Thieme

Progesterone – Effective for Tocolysis and Maintenance Treatment After Arrested Preterm Labour?

Critical Analysis of the Evidence

Progesteron – effektiv zur Wehenhemmung und zur Erhaltungstherapie nach Wehenstopp?

Kritische Analyse der Evidenz

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ABSTRACT

Numerous experimental studies indicate that natural progesterone, through various mechanisms, exerts an inhibitory effect on uterine contractility and sensitises the myometrium for tocolytics. It was therefore appropriate to investigate the possible benefits of oral/vaginal progesterone and the synthetic progesterone derivative 17-α-hydroxyprogesterone caproate, applied intramuscularly, in clinical studies on primary tocolysis, additively to established tocolytics ("adjunctive tocolysis") and as maintenance treatment after successful tocolysis in cases of threatened preterm birth. Three studies with a small number of cases do not yield any sufficient evidence for recommending progesterone/17-α-hydroxyprogesterone caproate as primary tocolysis in women with preterm labour. There is also no evidence that progesterone or 17-α-hydroxyprogesterone caproate combined with commonly used tocolytics leads to a prolongation of pregnancy and a significant decrease in the rate of preterm birth. The data on the use of progesterone as maintenance treatment is controversial. While randomised, controlled studies with low quality showed promising results, studies with high quality did not reveal any significant differences with regard to the rate of preterm birth < 37 weeks of gestation, the latency period until delivery and in the neonatal outcome between progesterone/17-α-hydroxyprogesterone caproate and placebo or no treatment. Significant differences in the methodology, the inclusion and outcome criteria, the mode of application and the dosages of the substances as well as the inadequate statistical power as a result of low numbers of cases make interpretation and comparability of the studies difficult. Therefore, well-designed randomised, placebo-controlled, double-blind studies with uniform primary outcome criteria are needed in order to clarify whether progesterone and via which route of administration and at which dosage is of clinical benefit for patients with manifest preterm contractions and as maintenance treatment after arrested preterm labour.

ZUSAMMENFASSUNG

Zahlreiche experimentelle Studien weisen darauf hin, dass natürliches Progesteron über verschiedene Mechanismen einen inhibitorischen Effekt auf die uterine Kontraktilität ausübt und das Myometrium für Tokolytika sensibilisiert. Daher war es sinnvoll, die möglichen Vorteile von oralem/vaginalem Progesteron und des intramuskulär applizierten synthetischen Progesteronderivats 17-α-Hydroxyprogesteroncaproat in klinischen Studien zur primären Tokolyse, additiv zu etablierten Tokolytika („adjunktive Tokolyse“) und zur Erhaltungstherapie nach erfolgreicher Wehenhemmung bei drohender Frühgeburt zu untersuchen. Aus drei Studien mit kleiner Fallzahl ergibt sich keine ausreichende Evidenz, Progesteron/17-α-Hydroxyprogesteroncaproat zur primären Tokolyse bei Frauen mit vorzeitiger Wehentätigkeit zu empfehlen. Es gibt ebenfalls keine Evidenz dafür, dass Progesteron oder 17-α-Hydroxyprogesteroncaproat in Kombination mit gebräuchlichen Tokolytika zu einer Verlängerung der Schwangerschaft und zu einer signifikanten Senkung der Rate an Frühgeburten führt. Die Datenlage zur Anwendung von Progesteron zur Erhaltungstherapie ist kontrovers. Während randomisierte, kontrollierte Studien mit niedriger Qualität vielversprechende Ergebnisse zeigten, ergaben sich aus Studien mit hoher Qualität keine signifikanten Unterschiede hinsichtlich der Frühgeburtenrate < 37 SSW, der Latenzzeit bis zur Geburt und im neonatalen Outcome zwischen Progesteron/17-α-Hydroxyprogesteroncaproat und Placebo oder keiner Behandlung. Erhebliche Unterschiede in der Methodologie, den Einschluss- und Zielkriterien, dem Applikationsmodus und den Dosierungen der Substanzen sowie die inadäquate statistische Power infolge niedriger Fallzahlen macht eine Interpretation und Vergleichbarkeit der Studien schwierig. Daher sind gut konzipierte, randomisierte, placebokontrollierte Doppelblindstudien mit einheitlichen primären Zielkriterien notwendig, um zu klären, ob Progesteron und auf welchem Applikationsweg und mit welcher Dosierung bei Patientinnen mit manifesten vorzeitigen Wehen und zur Erhaltungstherapie nach initialer Wehenhemmung von klinischem Nutzen ist.

Introduction

The work of A. Csapo in 1956, which indicated that progesterone inhibits the activity of the myometrium while prostaglandins promote it, was groundbreaking for the clinical use of progesterone [1]. In 1960, Fuchs and Stakemann [2] used high doses of progesterone applied intramuscularly in comparison to placebo for the treatment of preterm labour. They did not find any significant differences between the two investigation groups with regard to a prolongation of pregnancy with, however, an inadequate statistical power of the study.

With the development of effective tocolytics (e.g. beta sympathomimetics), the focus of interest shifted away from progesterone for the inhibition of preterm labour, and it was not until 1986 that Erny et al. [3] once again used oral progesterone for the treatment of preterm labour within the scope of a placebo-controlled study (see below).

In the past 20 years, experimental and clinical studies have greatly expanded our knowledge on the mode of action of progesterone on myometrium, placenta, membranes and cervix (overviews in [4, 5]).

