

# Hexoprenaline Compared with Atosiban as Tocolytic Treatment for Preterm Labor

## Vergleich der tokolytischen Therapie mit Hexoprenalin und Atosiban bei vorzeitiger Wehentätigkeit



### Authors

Ebba Kirchhoff<sup>1</sup>, Verena Schneider<sup>1</sup>, Gerhard Pichler<sup>2</sup>, Philipp Reif<sup>1</sup>, Josef Haas<sup>1</sup>, Maike Joksch<sup>1</sup>, Corinna Mager<sup>1</sup>, Christian Schmied<sup>1</sup>, Wolfgang Schöll<sup>1</sup>, Elisabeth Pichler-Stachl<sup>1</sup>, Daniela Gold<sup>1</sup>

### Affiliations

- 1 Universitätsklinik für Frauenheilkunde und Geburtshilfe der Med. Universität Graz, Graz, Austria
- 2 Klinische Abteilung für Neonatologie der Med. Universität Graz, Graz, Austria

### Key words

tocolysis, atosiban, hexoprenaline, efficacy

### Schlüsselwörter

Tokolyse, Atosiban, Hexoprenalin, Wirksamkeit

received 7. 10. 2021  
accepted after revision 10. 4. 2022

### Bibliography

Geburtsh Frauenheilk 2022; 82: 852–858

DOI 10.1055/a-1823-0176

ISSN 0016-5751

© 2022. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Georg Thieme Verlag KG, Rüdigerstraße 14,  
70469 Stuttgart, Germany

### Correspondence

Dr. Ebba Kirchhoff  
Universitätsfrauenklinik Graz  
Auenbruggerplatz 14, 8036 Graz, Österreich  
[ebba.kirchhoff@medunigraz.at](mailto:ebba.kirchhoff@medunigraz.at)

### ABSTRACT

**Introduction** Preterm birth is defined as a live birth before 37 weeks of gestation and is associated with increased neonatal morbidity and mortality. The aim of this study is to compare the efficacy of hexoprenaline and atosiban for short- and long-term tocolysis and their effects on neonatal and maternal outcomes.

**Methods** This retrospective cohort study included women with threatened preterm labor between 24 + 0 and 34 + 0 weeks of gestation without premature rupture of membranes. The tocolytic efficacy of hexoprenaline and atosiban was compared in women receiving one of the two medications for short- and long-term tocolysis. Continuous variables were compared using t-test or Mann–Whitney U test, as appropriate. Comparison of categorical variables between the two groups was done with  $\chi^2$  test after Pearson's and Fisher's exact test.

**Results** 761 women were enrolled in this study; 387 women received atosiban and 374 women received hexoprenaline as their primary tocolytic agent. Atosiban showed a higher efficacy as a primary tocolytic agent ( $p = 0.000$ ) within 48 hours. As regards long-term tocolysis, there were no differences between the treatment groups ( $p = 0.466$ ). Maternal side effects such as tachycardia ( $p = 0.018$ ) or palpitations ( $p = 0.000$ ) occurred more frequently after the administration of hexoprenaline, while there were no differences between the two drugs administered with regard to any other maternal or neonatal outcome parameter.

**Conclusion** Our retrospective study shows a significantly higher efficacy of atosiban in the first 48 hours, especially when administered at an early gestational age. There were no significant differences in terms of neonatal outcome but significantly more maternal adverse effects during the administration of hexoprenaline.

### ZUSAMMENFASSUNG

**Einleitung** Frühgeburtlichkeit ist definiert als eine Geburt vor vollendeter 37. Schwangerschaftswoche und ist assoziiert mit einer erhöhten Morbidität und Mortalität der Kinder. Ziel dieser Studie ist der Vergleich der Wirksamkeit von Hexoprenalin und Atosiban als Kurz- und Langzeittokolyse sowie die Auswirkungen auf das kindliche und maternale Outcome.

**Methoden** In dieser retrospektiven Kohortenstudie wurden Schwangere mit Frühgeburtsbestrebungen zwischen der 24 + 0 und 34 + 0 Schwangerschaftswoche ohne vorzeitigem Blasensprung eingeschlossen. Die tokolytische Wirksamkeit

von Atosiban und Hexoprenalin sowie die Wirksamkeit der Kurz- bzw. Langzeittokolyse wurden verglichen. Die Daten wurden mittels SPSS-Software ausgewertet und zum Vergleich der Daten wurde der t-Test oder der Mann-Whitney U-Test verwendet.

