

Hemmung vorzeitiger Wehentätigkeit – Stand 2010

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Medizin

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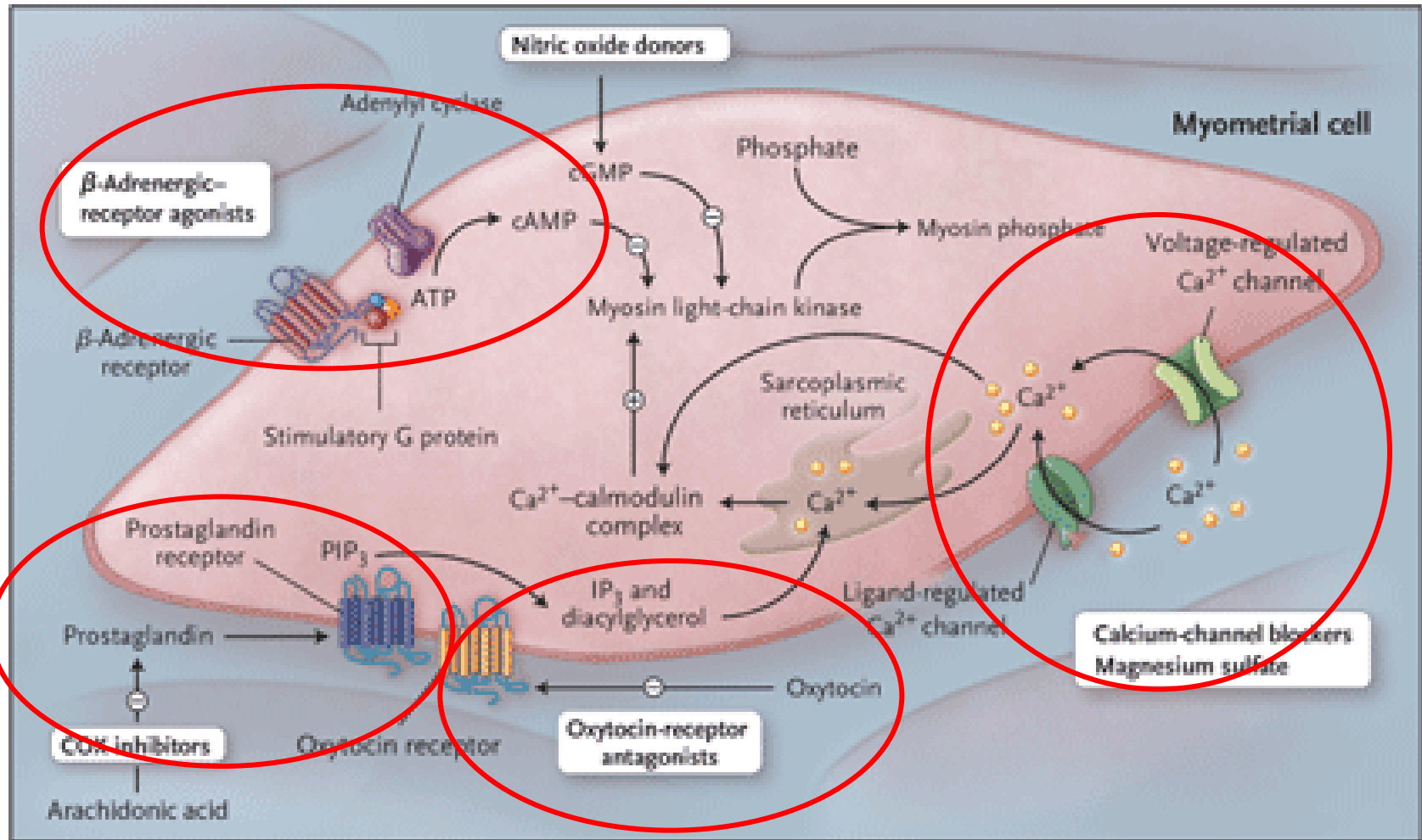
Conflict of Interests:

Ferring Arzneimittel Ges.m.b.H – Unterstützung für
Kongressreisen

Hologic Inc. – Advisory board

GlaxoSmithKline - Beratertätigkeit





Betamimetika vs. Atosiban

- Gleiche tokolytische Wirkung für 48h
- Atosiban hat bessere Wirkung für 7 Tage
- Betamimetika haben mehr Nebenwirkungen
- Kosten von Atosiban höher

Wirksamkeit und Sicherheit von Atosiban vs. pulsatiler Applikation von Fenoterol bei der Behandlung vorzeitiger Wehen

Effectiveness and Safety of Atosiban vs. Pulsatile Administration of Fenoterol in the Treatment of Preterm Labour

Autoren

A. Nonnenmacher, H. Hopp, J. Dudenhausen

Institut

Klinik für Geburtsmedizin, Charité-Universitätsmedizin Berlin

Randomisierte Studie, N=105, 51 Pat. Atosiban, 54 Pat. Fenoterol

24 + 0 bis 33 + 6 Wochen

≥ 4 Wehen in 30 min

Eröffnung des Muttermundes und /oder Zervix unter 25 mm bei

Einlingsschwangerschaften und unter 20 mm bei Mehrlingsschwangerschaften.

Outcome: Wirksamkeit 48h und 7d, Nebenwirkungen

Tab. 2 Wirksamkeit der Tokolyse mit Atosiban vs. Intervalltokolyse mit Fenoterol.

Schwangerschafts-Prolongation		Fenoterol	Atosiban	p-Wert
Einlingsgravidität	48 Std.	29/36 (80,6%)	32/36 (88,9%)	p = 0,5
Mehrlingsgravidität	48 Std.	14/18 (77,8%)	12/15 (80,0%)	p = 1,0
Gesamt		43/54 (79,6%)	44/51 (86,3%)	p = 1,0
Einlingsgravidität	7 Tage	23/36 (63,9%)	30/36 (83,3%)	p = 0,1
Mehrlingsgravidität	7 Tage	13/18 (72,2%)	10/15 (66,7%)	p = 1,0
Gesamt		36/54 (66,7%)	40/51 (78,4%)	p = 0,2

Tab. 3 Nebenwirkungen der Tokolyse mit Atosiban vs. Intervalltokolyse mit Fenoterol.

