Nifedipine versus Atosiban for Tocolysis in Preterm Labor

The APOSTEL III trial

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on behalf of the APOSTEL III study group

Studies in Obstetrics, Fertility & Gynaecology

nvog consortium 2.0

Disclosure

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- Dutch trial register no. 2947
- No conflicts of interest

ZonMw

nvog consortium 2.0

Preterm birth

- 5-12% of infants born <37 weeks of gestation

Preterm birth

- 7.7% of infants born <37 weeks of gestation
  - Mortality
  - Morbidity
    - IVH
    - Sepsis
    - NEC
    - BPD
    - Long term cognitive and motor development

Tocolytics in preterm labor

+

Labor <34 weeks of gestation

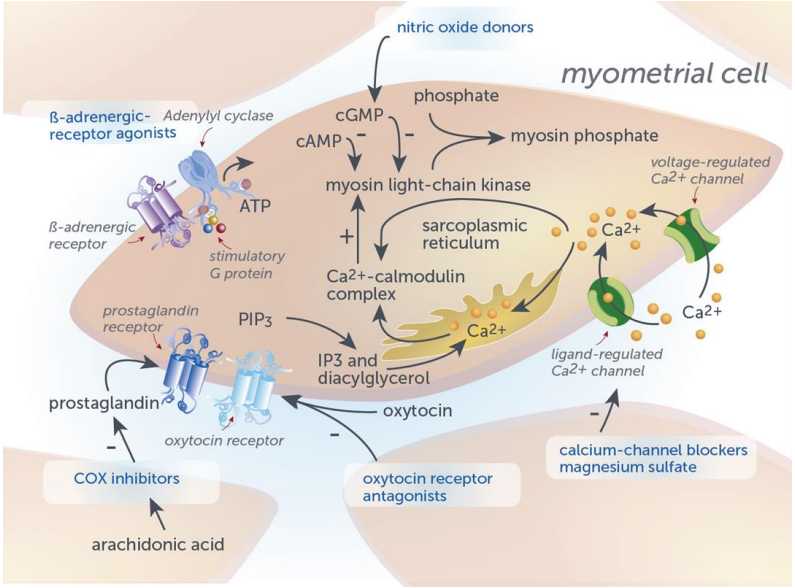
Antenatal corticosteroids for 48 hrs to optimize neonatal outcome

The optimal tocolytic drug

- Efficient in postponing preterm labor
- Favorable safety profile in mother and fetus
- Reduce neonatal morbidity and mortality
- Reasonable costs

Situation in 2012

- Nifedipine and Atosiban most used



Nifedipine and Atosiban

- Not compared directly in large RCT's
- Nifedipine off-label use
- Atosiban registered for preterm birth treatment
- Costs for 48 hours 1 euro versus 750 euro

APOSTEL III trial

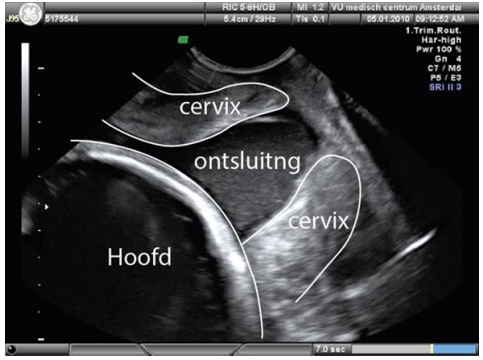
Aim: To compare the effectiveness of nifedipine with atosiban in preterm labor <34 weeks of gestation

Methods

Methods

Women between $25^{0/7}$ - $34^{0/7}$ weeks of gestation

With threatened preterm birth:
≥ 3 contractions every 30 minutes



AND:

Cervix ≤10 mm
or Cervix 11-30 mm + Fibronectin positive
or Rupture of membranes

Methods

Intervention

Nifedipine
2 x 10 mg in first hr
4 x 20 mg slow release
for 47 hrs

or

Atosiban
6,75 mg i.v. in 1 min
18 mg/hr for 3 hrs
6 mg/hr for 45 hrs

Outcome measures

Primary outcome measure:

Composite of adverse neonatal outcomes

- Perinatal death
- Pulmonary dysplasia
- Culture proven sepsis
- Intraventricular haemorrhage (IVH) > grade II
- Periventricular leukomalacia (PVL) > grade I
- Necrotizing enterocolitis (NEC) > grade I

