

# ASSESSMENT OF PERINATAL OUTCOME AFTER USING NIFEDIPINE VERSUS PLACEBO IN THE TREATMENT OF PRETERM PRELABOR RUPTURE OF MEMBRANES

(Randomized controlled study)

By

Mohamed Gamal El-Din Ahmed Shafey, Farid Ibrahim Hassan, Mofeed Fawzy Mohamed and Dalia Moneer El-Lahouny\*

Department of Obstetrics and Gynecology, Faculty of Medicine, Al-Azhar University

Department of Pediatrics\*, Faculty of Medicine, Al-Menoufia University

**Corresponding author:** Mohamed Gamal El-Din Ahmed Shafey,

**E-mail:** [gamalshafey66@gmail.com](mailto:gamalshafey66@gmail.com)

## ABSTRACT

**Background:** Preterm birth is the most common cause of neonatal morbidity and mortality worldwide and accounts for approximately 75% of all neonatal deaths and 50% of childhood neurological morbidities. Around one-third of preterm deliveries start with preterm pre-labor rupture of membranes (PPROM).

**Objective:** To assess the value of Nifedipine to change the perinatal outcome in cases of preterm pre-labor rupture of membranes.

**Patients and methods:** This was a randomized, controlled study that included and followed 200 pregnant women. One hundred pregnant women were recruited in the Nifedipine group in addition to 100 pregnant women were recruited as a control group from Obstetric Department of Shebin El Kom Teaching Hospital during the period from 2017-2019.

**Results:** In this randomized clinical trial among women with PPRM without contractions, we found no significant differences between treatment with nifedipine or placebo in terms of perinatal outcomes and prolongation of pregnancy.

**Conclusion:** On perinatal outcomes or prolongation of pregnancy in women with PPRM without contractions.

**Keywords:** Nifedipine versus placebo, preterm prelabor rupture of membranes.

## INTRODUCTION

Despite the high 25 prevalence of preterm birth following PPRM, the optimal management of PPRM remains a topic of debate and is hindered by a lack of evidence. After rupture of the membranes, there is a high risk that labor

will follow within days. Most women with PPRM who receive conservative management deliver within one week. Most clinical guidelines advise to administer a 48h course of corticosteroids and transfer to a tertiary care center to improve neonatal outcome (Flenady *et al.*, 2014). One mechanism by which tocolysis

might improve outcome is to delay delivery during this 48h period. However, the use of tocolysis in this period, but especially after 48 h, is subject to debate. The prevalence of adverse neonatal outcome is strongly related to gestational age at delivery declining from 77% at 24 to 27 weeks to less than 2% from 34 weeks onwards (*De Heus et al., 2011*).

Administration of tocolytic drugs after the 48h period may further increase the latency period and thereby improve gestational age at delivery. However, prolongation of pregnancy in PPRM does not automatically lead to an improvement of neonatal outcome. As infection is detected in a major part of all women with PPRM, prolongation of pregnancy may result in longer exposure of the fetus to a harmful infective environment. Therefore, the benefit of postponing delivery must be weighed against the potential harm of the increased risk on maternal and perinatal infection. A recent Cochrane review indicated that, when compared to placebo, tocolysis in PPRM is associated with an average 73 h longer latency of delivery and fewer births within 48 h. However, tocolysis was also associated with an increased risk of a 5 min Apgar score under 7 and an increased need for ventilation support. Different tocolytic drugs were compared, mostly betamimetics (ritodrine). Tocolysis significantly increased the duration of pregnancy without any significant effects on maternal and neonatal outcomes. Women with PPRM before 34 weeks of gestation tocolysis increased the rate of chorioamnionitis, neonatal outcome was comparable (*Jobe and Bancalari, 2010*).

**The aim of the study was to** assess the value of Nifedipine to change the perinatal outcome in cases of preterm pre-labor rupture of membranes.

## PATIENTS AND METHODS

This randomized, controlled, study included and followed 200 pregnant women. 100 pregnant women were recruited in the Nifedipine group in addition to 100 pregnant women were recruited as a control group from Obstetric Department of Shebin El Kom Teaching Hospital during the period from 2017-2019.

A written informed consent was obtained from every eligible woman. Women were informed about the study objectives, methodology, risk, and benefit. The study's protocol was reviewed and approved by IRB, ethics committee or Audit Department of Obstetrics and Gynecology, Shebin El Kom Teaching Hospital.