Nebenwirkungen	Fenoterol	Atosiban	p-Wert
Kardiovaskulär	42/54 (78%)	2/51 (4%)	p = 0,0
Gesamt	53/54 (98%)	8/51 (16%)	p = 0,0

„Auch bei der Intervalltokolyse mit Fenoterol kommt es zu einem erheblichen Profil an unerwünschten Wirkungen, insbesondere von kardiovaskulären Nebenwirkungen.“

Kalziumkanal Blocker - Nifedipin

The Cochrane Database of Systematic Reviews

Calcium channel blockers for inhibiting preterm labour

Author(s): King, JF; Flenady, VJ; Papatsonis, DNM; Dekker, GA; Carbonne, B

[Authors' conclusions](#): Kalziumkanal Blocker sind anderen Tokolytika überlegen, insbesondere den Betamimetika

Vorteile vs. Betamimetika:

- Bessere Wirkung
- Weniger Nebenwirkungen

Probleme:

- Dosierung, Art der Anwendung
- Welcher KKB (Nifedipin, Nicardipin...)
- Viele Studien mit geringer Fallzahl
- **Off-label Use**

MgSO₄

- Keine Schwangerschaftsverlängerung (sowohl <37 Wochen als auch <34 weeks)
- 7 Studien mit 727 Kindern, Mortalität (sowohl fetale als auch neonatale) höher bei Kindern unter Mg-Sulfat (RR 2.82; 95% CI, 1.20 to 6.62)

“...discontinuation of its use as a tocolytic agent”

*Hyagriv Simhan and Steve Caritis
Prevention of Preterm Delivery
N Engl J Med, Aug 2007;357:477-487*

Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus (Review)

Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D



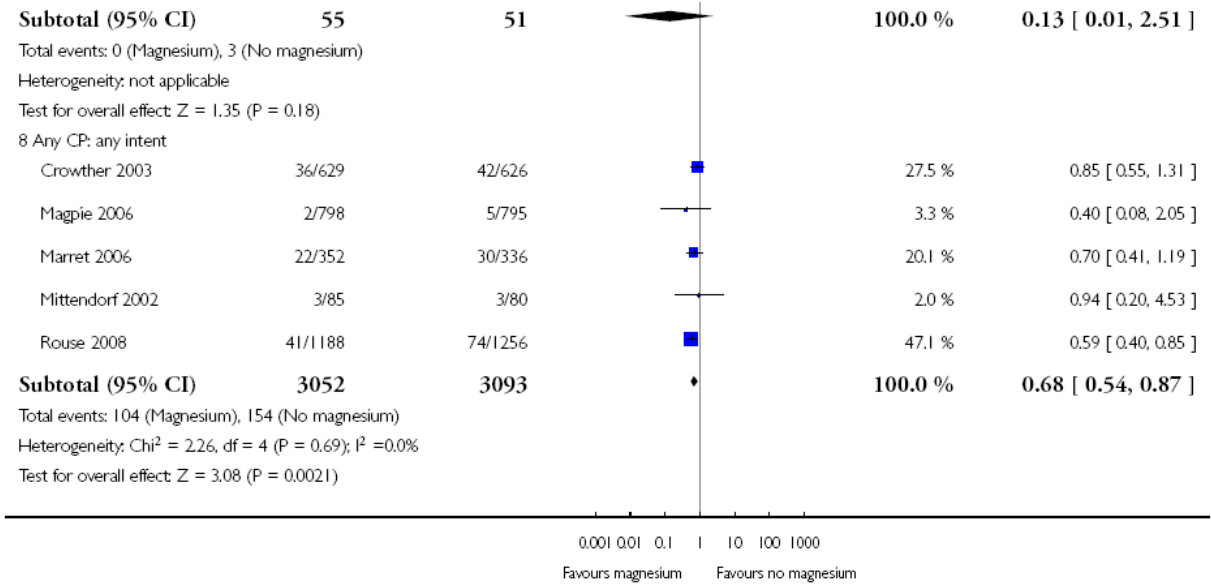
THE COCHRANE COLLABORATION®

Authors' conclusions

The neuroprotective role for antenatal magnesium sulphate therapy given to women at risk of preterm birth for the preterm fetus is now established. The NNT to benefit one baby by avoiding cerebral palsy is 63 (95% confidence interval 43 to 155)

Analysis 1.4. Comparison 1 Magnesium versus no magnesium, Outcome 4 Cerebral palsy.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus



Magnesium Sulfate for Neuroprotection

What Do We Do Now?

Offer magnesium sulfate for neuroprotection by using similar indications as used for prophylactic corticosteroid administration. This includes women before 28–32 weeks of gestation with uterine contractions or planned delivery.

2. Obtain informed consent.

3. Dosage: loading dose of 4–6 g of magnesium sulfate and 1–2 g/h for 12–24 hours; discontinue and restart with active labor or continue if delivery is imminent.

James R. Scott, MD, Editor-in-Chief
Obstet Gynecol 2009 VOL. 114, NO. 3,

PG-synthetase Inhibitoren/ Indomethacin

- Wirksamkeit:
 - Reduktion der Frühgeburten vor der 37.SSW in 3 randomisierten Studien (168 Frauen)
- Nebenwirkungen:
 - **Maternal:** Übelkeit, Reflux, Gastritis, Einschränkung der Thrombozytenfunktion
 - **Fetal:** Verschluß des Ductus arteriosus, Oligohydramnion

Tocolytic Therapy

A Meta-Analysis and Decision Analysis

David M. Haas, MD, MS, Thomas F. Imperiale, MD, Page R. Kirkpatrick, Robert W. Klein, Terrell W. Zollinger, DrPH, and Alan M. Golichowski, MD, PhD

Fifty-eight studies

Outcomes:

- Delay of delivery for 48 hours, 7 days, and until 37 weeks
- Adverse effects causing discontinuation of therapy
- Absence of respiratory distress syndrome
- Neonatal survival

Table 2. Weighted Percentages of Tocolytic Agents for Both Efficacy and Toxicity

Drug	Delay of Delivery			Neonates With RDS	Neonatal Death	Adverse Effects
	48 h	7 d	After 37 wk			
Placebo/control	53 (45–61) [9]	39 (28–49) [8]	36 (20–52) [3]	21 (17–26) [3]	2 (0–5) [3]	1 (0–2) [6]
Betamimetics	75 (65–85) [29]	65 (59–71) [26]	46 (36–56) [15]	13 (8–18) [17]	2 (1–3) [20]	14 (9–18) [32]
Calcium-channel blocker	76 (57–95) [17]	62 (56–69) [10]	47 (32–62) [12]	19 (4–33) [11]	1 (0–3) [12]	1 (0–3) [16]
Magnesium sulfate	89 (85–93) [11]	61 (39–84) [5]	42 (31–53) [7]	16 (11–20) [9]	1 (0–2) [9]	3 (1–6) [16]
Oxytocin receptor antagonists	86 (80–91) [8]	78 (68–88) [6]	No data	14 (8–21) [5]	1 (0–2) [6]	2 (0–5) [6]
Prostaglandin inhibitors	93 (90–95) [8]	76 (67–85) [3]	43 (6–79) [4]	11 (4–18) [4]	2 (0–4) [4]	0 (0–2) [6]

RDS, respiratory distress syndrome.

Data are % (95% confidence interval) of women experiencing the outcome and [number of studies reporting the outcome].

Adverse effects are those that required discontinuation of the medication.

48h: 80 of 1,000 women treated with prostaglandin inhibitors as compared with 182 to 416 for other treatments

7d: oxytocin antagonists and prostaglandin inhibitors were equivalent

Delay until 37w: No difference to placebo/control

RDS and neonatal death: no significant difference

Tocolytic Therapy

A Meta-Analysis and Decision Analysis

David M. Haas, MD, MS, Thomas F. Imperiale, MD, Page R. Kirkpatrick, Robert W. Klein, Terrell W. Zollinger, DrPH, and Alan M. Golichowski, MD, PhD

“Prostaglandin inhibitors may be the superior first-line tocolytic agent because of high tolerability and effectiveness at delaying delivery by at least 7 days.”

Adverse drug reactions to tocolytic treatment for preterm labour: prospective cohort study

Roel de Heus, registrar of obstetrics and gynaecology,¹ Ben Willem Mol, professor of perinatology and clinical epidemiology,^{2,3} Jan-Jaap H M Erwich, gynaecologist and perinatologist,⁴ Herman P van Geijn, professor of obstetrics,⁵ Wilfried J Gyselaers, gynaecologist and perinatologist,⁹ Myriam Hanssens, professor of obstetrics,¹⁰ Linda Härmark, pharmacologist,⁷ Caroline D van Holsbeke, gynaecologist and perinatologist,⁹ Johannes J Duvekot, gynaecologist and perinatologist,⁶ Fred F A M Schobben, professor of pharmacology,⁸ Hans Wolf, gynaecologist and perinatologist,³ Gerard H A Visser, professor of obstetrics¹

Cite this as: *BMJ* 2009;338:b744
doi:10.1136/bmj.b744

Setting 28 hospitals in the Netherlands and Belgium.

Participants 1920 consecutive women treated with tocolytics for threatened preterm labour.

Main outcome measures Maternal adverse events

Table 1 | Obstetrical characteristics of women who received tocolytic treatment. Values are numbers (percentages) of women

Variables	Single course treatment				Sequential courses (n=282)	Combined courses (n=311)
	Atosiban (n=575)	Nifedipine (n=542)	β mimetics (n=175)	Cyclo-oxygenase inhibitors (n=35)		
Singleton pregnancy	441 (77)	441 (82)	159 (81)	28 (80)	213 (76)	224 (72)
Parity 0	294 (51)	284 (52)	92 (53)	10 (29)	151 (54)	182 (59)
Preterm rupture of membranes	162 (28)	162 (30)	35 (20)	3 (9)	59 (21)	87 (28)
Cardiac history	15 (2.6)	10 (1.8)	3 (1.7)	0	3 (1)	4 (1.3)
Diabetes types 1 and 2 and gestational	5 (0.9)	4 (0.7)	0	0	3 (1)	2 (0.6)

Serious adverse event	Tocolytic	No of fetuses	Intensive care	Causality
Dyspnoea	Ritodrine	1	No	Probable
Dyspnoea	Fenoterol	1	No	Probable
Dyspnoea	Atosiban, nifedipine, and ritodrine*	1	No	Probable
Dyspnoea	Fenoterol	1	No	Probable
Dyspnoea	Nifedipine	2	No	Possible
Dyspnoea	Atosiban and fenoterol*	1	Yes	Possible
Hypotension	Nifedipine	1	No	Probable
Hypotension	Nifedipine	1	No	Certain
Hypotension	Nifedipine	2	No	Certain
Hypotension	Nifedipine	1	No	Certain
Cardiac failure	Atosiban then fenoterol†	1	Yes	Possible
Hypoxia	Nifedipine and ritodrine*	2	No	Probable
Lung oedema	Atosiban, nifedipine, and fenoterol*	2	Yes	Possible
Lung oedema	Atosiban and nifedipine*	1	Yes	Probable
Dyspnoea	Fenoterol	1	No	Unlikely
Deep vein thrombosis	Ritodrine then nifedipine†	2	No	Unlikely

*Combined courses: event occurred after simultaneous administration of all indicated tocolytics.
†Sequential courses: event occurred after administration of second tocolytic.