**Ergebnisse** Es wurden 761 Frauen in die Studie eingeschlossen; 387 Frauen erhielten Atosiban und 374 Frauen Hexoprenalin. Atosiban zeigte eine bessere Wirksamkeit als Hexoprenalin innerhalb von 48 Stunden ( $p = 0,000$ ). Es zeigte sich kein Unterschied in der Wirksamkeit der beiden Medikamente als Langzeittokolytika ( $p = 0,466$ ). Maternale Nebenwirkungen wie Tachykardie ( $p = 0,018$ ) oder Palpitationen ( $p = 0,000$ ) tra-

ten vermehrt nach der Gabe von Hexoprenalin auf. Sowohl im kindlichen Kurzzeit- als auch Langzeit-Outcome zeigten sich keine Unterschiede zwischen den beiden verabreichten Medikamenten.

**Schlussfolgerung** In unseren Ergebnissen zeigte sich eine signifikant bessere Wirksamkeit von Atosiban bei vorzeitigen Wehen innerhalb von 48 Stunden bei einer Applikation im niedrigeren Gestationsalter. Es zeigten sich keine wesentlichen Unterschiede in Bezug auf das neonatale Outcome, aber signifikant vermehrt maternale Nebenwirkungen während der Gabe von Hexoprenalin.

## Introduction

Preterm birth is defined as a live birth occurring before 37 weeks of gestation. Higher body mass index (BMI), advanced maternal age and prior use of assisted reproductive techniques such as in vitro fertilization (IVF) cause higher rates of preterm birth, especially in industrial nations. Other factors for preterm birth are a short cervix, infection, previous preterm birth or uterine overdistension. Preterm infants have higher risk of morbidity, mortality and neurodevelopmental impairment [1–3].

Around 10.6% of all deliveries worldwide are premature [4]. The number of premature deliveries in Germany has remained almost the same in recent years; in 2008, it was 8.0% and in Austria it was 7.9% in 2016 [5].

Several tocolytic agents exist; however, only few have been approved by the FDA or EMA [6]. Approved agents include  $\beta$ 2-adrenoceptoragonists (ritodrine, terbutaline, hexoprenaline), calcium channel blockers (e.g., nifedipine), magnesium sulfate, nitrates (e.g., nitroglycerin), oxytocin receptor antagonists (e.g., atosiban), and prostaglandin inhibitors (e.g., indomethacin) [6]. It is recommended that tocolytic agents are given for 48 hours to allow the administration of antenatal corticosteroids to reduce the risk of infant respiratory distress syndrome (IRDS) and intraventricular hemorrhage (IVH) [7] or permit the transfer of the mother to a tertiary hospital [8]. Hexoprenaline and atosiban have been deemed safe for the fetus [9]. In general, atosiban is known to have significant fewer side effects than beta-mimetics with similar efficacy [10, 11]. The most common side effects of hexoprenaline are palpitations, maternal tachycardia and chest pain [10].

Repeated or prolonged tocolysis is controversial; it is not recommended in most guidelines or not even mentioned. In some cases, maintenance tocolysis could be indicated to allow the fetus to achieve a higher gestational age [12]. The German S2k-guideline does not recommend long-term tocolysis as it does not significantly reduce the preterm birth rate or fetal morbidity and mortality. Long-term tocolysis may be useful in cases with very early gestational age or prolapse of the amniotic sac. In such cases, a risk-benefit assessment should be done together with the expectant mother [5]. In our institution, long-term tocolysis was used during the study period if considered necessary.

The aim of this study is to compare the efficacy of atosiban and hexoprenaline for both short- and long-term tocolysis in women

with preterm labor occurring between 24 + 0 and 34 + 0 weeks of gestation. Secondary outcome parameters are maternal side effects and neonatal short- and long-term neurological outcomes.

## Methods

For this retrospective cohort study, all women with threatened preterm labor between 24 + 0 and 34 + 0 weeks of gestation who gave birth at the hospital of the Medical University Graz between 2007 and 2017 were identified. Gestational age was determined according to the first day of the last period or by crown-rump-length measurement in cases of uncertainty.

## Inclusion and exclusion criteria

Women with threatened preterm labor defined by the presence of spontaneous and regular contractions ( $\geq 4$  contractions over 20 minutes) and cervical dilation from 0 to 3 cm for primigravida, and from 1 to 3 cm for multigravida, and a cervical length of less than 25 mm were included in the study [5, 13].

