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COMPARATIVE STUDY ON EFFICACY OF TRANSDERMAL NITROGLYCERINE PATCH AND ORAL NIFEDIPINE AS TOCOLYTIC IN PRETERM LABOUR

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ABSTRACT

Aim of The Study To Study the efficacy and usefulness of transdermal Nitro-glycerine patch and oral Nifedipine as a tocolytic in preterm labour. **Objective of The Study** To study maternal side effects and neonatal outcome of transdermal Nitro- glycerine patch and oral Nifedipine as a tocolytic in preterm labour. To study about perinatal mortality and morbidity of transdermal Nitro- glycerine patch and oral Nifedipine as a tocolytic in preterm labour. **Materials And Methods Study Design:** Prospective Comparative Study / Randomised Controlled Study **Sample Size:** 200 **Group A:** NITROGLYCERINE group, **Group B:** NIFEDIPINE group **Results:** The results from this study prerequisite to be future studies strengthened and validated by multicentric and larger sample size and to study the optimal dosage, dosage regimes, overall efficacy and foetal safety. **Conclusion** Out of the 97 in each group after dropouts, Nitro-glycerine groups 87 achieved Tocolysis and, 90 achieved Tocolysisin Oral Nifedipine group. In Nitro-glycerine group, the common side effects were Headache (22%) followed by Itching (12%). In Oral Nifedipine group, the common side effects were Tachycardia (10%) followed by Hypotension (5%). The common complication in Nitro-glycerine group is Respiratory Distress Syndrome (7%), followed by Sepsis (6%) and Aspyxia (5%). In Oral Nifedipine group, the common complication is Respiratory Distress Syndrome (5%) and Sepsis (4%).

KEYWORDS : Preterm labour, Prevention , Tocolysis, Respiratory Distress, sepsis.

INTRODUCTION

This is a prospective comparative study which was conducted in the Department of Obstetrics and Gynecology. preterm birth complications are the leading cause of death among children under 5 years of age, responsible for approximately 1 million deaths in 2015[Ref.No-1] Three-quarters of these deaths could be prevented with current, cost- effective interventions.[Ref.No-2] According to WHO - preterm labour is < 37 completed weeks (259 days) from the 1st day of last menstrual period.([Ref.No-3]) Preterm labour is one of the most challenging problem of obstetrician accounts for 7-12% of the pregnancies and causes about 75 - 80% of perinatal deaths occur in preterm infants[(Ref.No-4)]

If uterine contractions are perceived in the absence of cervical change the condition is called threatened preterm labour. Tocolysis is used to manage the preterm labour fundamentally wishes to prolong the pregnancy at least for 48-72 hours and so as to provide an satisfactory period to administer 2 doses of corticosteroids. This will help in preventing respiratory distress syndrome in new-born by allowing the corticosteroids to act on the lung maturity. [(Ref.No-5)] Currently, there is no clear first-line tocolytic agent although a meta- analysis proposed that Nifedipine seems to meet numerous characteristics of a perfect tocolytic agent) Both nitro-glycerine and Nifedipine have been shown to be effective in the management of preterm labour. This study is intended to compare the effectiveness of nitro-glycerine with Nifedipine as tocolytic for preterm labour in south Indian population.

Epidemiology And Contributing Factors

Race

Common among black women.

Age

Common in women under 20 and over 35.

Weight

Poor nutrition, poor weight gain and poor pre-pregnancy weight associated with preterm labour.

Stature

Short stature prone to produce preterm birth.

Socio Economic Status

Lower Socio economic status Less education Poor general and personal hygiene more prone for pre term labour.

Addictions

Cigarettes smoking and cocaine abuse and alcohol consumption are more prone for preterm labour.

Occupational

Women's involved in manual and strenous work are prone for preterm labour.

Contributing Factors

- Threatened abortion Birth defects
- Interval between pregnancies Coitus
- Stress
- Previous abortion and previous preterm delivery

AIM AND OBJECTIVES

AIM OF THE STUDY

To Study the efficacy and usefulness of transdermal Nitro-glycerine patch and oral Nifedipine as a tocolytic in preterm labour.

Objective of The Study

To study maternal side effects and neonatal outcome of transdermal Nitro- glycerine patch and oral Nifedipine as a tocolytic in preterm labour.

To study about perinatal mortality and morbidity of transdermal Nitro- glycerine patch and oral Nifedipine as a tocolytic in preterm labour.