WHAT THIS STUDY ADDS

β adrenoceptor agonists or multiple tocolytics for preventing preterm birth are associated with a high incidence of adverse drug reactions

Indometacin and atosiban are the only tocolytic drugs not associated with serious adverse drug reactions in women

- Betamimetika und kombinierte Tokolyse haben eine hohe Nebenwirkungsrate
- Indometacin und Atosiban zeigten keine schweren Nebenwirkungen

Research article

Open Access

Atosiban versus betamimetics in the treatment of preterm labour in Germany: an economic evaluation

Jaro Wex*^{†1}, Mark Connolly^{†2} and Werner Rath^{†3}

Table 3: Reported adverse events in all included trials

Adverse event	Frequency (%) Atosiban	Frequency (%) Betamimetics	Relative risk and Confidence Intervals	p-value
Tachycardia	3.90%	56.30%	RR = 0.07, 95% CI = 0.05, 0.1	<0.001
Palpitation	2.40%	20.40%	RR = 0.12, 95% CI = 0.06, 0.22	<0.001
Vomiting	5.90%	19.20%	RR = 0.27, 95% CI = 0.18, 0.4	<0.001
Headache	8.40%	14.10%	RR = 0.59, 95% CI = 0.43, 0.8	<0.001
Hyperglycaemia	7.80%	13.30%	RR = 0.57, 95% CI = 0.4, 0.89	0.001
Tremor	0.80%	12.20%	RR = 0.08, 95% CI = 0.04, 0.19	<0.001
Nausea	8.70%	10.50%	RR = 0.79, 95% CI = 0.57, 1.08	0.135
Dyspnoea	0.60%	8.50%	RR = 0.09, 95% CI = 0.04, 0.23	<0.001
Chest pain	1.70%	8.00%	RR = 0.18, 95% CI = 0.09, 0.38	<0.001
Hypokalemia	0.70%	7.10%	RR = 0.13, 95% CI = 0.05, 0.36	<0.001
Hypotension	2.80%	5.00%	RR = 0.6, 95% CI = 0.29, 1.11	0.1
Anxiety	1.50%	3.80%	RR = 0.43, 95% CI = 0.2, 0.91	0.027
Syncope	0.60%	0.50%	RR = 1.02, 95% CI = 0.17, 5.98	0.984
Pulmonary oedema	0.30%	0.50%	RR = 0.6, 95% CI = 0.08, 4.45	0.614
Myocardial ischemia	0.00%	0.30%	RR = 0.34, 95% CI = 0.01, 8.3	0.509
Foetal tachycardia	2.90%	21.10%	RR = 0.14, 95% CI = 0.08, 0.23	<0.001

Atosiban versus betamimetics in the treatment of preterm labour in Germany: an economic evaluation

Jaro Wex*⁺¹, Mark Connolly⁺² and Werner Rath⁺³

Table 1: Cost variables used as input in the economic model.

Variable	Value	95% uncertainty range	Reference	Comment
Atosiban (Tractocile) 6.5 mg	35.47€	31.93–39.02€	Ferring, data on file	Costs of diagnostics, monitoring and infusion fluids considered equal for all treatments; drug wastage accounted for; 19% VAT applied.
Atosiban (Tractocile) 37.5 mg	115.29€	103.76–126.82€	Ferring, data on file	Costs of diagnostics, monitoring and infusion fluids considered equal for all treatments; drug wastage accounted for; 19% VAT applied.
Fenoterol (Partusisten) 0.5 mg	3.75€	3.37–4.12€	Rote Liste [14]	Costs of diagnostics, monitoring and infusion fluids considered equal for all treatments; drug wastage accounted for; 19% VAT applied.
Preterm labour, one hosp. day	321.90€	Fixed value	G-DRG 2007/2008 [13]	G-DRG O64B
Preterm labour, more than one hosp. day	1,742.90€	Fixed value	G-DRG 2007/2008 [13]	G-DRG O64A
Chest pain	1,175.50€	Fixed value	G-DRG 2007/2008 [13]	G-DRG FZ4Z, min. 2 hosp. days were assumed for cases with chest pain.
Dyspnoea	2,470.80€	Fixed value	G-DRG 2007/2008 [13]	G-DRG E64D, min 2 hosp. days were assumed for cases with dyspnoea.

Research article

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Atosiban versus betamimetics in the treatment of preterm labour in Germany: an economic evaluation

Jaro Wex^{*†1}, Mark Connolly^{†2} and Werner Rath^{†3}

Cost-minimization analysis revealed, that from the payer's perspective, cost savings from using atosiban versus fenoterol were 423€ per patient.

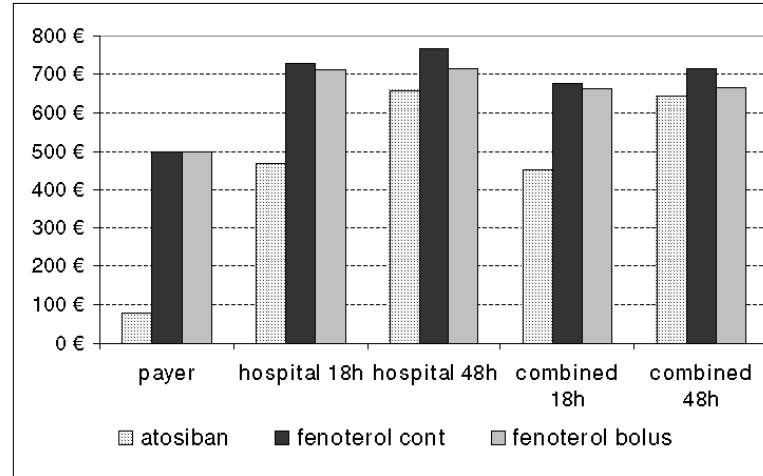
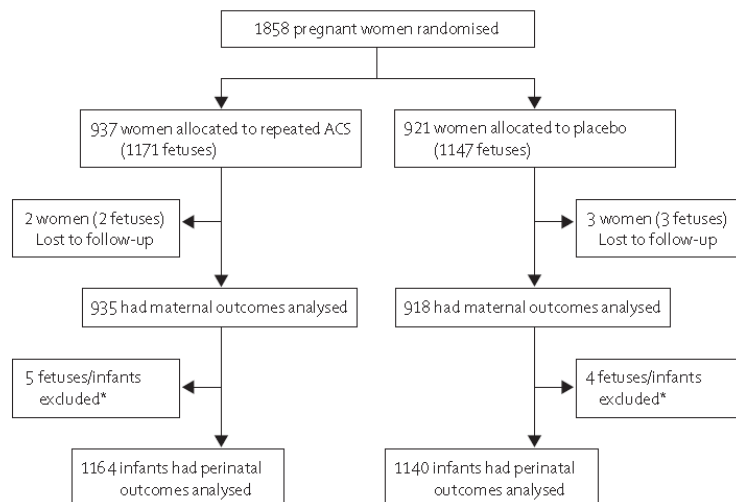


Figure 1
Cost results for the three perspectives for different time horizons based on evidence from the three double-blinded clinical trials.

