The Impact of Nifedipine on Maternal and Fetal Blood Stream on the Threat of Preterm Labor: an Experimental Study

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Abstract

Background: Preterm birth is a significant cause of perinatal morbidity and mortality and that becomes a major challenge in perinatal health care. Various pharmacological agents that inhibit uterine contractions are used in clinical practice to prevent preterm delivery. The maternal and fetal side-effect profiles of tocolytic agents are becoming an important consideration in selecting the drug of choice. Nifedipine, a dihydropyridine calcium entry blocker, is an effective tocolytic agent with low toxicity and teratogenicity, while carrying potential maternal as well as fetal vascular side effects due to its action on vascular smooth muscle. This study was performed to asses nifedipine use as tocolytic agent in preventing preterm birth, and assesing maternal as well as fetal vascular side effects.

Methods: This experimental study with one-group pretest-posttest design was performed in 30 pregnant women undergoing nifedipine as tocolytic. Doppler assessment of uterine, umbilical and fetal middle cerebral arteries, ductus venosus, and cerebroplacental ratio was performed before and 48 hours after nifedipine therapy. Wilcoxon's signed ranks test was used to analyze the difference between the two variables. A P-value of < 0.05 was considered significant.

Results: The result of the study showed nifedipine was associated with a significant decreased of pulsatility index uterine artery ($p = 0.016$; p-value<0.05) and umbilical artery ($p = 0.037$; p-value<0.05) after 48 hours therapy, while pulsatility index of fetal middle cerebral arteries, ductus venosus, and cerebroplacental ratio did not change significantly.

Conclusion: The study concluded that nifedipine as tocolytic increased blood flow of uterine artery and umbilical artery after 48 hours therapy.

Introduction

Preterm labor is the appearance of uterine contractions with sufficient intensity and frequency to cause cervical thinning and dilation before entering term pregnancy, between 20 to 37 weeks of pregnancy. [1]

Globally, an estimated 15 million babies are born prematurely, with a ratio of more than 1:10 births each year.[2] Complications from the occurrence of this prematurity cause almost 35% (about 3.1 million) neonatal deaths per year.[3,4] Based on WHO data in 2010, Indonesia ranks fifth after India, China, Nigeria and Pakistan with 675.700 preterm deliveries with a ratio of 15.5% per 100 live births.[5]

The exact cause of preterm labor is still unclear, but there are several risk factors for preterm labor, including idiopathic, iatrogenic, socio demographic (social and racial stress), maternal factors, medical illness and the state of pregnancy, infection and inflammation, and genetic factors. There are four main etiologies of spontaneous preterm labor, namely uterine distention, maternal-fetal stress, premature cervical changes, and infection. [1,6]

The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists in 2012 defined the threat of preterm when regular contractions occur before 37 weeks' gestation accompanied by cervical changes.[1] The guidelines for the Indonesian Fetomaternal Medical Association state that the diagnosis of preterm labor is established if uterine contractions are obtained based on Creasy and Heron criteria, namely a contraction of 4 times in 20 minutes or 8 times in 1 hour, accompanied by one of the following conditions, rupture of the amniotic sac, opening of the uterine sac, cervical dilation more than 2 cm, and cervical flattening more than 50%.[7]

Preterm labor is one of the significant problems in the field of obstetrics that causes various short-term and long-term complications for the baby. The threat of preterm labor can be recognized by the appearance of regular contractions accompanied by cervical changes. Various tocolytics have been developed to prevent the development of the threat of preterm labor. [1,8,9]

