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Progesterone for the Prevention of Preterm Birth – an Update of Evidence-Based Indications

Progesteron zur Prävention der Frühgeburt – ein Update evidenzbasierter Indikationen

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ABSTRACT

The prevention and treatment of preterm birth remains one of the biggest challenges in obstetrics. Worldwide, 11 % of all children are born prematurely with far-reaching consequences for the children concerned, their families and the health system. Experimental studies suggest that progesterone inhibits uterine contractions, stabilises the cervix and has immunomodulatory effects. Recent years have seen the publication of numerous clinical trials using progestogens for the prevention of preterm birth. As a result of different inclusion criteria and the use of different progestogens and their methods of administration, it is difficult to draw comparisons between these studies. A critical evaluation of the available studies was therefore carried out on the basis of a search of the literature (1956 to 09/2018). Taking into account the most recent randomised, controlled studies, the following evidence-based recommendations emerge: In asymptomatic women with singleton pregnancies and a short cervical length on ultrasound of ≤ 25 mm before 24 weeks of gestation (WG), daily administration of vaginal progesterone (200 mg capsule or 90 mg gel) up until 36 + 6 WG leads to a significant reduction in the preterm birth rate and an improvement in neonatal outcome. The latest data also suggest positive effects of treatment with progesterone in cases of twin pregnancies with a short cervical length on ultrasound of ≤ 25 mm before 24 WG. The study data for the administration of progesterone in women with singleton pregnancies with a previous preterm birth have become much more heterogeneous, however. It is not possible to make a general recommendation for this indication at present, and decisions must therefore be made on a case-by-case basis. Even if progesterone use is considered to be safe in terms of possible long-term consequences, exposure should be avoided where it is not indicated. Careful patient selection is crucial for the success of treatment.

ZUSAMMENFASSUNG

Die Prävention und Behandlung der Frühgeburt stellt nach wie vor eine der größten Herausforderungen in der Geburtshilfe dar. Weltweit werden 11 % aller Kinder zu früh geboren mit weitreichenden Konsequenzen für die betroffenen Kinder,

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ihre Familien und das Gesundheitssystem. Experimentelle Studien weisen darauf hin, dass Progesteron uterine Kontraktionen hemmt, die Cervix uteri stabilisiert und immunmodulatorisch wirksam ist. In den letzten Jahren ist eine Vielzahl von klinischen Studien, die Gestagene zur Prävention der Frühgeburt einsetzen, publiziert worden. Die Vergleichbarkeit dieser Studien untereinander ist durch unterschiedliche Einschlusskriterien, Anwendung verschiedener Gestagene sowie deren Applikationsmodi schwierig. Es wurde daher im Rahmen einer Literaturrecherche (1956 bis 09/2018) eine kritische Evaluation der Studienlage durchgeführt. Unter Berücksichtigung der neuesten randomisierten kontrollierten Studien ergeben sich folgende evidenzbasierte Empfehlungen: Bei asymptomatischen Frauen mit Einlingsschwangerschaften und sonografisch verkürzter Zervix ≤ 25 mm vor der 24. Schwangerschaftswoche (SSW) führt die tägliche Gabe von Progesteron vaginal (200 mg Kapsel oder 90 mg Gel) bis zur 36 + 6 SSW zu einer signifikanten Reduktion der Frühgeburtenrate und einer Verbesserung des neonatalen Outcomes. Neueste Daten weisen auch auf positive Effekte einer Behandlung mit Progesteron bei Geminischwangerschaften und einer sonografisch verkürzten Zervix ≤ 25 mm vor der 24. SSW hin. Dagegen ist die Studienlage für die Gabe von Progesteron bei Frauen mit Einlingsschwangerschaft mit vorausgegangener Frühgeburt deutlich uneinheitlicher geworden. Für diese Indikation kann derzeit keine generelle Empfehlung ausgesprochen werden, sie ist daher eine Einzelfallentscheidung. Auch wenn der Einsatz von Progesteron im Hinblick auf mögliche Langzeitfolgen als sicher gilt, sollte eine nicht indizierte Exposition vermieden werden. Entscheidend für den Therapieerfolg ist die präzise Selektion der Schwangeren.

