Thieme

Controversies about the Secondary Prevention of Spontaneous Preterm Birth

Kontroversen um die Sekundärprävention von spontanen Frühgeburten

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ABSTRACT

Preterm birth is one of the major global health problems and part of the Millennium Development goals because of the associated high number of perinatal or neonatal mortality and long-term risks of neurodevelopmental and metabolic diseases. Transvaginal sonography has meanwhile been established as a screening tool for spontaneous preterm birth despite its relatively low sensitivity when considering only the cervical length. Vaginal progesterone has been shown to reduce prematurity rates below 34 weeks in a screening population of singleton pregnancies. Up to now, no positive long-term effect could be demonstrated after 2 years. It seems to have no benefit to prolong pregnancies after a period of preterm contractions and in risk patients without cervical shortening. Meta-analyses still demonstrate conflicting results dependent on quality criteria used for selection. A cerclage is only indicated in singleton pregnancies with previous spontaneous preterm birth and a combined cervical shortening in the current pregnancy. Nevertheless, the short- and long-term outcome has never been evaluated, whereas maternal complications may be increased. There is no evidence for a prophylactic cervical cerclage in twin pregnancies even in cases with cervical shortening. Emergency cerclage remains an indication after individual counseling. The effect of a cervical pessary in singleton pregnancy seems to be more pronounced in studies where a few investigators with increasing experience have treated and followed the patients at risk for preterm birth. Mainly in twin pregnancies, pessary treatment seems to be promising compared to other treatment options of secondary prevention when the therapy is started at early stages of precocious cervical ripening. At present, several international trials with the goal to reduce global rates of prematurity are in progress which will hopefully allow to specify the indications and methods of intervention for certain subgroups. When trials are summarized, prospective meta-analyses carry a lower risk of bias than the meanwhile uncontrolled magnitude of retrospective meta-analyses with conflicting results.

ZUSAMMENFASSUNG

Frühgeburten gehören zu den wichtigsten Gesundheitsproblemen weltweit und gehören wegen der damit verbundenen hohen perinatalen und neonatalen Mortalitätsraten und der Langzeitrisiken für neurologische Entwicklungsstörungen und Stoffwechselkrankheiten zu den Millenniums-Entwicklungszielen. Obwohl die Sensitivität der transvaginalen Sonografie bei der Messung der zervikalen Länge relativ niedrig ist,

hat sich diese Methode als Screeninginstrument bei der Prävention von spontanen Frühgeburten etabliert. Die vaginale Verabreichung von Progesteron hat in einer Population werdender Mütter mit Einlingsschwangerschaft die Frühgeburtsraten vor der 34. Woche nachweislich verringert. Bislang wurden aber keine positiven Langzeitwirkungen nach 2 Jahren nachgewiesen. Es scheint, dass die Herauszögerung der Schwangerschaft nach einiger Zeit mit vorzeitigen Wehen sowie bei Risikopatientinnen ohne Zervixverkürzung keine Vorteile bietet. Die Ergebnisse von Metaanalysen sind nach wie vor widersprüchlich und hängen von den gewählten Qualitätskriterien ab. Eine Cerclage ist nur bei Einlingsschwangerschaften nach spontaner Frühgeburt in einer vorherigen Schwangerschaft verbunden mit einer Zervixverkürzung in der aktuellen Schwangerschaft indiziert. Die kurz- und langfristigen Auswirkungen wurden nicht untersucht, obwohl sie möglicherweise zu einer Erhöhung der mütterlichen Komplikationen führen könnten. Es gibt keine Hinweise, dass die prophylaktische zervikale Cerclage vorteilhaft ist bei Zwillingsschwangerschaften, selbst bei Frauen mit Zervixverkürzung. Je nach individueller Beratung mag eine Not-Cerclage indiziert sein. Die Wirkung eines zervikalen Pessars in Einlingsschwangerschaften war ausgeprägter in Studien, bei denen die Untersucher zunehmende Erfahrung hatten bei der Behandlung und Nachbetreuung von Frauen mit einem höheren Risiko für Frühgeburtlichkeit. Im Vergleich zu anderen Optionen für die Sekundärprävention scheint die Behandlung mit einem Pessar erfolgversprechend, vor allem bei Zwillingsschwangerschaften, wenn früh mit der Behandlung begonnen wird, d.h. in den ersten Stadien einer vorzeitigen Zervixreifung. Zurzeit laufen mehrere internationale Studien, die alle das Ziel haben, die Frühgeburtsraten weltweit zu reduzieren, und die hoffentlich weitere Hinweise auf die Indikationen und Interventionsmethoden für bestimmte Untergruppen liefern werden. Bei der Zusammenfassung von Studien wiesen prospektive Metaanalysen ein niedrigeres Verzerrungsrisiko auf als die inzwischen unkontrollierte Menge retrospektiver Metaanalysen mit ihren widersprüchlichen Ergebnissen.