Multiple courses of antenatal corticosteroids for preterm birth (MACS): a randomised controlled trial

Kellie E Murphy, Mary E Hannah, Andrew R Willan, Sheila A Hewson, Arne Ohlsson, Edmond N Kelly, Stephen G Matthews, Saroj Saigal, Elizabeth Asztalos, Susan Ross, Marie-France Delisle, Kofi Amankwah, Patricia Guselle, Amiram Gafni, Shoo K Lee, B Anthony Armson, for the MACS Collaborative Group*

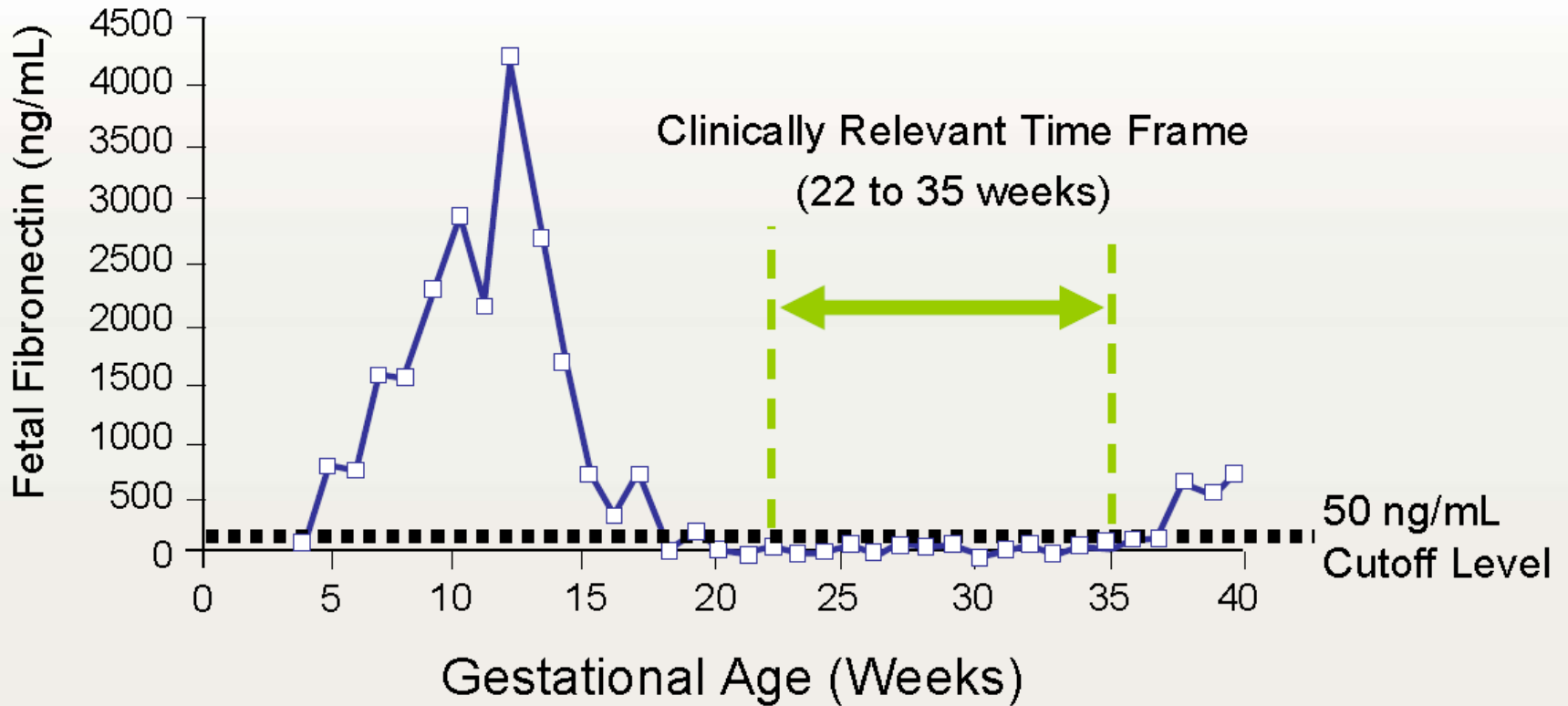


	Antenatal corticosteroids (N=935)	Placebo (N=918)	p value
Number of courses of study drug*			
0	5 (<1%)	5 (<1%)	
1	385 (41%)	365 (40%)	
2	305 (33%)	273 (30%)	
3	150 (16%)	169 (18%)	
4	90 (10%)	104 (11%)	
Fully compliant with study drug†	747 (80%)	722 (79%)	
Partly compliant with study drug	181 (19%)	189 (21%)	
Non-compliant, incorrect, or no study drug given	7 (<1%)	6 (<1%)	
Gestational age at birth (weeks)	34.5 (3.6)	34.9 (3.6)	