Exclusion criteria were preterm premature rupture of membranes (PPROM, examined with AmniSure [Qiagen GmbH, Germantown, USA]), signs of Triple I (intrauterine inflammation, infection or both), contraindications for the tocolytic agent, preeclampsia/HELLP syndrome, maternal concomitant disease, multiple gestation, severe peripartum bleeding, major fetal malformation or intrauterine death before the start of tocolysis.

## Tocolytics

The risk of preterm birth was examined using a fetal fibronectin test (PartoSure, Parsagen Diagnostics GmbH, Boston, USA). After taking the women's history, vaginal screening for infection was performed followed by obstetric ultrasound to assess the fetus and the cervix. In cases with threatened preterm labor, tocolysis was given for 48 hours according to the physician's preference, with tocolysis consisting either of atosiban (oxytocin receptor antagonist) or hexoprenaline (beta-mimetic) to allow lung maturation with corticosteroids (two doses of 12 mg betamethasone) [14]. Primary contraindications for hexoprenaline were hypersensitivity against the substance, liver or kidney insufficiency, general heart disease or (pre)eclampsia and for atosiban were also hypersensitivity, uterine bleeding, uterine infections and abnormal fetal heart rate [15]. Atosiban and hexoprenaline were given as contin-

► **Table 1** Maternal characteristics of women presenting with preterm labor at the time of hospital admission (n = 761).

	H (n = 374)	A (n = 387)	p value
Age (years)	29.4 (15.8–41.7)	29.8 (15.8–45.9)	0.328
Body mass index (kg/m <sup>2</sup> )	22.7 ± 3.8	22.6 ± 4.6	0.694
Gravidity	2.2 (1–11)	2.1 (1–9)	0.475
Parity	1.7 (1–6)	1.6 (1–7)	0.419
Gestational age at the start of tocolysis (weeks)	30.3 (20.1–40.9)	29.9 (21.9–38.6)	0.084
Gestational diabetes	20 (5.3%)	33 (8.5%)	0.000

Data are presented as numbers and percentages. H: hexoprenaline; A: atosiban

uous intravenous infusion with an initial loading dose followed by higher continuous doses (18 mg/hour for atosiban and 18 µg/hour for hexoprenaline), reduced after three hours to 6 mg/hour for atosiban and 4.3 µg/hour for hexoprenaline over a period of 48 hours in total. If one tocolytic agent failed, a switch to the other tocolytic agent was possible. Failure was determined as persistence of subjective and objective contractions and/or cervical opening. Long-term tocolysis was defined if a second course of tocolysis was given when contractions reappeared after 48 hours until 34 + 0 weeks of gestation at the latest. Tocolytic efficacy was present when women did not deliver within 48 hours without switching the tocolytic drug.

### Maternal and neonatal outcome parameters

Maternal and neonatal outcome parameters were compared between the two tocolytic agents. Maternal parameters included demographic data, mode of delivery and side effects of the tocolytic agents such as flushing, palpitations, nausea/vomiting or maternal tachycardia. Neonatal parameters included arterial and venous umbilical cord pH, Apgar scores at 1, 5 and 10 minutes, birth weight, hospital stay (days) in the neonatal intensive care unit (NICU), incidence of infant respiratory distress syndrome (IRDS) of any grade, intraventricular hemorrhage (IVH) of any grade, periventricular hemorrhage (PVH), periventricular leukomalacia (PVL) of any grade, retinopathy of prematurity (ROP) of any grade and, in addition, neonatal mortality.

All neonates born before 34 + 0 weeks of gestation or with a birthweight of less than 2000 g were admitted routinely to the NICU which is located next to our delivery ward.

At the age of two years, infants with very low birth weight (< 1500 g) or early onset impairment were routinely followed up with a cognitive and neurodevelopmental examination and Bayley II/III test at a corrected age of 2 years.

### Statistical analysis

SPSS version 23 was used for statistical analysis. Quantitative data are expressed as means and standard deviation, or median (minimum-maximum), depending on the skewness and normality of data distribution. Continuous variables were compared using t test or Mann–Whitney U test, as appropriate. Categorical variables were compared between the two groups using  $\chi^2$  test after Pearson's and Fisher's exact test. Statistical significance was defined as a p value of < 0.05.

## Results

During the study period 761 women fulfilled the inclusion criteria and received tocolysis for preterm labor with 374 women receiving hexoprenaline and 387 receiving atosiban. There were no significant differences between the two groups with regard to demographic parameters except for gestational diabetes (► **Table 1**).

