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REVIEW

Maintenance tocolysis: a reappraisal of clinical evidence

Patrick Stelzl[1] · **Sven Kehl**[1] · **Werner Rath**[2]

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Abstract

Introduction Maintenance tocolysis, mostly defined as the continuation of tocolytic treatment beyond 48 h, remains a matter of debate. There is no sufficient evidence from randomized controlled trials, that maintenance tocolysis is able to prolong pregnancy significantly and to reduce severe neonatal morbidity and mortality. Hence, it is not recommended in current guidelines. On the contrary, maintenance tocolysis is commonly used in clinical practice and subject of current clinical-scientific investigations.

Tocolytics for maintenance treatment None of the conventional tocolytics (beta-sympathomimetics, calcium-channel blockers, magnesium, cyclooxygenase inhibitors, and oxytocin receptor antagonists) have proven to be appropriate for maintenance treatment. Progesterone and 17-α-hydroxyprogesterone caproate have shown promising results in low-quality randomized trials, but not in high-quality studies.

Discussion Basically, the value of studies regarding maintenance tocolysis is limited by a considerable heterogeneity, its mostly low quality, significant differences in methodology as well as the inadequate statistical power due to the small number of women studied. So far, maintenance tocolysis is a case-by-case decision outweighing the benefits and harms of tocolytic treatment.

Keywords Threatened preterm birth · Maintenance tocolysis · Tocolytic agents · Progesterone · Efficacy · Recommendations

Introduction

The World Health Organization (WHO) defines preterm birth (PTB) as deliveries before 37 completed weeks of gestation or fewer than 259 days from the first day of a woman`s last menstrual period [1]. PTB, which occurs in 5–18% of pregnancies is the major reason for neonatal morbidity and mortality and ranks second concerning death in infancy under the age of 5 years [2–4]. Due to immatureness, PTB newborns are prone to diverse organ failures [e.g., respiratory distress syndrome (RDS), chronic lung disease (CLD), neonatal sepsis (NNS), necrotizing enterocolitis (NEC), etc.] and neurodevelopmental disabilities [e.g., cramping seizures, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVH), etc.]. Spontaneous PTB is considered a complex "syndrome", which is triggered by various pathological features, causing 70% of all PTBs [4, 5].

The prevention and treatment of PTB still remain one of the major challenges in obstetrics. While acute tocolysis over 48 h is an established "symptomatic" procedure to complete antenatal corticosteroid (ACS) administration and to enable the patient´s transfer to a tertiary perinatal centre, maintenance tocolysis is still a matter of debate. Although there exists no international uniform definition, maintenance tocolysis is mostly understood to mean the continuation of tocolytic treatment beyond 48 h. The rationale is to prolong pregnancy at least until 33 + 6 weeks of gestation to prevent severe neonatal morbidity and mortality [6–8].

It should be kept in mind that preterm contractions persist in 20–30% of pregnant women after acute tocolysis (48 h) and up to 60% experience the recurrence of preterm contractions after arrested labor following initial tocolytic therapy [9].

✉ Patrick Stelzl
patrick.stelzl@uk-erlangen.de

[1] Frauenklinik, Universitätsklinikum Erlangen, Universitätsstrasse 21-23, 91054 Erlangen, Germany

[2] Medizinische Fakultät Gynäkologie und Geburtshilfe, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Kiel, Germany

Due to the lack of evidence from randomized controlled trials (RCT) that maintenance tocolysis improves neonatal outcomes current guidelines do not recommend maintenance treatment [6, 9–12]. Nevertheless, it is commonly used in clinical practice and the subject of current clinical investigations.

Up to now, more than a dozen of different tocolytics and their modes of application have been studied. The aim of this review is to systematically reevaluate the current literature on maintenance tocolysis focusing on the different tocolytics used (Table 1).

Tocolytics for maintenance treatment

Beta-sympathomimetics

This substance class is approved for tocolysis in most countries worldwide. The most frequently used beta-sympathomimetic agent for tocolysis is terbutaline, a β_2-selective receptor agonist, which is capable of reducing uterine contractions by a cAMP-protein kinase-myosin light-chain kinase pathway [7, 13].

In Germany, fenoterol is the beta-mimetic of choice. It is administered as prolonged intravenous infusion, requiring hospitalization, immobilization, and close surveillance due to the high rate of cardiovascular and metabolic side effects, which applies to all beta-mimetics. If fenoterol is administered in a pulsatile manner, maternal side effects are decreased [14, 15].