Introduction

Preterm birth and specifically the 70% of preterm births with spontaneous onset (sPTB) are globally defined as birth before 37 weeks of gestation by the World Health Organization (WHO) which calculates that yearly 15 million babies are born preterm [1, 2]. The rates vary between countries with low incidences in Northern Europe of around 5%, 8–9% in Germany, 12% in the United States (US) up to 15–20% in regions of Sub-Saharan Africa [3]. A further considerable risk is the development of neurologic, pulmonary, cardiovascular and metabolic long-term complications in the children up to adulthood [4]. Over the past decades, various attempts have been made to prevent sPTB. Conventionally, prevention is divided into primary, secondary and tertiary prevention.

Primary prevention has the aim to reduce the risk of PTB in all women [5]. Smoking cessation [6, 7] and restriction of physical stress and certain diets [8, 9] have been identified as strategies to reduce sPTB in singular studies.

Secondary prevention has the purpose to identify patients at risk as early as possible and initiate preventive treatments. After the systematic description that cervical length (CL) obtained by transvaginal sonography (TVS) is closely related to the duration of pregnancy [10], approaches based on CL measurement such as vaginal progesterone, cerclage and cervical pessary have been reevaluated. This also holds true for twin pregnancies, which have a 6 to 8-fold increase of sPTB rates compared to singleton pregnancies [11]. *Tertiary prevention* by tocolysis, administration of corticosteroids and transfer of the mother to a perinatal center does not prevent sPTB, but may improve the neonatal outcome.

However, the primary endpoint of all preventive measures should be long-term health and life quality of both mother and child as suggested by the CROWN initiative [12].

Romero et al. already described preterm birth as a syndrome in 1994 [13] and expanded this concept in more recent publications [14]. Therefore, it is unrealistic that a single measure would be universally effective to prevent this condition [5].

In former times, clinical "opinion leaders" related their preferences to their own experience not necessarily based on evidence-based studies. Vice versa, meanwhile clinical investigators may disregard that prospective clinical trials should be registered in advance and it should be assured that the clinicians performing trials are experienced in the method they investigate according to good clinical practice (GCP) and that their communication helps that the patient is compliant in case of pharmacological treatments.

The "tsunami of retrospective meta-analyses" (expression used by Alfirevic) [15] has lead to conflicting results because of different selection criteria and interpretation of the quality of the included studies. The term "p-hacking" thereby describes meta-analyses, which include trials that were not registered before study start and/or not blinded [16]. In addition, p-hacking may also occur when diagnoses and treatments are insufficiently supervised during the study performance [16]. The present manuscript discusses controversies in recent publications related to secondary prevention of sPTB to help clinicians to make proper decisions for their patients within daily routine work.

Review

Controversies about progestagens

Singleton pregnancies

The preventive effect of progestagens with regard to sPTB was first discussed by Papiernik-Berkhauer [17] in 1971 and then by Keirse [18] in 1990.

Natural progesterone has a short half-life, is rapidly resorbed from the vaginal mucosa and should be distinguished from the *synthetic 17-alpha-hydroxyprogesterone capronate* (17-OHPC). Due to its long half-life the latter is administered intramuscularly at

weekly intervals [19]. The benefit of 17-OHPC is controversially discussed [19]. The still ongoing PROLONG trial is intended to investigate the use of 17-OHPC in high-risk pregnancies with previous sPTB. According to genetic analyses [20], it is believed that certain genes such as the NOS1t modify plasma levels and the susceptibility of 17-OHPC. Therefore, the efficacy depends on pharmacogenetic differences among individual patients [21]. It has not found a place in patients with clinical symptoms (short CL, contractions) of threatening preterm birth neither in singleton nor in twin pregnancies [22–25].