In the foreground of these investigations was the inhibition of myometrial contractions, among others, by a progesterone-mediated expression of connexin 43 resulting in reduced formation of gap junctions (intramyometrial cellular bridges which promote the propagation of contractions in the uterus), the modulation of the activity of calcium channels with direct inhibition of the contractile activity, as well as the decrease of oxytocin receptors in the myometrium. Progesterone binds to progesterone receptors and modulates the expression of specific target genes. Coactivators of the progesterone receptors (the cAMP-dependent protein kinase binding protein, among others) and the histone acetylation of myometrial cells are changed by progesterone and thus the contractility of the myometrium and the expression of proinflammatory cytokines are affected. Progesterone leads to a reduction in proinflammatory cytokines (such as TNFα, interleukin-2) through the production of PIBF (progesterone induced blocking factor), among others, and inhibits the synthesis of contraction-inducing and cervix-ripening prostaglandins.

In membranes, progesterone reduces apoptosis through the decreased production of proinflammatory cytokines and thus counteracts premature rupture of membranes.

In animal models, it was able to be shown that progesterone inhibits metalloproteinase-mediated collagen breakdown by inhibiting the synthesis of proinflammatory cytokines and thus prevents premature ripening of the cervix.

In vitro and animal experimental studies have shown that progesterone is able to increase the myometrial efficiency of nifedipine and indomethacin in comparison to the use of these tocolytics alone [6] and to sensitise the myometrium for beta sympathomimetics [7]. Using uterine electromyography, it was able to be demonstrated recently in a placebo-controlled study (n = 30) that the vaginal administration of 400 mg progesterone 48 hours after acute tocolysis significantly decreases the speed of propagation of electrical signals within the myometrium over 2 hours post-application in comparison to placebo and inhibits the myometrial activity [8].

These experimental and clinical investigations were the basis for using progesterone and 17-α-hydroxyprogesterone caproate (17-OHPC) within the scope of tocolysis as well, following promising results on the primary and secondary prevention of preterm birth [9, 10]. This involved use for primary tocolysis (initially and exclusively in the case of preterm labour), for adjunctive tocolysis (in combination with an established tocolytic) and as maintenance tocolysis/maintenance treatment following successful primary tocolysis.

Progesterone for Primary Tocolysis

After the first randomised placebo-controlled study by Fuchs and Stakemann in 1960 [2], the efficacy of treatment with 400 mg oral progesterone in addition to bed rest was investigated in a prospective, placebo-controlled study on pregnant women with preterm labour (n = 58). This yielded a significant reduction in contractions (tocographically measured decrease in contractions within 1 h after start of treatment) after progesterone in 80 % of cases versus 42 % in the placebo group [3]. Points of criticism regarding this study were the overall inadequate number of pregnant women, a lack of data on the prolongation of the pregnancy and neonatal outcome, as well as the inclusion of pregnant women with premature rupture of membranes.

In another randomised study by Chawanpaiboon et al. in 2010 [11], the tocolytic efficacy of nifedipine (20 mg orally initially, after 30 and 60 min, followed by 20 mg nifedipine retard every 12 h), 17-OHPC 250 mg intramuscularly/week or bed rest for the treatment of preterm labour between the 28th–35th week of gestation with a cervical length of < 30 mm was comparatively investigated in 50 pregnant women in each case. The greatest tocolytic efficacy (stopping contractions within 12 h) was demonstrated by nifedipine with a rate of 80 %, followed by 17-OHPC with 66 % and bed rest with 64 %; this was also the case for the most rapid onset of action (nifedipine 2.9 ± 2.1 h, 17-OHPC 4.6 ± 3.2 h, bed rest 6.2 ± 3.8 h); no significant differences were seen with regard to the mean gestational age at birth and the average birth weight. However, the statistical power of this study was inadequate. According to current findings, bed rest is no longer a suitable method for the treatment of pregnant women with threatened preterm birth.

Adjunctive Tocolysis

The prospective, placebo-controlled study by Noblot et al. in 1991 [12] investigated the efficacy of treatment – as a supplement to ridodrine – with oral progesterone (400 mg every 6 h in the first 24 h, 400 mg every 8 h in the next 24 h, followed by 300 mg every 8 h as maintenance dose) or placebo in 44 pregnant women with regular contractions (every 10 min) after 1 h bed rest, persistent contractions or contractions affecting the cervix between the 30th–33rd week of gestation. This did not reveal any significant differences between progesterone in comparison to placebo with regard to the rate of preterm birth < 37 weeks of gestation (27.2 vs. 36.4 %), however in the progesterone group, a significantly lower overall dose of the beta mimetic was necessary (245 vs. 875 mg, p < 0.01). Moreover, the length of hospitalisation of the pregnant patients was significantly shorter after progesterone (13.6 vs. 17.8 days, p < 0.05). However, the small number of pregnant patients and the inclusion of patients with multiple pregnancies and premature rupture of membranes limit the value of this study.

In another prospective randomised study which recruited 83 pregnant women between the 24th–34th week of gestation with regular preterm labour (> 6 contractions/30 min) and digitally verified cervical shortening, 200 mg progesterone/day vaginally until delivery or the 36 + 6 week of gestation was administered adjunctively to standard tocolysis with ritodrine intravenously (dose adjustment every 20 min until maximum dose of 0.35 mg/min until cessation of contractions or the appearance of serious maternal side effects with the need to discontinue treatment) [13]. A significant prolongation of the latency period until delivery (32.1 ± 17.8 vs. 21.2 ± 16.3 days) and a significant increase in birth weight (2983 ± 698 vs. 2585 ± 747 g) was able to be achieved by the additional administration of progesterone, however no significant reduction in the rate of preterm birth < 37 weeks of gestation (50 vs. 65 %). The small number of cases (n = 40 vs. 43), the lack of a placebo group and the late randomisation in week 32 of pregnancy on average were limiting factors in this study.