Numerous studies have investigated the effectiveness of maintenance therapy with β-receptor agonists in different application modes. A 2006 Cochrane meta-analysis summarized the evidence of oral beta-mimetics for maintenance therapy in threatened PTB. This review included 13 RCTs and 1551 women. PTB rate < 37 weeks of gestation was not reduced in 6 trials (risk ratio (RR) 1.11, 95% confidence interval (CI) 0.91–1.35, 644 patients), 4 studies compared ritodrine with placebo/no treatment, and 2 trials compared terbutaline with placebo/no treatment. NICU admission rate was not different between treatment and placebo (RR 1.28, 95% CI 0.68–2.41, 2600 patients) or magnesium (RR 0.80, 95% CI 0.43–1.46, 137 patients). Moreover, beta-mimetics did not reveal significant benefits concerning neonatal morbidity and mortality when compared to placebo, no treatment or other tocolytic agents. Because of potential maternal side effects, e.g., tachycardia, palpitations, tachypnea, hypotension, nausea/vomiting, hyperglycemia, and lack of evidence the authors concluded that oral beta-sympathomimetics should not be used for maintenance tocolysis [16].

An interesting approach for parenteral beta-sympathomimetic maintenance tocolysis was the introduction of a subcutaneous terbutaline pump in the late 1980ies [17]. The rationale of this method is to avoid tachyphylaxis—the most important problem, when beta-mimetics are given for a longer period (> 48 h)—inconsistent drug levels and lack of compliance [18–20]. The last Cochrane review on the effectiveness of terbutaline-pump maintenance tocolysis for prevention of PTB was published in 2002 and included only 2 studies with 94 patients. Compared to saline-placebo-pump the mean difference of gestational age at delivery was 0.14 weeks lower under terbutaline-pump therapy (95% CI 1.66–1.38), but 1.4 weeks higher compared to oral terbutaline (95% CI 1.13–3.93). There was no reduction of PTB < 37 week gestation (RR 1.17, 95% CI 0.79–1.73)

Table 1 Classes and substances for maintenance tocolysis

Substance class	Administration-mode	Substance	PTB rate-reduction	Improvement of neonatal outcomes	Side-effect risk	Recommendation for maintenance tocolysis
Beta-sympathomimetics	Oral parenteral: bolus, pump	Terbutaline, ritodrine Terbutaline, fenoterol, ritodrine	No No	No No	High High	Not recommended Not recommended
Calcium-channel blockers	Oral	Nifedipine	No	No	Intermediate	Case-by-case decision
Cyclooxygenase inhibitors	Oral/rectal/vaginal	Indomethacin	No	No	Intermediate	Case-by-case decision
Magnesium	Oral/parenteral	Magnesium sulfate	No	No	Intermediate	Not recommended
Nitric oxide donors	Transdermal	Nitroglycerine	No	No	High	Not recommended
Oxytocin receptor antagonists	Parenteral	Atosiban	No	No	Low	Not recommended
Progesterone	Oral/vaginal intramuscular	Micronized progesterone 17-Alpha-hydroxyprogesterone caproate	No No	No No	Low Low	Not recommended Not recommended

and PTB < 34 week gestation (RR 0.97, 95% CI 0.51–1.84) for terbutaline pump vs. saline-placebo-pump. Furthermore, terbutaline pump neither improved compliance nor reduced neonatal morbidity and mortality [19]. An in depth review by Elliott and Morrison in 2013 [21] analyzed 46 peer-reviewed published studies [17, 18, 22–64] reporting on terbutaline-pump maintenance tocolysis for PTB treatment. It was stated, that 44 of these studies including 21,595 patients, who received subcutaneous terbutaline maintenance tocolysis, showed higher gestational age at delivery, less adverse neonatal outcomes, and a reduction of financial expenses when compared to placebo or other treatments. Nevertheless, the evidence is low, since the review included 26 level II, 17 level III studies and only one level I study. Controversially, there were 2 level I studies, which did not find any differences between terbutaline pump and placebo. Elliott and Morrison questioned the methodology of both trials, because maintenance therapy was not adequately assessed, as it is administered in daily obstetrical routine (no uterine contraction monitoring, fixed dosages of tocolytic agents regardless maternal body weight and renal function) [21].

As serious maternal complications, e.g., pulmonary edema, cardiac arrhythmias and even cases of death caused by fatal hyperkalemia had been reported, US Food and Drug Administration (FDA) addressed a warning letter to health care providers in concerns of injectable terbutaline tocolysis and recommended to avoid prolonged treatment beyond 48–72 h [19, 21]. In Germany, a similar warning letter was published by the manufacturing company addressing the use of fenoterol beyond 48 h ("Rote Hand Brief").