On the contrary, the application of natural vaginal progesterone for the prevention of PTB has increased since the publication by DaFonseca et al. [26] in 2003. However, the patients in this study were not selected by CL measurements. Fonseca et al. [27] confirmed the utility of vaginal progesterone in patients with cervical shortening < 15 mm. However, this study failed to demonstrate a significant reduction in neonatal morbidity. In addition, it was only registered after the study was finished which increases risks of bias. The study by Hassan et al. [28] showed a significant reduction in the sPTB rate < 34, < 32 and < 28 weeks of gestation in asymptomatic women with a CL between 10 and 20 mm. Additionally, the authors observed a reduction in neonatal morbidity. However, it was criticized by statisticians of the FDA because the positive effects were mainly based on only 2 (out of 44!) centers in South Africa and Belarus. For instance, not even one US-center [29] found a significant reduction in sPTB-rate. In addition, the FDA statisticians found no evidence when correcting these data for maternal parameters and no difference in outcome after two years. This might have been a reason why the FDA did not agree that vaginal progesterone was approved in the US as a general preventive therapy [29].

The OPPTIMUM trial [30] investigated the long-term effect of vaginal progesterone application versus placebo for the prevention of PTB until the age of 2 years and generally found neither benefit nor harm related to the post-neonatal outcome, neither a significant prolongation of pregnancy. Therefore, Jane Norman concluded [22] that a drug for which no differences could be determined after two years should better not be given or at least would require patient's informed consent. Nevertheless, critics of this study were related to the variant inclusion criteria such as cervical shortening, positive fetal fibronectin or previous sPTB and a low compliance of only 60%. Meanwhile Romero et al. have conducted 3 meta-analyses, all published in the American Journal of Obstetrics and Gynecology, to underline the value of vaginal progesterone in asymptomatic singleton pregnancies with a short CL [31, 32]. Thereby, Romero et al. [33] still found a significant reduction of PTB even when data from Norman et al. were integrated [21]. In the most recent meta-analysis [31], the authors state that vaginal progesterone does not significantly work in normal weight nor in obese women, not in black and Asian women nor in US citizens, but also not in women < 18 or > 35 years. Although vaginal progesterone could reduce rates of PTB < 28 up to < 36 weeks, this was only significant if treatment was started in women between 22 and 25 weeks with a CL between 10 and 20 mm. Vaginal progesterone could not significantly reduce perinatal or neonatal mortality nor improve the long-term outcome after 2 years. In the last two meta-analyses, the authors thereby criticize the Opptimum-trial. On the contrary, Prior and Thornton [34] did not find any clinical value for vaginal progesterone when they included only studies with defined quality criteria in their meta-analysis (▶ **Table 1**). They also underlined that childhood outcomes matter more than surrogate markers of gestation at birth and early neonatal outcome [34].

Other topics of debate are the use of progestogens for prevention of sPTB in patients with a history of PTB and the use (similar to maintenance tocolysis) in women with a short cervix and after an episode of preterm contractions. O'Brien et al. [17] and DeFranco et al. [18] investigated the effect of vaginal progesterone in preventing sPTB between 28 and 36 weeks of gestation and found significant associations only if the CL was < 30 mm. Vaginal progesterone has not been successful to prolong pregnancy in women undelivered after their first preterm labor episode [35, 36].

Twin pregnancies

Up to now, most RCTs could not show any benefit to prolong pregnancy duration in selected or unselected twin gestations, e.g. regardless of CL [22, 36] and regardless of the dosage of vaginal progesterone of either 200 or 400 mg [37, 38]. Similarly, the Cochrane review by Dodd et al. [39] found no positive effect of progestogens in terms of reducing sPTB in multiple gestations. According to a meta-analysis of Schuit et al. [40], vaginal progesterone was found not to prolong pregnancy but in a subgroup of women with cervical shortening vaginal progesterone was suggested to reduce poor neonatal outcome.

By summarizing five negative trials and one positive trial in twin pregnancies with a short CL within a meta-analysis Romero et al. [41] concluded that vaginal progesterone reduces the risk of preterm birth in asymptomatic women with twin pregnancies and a short cervix in the mid-trimester. However, the authors admitted that the positive effect was only based on one non-registered and non-placebo-controlled trial from Egypt published in a low-impact journal [42], which would not match the criteria of Prior et al. (▶ **Table 1**). More conclusive data with selected inclusion and outcome criteria will be available from the large prospective meta-analysis currently on its way in the US.