Nifedipine is a tocolytic agent that has the greatest effectiveness and most minimal maternal side effects in the treatment of preterm labor threats.[10–12] Nifedipine is classified as a calcium channel blocker that works on the L-calcium channel that is found in all smooth muscle including the uterus and systemic vascular vessels. The mechanism of action of nifedipine at the calcium channel is blocking the entry of calcium ions into the cell and thereby preventing cell contraction. At the uterus, this will result in absent of contraction of uterine smooth muscle cells, resulting in uterine relaxation. Whereas in systemic blood vessels the effect will be vasodilation resulting in a decrease in systemic vascular resistance, including the uterine artery.[13,14] Nifedipine easily crosses the placenta with a fetal versus maternal ratio of 0.93 between umbilical cord blood and maternal serum concentrations. So that the administration of nifedipine in imminent preterm labor is expected to affect maternal arterial Doppler blood flow that can be assessed by a decrease uterine artery pulsatility index (PI). While its effect to fetal blood flow Doppler can be assessed by a decrease umbilical artery (UA) PI, increase middle cerebral artery (MCA) PI, increase cerebroplacental ratio (CPR), and decrease ductus venosus (DV) PI. [15–17] This research was performed to observe nifedipine use in imminent preterm labor and its effect to maternal blood flow assessed by the uterine artery PI and fetal blood flow assessed by the UA PI, MCA PI, DV PI and CPR.

Methods

This study was an experimental study with pre-test and post-test design. Data were collected with consecutive sampling method. Research subjects that met the inclusion and did not meet exclusion criteria were given informed consent before the study. After signing the agreement following the explanation, the subjects underwent ultrasound examination prior to therapy. The subjects then were given nifedipine as tocolytic with a loading dose of 10 mg orally every 10 minutes with a maximum dose of 40 mg followed with a maintenance dose of 20 mg per 8 hours. After 48 hours of the therapy, a Doppler uterus examination was performed.

The inclusion criteria were patients with the following characteristics: patients presented with imminent preterm labor, 24–36 weeks gestational age, singleton pregnancy with a live fetus, intact amniotic fluid,

adequate amniotic fluid. Exclusion criteria are if these following conditions present: preeclampsia, eclampsia, antepartum hemorrhage, hypertension, heart disease, hypothyroidism, hyperthyroidism, kidney disease, chronic lung disease, diabetes mellitus, congenital abnormalities in the fetus, maternal infections (such as systemic infections or urogenital tract infections based on history taking and clinical examinations). Drop out criteria: experiencing childbirth less than 48 hours after initiation of therapy, terminating therapy less than 48 hours after initiation of therapy due to side effects or refusing to continue therapy.

Results

Of the 30 study subjects who successfully underwent nifedipine therapy for 48 hours, the majority age range between 20–34 years old, or at optimal reproductive age (18 subjects; 60%). Based on the parity status, most were primigravida (16 subjects; 53.3%). The gestational age were majority > 32- <37 weeks (18 subjects; 60%), and the highest BMI > 26–29 kg m2 (15 subjects; 50%). Twelve subjects had anemia (40%), 5 subjects had a previous preterm birth (16.7%). Interestingly, oligohydramnios did not occur in almost all patients (Table 1).

Table 1
Characteristics of Research Subjects

Characteristics	N (n = 30)
Age (years)	
< 20	6
20–34	18
≥ 35	6
Gravida	
Primigravida	16
Multigravida	14
Gestational Age (weeks)	
24 - <28	3
28–32	9
>32-<37	18
Anemia	
Yes	12
No	18
History of Preterm Labor	
Yes	5
No	25
Body Mass Index	
< 19.8 kg/m^2	1
19.8–26 kg/m^2	6
>26–29 kg/m^2	15
> 29 kg/m^2	8
Oligohydramnios	
Yes	1
No	29

The results of Doppler measurements of uterine artery PI, UA PI, MCA PI, DV PI, and CPR were presented in Table 2. The normality of the collected data were then being analyzed.