Thus, in synopsis with lack of supporting evidence on the effectiveness of this procedure, parenteral beta-sympathomimetic maintenance tocolysis should no longer be used in obstetrical practice.

Calcium-channel inhibitors

The most commonly used and best investigated calcium-channel inhibitor is nifedipine, which was already described in 1980 to be a tocolytic drug with low maternal side effects [65, 66].

Its mechanism of action—supported by in vitro experiments—is the inhibition of an extracellular Ca^{2+} shift into myometrial cells, following relaxation of smooth muscles [66, 67]. Nifedipine is not approved for tocolytic therapy. Nevertheless, it is the most commonly used tocolytic agent in Germany for acute tocolysis [68]. While there is mounting evidence on its efficacy for acute tocolysis, maintenance treatment with nifedipine is questionable [69].

A 2013 Cochrane meta-analysis [70] including 6 trials with low risk of bias, evaluated nifedipine maintenance tocolysis within 794 study subjects. Neither a reduction of PTB incidence (RR 0.97, 95% CI 0.87–1.09, 681 patients) nor of neonatal mortality (RR 0.75, 95% CI 0.05–11.76, 133 patients) was found with nifedipine maintenance therapy compared to placebo/no treatment. Although a significant prolongation of pregnancy was achieved by a mean of 5.35 days (95% CI 0.49–10.21, 275 patients) within delivery subgroups < 34 and < 28 week gestation, there was no difference in giving birth within 7 days or gestational age at delivery when using nifedipine for maintenance treatment. Moreover, there were no benefits of nifedipine in the reduction of neonatal morbidity [70].

The Dutch multicenter, double-blind, placebo-controlled APOSTEL-II trial [69] included 406 patients between 26 + 0 and 32 + 2 weeks of gestation after arrested labor and completion of ACS administration. A total of 201 women were randomized to maintenance tocolysis with oral slow-release nifedipine (80 mg/day) and 205 to placebo for 12 days. Patients, investigators, clinicians, and nurses were blinded for assigned treatment. Pediatric charts were followed up until 6 months after birth. Composite adverse perinatal outcome (perinatal death, CLD, NNS, IVH > grade 2, PVL > grade 1, NEC) did not differ statistically significant between both groups (11.9% nifedipine, 95% CI 7.5–16.4% vs. 13.7% placebo, 95% CI 9.0–18.4%). Moreover, there were no differences in mean gestational age at delivery (34.1 weeks, standard deviation (SD) 4.0 vs. 34.2 weeks, SD 4.0), mean birth weight (2047 g, 95% CI 1950–2149 g vs. 2035 g, 95% CI 1938–2139 g), NICU admission rate (40.8% vs. 39.7%, RR 0.99, 95% CI 0.78–1.3), length of NICU stay (10 days for both groups, incidence rate ratio (IRR) 0.92, 95% CI 0.70–1.2), breathing aid (2 days vs. 3 days, IRR 0.74, 95% CI 0.43–1.3), and total hospital admission (23 days for both groups, IRR 0.97, 95% CI 0.82–1.1). In addition, subgroup analyses of patients randomized between 26 + 0–27 + 6, 28 + 0–29 + 6 and 30 + 0–32 + 1 week gestation showed no advantages of nifedipine maintenance tocolysis regarding perinatal mortality, composite adverse perinatal outcome, gestational age at delivery, and birth weight [69]. A later study on the APOSTEL-II data by De Lange et al. [71] analyzed the length of hospital stay of all subjects, who were admitted with threatened PTB < 32 week gestation to participating perinatal centers. Interestingly, mean length of hospital stay was significantly different before the start of the trial (9.3 days, 95% CI 8.98–9.62) compared to recruitment period (8.4 days, 95% CI 8.05–8.83) and time after the trial (8.1 days, 95% CI 7.64–8.61). This reduction in hospital stay was explained by the psychological upheaval of patients through "treatment" [8, 71].

The New Zealand NIFTY-trial [72], another multicenter, double-blind, placebo-controlled study included 60 patients in threatened PTB between 24 + 0–33 + 6 week gestation with positive fetal fibronectin (fFN) testing. A total of 29 patients were randomized to nifedipine (20 mg/8 h up to a

maximum of 160 mg/24 h) and 31 women to placebo. The dosage of acute and maintenance tocolysis was similar, and medication was continued until 36 + 6 weeks of gestation. Prolongation of pregnancy > 7 days was achieved in 76% of patients with nifedipine and 81% with placebo (RR 0.94, 95% CI 0.72–1.2). Mean gestational age at delivery was 0.7 weeks higher in the placebo group (36.1 weeks, SD 5.1 vs. 36.8 weeks, SD 3.6). Moreover, neonates of the nifedipine group showed a higher rate of NICU admissions (27.6% vs. 22.6%, RR 1.2, 95% CI 0.51–2.9), a mean of 11 days longer NICU stays (27 days, interquartile range (IQR) 24–41 vs. 16 days, IQR 8–37) and one case of perinatal death (RR 3.2, 95% CI 0.14–75) [72].