There are still some worrying publications [43] on long-term-effects of progesterone such as a dose-dependent increase in acute lymphoblastic leukemia and sympathetic tumors of the central nervous system in children whose mothers had been exposed to progesterone after infertility treatment whereby the authors discussed that the accelerated cell proliferation and increased mutation rate could be caused by epigenetic changes. These effects have not been described with dosages used for secondary prevention of sPTB, while the retrospective nature of the study cannot exclude a confounder. For the treatment with vaginal progesterone the patients' compliance is prerequisite, therefore communicative skills of the medical staff and methods to control a regular application by special tools (e.g. apps) are highly warranted in RCTs and clinical practice.

Controversies about cervical and abdominal cerclage

A cerclage was designed to mechanically close the cervical canal. Later, concepts proposed a prevention of ascending infection [44]. The prophylactic (primary) cerclage in patients with a history

▶ **Table 1** Evaluation criteria for randomized controlled trials and meta-analyses for prevention of preterm birth.

		Total number of patients randomized	Number of randomized cases with cervical shortening at study start	Registered trials with pre-specified primary outcomes (before study performance)*	Placebo-controlled study (only for progesterone)	Compliance evaluated (only for progesterone)	Clinical teaching/protocol before study start (Applicable only for cervical procedures)	Long-term postneonatal outcome evaluated
Author, year		**N**	**N**					
Vaginal Progesterone	Da Fonseca, 2003 (S) (RCT)	142	8	–	+	–		–
	Fonseca, 2007 (S) (RCT)	250	250	+	+	+		–
	De Franco, 2007 (S) (RCT)	620	46	–	+	+		–
	O'Brien, 2007 (S) (RCT)	659	0	+	+	+		–
	Norman, 2009 (T) (RCT)	500	Not evaluated	+	+	+		+
	Hassan, 2011 (S) (RCT)	465	465	+	+	+		–
	Rode, 2011 (T) (RCT)	677	Not evaluated	+	+	+		–
	Wood, 2012 (T) (RCT)	84	Not evaluated	+	+	+		–
	Romero, 2012 (S) (MA)	775	775	–	NA	NA		–
	Maher, 2013 (S) (RCT)	518	29	–	–	+		–
	Palacio, 2013 (S) (RCT)	265	265	+	+	+		–
	Serra, 2013 (T) (RCT)	294	5	+	+	+		+ (only morbidity)
	El-refaie, 2015 (T) (RCT)	250	250	–	–	+		–
	Schuit, 2015 (T) (MA)	3768	224	–	NA	NA		–
	Norman, 2016 (S) (RCT)	1228	712	+	+	+		+
	O'Brien, 2016 (S) (Review)	NA	NA	–	–	–		–
	Romero, 2016 (S) (MA)	974	974	–	+	NA		–
	Romero, 2017 (T) (MA)	303	96	–	+	NA		–
	Romero, 2018 (S) (MA)	NA	974	–	+	NA	NA	+
Pessary	Goya, 2012 (S) (RCT)	385	385	+	NA	NA	+	–
	Liem, 2013 (T) (RCT)	813	133	+			–	+
	Hui, 2013 (S) (RCT)	108	108	–			–	–
	Liem, 2015 (T) (RCT, secondary)	790	130	+			+	+
	Goya, 2016 (T) (RCT)	137	137	+			+	–
	Nicolaides, 2016 (S) (RCT)	935	935	+			–	–
	Nicolaides, 2016 (T) (RCT)	1180	215	+			–	–
	Van't Hooft, 2018 (T) (RCT)	133	133	+			+	+
	Dang et al. 2018 (T) (RCT)	300	85	+			+	–
Cerclage	Rust, 2001 (S) (RCT)	113	113	+	NA	NA	+	–
	To, 2004 (S) (RCT)	253	253	+			+	–
	Berghella, 2004 (S) (RCT)	61	31	–			+	–
	Rafael, 2014 (S & T) (Cochrane)	1577	55	–			NA	–
	Saccone, 2015 (T) (MA)	49	49	–			NA	–
	Alfirevic, 2017 (S) (Cochrane)	3490	344	–			NA	–

