Thieme

Acute Tocolysis – a Critical Analysis of Evidence-Based Data

Akuttokolyse – eine kritische Analyse evidenzbasierter Daten

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ABSTRACT

Tocolysis is among the most common obstetric measures. The objective is to prolong the pregnancy by at least 48 hours to complete foetal lung maturation and for the in-utero transfer of the pregnant woman to a perinatal centre. The indication for tocolysis is regular, premature contractions (≥ 4/20 min) and a dynamic shortening of the cervical length/cervical opening between 22 + 0 to 33 + 6 weeks of pregnancy. In this connection, the cervical length measured on ultrasound and the determination of biomarkers in the cervicovaginal secretions can be important decision-making aids. Beta sympathomimetics should no longer be used due to the high rate of severe maternal adverse effects. Given controversial data, magnesium sulphate is no longer recommended for tocolysis in current guidelines. Atosiban is as effective for prolonging pregnancy as beta sympathomimetics and nifedipine, has the lowest rate of maternal adverse effects, but also the highest drug costs. Nifedipine and indomethacin are recommended in international guidelines for acute tocolysis, however there are indications of increased neonatal morbidity following indomethacin. Current problems are, above all, the lack of randomised, controlled comparative and placebo-controlled studies, the data which are controversial to some extent, and the insufficient evidence of tocolytics to significantly improve the neonatal outcome.

ZUSAMMENFASSUNG

Die Tokolyse gehört zu den häufigsten geburtshilflichen Maßnahmen. Ziel ist die Verlängerung der Schwangerschaft um mindestens 48 Stunden zum Abschluss der fetalen Lungenreifung und zum In-utero-Transfer der Schwangeren in ein Perinatalzentrum. Die Indikation zur Tokolyse sind regelmäßige, vorzeitige Wehen (≥ 4/20 min) und eine dynamische Verkürzung der Zervixlänge/Zervixeröffnung zwischen 22 + 0 bis 33 + 6 SSW. In diesem Zusammenhang können die sonografisch gemessene Zervixlänge und die Bestimmung von Biomarkern im Zervikovaginalsekret wichtige Entscheidungshilfen sein. Betasympathomimetika sollten aufgrund der hohen Rate schwerer maternaler Nebenwirkungen nicht mehr eingesetzt werden. Bei kontroverser Datenlage wird Magnesiumsulfat in aktuellen Leitlinien nicht mehr zur Tokolyse empfohlen. Atosiban ist zur Schwangerschaftsverlängerung äquieffektiv zu Betasympathomimetika und Nifedipin, weist die geringste Rate maternaler Nebenwirkungen, aber auch die höchsten Arzneimittelkosten auf. Nifedipin und Indometacin werden in internationalen Leitlinien zur Akuttokolyse empfohlen, allerdings bestehen Hinweise für eine erhöhte neonatale Morbidität nach Indometacin. Derzeitige Probleme sind vor allem das Fehlen randomisierter, kontrollierter Vergleichs- und placebokontrollierter Studien, die z. T. kontroverse Datenlage und die unzureichende Evidenz von Tokolytika, das neonatale Outcome signifikant zu verbessern.

Introduction

For decades, drug-based inhibition of contractions has been a part of the treatment concept for preterm delivery whose rate in Europe, at 5–18%, remains high [1]; in Germany, it was 8.6% in 2017 [2].

As the perinatal statistics from 2017 show [2], approximately 18 800 cases of tocolysis are performed in Germany annually in the case of threatened preterm delivery, with a median duration of 3 days (up to 106 days).

For demonstrable reasons (for example, the pregnant woman's desire for "treatment", concerns about medical-legal disputes in the event of damage), tocolytics are used too frequently and too long. In approximately 30% of pregnant women with preterm contractions, these stop spontaneously [3]; about 50% of pregnant women deliver without tocolysis near term [4] and only 12–17% within one week [5]. In view of this, a differentiated indication is a precondition for performing tocolysis.

Indications for Tocolysis

According to the current recommendations of the European Association of Perinatal Medicine, tocolysis is indicated at the onset of regular preterm contractions, not fewer than 4 contractions within 20 minutes and dynamic cervical changes (shortening/expansion of the cervix) between 22 + 0 and 36 + 6 weeks of pregnancy [1].

The ACOG Practice Bulletin No. 171 2016 [3] recommends tocolysis in the case of regular preterm contractions and cervical dilation of ≥ 2 cm.

From earlier investigations, it is known that measuring cervical length using ultrasound (sensitivity 78.1%, specificity 82.7%) is superior to the digital examination (sensitivity 65.6%, specificity 72.4%) with regard to predicting preterm delivery within 7 days [6].

Pregnant women with preterm contractions and a cervical length of ≥ 30 mm have a risk of preterm delivery of < 2% within the next 7 days and an over 95% chance of delivering beyond the 35th week of pregnancy without treatment [7].

The indication for tocolysis increasingly includes the qualitative (quantitative) determination of biomarkers (foetal fibronectin, insulin-like growth factor-binding protein-1 and placental α-microglobulin-1) in the cervicovaginal secretion to predict preterm delivery within 7 days, in addition to the cervical length measured on ultrasound (overview in [1]).