Roos et al. [73] stratified women with threatened PTB into a high-risk and low-risk-population using fFN testing (fFN positive or fFN negative), cervical length (CL) measurements (CL < 15 mm or CL ≥ 15 mm) and evaluated the effectiveness of nifedipine maintenance tocolysis in both subgroups. Neither fFN testing nor sonographic CL evaluation changed the effect of maintenance therapy in regards of PTB reduction [73].

A 2016 systematic review by van Vliet et al. [74] performed an individual patient data meta-analysis including 6 randomized controlled trials ($n = 787$ patients between 24 + 0–36 + 6 weeks of gestation, $n = 390$ for nifedipine, $n = 397$ for placebo/no treatment) and evaluated the efficacy of nifedipine maintenance tocolysis on prolongation of pregnancy and neonatal outcomes. No significant differences regarding the incidence of perinatal death (RR 1.36, 95% CI 0.35–5.33), IVH ≥ grade II (RR 0.65, 95% CI 0.16–2.67), NEC (RR 1.15, 95% CI 0.50–2.65), RDS (RR 0.98, 95% CI 0.51–1.85), and prolongation of pregnancy (hazard ratio (HR) 0.74, 95% CI 0.55–1.01) could be demonstrated [74].

A more recent Indian study by Aggarwal et al. [75] included 50 women between 26 + 0–33 + 6 weeks of gestation after an episode of threatened PTB, who were randomized to a nifedipine intervention arm ($n = 25$) for 12 days or up to ≥ 33 + 6 week gestation and to a no treatment control arm (n = 25). The delivery rate at term was 20% higher (28% nifedipine vs. 8% control group), pregnancy prolongation was 6 days longer (20 days, IQR 2.5–51 vs. 14 days, IQR 1–27.5), and median NICU stay was 1.5 days shorter (4.0 days, IQR 2–10 vs. 5.5 days, IQR 2.25–12) within the treatment arm. However, these findings did not reach statistical significance. Interestingly, a statistically significant mean gain in birth weight of 386 g (2266 g, SD 726 g vs. 1880 g, SD 590 g) was observed in the nifedipine group. Finally, there were no beneficial effects of nifedipine maintenance tocolysis regarding pregnancy prolongation and reduction of NICU stays in advanced threatened PTB with a mean cervical dilatation of 2.5 cm [75].

Case reports have shown severe maternal and fetal complications such as severe hypotension, tachycardia, pulmonary edema, and even fetal death associated with nifedipine maintenance tocolysis [21, 76–78].

In conclusion, as there is insufficient evidence that nifedipine maintenance tocolysis reduces the rate of preterm birth significantly and improves neonatal outcomes, it cannot be recommended for clinical practice.

Cyclooxygenase inhibitors

The nonspecific cyclooxygenase (COX) inhibitor indomethacin is the most frequently used representative of this substance class. It has the potential to interfere with the inflammation-mediated pathway of PTB by inhibiting the synthesis of arachidonic acid to prostaglandins, which lead to uterine contractions and cervical ripening/dilatation [79]. Indomethacin may be the preferred tocolytic agent at lower gestational ages (< 30 weeks of gestation) when intrauterine inflammation/infection is suspected [80]. Recently, it has been hypothesized that COX expression/activity is enhanced with the beginning of human parturition, which might be the physiological explanation for the tocolytic effectiveness of COX inhibitors. However, a systematic review including 44 studies did not reveal evidence that this mechanism of action is involved in the commencement of PTB supporting COX-focused tocolysis [81].

According to a network meta-analysis 2012 [82], indomethacin is the most effective tocolytic agent for prolonging pregnancy by 48 h compared to placebo [82].

However, COX inhibitors rapidly cross the placental barrier and lead to the inhibition of fetal prostaglandin synthesis resulting among others in a decrease of renal blood flow and oligohydramnios as well as in premature closure of the ductus arteriosus Botalli [79].

Consequently, the use of indomethacin for tocolysis should be restricted to 48 h and to < 32 + 0 weeks of gestation [6].

