VIA MEDICA

ORIGINAL PAPER / OBSTETRICS

Ginekologia Polska
2022, vol. 93, no. 10, 820–826

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2021.0231

The use of calcium channel blockers as tocolytics may adversely affect pregnancy outcomes: a randomized clinical trial

Aysun Tekeli Taskomur[1], Ozlem Erten[2]

[1]*Department of Obstetrics and Gynecology, Amasya University, School of Medicine, Amasya, Turkey*
[2]*Department of Obstetrics and Gynecology, Kutahya Health Sciences University, Kutahya, Turkey*

ABSTRACT

Objectives: To investigate the effect of calcium channel blockers in tocolytic therapy on obstetric outcomes.

Material and methods: For our study, as a retrospective case control study, data were obtained from hospital records. During 2018, there were 65 patients hospitalized with a diagnosis of preterm labor and were treated with calcium channel blockers used as tocolytics (nifedipine, nicardipine) and these patients constituted the study group. Pregnant women with systemic disease were excluded from the total of 1552 patients who were followed and who gave birth in 2018. After exclusion to equalize the samples, we chose 65 healthy pregnant women from the remaining 646 healthy pregnancies using a simple random number table and these patients formed the control group. The obstetric and neonatal results of both groups were compared.

Results: There was no difference between the groups in terms of birth week, preterm labor rate, low birth weight, and delivery type. While birth weights were significantly lower, the need for neonatal intensive care and the number of infants weighing 2500–3000 g were higher in the study group ($p < 0.05$). When the results of pregnancies that gave birth at term weeks and were not administered steroids were compared, the birth weight was lower and the number of infants weighing 2500–3000 g was higher in the study group.

Conclusion: The use of calcium channel blockers in pregnancy may adversely affect birth weight gain and the need for intensive care.

Key words: preterm labor; low birth weight; calcium channel blocker, obstetric-neonatal outcomes

Ginekologia Polska 2022; 93, 10: 820–826

INTRODUCTION

One of the important causes of perinatal mortality and morbidity is preterm labor. Despite all efforts to reduce preterm labor throughout the world, the incidence of preterm labor in 2010 was 11.1% [1]. Diagnostic difficulties in determining preterm labor and difficult treatment are among the reasons for its high incidence. Seventy-five percent of preterm births occur spontaneously due to preterm labor, and various tocolytic agents are used to treat it [2].

Acute tocolysis treatment is given as a loading dose to stop contractions, and maintenance treatment is given to prevent the resumption of stopped contractions. Calcium channel blockers (CCBs) are one class of these treatment agents, which include nifedipine and nicardipine. CCBs act by preventing contraction of the myometrium by blocking calcium intake into myometrial cells. CCBs are recommended in the treatment of preterm labor because of their low maternal adverse effects and ease of use [2]. Some studies indicate that there are no adverse effects on the fetus or on neonatal results [3, 4]. However, other studies show conflicting results [5].

Objective

Nifedipine is an agent that continues to be used as a tocolytic. In order to use this agent comfortably, however, it is important to determine its effects on neonatal outcomes. Therefore, in this study, we evaluated whether CCBs used as tocolytics in the treatment of preterm labor influence obstetric and neonatal outcomes.

Corresponding author:
Aysun Tekeli Taskomur
Amasya University, Faculty of Medicine, Department of Obstetrics and Gynecology, Amasya, Turkey, Kirazlidere Neighborhood Turgut Ozal Street, Amasya, Turkey
e-mail: dr.isoon77@hotmail.com

Received: 22.06.2021 Accepted: 20.11.2021 Early publication date: 3.03.2022

MATERIAL AND METHODS

Approval was obtained from the ethics committee of Amasya University (Approval No.: 47). The study was conducted by examining the results of patients with a diagnosis of pre-term labor during 2018 who had treatment with nifedipine as a tocolytic. All patients had been admitted to the obstetrics and gynecology clinic of Amasya Sabuncuoğlu Şerefeddin Training and Research Hospital. In our hospital, the doses of nifedipine used for tocolysis are as follows: 4 x 10 mg nifedipine with 20-minute intervals for acute tocolysis and maintenance doses of 4 x 10 mg or 6 x 10 mg orally. While doses are being given, the blood pressure is monitored to avoid hypotension and to take precautions if necessary. Pregnant women diagnosed with pre-term labor under 34 weeks of gestation were administered steroids for lung maturation.