In a randomised, placebo-controlled study on a total of 112 pregnant women with preterm labour between the 22nd–35th week of gestation, Tan et al. [14] compared the treatment with nifedipine (initially 10 mg orally every 15 min up to 5 administrations, followed by 20 mg of a slow-release nifedipine preparation orally every 8 h up to 48 h) + placebo (NaCl) with the same nifedipine regimen combined with the single intramuscular application of 250 mg 17-OHPC. The primary outcome criterion of this study was prolongation of pregnancy by 48 h and 7 days. There were no significant differences between the two treatment groups with regard to the prolongation of pregnancy by 48 h (20.4 vs. 26.8 %, p = 0.50) and 7 days (25.0 vs. 35.2 %, p = 0.29). Likewise there were no significant differences with regard to the rate of preterm deliveries < 34th and < 37th week of gestation (44.2 vs. 46.3 %) as well as the neonatal outcome.

Here as well, the small number of cases resulting from early termination of the study due to insufficient recruitment of pregnant women as well as the lack of detailed information on the frequency of contractions and cervical status during randomisation limit the value of this study.

The objective of a randomised, placebo-controlled, double-blind study on 84 pregnant women between the 24th–34th week of gestation was to evaluate the additional oral administration of dydrogesterone 20 mg/day until delivery or until the 37th week of gestation in combination with nifedipine tocolysis (10–20 mg orally every 6 h) in comparison to placebo [15]. The primary outcome criterion of this investigation was the recurrence of regular contractions after 48 h. No significant differences with regard to the recurrence of contractions (87.5 vs. 91.7 %) were seen; likewise there were no significant differences in the latency period until birth (32.7 ± 20.2 vs. 38.2 ± 24.2 days) or in the rate of preterm birth < 34 (16.7 vs. 12.5 %) and < 37 weeks of gestation (33.3 vs. 37.5 %) and the neonatal outcome. However, this study had an overly low statistical power with regard to the prolongation of pregnancy, the rate of preterm birth < 34th/< 37th week of gestation, as well as the neonatal outcome.

The largest randomised, placebo-controlled, double-blind study so far on adjunctive tocolysis was published in 2014 by Martinez de Tejada et al. [16]. This multicentre study included 379 pregnant women between weeks 24^{0-7} and $33^{6/7}$ of pregnancy with preterm labour (at least 2 painful contractions in 10 min over 30 min) in conjunction with cervical shortening demonstrated on ultrasound (cervical length ≤ 30 mm up to the 31st week of gestation or ≤ 25 mm as of the 32nd week of gestation) or a cervical length of ≤ 10 mm confirmed on vaginal examination

▶ **Table 1** Randomised studies: Adjunctive tocolysis with and without maintenance treatment.

Author/year	n P vs. C	P/17-OHPC	Dose/ Interval (mg)	Controls	Tocolytics	Preterm birth < 37 weeks of gestation (%) [S]	Average latency period until delivery (days) [S]	Comments
Noblot et al. 1991	44 22 vs. 22	P oral	300 mg/ 8 h	Placebo	Ritodrine	27.2 vs. 36.4 [NS]	19 vs. 21 [NS]	Only adjunctive through P ritodrine dose ↓
Arikan et al. 2011	83 43 vs. 40	P vaginal	200/day	No treatment	Ritodrine	50 vs. 65 [NS]	32 vs. 21 [S]	Tocolysis until delivery/ 36 + 6 weeks of gestation
Tan et al. 2012	112 56 vs. 56	17-P i. m.	250/1 ×	Placebo	Nifedipine	44 vs. 46 [NS]	35 vs. 24 [NS]	Single application of 17-P
Areeruk 2016	84 24 vs. 24	Dihydro-P oral	200/day	Placebo	Nifedipine	33 vs. 37.5 [NS]	32 vs. 38 [NS]	Tocolysis until delivery/ 37th week of gestation Recurrence of contractions: 87.5 vs. 92 %
Martinez de Tejada 2015	379 193 vs. 186	P vaginal	200/day	Placebo	Atosiban/ Nifedipine	55 vs. 35 [NS]	45 vs. 52 [median, NS]	Tocolysis until delivery/ 36 + 6 weeks of gestation

n = Number of patients, P = Progesterone, 17-OHPC = 17-α-hydroxyprogesterone caproate, C = Controls, S = Significant ($p < 0.05$), NS = Not significant

or a Bishop score ≥ 6, progressive cervical shortening of ≥ 5 mm during two consecutive examinations or a positive qualitative fibronectin test, if available. The randomisation was performed within 48 h after the start of tocolysis. Depending on the centre, this was performed with beta sympathomimetics, oxytocin receptor antagonists or calcium channel blockers. In addition, either 200 mg progesterone vaginally/day or placebo was administered on an outpatient basis (self-medication) until delivery, premature rupture of membranes, or until 36 + 6 weeks of gestation.

The primary outcome criterion of the study was the rate of preterm birth < 37 weeks of gestation. There were no significant differences between the two treatment groups with regard to gestational age at birth (36.1 vs. 36.6 weeks of gestation), the frequency of preterm birth < 37 weeks of gestation (55.0 vs. 35.4 %, RR 1.20; 95 % CI 0.92–1.55), preterm deliveries < 34 weeks of gestation (20.3 vs. 12.4 %; RR 1.65; 95 % CI 1.01–2.67), in the readmission rate with preterm labour (6.7 vs. 10.3 %; RR 0.65; 95 % CI 0.33–1.28), in the latency period until delivery (median 45 vs. 52 days) and in the neonatal results and the rate of maternal adverse effects (5.7 vs. 6.5 %). The problem in this study, which was conducted in Switzerland and Argentina, was the inadequate compliance in 25 % of the pregnant women.

It should be noted that only the studies by Noblot et al. [12] and Tan et al. [14] involved exclusively adjunctive tocolysis. In the 3 other investigations, the administration of progesterone was continued in terms of maintenance treatment (▶ **Table 1**).