There are no randomized controlled trials on the use of indomethacin for maintenance treatment. A retrospective chart review by Dutta et al. [83], including 73 women with threatened PTB < 32 weeks of gestation, compared perinatal outcomes after a prolonged course > 48 h ($n = 32$) vs. a standard course ≤ 48 h ($n = 41$) of indomethacin. In the prolonged group, the interval from hospital admission to delivery was a mean of 1.4 weeks longer compared to the standard group (1.8 weeks, 95% CI 1.1–3 vs. 0.4 weeks, 95% CI 0.1–0.8) and there was no significant increase in composite adverse neonatal outcomes after prolonged treatment [83].

Because of the lack of evidence and concerns regarding fetal side effects, indomethacin maintenance tocolysis cannot be recommended. It may be an option in exceptional cases, particularly in women with threatened very PTB [83]. According to the Recommendations from the European Association of Perinatal Medicine [2], indomethacin

tocolysis may be repeated, if necessary after a 5-day break. During indomethacin treatment, the pulmonary trunk blood flow should be checked and the severity of regurgitation at the level of the tricuspid valve should be assessed at least once a week. The volume of amniotic fluid should be measured two times a week [2].

Magnesium

The basis of magnesium sulfate tocolytic action is still unclear, although it is presumed to involve competition with calcium for entry into muscle cells through voltage-gated calcium channels or competitively binds to calcium storage sites in the endoplasmatic reticulum, thus inhibiting the cellular influx of calcium necessary for smooth muscle contraction [84].

The evidence for magnesium sulfate as a tocolytic agent is controversial [68]. Data on magnesium sulfate maintenance tocolysis are insufficient.

Martin et al. [85] compared the tocolytic efficacy of oral magnesium gluconate with that of ritodrine hydrochloride in 50 patients after arrested labor; 25 women received 1 g oral magnesium, the others 10 mg of ritodrine every 2–4 h. Pregnancy prolongation was similar in both groups [85].

A further study by Martin et al. [86] within a subgroup of 31 women at high PTB risk receiving home uterine contraction monitoring, found no significant difference in prolonging pregnancy between 1 g magnesium gluconate 4 times/day vs. placebo [86].

The trial by Rust et al. [87] comparing oral magnesium chloride to placebo for maintenance tocolysis showed no significant differences between both groups regarding the rate of PTB < 37 weeks of gestation, the mean birth weight and the rate of NICU admissions [21, 87].

In the trial of Ridgway et al. [88], 23 patients received 200 mg magnesium oxide and 27 patients 2.5–5 mg terbualine sulfate orally for maintenance treatment every 3–4 h after arrested labor until 36 week gestation. There were no significant differences in the rate of PTB < 36 weeks of gestation (18.5 vs. 17.4%, RR 0.94, 95% CI 0.29–3.09) [88]. These trials on oral magnesium use for maintenance tocolysis were published more than 25 years ago and are limited among others by the small number of patients included.

A Cochrane Review by Han et al. [84] including 4 randomized controlled trials with 422 women did not find any significant differences between magnesium maintenance therapy (neither oral nor parenteral administration) and placebo in the prevention of PTB < 37 weeks of gestation or in the number of perinatal deaths [84]. Again, the number of patients included was too small to deduce clinical recommendations.

In summary, because of the lack of evidence magnesium cannot be recommended for maintenance tocolysis.

Nitric oxide (NO) donors

Nitroglycerine, which is a powerful smooth muscle relaxant, has been off-label used for tocolysis mostly as transdermal patch (10 mg/24 h).

A Cochrane Review 2014 [89] includes only trials with NO donors for acute tocolysis concluding that there is insufficient evidence to advocate NO donors for tocolytic treatment [89].

There is one randomized study [90], including 132 patients with threatened PTB, which compared transdermal nitroglycerine ($n = 67$) administered up to 5 days after initial tocolysis with intravenous ritodrine ($n = 62$) applied for a maximum of 3 days. Recurrent episodes of uterine contractions were also treated by the same regime as randomized. Nitroglycerine was superior to ritodrine regarding the delivery rate > 34 and 37 weeks of gestation, birth weight > 2500 g, and the necessity of NICU admissions [90]. However, the study design has to be labelled as unsuitable in terms of maintenance treatment.

In accordance with current guidelines, NO donors are neither recommended for acute nor maintenance tocolysis [9–12, 68, 91].

Oxytocin receptor antagonists

Atosiban, a synthetic oxytocin receptor antagonist, acts by competing with oxytocin for receptors in the myometrium and potentially in the decidua and fetal membranes as well. It inhibits oxytocin-stimulated inositol triphosphate production and subsequent intracellular shift of Ca^{2+} from the sarcoplasmatic reticulum into the cytoplasm [92, 93]. Atosiban is approved for acute tocolysis, and repeated cycles of treatment are possible.