Evaluation of randomized-controlled trials or meta-analyses on prevention of sPTB according to criteria of Prior, clinical audit and compliance.
N = Number, S = Singletons, T = Twins
RCT = Randomized Controlled Trial, MA = Metaanalysis, Cochrane = Cochrane Review
NA = not applicable, + = affirmative/evaluated, – = Negative/not evaluated
Secondary = secondary analysis
* Source: Clinicaltrials.gov and Prior et al. 2017

of preterm birth or multiple gestation has been enthusiastically and uncritically used for decades. It should be distinguished from the therapeutic (secondary or tertiary) vaginal cerclage. The most frequently used methods are the Shirodkar and McDonald operations, which do not seem to differ from one another in the general outcome [45]. In very rare cases without cervical tissue after trachelectomy or repeated radical conization an abdominal cerclage is described to be a better option [46, 47]. The Total Cervix Occlusion (TCO) should be differentiated from the cerclage since it closes the cervical canal like a total barrier and thus prevents ascension of microorganisms, while the cerclage only tightens the canal. The early TCO is an early preventive measure for women with a history of two or more late abortions or early PTB (before 32 weeks). Depending on the experience of the operator and available results the early TCO is a promising efficient operative measure for the prevention of sPTB [48–50]. In the absence of randomized trials regarding the TCO we would like to focus in the current manuscript only on the treatment with cerclage.

Singleton pregnancies

Meanwhile, systematic reviews have shown that a prophylactic cerclage is only indicated in high-risk pregnancies with 3 or more preterm births due to cervical insufficiency. Althuisius and van Geijn [51] showed that, with exception of this high-risk group, the expectant observation of the CL by TVS is the better alternative to the prophylactic cerclage.

A secondary cerclage is performed in cases with shortened cervix, while tertiary or emergency cerclage is carried out in cases with an opening of the entire cervix or a prolapse of the amniotic sac. Berghella et al. [52] showed a reduction of the premature births before 35 weeks after treatment with a cerclage in singleton pregnancies with a cervical shortening under 25 mm and a history of previous sPTB. However, in his first meta-analysis the reduction of prematurity did not achieve significant results in patients with funneling or CL length < 15 mm. Only after inclusion of the study data of Owen et al. [53], Berghella et al. [54] showed in a further meta-analysis a significant reduction of prematurity in singleton pregnancies with previous premature birth and a CL of either < 25 mm or < 15 mm. Nevertheless, there is no evidence that the therapeutic cerclage can be useful in cases without previous sPTB even in the presence of cervical shortening in the index pregnancy [55, 56]. A Cochrane review by Alfirevic et al. [57] including singleton pregnancies concluded that "cervical cerclage reduces the risk of preterm birth in women at high-risk of preterm birth and probably reduces risk of perinatal deaths. There was no evidence of any differential effect of cerclage based on previous obstetric history or short cervix indications, but data were limited for all clinical groups. The question of whether cerclage is more or less effective than other preventative treatments remains unanswered".

Twin pregnancies

A Cochrane review by Rafael et al. [58] investigated five prospective RCTs including 122 twin pregnancies with cerclage. The authors even found a statistically significant increase of cases with low or very low birth weight and with Respiratory Distress Syndrome (RDS) after cerclage compared to expectant management, regardless of a further increase in maternal morbidity. These findings could be confirmed by the meta-analysis of Saccone et al. [59] analyzing twin pregnancies with cervical shortening. Following these data, the Society for Maternal-Fetal Medicine (SMFM, choosing wisely criteria) advises against the placement of a cerclage in women with short cervix who are pregnant with twins [60].

Controversies within observational studies may also be contributed to different operative skills and clinical surveillance. Only a cerclage height of 18 mm or greater (from the external os) has been shown to be associated with a reduction in sPTB for women with an ultrasound-indicated cerclage [61]. It can hardly be denied that vaginal cerclage and even more abdominal cerclage demand experience of the operator and unfortunately, this has not sufficiently been considered or audited in prospective or retrospective trials. The clinical risks of cerclage are rare, but if they occur, they can be dramatic up to blood loss, severe sepsis, perinatal, neonatal or maternal death [62]. Within many trials and meta-analyses differences in operative skills and surveillance may cause conflicting results but have even been described after negative amniocentesis [63].