In a retrospective observational study from Poland [17], 96 pregnant women between the 24th and 34th weeks of gestation and following successful tocolysis with fenoterol were administered either 100 mg progesterone vaginally twice daily until the 34th week of gestation (time period 2009–2010) or no treatment (observation period 2007–2008). There were no significant differences with regard to the mean gestational age at delivery (35 vs. 34 weeks of gestation) and in the rate of preterm birth < 34 weeks of gestation (23 vs. 34 %), but instead in the prolongation of pregnancy by an average of 7.6 vs. 6.3 weeks.

The retrospective study design, the lack of definition of preterm labour as well as the low number of cases considerably limit the value of this study.

Maintenance Tocolysis/Treatment

To date there has been no uniform and authoritative definition of "maintenance tocolysis/treatment". It is mostly understood to mean the continuation of drug-based tocolysis beyond 48 hours. Contractions still persist in 20–30 % of pregnant women after initial tocolysis and up to 60 % experience the recurrence of contractions at various intervals after initial tocolysis [9]. Maintenance tocolysis/treatment is not an evidence-based measure for reducing neonatal morbidity and mortality and is therefore not recommended in the current guidelines [18–20], however it is repeatedly discussed in clinical practice as an option for prolongation of pregnancy and is the subject of current clinical-scientific investigations.

Due to the loss of efficacy through tachyphylaxis, beta sympathomimetics are not suitable and ineffective for use beyond 48 h. Oxytocin receptor antagonists are not approved for maintenance tocolysis and the data in this regard are wholly inadequate (only one randomised, placebo-controlled, double-blind study); with regard to the use of prostaglandin synthetase inhibitors, there are no randomised, controlled studies on maintenance treatment tocolysis available, and magnesium sulphate, in view of the inadequate data beyond 48 h, is not associated with a decrease in the rate of preterm birth (overview in [21]). According to a 2016 meta-analysis [22] which included 6 randomised, controlled studies with 787 pregnant women, oral nifedipine used beyond 48 h is not more effective for prolonging pregnancy in comparison to

placebo and does not lead to any reduction in perinatal and neonatal morbidity.

New investigations therefore focus on the use of progesterone and 17-OHPC for maintenance treatment after arrested preterm labour.

A 2014 Cochrane analysis [23] included 7 randomised, controlled studies with 538 pregnant women. It evaluated investigations between 1960 and 2012 with the use of progesterone and synthetic progesterone derivatives for primary tocolysis or for adjunctive and/or maintenance tocolysis with/after ritodrine [12, 13], nifedipine [14] or atosiban [24]. Given the significant heterogeneity and inadequate statistical power of the individual studies, the Cochrane analysis concluded that the evidence for the use of progesterone/17-OHPC in pregnant women with preterm labour is insufficient. A summary overview of these studies including the randomised, controlled study by Martinez de Tejada et al. [16] is also found in Navathe and Berghella 2016 [25].

In 2015 two meta-analyses on the use of vaginal progesterone [26] and intramuscular 17-OHPC [27] for maintenance tocolysis were published. The meta-analysis of Suhag et al. [26] included 5 randomised, controlled studies (441 singleton pregnancies) with vaginal progesterone versus placebo/no treatment [13, 28 – 31]. The daily vaginal progesterone dose in 3 studies was 200 mg and in 2 studies, it was 400 mg. Primary tocolysis was performed using magnesium sulphate (3 studies), ritodrine (1 study) and atosiban (1 study). Preterm labour was defined as at least 6 contractions/30 min or 4 contractions/20 min in combination with cervical shortening confirmed digitally or on ultrasound. Progesterone led to a significant decrease in the rate of preterm birth < 37th week of 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 greater gestational age at birth (mean difference 1.3 weeks) in 4 studies, a significantly lower frequency of the recurrence of contractions (24 vs. 46 %; RR 0.51; 95 % CI 0.31–0.84) as well as a lower rate of neonatal sepsis (2 vs. 7 %, RR 0.34; 95 % CI 0.12–0.98) in 4 studies. Despite promising results in individual studies, the meta-analysis concluded that, based on the considerable heterogeneity between the studies, their low quality (no double-blind studies, selection bias, among others) and the inadequate statistical power, no recommendation for the use of vaginal progesterone as maintenance tocolysis can be made.

The meta-analysis of Saccone et al. [27] evaluated 5 randomised, controlled studies with 426 pregnant women who, after arrested labour (atosiban, nifedipine, magnesium sulphate), received 250 mg 17-OHPC (3 studies) weekly or 341 or 500 mg 17-OHPC twice per week intramuscularly vs. no treatment or placebo (1 study) [24, 31 – 34]. It revealed no significant differences with regard to 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 as well as the rate of neonatal complications and transfers to the neonatal intensive care unit in comparison to the control groups. However, after intramuscular 17-OHPC, there was a significantly longer latency period until birth (mean difference 8.4 days) and a significantly higher birth weight (mean difference 224 g). The value of this meta-analysis is limited by the lack of data on risk factors for preterm birth in the studies, the different dosages and application intervals for 17-OHPC, the different primary outcome criteria of the investigations, as well as the low numbers of cases with inadequate statistical power.

According to the authors, the intramuscular application of 17-OHPC is indeed promising, however it cannot be recommended for routine clinical practice due to the insufficient data.

Three additional meta-analyses from 2016 also addressed the use of progesterone/17-OHPC for maintenance tocolysis, however the selection of the randomised, controlled trials (RCT) was entirely different.

Eke et al. [35] thus analysed four of the RCTs already cited with 362 pregnant women [12, 24, 28, 32] in which vaginal/oral progesterone and 17-OHPC were compared with placebo/no treatment. Here, the search strategies/criteria are unclear in view of the large number of studies published by then and not taken into account in this meta-analysis. The outcome criteria of this meta-analysis were the latency period from randomisation until delivery and the rate of preterm birth < 37 and < 34 weeks of gestation. With regard to these criteria, there were no significant differences between the treatment groups and the mean birth weight was 203 g higher on average following progesterone/17-OHPC than in comparative groups.