A Cochrane Review from 2013 [94] includes only one double-blind, placebo-controlled trial [95]; 503 patients who responded to acute tocolytic treatment with atosiban received either atosiban ($n = 252$) or placebo ($n = 251$). Maintenance treatment was performed using a subcutaneous infusion pump (30 µg/min) until the 36 + 6 weeks of gestation. Patients with recurrent episodes of contractions received a rescue therapy with intravenous atosiban until "uterine quiescence" was obtained followed by continuation of the study medication. Atosiban led to a significant prolongation of the interval between the beginning of maintenance therapy to the recurrence of contractions (up to 5 days compared to placebo). However, it did not reduce preterm birth rates < 37 (RR 0.89, 95% CI 0.71–1.12), < 32 (RR 0.85, 95% CI 0.47–1.55) or < 28 weeks of gestation (RR 0.75, 95% CI 0.28–2.01). No differences were found in neonatal morbidity or in perinatal mortality [94, 95].

In conclusion, there is not sufficient evidence to support maintenance treatment with oxytocin receptor antagonists.

Progesterone

Numerous experimental and clinical studies have shown that natural progesterone exerts an inhibitory effect on uterine contractility through various mechanisms and may sensitize the myometrium for tocolytics [96–101]. A recent review highlighted the evidence of progesterone for tocolysis and maintenance treatment [102].

In 2015, two meta-analyses [103, 104] (Table 2) on the use of vaginal progesterone (200–400 mg/day) and intramuscular 17-alpha-hydroxyprogesterone caproate (17-OHPC, 250 mg/week) vs. placebo/no treatment for maintenance treatment were published. In the meta-analysis of Suhag et al. [103] (Table 2), including 5 randomized controlled trials (RCT) and 441 patients, vaginal progesterone led to a significant decrease in the rate of preterm birth < 37 + 0 week gestation (42 vs. 58%, RR 0.71, 95% CI 0.57–0.90) in 3 studies, a significant prolongation of the latency period until birth (mean difference 13.8 days) in 4 studies, a higher gestational age at birth (mean difference 1.3 weeks), a significantly lower frequency of the recurrence of contractions (24 vs. 48%, RR 0.51, 95% CI 0.31–0.84) as well as a lower rate of NNS (2 vs. 7%, RR 0.34, 95% CI 0.12–0.98) in 4 studies. Despite promising results in individual studies, the meta-analysis came to the conclusion that based on the considerable heterogeneity between the studies, their low quality, and the inadequate statistical power, no recommendation for the use of vaginal progesterone as maintenance treatment can be made [103].

The meta-analysis of Saccone et al. [104] (Table 2), including 5 RCTs with 426 patients, compared the intramuscular administration of 17-OHPC with placebo/no treatment. Although a longer latency period until birth (mean difference 8.4 days) was found, there were no significant differences in the rate of preterm birth < 37 weeks of gestation (42 vs. 51%, RR 0.78, 95% CI 0.50–1.22) and < 34 weeks of gestation (25 vs. 34%, RR 0.60, 95% CI 0.28–1.12), the frequency of the recurrence of contractions and the rate of neonatal complications. The authors concluded that the intramuscular application of 17-OHPC is promising [104]. However, it cannot be recommended for routine clinical practice due to the insufficient data.

The meta-analysis of Eke et al. 2016 [105] (Table 2), including 4 RCTs and 362 pregnant women, compared vaginal/oral progesterone, and intramuscular 17-OHPC with placebo/no treatment for maintenance tocolysis after arrested labor. No significant differences were seen between the study groups regarding the latency period from randomization until delivery and the rates of preterm birth < 37 and < 34 weeks of gestation [105].

A further meta-analysis by Ding et al. [106] evaluated 10 RCTs, of which 5 used oral nifedipine and 5 oral/vaginal progesterone for maintenance treatment. In comparison with placebo/no treatment, a significant prolongation of pregnancy (on average by 1.6 weeks), a reduction in the rate of preterm birth < 37 weeks of gestation (RR 0.63; 95% CI 0.47–0.83), and a significant increase in mean birth weights (by 318 g on average) were achieved when using progesterone, while maintenance tocolysis with nifedipine compared to placebo/no treatment did not result in any significant prolongation of pregnancy. The authors concluded that progesterone, but not nifedipine is beneficial for maintenance treatment after arrested labor [106].