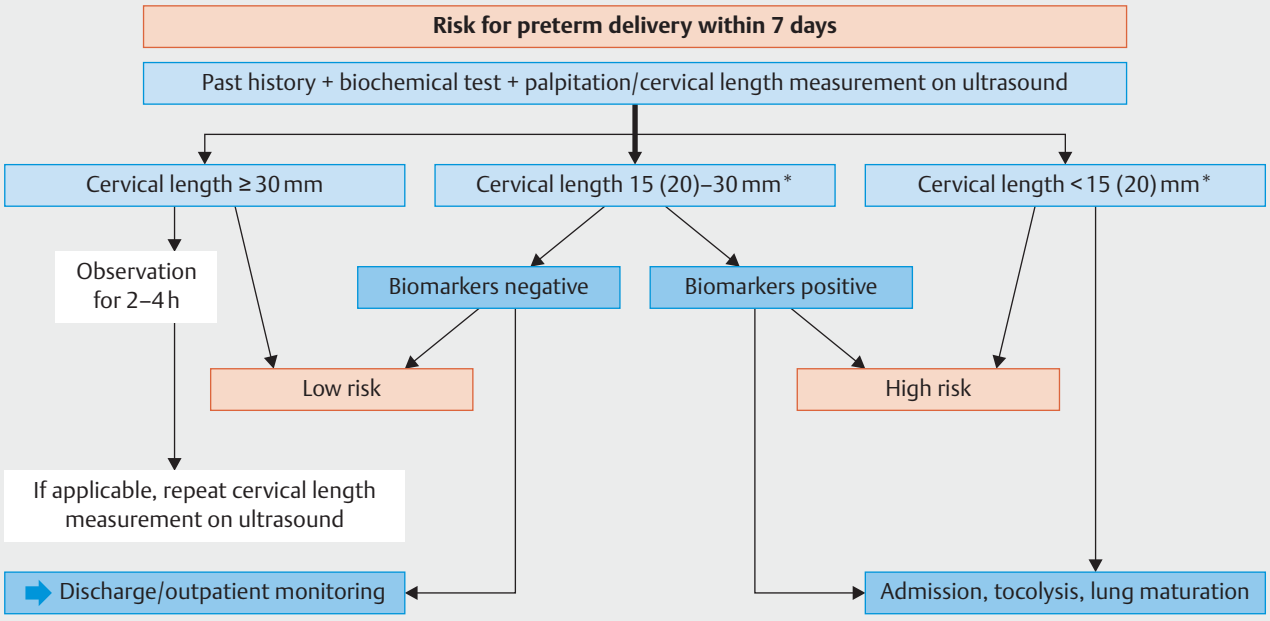
According to a systematic overview of prospective cohort and observational studies, the determination of the placental α-microglobulin-1 over all areas of risk has the highest positive predictive value for a preterm delivery within 7 days in comparison to the two other biomarkers [8]; however, it should be taken into account here that these included non-randomised, controlled studies must be viewed critically due to possible bias.

The combination of cervical length measurement on ultrasound and biomarker testing in the cervicovaginal secretions should enable a differentiation to be made in pregnant women at low risk (< 2–5%) for a preterm delivery within 7 days who do not need tocolysis and pregnant women at high risk for whom an inpatient admission and tocolysis as well as induction of foetal lung maturation is recommended. Indicative for this recommendation were a meta-analysis by De Franco et al. [9] as well as the results of a prospective cohort study (n = 665, 24th-34th weeks of pregnancy) from the Netherlands, with disproportionate inclusion of later weeks of the time period mentioned and thus a significant bias [10]. Pregnant women with preterm contractions and a cervical length > 30 mm or a cervical length of 15–30 mm and negative fibronectin have a preterm delivery rate < 5% within a week. As a subsequent randomised study from the same working group [11] showed, no significant decrease in the preterm delivery rate within 7 days (8.1 vs. 2.8%) and no significant differences with regard to the median gestational age at birth were able to be achieved in this low-risk collective (cervical length 10–30 mm, negative fibronectin test, intact amniotic sac) by the oral administration of nifedipine in comparison to placebo.

Pregnant women with regular preterm contractions, a cervical length < 15 mm or a cervical length of 15–30 mm and a positive fibronectin test had a risk of preterm delivery within 7 days of 52 and 11–17% respectively and thus an indication for tocolysis [10]. In a subgroup analysis of the APOSTEL-I study, the combination of cervical length measurement on ultrasound and the determination of foetal fibronectin proved to be cost-effective through the reduction in inpatient admissions, tocolysis and induction of foetal lung maturation [12]. In another subanalysis of this study, the introduction of this approach resulted in a significant shortening of the inpatient hospital stay [13]. However, according to a recent meta-analysis from 6 randomised, controlled studies (n = 546), the fibronectin determination alone does not lead to a reduction in the preterm delivery rate < 28, < 32 and < 37 weeks of pregnancy and not within 7 days or to a decrease in inpatient hospitalisations and cases of tocolysis, but to higher inpatient costs [14]. It is currently being discussed whether, in addition to cervical length measurement on ultrasound, the additional determination of a biomarker such as fibronectin significantly improves the prediction of preterm delivery and thus should be included in the clinical management in the event of threatened preterm delivery (overview in [15]). In the case of a cervical length of > 30 mm or < 20 mm, the additional determination of a biomarker such as fibronectin is not recommended since the risk of preterm delivery within a week in these cases is < 2–5% and > 25% respectively [16].

Navathe and Berghella 2016 [17] define "true preterm labour" as regular preterm contractions in connection with a cervical length measured transvaginally of < 20 mm or 20–29 mm and a positive fibronectin test in the cervicovaginal secretions; in the case of these pregnant women, they see an indication for inpatient admission, tocolysis and induction of foetal lung maturation.