Introduction

The prevalence of preterm birth is between 5 and 18% worldwide [1], and was 8.4% in Germany in 2017 [2]. According to WHO estimates, approx. 10 million babies were born before 37 + 0 WG in 2010, which means that preterm birth affects approximately 11% of all pregnancies [1]. Worldwide, more than a million babies a year born prematurely die from complications in the first month of life, with a clear disparity between industrialised and developing countries that is impossible to ignore. Whereas babies born prematurely between 28 and 32 WG survive in over 90% of cases in industrialised countries (more than 90% without disabilities), this rate is just 30% in most developing countries [1]. Despite a worldwide decline in neonatal mortality (from 93 deaths per 1000 live births in 1990 to 41 deaths per 1000 live births in 2016), this mortality is still 35% overall among preterm babies and preterm birth is responsible for 16% of all deaths of children under the age of 5 years [3]. Preterm births account for up to 75% of perinatal mortality [2].

In addition, extremely preterm birth in particular is associated with a significantly increased risk of severe neonatal morbidity (e.g. respiratory distress syndrome, necrotising enterocolitis, intraventricular haemorrhage) and of severe long-term neurological problems (e.g. cognitive developmental delays, hearing and sight impairment). Finally, there is evidence that children born prematurely are at significantly increased risk in the long term of developing cardiovascular disease, hypertension, diabetes mellitus and metabolic syndrome [4]. A recent Swedish cohort study showed that the educational prospects of preterm infants are considerably limited compared with children born at term [5].

According to Goldenberg et al. (2008), 65–70% of preterm births are spontaneous, and approx. 30% are iatrogenic due to preterm delivery on the basis of maternal or foetal indications [6].

In the context of preterm birth prevention, the treatment of premature labour represents merely "symptomatic therapy" (for overview, see [7]). For primary and secondary prevention, in the light of a large number of new studies, the administration of progesterone is increasingly becoming a focus of interest and is currently the subject of some controversy [8].

The use of natural progesterone and its synthetic derivatives, often referred to collectively as progestogens, in this connection is based on basic research and the latest clinical trial results. Molecular and experimental (animal) studies suggest that progesterones are capable of both inhibiting uterine contractions (including directly tocolytic effects via membrane-bound progesterone receptors [9]; influence on the expression of contraction-promoting proteins such as connexin 43, Ca^{+} channels, oxytocin receptors [10]; reduction in pro-inflammatory cytokine levels and consecutively of prostaglandin levels [11]) and of having a significant effect on the biochemical components of the cervix (including reduced degradation of cervical collagen [12]). In recent years, numerous new clinical trials have appeared, some of a high quality, which means that the evidence supporting progesterone use in the prevention and treatment of preterm birth in certain indications (see below) has become clearer. Of no less importance are the studies with negative results, as these help to identify those women who do not benefit from progesterone and should therefore not be exposed to it unnecessarily. In view of the large number of new studies and the considerable heterogeneity between these studies (including differences in methodology, inclusion criteria, natural progesterone vs. 17α-hydroxyprogesterone caproate (17-OHPC), different methods of administration and different dosage, start and duration of therapy, see ▶ **Table 1**), there is an urgent need for an up-to-date critical analysis of the study data taking into account the multifactorial aetiology of preterm birth.

Material and Methods

A search of the literature was performed in PubMed for the period 1956 to September 2018. It was based on the following search terms: preterm birth and progesterone or 17-OHPC or progestin. Publications in both English and German were included. The aim of this study is to describe the available data on the use of progesterone for the primary (after previous preterm birth) and secondary (with a short cervix in the current pregnancy) prevention of

▶ **Table 1** Progesterone therapy for the prevention of preterm birth: type, method of administration, dose and interval.

Type	Method of administration	Dose (mg)	Interval
17-OHPC	Intramuscular injection	250	Weekly
Natural micronised progesterone	Vaginal pessary	100, 200, 400	Daily
	Vaginal gel	90	Daily
	Oral (capsule)	200, 400	Daily

17-OHPC: 17α-hydroxyprogesterone caproate

preterm birth. Other possible indications such as progesterone use for premature rupture of membranes or premature labour shall not be evaluated in this review.

Results I – Primary Prevention

Singleton pregnancies with a previous preterm birth

The rationale for using progesterone is the significantly increased risk of preterm birth after a previous spontaneous preterm birth (OR 3.6; 95% CI 3.2–4.0) [13].

▶ **Table 2** presents an overview of the randomised, placebo-controlled studies on progesterone therapy for the prevention of preterm birth in women with singleton pregnancies after a previous preterm birth.

The randomised, placebo-controlled, double-blind study conducted by O'Brien et al. showed no significant differences with regard to the preterm birth rate at ≤ 32 WG (primary endpoint of the study) or neonatal morbidity and mortality. 659 pregnant women with a history of spontaneous preterm birth were included in the study between 18 and 23 WG and the efficacy of 90 mg progesterone (vaginal gel) was evaluated vs. placebo [14]. The authors of the study suggested as long ago as 2007 that the selection criterion of "previous preterm birth" is not sufficient to identify the group of patients who benefit from administration of progesterone (differentiation between responders and nonresponders) [14].