The study group consisted of 65 pregnant women who were hospitalized in 2018 due to pre-term labor and who were started on treatment with a CCB. The control group was formed by selecting from 1552 pregnant women who were followed up and gave birth in 2018. Pregnant women were not included in the study or control group if they had hypertensive disease of pregnancy, abortion imminence, thrombophilia, hyperemesis gravidarum, gestational diabetes, diabetes mellitus, or any systemic disease. Figure 1 shows a flow chart according to the diagnoses of the pregnant women in 2018. As shown, after excluding pregnant women who were diagnosed with the diseases mentioned, there remained 646 healthy pregnancies without a diagnosis of any disease, and 65 healthy pregnant women were selected using a simple random number table to equalize the sample size to form the control group.

The demographic characteristics (age, height, weight, body mass index (BMI), parity, education level), obstetric results (birth week, infant weight, number of pre-term labors, intrauterine growth retardation, number of post-maturity, delivery type, low-birth-weight infants) and neonatal results (infant intensive care rates) of these groups were compared. The groups were also compared in terms of smoking, alcohol use and steroid administration for lung maturation, which may affect obstetric and neonatal outcomes. The World Health Organization defines low birth weight as a birth weight below 2500 g, regardless of gestational week [6–8]. Intrauterine growth restriction is defined as pathological inhibition of intrauterine fetal growth and the fetus's inability to reach growth potential [9]. However, this growth restriction does not mean that fetal weight is below 2500 g. In our study, following the WHO definition, the low-birth-weight group included all such babies, including those with intrauterine growth retardation and pre-term births below 2500 g, regardless of gestational week.

Delivery at post-term/pre-term weeks and administration of steroids have adverse effects on obstetric and neonatal outcomes [10–12]. To exclude these negative effects and to show the isolated effect of nifedipine on obstetric and neonatal outcomes, within the groups we separately compared the results of women who gave birth at term (370/7–406/7 weeks) and who were not administered steroids.