The NICE guideline "Preterm labour and birth" 2015 [18] discusses "diagnosed preterm labour" in pregnant women with regular preterm contractions and a cervical length on ultrasound of ≤ 15 mm. If cervical length measurement via vaginal ultrasound is not available/feasible, the fibronectin test for risk stratification should be used in the event of threatened preterm delivery ≥ 30 weeks of pregnancy; a combination of both methods is not recommended.



▶ **Fig. 1** Possible algorithm for actions to be taken in the case of regular preterm contractions: $23^{0/7}$ – $33^{6/7}$.

Tocolysis should be performed in pregnant women between 24 + 0–25 + 6 weeks of pregnancy with intact amniotic sac and "suspected preterm labour" (regular, painful contractions and cervical shortening/opening verified by vaginal examination, but not ≥ 4 cm) as well as between 26 + 0–33 + 6 weeks of pregnancy in the case of "suspected" or "diagnosed preterm labour".

A possible algorithm for actions to be taken, published by some authors in the meantime [1, 17 – 19], is shown in ▶ **Fig. 1**.

Objectives of Tocolysis

There is no evidence to date from placebo-controlled studies that tocolytics lead to a significant decrease in perinatal and neonatal mortality as well as in neonatal morbidity [20 – 22]. However, the studies in this regard should be assessed critically owning to the considerable heterogeneity and insufficient quality in studies/meta-analyses (among other things, inclusion of pregnant women with advanced gestational age, no antenatal induction of lung maturation or transfer to a perinatal centre, inadequate statistical power for rare complications, e.g. neonatal death) [23]. According to the current view, [1, 3, 18, 22, 24] the objective of tocolysis is the prolongation of the pregnancy by at least 48 hours to ensure completion of induction of lung maturation using corticosteroids, to enable an in-utero transfer of the pregnant woman to a perinatal centre with a neonatal intensive care unit and to complete foetal neuroprotection using magnesium sulphate < 32 weeks of pregnancy [3]. These measures are evidence-based methods to decrease neonatal morbidity and mortality [24].

Choice of tocolytic

The following criteria should be taken into account:

- Approved or off-label use
- Tocolytic effectiveness to prolong the pregnancy by at least 48 hours
- Rate of maternal adverse effects/complications
- Rate of foetal adverse effects/complications
- Early, late, long-term morbidity
- Practicability (e.g. mode of application), need for monitoring
- Costs, cost effectiveness

Beta Sympathomimetics

For several decades, since the 1970s, fenoterol has been the most frequently used tocolytic in Germany. According to a 2009 meta-analysis [25], a prolongation of the pregnancy by 48 hours can be achieved in 75 % and by 7 days in 65 % of cases using beta sympathomimetics.

According to a 2012 network meta-analysis [26], beta sympathomimetics are indeed effective in prolonging pregnancy for 48 hours (OR 2.41; 95 % CI 1.27–4.55), but significantly less effective than calcium channel blockers and indomethacin and also have the highest rate of maternal adverse effects of all tocolytics in comparison to placebo (OR 22.67; 95 % CI 7.51–73.67, see below).

A Cochrane Review published in 2014 [27] of 28 randomised, controlled studies from 1974–2010 (all application forms) revealed for beta sympathomimetics – in comparison to placebo (10 studies, n = 1209) – a significant decrease in the preterm delivery rate within 48 hours (RR 0.68; 95 % CI 0.53–0.87) and within

7 days (RR 0.80; 95% CI 0.65–0.89). However, there was no significant decrease in the frequency of preterm deliveries before the 37th week of pregnancy (RR 0.95; 95% CI 0.88–1.03, 10 studies, n = 1212), perinatal mortality (RR 0.89; 95% CI 0.46–1.55, 6 studies, n = 1174 children) as well as the rate of RDS (RR 0.87; 95% CI 0.71–1.08, 8 studies, n = 1239 children), cerebral pareses, necrotising enterocolitis and transfer to the neonatal intensive care unit. One point of criticism is that this Cochrane Review included 24 (out of 28) studies prior to 1990 and at that time, induction of foetal lung maturation with corticosteroids was not a standard practice. In addition, the target parameters such as preterm deliveries before the 37th week of pregnancy should be looked at critically, since in many countries, no tocolysis is given starting from 34 + 0 weeks of pregnancy. Certain morbidities such as RDS are especially relevant in the case of an early gestational age and therefore can also, depending on the study collective (e.g. large percentage of pregnancies beyond week 30) still demonstrate significances with difficulty.

Beta sympathomimetics do not influence the long-term development of the child (overview in [28]). In twin pregnancies, the prophylactic administration of beta sympathomimetics does not decrease the rate of preterm deliveries < 37 weeks [29]. According to a Cochrane Review from 2012 [30] which included 13 randomised, controlled studies (n = 1551), the oral use of beta sympathomimetics following initial tocolysis in comparison to placebo/no treatment does not lead to any significant decrease in the rate of preterm delivery < 37 weeks (RR 1.11; 95% CI 0.91–1.35) or to any decrease in the transfer rate of children to the neonatal intensive care unit (RR 1.28; 95% CI 0.68–2.41).

Based on the pharmacological effects with an increase in heart rate and cardiac output as well as peripheral vasodilatation, beta sympathomimetics are above all burdened with adverse cardiovascular effects in up to 80% of cases [27]: significantly higher incidence of palpitations (RR 10.11; 95% CI 6.56–15.58), tachycardia (RR 4.08; 95% CI 1.55–10.73), chest pain (RR 11.3; 95% CI 3.8–33.46), dyspnoea (RR 3.86; 95% CI 2.21–6.77) and headaches (RR 4.1; 95% CI 2.6–6.35) in comparison to placebo. In addition, there are neurological symptoms, particularly tremors (RR 10.74; 95% CI 6.2–18.6), inner restlessness/anxiety and insomnia. Metabolic adverse effects involve, in particular, hyperglycaemia and hypokalaemia.