**Inclusion Criteria:** Pregnant women during aged 20 – 30 years, patients accepted to join the study after signing informed consent, women with gestational age between 28 and 37 weeks, recent onset of rupture of membranes within 24h, ruptured membranes without signs of active labor and ruptured membranes without signs of infection.

**Exclusion Criteria:**  $\geq 3$  contractions per 10 min (signs of active labor), previous treatment with tocolysis in the last 7 days (tocolysis for  $< 6$  h for transportation was allowed), ruptured membranes  $\geq 72$ h, signs of chorioamnionitis or intra uterine infection, signs of fetal distress, fetal major congenital anomaly, contraindication for the use of nifedipine,

maternal disease as reason for delivery (such as hypertension, HELLP syndrome or preeclampsia) and patient who refuse to take part in the study.

To detect a reduction in adverse perinatal outcome from 30% in the placebo group to 10% in the nifedipine group, 200 women (100 per group) were needed (two-sided test, type I error= 0.05, power = 80%).

**Baseline characteristics of the included patients:** Baseline demographics of the patient entered in a web-based database. We collected Gestational age at study entry, maternal age, body mass index, smoking status, nulliparity, prior preterm birth, twin gestation, laboratory results at entry, prophylactic antibiotic therapy and corticosteroid administration.

Study medication consisted of one tablet every six hours, administered orally (containing 20 mg nifedipine slow release or placebo). The medication was given until the start of active labor (>3 contractions per 30 min), with a maximum of 18 days or until gestational age of 34+0 weeks. The length of the therapy was limited to 18 days, based on the assumption that prolongation of pregnancy of more than two weeks, if clinically relevant, should show an effect on perinatal outcome. The medication package was stored by the patient, and the administration of the study medication was noted in her medical record. Antenatal corticosteroids were

administered according to national guidelines, advising antenatal corticosteroids to women in preterm labor <34 weeks of gestation. Prophylactic antibiotic therapy and magnesium sulphate were administered according to local protocol, as was maternal 121 and fetal monitoring.

Laboratory investigations were done in the form of leukocytes and CRP.

#### **Statistical Analysis:**

An Excel spreadsheet was established for the entry of data. We used validation checks on numerical variables and option-based data entry method for categorical variables to reduce potential errors. The analyses were carried with SPSS software (Statistical Package for the Social Sciences, version 24, SSPS Inc, Chicago, IL, USA). Frequency tables with percentages were used for categorical variables and descriptive statistics (median and interquartile range [IQR]) were used for numerical variables. Independent Student t-test or Mann-Whitney test were used to compare quantitative variables, while Chi-square test or was used to analyze categorical variables. The main outcome variable, adverse perinatal outcome and secondary neonatal outcomes were assessed by calculating rates in the two groups, relative risks and 95% confidence interval. A p-value < 0.05 is considered statistically significant.

## RESULTS

The mean gestational age was 33.6 ( $\pm 2.48$ ) in Nifedipine group and 33.4 ( $\pm 2.52$ ) in placebo group. The mean maternal age was 27.1 ( $\pm 5.73$ ) in Nifedipine group and 25.6 ( $\pm 5.52$ ) in placebo group. Mean body mass index is 25.8 (2.2) in Nifedipine group and 24.1 (1.5) in placebo group. The mean parity was 0.89 (0.76) in nifedipine group and 0.70 (0.79) in placebo group. Only 1.0% of the participants were smoker in nifedipine group and no smoker in the control group. Only 6.0% of the participants experienced prior preterm

birth in nifedipine group and 5.0% of the participants experienced prior preterm birth in control group. Only 3.0% of the participants reported twin gestation in nifedipine group and 3.0% of the participants reported twin gestation in control group. There were no statistically significant differences between nifedipine group and control group regarding gestational age, maternal age, body mass index, parity, smoking, prior preterm birth, and twin gestation ( $p$  value  $> 0.05$ ) (Table 1).