A multicentre, randomised and placebo-controlled study from Australia, New Zealand and Canada published in 2017 was not able to show any significant reduction in the rate of neonatal respiratory distress syndrome (primary endpoint; 10.5% in the progesterone vs. 10.6% in the placebo group) and preterm births before 37 WG (36.5% in the progesterone vs. 37.2% in the placebo group) in 787 pregnant women (including 12 twin pregnancies) with a previous preterm birth (spontaneous onset of labour and cervical shortening or premature rupture of membranes) who received 100 mg vaginal progesterone or placebo starting between 20 and 24 WG up until 34 WG [15]. The authors call for a meta-analysis of the individual patient data from clinical trials ("individual participant data meta-analysis") in order to identify the subgroup which benefits from progesterone administration. In our opinion, the results of the randomised, placebo-controlled OPPTIMUM study [16] should also be included in such a meta-analysis. This study included a heterogeneous population of 1228 women with singleton pregnancies who were treated daily either with 200 mg vaginal progesterone or with placebo starting at 22–24 WG up until 34 WG. Not only pregnant women with a previous spontaneous preterm birth at ≤ 34 WG were evaluated but also pregnant women with a cervical length of ≤ 25 mm and with a positive fetal fibronectin test combined with other clinical risk factors for a preterm birth. The criticism of the OPPTIMUM study will be addressed in more detail under "Discussion".

There is also a recent, single-centre, randomised and placebo-controlled study from Egypt on the oral method of administration that has not been possible to include in the 2013 Cochrane analysis (see below) [17]. In this study, 212 women with singleton pregnancies and a previous spontaneous preterm birth were treated either with 100 mg oral progesterone every 6 hours (daily dose 400 mg) or placebo, starting at 14–18 WG up until 37 WG [17]. No significant differences were observed in this study with regard to the frequency of additionally required cerclage (72.9% in the progesterone and 80.2% in the placebo group, $p = 0.25$). The serum progesterone levels were significantly higher at 20 and 28 WG after progesterone administration compared with placebo (e.g. at 20 WG: 30.7 ± 3.4 ng/ml vs. 15.7 ± 1.4 ng/ml, $p < 0.001$). The gestational age at birth was significantly higher in the progesterone group than in the placebo group (35.4 vs. 33.9 WG, $p = 0.01$) and the rate of preterm births before 37 WG significantly lower (44.7 vs. 63.7%, $p = 0.01$). The administration of oral progesterone was also associated with significantly lower neonatal morbidity (e.g. rate of neonatal respiratory distress syndrome 21.8 vs. 42.8%, $p = 0.004$) and a shorter stay in the Neonatal Intensive Care Unit for the infant (15.4 days in the progesterone vs. 19.5 days in the placebo group) [17].

In the United States of America, intramuscular (i. m.) administration of 17-OHPC is common. The synthetic progesterone derivative is not commercially available in Germany and is available only through foreign pharmacies.

Because of its longer half-life (7.8 days compared with 35–55 hours for natural progesterone), 17-OHPC only has to be administered once weekly [18]. Meis et al. were able to identify a significant reduction in the preterm birth rate before 37 WG in pregnant women with a previous preterm birth ($n = 310$) who received 17-OHPC (250 mg/week) compared with placebo starting at 16–20 WG up to 36 WG (36.3 vs. 54.9%, $p < 0.001$). There was also a significantly lower rate of necrotising enterocolitis (none in the progesterone vs. 2.6% in the placebo group), intraventricular haemorrhage (1.3 vs. 5.2%) and oxygen therapy (14.9 vs. 23.8%) in the newborns in the 17-OHPC group. Critics of the study by Meis et al. [17] point out the high rate of preterm births in the

▶ **Table 2** Randomised placebo-controlled studies: Progesterone for the prevention of preterm birth in women with singleton pregnancies and a previous preterm birth.