Controversies about cervical pessaries

An alternative approach for secondary prevention of sPTB is represented by the placement of a cervical pessary. The use of a ring pessary has been proposed in 1959 [64] followed by some other models during the years [65]. The meanwhile mostly used model represents a negative re-print of the upper vaginal vault and was developed for pregnant women with clinically short cervix and a risk for sPTB [66]. Only 25 years later it was re-evaluated in patients with a short CL based on TVS [67]. This pessary is meanwhile approved for the prevention of preterm birth within Europe and several countries (CE0482/EN ISO 13485:2003 Annexe/III of the Council Directive 93/42 EEC) and by the FDA as an Investigational Device Exemption (IDE) for study use.

Using magnetic resonance imaging it has been shown that the pessary produces a sacralisation of the cervix, and may lead to a change of the utero-cervical angle or even a reduction in funneling and a cervical length prolongation [68]. Consequently, this may have an impact on stretching of the cervical cells and prevent atypical interleukin production [69]. A study using TVS showed that the cervix is prolonged during pessary treatment and that this is associated with a prolongation of pregnancy [70].

Singleton pregnancies

The first large RCT by Goya et al. [71] with this model investigated 385 singleton pregnancies with cervical shortening < 25 mm after teaching and audit of the staff in special preterm birth clinics in Barcelona. They found that prematurity before 34 weeks was significantly reduced and that the neonatal outcome was improved in the pessary group. An RCT by Hui et al. [72] in Hong Kong could not show a reduction of sPTB. However, the quality of this study is questionable because it was not registered, disengaged from the power analysis before reaching the number of patients and was designed as "double blind study", which is not only impossible for operational procedures but also leaving ethical issues unanswered. In addition, a concurrent study from the same center

showed that a pessary was effective to prolong the duration in high-risk pregnancies for sPTB, so there might have also be a selection bias [73].

Nicolaides and co-workers [74] applied pessaries in patients with singleton pregnancies and cervical shortening in a multicontinental prospective study with involvement of many clinicians, not experienced in the therapy. The authors could not find any differences between pessary treatment and the control group. However, 40% of the study population was treated parallel with progesterone. In addition, the high rate of premature removal of the pessaries and the application of antibiotics (33.5%) for a so-called "infection" signalizes that instructions in clinical surveillance such as the differential diagnosis between asymptomatic discharge, premature rupture of membranes (PPROM) and "infection" were not defined. Similarly, Watts et al. [75] have demonstrated a case in which the watery discharge and pooling of fluid in the posterior fornix after pessary insertion was suspected for preterm premature rupture of the membranes although it was later excluded. Predefined instructions and surveillance protocols may prevent redundant interventions such as corticosteroids or antibiotics. Alterations of the microbiome due to unnecessary antibiotic exposure could have adversely affected the outcome [76]. The multicontinental character of the study of Nicolaides [55] also indicates methodological weaknesses as clinical experience with pessary treatment within many study centers was neither present before nor personally taught or audited [77]. Franca et al. [78] investigated the impact of a learning curve in pessary treatment and found significant differences in outcome between early and late recruitment in a prospective study. Accordingly, the recent European guidelines on preterm labor and birth management [72] recommend pessary treatment for secondary prevention of sPTB only after proper training and suggest further RCTs with training to clarify the usefulness of pessary treatment.

The most recent RCT in singleton pregnancies with a short CL could demonstrate a significant reduction of preterm birth rates < 34 weeks [79].

To date, there is only one Cochrane review [80] on pessary treatment, which indicates positive effects and a potentially favorable cost–benefit ratio in countries with high preterm birth rates.

Pregnant women with either a history of sPTB and/or a conisation constitute a special subgroup. Alfirevic et al. [47] retrospectively examined the perinatal outcome of patients with previous sPTB receiving vaginal progesterone, cerclage or pessary and found that the pessary was associated with a lower rate of sPTB before 34 weeks compared to progesterone (12 vs. 32%, RR 2.70). However, these data should be interpreted with caution because of the retrospective nature of the study. After a conisation, Ortoft et al. [50] reported a 2.8-fold increased perinatal death rate, an almost 5-fold risk for sPTB after a single and a 10-fold risk after two cone biopsies in subsequent pregnancies [81]. While a cerclage could not reduce sPTB rates in these high-risk pregnancies [82, 83], a prolongation of pregnancy was observed after pessary application during the first trimester within a pilot observational study [84]. However, neither for patients with a history of sPTB nor for patients with a conisation RCTs have been published.