### Short-term maternal outcome

► **Table 2** shows the obstetric outcomes and maternal side effects of the two tocolytic agents. No significant differences were observed for any obstetric parameter between the groups. 15% of women in both groups were overdue after successful tocolysis and had to be induced. Mean gestational age at delivery was 34 weeks in the Hexoprenaline group and 35 weeks in the Atosiban group. 55% and 60% of women in the Hexoprenaline and Atosiban group, respectively, had a vaginal delivery; the remaining women had an operative vaginal delivery or cesarean section. In the Hexoprenaline group more women had a vaginal delivery and primary cesarean section and fewer had a secondary cesarean section compared to the Atosiban group (p = 0.035). In terms of complications, hexoprenaline caused significantly more palpitations (p = 0.000) and maternal tachycardia (p = 0.018). Other than this, the rate of side effects was low, with similar incidences for hypotension, flushing, nausea or vomiting in both groups.

### Efficacy of atosiban versus hexoprenaline and long-term tocolysis

Tocolytic efficacy is shown in ► **Table 3**. Atosiban showed significantly better efficacy in the first 48 hours of tocolysis and the initial course of tocolysis (p = 0.000) with 63% of women not giving birth in the Atosiban group and 56% of women in the Hexoprenaline group across all gestational ages. A switch to another tocolytic agent was carried out in 15% of cases, with a further 114 women not being delivered within 48 hours (► **Table 2**).

When calculating the significance based on the start of tocolysis according to gestational age, ► **Table 4** shows that there were no significant differences in efficacy between the tocolytic agents. However, it seems that hexoprenaline showed a higher efficacy with regard to short-term tocolysis at later gestational ages while atosiban was more efficient when threatened preterm labor occurred at an earlier gestational age.

► **Table 2** Maternal outcomes associated with tocolytic therapy (n = 761).

	H (n = 374)	A (n = 387)	p value
Gestational age at delivery	34.5 (± 4.4)	35.2 (± 4.0)	0.047
Induction of labor	58 (15.5%)	59 (15.2%)	1.000
Mode of delivery			
▪ Vaginal	223 (59.6%)	214 (55.3%)	0.035
▪ Operative vaginal delivery (vacuum/forceps)	18 (4.8%)	24 (6.2%)	
▪ Primary cesarean section	49 (13.1%)	44 (11.4%)	
▪ Secondary cesarean section	84 (22.5%)	105 (27.1%)	
Palpitations	26 (7.0%)	7 (1.8%)	0.000
Hypotension	4 (1.1%)	1 (0.3%)	0.268
Flushing	1 (0.3%)	0 (0%)	0.553
Nausea and vomiting	14 (3.7%)	13 (3.4%)	0.144
Maternal tachycardia	13 (3.5%)	4 (1.0%)	0.018
Unspecific side effects	18 (4.8%)	6 (1.6%)	0.005

Data are presented as numbers and percentages. H: hexoprenaline; A: atosiban

► **Table 3** Tocolytic efficacy of atosiban and hexoprenaline in women presenting with preterm labor between 24 and 34 weeks of gestation (n = 761).

	H (n = 374)	A (n = 387)	p value
Short-term tocolysis			
Tocolytic efficacy			
▪ No failure at 48 h	208 (55.6%)	245 (63.3%)	0.000
▪ No failure at 7 days	37 (9.9%)	25 (6.5%)	0.500
Long-term tocolysis	H (n = 203)	A (n = 258)	
▪ Tocolytic efficacy up to 34 weeks	140 (69.0%)	180 (69.7%)	0.466

Data are presented as numbers and percentages. H: hexoprenaline; A: atosiban

► **Table 4** Tocolytic efficacy of atosiban and hexoprenaline in women presenting with preterm labor according to gestational age at the start of tocolysis.

Tocolytic efficacy depending on GA at start of tocolysis	Gestational age (weeks + days)	Hexoprenaline	Atosiban	p value
No failure at 48 h	24 + 0–26 + 6	29 (56.9%)	44 (72.1%)	0.112
	27 + 0–28 + 6	27 (56.3%)	46 (66.7%)	0.332
	29 + 0–31 + 6	77 (64.7%)	83 (62.4%)	0.793
	32 + 0–34 + 6	66 (55.5%)	64 (59.8%)	0.590
No failure at 7 days	24 + 0–26 + 6	29 (56.8%)	44 (72.1%)	0.368
	27 + 0–28 + 6	27 (56.2%)	46 (66.6%)	0.295
	29 + 0–31 + 6	77 (64.7%)	83 (62.4%)	0.342
	32 + 0–34 + 6	66 (55.5%)	64 (60.3%)	0.113

Data are presented as numbers and percentages. H: hexoprenaline; A: atosiban

► **Table 5** Short-term neonatal outcomes according to the maternal tocolytic therapy for preterm labor.