A.Preterm Labour:

Preterm labour is defined as "regular contractions of the uterus resulting in changes in the cervix that commence before 37 weeks of pregnancy. Changes in the cervix comprise of effacement (the cervix thins out) and dilation (the cervix opens so that the foetus can enter the birth canal)." By American College of Obstetricians and Gynaecologists. [(Ref.No-6)3]

World health Organisation(WHO) defines Preterm as "babies born alive before 37 weeks of pregnancy are completed". There are sub-categories of preterm birth, based on

gestational age:
a. Extremely preterm (less than 28 weeks)
b. Very preterm (28 to 32 weeks)
c. Moderate to late preterm (32 to 37 weeks).(2)

B .Tocolysis:
Tocolysis is used for postponement preterm delivery. It is an important intervention in obstetrics. Thoughtocolyticshave not been shown to improve neonatal outcomes, they can postpone preterm delivery long enough for antenatal corticosteroids to be administered and creating time for the corticosteroids to act. (Ref.No-8) In premature neonates, antenatal corticosteroids has been documented to reduce morbidity and mortality(Ref.No-9). The primary goal of a tocolysis is the prevention of a preterm delivery before the end of the 37th week of gestation. The following table represents the indications for Tocolysis, (Ref.No-10)

Drugs in Tocolysis:
The following table represents the drugs used in the tocolysis, their primary usage and most common side effects, The following table represents the drugs used in Tocolysis, its dosage, description and rationale.(Ref.No-7)

Medication or Drug Class	Dosage	Description	Rationale
Nifedipine	30 mg loading dose, 10–30 mg q 4–6 hr	Calcium channel blocker; tocolytic	Inhibits contraction of smooth muscles by reducing intracellular calcium influx
Indomethacin	100 mg PR, then mg PO every 6 hr for 8 doses	Prostaglandin synthetase inhibitor; tocolytic (labor repressant)	Reduces prostaglandin systhesis and decreases inflammation
Magnesium sulfate (contraindicated in myasthenia gravis)	4–6 g IV loading dose, 1–4 g/hr of IV maintenance	Central nervous system depressant; tocolytic	Decreases contraction of smooth muscles by reducing intracellular calcium influx; some controversy about its effectiveness
Terbutaline (Brethine)	Initially, 2.5 mcg/min; increase to a max of 20 mcg/min OR 0.25 mg SQ q 20 min × 3 doses, then q 3 hr; after IV is discontinued, follow with 5 mg PO q 4–6 hr	Beta-adrenergic	Relaxes smooth muscle, inhibiting uterine contractions; use has been curtailed due to side effects such as palpitations, tachycardia, and transient hyperglycemia, hypokalemia, and myocardial ischemia in the mother and fetus
Betamethasone (Celestone)	12 mg IM q 24 hr × 2	Glucocorticoid	Hastens fetal lung maturity; indicated if delivery is anticipated between 24 and 34 wk

Class of drugs	Primarily licensed for	The most frequent side effects
Beta-adrenergic agonists	bronchial asthma	Maternal: tachycardia, hyperglycemia, pulmonary oedema Foetal: tachycardia, RDS
Cyclooxygenase inhibitors	inflammation, pain, fever	Foetal: premature closure of ductus arteriosus, reduced amniotic fluid index
Gestagens	hormonal substitution, contraception	no relevant side effect
Magnesium sulphate	hypomagnesaemia, eclampsia in pregnancy	Maternal: constipation, visual blurring, headache
CCBs (DHPs)	hypertension	Maternal: headache, tachycardia, hypotension
Oxytocin antagonists	tocolysis	Maternal: tachycardia, chest pain

METHODOLOGY

Study Subjects:
- Preterm mothers (SAMPLE SIZE- 200) admitted for tocolysis in our department of Obstetrics and Gynecology.

Study Design:
- Prospective Comparative Study / Randomized Controlled Study

Inclusion Criteria:
a. Gestational age between 28 to 37 weeks
b. Presence of regular uterine contractions 2 in 10minutes each contractions lasting for more than 40 seconds.
c. Cervical changes - cervical effacement >25% or dilatation of >1 cm. with intact membranes.
d. No previous administration of tocolytics.