Author	Year	Number of patients (progesterone vs. control)	Inclusion criteria	Progestogen type	Dose and interval	Period of use (WG)	Primary outcome	Reduction in preterm birth
A) 17α-OHPC								
Meis et al. [51]	2003	310 vs. 153	Previous sPB	i. m. 17α-OHPC	250 mg/ week	16–20 to 36	PB < 37 WG: 36.3 vs. 54.9 % (p < 0.001)	Yes
B) Vaginal progesterone								
Fonseca et al. [60]	2003	72 vs. 70	Previous sPB, uterine anomalies, cervical incompetence	Vaginal pessaries	100 mg/ day	24 to 34	PB < 37 WG: 13.8 vs. 28.5 % (p < 0.030)	Yes
O'Brien et al. [14]	2007	309 vs. 302	Previous sPB	Vaginal gel	90 mg/day	18–24 to 36	PB < 32 WG: 10 vs. 11.3 % (p > 0.050)	No
Cetingoz et al. [33]	2011	80 vs. 70	Previous sPB, uterine anomalies (n = 67, twin pregnancies)	Vaginal pessaries	100 mg/ day	24 to 34	PB < 37 WG: 40 vs. 57.2 % (p < 0.036)	Yes
Azargoon et al. [61]	2016	50 vs. 50	Previous PB, uterine anomalies, intramural fibroid ≥ 7 cm	Vaginal pessaries	400 mg/ day	16–22 to 36	PB < 37 WG: 36 vs. 68 % (p < 0.001)	Yes
Norman et al. [16]	2016	610 vs. 618	Previous sPB, cervical length ≤ 25 mm, pos. fetal fibronectin combined with other PB risk factor	Vaginal pessaries	200 mg/ day	22–24 to 34	PB or fetal death < 34 WG: 16 vs. 18 % (p = 0.670) Neonatal outcome[a]: 7 vs. 10 % (p = 0.072) Cognitive score [at 2 y]: 17.9 vs. 17.5 % (p = 0.680)	No
Crowther et al. [15]	2017	398 vs. 389	Previous sPB (n = 12, twin pregnancies)	Vaginal pessaries	100 mg/ day	18–24 to 34	Acute respiratory distress syndrome: 10.5 vs. 10.6 % (p = 0.905) Severity: no difference (p = 0.905) PB < 37 WG[b]: 36.5 vs. 37.2 % (p = 0.765)	No
C) Oral progesterone								
Rai et al. [62]	2009	74 vs. 74	Previous sPB	Oral	200 mg/ day	18–24 to 36	PB < 37 WG: 39.2 vs. 59.5 % (p = 0.002)	Yes
Glover et al. [63]	2011	19 vs. 14	Previous sPB	Oral	400 mg/ day	16–20 to 33	PB < 37 WG: 26.3 vs. 57.1 % (p = 0.150)	Yes
Ashoush et al. [17]	2017	106 vs. 106	Previous sPB	Oral	400 mg/ day	14–18 to 37	PB < 37 WG: 44.7 vs. 63.7 % (p = 0.010)	Yes

WG: weeks of gestation, 17-OHPC: 17α-hydroxyprogesterone caproate, PB: preterm birth, sPB: spontaneous preterm birth, [a] combination of neonatal death, brain damage or bronchopulmonary malformation, [b] secondary outcome

placebo group (54.9 %) compared with other studies, however. In addition, the frequency of preterm births with 17-OHPC (36.3 %) was similar to that in other studies after previous preterm birth without therapy [19].

Three clinical trials and 2 meta-analyses carried out a direct comparison between vaginal progesterone and 17-OHPC in pregnant women with a previous preterm birth [20 – 24]. Contrary to the results of the double-blind study conducted by O'Brien et al. in 2007 already cited, both meta-analyses from 2017 (direct comparison of vaginal progesterone vs. 17-OHPC) indicated a significantly lower rate of preterm births at < 32 and < 34 WG with vaginal progesterone compared with 17-OHPC in singleton pregnancies with a history of preterm birth [23, 24]. The use of vaginal progesterone was also associated with a significantly lower adverse effect rate (7.1 vs. 13.2 % with 17-OHPC use) and a lower frequency of infant admissions to the Neonatal Intensive Care Unit (18.7 vs. 23.5 %) [23].

A Cochrane analysis was published as long ago as 2013, although this did not include the new studies mentioned (e.g. Norman et al., 2016, Crowther et al., 2017, Ashoush et al., 2017)

with large sample sizes. Eleven randomised, controlled studies were analysed involving 1936 pregnant women with a previous preterm birth [25]. This revealed a significant reduction in the preterm birth rate at < 34 WG (5 studies, n = 602, RR 0.31; 95 % CI 0.14–0.69), < 37 WG (10 studies, n = 1750, RR 0.55; 95 % CI 0.42–0.74) and a significant reduction in perinatal mortality (6 studies, n = 1453, RR 0.5; 95 % CI 0.33–0.75), neonatal morbidity (e.g. necrotising enterocolitis: 3 studies, n = 1170; RR 0.30; 95 % CI 0.10–0.89) and admission to the Neonatal Intensive Care Unit (3 studies, n = 389, RR 0.24; 95 % CI 0.14–0.40). This meta-analysis is limited by the fact that no distinction was made between the different progestogens, their dosages and methods of administration, however, which means that the review covers an extremely heterogeneous population: 4 studies with weekly administration of 250 mg 17-OHPC i. m., including 3 studies vs. placebo and 1 study vs. standard care, 5 studies with daily administration of intravaginal progesterone, including 3 studies vs. placebo and 2 studies vs. standard care, 2 studies with daily administration of oral progesterone vs. placebo, dosages in the studies with natural progesterone between 90 and 400 mg/day.