Table 2
Pre and post nifedipine therapy PI measurements

Variable	PI Measurement			Normality test (p value)
	Mean (SD)	Median	Range	
1. Uterine artery before therapy	0.79(0.21)	0.70	0.60–1.30	< 0.001
Uterine artery 48 hours of therapy	0.70(0.22)	0.68	0.42–1.56	< 0.001
2. UA before therapy	0.97(0.31)	0.90	0.52–2.30	< 0.001
UA 48 hours of therapy	0.88(0.15)	0.91	0.44–1.08	0.025
3. MCA before therapy	1.67(0.48)	1.55	0.75–3.06	0.297
MCA 48 hours of therapy	1.64(0.50)	1.52	0.71–3.19	0.006
4. DV before therapy	0.50(0.17)	0.50	0.21–0.84	0.234
DV 48 hours of therapy	0.50(0.18)	0.46	0.21–1.10	0.020
5. CPR before therapy	1.79(0.54)	1.81	0.94–3.04	0.566
CPR 48 hours of therapy	1.89(0.58)	1.76	1.00-3.14	0.013
Note: data is normally distributed if the value of $p > 0.05$ (Shapiro-Wilk test)				
We further analyze the significany of the results of Doppler measurements of uterine artery PI, UA PI, MCA PI, DV PI, and CPR, and data were presented in Table 3. Of the five variables studied, two variables, uterine artery PI and UA PI showed significant difference before therapy compared to that of post therapy ($p < 0.05$).				

Table 3
Comparison PI measurements pre and post nifedipine therapy

Variable	PI Measurement		P value
	Before therapy	48 hours of therapy	
1. Uterine artery PI			0.016*
Mean ± SD	0.79 ± 0.21	0.70 ± 0.22	
Median	0.70	0.68	
Range	0.60–1.30	0.42–1.56	
2. UA PI			0.037*
Mean ± SD	0.97 ± 0.31	0.88 ± 0.15	
Median	0.90	0.91	
Range	0.52–2.30	0.44–1.08	
3. MCA PI			0.636
Mean ± SD	1.67 ± 0.48	1.64 ± 0.50	
Median	1.55	1.52	
Range	0.75–3.06	0.71–3.19	
4. DV PI			0.721
Mean ± SD	0.50 ± 0.17	0.50 ± 0.18	
Median	0.50	0.46	
Range	0.21–0.84	0.21–1.10	
5. CPR PI			0.821
Mean ± SD	1.79 ± 0.54	1.89 ± 0.58	
Median	1.81	1.76	
Range	0.94–3.04	1.00–3.14	
Note: *) $p < 0.05$ was considered significant (Wilcoxon test)			

Discussion

The study was conducted to 32 patients who visited Emergency Room of Dr. Hasan Sadikin General Hospital Bandung during the period from December 2017 to February 2018. Two patients experienced a drop-out due to labor occuring less than 48 hours after receiving nifedipine therapy.

Subjects' Characteristics

Majority of patients in this study were in the optimal reproductive age range of 20–34 years with 18 patients (60%), the remaining 6 patients (20%) aged < 20 years, and 6 patients (20%) belonged to the age > 34 years. Previous study reported that maternal age < 20 years is a risk factor for preterm labor. Likewise, maternal age > 35 years is also a risk factor for preterm labor because at the age > 35 years women are prone to suffer from degenerative diseases such as diabetes mellitus and hypertension during pregnancy.[18,19] Yet, our study did not show similar results with these studies. The reason may be Dr. Hasan Sadikin General Hospital Bandung is a referral hospital, and therefore, the patients who refer to this hospital may represent the West Java population in general. Indeed West Java has a high population women with reproductive age, thus these subjects represent the West Java population that consists of pregnant women at optimal reproductive age.[20]

In this study 6 subjects (53.3%) were primigravida. This result was inline with a study in Egypt that found that primigravida was a risk factor for preterm labor. Primigravida increases the risk of preterm labor associated with young age at first pregnancy and lack of knowledge and awareness from mothers about the importance of good antenatal care.[21,22]

The highest incidence of preterm labor in this study occurred at gestational age > 32- < 37 weeks 18 subjects (60%) or the most at the age of late preterm. Consistent with previous finding, the majority of preterm deliveries in the United States occur in the late preterm period. In 2015, 71.4% of all preterm births (6.87% of all births) occurred in the late preterm period.[23]