Exclusion criteria:
I. Systemic diseases like
a. Diabetes Mellitus,
b. Cardiac Diseases,
c. Liver Or Renal Diseases,
d. Hypotension.

ii. Obstetric complications like
a. Hypertensive Disorders of Pregnancy,
b. Antepartum Haemorrhage,
c. Ruptured Membranes.

iii. Foetal complications like
- Chorioamnionitis,
- IUGR,
- Congenital Anomaly,
- Foetal Distress.
- MultifoetalGestation,
- Polyhydramnios,
- Oligohydramnios

Sample Size:200

GROUP A:NITROGLYCERINE group GROUP B:NIFEDIPINE group

Study procedure:
Pregnant women with preterm pains in Labour ward of department of Obstetrics and Gynaecology. All patients presenting with preterm labour were scrutinized to select the patient for tocolysis.

After fulfilling the inclusion criteria and after explaining the procedure and obtaining written consent patients were enrolled for the study. Patients were be randomly assigned to GROUP A and GROUP B.Randomization done by table of random numbers or computer generated list which eliminates bias and allows comparability.

Both groups should be alike with regards to certain variables that might affect the outcome of the experiment. Cross matching of the two groups was performed regarding age, previous obstetric history, gestational age, height of fundus, temperature and blood pressure at the time of admission.

PROCEDURE OF STUDY :
A detailed history, complete physical examination and routine investigation, USG for cervical length, dilatation, was done for all patients. All women were screened for urinary tract infections (UTI)/bacterial vaginosis with a mid-stream clean catch sample & a high vaginal swab respectively and antibiotic treatment was instituted. All patients received two doses of 12 mg betamethasone intramuscularly, first at admission and a second dose 24 hours later in order to accelerate the foetal lung maturity.

Patients were randomly assigned to group A (NITROGLYCERINE) and group B(NIFEDIPINE)

Patients in the study were admitted with strict bed rest to the labour ward. At the onset of treatment, maternal and foetal measurements were recorded 15 minutes during first two hours and then followed by hourly recording.

After pelvic examination, the patient was placed in lateral recumbent position and externally monitored for foetal heart rate and contractions. Intravenous boluses of 500 ml of normal saline was infused in order to prevent hypotensive effect of two drugs and it diminishes the contractions of an irritable uterus which also helps to differentiate this condition from pretermlabour.

5. Mode of Delivery:

In the study population majority were undergoing vaginal delivery (88, 90 in Nitro-glycerine and Oral Nifedipine groups respectively), followed by LSCS (9, 7 in Nitro-glycerine and Oral Nifedipine groups respectively).3 were lost to follow up in each of these groups. .

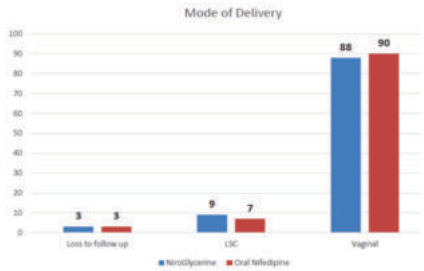

Fig. 5 Bar chart. Mode of delivery between Nitro-glycerine and Oral Nifedipine groups:

6. Side effects:

The major side effects reported among the Nitro-glycerine and Oral Nifedipine groups are HA and TA respectively.

Table. 2 Side effects among the Nitro-glycerine and Oral Nifedipine groups:

Side effects			
Nitro-glycerine		Oral Nifedipine	
HA	22	FAS	2
IT	12	HY	5
NAU+V	2	HY/TA	4
RASH	1	NAU	4
		Tachycardia	10

7. NICU Complications:

The major NICU complications reported among the Nitro-glycerine and Oral Nifedipine groups are Respiratory Distress Syndrome. Sepsis was present in 6 and 4 newborns in Nitro-glycerine and Oral Nifedipine groups respectively.

Table-3 NICU complications among the Nitro-glycerine and Oral Nifedipine groups:

NICU complications			
Nitro-glycerine		Oral Nifedipine	
ASP	5	ASP	1
IVH	1	CONG	1
RDS	7	IVH	1
SEPS	6	RDS	5
		SEPS	4

8. Tocolysis:

Out of the total study population, 6 (3 from each group) were drop outs from the study.in the remaining 194, Tocolysis was achieved in 177 (88.5%) followed by 17 (8.5%).