	H (n = 374)	A (n = 387)	p value
Weight (g)	2361 (± 852)	2487 (± 827)	0.001
Length (cm)	47.0 (± 4.0)	47.7 (± 4.0)	0.078
Head circumference (cm)	33.1 (± 2.4)	33.2 (± 2.6)	0.217
Length percentile	36.6 ± 26.4	36.8 ± 23.3	0.975
Weight percentile	44.5 ± 24.9	43.3 ± 23.2	0.757
Head circumference percentile	43.8 ± 26.0	40.8 ± 25.5	0.116
Apgar 1 score	7.8 ± 1.8	8.2 ± 1.5	0.028
Apgar 5 score	9.2 ± 1.3	9.4 ± 1.1	0.157
Apgar 10 score	9.5 ± 1.0	9.6 ± 1.0	0.241
Umbilical artery pH	7.28 ± 0.09	7.29 ± 0.07	0.076
Umbilical vein pH	7.35 ± 0.07	7.36 ± 0.07	0.037
NICU admission (days)	13 (8.2)	12 (7.3)	0.201
Mortality	0	0	not applicable
IRDS	82 (45.3%)	84 (47.7%)	0.241
IVH	18 (9.7%)	13 (7.0%)	0.805
PVH	2 (1.1%)	1 (0.5%)	0.795
PVL	9 (4.9%)	13 (7.0%)	0.541
ROP	89 (23.8%)	125 (32.3%)	0.651
Abnormal neurological behavior	20 (12.3%)	12 (7.0%)	0.094

Data are presented as numbers and percentages. H: hexoprenaline; A: atosiban; IRDS: infant respiratory distress syndrome (of any grade); IVH: intra-ventricular hemorrhage (of any grade); PVH: periventricular hemorrhage (of any grade); PVL: periventricular leukomalacia; ROP: retinopathy of prematurity (of any grade)

66% (n = 258/387) of women in the Atosiban group and 54% (n = 203/374) in the Hexoprenaline group received long-term tocolysis of similar efficacy up to 34 + 0 weeks of gestation (p = 0.466).

### Short-term neonatal outcomes

Neonatal outcome parameters are presented in ► **Table 5**. Birthweight was significantly lower in the Hexoprenaline group (p = 0.001), although these neonates were born slightly earlier than the neonates in the Atosiban group. No differences between the groups were observed for any other neonatal parameter or for neonatal mortality or morbidity.

### Long-term neonatal outcomes

At 2-years follow-up, preterm-born infants were assessed for long-term neurodevelopmental outcomes. Data were available for 104 infants. Half of the infants from the Hexoprenaline group (49%, n = 30/61) and the Atosiban group (51%, 22/43) showed no neurodevelopmental impairment. Severe impairment was recorded in 26% in both groups. Neurodevelopmental assessment by Bayley test was available for 61 infants. 50% of infants in the Hexoprenaline group and 65% of infants in the Atosiban group did not show any impairment; only 5% and 9% of infants, respectively, showed severe impairment (► **Table 6**).

## Discussion

The present retrospective cohort study compares the tocolytic efficacy of atosiban and hexoprenaline as tocolytic agents in pregnancies with threatened preterm labor and found that atosiban showed a better efficacy in the first 48 hours of tocolysis while there was no significant difference in efficacy with regard to maintenance tocolysis up to 34 + 0 weeks of gestation.

These findings are contrary to those of a Cochrane review by Flenady et al., where no benefits were reported for atosiban compared to beta-mimetics with regard to the prolongation of pregnancy or neonatal outcomes [16].

The significance of atosiban's efficacy disappeared when efficacy was calculated according to gestational age at the time when tocolysis was initiated. It seems that atosiban is especially beneficial in early pregnancy but this may not be the case at later gestational ages. There is evidence that the number of oxytocin receptors in the myometrium increases at later gestational ages but also in cases with preterm labor [17], which could be a possible explanation for our findings.