Twin pregnancies

Pessary treatment was proposed to be effective in twin pregnancies with a short CL [67]. However, in the Pro-Twin trial [62] unselected patients (n = 813) with twin pregnancies between 16 and 20 weeks were randomized to pessary versus control group. Although the authors did not find – as expected – any differences with regard to the primary outcome (sPTB before 34 weeks), in a subgroup of patients with cervical shortening below 38 mm (< 25th centile) there was a significant 6-fold reduction in perinatal mortality in the pessary group and similarly a significant reduction of severe morbidity. These findings indicate that early screening and early therapy are important in high-risk groups [85] and correspond with previous studies demonstrating that the likelihood of sPTB is 10 times higher in patients with a short CL before than that of after 20 weeks [11].

A second RCT by Goya et al. [86] also showed a significant reduction in the rate of sPTB in twins with a CL < 25 mm at 20–24 weeks after pessary treatment compared to a control group. The differences were less pronounced compared to the subgroup with early shortening between 16 and 20 weeks in the Pro-Twin study. Similarly, Fox et al. [87] reported a significant reduction of sPTB in twins before 32 weeks (4.8 vs. 28.6%), a significant prolongation of pregnancy (65.2 vs. 52.1 days) and a significant reduction of neonatal morbidity (9.5 vs. 34.9%). Two smaller studies were published: A small historic control study by Carreras et al. [88] investigated monochorionic twin pregnancies with severe twin-to-twin transfusion syndrome after laser surgery and reported a clinically significant prolongation of pregnancy by more than 4 weeks in cases with cervical shortening < 25 mm. Based on this pilot study, meanwhile we (IK and FB) are already recruiting patients in an RCT run by the team of Hebron Barcelona and included all monochorionic twin pregnancies undergoing laser treatment [89]. Di Tommaso et al. [90] conducted a case-control study comparing 40 twin pregnancies with a CL < 25 mm between 20 and 31 weeks treated with a pessary with a control group. Patients with a pessary delivered at a higher gestational age compared to the controls (35 vs. 33 weeks, p = 0.02), showed a prolongation of pregnancy and their infants had a shorter stay at the hospital (p = 0.03).

The only study that showed no benefit was a study by Nicolaides et al. [91]. The authors admitted that the quality of the study was limited because of no audit and the fact that a high proportion of pessaries were removed too early due to similar reasons as described for singleton pregnancies: too many unexperienced clinicians were involved [92]. Recently, Berghella et al. [93] reported on a trial to prevent prematurity in twin pregnancies using a pessary which was developed to treat cystoceles. The study was interrupted and strongly underpowered. Although many aspects of this study were criticized, the readers who only study abstracts may falsely cite the results when they wish to argue against pessary use in twins [65].

Patients from the Pro-Twin Trial were evaluated in secondary analyses showing that the effect of a pessary even improved when patients who were not treated according to GCP were removed from evaluation [94]. In addition, specific subgroups, which were more responsive to pessary treatment, were evaluated by a validated multivariable selection model, with CL, chorionicity, preg-

nancy history and number of fetuses. Primiparous women with monochorionic twins seemed to benefit best from pessary treatment [95].

More importantly, the twins of the Pro-Twin trial were followed up to 3 years of age after pessary treatment and compared with a control group. There was a significantly higher survival rate without neurological impairment in the pessary group compared to controls (92.4 vs. 73.8%, p = 0.006) [96]. Similar findings in twins are still not available after treatment with vaginal progesterone or cerclage.

Last but not least, Dang and colleagues [97] recently presented the first randomized trial comparing a cervical pessary versus vaginal progesterone in twin pregnancies with a cervix < 38 mm and a pre-defined subgroup of women with a CL < 28 mm. Hereby, in this pre-specified subgroup they found a significant reduction of 54 and 35% in sPTB < 34 (RR 0.46, 95% CI 0.24–0.89) and < 37 (RR 0.65, 95% CI 0.45–0.93) weeks respectively and a better neonatal outcome after the use of a cervical pessary compared to vaginal progesterone. As such the admission rate of neonates in the NICU in the pessary group was 15.6% compared to 44.4% in the progesterone group (RR 0.35, 95% CI 0.11–0.49). Most important, the neonatal sepsis rates in the pessary group were 6.7% in the pessary group versus 23.8% in the progesterone group (RR 0.28, 95% CI 0.08–0.63).