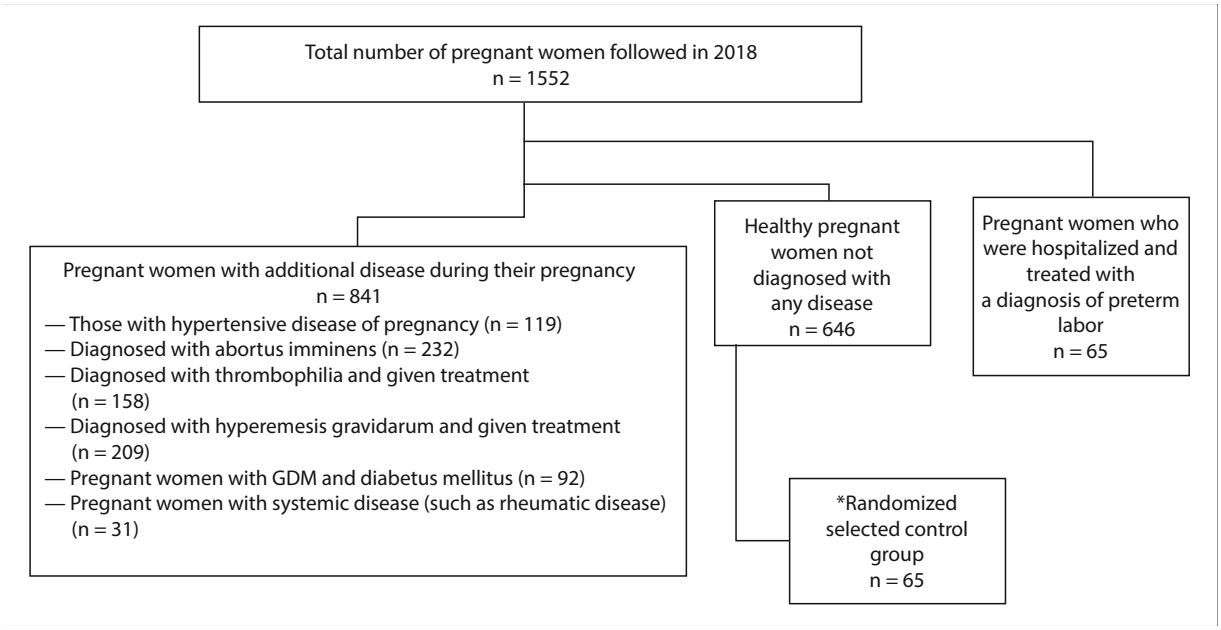

Figure 1. Flow chart according to the diagnoses of the pregnant women in 2018

Power analysis

The program G Power 3.1 was used to calculate the sample size for the study. The calculation was made according to the comet hypothesis method based on the study by Sayın et al. [13] after considering the incidence of the disease being 8.9%, the number of women newly diagnosed with pregnancy in the health institution where the study was planned to be conducted (n = 1600–1700 cases), the effect width (w = 0.75), and doubling the result. The confidence interval was determined as 95% and the margin of error was 5%. As a result of the calculation, it was determined that there should be 60 women for the control group and 60 women for the experimental group.

Statistical analysis

Data were analyzed with IBM SPSS V23. The chi-squared test was used to compare categorical variables according to groups. Mann-Whitney U test was used to compare non-normally distributed data according to paired groups, and an independent two-sample t test was used for comparison of normally distributed data. The significance level was considered as $p < 0.05$.

RESULTS

The distributions of both groups were homogeneous in terms of age, parity, height, weight, BMI, and education level (Tab. 1). The groups were evaluated in terms of smoking, alcohol use, and steroid administration for fetal lung maturation, which may affect obstetric and neonatal results. While there was no difference between the groups in terms of smoking and alcohol use, steroid administration due to the risk of pre-term labor was significantly higher in the study group using CCBs than the control group ($p > 0.05$).

The birth week was week 38.05 ± 2.06 in the study group using CCBs and week 38.53 ± 1.89 in the control group, but the difference was not significant ($p = 0.194$). The average infant weight in the study group was 2954.31 ± 479.24 g, whereas it was 3226.15 ± 502.48 g in the control group. Although the mean week of both groups was 38, infant birth weight was significantly lower in the study group using CCBs ($p = 0.002$) (Tab. 2).

There were two infants with fetal growth restriction (FGR) in the study group and none in the control group, but the difference was not significant ($p = 0.496$). One of the FGR infants in the study group was born at 2400 g, and the other was 2740 g. In other words, one of these infants had low birth weight. The number of infants with low birth weight was 9/65 infants (13.8%) in the study group and 4/65 infants (6.2%) in the control group. The number of infants with low birth weight was higher in the study group, but the difference between the groups was not statistically significant ($p = 0.144$) (Tab. 2). In addition, in order to examine the effect of CCBs on birth weight in more detail, the number of infants between 2500 and 3000 g was compared. This revealed that 43.1% (n = 28/65) of the study group and 16.9% (n = 11/65) of the control group were between 2500 and 3000 g, and the difference between the groups was statistically significant ($p = 0.001$) (Tab. 2).

There was no difference between the groups in terms of cesarean rates ($p = 0.599$) (Tab. 2). Pre-term labor occurred in

Table 1. Comparison of the groups in terms of demographic characteristics, smoking, alcohol use, and steroid administration for lung development