The randomized, placebo-controlled double-blind trial by Palacio et al. (PROMISE-TRIAL [107]) (Table 2) included 248 pregnant women. After arrest of labor by acute tocolysis, the patients were discharged from the hospital with a cervical length < 25 mm; 126 women received vaginal progesterone (200 mg/day) and 132 women placebo until 36 + 6 weeks of gestation or until delivery. The

Table 2 Meta-analyses of maintenance tocolysis with Progesterone/17-OHPC vs. placebo/no treatment after acute tocolysis

Author	Studies	*n*	P/17-OHPC (number of studies)	PTB < 37 + 0 week gestation (%) RR (95% CI)	PTB < 34 + 0 week gestation (%) RR (95% CI)	Pregnancy prolongation (days, mean difference range)
Saccone et al. 2015	5	426	17-OHPC i.m	42 vs. 51 0.78 (0.5–1.2)	25 vs. 34 0.60 (0.28–1.12)	8.4 (S) (3.2–13.5)
Suhag et al. 2015	5	441	Vaginal P	42 vs. 58 (S) 0.71 (0.57–0.9)	N/A	13.8 (S) (4.0–23.6)
Palaccio et al. 2016	16	1917	P (12) 17-OHPC (4)	38.2 vs. 44.3 (S) 0.79 (0.65–0.97)	15.6 vs. 18.3 0.77 (0.53–1.12)	8.1 (S) (3.8–12.4)
Eke et al. 2016	4	362	P (2) 17-OHPC (2)	N/A RR 0.8 (0.58–1.1)	N/A RR 0.69 (0.4–1.2)	2.4 (− 1.5 to 6.3)
Wood et al. 2017	15	1742	P (11) 17-OHPC (4)	N/A OR 0.77 (S) (0.62–0.96)	N/A OR 0.80 (0.60–1.08)	9.1 (S) (3.7–14.5)

n number of patients, *P* progesterone, *17-OHPC* 17-alpha-hydroxyprogesterone caproate, *RR* relative risk, *CI* confidence interval, *i.m.* intramuscular, *(S)* statistically significant ($p < 0.05$), *N/A* non applicable, *OR* odds ratio

Data from Rath et Kuon 2019 [102]

study was terminated prematurely due to financial problems. There were no significant differences regarding the rate of preterm birth < 34 (7.1 vs. 7.6%) and < 37 weeks of gestation (28.6 vs. 22%) as well as in the mean gestational age at birth [107].

A subsequent meta-analysis by the same group [108], including 16 RCTs and 1917 patients compared vaginally or orally administered progesterone (12 trials, dose: 200–400 mg/day) and intramuscular 17-OHPC (4 trials, dose: 250–500 mg/week) to placebo/no treatment.

The use of 17-OHPC led to a significant decrease in the rate of preterm birth < 37 weeks of gestation (44.3 vs. 38.2%, RR 0.79; 95% CI 0.65–0.97), but not < 34 weeks of gestation (15.6 vs. 18.3%; RR 0.77; 95% CI 0.53–1.12). When evaluating only high-quality studies ($n = 5$) no significant differences were seen in all of the outcome criteria. The authors concluded, that based on the lack of qualified studies and the significant heterogeneity between studies, the data are insufficient to support the use of progesterone and 17-OHPC for maintenance treatment [108].

A randomized, controlled multicenter trial from Italy [109] with 254 patients between 22 + 0 and 31 + 6 weeks of gestation and a cervical length < 25 mm compared the vaginal application of 200 mg/day ($n = 84$) and 341 mg 17-OHPC/week administered intramuscularly ($n = 87$) to no treatment for maintenance tocolysis until the 36 + 6 weeks of gestation. The recruitment of 160 women/study arm was planned. However, after an interim-analysis the study was stopped prematurely by an independent monitoring committee, because no significant differences were found between treatment groups and controls regarding primary outcome criteria (rate of preterm birth < 37 and < 35 weeks of gestation) [109].

A further RCT compared vaginal progesterone (200 mg/day) to placebo for maintenance treatment in patients 12 h after arrested labor and positive fibronectin testing [110]. This study, planning to recruit 60 women/study arm, was also terminated prematurely due to inadequate recruitment and the lack of patients' compliance. The following meta-analysis by the same investigators [110] (Table 2) evaluated 15 RCTs and 1742 patients comparing intramuscular 17-OHPC ($n = 5$), oral progesterone ($n = 2$) and vaginal progesterone ($n = 8$) to placebo/no treatment; 5 studies were classified as "high" and 10 as low quality using the Jaddad criteria [110].

In accordance to the meta-analysis of Palacio et al. [108] a significant reduction in the rate of preterm birth could only be demonstrated in the low quality but not in the high-quality studies [110].

Following the authors' conclusion neither vaginal/oral progesterone nor intramuscular 17-OHPC as maintenance treatment are appropriate for clinical practice.