41% of all tocolysis in Austria is maintenance tocolysis administered for longer than 48 hours [18]. The reason for the discrepancy compared to other countries could be a lack of knowledge about the harms and uses of tocolysis, especially in terms of long-term outcomes. At our institution, long-term tocolysis is prescribed on a case-by-case basis with the decision made by the at-

► **Table 6** Long-term neurodevelopmental outcomes of infants according to maternal tocolytic therapy for preterm labor.

			p value
<b>Clinical investigation/neuromotor impairment</b>	<b>H (n = 61)</b>	<b>A (n = 43)</b>	
▪ No impairment	30 (49%)	22 (51%)	1.000
▪ Mild impairment	15 (25%)	10 (23%)	
▪ Severe impairment	16 (26%)	11 (26%)	
<b>Bayley test</b>	<b>H (n = 38)</b>	<b>A (n = 23)</b>	
▪ No impairment	19 (50%)	15 (65%)	0.408
▪ Mild impairment	17 (45%)	6 (26%)	
▪ Severe impairment	2 (5%)	2 (9%)	

Data are presented as numbers and percentages. H: hexoprenaline; A: atosiban

tending obstetrician together with the expectant mother. Prematurity is associated with higher morbidity and mortality rates; therefore, it seems obvious that prolongation of the pregnancy should improve the outcome. However, there are only a few studies which demonstrate that maintenance tocolysis improves maternal and neonatal (long-term) outcomes and does not merely prolong pregnancy [12, 18, 19]. Short-term tocolysis should be given for 48 h to allow the administration of antenatal corticosteroids to improve the neonatal outcome [20], and it is often recommended that maintenance tocolysis should be avoided [8, 21–23]. In our series receiving maintenance tocolysis, maintenance tocolysis appeared to successfully prevent preterm labor in many patients without incurring any severe maternal or neonatal side effects. Based on our series, however, due to the retrospective analysis it cannot be definitively stated whether long-term tocolysis was responsible for a delay in delivery in women with ongoing contractions after 48 hours.

It is well-known that hexoprenaline causes more side effects such as palpitations, maternal tachycardia or chest pain in comparison to atosiban, and our study confirms these observations [8, 11, 16, 24]. However, both tocolytic agents seem to be quite well tolerated. Nevertheless, atosiban is recommended as the first choice tocolytic agent, especially in women with multiple gestations or maternal disease [9]. According to Berger et al.'s review of the literature, the prophylactic administration of aspirin as a tocolytic agent should also be further investigated, as it both reduces the risk of preeclampsia and fetal growth restriction and leads to a reduction of preterm labor [25].

Neonatal morbidity and mortality rates were similar in both groups. Birth weight of the neonates in the Atosiban group was slightly higher but these neonates were also born at slightly later gestational ages. This is in line with a multicenter randomized controlled trial in Belgium and the Netherlands (APOSTEL III) that compared neonatal outcomes after using atosiban or nifedipine for tocolysis [26]. Van Vliet et al. highlighted the improvement in primary neonatal outcomes as the main goal of tocolysis, not merely prolongation of the pregnancy. Our results are similar to the findings of the APOSTEL III trial with regard to neonatal outcomes and maternal side effects.

A cohort study by Pinto Cardoso et al. showed a reduced risk of neonatal death as well as a reduced risk of severe intraventricular

hemorrhage after using tocolysis in general, that was similar to our findings. Atosiban may affect neuroprotection and prepares the fetus for labor [27] while corticosteroids stabilize arterial blood pressure and have an anti-inflammatory effect [28, 29]. Both Gilard et al. and Di Renzo et al. discussed the occurrence of IVH and white matter lesions in preterm infants; they believe that the use of steroids and magnesium sulfate and not the tocolytic drug itself are responsible for decreased numbers of cases with IVH and other complications.

Prematurity is the most common cause of increased morbidity and mortality in infancy. Follow-ups can identify risk factors for cognitive, neurological and behavioral disorders and establish new treatment options [30]. Sixty-one children in the Hexoprenaline group and 43 children in the Atosiban group were available for follow-up. The number of cases in our follow-up cohorts are small because only infants with a birth weight of up to 1500 g were invited for assessment of their 2-year neurodevelopmental outcome. 25% of these children showed severely impaired neuromotor development on clinical examination. In two thirds (hexoprenaline) and half of the infants (atosiban), respectively, a Bayley test was performed to identify any impairment more precisely. At this follow-up, 50% of the infants in the Hexoprenaline group and 65% in the Atosiban group showed no impairment, while 5% and 9%, respectively, showed severe impairment. These findings are in accordance with the current literature. The APOSTEL III trial was followed in 2020 by the first published follow-up trial that compared neonatal outcomes after tocolysis with nifedipine or atosiban. 46% of the children of the first trial participated in the follow-up study, which was comparable with our follow-up data. Abnormal development was found in 38% in the Atosiban group but there were no differences with regard to neurodevelopment, executive function, behavior or health [31].