A meta-analysis by Ding et al. [36] investigated 10 RCTs, 5 of which had oral nifedipine and 5 had oral/vaginal progesterone in comparison to placebo/no treatment for maintenance tocolysis between the 24th–34th week of gestation in the period from 1980–2014 [13, 28, 30, 37, 38]. Not included were studies with intramuscular 17-OHPC; the progesterone dosages were 200 and 400 mg/day, primary tocolysis was performed with nifedipine, magnesium sulphate, ritodrine or atosiban.

In comparison to 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 the birth weight (by 318 g on average) was able to be achieved with progesterone. The treatment had no effect on the neonatal outcome. By contrast, maintenance tocolysis with nifedipine, compared to placebo/no treatment, did not result in any significant prolongation of pregnancy. A randomised study [37] included in this meta-analysis compared 20 mg oral nifedipine every 8 h directly with the administration of 400 mg vaginal progesterone: 10 % of the pregnant women in the nifedipine group and 61 % of the pregnant women in the progesterone group reached term (p: 0.000). The mean prolongation of pregnancy was 16.6 vs. 40.1 days, the adverse effects following nifedipine were significantly higher than after vaginal progesterone (e.g. hypotension 15.7 vs. 0 %).

The authors conclude from their results that, in contrast to nifedipine, progesterone is beneficial for maintenance treatment after arrested labour.

It is unclear why other RCTs published during the observation period were not included in this meta-analysis (among others [13, 29, 31, 39]), which limits its value.

The randomised, placebo-controlled, double-blind study by Palacio et al. published in 2016 (PROMISE-Trial [40], EL1) was not taken into account in the meta-analyses previously cited. This in-

▶ **Table 2** Meta-analyses: Progesterone/17-OHPC vs. placebo/no treatment as maintenance tocolysis* after arrested preterm labour.

Author/year	Suhag 2015	Saccone 2015	Palacio 2016	Eke 2016	Wood 2017
Number of studies included	5	5	16	4	15
Total number of pregnant women	441	426	1917	362	1742
P/17-OHPC (number of studies)	vag. P	17-OHPC i.m.	P (12) 17-OHPC (4)	P (2) 17-OHPC (2)	P (11) 17-OHPC (4)
Preterm birth < 37th week of gestation (%) RR (95% CI)	42 vs. 58+ 0.71 (0.57–0.9)	42 vs. 51 0.78 (0.5–1.2)	38.2 vs. 44.3+ 0.79 (0.65–0.97)	RR 0.8# (0.58–1.1)	OR 0.77+# (0.62–0.96)
Preterm birth < 34th week of gestation (%) RR (95% CI)	N/I	25 vs. 34 0.60 (0.28–1.12)	15.6 vs. 18.3 0.77 (0.53–1.12)	RR 0.69# (0.4–1.2)	OR 0.80 (0.60–1.08)
Latency period until delivery (days, mean difference range)	13.8+ (4.0–23.6)	8.4+ (3.2–13.5)	8.1+ (3.8–12.4)	2.4 (−1.5–6.3)	9.1+ (3.7–14.5)

* = Maintenance treatment until delivery or 35th – < 37th week of gestation, + = Significant results ($p < 0.05$), # = No percent values, N/I = No information, P = Progesterone, 17-OHPC = 17-α-hydroxyprogesterone caproate, RR = Relative risk, OR = Odds ratio

vestigation included 248 pregnant women with randomisation between 24 + 0 to 30 + 6 weeks of gestation and 31 + 0 to 33 + 6 weeks of gestation. Preterm labour was defined as 2 painful contractions/10 min in conjunction with shortening/opening of the cervix. After successful primary tocolysis (atosiban, nifedipine), the pregnant women were discharged from the hospital with a cervical length of < 25 mm: 126 pregnant women received 200 mg vaginal progesterone/day and 132 placebo until delivery or until 36 + 6 weeks of gestation. It was planned to recruit a total of 350 pregnant women; however this study was discontinued early due to financial problems.

There were no significant differences with regard to the rate of preterm deliveries < 34 weeks of gestation (7.1 vs. 7.6%) and < 37 weeks of gestation (28.6 vs. 22%), nor when the stratification of the investigational groups was considered as a function of gestational age. The differences in gestational age at birth were also non-significant (38.0 vs. 38.2 weeks of gestation).

It is debatable whether the study would have achieved different results if the entire planned number of pregnant women had been recruited than in the case of the 75.7% achieved upon premature termination of the study.

Palacio et al. included their study in their own subsequent meta-analysis with 16 RCTs and 1917 pregnant women (reporting period 1991 to June 2015) [41]. Primary tocolysis was performed in most cases with magnesium sulphate (7 studies); in 11 RCTs, progesterone was administered vaginally or orally at dosages of 200–400 mg/day for maintenance treatment either in addition to acute tocolysis or after arrested preterm labour, in 5 RCTs, 17-OHPC was administered intramuscularly at dosages between 250–500 mg once to twice per week. Randomisation was performed between 24 + 0–34 + 6/7 weeks of gestation. Pregnant women with a previous preterm birth were also included. The definitions of preterm labour differed: in most cases, ≥ 6 contractions/30 min or 4 contractions/20 min associated with cervical shortening confirmed digitally or on ultrasound. The number of pregnant women recruited was between 40 [42] and 379 [16]. In comparison to placebo/no treatment, a significant decrease in the rate of preterm birth < 37th week of gestation from 44.3 to 38.2% (RR 0.79; 95% CI 0.65–0.97) was achieved overall through the use of progesterone/17-OHPC. The prolongation of pregnancy after progesterone/17-OHPC was 8.1 days on average (95% CI 3.8–12.4 days). No significant differences were seen in the rate of preterm birth < 34th week of gestation (15.6 vs. 18.3%, RR 0.77; 95% CI 0.53–1.12). In the sensitivity analysis which included 5 "high-quality" studies, no significant differences were seen with regard to the rate of preterm birth < 37 weeks of gestation in comparison to placebo/no treatment (37.2 vs. 36.9%; RR 0.91; 95% CI 0.67–1.21) nor in the latency period between randomisation and delivery (mean difference 0.6 days; 95% CI −3.7–4.9).