	Antenatal corticosteroids	Placebo	Mean difference (95% CI)	p value
Total number of infants	1164	1140		
Composite primary outcome*†	150 (13%)	143 (13%)	1.04 (0.77 to 1.39)	0.83
Singletons	88/737 (12%)	83/726 (11%)		
Multiples	62/427 (15%)	60/414 (15%)		
Stillbirth or neonatal death \leq 28 days after birth or before discharge, whichever happened later	43 (4%)	40 (4%)	1.08 (0.67 to 1.66)	0.82
Number of surviving infants‡	1121	1100		
Severe RDS	87 (8%)	77 (7%)	1.14 (0.80 to 1.58)	0.51
BPD	19 (2%)	11 (1%)	1.50 (0.68 to 2.95)	0.37
IVH (grade III or IV)	6 (<1%)	9 (<1%)	0.92 (0.37 to 1.88)	0.68
Cystic PVL	9 (<1%)	10 (<1%)	1.07 (0.41 to 2.33)	0.95
NEC	10 (<1%)	12 (1%)	1.03 (0.38 to 2.29)	0.87
Total number of infants	1164	1140		
Male	616 (53%)	598 (53%)		
Female§	546 (47%)	540 (48%)		
Birthweight (g)	2216 (28.3)	2330 (28.7)	-113.1 (37.3) (-187.0 to -41.17)	0.0026
Length at birth (cm)	44.5 (0.2)	45.4 (0.2)	-0.9 (0.25) (-1.34 to -0.37)	<0.001
Mean head circumference (cm)	31.1 (0.1)	31.7 (0.1)	-0.6 (0.15) (-0.90 to -0.32)	<0.001

Wiederholte Gabe antenataler Kortikosteroide führen zu vermindertem fetalen Körperwachstum ohne Verbesserung des neonatalen Outcome.

Fetales Fibronectin



Adapted from Garite TJ et al. *Contemp Obstet Gynecol.* 1996;41:77-93.

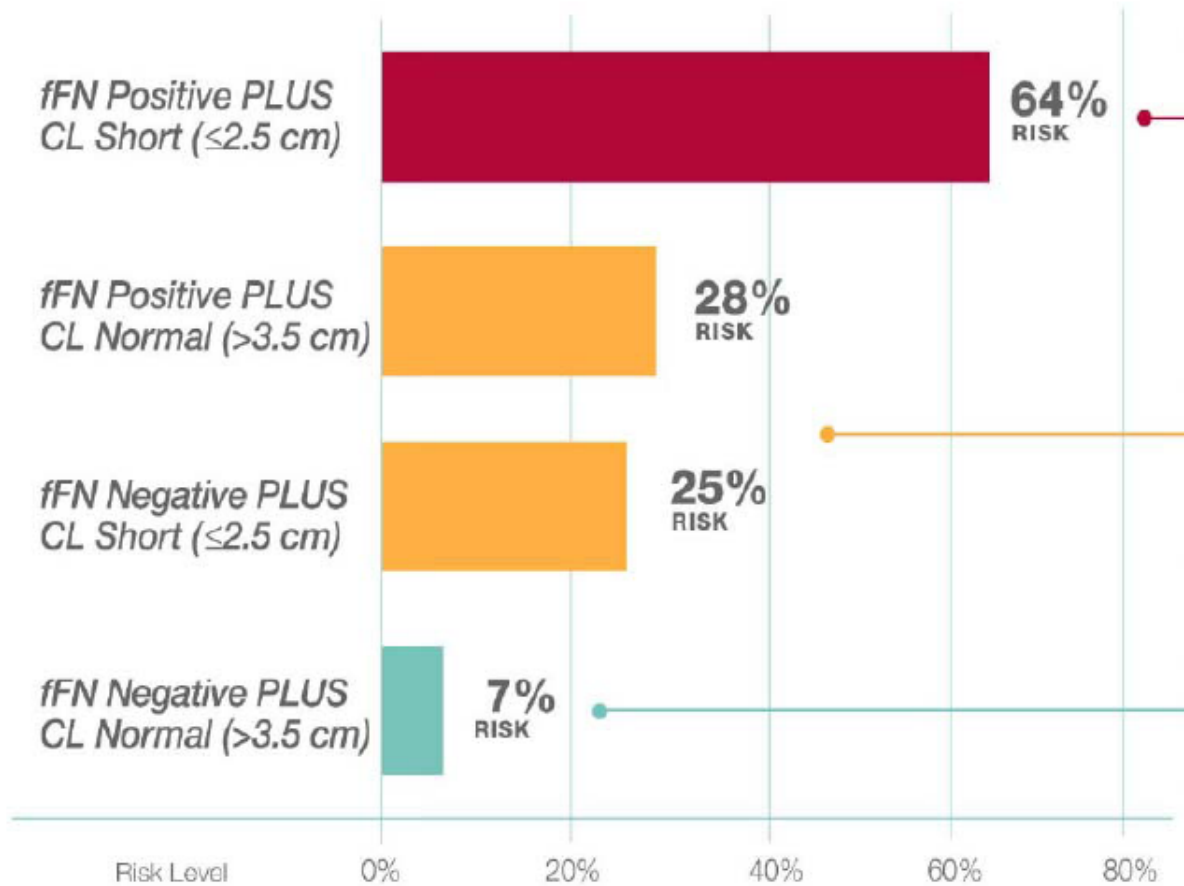
Cervicovaginal fetal fibronectin testing among symptomatic women and number of women needed to be treated (NNT) at 31 weeks' gestation with antenatal steroids to prevent one case of neonatal respiratory distress syndrome (RDS) associated with spontaneous preterm birth within 7-10 days of testing

Test result	Probability of spontaneous preterm birth within 7-10 days of testing (%)	Risk of RDS at 32 weeks' gestation^{56 57}	Rate of RDS* at 32 weeks' gestation (%)	NNT†
No testing	4.5 [‡]	0.53	2.0	109
Test positive	20.6 [§]	0.53	11.0	17
Test negative	1.0 [§]	0.53	0.4	509

Honest Honest et al.