According to a prospective cohort study [31], the rate of serious, primarily maternal adverse effects is 1.7% and thus around 3.8 times higher in comparison to other tocolytics. Overall, the therapy discontinuation rate is between 6 and 38% (RR 11.38; 95% CI 5.2–24.9) [21, 27].

The most serious complication of beta sympathomimetics is pulmonary oedema in approx. 0.3% of pregnant women to the point of maternal death in individual cases [21]. The decrease in diastolic cardiac filling in tachycardia promotes the development of pulmonary oedema, particularly in unbalanced and increased volume replacement, concomitant corticosteroid administration, preeclampsia, blood transfusions and multiple pregnancies [32]. In comparison to the continuous application of beta sympathomimetics (fenoterol), bolus tocolysis with fenoterol has a significantly lower rate of maternal adverse effects [33].

No teratogenic effects are known for beta sympathomimetics; they cross the placental barrier and can therefore lead to foetal tachycardia (in up to 28% of cases), limitations in heart sound variability as well as neonatal hyperinsulinaemia/hypoglycaemia.

CONCLUSION FOR CLINICAL PRACTICE

- Approved for tocolysis
- Effective for prolonging the pregnancy by 48 h (7 days)
- Unfavourable adverse effect profile of all tocolytics and the highest therapy discontinuation rate
- Immobilisation of the pregnant woman in the case of parenteral use
- Significant monitoring needed (e.g. ECG, laboratory testing), close circulatory monitoring necessary (see [1])

In current guidelines, beta sympathomimetics are no longer recommended for tocolysis [18, 22, 24].

NO donors

The transdermal application of nitroglycerin (patches, 10 mg/24 h) was considered for some years to be a new, innovative method for tocolysis since it is effective, has few side effects, is easy to apply and cost-efficient. While NO donors were not mentioned in the 2009 meta-analysis of Haas et al. [25], the 2012 network meta-analysis [26] classified NO donors as the least effective tocolytics in comparison to placebo for prolonging delivery by 48 hours (RR 1.19; 95% CI 0.64–5.33).

A meta-analysis from 2013 (13 randomised, controlled studies, n = 1302) was not able to show any significant differences in two studies with a small number of cases (total n = 186) between transdermal nitroglycerin and placebo with regard to prolongation of pregnancy by 48 hours [34]. However, transdermal nitroglycerin, in comparison to beta sympathomimetics (9 studies, n = 1024) led to a significant reduction in the rate of preterm delivery < 34 weeks of pregnancy (20 vs. 28%, RR 0.71; 95% CI 0.51–0.99) and < 37 weeks of pregnancy (44 vs. 57%, RR 0.76; 95% CI 0.60–0.96) without an influence on neonatal morbidity. Moreover, transdermal nitroglycerin had a significantly lower rate of maternal adverse effects except for headaches and hypotension. Two other randomised, controlled studies compared transdermal nitroglycerin with nifedipine and magnesium sulphate without significant differences with regard to prolongation of pregnancy by 48 hours. The meta-analysis came to the conclusion that the evidence for the use of transdermal nitroglycerin for tocolysis is insufficient [34]. A Cochrane Review from 2014, which also came to comparable results and conclusions [35], included 12 randomised, controlled studies with 1227 pregnant women with the indication that the studies have inadequate statistical power with regard to most variables.

In current international guidelines, NO donors are not mentioned for tocolysis or are not recommended [1, 3, 18, 22, 24].

CONCLUSION FOR CLINICAL PRACTICE

- Not approved for tocolysis (off-label use)
- More effective in comparison to beta sympathomimetics with regard to prolongation of pregnancy by 48 hours
- Possibly decreased acceptance due to high rate of headaches
- Inadequate data, no recommendation in international guidelines

Cyclooxygenase Inhibitors

The nonspecific cyclooxygenase inhibitor indomethacin (initial dosage 50–100 mg oral or rectal, followed by 25–50 mg every 4–6 h) is used most frequently for tocolysis and is the only tocolytic with an anti-inflammatory effect. According to a 2009 meta-analysis [25], delivery was postponed by 48 hours in 93 % of cases and over 7 days in 76 % of cases with indomethacin < 32 weeks of pregnancy, however the low number of pregnant women included (n = 442) limits the significance of this meta-analysis.

A subsequent network meta-analysis from 2012 [26] which included 18 studies (1980–2007) showed that COX inhibitors were the most effective tocolytics for prolonging pregnancy by 48 hours in comparison to placebo (OR 5.39; 95 % CI 2.14–12.34) – with concomitantly the lowest rate of maternal adverse effects and good neonatal outcome (see ▶ **Table 1**). It is surprising that a Cochrane Review from 2015 [36] which included 20 randomised, controlled studies (n = 1509) from 1980–2012, 15 of which were studies with indomethacin, found different results although the same studies, for the most part, were evaluated. In this Cochrane Review, no significant decrease in the rate of premature delivery < 48 hours was able to be demonstrated in comparison to placebo (3 studies, n = 102) (RR 0.20; 95 % CI 0.03–1.28). In comparison to beta sympathomimetics, COX inhibitors led to a significant decrease in the preterm delivery rate < 48 hours (RR 0.27; 95 % CI 0.08–0.96) and to a greater decrease in the preterm delivery rate < 37 weeks of pregnancy (RR 0.53; 95 % CI 0.28–0.99; 4 studies, n = 180) without an impact on neonatal morbidity and mortality. Compared to beta sympathomimetics, COX inhibitors had significantly lower rates of maternal adverse effects (RR 0.19; 95 % CI 0.11–0.31; 5 studies, n = 248) and a lower rate of discontinuation of therapy (RR 0.39; 95 % CI 0.25–0.62; 5 studies, n = 635).

