it 35% %age of 3.1 million of death cases happened in a year as its total, and also are one of the cause behind under-5 mortality in worldwide after Pneumonia. While in high and also middle-income nations claimed that the condition of preterm birth causes the most factor of child death cases. Baby who born premature has bigger risk of dying because

of other causes, mainly because of neonatal infections which predicted to be in 50% of neonatal deaths.<sup>7</sup> Preterm birth complications are the main reason led to mortality, whether being such neonatal period and also the global under-5 mortality.<sup>8</sup>

In Indonesia itself, the most factor led to neonatal deaths cases that occurred around year 2015 which prematurity which results (35.5 %), of asphyxia of having birth and also because of trauma (21.6 %) and for congenital anomalies (17.1%).<sup>9</sup> In 2019, neonatal mortality rate for Indonesia was 12.4 deaths cases each of 1,000 living births.<sup>10</sup>

Tocolysis is an obstetric procedure performed using method of giving medications in a purpose to get delaying the delivery of the fetus inside women who have premature contraction.<sup>11,12</sup>

The term of tocolysis is defined as a prolong of pregnancy between two until seven days and also acts more in making such an atmosphere happened in the uterus, in hope that it will decrease the fetal morbidity and mortality. The effectivity of tocolysis lies in its focus of delaying and weakening the uterine contraction. Myometrium as the smooth muscle in the uterus is it's pharmacological targets. Labor can start earlier regardless of the normal average gestation age is 40 weeks. It's believed that the sudden condition happen because a change of balance in proinflammatory and also in anti-inflammatory cytokines.<sup>13</sup>

Predisposition factor from preterm labor which are the infection, uterine happened to distention stress, complication in vascular and decidual senesence. Fetus has smaller chance of survival if the contractions begin too early. Calcium channel of blockers (Nifedipine) precisely go on T-type of calcium type of channels to prevent the contraction of uterus by prohibiting the way calcium goes to uterine smooth muscle.<sup>11,12</sup> Our main objective is evaluating the role of nifedipine as a tocolytic when compared to controls including side effects to pregnant women and neonates.

## METHODS

Literature searches use medical search engines such as Pubmed, Google Scholar and Medical Scientific journals, for example the American of Journal which is learning Obstetrics and also learning Gynecology. The literature used ranges from 1986 to 2020. The key word are ("pregnant woman" OR pregnancy) AND ("preterm birth"

OR “preterm labor”) AND nifedipine. The main data extraction was in the form of an extended gestation period, divided into 48 hours, 7 days, and 37 weeks with data analysis using the RevMan 5.4 application. The inclusion criteria for the research subjects were pregnant women gets the risk of experiencing preterm labor with a gestational age range of 20 - 36 weeks. Using nifedipine as tocolytic and there is a control group, the research design is in the form of clinical trials, systematic reviews, and metanalysis.

**RESULTS**

Twenty-four clinical trials were analyzed with a total of 2,889 study subjects. The purpose of using nifedipine to be tocolytic which seem to have no significant difference, within 48 hours (RR 1.06; 95% CI, 0.99 - 1.13; p = 0.12) (figure 1), 7 days or the same with (RR 1.02; 95% CI, 0.95 - 1.09; p shown = 0.57) (figure 2), and comes around 37 weeks (RR 1.22; 95% CI, 0.96 - 1.54; p = 0.10) (figure 3) which was being compared with the group of control. Likewise with side effects in pregnant women (RR 0.99; 95% CI, 0.74 - 1.31; p = 0.92) and neonates (RR 0.93; 95% CI, 0.83 - 1.04; p shown = 0.21), there claimed not to have any difference with the group of control.