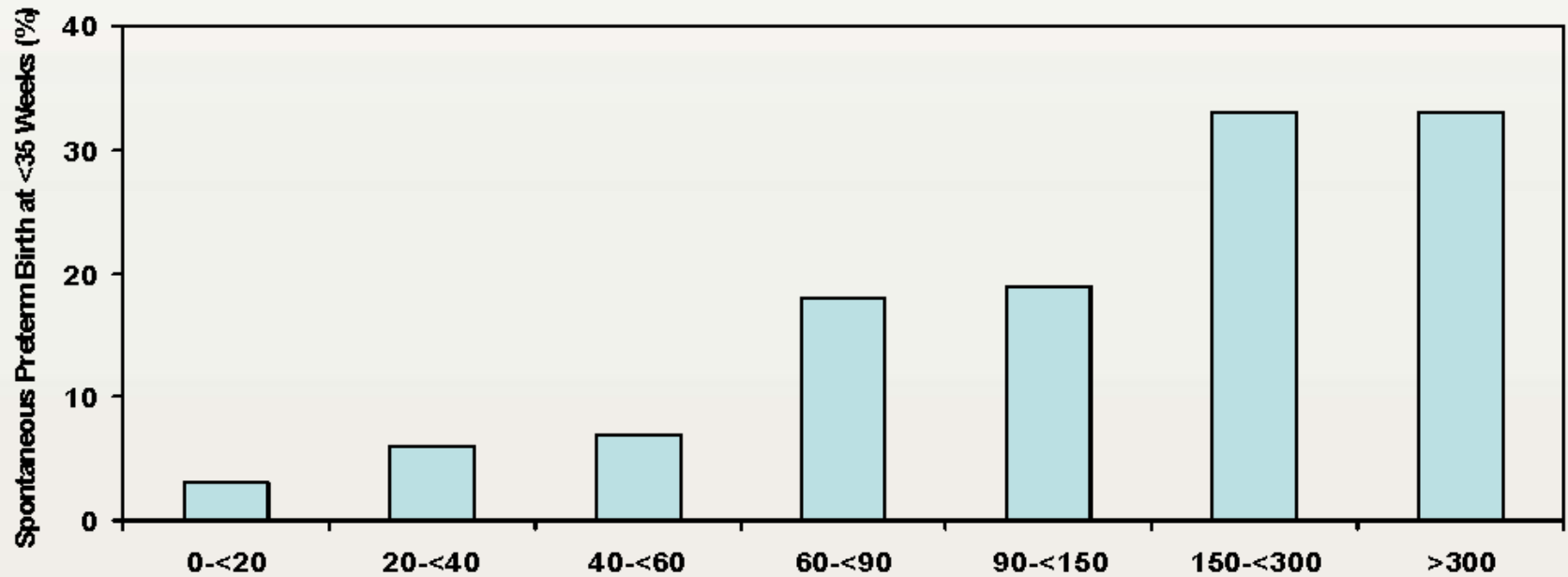
Accuracy of cervicovaginal fetal fibronectin test in predicting risk of spontaneous preterm birth: systematic review
BMJ 2002;325:301

Risk of Recurrent PTB (<35 weeks)



1. Iams JD, Goldenberg RL, Mercer BM, et al. The preterm prediction study: recurrence risk of spontaneous preterm birth. *Am J Obstet Gynecol.* 1998;178:1035-40.

Highest Cervical or Vaginal Fetal Fibronectin Value (ng/ml) at 24 Weeks



Goepfert et al, Am J Obstet Gynecol 2000;183(6):1480-1483

pPROM

BJOG: an International Journal of Obstetrics and Gynaecology
March 2005, Vol. 112, Supplement 1, pp. 32–37

Preterm premature rupture of membranes: diagnosis, evaluation and management strategies

Hyagriv N. Simhan, Timothy P. Canavan

The literature currently does not support the use of maintenance or prophylactic labour inhibiting agents beyond the initial 48-hour steroid window.

Zukunftsaspekte

Study protocol

Open Access

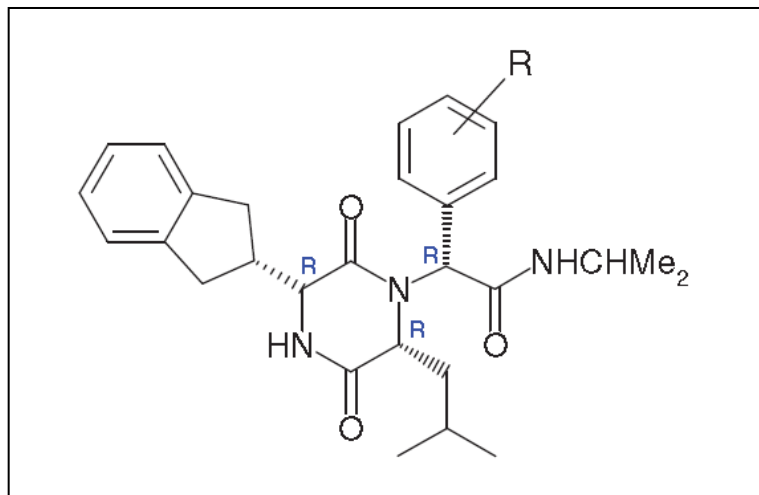
Assessment of perinatal outcome after sustained tocolysis in early labour (APOSTEL-II trial)

Carolien Roos*¹, Liesbeth HCJ Scheepers², Kitty WM Bloemenkamp³, Annemiek Bolte⁴, Jerome Cornette⁵, Jan B Derks⁶, Hans JJ Duvekot⁵, Jim van Eyck⁷, Joke H Kok⁸, Anneke Kwee⁶, Ashley Meri n⁹, Brent C Opmeer¹⁰, Mari lle G van Pampus¹¹, Dimitri NM Papatsonis¹², Martina M Porath⁹, Joris AM van der Post¹³, Sicco A Scherjon³, Krystyne Sollie¹¹, Marc EA Spaanderman¹, Sylvia MC Vijgen¹³, Christine Willekes², Ben Willem J Mol¹³ and Fred K Lotgering¹

- Multicentre placebo-controlled study. N=406
- Women who have been treated with 48 hours corticosteroids and tocolysis 26+0 and 32+2 weeks
- Nifedipine (intervention) or placebo (control) for twelve days or until delivery
- Primary outcome: composite of perinatal death, and severe neonatal morbidity up to evaluation at 6 months after birth.