The Cochrane Review concludes that because of the low number of cases in studies, the insufficient information on the safety profile and long-term consequences, the evidence for the use of COX inhibitors for tocolysis is not sufficient.

COX inhibitors rapidly cross the placental barrier and lead to inhibition of foetal prostaglandin synthesis with potential consequences for the foetus: as a result of an increased vasopressin effect with decrease in the renal blood flow [37], there can be decreased urine production (rarely to the point of renal failure) following indomethacin in foetuses, resulting in oligohydramnios in 5–15 % of cases, and even in up to 70 % of cases in the case of use for more than 72 h [38]. After stopping indomethacin, the amount of amniotic fluid should normalise once again within 24 (– 96) h [39]. According to the recommendations of the European Association of Perinatal Medicine 2017 [1] the amount of amniotic fluid should be checked prior to starting therapy and after 48–72 h. Indomethacin should only be given if there is a normal amount of amniotic fluid and if oligohydramnios occurs, it should be discontinued or at least the dose should be reduced [1].

To avoid premature closure of the ductus arteriosus, it is recommended to administer COX inhibitors only up to the 32nd

▶ **Table 1** Network meta-analysis of 95 randomised, controlled studies (1982–2012). Placebo as reference: median OR (95 % CI).

Tocolytics	Prolongation of pregnancy 48 h[+]	Probability of being best	Neonatal mortality[*]	Probability of being best	RDS[*]	Probability of being best	Maternal adverse effects[#]	Probability of being best
Betamimetics	2.41 (1.27–4.55)	0.01	0.62 (0.14–2.48)	0.12	0.85 (0.5–1.45)	0.14	22.68 (7.5–73.7)	< 0.01
PG inhibitors	5.39 (2.14–12.34)	0.83	0.62 (0.04–4.63)	0.28	0.87 (0.4–1.75)	0.20	1.63 (0.4–6.85)	0.21
Calcium channel blockers	2.71 (1.17–5.9)	0.06	0.39 (0.09–1.5)	0.41	0.71 (0.37–1.43)	0.47	3.50 (1.0–16.9)	0.01
Magnesium sulphate	2.76 (1.58–4.94)	0.02	0.97 (0.3–3.3)	0.03	0.99 (0.55–1.7)	0.03	8.15 (2.47–27.7)	< 0.01
Atosiban	2.02 (1.1–3.8)	0.01	0.62 (0.16–2.35)	0.13	0.89 (0.55–1.37)	0.10	1.99 (0.61–6.94)	0.08
NO donors	1.91 (0.64–5.33)	0.04	No information	–	No information	–	3.2 (0.4–20.84)	0.10

[+] Odds ratio > 1 favour active class

[*] Odds ratio < 1 favour active class

[#] Odds ratio > 1 favour placebo

Conclusion: Indomethacin and calcium channel blockers have the highest probability of delaying delivery and improving neonatal and maternal outcome

Haas DM et al. BMJ 2012; 345: e6226 [26]

week of pregnancy for 48 hours. Under these conditions, only one case with antenatal closure of the ductus arteriosus was identified among 403 pregnant women with indomethacin exposure [40, 41]. Prior to 32 weeks of pregnancy, an echocardiographic examination of the foetal ductus arteriosus with assessment of the tricuspid valve (tricuspid regurgitation) is recommended if treatment lasts > 48 hours [1]. In accordance with this in the Cochrane Review from 2015 and in a subsequent meta-analysis [42], there was not found to be an elevated risk of a significant increase in neonatal mortality or the rate of RDS, bronchopulmonary dysplasia, patent ductus arteriosus and pulmonary hypertension or intraventricular bleeding of all levels of severity. However, in the meta-analysis [42] which included 27 observational studies, (n = 1731) there was a significantly increased risk of

- Intraventricular bleeding, grade III/IV RR 1.29 (95% CI 1.06–1.50),
- necrotising enterocolitis RR 1.36 (95% CI 1.08–1.71) and
- periventricular leucomalacia RR 1.59 (95% CI 1.17–2.17).

However, in this meta-analysis, there was no information provided on the dosage and duration of the indomethacin administration and also no details given on the percentage of pregnant women who received antenatal induction of lung maturation with corticosteroids. Likewise, it should be taken into account that indomethacin was/is used in the very early weeks of pregnancy in which the previously described complications naturally occur more frequently.

CONCLUSION FOR CLINICAL PRACTICE

- Off-label use
- Easy application, cost-effective
- Use only until 32 weeks of pregnancy for 48 hours
- Indications of increased neonatal morbidity (severe intraventricular bleeding, necrotising enterocolitis, periventricular leucomalacia): inform paediatrician of administration!
- Varying recommendations (controversial data, to some extent)
  - not recommended/insufficient data: Cochrane Review 2015 [36], Hammers et al. 2015 [42], Nijman et al. 2016 [5]. WHO Recommendations 2015 [24]
  - recommended with restrictions: Navathe and Berghella 2016 [17], European recommendations 2017 [1]
  - recommended: among others: 2009 meta-analysis [25], 2012 network meta-analysis [27], ACOG Practice Bulletin 2016 [3]

