

Diagnosis, prevention and treatment of preterm parturition

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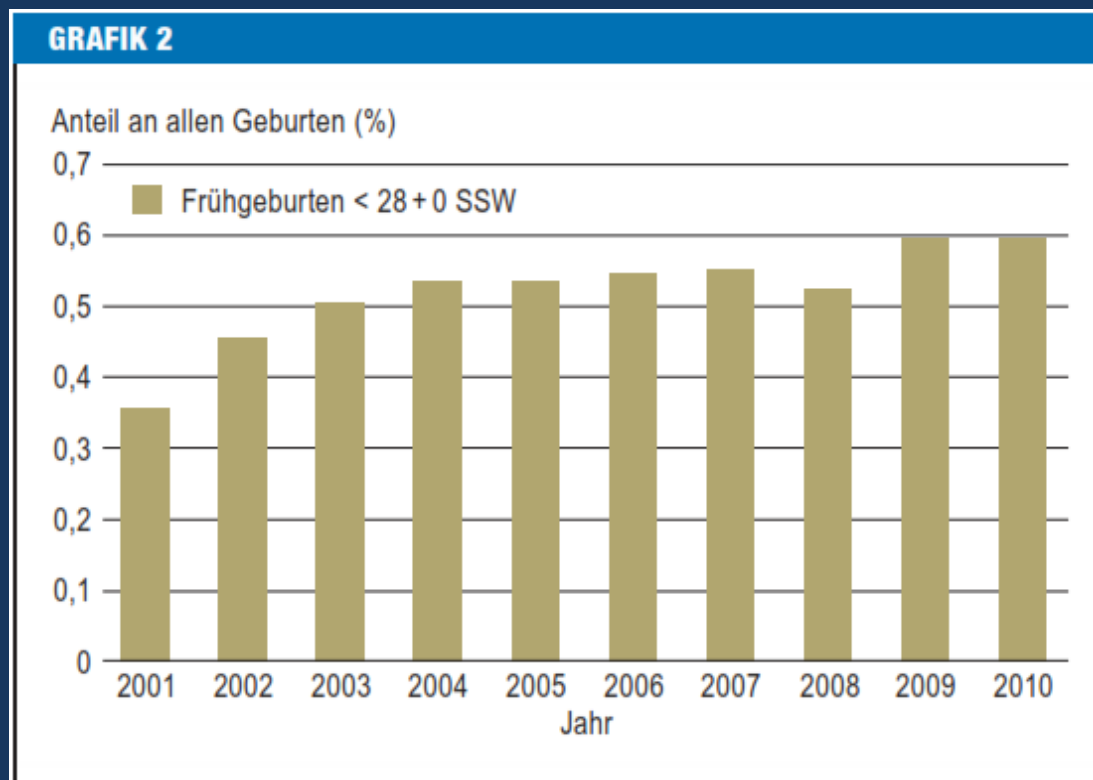
Bremen

The clinical problem

In the last decades annual rate of preterm births in Germany increased approximately to 9%, which is a relative high level compared to other European countries.

In the United States, the annual rate of preterm births reached a peak of 12.8% in 2006 and was 11.7% in 2011.

Increase of extremely preterm births < 28th week of gestation in Germany



Prevention of preterm parturition

Annual rate of preterm births (< 37 weeks of gestation) worldwide is 5 – 18 %.

Despite advances in antenatal and neonatal care as well, preterm birth remains a leading cause of neonatal mortality and infant death (27% in 2010), resulting in over one million deaths annually worldwide.