	Study group n (65)	Control group n (65)	p
Age (year)	27.08 ± 5.84	27.85 ± 5.32	0.327
Height (cm)	161.80 ± 5.30	161.86 ± 4.13	0.774
Weight (cm)	78.83 ± 9.76	77.08 ± 10.65	0.243
BMI [kg/m^2]	30.14 ± 3.69	29.39 ± 3.74	0.199
Parity			
Nulliparity	27 (41.5%)	20 (30.8%)	0.201
Multiparity	38 (58.5%)	45 (69.2%)	
Education			
Primary school	21 (32.3%)	21 (32.3%)	0.958
Middle school	7 (10.8%)	9 (13.8%)	
High school	24 (36.9%)	23 (35.4%)	
University	13 (20%)	18.4%)	
Smoking	0 (0.0%)	4 (6.2%)	0.119
Alcohol use	0 (0.0%)	0 (0.0%)	-
Steroid administration	39 (60.0%)	0 (0.0%)	**< 0.001**

p-values were calculated with the independent t test (age, height, weight, BMI) and chi-squared test

Table 2. Comparison of obstetric and neonatal results of the groups

	Study group n (65)	Control group n (65)	p
Infant weight (g)	2954.31 ± 479.24	3226.15 ± 502.48	0.002
Birth week (week)	38.05 ± 2.06	38.53 ± 1.89	0.194
Preterm birth	13 (20.0%)	6 (9.2%)	0.082
IUGR	2 (3.1%)	0 (0.0%)	0.496
Delivery type			
Vaginal birth	33 (50.8%)	30 (46.2%)	0.599
Cesarean	32 (49.2%)	35 (53.8%)	
Post-maturity	1 (1.5%)	3 (4.6%)	0.619
Neonatal intensive care needs	16 (24.6%)	7 (10.8%)	0.039
Low-birth-weight infants	9 (13.8%)	4 (6.2%)	0.144
Infants with 2500–3000 g birth weight	28 (43.1%)	11 (16.9%)	0.001
Comparison of the groups' indications for admission to the infant intensive care unit			
	Study group n (16)	**Control group n (7)**	**p**
RDS	6 (37.5%)	3 (42.9%)	0.304
Neonatal pneumonia	3 (18.8%)	0 (0.0%)	
Temporary tachypnea of the newborn	7 (43.7%)	3 (42.9%)	
Neonatal sepsis	0 (0.0%)	1 (14.2%)	

p-values were calculated with the Mann Whitney U test (birth week), the independent t test (infant weight), and chi-squared test. IUGR — Intrauterine growth retardation; RDS — Respiratory distress syndrome

Table 3. Comparison of the study group steroid-free cases between $37^{0/7}$-$40^{6/7}$ weeks with the control group in terms of infant weight, 2500–3000 g birth weight infants, low-birth-weight infants, and need for intensive care

	CCB used (Steroid free) n (24)	Control group (Steroid free) n (56)	p
Infant weight (g)	2992.29 ± 482.65	3301.88 ± 406.15	0.004
Birth week (week)	38.81 ± 0.98	38.87 ± 1.15	0.801
IUGR	0 (0.0%)	0 (0.0%)	-
Delivery type			
Vaginal birth	11 (45.8%)	25 (44.6%)	0.922
Cesarean	13 (54.2%)	31 (55.4%)	
NICN	5 (20.8%)	5 (8.9%)	0.157
Low-birth-weight infants	2 (8.3%)	1 (1.8%)	0.213
2500–3000-g birth weight infants	11 (45.8%)	9 (16.1%)	0.005

p-values were calculated with the Mann Whitney U test (birth week), the independent t test (infant weight), and chi-squared test. NICN — Neonatal intensive care needs; CCB — calcium channel blockers; IUGR — Intrauterine growth retardation

13/65 (20.0%) (4 were low birth weight) women in the study group and 6/65 (9.2%) (3 were low birth weight) women in the control group. There was 1/65 (1.5%) post-maturity pregnancy in the study group and 3/65 (4.6%) cases in the control group. There was no difference between the groups in terms of pre-term labor and post-maturity ($p > 0.05$) (Tab. 2).

Intensive care was needed for 16 (24.6%) infants in the study group and for seven (10.8%) in the control group. The need for intensive care was higher in the study group, regardless of the gestational week, and the difference was statistically significant ($p = 0.039$) (Tab. 2). In the study group, there were six infants admitted to the intensive care unit for respiratory distress syndrome (RDS), three for a lung infection, and seven for temporary tachypnea. In the study group, three infants were admitted to the intensive care unit for RDS, three for transient tachypnea, and one for neonatal sepsis (Tab. 2).