Most patients were presented with BMI > 26–29 kg/m^2 (15 subjects; 50%). Our result was compared to the standard set by Gustaaf Dekker et al. that stated a low BMI < 20 increases the risk of preterm labor (OR 2.1; 95% CI: 0.93–4.54). Previously a low BMI was associated with undernutrition, but now obesity is a low socioeconomic marker with excessive consumption of high-calorie foods but low levels of micronutrients.[24]

In this study 12 patients (40%) had anemia, this is in accordance with the data from WHO in 2016 that 42% of pregnant women in Indonesia was found with anemia. Anemia is known as an important risk for preterm labor, and poor labor outcomes.[25,26]

The number of subjects with history of prematurity was as many as 5 patients (16.7%), and only 1 subject (3.3%) had oligohydramnios. Our data is not supported by previous study that described a history of preterm labor or abortion increases the risk of preterm labor. History of prematurity may indicate increase risk, since factors such as abnormalities of uterus, or cervical incompetence can cause repeated preterm labor.[27] Unlike in our study, other researchers found that oligohydramnios increased the risk for impending preterm delivery and intra-amniotic inflammation. Patients with oligohydramnios had a higher frequency of amniotic fluid infection and/or inflammation than those without oligohydramnios. The reason may be patients with oligohydramnios had a higher median amniotic fluid MMP-8 concentration

than those without oligohydramnios. Moreover women with preterm labor associated with oligohydramnios had a shorter interval to delivery than those without oligohydramnios.[28]

Decreased PI of uterine arterial blood flow 48 hours after nifedipine therapy

Doppler examination of uterine arterial blood flow is one indicator of maternal blood flow that can be used as a reference for assessing uteroplacental flow. Interference to the uterine artery blood flow carries detrimental impact on the development of intrauterine fetus.[29]

Doppler blood flow resistance assessment can use various parameters such as PI, resistance index, systolic/diastolic ratio (S/D). However, in this study we used the PI parameter with the consideration that the PI has a minimum range of variation values, has the smallest error rate. Unlike SD ratio parameter, PI has defined value. Lastly the PI value is directly proportional to blood flow resistance.

Based on Table 4.3 the mean value PI of uterine artery before therapy was 0.79 ± 0.21 with a median of 0.70, whereas 48 hours after therapy the mean value of PI uterine artery was 0.70 ± 0.22 with a median of 0.68 that is statistically significant.

Nifedipine is a calcium channel blocker that works on the L- calcium channel that is found in all smooth muscle including the uterus and systemic vascular vessels. Nifedipine shows effect by blocking the entry of calcium ions into the cell so that calcium cannot pass through the voltage gate calcium channel (VGCC) / L-type calcium channel, so that calcium cannot bind to calmodulin. By not forming the calcium calmodulin complex, myosin light chain kinase (MLCK) cannot phosphorylate serine 19 in the regulatory light chain of myosin (MLC20) causing no crossbridge cycling, thus preventing cell contraction. In blood vessels this causes a vasodilation effect resulting in a decrease in vascular resistance. This is in line with what we found in this study that there was a significant decrease in uterine artery PI after 48 hours of nifedipine therapy. A decrease in uterine artery PI represents the vasodilation of uterine arteries, assuming that there is an increase in uterine artery blood flow so that it has a positive effect on uteroplacental blood flow.[14,30]

The same finding was obtained by previous study that administration of nifedipine in maintenance doses caused a decrease in uterine artery PI at earlier observation, 24 hours and als long as 48 hours of therapy.[17,31]

Decreased of UA PI 48 hours after nifedipine therapy

Based on Table 4.3, UA PI before nifedipine, the mean was 0.97 ± 0.31, whereas after 48 hours of nifedipine therapy the mean was 0.88 ± 0.15 with a significant decrease in UA blood flow after nifedipine therapy.