Magnesium Sulphate

The data on magnesium sulphate as a tocolytic are controversial. According to the meta-analysis from 2009 [25], a prolongation of pregnancy by 48 hours can be achieved in 89% of cases with magnesium sulphate and by up to 7 days in 61%. A network meta-analysis from 2012 [26] which included 29 studies confirmed the high tocolytic efficacy of magnesium sulphate for prolonging pregnancy by 48 hours (OR 2.76; 95% CI 1.58–4.94) without influencing neonatal mortality (OR 0.97; 95% CI 0.29–3.29). However, in a probability analysis, this work concluded that magnesium sulphate is not the most effective tocolytic with the fewest adverse effects. Contrary results were seen in the Cochrane Review from 2014 [43] which included 37 studies with 3571 pregnant women (period from 1982–2012). This did not reveal any evidence (4 studies) that magnesium sulphate, in comparison to placebo/no treatment, is more effective for prolonging pregnancy by 48 hours (RR 0.57; 95% CI 0.28–1.15) and increasing the gestational age until delivery. In addition, a borderline increase in cases of perinatal/neonatal death following magnesium sulphate was seen (risk ratio 4.56; 95% CI 1.00–20.86, 2 studies, 257 children). According to this, the Cochrane Analysis concluded that magnesium sulphate is ineffective for prolonging pregnancy or avoiding preterm delivery. With regard to these controversial results, it is interesting that the network meta-analysis (2012) and the Cochrane Review (2014) evaluated nearly the same studies covering a comparable period – in the Cochrane Review, only one study after the period covered by the network meta-analysis was included [44].

The myometrium-relaxing effect of magnesium sulphate as well as the scope and frequency of adverse effects are dose-dependent (overview in [45]). Thus at an initial dose of 4 g and a maintenance dose of 2 g/hour as an infusion, the rate of success with regard to prolongation of pregnancy by 48 hours was between 60–77%; at an initial dose of 6 g followed by 2 (4) g/hour, it was between 84–94% [46]. In a randomised comparative study between nifedipine and magnesium sulphate (4 g magnesium sulphate initially, followed by 2–4 g as maintenance dose), prolongation of pregnancy by 48 hours was able to be achieved in 87% of cases with magnesium sulphate, however the rate of maternal adverse effects – 62% – was high (including 3 cases of pulmonary oedema) [47]. According to a current retrospective case-control study (n = 150), magnesium sulphate significantly increases the risk of pulmonary oedema (adjusted OR 3.51; 95% CI 1.26–9.76; [48]). This is in line with a Cochrane Review from 2015 on tocolysis with magnesium sulphate at various dosages [49].

According to Elliott et al. [50], magnesium sulphate is equieffective to other tocolytics at a sufficiently high dose reaching magnesium levels between 5.0–8.0 mg/100 ml (Note: The patellar tendon reflex disappears between 9–13 mg/100 ml).

Except in the U.S., magnesium sulphate is no longer recommended for tocolysis [51] in current reviews and guidelines [1, 4, 17, 22, 43, 52].

Oxytocin Receptor Antagonists (Atosiban)

The advantage of the selective oxytocin receptor antagonist atosiban approved for tocolysis, in comparison to other "ubiquitously" effective tocolytics is the primarily uterus-specific effect without a significant influence on the cardiovascular system, the CNS, the kidney and the lung as well as without negative metabolic effects (overview in [53]). With low placental passage of 10–12%, no relevant adverse effects on the foetus/child are known, even after a 2-year observation period. Except for "hypersensitivity to the drug", there are no substance-specific contraindications. Disadvantages are the i.v. application and associated immobilisation

of the pregnant woman as well as the drug costs which are significantly higher as compared to other tocolytics. A Cochrane Review from 2014 [54] included 14 studies with 2485 pregnant women with the following results: oxytocin receptor antagonists (atosiban and barusiban) did not prove to be significantly more effective, compared to placebo, in prolonging pregnancy by 48 hours (4 studies, n = 854; RR 1.05; 95% CI 0.15–7.43) and no significant differences were seen with regard to the rate of preterm delivery < 37 weeks of pregnancy, perinatal mortality and neonatal morbidity.

In 8 studies (n = 1402) atosiban was compared to beta sympathomimetics; this revealed no significant differences between both tocolytics with regard to prolongation of pregnancy by 48 hours (RR 0.89; 95% CI 0.66–1.22) as well as perinatal mortality (RR 0.55; 95% CI 0.21–1.48; 3 studies with 812 children). The difference in the rate of maternal adverse effects (RR 0.38; 95% CI 0.21–0.68) and treatment discontinuations (RR 0.05; 95% CI 0.02–0.11; 5 studies, n = 1161) was significant. A large prospective cohort study revealed mild adverse effects in 0.2% of the pregnant women, but no severe adverse effects (RR 0.07; 95% CI 0.01–0.4; [31]).

In the meta-analysis of Haas et al. from 2009 [25], which included 1249 pregnant women, prolongation of pregnancy by 48 hours was achieved in 86% of cases and by 7 days in 78% of cases. The network meta-analysis from 2012 [26] revealed a significant tocolytic effect for atosiban in the prolongation of pregnancy by 48 hours (OR 2.02; 95% CI 1.10–3.80) without an influence on the rate of RDS and perinatal mortality.