The obstetric and neonatal outcomes of pregnant women who gave birth at term (370/7–406/7 weeks) and were not administered steroids were compared (Tab. 3). In

the study group, there were 13 pregnant women in pre-term weeks, one pregnant woman in post-term weeks, and 27 pregnant women who were given steroids and delivered at term. In the control group, there were six pregnant women who gave birth in pre-term weeks and three women who gave birth in post-term weeks. Obstetric and neonatal outcomes of 24 pregnant women in the study group were compared with the results of 56 pregnant women in the control group by extracting the results of these pregnant women. In this comparison, the groups did not have cases of FGR. There was no significant difference between the groups in terms of the birth week, delivery type, low birth week, and neonatal intensive care need ($p > 0.05$). However, infant weight was significantly lower in the study group, and the number of infants weighing 2500–3000 g was significantly higher ($p < 0.05$).

DISCUSSION

Many agents for tocolytic purposes are used in the treatment of pre-term labor. One of the agent classes is calcium channel blockers. Although the efficacy, superiority, and side effects of calcium channel blockers in the treatment of pre-term labor with other tocolytic agents (beta blockers, atosiban and indomethacin) have been compared in previous studies, the effects of calcium channel blockers on pregnancy have not been thoroughly investigated [14–16]. Therefore, in this study, we compared the obstetric and neonatal outcomes of pregnant women diagnosed with pre-term labor and receiving calcium channel blockers as tocolytic therapy with those of healthy pregnant women. In the comparison, there was no significant difference between the groups in terms of the birth week, number of preterm births, FGR, delivery type, post-maturity, and low birth weight. Birth weight was significantly lower and need for neonatal intensive care and the number of infants at 2500–3000g were significantly higher in the study group than the control group (Tab. 2). In this comparison, it can be thought that the study group consisting of pregnant women diagnosed with pre-term labor may have affected the study results. However, the fact that the average birth week of both groups was 38 rules out this situation.

In order to evaluate the effects of CCBs on pregnancy more clearly, the results of the pregnant women who gave birth at pre-term/post-term weeks and were diagnosed with pre-term labor and were administered steroids under 34 weeks, which are the factors affecting obstetric and neonatal outcomes in our study, were extracted and the comparison was made again. In this comparison, birth weight was significantly lower, and the number of birth weight infants between 2500-–3000 g was significantly higher in the study group. There was no significant difference between the groups regarding the birth week, FGR, delivery type, NICN, and the number of low birth weight infants.

The first time that calcium channel blockers were used as tocolytics in the treatment of pre-term labor was 1980 [17]. However, the effectiveness of these agents in this indication is still under investigation. While some of the studies done so far show that nifedipine is not effective in prolonging pregnancy or improving perinatal outcomes [18, 19], others show that nifedipine is effective in stopping contractions with acute tocolysis treatment, preventing recurrence when treatment is continued, prolonging pregnancy, and improving neonatal outcomes [20]. Although its effectiveness in preventing preterm labor has not been fully clarified, it has been used for this indication in clinics for nearly 40 years [3]. It is preferred in clinical practice, especially since it has fewer side effects than other tocolytics, low cost, and is easy to administer in maintenance therapy since it can be taken orally [21].

CCBs have no known teratogenic effects [22, 23]. They cross the placenta to varying degrees and are detected in fetal serum, amniotic fluid, and breast milk [24]. There are studies that say CCBs have no adverse effects on the human fetus [3, 4]. However, the results of animal experiments have been controversial [25–28]. In animal studies, the primary cause of adverse fetal effects is decreased uteroplacental blood flow developing secondary to maternal hypotension. Accordingly, it has been shown that hypoxemia and acidosis develop in the fetus (3). Furthermore, it has even been reported to cause bradycardia and fetal death [28].