This proves that nifedipine can cross the placental barrier with a high ratio, and maternal administration of nifedipine will be followed by increased levels of nifedipine in fetal serum. In addition, this preparation

has a direct effect on vascular structure and acts on receptors throughout the body, so that nifedipine can decrease UA PI.[32]

An umbilical arterial blood flow Doppler examination is one indicator of fetal blood flow that can provide an overview of intrauterine fetal conditions. Disrupted UA blood flow can cause fetal hypoxia and a unfavorable outcome on intrauterine fetal development. Changes in hemodynamics and intrauterine oxygenation will show initial efecet on UA blood flow.[16,17] This finding contradicts with that by Guclu *et al*, that administration of nifedipine maintenance dose did not cause differences in UA PI after 24 hours and 48 hours of therapy.[33]

Changes in MCA PI blood flow before and after 48 hours after nifedipine therapy

From table 4.3 the mean MCA PI before therapy was 1.67 ± 0.48, while the average MCA PI after 48 hours of nifedipine therapy was 1.64 ± 0.50 without any statistical significant difference. So it can be explained that Doppler changes in fetal blood flow only affect the early fetal hemodynamic stage, which is UA blood flow. Applying nifedipine does not cause redistribution of blood flow to the cerebral.[34]

Changes in CPR PI blood flow before and after 48 hours after nifedipine therapy

The mean of CPR PI before therapy was 1.79 ± 0.54, while the mean of CPR PI after 48 hours of nifedipine therapy was 1.89 ± 0.58 without statistically significant. CPR is an important indicator that describes fetal well-being and as a predictor of fetal output. CPR can also describe the presence or absence of placental insufficiency. Based on these results it can be concluded that administration of nifedipine does not affect the welfare of the fetus, and does not cause any signs of placental insufficiency.[34]

DV PI changes in blood flow before and after 48 hours after nifedipine therapy

Table 4.3 showed the mean DV PI before therapy was 0.50 ± 0.17, while the mean of DV PI after nifedipine therapy for 48 hours was 0.50 ± 0.18 without any significancy. The DV is a blood vessel that has a thin muscle. Nifedipine works in vascular smooth muscle by blocking the entry of calcium into vascular smooth muscle. This indicates the administration of nifedipine does not greatly affect the blood flow of the fetal venous system.

Hemodynamic changes in venous fetal blood flow occur in an advanced stage, i.e. if the changes in arterial system blood flow in uncompensated stage. This means that changes in venous fetal blood flow will only occur if there has been a change in the blood flow parameters UA, MCA, and CPR.[35]

Conclusion

Our study found administration of nifedipine can increase uteroplacental blood flow, increase fetal blood flow, no redistribution of cerebral blood flow, and no changes in venous fetal blood flow. Therefore it is evident that nifedipine is harmless for the fetus.

Declarations

Ethics Approval and Informed Consent to Participate

This research was conducted after obtaining approval and recommendations from the Ethics Committee Review Board of Dr. Hasan Sadikin General Hospital – Faculty of Medicine, Universitas Padjadjaran.

Consent for publication

All authors declare that written informed consent was obtained from every patient, regarding detail information and images to be described in this publication.

Availability of data and materials section

The authors declare that the personal data from any patients involved in this study will not be shared based on patients' confidentialities.

Competing Interest

The authors have declared that no competing interest exist.

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Authors' contributions

ADA, IMT, JSE did the conception and design of the study, acquisition of data, analysis and interpretation of the data, drafting the manuscript and revising the manuscript critically for important intellectual content.

ENA, RTR did the conception and design of the study, acquisition of data, and analysis and interpretation of the data.

KIM drafted the manuscript and revising the manuscript critically for important intellectual content.