Outcome measures

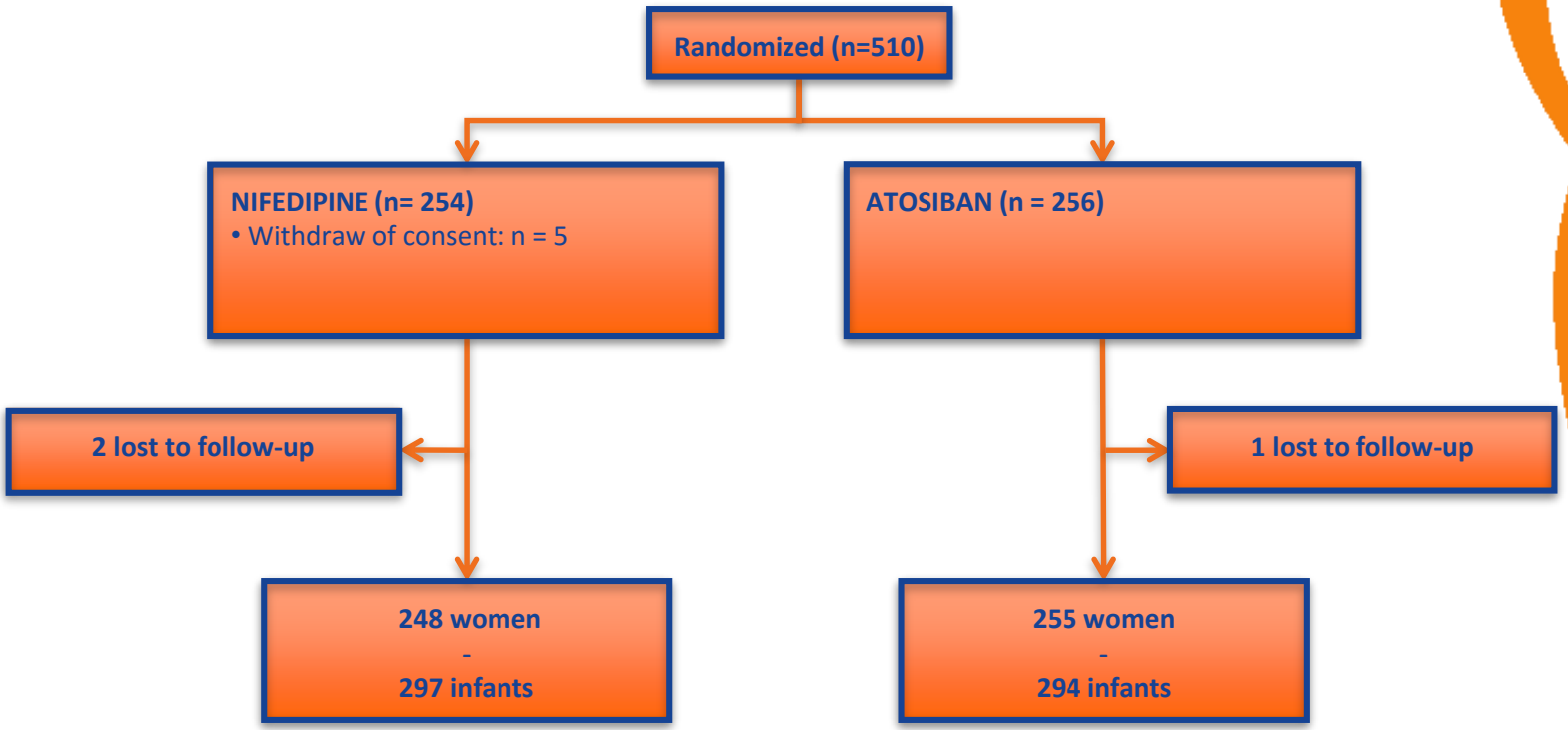
Secondary outcome measures:

- Gestational age at delivery
- Prolongation of pregnancy
- Undelivered after 48 hours
- Maternal death
- Discontinuation of study medication

Sample size

- Expected difference in reduction primary outcome: 25% to 15%
- β of 0.2 α of 0.05
- 500 patients are needed to detect this difference

Results


Randomized (n=510)
NIFEDIPINE (n= 254)
• Withdraw of consent: n = 5
ATOSIBAN (n = 256)
2 lost to follow-up
1 lost to follow-up
248 women
-
297 infants
255 women
-
294 infants

Baseline characteristics

	Nifedipine (n= 249)	Atosiban (n= 256)
Maternal age, years	30.7 (5.2)	30.2 (5.1)
BMI, median (IQR)	23.1 (20.8 – 25.8)	22.8 (20.6 – 25.5)
Caucasian, n (%)	180 (73%)	184 (72%)
Nulliparous, n (%)	160 (65%)	170 (67%)
Previous PTB, n (%)	33 (13%)	30 (12%)
Gestational age, wk median (IQR)	30.3 (28.4 – 32. 1)	30.3 (28.1 – 31.7)
Multiple pregnancy, n (%)	49 (20%)	38 (15%)
PPROM, n (%)	85 (34%)	88 (35%)

Primary outcome

	Nifedipine (n = 297)	Atosiban (n = 294)	R.R. (95%-C.I.)
Composite outcome	14.1 % (n= 42)	15.3 % (n= 45)	0.91 (0.61-1.37)