Overall, the available data on the use of vaginal/oral progesterone and of i. m. 17-OHPC for the prevention of preterm birth with a previous spontaneous preterm birth appear to be heterogeneous and in some cases contradictory.

Twin pregnancies without additional selection criteria

A recent Cochrane analysis from 2017 included 17 studies (n = 4773) involving multiple pregnancies without additional selection criteria investigating vaginal progesterone or 17-OHPC vs. placebo/no treatment for the prevention of preterm birth [26]. With considerable heterogeneity between the studies and predominantly poor study quality, no significant differences were observed in terms of the preterm birth rate either for 17-OHPC at < 37 WG (RR 1.05; 95 % CI 0.98–1.13) and < 28 WG (RR 1.08; 95 % CI 075–1.55) compared with placebo/no treatment or for vaginal progesterone (preterm birth rate at < 28 WG: RR 1.22; 95 % CI 0.68–2.21; preterm birth rate at < 37 WG: RR 0.97; 95 % CI 0.89–1.06), and there were also no significant differences in the neonatal outcome.

As a randomised, placebo-controlled double-blind study in non-selected dichorionic and diamniotic twin pregnancies showed (n = 290), an increase in dose from 200 to 400 mg progesterone/day vs. placebo did not result in any significant reduction in the preterm birth rate, perinatal mortality and neonatal morbidity [27].

Results II – Secondary Prevention

Singleton pregnancies before 24 + 0 WG with a short cervical length on ultrasound of ≤ 25 mm

A cervical length on ultrasound of ≤ 25 mm in the 2nd trimester is associated with a significantly increased risk of spontaneous preterm birth [28]. ▶ **Table 3** summarises the existing randomised, placebo-controlled studies on progesterone administration for the prevention of preterm birth in asymptomatic women with singleton pregnancies and a short cervix.

A recent individual patient data meta-analysis (IPDMA) by Romero et al. is available from 2018 which includes the data from the OPPTIMUM trial (Norman et al.) [29]. Asymptomatic pregnant women with a short cervix on ultrasound (≤ 25 mm) before 24 + 0 WG who were treated with vaginal progesterone (daily

▶ **Table 3** Randomised, placebo-controlled studies: Progesterone for the prevention of preterm birth in asymptomatic women with singleton pregnancies and a short cervix.

Author	Year	Number of patients Screening	Number of patients (progesterone vs. control)	Inclusion criteria	Progesterone type	Dose and interval	Period of use (WG)	Primary outcome	Reduction in preterm birth
A) 17-OHPC									
Winer et al. [68]	2015	–	51 vs. 54	High PB risk[a], cervical length < 25 mm at 20–31 WG	17α-OHPC i. m.	500 mg/ week	20–31 to 36	Interval (days) until birth: 76 ± 5 days vs. 72 ± 5 days (p = 0.480)	No
B) Vaginal progesterone									
Fonseca et al. [31]	2007	24620	125 vs. 125	Cervical length < 15 mm (n = 24 twin pregnancies) at 20–25 WG	Vaginal pessaries	200 mg/ day	24 to 34	PB < 34 WG: 19.2 vs. 34.4 % (p = 0.020)	Yes
Hassan et al. [34]	2011	32091	235 vs. 223	Cervical length 10–20 mm at 20–24 WG	Vaginal gel	90 mg/ day	20–24 to 36	PB < 32 WG: 8.9 vs. 16.1 % (p = 0.020)	Yes

WG: weeks of gestation; PB: preterm birth, 17-OHPC: 17α-hydroxyprogesterone caproate

[a] history of PB (55 % in active treatment vs. 57 % in placebo group), previous surgery on the cervix (4 vs. 8 %), uterine anomalies (20 vs. 19 %) or prenatal exposure to diethylstilbestrol (8 vs. 11 %)

▶ **Table 4** Individual patient data meta-analysis: Prevention of preterm birth with vaginal progesterone in asymptomatic pregnant women (singleton pregnancies) with a short cervix on ultrasound (≤ 25 mm) before 24 + 0 WG [29].