Although studies state that CCBs do not have adverse effects on the human fetus, it has been reported that low dose (10mg) sublingual nifedipine is used to control severe hypertension during pregnancy, causing severe hypotension and fetal distress [29]. In fact, it is stated in the latest case reports in the literature that CCBs cause severe hypotension and fetal death [30]. Fetal death can be considered as an early secondary effect of CCBs on severe maternal hypotension. Depending on the maintenance treatment, there may be long-term effects. Indeed, maternal and fetal effects of maintenance therapy are not yet known [21].

In the human study of Sayın et al., it was reported that fetal weight gain was decreased due to CCB use [5]. Other studies report that fetal weight gain is affected in those using CCBs even if they are born at term weeks [31, 32]. Birth weight was lower in the study group using CCBs than in the healthy group in our study. While there was no significant difference between the groups in terms of low birth weight, the number of infants weighing 2500-3000g was higher in the study group (Tab. 2). In the comparison we made by subtracting the results of pre-term/post-term births and steroid administered pregnant women, birth weight was lower and the number of infants weighing 2500–3000 g was significantly higher in the study group than in the control group (Tab. 3).

In a study of 50 nulliparous pregnant women, it was found that neonatal hospitalization times were shorter with acute and maintenance tocolysis therapy with nifedipine, but the difference was not statistically significant. The main reason nifedipine is beneficial for neonatal results is the delay of birth and gestational week to the future, thus allowing for lung maturation [20]. Contrary to this study, we found that more infants needed hospitalization in the neonatal intensive care unit in the study group using nifedipine, independent of gestational week (p = 0.039) (Tab. 2).

The CCBs used for pre-term labor in the study were applied for a minimum of 48 hours and a maximum of many weeks. In other words, there was no standard duration for using CCBs in the study. Since the long-term use of CCBs may affect the study results, the lack of a standard usage period of CCBs in our study constitutes a limitation. Although there are cases where CCBs were used for a short time, such as 48 hours, a lower fetal weight in the study group was observed. We suggest that this situation adds value to the results of the study. In our study, the high number of babies with low birth weight in the study group, although not statistically significant, makes it even more important to investigate the possibility of this result being due to the use of CCBs. Low birth weight is one of the essential indicators of both maternal and child health. The low number of cases in our study may not have been sufficient to allow low birth weight results to be meaningful, which may be another limitation.

The strength of our study was that although the average birth weeks of the groups were matched at 38 weeks, we could show that the study group had lower birth weight and a higher need for infant intensive care. In addition, in our study there was low birth weight in the group using CCBs in the $37^{0/7}$–$40^{6/7}$ weeks remaining after the exclusion of pre-term births (which are likely to have low birth weight and need more infant intensive care) and postmature births (which are likely to have a greater need for infant intensive care). This strengthens the conclusion that weight gain is affected using CCBs.

CONCLUSIONS

The data obtained in our study regarding tocolytic use of CCBs suggests that infant weight gain may be negatively affected and may lead to a greater need for neonatal intensive care.

Conflict of interest

All authors declare no conflict of interest.