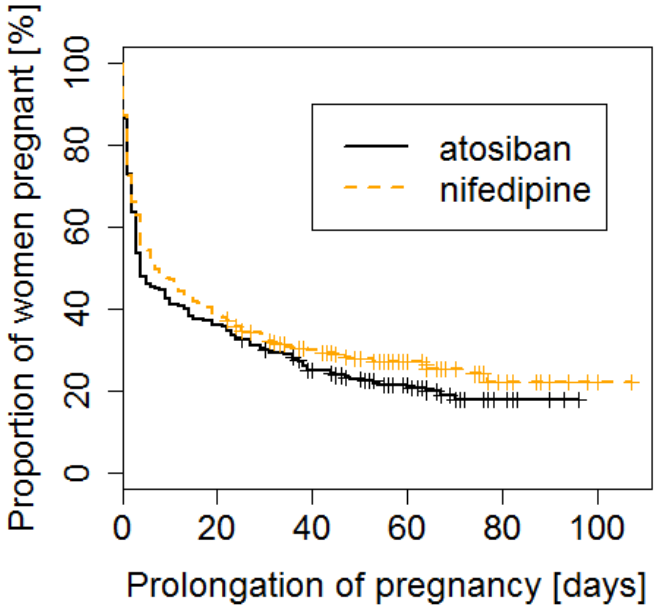
Primary outcome

	Nifedipine (n = 297)	Atosiban (n = 294)	R.R. (95%-C.I.)
Composite outcome	14.1% (n= 42)	15.3% (n= 45)	0.91 (0.61-1.37)
Perinatal death	5.4% (n= 16)	2.4% (n = 7)	2.20 (0.91-5.33)
Pulmonary dysplasia	3.7%	7.1%	0.55 (0.27 -1.15)
Sepsis	8.1%	8.6%	0.97 (0.55-1.70)
IVH > grade II	1.7%	0.7%	2.47 (0.48- 12.75)
PVL > grade I	0.3%	0.7%	0.49 (0.05-5.46)
NEC > grade I	2.4%	1.0%	1.72 (0.51 -5.83)

Secondary outcomes

	Nifedipine (n = 248)	Atosiban (n = 255)	H.R./R.R. (95%- C.I.)
Gestation age delivery (wk)	33.1 (30.5 – 37.0)	32.4 (30.1 – 35.8)	0.86 (0.70 -1.05)
Prolongation of pregnancy (d)	7 (1.0 – 40.0)	4 (1.0 - 38.0)	0.88 (0.72-1.07)
Undelivered after 48 hours	169 (68%)	168 (66%)	1.04 (0.92-1.17)
Maternal death	0 (0%)	0 (0%)	
Discontination of medication	74 (30%)	75 (30%)	1.01 (0.77-1.32)

Secondary outcomes



Log rank test: $p = 0.12$

Conclusion APOSTEL III

- In women with threatened preterm labor, tocolysis with nifedipine and atosiban results in comparable adverse perinatal outcome rates.
- The higher perinatal death rate in the nifedipine group is of concern.

Conclusion APOSTEL III

Nifedipine versus atosiban for threatened preterm birth (APOSTEL III): a multicentre, randomised controlled trial

Elvira O G van Vliet, Tobias A J Nijman, Ewoud Schuit, Karst Y Heida, Brent C Opmeer, Marjolein Kok, Wilfried Gyselaers, Martina M Porath, Mallory Woiski, Caroline J Bax, Kitty W M Bloemenkamp, Hubertina C J Scheepers, Yves Jacquemyn, Erik van Beek, Johannes J Duvekot, Maureen T M Franssen, Dimitri N Papatsonis, Joke H Kok, Joris A M van der Post, Arie Franx, Ben W Mol, Martijn A Oudijk

Implementation

Discussion

- Dutch guideline
- Off-label use nifedipine
- Adverse effects nifedipine
- Atosiban

Acknowledgements

Thank you for your attention!

Subgroup analysis

- PPROM versus no PPROM
- Fibronectine positive versus negative
- Singleton versus multiplets
- Previous preterm birth yes/no
- Gestational age at randomisation < / >= 30 weken
- Cervical length at randomisation < / >= 10 mm

Perinatal death, n = 22

	Nifedipine (n=16)	Atosiban (n = 6)
GA at birth	27.5 (2.2)	28.0 (2.1)
Prolongation of pregnancy, hrs	66.2 (78.6)	165.8 (234.0)
Interval from birth to death, days	10.6 (12.1)	6.8 (6.2)
Crossover, n(%)	1 (6%)	0 (0%)
Twins, n (%)	5 (31%)	1 (17%)
Congenital malformations, n (%)	3 (19%)	2 (33%)

EXCLUSION CRITERIA

- Cervical dilatation > 5 cm
- Vaginal blood loss (if contra-indication for tocolysis)
- Cerclage
- Previous treatment for PTL in current pregnancy
- Hypertensive disease / anti-hypertensive treatment
- Myocardial infarction
- Angina pectoris
- Fetal congenital abnormalities
- Fetal distress or signs of intrauterine infection