Outcome	Relative risk (RR) (95% CI)	p-value	NNT
Preterm birth < 28 WG	0.67 (0.45–0.99)	0.04	27
Preterm birth < 33 WG*	0.62 (0.47–0.81)	0.0006	12
Preterm birth < 35 WG	0.72 (0.58–0.89)	0.003	12
Respiratory distress syndrome	0.47 (0.27–0.81)	0.007	18
Total neonatal morbidity and mortality[a]	0.59 (0.38–0.91)	0.02	18
Birth weight < 1500 g	0.62 (0.44–0.86)	0.004	16
Admission to NICU[b]	0.68 (0.53–0.88)	0.003	13

[a] total neonatal morbidity and mortality: defined as the occurrence of one of the following events: respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, documented neonatal sepsis, neonatal death

[b] NICU = Neonatal Intensive Care Unit

NNT = number needed to treat, * = primary outcome

dose 90–200 mg) showed a significant reduction in preterm birth rate and an improved neonatal outcome (▶ **Table 4**) [29]. The significances were detectable for pregnant women both with and without a previous preterm birth, and the results are consistent with a previous meta-analysis from 2016 by the same team [30].

Five high quality clinical trials (assessed using the GRADE system) involving a total of 974 women with a cervical length of ≤ 25 mm before 24 + 0 WG were included in the individual patient data meta-analysis by Romero et al. (Da Fonseca et al. 2007, n = 226: 200 mg/d vaginal progesterone; O'Brien et al. 2007, n = 31: 90 mg/d progesterone gel; Cetingoz et al. 2011, n = 8: 100 mg/d vaginal progesterone; Hassan et al. 2011, n = 458: 90 mg/d progesterone gel; Norman et al. (OPPTIMUM study) 2016, n = 251: 200 mg/d vaginal progesterone [16, 31 – 34]). With regard to the method of administration as a vaginal gel compared with the capsule form, and also to the progesterone dosage of 90–100 mg or 200 mg/day, no significant differences in efficacy were observed [29]. It was also not possible to detect any negative effect of vaginal progesterone on the mothers or on the neurological development of children exposed in utero (studied up to the age of 2 years and initial data also up to 6 years) [35, 36]. A Cochrane analysis dating back to 2013 also came to similar conclusions [25]. A number of meta-analyses suggest that, in asymptomatic singleton pregnancies, a combination of cervical length screening by means of transvaginal ultrasound and the use of vaginal progesterone in pregnant women with a cervical length of ≤ 25 mm before 24 + 0 WG leads to a significant reduction in the preterm birth rate and an improvement in neonatal outcome [29, 30, 37 – 45].

No data from clinical trials are available at present for the prophylactic use of progesterone in the presence of a short cervix after 24 + 0 WG. This is therefore a decision that should be made on a case-by-case basis.

Twin pregnancies before 24 + 0 WG with a short cervical length on ultrasound of ≤ 25 mm

An individual patient data meta-analysis by Romero et al. from 2017 with 6 studies [27, 33, 46 – 49], that investigated the administration of vaginal progesterone versus placebo or no treatment in 303 asymptomatic twin pregnancies with a cervical length of ≤ 25 mm in the 2nd trimester was able to demonstrate a significant reduction in the preterm birth rate at < 33 WG (31.4 vs. 43.1%; RR 0.69; 95% CI 0.51–0.93, primary outcome) and an improvement in neonatal outcome, e.g. reduction in neonatal mortality (RR 0.53; 95% CI 0.35–0.81), respiratory distress syndrome (RR 0.70; 95% CI 0.56–0.89) and a reduction in babies with a birth weight of < 1500 g (RR 0.53; 95% CI 0.35–0.80) [50]; 70.4% of the patients included in this meta-analysis are taken from the study by El-Refaie et al., in which vaginal progesterone was used in a daily dosage of 400 mg vs. no treatment [48].

Results III – Safety and Possible Adverse Effects of Progesterone and 17-OHPC

17-OHPC

In the study by Meis et al., in which 250 mg 17-OHPC i. m./week was used for the prevention of preterm birth in women with singleton pregnancies and a previous preterm birth, no increased rates of miscarriage or stillbirth could be detected in the 17-OHPC group [51]. However, a higher rate of miscarriages was observed in the active treatment group before 20 WG (n = 5 [1.6%] in the 17-OHPC group vs. n = 0 [0%] in the placebo group [51]. A follow-up observational study between 30 and 60 months showed no significant differences in terms of the outcome for the child (including neurological and motor development parameters) [52]. The US medicines agency authorised the product Makena® for the prevention of preterm birth in 2011 subject to a confirmatory study (PROLONG trial) which was to include over 1700 pregnant women. The results of this study are eagerly awaited in spring 2019.