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References

1. Cunningham F, Leveno K, Bloom S, Hauth J WK. Preterm Birth, William Obstetrics. 24th ed. New York: McGraw-Hills; 2014. 829–61 p.
2. Kinney M V., Lawn JE, Howson CP, Belizan J. 15 million preterm births annually: What has changed this year? Vol. 9, Reproductive Health. BioMed Central; 2012. p. 28.
3. Nadin M. Abdel Razeq, Yousef S. Khader and AMB. The incidence, risk factors, and mortality of preterm neonates: A prospective study from Jordan (2012-2013). Turk J Obs Gynecol. 2017;14(1):28–36.
4. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller AB, et al. Born Too Soon: The global epidemiology of 15 million preterm births. Reprod Health. 2013;10(SUPPL. 1):S2.
5. WHO. WHO | Born Too Soon: The Global Action Report on Preterm Birth. who web site. 2013. https://www.who.int/pmnch/media/news/2012/preterm_birth_ report/en/index3.html. Accesed 14 Jul 2020.
6. Handono B. Mekanisme Persalinan Prematur. In: Krisnadi S, Jusuf E, Adhi P, editors. Prematuritas. 1st ed. Bandung: Reflika Aaditama; 2009. p. 7–17.
7. Mohsen Sabaa HA. Value of Urocortin as a Marker for Preterm Labor. J Gynecol Womens Heal. 2016 May 25;1(2):555559.
8. Wirakusumah F. Penentuan Usia Kehamilan. In: Krisnadi S, Effendi J, Pribadi A, editors. Prematuritas. 1st ed. Bandung: Reflika Aditama; 2009. p. 7–17.
9. Martin J a, Hamilton BE, Ventura SJ, Osterman MJK, Wilson E, Mathews TJ. Final Data for 2010. Natl Vital Stat Reports. 2012;61(1):1–104.
10. Conde-Agudelo A, Romero R, Kusanovic JP. Nifedipine in the management of preterm labor: A systematic review and metaanalysis. Am J Obstet Gynecol. 2011;204(2):134.e1-134.e20.
11. Singh N, Singh U, Seth S. Comparative study of nifedipine and isoxpurine as tocolytics for preterm labor. J Obstet Gynecol India. 2011 Oct;61(5):512–5.
12. Seema B, Pujar T V. Comparison of safety, efficacy and perinatal outcome of isoxsuprine and nifedipine in women with preterm labour. Int J Reprod Contraception, Obstet Gynecol. 2017 Jan 31;6(2):400.
13. Vinken MPGC, Rabotti C, Mischi M, van Laar JOEH, Oei SG. Nifedipine-Induced Changes in the Electrohysterogram of Preterm Contractions: Feasibility in Clinical Practice. Obstet Gynecol Int. 2010;
14. Hajagos-Tth J, Kormnyos Z, Falkay G, Pl A, Gspr R. Potentiation of the uterus-relaxing effects of β-adrenergic agonists with nifedipine: Studies on rats and the human myometrium. Acta Obstet Gynecol Scand. 2010 Oct;89(10):1284–9.
15. Aguilar HN, Mitchell BF. Physiological pathways and molecular mechanisms regulating uterine contractility. Hum Reprod Update. 2010;16(6):725–44.
16. Grzesiak M, Ahmed RB, Wilczynski J. 48-hours administration of nifedipine in spontaneous preterm labor-Doppler blood flow assessment of placental and fetal circulation-780X • www.nel.edu. Vol. 34, Neuroendocrinology Letters. 2013.