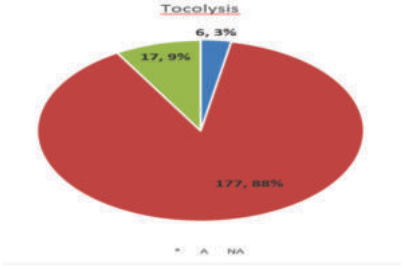

Fig.6 Pie chart Tocolysis among the Nitro-glycerine and Oral Nifedipine groups:

b. Inferential Statistics:

I. Comparison of Tocolysis between groups:

Out of the total study population, 6 (3 from each group) were drop outs from the study.in the remaining 194, Tocolysis was achieved in 177 (88.5%) followed by 17 (8.5%). Out of the 97 Nitro-glycerine groups 87 achieved Tocolysis. And in Oral Nifedipine group out of 97, 90 achieved Tocolysis. This difference is not statistically significant using chi-square test with p-value of 0.446.

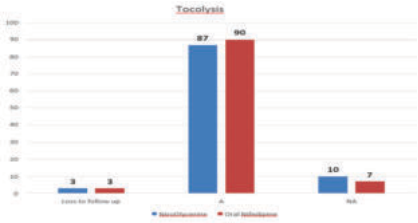

Fig.7 Bar Chart. Tocolysis among the Nitro-glycerine and Oral Nifedipine groups:

I.Comparison of Live status of the babies delivered between groups:

Out of the 97 studied in each group only one still birth was reported in Oral Nifedipine group.

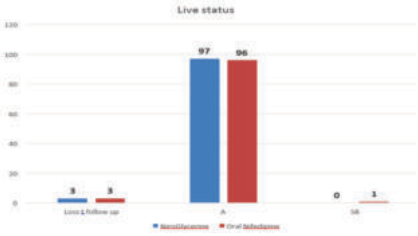

Fig.8 Bar chart. Live status of the babies delivered between groups

ii.Comparison of mode of delivery between groups:

Out of the total study population, 6 (3 from each group) were drop outs from the study. Out of the 97 Nitro-glycerine group, 88 undergone vaginal delivery. And in Oral Nifedipine group out of 97, 90 undergone vaginal delivery. This difference is not statistically significant using chi-square test with p-value of 0.602.

Table 4. Mode of Delivery among the Nitro-glycerine and Oral Nifedipine groups:

		Group		Total	p-value
		Nitro-glycerine	Oral Nifedipine		
MOD	LSCS	9	7	16	0.602
	VD	88	90	178	
Total		97	97	194	

iv. Comparison of side effects between groups:

There were no side effects reported in the 60 and 72 patients in Nitro- glycerine and Oral Nifedipine groups respectively. In Nitro-glycerine group, the common side effects were Headache (22) followed by Itching (12). In Oral Nifedipine group, the common side effects were Tachycardia (10) followed by Hypotension (5). Hypotension and Nausea/vomiting were present in Oral Nifedipine group only. These difference are statistically significant with p- value of <0.001. (As many cell values were zero, considering the p-value may not be fair).

Table 5. Comparison of side effects between groups:

		Group		Total	p-value
		Nitro-glycerine	Oral Nifedipine		<0.001
Side effects	NIL	60	72	132	
	Facial flushing	0	2	2	
	Headache	22	0	22	
	Hypotens ion	0	5	5	

Group A:
Study participantswere given transdermal nitro-glycerine patch, which delivers 10 mg NTG over twenty-four hours and it is applied to the woman's abdomen. If contractions persisted at the end of 1 hour, an additional patch of 10 mg is applied. No more than two patches were worn simultaneously (20 mg). At the end of 24 hours, a fresh patch replaced these. Mild headaches were treated usingparacetamol. Patches remained in place for 12 hrs if the contractions had ceased, if it persists it were kept in place for full 24 hours. At the end, the patches were removed and the women were reassessed.

Group B:
Study participants in this group were given loading dose of oral Nifedipine 20 mg, if contractions persists after one hour 10mg were repeated, followed by maintenance dose of 10mg 8th hourly for two days.

If uterine contractions does not arrest even after giving 40 mg of Nifedipine then it is considered as tocolysis not achieved.3

Patients were monitored from the time of admission to the time of discharge.

Treatment Success:
Treatment is considered successful if uterine contraction subsided and Tocolysis achieved for > 48 hours.

STATISTICAL METHODS:
Descriptive Statistics:
1. Numerical variables like age are represented in mean, median, mode and standard deviation.
2. Categorical variables like gender are represented in frequencies and percentages. Pie-charts and bar diagrams are used as appropriate.