The strength of our study is its large sample size and the absence of differences with regard to maternal characteristics. Since the tocolytic agents used at our institution are not necessarily available in other industrialized countries, only very little data is available which specifically compares these two drugs. In addition, long-term follow-up data of low birthweight infants was available in our study.

Our study has some major limitations. The first is its retrospective design without randomization to treatment groups. Further-



more, long-term follow-up is not available for all infants, possibly leading to data bias.

## Conclusion

In conclusion, there is a significant difference in efficacy between the two tocolytic agents, with atosiban showing a higher efficacy during the first course of administration, especially when administered at an early gestational age, although this effect was not seen for long-term administration. There was no significant difference between the two tocolytic agents in regard to maternal or neonatal outcomes; however, hexoprenaline is associated with a higher rate of known maternal side effects.

## Conflict of Interest

The authors declare that they have no conflict of interest.

## References

- Zeitlin J, Szamotulska K, Drewniak N et al. Preterm birth time trends in Europe: a study of 19 countries. *BJOG* 2013; 120: 1356–1365. doi:10.1111/1471-0528.12281
- Gilbert WM. The cost of preterm birth: the low cost versus high value of tocolysis. *BJOG* 2006; 113 (Suppl. 3): 4–9. doi:10.1111/j.1471-0528.2006.01117.x
- Lawn JE, Cousens S, Zupan J; Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: when? Where? Why? *Lancet* 2005; 365: 891–900. doi:10.1016/S0140-6736(05)71048-5
- Stubert J, Gründler K, Gerber B et al. Prediction of Spontaneous Preterm Birth in At-risk Women Using Thrombospondin 1 from Cervicovaginal Fluid: A Prospective Observational Study. *Geburtshilfe Frauenheilkd* 2021; 81: 1055–1064. doi:10.1055/a-1486-7148
- Berger R, Abele H, Bahlmann F et al. Prevention and therapy of preterm labour. Guideline of the DGGG, OEGGG and SGGG (S2k-Level, AWMF Registry No. 015/025, February 2019). Part 1 with Recommendations on the Epidemiology, Etiology, Prediction, Primary and Secondary Prevention of preterm Birth. *Geburtshilfe Frauenheilkd* 2019; 79: 800–812
- Younger JD, Reitman E, Gallos G. Tocolysis: Present and future treatment options. *Semin Perinatol* 2017; 41: 493–504. doi:10.1053/j.semperi.2017.08.008
- Roberts D, Brown J, Medley N et al. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev* 2017; (3): CD004454. doi:10.1002/14651858.CD004454.pub3
- Haram K, Mortensen JH, Morrison JC. Tocolysis for acute preterm labor: does anything work. *J Matern Fetal Neonatal Med* 2015; 28: 371–378. doi:10.3109/14767058.2014.918095
- Lamont CD, Jorgensen JS, Lamont RF. The safety of tocolytics used for the inhibition of preterm labour. *Expert Opin Drug Saf* 2016; 15: 1163–1173. doi:10.1080/14740338.2016.1187128
- Wex J, Abou-Setta AM, Clerici G et al. Atosiban versus betamimetics in the treatment of preterm labour in Italy: clinical and economic importance of side-effects. *Eur J Obstet Gynecol Reprod Biol* 2011; 157: 128–135. doi:10.1016/j.ejogrb.2011.04.009
- Wex J, Connolly M, Rath W. Atosiban versus betamimetics in the treatment of preterm labour in Germany: an economic evaluation. *BMC Pregnancy Childbirth* 2009; 9: 23. doi:10.1186/1471-2393-9-23
- Dehaene I, Bergman L, Turtiainen P et al. Maintaining and repeating tocolysis: A reflection on evidence. *Semin Perinatol* 2017; 41: 468–476. doi:10.1053/j.semperi.2017.08.005