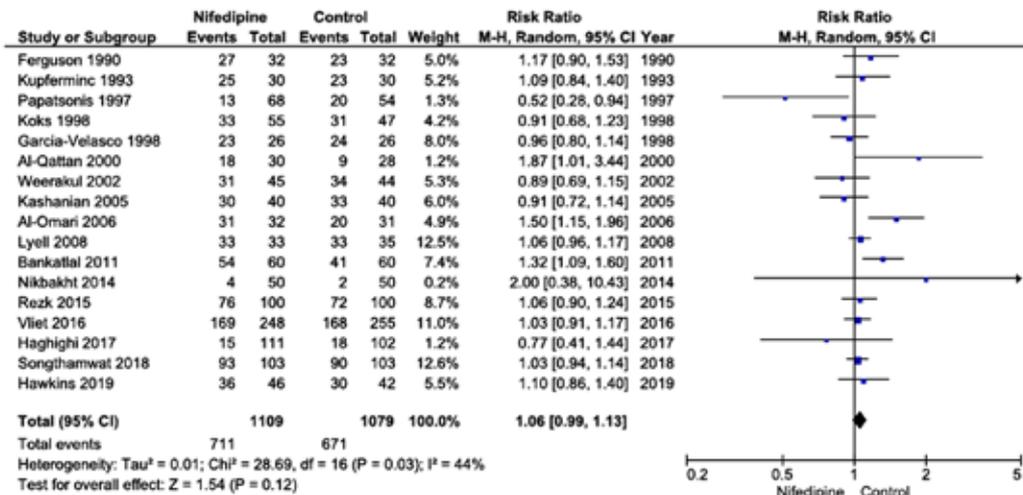


Figure 1. Forest plot showing the prolongation of pregnancy up to 48 Hours

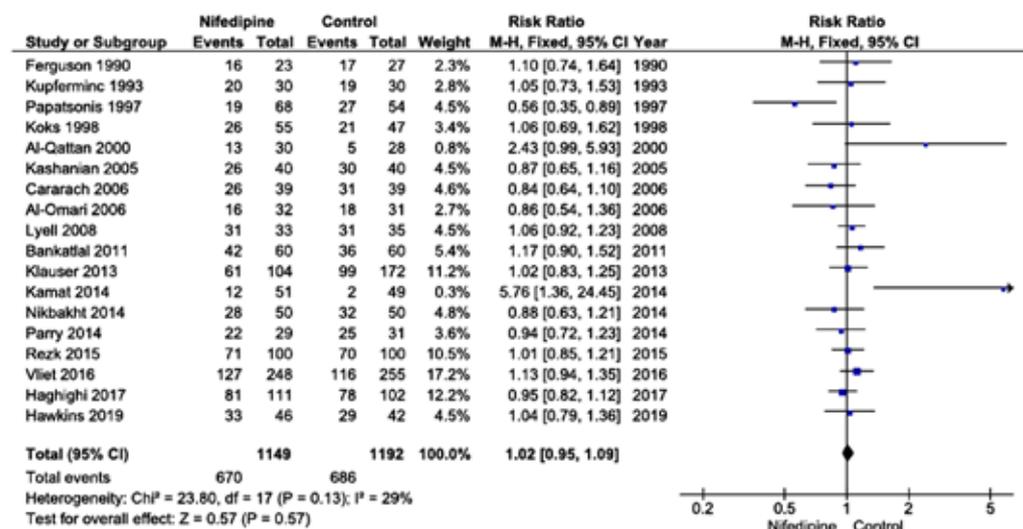


Figure 2. Forest plot showing the prolongation of pregnancy up to 7 days

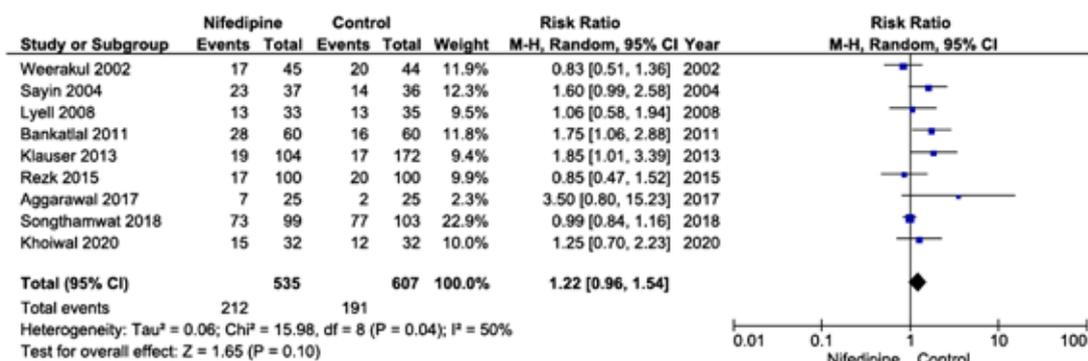


Figure 3. Forest plot showing the prolongation of pregnancy up to 37 weeks

## DISCUSSION

Using meta-analysis in this study has the purpose to define it as based on two latest pre-existing meta analyzes. The two previous meta-analyzes examined the role of nifedipine as a tocolytic. Both in terms of effectiveness, or safety of pregnant women and their babies.