Points of interest

Primary prevention

Healthy pregnant women and women with high risk for preterm parturition

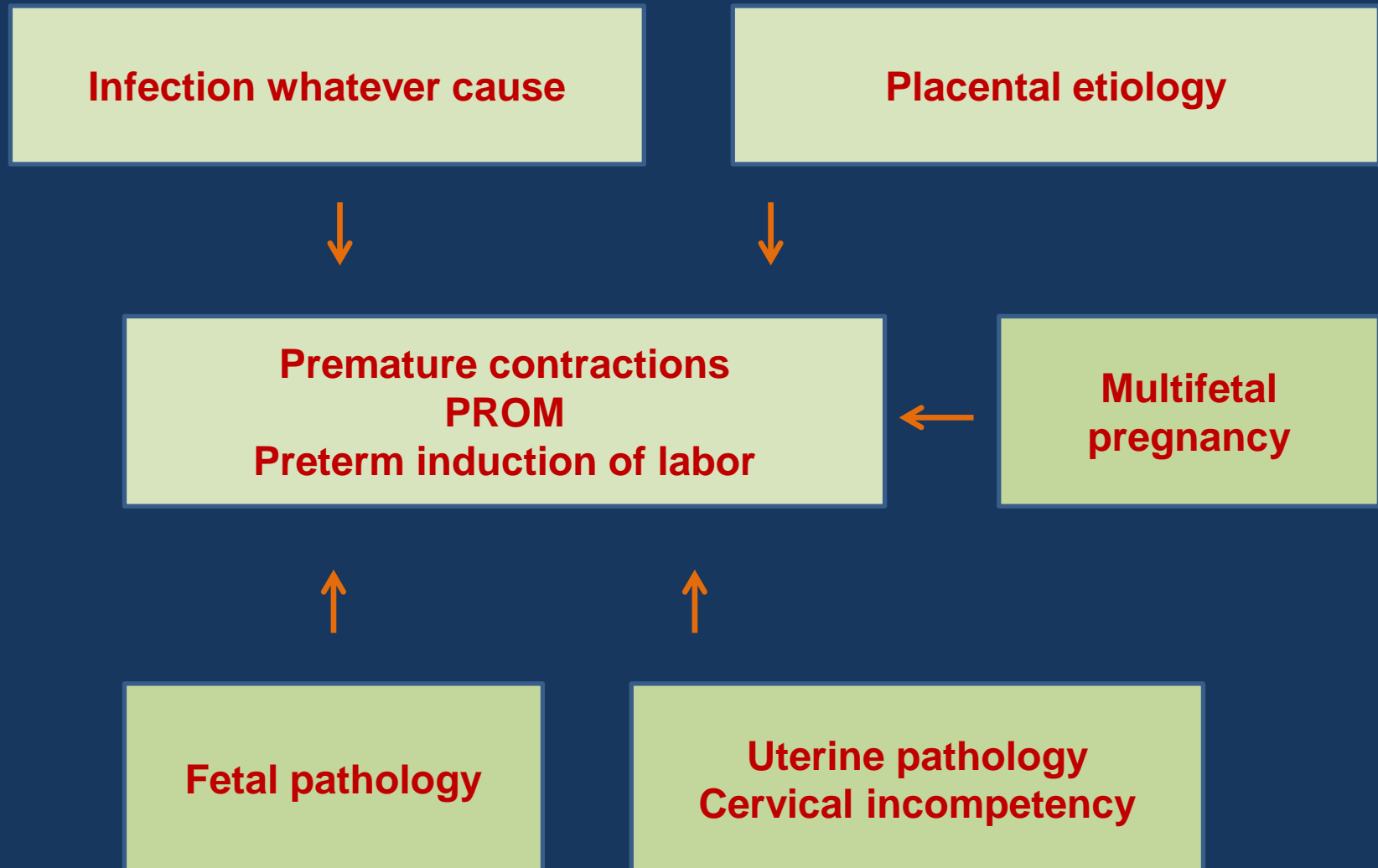
Secondary prevention

Pregnant women with clinical signs of preterm parturition

Tertiary prevention

Options to optimize neonatal care in pregnant women who are candidates for preterm parturition

Pathogenesis of spontaneous preterm birth



Major risk factors for preterm birth

- Previous pregnancy with an adverse outcome
 - Social and economic disadvantages, racial/ethnic disparities
- Smoking
- Periodontal disease
 - Assisted fertility and multifetal pregnancy
 - Extremes of body weight (BMI > 35)
 - Maternal age (< 20 and > 40)
- Genitourinary infection
 - Maternal depression
 - Prepregnancy stress
 - Poor diet
- Impatience of the obstetricians and particular interests of hospital managers

Prevention of preterm parturition

Strategies to identify and treat medical risk factors in early pregnancy (e. g., genitourinary infection and poor nutrition) have unfortunately not been effective in reducing preterm birth rates in most cases .