In comparison to the meta-analyses of Suhag et al. [26] and Saccone et al. [27], the meta-analysis of Palacio et al. [41] evaluated 6 additional RCTs between 2009 and 2016, primarily from India, Egypt and Iran [38, 39, 42, 43], and studies with adjunctive tocolysis with and without the continuation of the progesterone treatment as maintenance treatment were also included (see ▶ **Table 2**).

Taking the Cochrane risk of bias tool [44] into account revealed significant heterogeneity between the studies, especially with regard to the rate of preterm birth < 37, < 34 weeks of gestation and the latency period until delivery. In 10 out of 16 studies, a selection bias can be assumed (no double-blind studies, inadequate randomisation, different inclusion criteria).

Only 5 studies met the Jadad criteria (validated scale for assessing the methodological study quality [45]); in the sensitivity analysis, they did not demonstrate any significant differences with regard to the outcome criteria.

In the authors' opinion, based on the lack of qualified studies and the significant heterogeneity between the studies, the data are insufficient for using progesterone as maintenance treatment after arrested preterm labour with the goal of decreasing the preterm birth rate and prolonging pregnancy.

A randomised, controlled, multicentre study from Italy published in 2017 with 254 pregnant women between $22^{0/7}$ – $31^{6/7}$ weeks of gestation and a cervical length ≤ 25 mm compared the application of 200 mg progesterone vaginally/day vs. 341 mg 17-OHPC/week intramuscularly vs. no treatment until the end of

the 36th week of gestation after arrested labour with atosiban, nifedipine or indomethacin [46]. The recruitment of 160 pregnant women/study arm was planned. The primary outcome criterion was indicated as the rate of preterm birth < 37 weeks of gestation. Following an interim analysis of more than 50% of the pregnant women included up to that point, the study was discontinued prematurely by an independent monitoring committee, since even after the originally planned number of pregnant women was reached, no statistically significant advantages with regard to the primary outcome criterion through the use of progesterone/17-OHPC could be expected. The initial hypothesis was that the risk of a preterm birth < 37 weeks of gestation can be reduced by 50% when using progesterone. Taking the evaluated cases into account, the rate of preterm birth < 37 weeks of gestation was 39% after vaginal progesterone, 23% after 17-OHPC and 22% in the control group, thus without statistically significant differences. Likewise there were no significant differences between the treatment groups with regard to the rate of preterm birth < 35 and < 32 weeks of gestation.

The conclusion of the study is that progesterone/17-OHPC as maintenance tocolysis does not decrease the rate of preterm births.

In the same year (2017) Wood et al. [47] conducted another randomised, placebo-controlled study and an update of previous meta-analyses. Included were pregnant women between 23 + 0–32 + 6 weeks of gestation with cessation of contractions at least 12 h after initial tocolysis or after spontaneous cessation of contractions and positive fibronectin test, who received either 200 mg vaginal progesterone/day or placebo until the 35th week of gestation. The recruitment of 60 pregnant women in each treatment arm was planned. Because of the inadequate recruitment and the fact that the study medication ran out, the investigation was discontinued prematurely after the inclusion of 41 pregnant women (19 with progesterone, 22 with placebo); added to this was the lack of compliance by the pregnant women.

The meta-analyses incorporated 15 RCTs (n = 1742) including the results from their own study. In contrast to the meta-analysis by Palacio et al. [41], 3 RCTs which are in part not listed in PubMed [42, 43], are not taken into account, but the randomised, controlled study of Kamat et al. was, however [37]; 4 randomised, controlled studies related to the use of 17-OHPC, 2 to the use of oral progesterone and 8 to the use of vaginal progesterone; 5 studies were assessed as "high-quality" and 10 as "low-quality". The 5 "high-quality" studies included, in addition to their own study, the 4 which also have this quality feature in the meta-analysis of Palacio et al. The results of this meta-analysis can be summarised as follows: overall, the use of progesterone/17-OHPC decreased the rate of preterm birth < 37th week of gestation significantly (OR 0.77; 95% CI 0.62–0.96), however significances for vaginal/oral progesterone and 17-OHPC alone could not be identified. Not significant for both was also the rate of preterm birth < 34 weeks of gestation (OR 0.80; 95% CI 0.60–1.08). In comparison to the control groups (placebo/no treatment), the latency period overall until delivery was able to be prolonged through progesterone by an average of 9.1 days (95% CI 3.7–14.5 days). Comparable with the meta-analysis of Palacio et al. [41], this meta-analysis also revealed in the "low-quality" studies a significant decrease in the rate of preterm birth < 37 weeks of gestation (OR 0.47; 95% CI 0.34–0.64), < 34 weeks of gestation (OR 0.55; 95% CI 0.35–0.86) and the mean latency period until delivery (16 days; 95% CI 14.1–17.8 days), however not in the "high-quality" studies (rate of preterm birth < 37 weeks of gestation: OR 1.23; 95% CI 0.91–1.67, < 34 weeks of gestation: OR 1.22; 95% CI 0.74–1.69 and latency period until delivery: − 0.95 days; 95% CI − 5.5–3.6 days).