**Table (1): Baseline characteristics of the study cohort**

Parameters		Nifedipine (n=100)		Placebo (n=100)		P-value
		Mean	SD	Mean	SD	
Gestational age		33.6	2.48	33.4	2.52	>0.05
Maternal age		27.1	5.73	25.6	5.85	>0.05
Body mass index		25.8	2.2	24.1	1.5	<0.001
Parity		0.89	0.76	0.70	0.79	0.241
		N	%	N	%	
Smoking	Yes	1	1.0%	0	0.0%	>0.05
	No	99	99.0%	100	100.0%	
Prior preterm birth	Yes	6	6.0%	5	5.0%	>0.05
	No	94	94.0%	95	95.0%	
Twin gestation	Yes	3	3.0%	2	2.0%	>0.05
	No	97	97.0%	98	98.0%	

Median leukocytic count was 11.2 in nifedipine group and 12.1 in control group. Median CRP count was 5.0 in nifedipine group and 7.0 in control group. Prophylactic antibiotic therapy was reported in 16.0% of the participants of nifedipine group and placebo group. Corticosteroid administration was reported in 30.0% of the participants of

nifedipine group and 25.0% of the participants in placebo group. There were no statistically significant differences between nifedipine group and control group regarding leukocytes, CRP, prophylactic antibiotic therapy, and corticosteroid administration ( $p$  value  $> 0.05$ ) (Table 2).

**Table (2): Laboratory and treatment data of the study cohort**

Parameters		Nifedipine (n=100)		Placebo (n=100)		P value
		Median	IQR	Median	IQR	
Leukocytes		11.2	9.4 – 12.5	12.1	9.5 – 13.1	>0.05
CRP		5.0	3.0 – 6.0	7.0	3.0 – 11.0	>0.05
		N	%	N	%	
Prophylactic antibiotic therapy	Yes	16	16.0%	16	16.0%	>0.05
	No	84	84.0%	84	84.0%	
Corticosteroids administered	Yes	30	30.0%	25	25.0%	>0.05
	No	70	70.0%	75	75.0%	

Perinatal mortality was reported in 2.0% of the participants of nifedipine group and 3.0% of the participants in placebo group. Broncho pulmonary dysplasia was reported in 0.0% of the participants of nifedipine group and 6.0% of the participants in placebo group. PVL > grade I was reported in 1.0% of the participants of nifedipine group and 2.0% of the participants in placebo group. IVH > grade II was reported in 2.0% of the participants of nifedipine group and 2.0% of the participants in placebo group. NEC > grade I was reported in 2.0% of the participants of nifedipine group and 5.0%

of the participants in placebo group. Culture proven sepsis was reported in 10.0% of the participants of nifedipine group and 15.0% of the participants in placebo group. There were no statistically significant differences between nifedipine group and control group regarding perinatal mortality, PVL > grade I, IVH > grade II, and corticosteroid administration, NEC > grade I, and culture proven sepsis (p value > 0.05). However, broncho pulmonary dysplasia was significantly higher in placebo group than nifedipine group (p value = 0.021) (**Table 3**).

**Table (3): Primary and secondary outcomes of our study**

Parameters		Nifedipine (n=100)		Placebo (n=100)		P value
		N	%	N	%	
Perinatal mortality	Yes	2	2.0%	3	3.0%	>0.05
	No	98	98.0%	97	97.0%	
Broncho pulmonary dysplasia	Yes	0	0.0%	6	0.0%	0.021
	No	100	100.0%	94	94.0%	
PVL > grade I	Yes	1	1.0%	2	2.0%	>0.05
	No	99	99.0%	98	98.0%	
IVH > grade II	Yes	2	2.0%	2	2.0%	>0.05
	No	98	98.0%	98	98.0%	
NEC > grade I	Yes	2	5.0%	5	5.0%	>0.05
	No	95	95.0%	95	95.0%	
Culture proven sepsis	Yes	10	10.0%	15	15.0%	>0.05
	No	90	90.0%	85	85.0%	

Mean birth weight was 1810 in nifedipine group and 1524 in control group. NICU admittance was found in 20.0% of the participants of nifedipine group and 23% in placebo group. Median NICU Length was 11.0 in nifedipine group and 20.0 in control group. Ventilatory support was found in 5.0% of the participants of nifedipine group and

6% in placebo group. Median ventilatory support length was 1.0 in nifedipine group and 4.0 in control group. There were no statistically significant different between nifedipine group and control group regarding birth weight, NICU admittance, NICU length, ventilation support, and ventilation support length (p value > 0.05) (**Table 4**).