Asymptomatic bacteriuria in pregnancy

Small, F, and Vazques JC.

Cochrane Database Syst. Rev. 2007

Fourteen studies were included. Overall the study quality was poor.

Antibiotic treatment compared to placebo or no treatment was effective in clearing asymptomatic bacteriuria (RR 0.25, 95% - CI 0.14 to 0.48). The incidence of pyelonephritis was reduced (RR 0.23, 95% - CI 0.13 to 0.41).

Antibiotic treatment was also associated with a reduction in the incidence of low birth weight babies (RR 0.66 - 95% CI 0.49 to 0.89) **but a difference in preterm delivery was not seen.**

Different antibiotic regimens for treating asymptomatic bacteriuria in pregnancy.

Guinto V.T., De Guia B., Festin M.R., Dowswell T.

Cochrane Database Syst. Rev. 2010

We cannot draw any definite conclusion on the most effective and safest antibiotic regimen for the initial treatment of asymptomatic bacteriuria in pregnancy. One study showed advantages with a longer course of nitrofurantoin, and another showed better tolerability with ampicillin compared with pivmecillinam; otherwise, there was no significant difference demonstrated between groups treated with different antibiotics. Given this lack of conclusive evidence, it may be useful for clinicians to consider factors such as cost, local availability and side effects in the selection of the best treatment option.

Smoking and preterm birth

**Stopping smoking prior to pregnancy reduces
the risk of preterm birth**

OR 0,84 – CI 0.7 – 0.98

Rood, K. and Malone, F.D.

Seminars Fetal Neonat. Med. 17 (2012) 68 - 63

Clinical manifestations

Early signs and symptoms

- **Menstrual-like cramping**
- **Mild, irregular contractions**
- **Low back ache**
- **Pressure sensation in the vagina**
- **Vaginal discharge of mucus, which may be clear, pink, or slightly bloody (i. e. mucus plug, bloody show)**

Clinical manifestations of true labor

- **Uterine contractions**

Increased frequency accompanied by increased intensity and duration (3 every 10 min, 4 every 20 or 8 every 60 min, respectively)

- **Cervical changes**

Transvaginal sonographic identification of a short cervix (≤ 25 mm) is predictive of an increased risk of preterm labor and birth; the shorter the cervical length-cut off, the higher the risk of preterm birth.

**Transvaginal sonographic measurement of cervical length to predict preterm birth in asymptomatic women at increased risk:
a systematic review**