- American College of Obstetricians and Gynecologists; Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin no. 127: Management of preterm labor. *Obstet Gynecol* 2012; 119: 1308–1317. doi:10.1097/AOG.0b013e31825af2f0
- Medley N, Poljak B, Mammarella S et al. Clinical guidelines for prevention and management of preterm birth: a systematic review. *BJOG* 2018; 125: 1361–1369. doi:10.1111/1471-0528.15173
- Pschyrembel W. *Pschyrembel Klinisches Wörterbuch*. 260. Aufl. Berlin: de Gruyter; 2004
- Flenady V, Reinebrant HE, Liley HG et al. Oxytocin receptor antagonists for inhibiting preterm labour. *Cochrane Database Syst Rev* 2014; (6): CD004452. doi:10.1002/14651858.CD004452.pub3
- Arrowsmith S, Wray S. Oxytocin: its mechanism of action and receptor signalling in the myometrium. *J Neuroendocrinol* 2014; 26: 356–369. doi:10.1111/jne.12154
- Nazifovic E, Husslein H, Lakovscek I et al. Differences between evidence-based recommendations and actual clinical practice regarding tocolysis: a prospective multicenter registry study. *BMC Pregnancy Childbirth* 2018; 18: 446. doi:10.1186/s12884-018-2078-5
- Stelzl P, Kehl S, Rath W. Maintenance tocolysis: a reappraisal of clinical evidence. *Arch Gynecol Obstet* 2019; 300: 1189–1199. doi:10.1007/s00404-019-05313-7
- Schmitz T. [Prevention of preterm birth complications by antenatal corticosteroid administration]. *J Gynecol Obstet Biol Reprod (Paris)* 2016; 45: 1399–1417. doi:10.1016/j.jgyn.2016.09.008
- Doret M, Kayem G. [Tocolysis for preterm labor without premature preterm rupture of membranes]. *J Gynecol Obstet Biol Reprod (Paris)* 2016; 45: 1374–1398. doi:10.1016/j.jgyn.2016.09.018
- Sentilhes L, Sénat MV, Ancel PY et al. Prevention of spontaneous preterm birth: Guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF). *Eur J Obstet Gynecol Reprod Biol* 2017; 210: 217–224. doi:10.1016/j.ejogrb.2016.12.035
- Nakamura M, Hasegawa J, Arakaki T et al. Comparison of perinatal outcomes between long-term and short-term use of tocolytic agent: a historical cohort study in a single perinatal hospital. *J Obstet Gynaecol Res* 2016; 42: 1680–1685. doi:10.1111/jog.13104
- Nonnenmacher A, Hopp H, Dudenhausen J. [Effectiveness and safety of atosiban vs. pulsatile administration of fenoterol in the treatment of preterm labour]. *Z Geburtshilfe Neonatol* 2009; 213: 201–206. doi:10.1055/s-0029-1225640
- Berger R, Kyvernitakis I, Maul H. Spontaneous Preterm Birth: Is Prevention with Aspirin Possible? *Geburtshilfe Frauenheilkd* 2021; 81: 304–310. doi:10.1055/a-1226-6599
- van Vliet EOG, Nijman TAJ, Schuit E et al. Nifedipine versus atosiban for threatened preterm birth (APOSTEL III): a multicentre, randomised controlled trial. *Lancet* 2016; 387: 2117–2124. doi:10.1016/S0140-6736(16)00548-1
- Pinto Cardoso G, Houivet E, Marchand-Martin L et al. Association of Intraventricular Hemorrhage and Death With Tocolytic Exposure in Preterm Infants. *JAMA Netw Open* 2018; 1: e182355. doi:10.1001/jamanetworkopen.2018.2355
- Gilard V, Tebani A, Bekri S et al. Intraventricular Hemorrhage in Very Preterm Infants: A Comprehensive Review. *J Clin Med* 2020; 9: 2447. doi:10.3390/jcm9082447
- Di Renzo GC, Al Saleh E, Mattei A et al. Use of tocolytics: what is the benefit of gaining 48 hours for the fetus? *BJOG* 2006; 113 (Suppl. 3): 72–77. doi:10.1111/j.1471-0528.2006.01127.x
- Ream MA, Lehwald L. Neurologic Consequences of Preterm Birth. *Curr Neurol Neurosci Rep* 2018; 18: 48. doi:10.1007/s11910-018-0862-2
- van Winden T, Klumper J, Kleinrouweler CE et al. Effects of tocolysis with nifedipine or atosiban on child outcome: follow-up of the APOSTEL III trial. *BJOG* 2020; 127: 1129–1137. doi:10.1111/1471-0528.16186