Discussion

Maintenance tocolysis, mostly defined as the continuation of tocolytic treatment beyond 48 h, is still a controversial issue. Due to the lack of evidence from qualified RCTs, that maintenance treatment significantly prolongs pregnancy and improves neonatal outcomes, it is not recommended by current guidelines [2, 6, 9–12]. On the contrary, maintenance tocolysis is commonly used in many countries [111–117]. However, this assumption is based on mostly "historical" surveys from practitioners or from retrospective observations of tocolytic management in women with threatened PTB [118].

Basically, the obstetrician has to acknowledge the woman´s fear of delivering a preterm baby and her fear of neonatal complications and even neonatal death.

Many surveys have been published, reflecting the common practice of maintenance tocolysis in different countries. In a mail-based survey among 827 members of the Society for Maternal–Fetal Medicine (response rate 46%) 29% would suggest maintenance tocolysis [111]. In the survey of the Royal Australian and New Zealand College of Obstetricians and Gynecologists including 813 participants (18.9% response rate for Australia; 27.1% response rate for New Zealand) 34% of the members stated to use maintenance tocolysis in obstetrical practice [113]. A 2014 French declarative practice survey reported, that 50% of French maternity hospitals would prescribe maintenance tocolysis [115]. Between two Canadian cross-sectional surveys in 1997–1998 ($n = 1313$; 46.4% response rate) and 2004 ($n = 1508$; 43.4% response rate) a decrease of 10.4% maintenance treatment recommendations was observed (20% in 1997–1998 vs. 9.6% in 2004) [116]. The EVAPRIMA study, a cross-sectional French practice survey including 107 hospitals and 734 admissions with threatened PTB, reported a maintenance tocolysis rate of 59.8% in patients without PPROM [114]. A further evaluation of the EVAPRIMA data revealed a "maternity unit effect". Maintenance treatment was more common in maternity units of low- and intermediate-risk pregnancies, and smaller obstetrical divisions in certain provinces of France [117]. A more recent prospective multicenter registry study [112] including 10 Austrian maternity units and totally 309 cases reported on repeated tocolysis in 41.7% of women with threatened PTB, of which 40.8% received maintenance therapy during the first course of tocolytic treatment [112].

The question, which tocolytic agent may be appropriate for maintenance treatment is still unanswered.

Due to the loss of efficacy through tachyphylaxis orally or parenterally applied beta-sympathomimetics are not suitable for maintenance treatment.

According to a 2016 meta-analysis [74] oral nifedipine use beyond 48 h is not more effective in prolonging pregnancy compared with placebo and does not lead to any reduction in perinatal and neonatal morbidity [74].

There exists no RCT on the use of COX inhibitors for maintenance treatment and according to current recommendations indomethacin should only be given for 48 h until 32 weeks of gestation [6, 83].

Oral or intravenous magnesium was shown to be insufficient for maintenance treatment in mostly "historical" studies, which was confirmed by a Cochrane Review [84].

Data on the use of oxytocin receptor antagonists for maintenance treatment are also insufficient, since there exists only one RCT [95].

NO donors have never been investigated for maintenance treatment in RCTs.

The data on the use of native progesterone and intramuscular 17-OHPC for maintenance treatment are conflicting. While RCTs of low quality have shown promising results, studies of high quality did not reveal any significant differences compared to placebo/no treatment regarding the rate of preterm birth < 37 and < 34 weeks of gestation, the latency period until delivery and neonatal outcomes [102].

Several shortcomings become overt when evaluating the literature critically. Major problems are the lack of placebo-controlled randomized trials and the low quality of published studies, which applies to most of the tocolytic agents. Another problem is the high degree of heterogeneity between the studies, which limits the validity of pooled data in meta-analyses. Crucial points in this context, which make the interpretation and comparability of studies difficult, especially, are different inclusion and exclusion criteria with the risk of a selection bias.

In addition, there are significant methodological differences between the studies (e.g., nature and quality of randomization, placebo-controlled trials vs. no treatment, selection of primary outcome criteria) as well as in the approach (e.g., mode of application, differences in dosage and application frequency). A further problem is the insufficient number of cases in studies associated with inadequate statistical power.

Meta-analyses have failed to prove that maintenance treatment is able to reduce severe neonatal morbidity and mortality. This may be due to the low prevalence of serious neonatal complications and neonatal deaths. It requires high numbers of cases to demonstrate a significant reduction in severe neonatal morbidity and mortality.

Furthermore, well-designed randomized placebo-controlled trials are necessary to evaluate the clinical value of maintenance treatment.

So far, maintenance tocolysis in daily obstetrical practice remains a case-by-case decision outweighing the benefits and harms of tocolytic medication and acknowledging the woman's wish to prolong pregnancy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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