17. Ulubaşoğlu H, Özmen Bayar Ü, Kaya C, Ungan B. The effect of nifedipine tocolysis on Doppler indices of the uterine and umbilical Arteries. J Clin Ultrasound. 2015 Jun 1;43(5):322–6.
18. Fuchs F, Monet B, Ducruet T, Chaillet N, Audibert F. Effect of maternal age on the risk of preterm birth: A large cohort study. Gutman J, editor. PLoS One. 2018 Jan 31;13(1):e0191002.
19. Matsuda Y, Kawamichi Y, Hayashi K, Shiozaki A, Satoh S, Saito S. Impact of maternal age on the incidence of obstetrical complications in Japan. J Obstet Gynaecol Res. 2011 Oct 1;37(10):1409–14.
20. Badan Pusat Statistik. Statistik Indonesia 2020. https://www.bps.go.id/publication/2020/04/29/e9011b3155d45d70823c141f/statistik-indonesia-2020.html. Accessed 28 Juni 2020.
21. Mahaseth B, Srivastav M, Das C, Malla T. Preterm Delivery Associated Risk Factor And Its Incidence. IOSR J Dent Med Sci e-ISSN. 2017;17(01):51–5.
22. Indarti J, Nanda A, Fattah A, Dewi Z, Dediat R, Hasani K, et al. Teenage Pregnancy: Obstetric and Perinatal Outcome in a Tertiary Centre in Indonesia. Obstet Gynecol Int. 2020;
23. Purisch SE, Gyamfi-Bannerman C. Epidemiology of preterm birth. Vol. 41, Seminars in Perinatology. W.B. Saunders; 2017. p. 387–91.
24. Dekker GA, Lee SY, North RA, McCowan LM, Simpson NAB, Roberts CT. Risk factors for preterm birth in an international prospective cohort of nulliparous women. PLoS One. 2012 Jul 16;7(7):e39154.
25. WHO. Prevalence of anemia among pregnant women (%) - Indonesia | Data [Internet]. The World Bank. 2016 [cited 2020 Jul 17]. Available from: https://data.worldbank.org/indicator/SH.PRG.ANEM?locations=ID&most_recent_year_d
26. Pinho-Pompeu M, Surita FG, Pastore DA, Paulino DSM, Pinto e Silva JL. Anemia in pregnant adolescents: impact of treatment on perinatal outcomes. J Matern Neonatal Med. 2017 May 19;30(10):1158–62.
27. Roozbeh N, Moradi S, Soltani S, Zolfizadeh F, Tadris Hasani M, Pormehr Yabandeh A. Factors associated with preterm labor in Hormozgan province in 2013. Electron physician. 2016 Sep 20;8(9):2918–23.
28. Kim BJ, Romero R, Lee SM, Park CW, Park JS, Jun JK, et al. Clinical significance of oligohydramnios in patients with preterm labor and intact membranes. J Perinat Med. 2011 Mar 1;39(2):131–6.
29. Stampalija T, Gyte GM, Alfirevic Z. Utero-placental Doppler ultrasound for improving pregnancy outcome. Cochrane Database Syst Rev. 2010 Sep 8;(9).
30. Gáspár R, Hajagos-Tóth J. Calcium channel blockers as tocolytics: Principles of their actions, adverse effects and therapeutic combinations. Vol. 6, Pharmaceuticals. Multidisciplinary Digital Publishing Institute (MDPI); 2013. p. 689–99.
31. Samy S, Elshourbagy S. Assessment of Maternal Nifedipine as a Tocolytic Agent on the Doppler Indices of Uterine and Fetal Umbilical and Middle Cerebral Arteries. Gynecol Obs Res Open J. 2017;4(2):44–9.
32. de Heus R, Mulder EJH, Visser GHA. Management of preterm labor: Atosiban or nifedipine? Vol. 2, International Journal of Women's Health. Dove Medical Press; 2010. p. 137–42.

33. Guclu S, Saygili U, Dogan E, Demir N, Baschat AA. The short-term effect of nifedipine tocolysis on placental, fetal cerebral and atrioventricular Doppler waveforms. Ultrasound Obstet Gynecol. 2004 Dec;24(7):761–5.
34. Baykal BÖ, Avcıoğlu SN. Comparison of effects of nifedipine and ritodrine on maternal and fetal blood flow patterns in preterm labor. J Turkish Ger Gynecol Assoc. 2015;16(2):80–5.
35. Armangil D, Yigit S, Velipasaoglu M. Fetal arterial and venous Doppler in growth restricted fetuses for the prediction of perinatal complications. Turk J Pediatr. 2010;52:384–92.