Inferential Statistics:
1. When a Numerical variable is associated with the Numerical variables such as Pearson's correlation testis used after checking for normality.
2. When a Categorical Variable is associated with a categorical variable, the variablesare represented in both by tables and bar diagrams. For test ofsignificance, chi-square test is used. Fisher's exact test is used when more than 20% of the cell values have expected cellvalue less than 5.
3. P-values less than 0.05 were considered statistically significant.
4. Data was entered in MS excel sheet and analysed using SPSS software version 16.
5. When a numerical variable (No. of days) is compared between two groups, Independent t test was used after checking for normality.

1. Age:
In the study population, the Mean, Median, Mode, Std. Deviation, Minimum and Maximum values of the age in the Nitro-glycerine and Oral Nifedipine groups are similar.

Table -1 Age distribution among Nitro-glycerine and Oral Nifedipine groups:

Measure	Nitro-glycerine	Oral Nifedipine
Mean	24.30	25.33
Median	24.00	26.00
Mode	22	28
Std. Deviation	3.535	3.590
Minimum	18	18
Maximum	34	35

2.Obstetric Code:
Among the study population, majority were Primi gravidae (66, 71 inNitro-glycerine and Oral Nifedipine groups respectively). This is followed by G2P1L1 (21, 16 in Nitro-glycerine and Oral Nifedipine groups respectively). Fig.1 Bar Chart. Obstetric code among Nitro-glycerine and Oral Nifedipine groups:

ontraction in the groups:
Among the Nitro-glycerine group, 75% were having 2 contractions and among the Oral Nifedipine group, 68% were having 2 contractions.

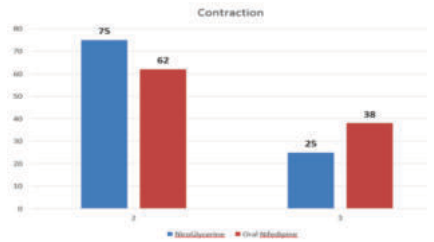

Fig.2 Bar Diagram. Contractions among the Nitro-glycerine and Oral Nifedipine groups:

3. Birth weight, GOA, GOD:
In the study population, the Mean, Median, Mode, Std. Deviation, Minimum and Maximum values of the Birth Weight, GOA and GOD in the Nitro-glycerine and Oral Nifedipine groups are similar

A. CD in CMCS:

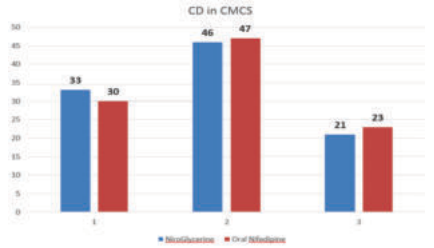

Figure.3

4. Effacement:
In the study population, the majority were having 50 % effacement (46, 47 in Nitro-glycerine and Oral Nifedipine groups respectively), followed by 25% effacement (33, 30 inNitro-glycerine and Oral Nifedipine groups respectively) and 75% effacement in (21, 23 in Nitro-glycerine and Oral Nifedipine groups respectively).

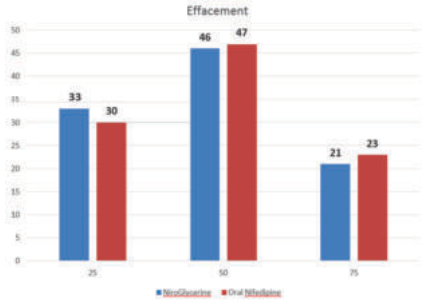

Fig. 4 Effacement between Nitro-glycerine and Oral Nifedipine groups:

	HY/TA	0	4	4	
	IT	12	0	12	
	NAU	0	4	4	
	NAU+V	2	0	2	
	RASH	1	0	1	
	TA	0	10	10	
Total		97	97	194	

V. Comparison of mean days of prolongation after Tocolysis between groups:

The mean Days of Prolongation among the Nitro-glycerine group is 7.58 and Oral Nifedipine group is 7.29. This difference is statistically not significant using t test with p-value of 0.672.