After intramuscular administration of 17-OHPC, short-term local reactions such as pain (34.2%), swelling (14.1%), itching (11.3%) and redness (6.7%) are to be expected [51].

Progesterone

Depending on the method of administration, progesterone administration can result in various adverse effects, some of them systemic. For oral administration, an increased rate of headache (no data available [53]), dizziness (29.1 vs. 9.8%) and fatigue (41.6 vs. 19.7%) has been described compared with placebo [17, 54, 55]. As a result of vaginal progesterone administration, the initial metabolism in the liver is bypassed, which leads to lower systemic at the same time as increased local bioavailability. This has been referred to as the "first uterine pass effect" [56]. This also results in a reduction in the systemic adverse effects described with oral progesterone administration [54, 57]. Studies point to an increase in vaginal discharge when progesterone is administered vaginally [31, 58].

There is currently no evidence of a negative effect of vaginal progesterone on the neurological development of the foetus (studied up to the age of 2 years and initial data also up to 6 years) [29, 35, 36]. Vedel et al. pointed out that progesterone administration in the 2nd and 3rd trimester in twin pregnancies (n = 492 pregnant women in the progesterone and n = 497 in the placebo group) did not show any detrimental effects on child development up to the 8th year of life [36]. A recent meta-analysis from 2017 that included 1188 newborns from 22 randomised, controlled studies was unable to show any negative effects of progesterone or 17-OHPC sui generis on neonatal mortality [59].

Other studies over a longer follow-up period are needed before a final assessment can be delivered. The use of progesterone for the prevention of preterm birth is an off-label use.

Discussion

Progestogens are capable of preventing preterm birth and significantly reducing neonatal morbidity and mortality. In this regard, as recent studies show, the pregnant women eligible need to be selected carefully, however. This problem will be addressed in more detail below.

The multifactorial aetiology of preterm birth has a decisive influence on study results [6]. For example, pregnant women with a previous preterm birth represent a heterogeneous at-risk population because of the differences in the causes leading to this preterm birth. The selection criterion of "previous preterm birth" is therefore not sufficient by itself to identify those pregnant women who benefit from progesterone administration. Whereas studies without any detailed characterisation of the causes of the previous preterm birth [15, 16] produced negative results, studies with additionally defined causes for the previous preterm birth (e.g. uterine anomalies, cervical incompetence) showed a significant reduction in the preterm birth rate [33, 60, 61].

The different pharmaceutical forms, methods of administration and dosages of progesterone/17-OHPC represent another problem with regard to the assessment and comparability of studies. The different metabolic and pharmacokinetic properties of oral and vaginal progesterone need to be taken into account (intestinal absorption with systemic effects vs. mainly local effect with predominant "first uterine pass effect"). A differentiated approach is therefore needed for studies with oral or vaginal progesterone. Even if the results still need to be confirmed in studies with higher sample sizes, oral progesterone administration represents a promising alternative for pregnant women with a previous spontaneous preterm birth [17, 62, 63].

On the basis of the study by Meis et al. (2003), weekly intramuscular administration of 250 mg 17-OHPC between 16 + 0 and 36 + 0 WG was authorised by the Food and Drug Administration (FDA) in the USA in 2011 for the prevention of preterm birth in singleton pregnancies with a previous preterm birth [51]. Mainly because of the increase in the miscarriage rate before 20 WG after 17-OHPC, the FDA requested a confirmatory study, which was initiated in 2009. As our own enquiry revealed, the PROLONG (Progestin's Role in Optimizing Neonatal Gestational Length) study has now been completed successfully with over 1700 pregnant women being recruited. The first results should be presented at the Annual Meeting of the Society for Maternal-Fetal Medicine in spring 2019. Contrary to the 2012 recommendations of the Society for Maternal-Fetal Medicine [64], in which progesterone was named as a possible alternative to 17-OHPC for the prevention of preterm birth in pregnant women with a previous preterm birth, the Society states in its 2017 update of these recommendations that, on the basis of the current data now collected, only 17-OHPC can still be recommended in this indication [65]. This decision is probably due mainly to the results of the OPPTIMUM study and those of Crowther et al. (2017) [15, 16]. Criticisms of the study by Crowther et al. include the inadequate characterisation of the risk factor of "previous preterm birth" and the inclusion of twin pregnancies.

In particular, however, the high-profile OPPTIMUM study published in leading journals has increasingly become the target of criticism [16]. This relates to the inclusion criteria in particular. Initially (2009), singleton pregnancies with the risk factor of previous preterm birth (defined as a previous preterm birth, previous premature rupture of membranes or previous cone biopsy) and a positive foetal fibronectin test were included. The next year, the exclusion criteria were widened to include singleton pregnancies with a previous preterm birth before 34 + 0 WG and a negative foetal fibronectin test and singleton pregnancies with a cervical length of ≤ 25 mm between 18 and 24 + 0 WG and a positive or negative fetal fibronectin test.