Of interest is a prospective, randomised study from Germany [55] on 105 pregnant women between 24 + 0 to 33 + 6 weeks of pregnancy in which the pulsatile application of fenoterol was compared to atosiban at a standard dosage. This revealed no significant differences with regard to prolongation of pregnancy by 48 hours (79.8 vs. 86.3%) and by 7 days (66.7 vs. 78.4%). However, on fenoterol, adverse cardiovascular effects were observed in 78% of cases and on atosiban in only 4% of cases (treatment discontinuation rate 9% versus 0). The data on the comparison of nifedipine and atosiban for acute tocolysis were unclear since 3 randomised studies with small numbers of cases had controversial results (overview in [56]). This was clarified by the APOSTEL-III study, a randomised, controlled study (n = 510) on pregnant women with regular preterm contractions, a cervical length of ≤ 10 mm or a cervical length of 11–30 mm and a positive fibronectin test [57]. In this study, 20 mg nifedipine were given in the first hour, followed by 20 mg nifedipine sustained-release every 6 h (up to 48 h) and compared to a standard dosage of atosiban. No significant differences were seen between nifedipine and atosiban with regard to prolongation of pregnancy by ≥ 48 hours (68 vs. 66%) and by 7 days (51 vs. 45%), no significant differences with regard to perinatal mortality (5 vs. 2%) and neonatal morbidity (14 vs. 15%); given a higher rate of maternal adverse effects, the treatment discontinuation rate following nifedipine was not significantly higher (6 vs. 3%).

CONCLUSION FOR CLINICAL PRACTICE

- Approved (not in the USA)
- Tocolytic efficacy comparable to beta sympathomimetics and nifedipine
- Associated with few adverse effects for mother and child
- Intravenous application and immobilisation necessary
- High drug costs
- Recommendations: particularly in the case of contraindications to nifedipine and indomethacin [18] or as a first-line tocolytic [1], suitable tocolytic in the case of pre-existing metabolic and cardiovascular diseases in the mother [23]

Calcium Channel Blockers (e.g. Nifedipine)

Nifedipine is used most frequently (half-life 2–3 hours, maximum plasma concentration after a 10-mg tablet 30–60 min); it is not approved for tocolysis. The dosage recommendations differ, e.g.

- NICE 2015 [18]: initially 20 mg oral, followed by 10–20 mg three to four times daily, depending on uterine activity (see also [24]).
- ACOG 2016 [3]: 30 mg nifedipine initially, then 10–20 mg every 4–6 h.

Dose-dependent adverse effects such as flushing, headaches, dizziness, palpitations, tachycardia and hypotension may occur. The rate of serious maternal adverse effects is 0.9% and is significantly higher than after atosiban; the rate of treatment discontinuation as a result of marked hypotension is < 0.5% [31] and isolated cases with intrauterine death have been described in this connection [58, 59] whereby a causal connection must be critically scrutinised.

Caution is needed in the case of pre-existing cardiac diseases and pre-existing hypotension: The use of slow-release preparations can lead to maternal hypotension which persists for hours [60] and the sublingual application of nifedipine can lead to sudden and rapid decreases in blood pressure with consecutive foetal hypoxia [61].

According to a meta-analysis from 2010 [62], an approximately 4-fold increase in maternal adverse effects should be expected if a daily dose of > 60 mg is exceeded (OR 3.78; 95% CI 1.27–11.2); in particular, there is a three-fold increase in tachycardia and an 8- to 9-fold increase in hypotension which can have serious consequences for the patient with cardiac problems. Isolated cases of myocardial infarcts have been published [63], however also of pulmonary oedema, above all, following nicardipine and also following nifedipine at daily dosages ≥ 150 mg in connection with multiple pregnancies, intramuscular corticosteroid administration and high volume replacement [63].

Calcium channel blockers do not have any significant negative effects on the child, also not on utero-foetoplacental circulation, in particular [64].

Long-term investigations on children following in-utero exposure with nifedipine did not reveal any negative effects in children aged 9–12 years [65].

According to a meta-analysis of Conde-Agudelo et al. in 2011 (26 studies, n = 2124; [66]) in 2014, a Cochrane Review [67] was published which took 38 studies (n = 3550) into account, 35 of which were with nifedipine. The significant heterogeneity and the quality of the studies, which is to some extent low, should be pointed out. In comparison to placebo/no therapy (2 studies, n = 173) there was a significant decrease in the rate of preterm delivery within 48 hours (RR 0.30; 95% CI 0.21–0.43) with an increased rate of maternal adverse effects. Calcium channel blockers demonstrated significant advantages over beta sympathomimetics: a prolongation of pregnancy by a median of 4.4 days, a decrease in the rate of preterm delivery < 32 weeks of pregnancy (RR 0.89; 95% CI 0.80–0.89), the rate of RDS (RR 0.64; 95% CI 0.48–0.86), of necrotising enterocolitis (RR 0.25; 95% CI 0.05–0.96), of intraventricular haemorrhage (RR 0.53; 95% CI 0.34–0.84) as well as admissions to the neonatal intensive care unit (RR 0.74; 95% CI 0.63–0.87). Moreover, there was a significantly lower rate of maternal adverse effects (RR 0.36; 95% CI 0.24–0.53). The studies comparing calcium channel blockers to magnesium sulphate, NO donors and indomethacin are inadequate.

In the meta-analysis from 2009 [25] delivery was able to be postponed by 48 hours with calcium channel blockers in 66% of cases and by 7 days in 62% of cases. According to the network meta-analysis from 2012 [26], calcium channel blockers are the most effective tocolytic, after indomethacin, for postponing delivery by 48 hours, with a low rate of maternal adverse effects and good neonatal outcome.