Table 6. Comparison of mean days of prolongation after Tocolysis between groups:

	Group	N	Mean	Std. Deviation	p-value
Days of Prolongation	Nitro-glycerine	97	7.58	4.39	0.672 (Not Significant) t test used.
	Oral Nifedipine	97	7.29	5.06	

vi. Comparison of NICU Complications between groups:

78 in Nitro-glycerine group and 85 in Oral Nifedipine group had no complications in new born. The common complication in Nitro-glycerine group is RDS (7), followed by Sepsis (6) and Asp (5).In Oral Nifedipine group, the common complication is RDS (5) and Sepsis (4). This difference is statistically not significant using Fisher's Exact test with p-value of 0.453.

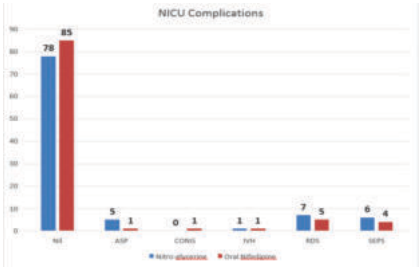

Fig.9 Bar Chart. Comparison of NICU complications between groups:

DISCUSSION

The main objective of the study isto Study the efficacy and usefulness of transdermal Nitro-glycerine patch and oral Nifedipine as a tocolytic in preterm labour.The rate of preterm delivery has not come down because of the unknown aetiology and subtle signs and symptoms. World Health Organisation recommends nine salient interventions for managing the preterm labour. Tocolysis is one among the nine key recommendations. Preterm labour has multiple aetiologies and some remain grey areas to the experts. Hence, the measurement of the effectiveness of tocolytic in delaying the labour itself is determined by various factors.

GTN is compared with the other tocolytics likeritodrine, magnesium sulphate (MgSO4), fenoterol magnesium sulphate, or salbutamol magnesium sulphate, as well as one case series and yielded a favourable results for Nitro-glycerine.

RESULTS :

The results from this study prerequisite to be future studies strengthened and validated by multicentric and larger sample size and to study the optimal dosage, dosage regimes, overall efficacy and foetal safety.

CONCLUSION

Out of the 97 in each group after dropouts, Nitro-glycerine groups 87 achieved Tocolysis and, 90 achieved Tocolysisin Oral Nifedipine group. In Nitro-glycerine group, the common side effects were Headache (22%) followed by Itching (12%). In Oral Nifedipine group, the common side effects were Tachycardia (10%) followed by Hypotension (5%).

The common complication in Nitro-glycerine group is Respiratory Distress Syndrome (7%), followed by Sepsis (6%) and Aspyxia (5%). In Oral Nifedipine group, the common complication is Respiratory Distress Syndrome (5%) and Sepsis (4%).

REFERENCES

1. Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, et al. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet. 2016 Dec 17;388(10063):3027–35.
2. Preterm birth [Internet]. [cited 2019 Oct 27]. Available from: https://www.who.int/news-room/fact-sheets/detail/preterm-birth
3. WHO. WHO | International Classification of Diseases, 11th Revision (ICD-11) [Internet]. Who. 2019 [cited 2019 Oct 28]. Available from: https://www. who.int/classifications/icd/en/
4. Sandhya RM, Lakshmi VAA. Comparative Study of transdermal NTG patch versus Oral Nifedipine in the pevention of Preterm Labour. IOSR J Dent Med Sci [Internet]. 2015 [cited 2019 Oct 26];14(4):2279–861. Available from: www.iosrjournals.org
5. Crowley P. Prophylactic corticosteroids for preterm birth. Crowley P, editor. Cochrane Database Syst Rev [Internet]. 2006 Apr 22 [cited 2019 Oct 28]; Available from: http://doi.wiley.com/10.1002/14651858.CD000065.
6. Preterm Labor and Birth - ACOG [Internet]. [cited 2019 Oct 27]. Available from: https://www.acog.org/Patients/FAQs/Preterm-Labor- and-Birth?IsMobileSet=false.
7. Preterm labor | definition of preterm labor by Medical dictionary [Internet]. [cited 2019 Oct 28]. Available from: https://medical- dictionary.thefreedictionary.com/preterm+labour.
8. Haas DM, Imperiale TF, Kirkpatrick PR, Klein RW, Zollinger TW, Golichowski AM. Tocolytic therapy: A meta-analysis and decision analysis. Obstet Gynecol. 2009 Mar;113(3):585–94.
9. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Vol. 2017, Cochrane Database of Systematic Reviews. John Wiley and SonsLtd;2017.
10. Simhan HN, Caritis SN. Prevention of preterm delivery. Vol. 357, New England Journal of Medicine. Massachussetts Medical Society; 2007. p. 477.