J. M. Crane and D. Hutchens; Ultrasound Obstet. Gynecol. 31 (2008) 579 - 587

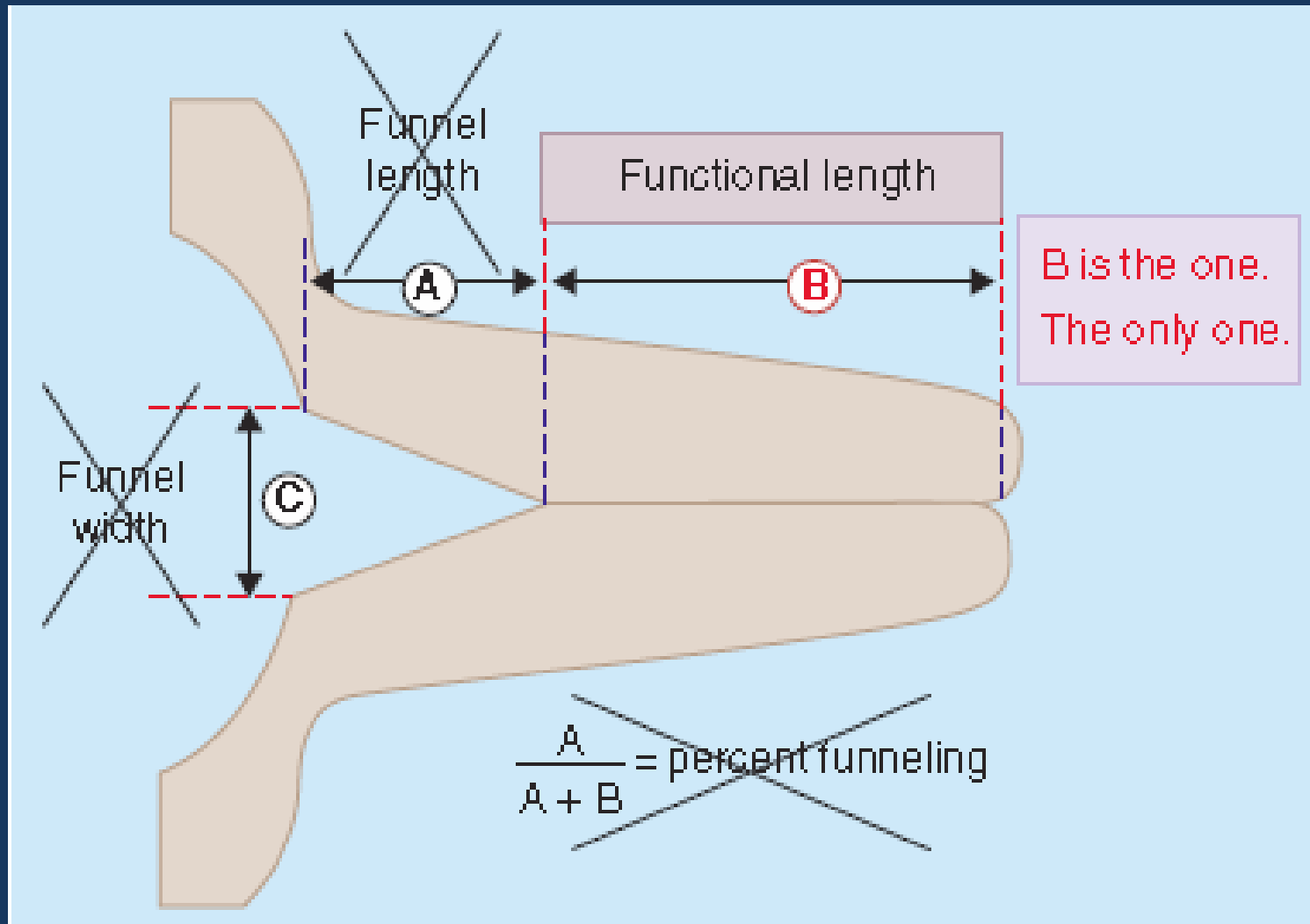
- **1980 – 2006 Medline, Pubmed, EMBASE, Cochrane Library**
- **Asymptomatic women considered at high risk with**
 - **a history of spontaneous preterm birth,**
 - **uterine abnormalities,**
 - **a history of excisional cervical procedures,**
 - **intact membranes**

**Transvaginal sonographic measurement of cervical length to predict preterm birth in asymptomatic women at increased risk:
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- **Short cervical length < 32 week of gestation as measured by transvaginal ultrasonography is predictive of preterm birth in all populations studied**
- **Previous preterm birth and a short cervix (≤ 25 mm) < 24 weeks of gestation are major risk factors for preterm birth (OR 2.76 - CI 2.41 – 3.17)**
- **With a negative predictive value of 92 % preterm parturition can be ruled out if the cervix length is > 25 mm**

How to measure cervical length



Cerclage for short cervix (< 25 mm before 24 week of gestation) on transvaginal ultrasonography in women with singleton gestations and previous preterm birth

A meta-analysis

Berghella V., Rafael T. J., Szychowski J. M., Rust O. A., Owen J.

Obstet. Gynecol. 117 (2011) 663 - 671

In asymptomatic women with a history of spontaneous preterm birth, singleton gestation and ultrasonographically diagnosed short cervical length (< 25 mm) prior to 24 weeks of gestation, cervical cerclage significantly prevents preterm birth and composite perinatal mortality and morbidity.

Cerclage for short cervix in women with singleton gestations and previous preterm birth - A meta-analysis

Berghella V. et al.; *Obstet. Gynecol.* 2011, 117:663 - 671

	Cerclage	No cerclage	
Preterm birth < 35 weeks of gestation	28.4 % 71/250	41.3% 105/254	RR 70% CI 0.55 – 0.89
Composite perinatal mortality and morbidity***	15.6%	24.8%	RR 64% CI 0.45 – 0.91

*** Resp. distress syndrome, intraventricular hemorrhage grades III and IV, necrotizing enterocolitis, sepsis and chronic lung disease

Cerclage for short cervix in prevention of preterm parturition

It is unclear whether ultrasonographic cervical length assessment has significant advantages over clinical examination alone after elective or emergency cervical cerclage placement, although some signs, such as funneling to the stitch, are associated with a high risk of preterm premature rupture of membranes.