In the "low-quality" studies, the progesterone treatment was associated with a significant reduction in perinatal mortality (OR 0.39; 95% CI 0.12–0.87), however not in the "high-quality" studies (OR 0.52; 95% CI 0.14–1.95).

The authors conclude that, at present, neither vaginal/oral progesterone nor 17-OHPC as maintenance treatment is suitable for clinical practice and the results of further randomised, controlled (double-blind) studies should be awaited.

Discussion

In view of a preterm birth rate in Europe between 5–18% (in Germany 2017: 8.6%), tocolysis is among the most frequent obstetric measures. In pregnant women with preterm labour, common tocolytics are able to prolong the pregnancy by 48 h in 75–93% of cases and by 7 days in 61–78% of patients [48]. The increase in the tocolytic efficacy with a simultaneous reduction in maternal adverse effects through additional measures is a worthwhile pursuit of clinical research for practical application. Another objective following acute tocolysis is to develop new therapeutic methods which effectively prolong pregnancy until near term and are able to significantly reduce the rate of preterm deliveries and associated neonatal morbidity.

As shown in experimental and clinical studies, progesterone inhibits the contractility of the myometrium through a number of various mechanisms [6 – 8, 49].

According to in-vitro studies [6], progesterone has synergistic effects in combination with nifedipine, indomethacin and beta sympathomimetics. According to clinical investigations, the tocolytic efficacy, particularly of beta sympathomimetics, can be increased by progesterone and the dosage of the tocolytic can be significantly reduced [3, 10, 12, 13]. However, the randomised placebo-controlled study of Martinez de Tejada et al. [16] arrived at contrary results in this regard.

There are only 3 studies from 1960, 1986 and 2011 on primary tocolysis with progesterone/17-OHPC with small numbers of cases, different study design and different primary outcome criteria. In two studies, 17-OHPC (n = 276) was used, in one study (n = 57) oral progesterone was used and in *no* study was vaginal progesterone used. While an inhibition of uterine contractions through progesterone/17-OHPC was unanimously confirmed, no details were given regarding a decrease in the rate of preterm birth and the interval between the start of treatment and delivery.

Because of these insufficient data, it is unclear whether or not progesterone/17-OHPC is suitable for primary tocolysis. In this connection, the question arises as to the optimal mode of application, the effective, contraction-inhibiting dosage and the suitable application intervals of the substances. Of note is the fact that, since 2011, no study on primary tocolysis with progesterone/17-

OHPC has been published and thus here as well, there is evidently considered to be no need for research.

The data on adjunctive tocolysis are also completely inadequate, especially as oral progesterone and 17-OHPC were used concomitantly/in addition to conventional tocolytics in only 2 out of 5 studies [12, 14]. A limiting factor in the placebo-controlled study by Noblot et al. [12] is the small number of cases (n = 44), in the study of Tan et al. [14], it is its premature termination with 112 out of 254 planned pregnant women who actually should have been included in the study in view of an adequate statistical power. The randomised, placebo-controlled, double-blind study of Martinez de Tejada et al. [16], which is the largest to date and which has precise inclusion criteria, clear information on the randomisation and defined outcome criteria (evidence level I), is of great clinical significance. In this study, vaginal progesterone was applied within 48 h additively to tocolysis and then as maintenance treatment until delivery or up to 36 + 6 weeks of gestation. During an interim analysis (n = 302), the power analysis revealed that even if the planned number of patients is reached, the probability of an advantage of progesterone in comparison to placebo with regard to the primary outcome criterion (rate of preterm birth < 37 weeks of gestation) would be 0 %. Independent of this, the authors conclude that the daily administration of 200 mg vaginal progesterone does not decrease the rate of preterm birth or improve the neonatal outcome.

One problem of this and other studies [47] which is difficult to overcome is the self-medication of progesterone by the pregnant woman after discharge from the hospital which leads to an incalculable influence on the results. The repeated weekly i. m. administration of 17-OHPC may demonstrate even lower compliance [47].

Whether exclusively adjunctive tocolysis with progesterone is effective can only be clarified in randomised, placebo-controlled studies with an adequate number of cases without additional maintenance treatment. In light of this, the extent to which this approach decreases the rate of preterm birth without further maintenance treatment is questionable.

The objective of maintenance tocolysis (treatment) is the prolongation of the latency period until delivery and thus a reduction in the rate of preterm birth < 37 [34] weeks of gestation, as well as a decrease in neonatal morbidity and mortality. This objective could not be achieved for various reasons with the use of beta sympathomimetics, calcium channel blockers, cyclooxygenase inhibitors, magnesium sulphate and the selective oxytocin receptor antagonist atosiban in comparison to placebo [26]. Particularly in regard to a reduction of serious neonatal complications/neonatal mortality, their low prevalence calls for high numbers of cases which are not reached in previous randomised, controlled studies, however. Whether this objective can be achieved with progesterone/17-OHPC was and is the subject of clinical research in the past 10 years to date. Overall, the results of this research are contradictory. Notwithstanding the considerable heterogeneity between the studies, the meta-analysis of Suhag et al. [26] revealed a significant prolongation of the latency period until delivery and a significant decrease in the rate of preterm birth < 37 weeks of gestation following vaginal progesterone. The contemporaneous meta-analysis of Saccone et al. [27] achieved opposite results after the use of intramuscular 17-OHPC as maintenance treatment. In both meta-analyses, no subgroup analysis with regard to the quality of RCTs evaluated was performed.