**Table (4): Secondary outcomes on the child level**

Parameters	Groups	Nifedipine (n=100)		Placebo (n=100)		P value
		Mean	SD	Mean	SD	
Birth weight (g)		1810	210	1524	240	<0.001
NICU admittance		N	%	N	%	
	Yes	20	20.0%	23	23.0%	>0.05
	No	80	80.0%	23	23.0%	
NICU Length (days)		Median	IQR	Median	IQR	>0.05
		11	3 - 22	20	5 - 55	
Ventilation support		N	%	N	%	>0.05
	Yes	5	5.0%	6	6.0%	
	No	95	95.0%	6	94.0%	
Ventilation support length (days)		Median	IQR	Median	IQR	>0.05
		1	1 - 9	4	1 - 8	

Median gestational age at delivery was 32.0 in nifedipine group and 30.0 in control group. Median length of prolongation of pregnancy at delivery was 11.0 in nifedipine group and 8.0 in control group. Prolongation of pregnancy  $\geq 48$  h was reported in 23.0% of the participants of nifedipine group and 25.0% of the participants in placebo group. Prolongation of pregnancy  $\geq 7$  days was reported in 16.0% of the participants of nifedipine group and 15.0% of the participants in placebo group. There was no maternal mortality reported in both groups. Discontinuation of study medication was reported in 19.0% of the participants of nifedipine group and 18.0% of the participants in placebo group. Discontinuation of due to progression into labor was reported in 15.0% of the participants of nifedipine

group and 14.0% of the participants in placebo group. Discontinuation due to side effects was reported in 2.0% of the participants of nifedipine group and 0.0% of the participants in placebo group. Discontinuation due to signs of intra uterine infection was reported in 6.0% of the participants of nifedipine group and 8.0% of the participants in placebo group. There were no statistically significant difference between nifedipine group and control group regarding gestational age at delivery, prolongation of pregnancy, prolongation of pregnancy  $\geq 48$  h, prolongation of pregnancy  $\geq 7$  days, maternal mortality, discontinuation of study medication, discontinuation of due to progression into labor, discontinuation due to side effects, and discontinuation due to signs of intra uterine infection (p value > 0.05) (**Table 5**).

Table (5): Secondary outcomes on the maternal level

Parameters	Groups	Nifedipine (n=100)		Placebo (n=100)		P value
		Median	IQR	Median	IQR	
Gestational age at delivery, weeks		32.0 (29.1–33.3)		30.0 (26.3–32.1)		>0.05
Prolongation of pregnancy, days		11 (7-19)		8 (5-25)		>0.05
Prolongation of pregnancy $\geq$ 48 h		N	%	N	%	>0.05
	Yes	23	23.0%	25	25.0%	
	No	77	77.0%	75	75.0%	
Prolongation of pregnancy $\geq$ 7 days	Yes	16	16.0%	15	15.0%	>0.05
	No	84	84.0%	85	85.0%	
Maternal mortality	Yes	0	0.0%	0	0.0%	>0.05
	No	100	100.0%	100	100.0%	
Discontinuation of study medication	Yes	19	19.0%	18	18.0%	>0.05
	No	81	81.0%	82	82.0%	
Discontinuation of due to progression into labor	Yes	15	15.0%	14	14.0%	>0.05
	No	85	85.0%	86	86.0%	
Discontinuation due to side effects	Yes	2	2.0%	0	0.0%	>0.05
	No	98	98.0%	0	100.0%	
Discontinuation due to signs of intra uterine infection	Yes	2	2.0%	4	4.0%	>0.05
	No	98	98.0%	96	96.0%	

## DISCUSSION

In this randomized clinical trial among women with PPROM without contractions, we found no significant differences between treatment with nifedipine or placebo in terms of perinatal outcomes and prolongation of pregnancy. Our results were in line with previous studies in which women with PPROM did not seem to benefit from treatment with prolonged tocolysis (*Jobe and Bancalari, 2014*).

Although we found a comparable rate of composite adverse perinatal outcome, our small sample size indicated that we might have missed a relevant difference. Therefore, it may still be possible that use of nifedipine resulted in a clinically

relevant difference in perinatal outcomes in women with PPROM without contractions.

Results of a Cochrane review showed no improvement in neonatal outcomes. Not all trials used standard corticosteroid therapy and antibiotics.

They found that CCBs, specifically nifedipine, is better than no tocolytics for postponing preterm birth for 48 hours, which may help improve outcomes for babies. Compared with betamimetics, CCBs were more effective at postponing birth, had fewer side effects for women, and appeared to improve some important short-term outcomes for the baby (breathing difficulties, gut infections, and admission to special care units).