REFERENCES

1. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012; 379(9832): 2162–2172, doi: 10.1016/S0140-6736(12)60820-4, indexed in Pubmed: 22682464.
2. King JF, Grant A, Keirse MJ, et al. Beta-mimetics in preterm labour: an overview of the randomized controlled trials. Br J Obstet Gynaecol. 1988; 95(3): 211–222, doi: 10.1111/j.1471-0528.1988.tb06860.x, indexed in Pubmed: 2897207.
3. Economy KE, Abuhamad AZ. Calcium channel blockers as tocolytics. Semin Perinatol. 2001; 25(5): 264–271, doi: 10.1053/sper.2001.27165, indexed in Pubmed: 11707015.
4. Papatsonis DNM, van Geijn HP, Bleker OP, et al. Hemodynamic and metabolic effects after nifedipine and ritodrine tocolysis. Int J Gynaecol Obstet. 2003; 82(1): 5–10, doi: 10.1016/s0020-7292(03)00145-0, indexed in Pubmed: 12834935.
5. Oei SG. Calcium channel blockers for tocolysis: a review of their role and safety following reports of serious adverse events. Eur J Obstet Gynecol Reprod Biol. 2006; 126(2): 137–145, doi: 10.1016/j.ejogrb.2006.03.001, indexed in Pubmed: 16567033.
6. Tshotetsi L, Dzikiti L, Hajison P, et al. Maternal factors contributing to low birth weight deliveries in Tshwane District, South Africa. PLoS One. 2019; 14(3): e0213058, doi: 10.1371/journal.pone.0213058, indexed in Pubmed: 30822317.
7. UNICEF, WHO, Low Birthweight Estimates: Level and Trends 2000–2015, WHO Publications, Geneva, Switzerland, 2019. http://www.who.int/nutrition (05.06.2021).
8. World Health Organization, World Health Assembly Global Nutrition Targets 2025: Low Birth Weight Policy Brief, World Health Organization, Geneva, Switzerland, 2014, http://www.who.int/nutrition/topics/global-targets_stunting_policybrief. (05.06.2021).
9. Albu AR, Anca AF, Horhoianu VV, et al. Predictive factors for intrauterine growth restriction. J Med Life. 2014; 7(2): 165–171, indexed in Pubmed: 25408721.
10. Sangkomkamhang U, Pattanittum P, Laopaiboon M, et al. Mode of delivery and outcomes in preterm births. J Med Assoc Thai. 2011; 94(4): 415–420, indexed in Pubmed: 21591525.
11. Galal M, Symonds I, Murray H, et al. Postterm pregnancy. Facts Views Vis Obgyn. 2012; 4(3): 175–187, indexed in Pubmed: 24753906.
12. Braun T, Weichert A, Gil HC, et al. Fetal and neonatal outcomes after term and preterm delivery following betamethasone administration. Int J Gynaecol Obstet. 2015; 130(1): 64–69, doi: 10.1016/j.ijgo.2015.01.013, indexed in Pubmed: 25872453.
13. Sayin NC, Varol FG, Balkanli-Kaplan P, et al. Oral nifedipine maintenance therapy after acute intravenous tocolysis in preterm labor. J Perinat Med. 2004; 32(3): 220–224, doi: 10.1515/JPM.2004.041, indexed in Pubmed: 15188794.
14. van Vliet EOG, Nijman TAJ, Schuit E, et al. Nifedipine versus atosiban for threatened preterm birth (APOSTEL III): a multicentre, randomised controlled trial. Lancet. 2016; 387(10033): 2117–2124, doi: 10.1016/S0140-6736(16)00548-1, indexed in Pubmed: 26944026.
15. García-Velasco JA, González González A. A prospective, randomized trial of nifedipine vs. ritodrine in threatened preterm labor. Int J Gynaecol Obstet. 1998; 61(3): 239–244, doi: 10.1016/s0020-7292(98)00053-8, indexed in Pubmed: 9688484.
16. Abou-Ghannam G, Usta IM, Nassar AH. Indomethacin in pregnancy: applications and safety. Am J Perinatol. 2012; 29(3): 175–186, doi: 10.1055/s-0031-1284227, indexed in Pubmed: 21786219.
17. Ulmsten U, Andersson KE, Wingerup L. Treatment of premature labor with the calcium antagonist nifedipine. Arch Gynecol. 1980; 229(1): 1–5, doi: 10.1007/BF02109822, indexed in Pubmed: 7362274.
18. Roos C, Spaanderman MEA, Schuit E, et al. APOSTEL-II Study Group. Effect of maintenance tocolysis with nifedipine in threatened preterm labor on perinatal outcomes: a randomized controlled trial. JAMA. 2013; 309(1): 41–47, doi: 10.1001/jama.2012.153817, indexed in Pubmed: 23280223.
19. Parry E, Roos C, Stone P, et al. The NIFTY study: a multicentre randomised double-blind placebo-controlled trial of nifedipine maintenance tocolysis in fetal fibronectin-positive women in threatened preterm labour. Aust N Z J Obstet Gynaecol. 2014; 54(3): 231–236, doi: 10.1111/ajo.12179, indexed in Pubmed: 24506318.
20. Aggarwal A, Bagga R, Girish B, et al. Effect of maintenance tocolysis with nifedipine in established preterm labour on pregnancy prolongation and neonatal outcome. J Obstet Gynaecol. 2018; 38(2): 177–184, doi: 10.1080/01443615.2017.1331340, indexed in Pubmed: 28784001.
21. Gaunekar NN, Crowther CA. Maintenance therapy with calcium channel blockers for preventing preterm birth after threatened preterm labour.