The Design of Orally Bioavailable 2, 5 diketopiperazine Oxytocin Antagonists: From Concept to Clinical Candidate for Premature Labor

Department of Medicinal Chemistry, GlaxoSmithKline Research and Development, Medicines Research Centre,



Retosiban is >15-fold more potent at the human oxytocin receptor than Atosiban

Has been shown to be an effective tocolytic by i.v. and by oral administration in rats

Was selected for progression as a potential clinical candidate for preterm labor

Genetic Polymorphisms and Spontaneous Preterm Birth

Catherine S. Gibson, PhD, Alastair H. MacLennan, MD, Gustaaf A. Dekker, PhD, Paul N. Goldwater, MD, James M. Dambrosia, PhD, David J. Munroe, PhD, Shirley Tsang, PhD, Claudia Stewart, BS, and Karin B. Nelson, MD

Table 3. Single Nucleotide Polymorphisms Studied

Symbol	Gene Name	rs No.	Location	SNP
F2	Coagulation factor II	1799963	11q11.2	G20210A
F5	Coagulation factor V	6025	1q23	R506Q
F7	Coagulation factor VII	5742910	13q34	-323 indel
F7	Coagulation factor VII	6046	13q34	R353Q
TFPI	Tissue factor pathway inhibitor	11896231	2q31-q32.1	-33 T/C
IL-8	Interleukin 8	4073	4q13-q21	-251 A/T
LTA	TNF β lymphotoxin α precursor	1041981	6p21.3	T26N
MTHFR	5,10-@ methylene tetrahydrofolate reductase	1801133	1p36.22	677 C/T
CBS	Cystathionine- β synthase	12329790	21q22.3	L278T
ANX5	Annexin 5A	8145113	4q26-q28	1 C/T
ADD1	Adducin 1 (α)	4961	4p16.3	G460W
NOS2A	Nitric oxide synthase 2a isoform 1	1137933	17q11.2-q12	-231 C/T
eNOS3	Nitric oxide synthase 3	1800779	7q36	-922 A/G
eNOS3	Nitric oxide synthase 3	1799983	7q36	E298D
NOS3	Nitric oxide synthase 3	3918226	7q36	690 CT
EPCR	Endothelial protein C receptor precursor	867186	20q11.2	4600 A/G
THBD	Thrombomodulin	1800576	20p11.2	G127A
PAI1_1	Nexin, Plasminogen activator inhibitor 1	1799768	7q22.1	675 4G/5G
PAI1_2	Nexdin, Plasminogen activator inhibitor 1	7242	7q22.1	11053 G/T
PAI2_1	Plasminogen activator inhibitor 2 precursor	6098	18q21.3	Asn 120 Asp
PAI2_2	Plasminogen activator inhibitor 2 precursor	6103	18q21.3	Asn 40L Lys
PAI2_3	Plasminogen activator inhibitor 2 precursor	6104	18q21.3	Ser 423 Cys
PDE4D	Phosphodiesterase 4D	12188950	5q12.1	SNP45 (C more than T)
PLAT	Tissue Plasminogen Activator	2020918	8p11.2	-7351 C/T
ADRB2	β -2 adrenergic receptor	1042714	5q31-q32	Q27E
FGB_1	Fibrinogen β polypeptide	4220	4q31.3	R448K
FGB_2	Fibrinogen β polypeptide	1800790	4q31.3	-455G>A
ALOX5AP_1	Arachidonate 5-lipoxygenase activating protein	1769874	13q12	SQ13S89
ALOX5AP_2	Arachidonate 5-lipoxygenase activating protein	NA	13q12	SG13S32
ALOX5AP_3	Arachidonate 5-lipoxygenase activating protein	NA	13q12	SG13S25

rs, reference SNP accession number; SNP, single nucleotide polymorphism; NA, not applicable.

(*Obstet Gynecol* 2007;109:384-91)

LEVEL OF EVIDENCE: II

„We confirm previous observations that variants of the beta-adrenergic receptor and of nitric oxide synthase are associated with prematurity.“

(Obstet Gynecol 2007;109:384–91)

LEVEL OF EVIDENCE: II

AWMF online		Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG)		
AWMF-Leitlinien-Register	Nr. 015/025	Entwicklungsstufe: 1
Medikamentöse Wehenhemmung bei drohender Frühgeburt		

Off label Use

Wenn Medikamente im Rahmen einer Off-Label-Anwendung zur Tokolyse eingesetzt werden, ergeben sich daraus mehrere Problemfelder:

- o Eine Leistungspflicht der Krankenkasse besteht bei einem Off-Label-Gebrauch von Medikamenten nicht. Da für die Tokolyse alternative Medikamente zur Verfügung stehen, ist es fraglich, ob eine Kostenerstattung für diese Medikamente zur Tokolyse erfolgen würde.

- o Es bleibt dem einzelnen Arzt überlassen, das Medikament in eigener Verantwortung und mit dem Risiko der Haftung für entstehende Gesundheitsschäden außerhalb des Anwendungsgebietes zu benutzen.

- o Beachtet werden muss auch, dass Patienten erheblich verunsichert werden, wenn diese die Anwendungsbeschränkungen im Beipackzettel lesen und über die Gründe der dennoch erfolgten Anwendung nicht ausreichend aufgeklärt wurden

Aus dem Gesagten muss gefolgert werden, dass nicht zugelassene Tokolytika nur nach ausführlicher Information der Patientin und Einholen des Einverständnisses für die Anwendung ausserhalb der Zulassung angewendet werden sollten.

Zusammenfassung

- Atosiban vs. Betamimetika – Nebenwirkungen
– Kosten
- Off label Präparate – Unterstützung durch Leitlinien
- Nifedipin – Wirksamer als Betamimetika mit weniger Nebenwirkungen
- Indometacin – Zunehmende Evidenz für geringe Nebenwirkungen
- Lungenreifung – 1x
- Ausschöpfung aller diagnostischer Möglichkeiten
- Magnesium – Vermeidung der Zerebralparese

„Primum non Nocere“

„Zuerst einmal nicht schaden“