The relatively late start of treatment between 22 and 24 WG, particularly in the "previous preterm birth" subgroup that dominates the results (921 of 1228 recruited women) is also open to criticism. The SMFM recommends starting 17-OHPC use between 16 and 20 WG [65]. Furthermore, the subgroup (n = 256) with a short cervix between 18 and 24 + 0 WG in the OPPTIMUM trial is not comparable with those groups of patients in other studies investigating the use of progesterone in patients with a short cervix before 24 + 0 WG [31, 34] because pregnant women in these studies were documented and treated in a systematic screening programme.

Even when the results from the OPPTIMUM study were included, a subsequent individual patient data meta-analysis came to different conclusions [29]. This showed that vaginal administration of progesterone (n = 498) compared with placebo (n = 476) in 5 high-quality studies in singleton pregnancies before 24 + 0 WG and a cervical length on ultrasound of ≤ 25 mm resulted in a significant reduction in the preterm birth rate at

< 33 WG (RR 0.62; 95 % CI 0.47–0.81, p = 0.006) and < 36 WG (RR 0.80; 95 % CI 0.67–0.97, p = 0.02) and a reduction in neonatal morbidity and mortality, the rate of respiratory distress syndrome and of babies with a birth weight of < 2500 g (RR between 0.47 and 0.82) without any significant impact on infant development up to the 2nd year of life [29].

Being pregnant with twins increases the risk of preterm birth by a factor of approx. 6 [2], and having a short cervix at the same time further increases this risk significantly [66]. There are as yet no effective evidence-based strategies for the prevention of preterm birth in twin pregnancies. The individual patient data meta-analysis by Romero et al. (2017) showed promising results, but other, well designed, randomised, double-blind studies are needed [50]. Three of the clinical trials that are currently recruiting may lead to clear recommendations for practice (NCT02697331: 200 mg vaginal progesterone/day vs. placebo; NCT02518594: 3 treatment arms: 200 mg vaginal progesterone/day or Arabin pessary vs. placebo; NCT02329535: 400 mg vaginal progesterone/day vs. standard care [no treatment]).

Even if the use of natural progesterone in the 2nd and 3rd trimester is considered safe on the basis of the data available at present, there is a need for further follow-up studies of children exposed in utero over a longer period of time (> 2 years).

Further prospective controlled studies are needed to show whether pregnant women with progressive cervical shortening verified on ultrasound following cerclage benefit from progesterone, as demonstrated recently in a retrospective case-control study [67].

Conclusion

The current evidence from clinical trials with progesterone on the prevention of preterm birth suggests that strict selection criteria are necessary in order to identify those patients who actually benefit from progesterone administration. From this point of view, further studies with clearly defined inclusion criteria and (primary) endpoints which also take into account the most common and clinically relevant risk factors are essential. Because the available data are heterogeneous, the administration of natural vaginal progesterone to pregnant women, particularly those with a "previous preterm birth" in their history as a risk factor, cannot generally be recommended.

Although the results on oral progesterone use in pregnant women with a previous preterm birth are promising, they do not yet provide a sufficient basis (3 studies with 199 treated patients) for making definitive clinical recommendations.

The data from the confirmatory PROLONG trial, to be expected soon, will show the extent to which pregnant women with a previous preterm birth benefit from preventive treatment with 17-OHPC. According to a recent Cochrane analysis, neither natural progesterone nor 17-OHPC can be recommended for pregnant women with twin pregnancies without additional risk factors for preterm birth. There is not yet sufficient evidence to confirm whether increasing the dose in these cases from 200 to 400 mg progesterone/day leads to better results.

On the basis of current scientific knowledge, the following are evidence-based indications for progesterone administration for the prevention of preterm birth:

- Women with singleton pregnancies with a cervical length on ultrasound of ≤ 25 mm before 24 + 0 WG: vaginal administration of progesterone 200 mg capsules or 90 mg gel/day up until 36 + 6 WG.
- Women with twin pregnancies with a cervical length on ultrasound of ≤ 25 mm before 24 + 0 WG: vaginal progesterone 200–400 mg capsules/day up until 36 + 6 WG.

Conflict of Interest

PD Dr. Kuon received speaker's fees from DR. KADE/BESINS Pharma GmbH. Pauline Voß and Prof. Dr. Rath state that they have no conflict of interest.

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