Cochrane Database Syst Rev. 2004(3): CD004071, doi: 10.1002/14651858.CD004071.pub2, indexed in Pubmed: 15266515.
22. Magee LA, Schick B, Donnenfeld AE, et al. The safety of calcium channel blockers in human pregnancy: a prospective, multicenter cohort study. Am J Obstet Gynecol. 1996; 174(3): 823–828, doi: 10.1016/s0002-9378(96)70307-1, indexed in Pubmed: 8633650.
23. Sørensen HT, Steffensen FH, Olesen C, et al. Pregnancy outcome in women exposed to calcium channel blockers. Reprod Toxicol. 1998; 12(3): 383–384, doi: 10.1016/s0890-6238(98)00012-4, indexed in Pubmed: 9628561.
24. Blea CW, Barnard JM, Magness RR, et al. Effect of nifedipine on fetal and maternal hemodynamics and blood gases in the pregnant ewe. Am J Obstet Gynecol. 1997; 176(4): 922–930, doi: 10.1016/s0002-9378(97)70622-7, indexed in Pubmed: 9125622.
25. Ferguson JE, Schutz T, Pershe R, et al. Nifedipine pharmacokinetics during preterm labor tocolysis. Am J Obstet Gynecol. 1989; 161(6 Pt 1): 1485–1490, doi: 10.1016/0002-9378(89)90909-5, indexed in Pubmed: 2603904.
26. Csapo AI, Puri CP, Tarro S, et al. Deactivation of the uterus during normal and premature labor by the calcium antagonist nicardipine. Am J Obstet Gynecol. 1982; 142(5): 483–491, doi: 10.1016/0002-9378(82)90749-9, indexed in Pubmed: 7058850.
27. Richichi J, Vasilenko P. The effects of nifedipine on pregnancy outcome and morphology of the placenta, uterus, and cervix during late pregnancy in the rat. Am J Obstet Gynecol. 1992; 167(3): 797–803, doi: 10.1016/s0002-9378(11)91592-0, indexed in Pubmed: 1530041.
28. Parisi VM, Salinas J, Stockmar EJ. Fetal vascular responses to maternal nicardipine administration in the hypertensive ewe. Am J Obstet Gynecol. 1989; 161(4): 1035–1039, doi: 10.1016/0002-9378(89)90779-5, indexed in Pubmed: 2801819.
29. Impey L. Severe hypotension and fetal distress following sublingual administration of nifedipine to a patient with severe pregnancy induced hypertension at 33 weeks. Br J Obstet Gynaecol. 1993; 100(10): 959–961, doi: 10.1111/j.1471-0528.1993.tb15120.x, indexed in Pubmed: 8217985.
30. van Veen AJ, Pelinck MJ, van Pampus MG, et al. Severe hypotension and fetal death due to tocolysis with nifedipine. BJOG. 2005; 112(4): 509–510, doi: 10.1111/j.1471-0528.2004.00480.x, indexed in Pubmed: 15777455.
31. Ahokas RA, Sibai BM, Mabie WC, et al. Nifedipine does not adversely affect uteroplacental blood flow in the hypertensive term-pregnant rat. American Journal of Obstetrics and Gynecology. 1988; 159(6): 1440–1445, doi: 10.1016/0002-9378(88)90571-6.
32. Karahanoglu E, Altinboga O, Akpinar F, et al. Nifedipine increases feto-placental perfusion. J Perinat Med. 2017; 45(1): 51–55, doi: 10.1515/jpm-2016-0072, indexed in Pubmed: 27387329.