Calcium channel blockers were better than other types of tocolytics for some outcomes only. Oxytocin receptor antagonists (ORAs) appear to have fewer side effects for women than CCBs, but ORAs are not as good at reducing preterm birth. Another type of CCB, nifedipine, was only used in three trials, but was not more effective than other tocolytics. Longer-term infant and childhood outcomes were not able to be assessed due to lack of available information. In general, CCBs are more effective than betamimetics, but only sometimes more effective than other types of tocolytics (*Mackeen et al., 2014*).

In otherwise symptom free women with PPROM is that we found no effect from nifedipine on time to delivery. Furthermore, the number of women that discontinued study medication because of progression into labor was high, and comparable between the groups (19% in the nifedipine group versus 18% in the placebo group).

In absence of such an effect on duration of pregnancy, it is unlikely that children born from women with PPROM will benefit directly from nifedipine. This is in line with our previous study on prolonged tocolysis in women with arrested preterm labor, the APOSTEL II study, that did not show a difference in short term perinatal outcome or at 2-year follow-up.

*Roos et al. (2016)* women with threatened preterm labor between 26 weeks (plus 0 days) and 32 weeks (plus 2 days) gestation, who had not delivered after 48 hours of tocolysis and a completed course of corticosteroids, were

enrolled. Surviving infants were followed up until 6 months after birth.

Analyses completed on an intention-to-treat basis. Age at randomization was 29.2 (1.7) weeks for both groups. They concluded that, in patients with threatened preterm labor, nifedipine-maintained tocolysis did not result in a statistically significant reduction in adverse perinatal outcomes when compared with placebo (*Nijman et al., 2016*).

Although the lower than anticipated rate of adverse perinatal outcomes in the control group indicated that a benefit of nifedipine cannot completely be excluded, its use for maintenance tocolysis did not appear beneficial at this time. *Nijman et al. (2016)*, it was a nationwide multicentre randomized placebo controlled trial. We included women with PPROM without contractions between 24+0 and 33+6 weeks of gestation. Participants were randomly allocated to daily 80 mg nifedipine or placebo, until the start of labor, with a maximum of 18 days.

The primary outcome measure was a composite of poor neonatal outcome, including perinatal death, bronchopulmonary dysplasia, periventricular leukomalacia > grade 1, intraventricular hemorrhage > grade 2, necrotizing enterocolitis > stage 1 and culture proven sepsis. Secondary outcomes were gestational age at delivery and prolongation of pregnancy (*Roos et al., 2013*).

Analysis was by intention to treat. To detect a reduction of poor neonatal outcome from 30% to 10%, 120 women needed to be randomized. The median gestational age at randomization was 29.9 weeks (IQR 27.7–31.3) in the nifedipine

group and 27.0 weeks (IQR 24.7–29.9) in the placebo group (*Roos et al., 2013*).

Other baseline characteristics were comparable. The adverse perinatal outcome occurred in neonates (33.3%) in the nifedipine group and 32.1% in the placebo group. Two perinatal deaths occurred, both in the nifedipine group. Bronchopulmonary dysplasia was seen less frequently in the nifedipine group. Prolongation of pregnancy did not differ between the nifedipine and placebo group. They concluded that randomized trial did not show a beneficial effect of prolonged tocolysis on neonatal (*Roos et al., 2013*).

No deaths occurred in the nifedipine group and no causal relation could be determined between death and possible side effects of nifedipine. We cannot exclude an indirect effect. It may be hypothesized that the administration of nifedipine in pregnant women has an adverse effect on the fetus, for example by lowering maternal blood pressure and reducing placental perfusion. However, previous studies have shown contradictory results, thus no final conclusions can be drawn (*Roos et al., 2013*).

Primary outcome measures were the effects on fetal heart rate (FHR) and its variation. Secondary endpoints were the effects on fetal movement and blood flow (pulsatility index - PI) of the umbilical (UA) and medial cerebral arteries. One-hour recordings of FHR and fetal movements were made on each of five successive days (days 0-4). Fetal blood flow velocity patterns were studied daily by Doppler ultrasound. Baseline characteristics of 31 women who had not delivered at day 0 and needed no escape tocolysis did not differ between the study

groups. Multilevel analysis showed no significant effect of either tocolytic on FHR and movement parameters over the 5-day study period. The use of tocolytics also did not significantly alter the time courses of PI-values for UA and MCA. This study demonstrated for the first time the direct effects of atosiban on fetal movement, heart rate and blood flow. Tocolysis with either atosiban or nifedipine combined with betamethasone administration appears to have no direct fetal adverse effects (*Ugwumadu, 2011*).