There is no consensus on the frequency or timing of ultrasonographic cervical length assessment post cerclage.

Management of preterm delivery < 34 weeks of gestation

- Hospitalization and bed rest
- A course of 12 mg betamethasone (2 x 12 mg/24 h) to reduce neonatal morbidity and mortality associated with preterm birth
- Tocolytic drugs for up to 48 hours to delay delivery so that betamethasone given to the mother can achieve its maximum fetal effect
- B-streptococcal culture
- Urine culture
- Progesterone supplementation
- Swab for fetal fibronectin (fFN)

ANTENATAL CORTICOSTEROIDS TO REDUCE NEONATAL MORBIDITY AND MORTALITY

Roberts D., Dalziel S. R.

**Antenatal corticosteroids for accelerating fetal lung maturation for women
at risk of preterm birth.**

Cochrane Database of Systematic Reviews, 2006 (3)

**The use of antenatal steroid is most effective in reducing
the incidence of respiratory distress syndrome in pregnancies
that deliver 24 hours after the initial dose and up to 7 days after
administration of the second dose of antenatal corticosteroids.**

Management of preterm delivery < 34 weeks of gestation

- Tocolytic therapy either with fenoterol, atosiban or nifedipin
- Antibiotics for GBS chemoprophylaxis, when appropriate
- Appropriate antibiotics to women with positive urine culture results
- Magnesium sulfate for pregnancies at 24 to 32 weeks of gestation. In utero exposure to magnesium sulfate provides neuroprotection against cerebral palsy and other types of severe motor dysfunction in offspring born preterm (Doyle et al 2009; Cochrane Database Syst. Reviews)

Neuroprotection against cerebral palsy with magnesium sulfate

Controversy

Schleußner E. und Göpel, W. Frauenarzt 52 (2011) 570 - 571

The recent evaluation of German Neonatal Network revealed in a group of 1.965 preterm neonates with a birth weight < 1.500g significant more severe intracerebral bleedings if the mothers of the neonates have been treated with a combination of magnesium sulfate and fenoterol during their pregnancies.

Primary prevention of preterm parturition

The use of progesterone supplementation in women with a previous preterm birth was shown in randomized trials to reduce the frequency of preterm birth and is recommended for women with these risk factors.

Progesterone supplementation is also effective in patients without a history of preterm birth but a short cervix in the second trimester.

Agents in clinical use for tocolytic therapy

Substances and mechanism	Trade name	Clinical use
Betasympathomimetics (BS) Fenoterol, only in D and A, Ritodrine and Terbutaline (intern.)	Prolongation of pregnancy 2 – 7 days, no change in perinatal mortality	Approved, side effects ↑↑↑ Bolus appl. effective
Oxytocin antagonist Atosiban	Tractocile As effective as BS	Approved, side effects ↓↓↓
Calcium channel blocker	Nifedipine More effective than BS	Off label, Moderate side effects
Inhibitors of prostaglandin synthesis	Indomethacin	off label, fetal side effects possible
Donators of nitric oxide	Glyceroltrinitrate	Off label, side effects ↓↓↓
Competition to Ca ⁺⁺ in the muscle	Magnesiumsulphate	Not effective side effects ↓↓↓

Maintenance tocolysis – yes or no?