Two other meta-analyses from 2016 [35, 36] which included 4 and 5 RCTs also yielded contradictory statements. While Eke et al. [35] included RCTs with oral/vaginal progesterone *and* 17-OHPC in their analysis and found no significant reduction in the rate of preterm birth < 37/<34 weeks of gestation, Ding et al. [36] evaluated only RCTs with oral/vaginal progesterone as maintenance treatment. In comparison to oral nifedipine, a significant prolongation of pregnancy and a significant decrease in the rate of preterm birth < 37 weeks of gestation were able to be achieved with progesterone. For both meta-analyses, there is evidence of a publication bias [41], since other RCTs published during the period covered by these meta-analyses were not taken into account. Moreover, the low number of cases (n = 362 and n = 410) in both meta-analyses limits their value.

The most comprehensive and qualitatively best meta-analysis to date, which included 16 RCTs with 1917 pregnant women, was published in 2016 by Palacio et al. [41]. A detailed analysis of the RCTs regarding heterogeneity and an assessment of their quality was performed using the Cochrane risk of bias tool and the Jadad criteria. In "low-quality" studies, there was a significant decrease in the rate of preterm birth < 37 weeks of gestation and a significant prolongation of pregnancy following progesterone/17-OHPC; this could not be demonstrated in 5 "high-quality" studies. Comparable results were also found in the meta-analysis of Wood et al. 2017 (15 RCTs with 1742 pregnant women) which was not able to demonstrate any significant differences in the 5 "high-quality" studies with regard to the primary outcome criteria [47]. In doing so, in both meta-analyses, the same RCTs were classified as "high quality" 4 times in each case [12, 16, 34, 40]; in the meta-analysis of Palacio et al. [41] additionally the RCT of Choudhary et al. [38], in that of Wood et al. [47] their own RCT which was, however, prematurely terminated after recruiting 41 pregnant women. According to the conclusion from both meta-analyses, there is no sufficient evidence to date that maintenance treatment with progesterone/17-OHPC, in comparison to placebo/no treatment, significantly decreases the rate of preterm deliveries and is thus suitable for clinical use.

Two other recently published RCTs [40, 46] also support this statement. The randomised, placebo-controlled, double-blind study by Palacio et al. [40] was discontinued prematurely after recruiting 258 pregnant women (350 planned) after no significant differences were seen between maintenance treatment with 200 mg vaginal progesterone/day vs. placebo with regard to the rate of preterm birth < 37 and < 34 weeks of gestation. A randomised, controlled, multicentre study from Italy [46] was also terminated prematurely after the interim analysis which revealed no significant differences with regard to the primary outcome criterion (rate of preterm birth < 37 weeks of gestation) following maintenance treatment with vaginal progesterone and intramuscular 17-OHPC versus no treatment.

As is evident from the different clinical results of the meta-analyses of Suhag et al. [26] and Saccone et al. [27], differences in effect with regard to the tocolytic potency between natural progesterone and synthetic progesterone derivates which affect the metabolisation and receptor affinity, among others (discus-

sion in [4]), can be assumed. In-vitro investigations have shown that not 17-OHPC but rather natural progesterone inhibits myometrium contractions dose-dependently [49, 50]. In comparison to natural progesterone, 17-OHPC has a lower relative binding affinity of 26–30 % to the progesterone receptors [51]. In animal models, birth processes could be fully inhibited only by the substitution of progesterone and not by 17-OHPC, however [52]. Moreover, the mode of application and the solvent used (castor oil in the case of 17-OHPC, stimulating effect on the uterus) in particular play a further role [52]. The direct transport of the substance from the vagina to the uterus (first uterine pass effect [53]) is considered to be an advantage of vaginally applied progesterone as compared to systemically administered 17-OHPC.

Natural progesterone is commercially available in Germany, however 17-OHPC is only available via the international pharmacy.

Problems become clear from the critical analysis of published data which apply not only for the evaluation of RCTs and resultant meta-analyses on progesterone/17-OHPC, but rather clearly for other treatment studies as well. The high degree of heterogeneity between the studies limits the validity of pooled data in meta-analyses. Crucial problems in this connection which make the interpretation and comparability of studies difficult are especially different inclusion criteria with the risk of a selection bias (differences in the definition of preterm labour, gestational age and cervical status at randomisation, in the assessment of the cervix using palpation or ultrasound, in the exclusion or inclusion of risk factors for preterm birth such as a prior preterm birth or ethnic affiliation, among others). Added to this are the considerable methodological differences between the studies (e.g. nature and quality of the randomisation, double-blind study vs. no blinding, placebo-controlled study vs. no treatment, selection of primary outcome criteria) as well as in the approach (e.g. local vs. systemic application, dosages, application frequency). Another problem is the insufficient number of cases in studies with inadequate statistical power. Studies with low numbers of cases often arrive at different results with regard to the primary outcome criteria in comparison to studies with high numbers of cases. Thus, in comparison to studies with small numbers of cases ($n < 100$, e.g. [28, 30, 33, 37, 38]) in the largest RCT to date of Rozenberg et al. ($n = 184$ [32]) with 17-OHPC and in that of Martinez de Tejada et al. ($n = 385$ [16]) with vaginal progesterone, no significant differences in the latency period until delivery and in the rate of preterm birth could be demonstrated.

Not to be underestimated with regard to the results is also the lack of compliance during self-medication of progesterone after discharge from the hospital [16, 47] and during repeat outpatient application of 17-OHPC [14]. The controversial data on progesterone in meta-analyses is the subject of current discussions [54].

Conclusion

Based on current knowledge, progesterone/17-OHPC is not suitable either for primary or adjunctive tocolysis. In line with the forthcoming AWMF guideline “Prävention und Therapie der Frühgeburt” [Prevention and treatment of preterm birth], maintenance treatment with progesterone, after arrested preterm labour, is also not a suitable measure for the prevention of preterm birth.

Conflict of Interest

Prof. Dr. Rath states that there is no conflict of interest. PD Dr. Kuon received speaker’s fees from DR. KADE/BESINS Pharma GmbH.

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