The first one showed that being compared to progesterone, nifedipine was better at prolonging pregnancy (RR 23.50; 95% CI, 18.40 - 28.60). However, there was no difference which the time it is compared with the placebo (RR 2.21; 95% CI, -3.63 - 8.05). For neonatal side effects, there was no difference with neonates weight (RR 5.58; 95% CI, -103.28 - 114.43).<sup>14</sup>

For a second meta-analysis, showed that when compared to atosiban nifedipine there claimed not to have any significant difference onto the prolongation period of having pregnancy to 48 hours or more. Both include the condition from having efficacy (RR 1.06; 95% CI, .92 - 1.22) and effectiveness (RR 0.93; 95% then CI, 0.84 - 1.03). The same thing happened in the extension of the gestation period to 7 days or more.<sup>15</sup>

There was no difference in maternal side effects (RR 0.47; 95% CI, .22 - 0.99,  $p = 0.05$ ), palpitations (RR 0.37; 95% CI, 0.10 - 1.33,  $p = 0.13$ ), hypotension (RR 0.30). ; 95% CI, 0.80 - 1.19,  $p = 0.09$ ), vomiting (RR 1.55; 95% CI, 0.28 - 8.64,  $p = 0.62$ ), nausea (RR 2.44; 95% CI, 0.13 - 46.73,  $p = 0.55$ ). However, there were differences in tachycardia (RR 0.20; 95% CI, 0.05 - 0.74,  $p = 0.02$ ).<sup>16</sup>

Likewise, there claimed not to have any significant difference of side effects for neonates alone with respect to respiratory failure (RR 0.79; 95% CI, 0.27 - 2.34,  $p = 0.67$ ), intraventricular bleeding (RR 0.79; 95% CI, 0.26 - 2.41,  $p = 0.68$ ), neonatal sepsis (RR 0.98; 95% CI, 0.60 - 1.60,

$p = 0.93$ ), necrotizing enterocolitis (RR 1.75; 95% CI, 0.11-29.02,  $p = 0.69$ ).<sup>15</sup>

Based on the results of several previous meta-analyzes, there is no difference between nifedipine as a tocolytic and others tocolytic as a control. The control group here was atosiban, indomethacin, MgSO<sub>4</sub>, progesterone, ritrodine, terbutaline, nicorandil, isoxsuprine, and placebo. Coming back from the term of Preterm Labor and also Birth guidelines which learnt from the National of Institute that learn about Health and also Care Excellence (NICE), nifedipine is still a recommendation in choosing tocolytics. This guide has been coming up in 2020.<sup>16</sup>

According to the National of Institute that learn about Health issues and also Care of Excellence (NICE), Nifedipine as a tocolytic offer to woman between 26<sup>0</sup> and 33<sup>+6</sup> weeks of having pregnancy those have such as intact of membranes and also being judged to be had kind of preterm labor.<sup>16</sup>

Calcium channel of blockers (CCBs) claimed as non- specific of soft muscle that is claimed to be relaxants, then predominantly is intended for the maintenance of hypertension and is claimed to get used in many doses to be a tocolytic for women in having kind of preterm labor.<sup>17</sup> Nifedipine is defined as dihydropyridine calcium channel of blocker that giving action onto L-type calcium of channels to get calcium influx moves to become myometrial of cells. Reducing Intracellular of calcium concentrations avoid the process of activating the myosin of light chain from kinase, and also the term thereby myometrium contraction.<sup>18</sup> Then, nifedipine gets contraindicating inside women whom have cardiac disease.<sup>19</sup>

The process of managing the condition of preterm labor defines are having rest in bed, adequate of having hydration, prophylactic cervical cerclage and using tocolytic drugs.

Nevertheless the tocolytics haven't proofed to get improved the neonatal outcomes, it may deal with the delaying so antenatal of corticosteroid t administers or the mother being moved to a tertiary care facility.<sup>16,20</sup>

## CONCLUSION

In our study, administration of nifedipine as a tocolytic did not have a statistically significant difference, both in prolonging pregnancy and side effects for pregnant women and neonates compared to the control group. We are looking forward for further study/research about nifedipine and other tocolytic agent in inhibiting Premature Birth in Reducing the Risk of Neonatal Death in Childbirth.

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