CONCLUSION FOR CLINICAL PRACTICE

- Not approved
- Simple application mode
- High tocolytic efficacy, equieffective to beta sympathomimetics and atosiban
- Low rate of maternal adverse effects
- No negative effects on the foetus/newborn, no negative long-term effects on the child
- Recommended as first-line tocolytic: NICE 2015 [18], WHO 2015 [24], French guideline 2017 [22]

An overview of the tocolytics currently used can be found in ▶ **Table 2**.

Discussion

Next to induction of labour, tocolysis is among the most common obstetric interventions. The lack of current, randomised, controlled and, above all, placebo-controlled studies is noteworthy, and despite efforts regarding innovative new developments, the stagnation in the clinical approval and availability of new tocolytics. Taking the current indications for tocolysis into account – not only to treat the symptom of "preterm contractions" but only those which have an effect on the cervix – placebo-controlled studies should, for understandable reasons, be a thing of the past. The implementation of randomised, controlled studies has become increasingly more difficult not only in Germany in recent years. The recruitment of a sufficiently high number of "study participants" has, among other things, also become more difficult, particularly in the case of off-label use of the tocolytic (only fenoterol and atosiban are approved) in light of the pregnant women's increased need/desire for information, given a rapid increase in easily accessible sources of information, resulting in uncertainty or even a refusal of the pregnant women to take part in studies.

▶ **Table 2** Overview: common tocolytics.

Tocolytics	Approved	Prolongation of pregnancy* by 48 h	Adverse effects – mother	Adverse effects – child	Mode of application	Amount of monitoring needed	Drug costs
Beta sympathomimetics (continuous i. v.)	+	++	+++	++	i. v.	high	moderate
Indomethacin	–	++(+)	(+)	+(+)	rectal/oral	low	very low
Atosiban	+	++	(+)	–	i. v.	low	high
Magnesium sulphate	–	Controversially dose-dependent	Dose-dependent ++	++	i. v.	moderate	moderate
Calcium channel blockers (nifedipine)	–	++(+)	+	(+)	oral	low	very low
NO donors	–	++	++	–	transdermal	low	low

*evaluated according to meta-analyses of Haas et al. 2009 and 2012 [25, 26]

To some extent no direct comparative studies

Preference: Nifedipine, indomethacin < 32 weeks of pregnancy (48 h) (off-label use); Atosiban: approved

The legal and bureaucratic hurdles for conducting randomised-controlled studies have grown, while at the same time, there has been a significant decrease in third-party funding for obstetrical clinical studies and the financial support of the industry for studies in which affordable drugs which have already been introduced and are established in other areas of indication are used. As our own research revealed, the manufacturer of nifedipine, for example, is not interested in conducting costly placebo-controlled studies as a precondition for approval during pregnancy in the case of such a "low-price product". It is therefore hardly surprising that, since 2016, no randomised, controlled studies on acute tocolysis with indomethacin and only one randomised, controlled study on acute tocolysis with nifedipine has been published; according to PubMed research, there have also been no new studies on atosiban since 2014.

Another problem is the inconsistent and, to some extent, controversial data on the use of tocolytics. The small amount of evidence, particularly of the serious maternal adverse effects of tocolytics and the neonatal morbidity and mortality from Cochrane and meta-analyses, primarily stems from the considerable heterogeneity (e.g. different indications, inclusion of pregnant women with advanced gestational age, no antenatal induction of lung maturation and no in-utero transfer to a perinatal centre, cumulative data for different forms of application and dosages) and the mostly moderate to low quality of the studies included as well as the inadequate statistical power for rare, serious complications or perinatal/neonatal death. For these reasons, meta-analyses have been unable to prove to date that tocolytics are able to reduce the serious neonatal morbidity and mortality. On the other hand, it should be understandable that, through prolongation of pregnancy by 48 hours which can be achieved with tocolytics in approximately 80 % of cases which enables completion of induction of foetal lung maturation and the in-utero transfer to a perinatal centre as well as the implementation of foetal neuroprotection with magnesium sulphate, especially before the 30th week of pregnancy, a decrease in the serious neonatal morbidity and mortality can be reached. Upon critical review, it is also striking that Cochrane and meta-analyses, despite including nearly identical studies, arrive at contrary statements (e.g. magnesium sulphate: Cochrane Review 2014 versus network meta-analysis 2012) and in addition, predominantly "older" studies published before the turn of the millennium influence the results in which the above-mentioned evidence-based measures were not yet standard. For example, in the Cochrane Review from 2015 [36] on the COX inhibitors which covered 20 studies, 12 studies were published prior to 2000; in the Cochrane Review by Crowther et al. [43] on magnesium sulphate as a tocolytic, 25 of 37 studies were published prior to 2000. The uncertainty of the data is also reflected by the fact that nearly unanimously at the end of current reviews and meta-analyses, there is a call for additional placebo-controlled or randomised, controlled studies which, however, are clearly not being performed.

Independent of the insufficient data and lack of evidence, particularly with regard to the improvement in neonatal outcome, and this is a priority, drug tocolysis is and remains an indispensable measure in everyday obstetrical practice. To date, there is no "ideal" tocolytic. In the authors' opinion, nifedipine and atosiban are suitable tocolytics with regard to efficacy, adverse effect profile and effects on the child. Indomethacin is a potent tocolytic with anti-inflammatory effects and a low rate of maternal adverse effects and should be justified, especially in early preterm delivery, however it is not clear whether or not indomethacin leads to an increase in foetal complications.

Beta sympathomimetics should no longer be used for tocolysis due to the high rate of maternal and foetal adverse effects and magnesium sulphate should not be used due to the controversial study results and the adverse effect profile at a high dose.

Conflict of Interest

The authors declare that they have no conflict of interest.

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