Looking at separate components, we found a significantly lower rate of bronchopulmonary dysplasia in women treated with nifedipine (0% in the nifedipine group compared to 6% in the placebo group). A possible explanation for this difference could be the higher gestational age at study entry and delivery in the nifedipine group, since the occurrence of bronchopulmonary dysplasia decreases with increasing gestational age at delivery (*Weijerman et al., 2010*).

All cases of bronchopulmonary dysplasia occurred in neonates born before 30 weeks of gestation. bronchopulmonary dysplasia can only be diagnosed if survival occurs to a corrected age of 36 weeks of gestation.

## CONCLUSION

No beneficial effect of prolonged tocolysis with nifedipine on perinatal outcomes or prolongation of pregnancy in women with PPROM without contractions.

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## تقدير نتائج ما بعد الولادة عقب استخدام اقراص النيفديبين مقابل البلاسيبو في علاج الانفجار المبكر لجيب المياه

محمد جمال الدين أحمد الشافعي، فريد إبراهيم حسن، مفيد فوزي محمد، داليا منير  
اللاهوني\*

قسم النساء و التوليد، كلية الطب، جامعة الأزهر

\*قسم الأطفال، كلية الطب، جامعة المنوفية

**خلفية البحث:** تعرف الولادة المبكره بالولاده قبل الاسبوع 37 مما يسبب ارتفاع نسبة وفيات الاطفال والحاق الاضرار بهم مثل الاضرار الذهنيه والعقليه للاطفال بعد الولاده. اكثر من ثلث اسباب الولاده المبكره هو انفجار جيب المياه مع احتمالية الدخول في ولاده خلال ايام بعد انفجار جيب المياه. اغلب حالات انفجار جيب المياه يحتاج للملاحظه لفترة لاتقل عن اسبوع مع اعطاء المريضه جرعه من الكورتيزون لاسيما تكوون رئه الطفل مع اعطاء المريضه مهدئات لانقباض الرحم حتي تتمكن الام من الاستفاده بجرعه الكورتيزون وتحسين فرص الطفل في الاستشفاء بعد الولاده.

**الهدف من البحث:** تقييم نتائج ما بعد الولادة عقب استخدام اقراص النيفديبين مقابل البلاسيبو في علاج الانفجار المبكر لجيب المياه.

**المرضي وطرق البحث:** تم تنفيذ هذه الدراسة علي 200 مريضه يعانون من انفجار لجيب المياه بقسم النساء والتوليد بمستشفى شبين الكوم التعليمي 100 مريضه قاموا باستخدام عقار النيفديبين و100 مريضه قاموا باستخدام البلاسيبو (عينه للمقارنه) من نفس الجنس والفئه العمرية ويتم عمل الدراسة علي السيدات الحوامل ما بين 28-37 اسبوع. تتراوح أعمارهم بين (20 – 35) سنة ما بين 28-37 اسبوع من أسابيع الحمل ويعانون من انفجار مبكر لجيب المياه بقسم النساء والتوليد بمستشفى شبين الكوم التعليمي وعمل مقارنه مع 100 مريضه أخري يعانون من انفجار مبكر من جيب المياه من نفس الجنس والفئه العمرية (عينه للمقارنه) من الفترة 2017 حتي 2019.

**نتائج البحث:** تم مقارنة 100 حالة تعاني من إنفجار مبكر لجيب المياه مع استخدام عقار النيفديبين و100 حالة أخرى تعاني من إنفجار مبكر لجيب المياه مع استخدام البلاسيبو. ومع مقارنة النتائج وجد عدم وجود تحسن لنتائج ما بعد الولادة عقب استخدام اقراص النيفديبين مقابل البلاسيبو في علاج الإنفجار المبكر لجيب المياه.

**الاستنتاج:** عقار النيفديبين من احسن الادويه في علاج الانقباضات المبكره للرحم. لا يستخدم عقار النيفديبين كمثبطات للرحم مده طويله لتجنب الاثار الجانبيه للعقار بل يستخدم لمده لا تتجاوز 48 ساعه لاعطاء جرعه الديكساميثازون.

**الكلمات الدالة:** نيفديبين مقابل الدواء الوهمي ، تمزق الأغشية قبل الولادة قبل الأوان.