A never ending story

Effect of maintenance tocolysis with nifedipine in threatened preterm labor on perinatal outcomes: A randomized controlled trial

Assessment of Perinatal Outcome by use of
Specific Tocolytics in Early Labor

APOSTEL III -STUDY

Roos et al, JAMA 309 (2013) 41 - 47

From: **Effect of Maintenance Tocolysis With Nifedipine in Threatened Preterm Labor on Perinatal Outcomes: A Randomized Controlled Trial**

AA
APOSTEL II-Trial

Table 1. Baseline Demographics and Clinical Characteristics

Characteristics	Participants by Study Group, No. (%)		
	Nifedipine (n = 201)	Placebo (n = 205)	Nonrandomization (n = 230)
Age, mean (SD), y	30.2 (5.1)	30.2 (5.1)	28.7 (5.5) ^a
Body mass index, mean (SD) ^b	23.3 (4.7)	23.3 (4.3)	23.5 (5.0)
White race	166 (82.6)	155 (75.6)	166 (72.2)
Nulliparous	116 (57.7)	106 (51.7)	134 (58.3)
Prior preterm birth	39 (19.4)	55 (26.8)	40 (17.4)
Gestational age at study entry, mean (SD), wk	29.2 (1.7)	29.2 (1.7)	29.2 (1.9)
Multiple gestation	42 (20.9)	48 (23.4)	45 (19.6)
Twins	40 (19.9)	44 (21.5)	42 (18.3)
Triplets	2 (1.0)	4 (1.9)	3 (1.5)
pPROM at study entry	53 (26.4)	48 (23.4)	44 (19.1)
Vaginal bleeding at study entry	38 (18.9)	38 (18.5)	43 (18.7)
Additional tocolysis	12 (6.0)	9 (4.4)	NA
Vaginal examination at study entry	(n = 134)	(n = 132)	(n = 111)
Dilatation, median (IQR), cm	0 (0-1)	1 (0-2)	1 (0-1)
Cervical length, median (IQR), mm	25 (15-35)	23 (15-30)	24 (17-31)

Abbreviations: IQR, interquartile range; NA, not applicable; pPROM, premature rupture of the membranes before 37 weeks' gestation.
^aP = .01.
^bBody mass index is calculated as weight in kilograms divided by height in meters squared.

Effect of maintenance tocolysis with nifedipine in threatened preterm labor on perinatal outcomes

A randomized controlled trial

APOSTEL II Trial

Table 2. Perinatal Outcome

Primary Outcome	Participants by Study Group, No. (%)		RR (95% CI)	IRR (95% CI)
	Nifedipine (n = 201)	Placebo (n = 205)		
Adverse perinatal outcome ^a	24 (11.9)	28 (13.7)	0.87 (0.53-1.45)	
Perinatal death	5 (2.5)	4 (2.0)	1.3 (0.35-4.7)	
Chronic lung disease	5 (2.5)	6 (2.9)	0.85 (0.26-2.7)	
Neonatal sepsis	16 (8.0)	18 (8.8)	0.91 (0.48-1.7)	
IVH >grade 2	2 (1.0)	5 (2.4)	0.41 (0.08-2.1)	
PVL >grade 1	0	0	NA	
Necrotizing enterocolitis	5 (2.5)	3 (1.5)	1.7 (0.41-7.0)	
Secondary outcome	(n = 245)	(n = 257)		
Geometric birth weight, mean (95% CI), g ^b	2047 (1950-2149)	2035 (1938-2138)		
Neonatal intensive care unit admission, No. (%)	100 (40.8)	102 (39.7)	0.99 (0.78-1.3)	
Length, median (IQR), d	10 (6-19)	10 (5-24)		0.92 (0.70-1.2)
Ventilation support, No. (%)	35 (14.3)	34 (13.2)	1.1 (0.67-1.7)	
Length, median (IQR), d	2 (1-4)	3 (1-6)		0.74 (0.43-1.3)
Total hospital admission, No. (%)	216 (88.2)	220 (85.6)	1.0 (0.95-1.1)	
Length, median (IQR), d	23 (5-42)	23 (4-45)		0.97 (0.82-1.1)

Abbreviations: IQR, interquartile range; IRR, incidence rate ratio; IVH, intraventricular hemorrhage; NA, not applicable; PVL, periventricular leukomalacia; RR, relative risk.

^aAdverse perinatal outcome was a composite of perinatal death, chronic lung disease, neonatal sepsis, IVH greater than grade 2, PVL greater than grade 1, and necrotizing enterocolitis.

^bThe geometric mean difference is 27 g (95% CI, -128 to 195).

APOSTEL III -STUDY

Assessment of Perinatal Outcome by use of
Specific Tocolytics in Early Labor.

Nifedipine versus Atosiban

in the treatment of threatened preterm labor.