Meanwhile, several more RCTs in twin pregnancies are registered (NCT03418311, NCT02235181 and NCT02518594) and will be summarized in a prospective meta-analysis in the future called "the prospective meta-analyses of pessary trials" (PROMPT) using all CORE outcome parameters.

Meta-analyses using two or three studies [98] including data where teaching was questionable will soon be overruled by outcome data of more trials whatever the outcome may be.

Combinations of treatments

Within the first study when a cervical pessary was placed due to TVS, it was placed out of despair as a sort of last attempt in a patient with a history of two fetal losses, twins and a non-functioning cerclage (endocervical length of 0, personal communication Birgit Arabin). Although the patient had already lost 2 children due to sPTB at 20 weeks, pregnancy continued until 36 weeks when two heathy twins were born. Systematic reports on a combined treatment with cerclage and pessary are currently missing. However, they may be theoretically useful considering that the cerclage may prevent the prolapse of the membranes while the pessary would relieve the strain from the stitches. Smaller studies comparing either the pessary with combined treatment with pessary and progesterone [99] or progesterone alone with combined treatment of progesterone with pessary [100] have not shown any significant difference in the preterm birth rate. In a cohort study by Stricker et al. [99] pessary treatment was compared with the combination of pessary and vaginal progesterone (200 mg daily) in a screening and in a high-risk group of patients with short CL. Although the preterm birth rate could not be reduced through the additional application of progesterone, neonates from the combined treatment screening group stayed shorter at the neonatal intensive care unit compared to the pessary group. Whether this trend was the result of an anti-inflammatory effect of progesterone [101] or just a confounder due to the historic cohort shall be answered in larger future trials. Since both treatments, vaginal progesterone and cervical pessary are relatively cheap, non-invasive and carry low risks it may be optional to use both treatments until larger prospective cohorts allow a more directed treatment within specific subgroups.

A further 3-armed study reported that the additional application of a cervical pessary compared to cerclage or progesterone alone resulted in a significant reduction of dysbiosis, vaginal bleeding and chorioamnionitis [102]. This was mainly true in patients with placenta praevia where a pessary led to a 3-fold reduction of severe bleeding and prematurity (Borinov, personal communication).

At present, large systematic studies comparing vaginal progesterone and pessary in screening groups (NCT03058536) or cerclage and pessary in high-risk groups or even trials with three arms (progesterone, pessary and cerclage in high risk groups with singleton pregnancy) (NCT02673359) are still ongoing. Similarly, in twin pregnancies, comparative studies are on their way to compare the effect of vaginal progesterone and cervical pessary (NCT02518594 and NCT02623881).

Mainly in risk patients such as patients with a history of early preterm birth or multiple gestation, it is essential to screen before 20 gestational weeks due to the increased likelihood for preterm birth with early precocious cervical ripening [11].

Conclusions

Although TVS is recognized as a screening tool for high-risk pregnancies and used in most trials for selection of risk patients, the sensitivity for sPTB is still relatively low and more specific (combinations of) prognostic tools are desired. In this regard, rapid bedside tests for prediction of sPTB such as Placental alpha macroglobulin-1 (PAMG-1) and fetal fibronectin are available for women with cervical ripening. According to the most recent findings, PAMG-1 demonstrated statistical superiority against fetal fibronectin in predicting sPTB [103]. Due to controversial study results, it may be difficult for clinicians who do not have the chance to analyze study designs to get to proper conclusions for their patients.

Large studies, which are not conducted with scientific correctness (e.g. not registered, not placebo-controlled in case of progesterone, no teaching nor audit of a clinical protocol for cerclage and pessary) can bias study results and meta-analyses.

By addressing the controversies for each form of secondary prevention, and by classifying RCTs and meta-analyses which can be permanently renewed (▶ **Table 1**) we tried to optimize transparency for clinicians who need to make decisions on a daily basis.

In addition, we try to summarize the essentials in our perspective:

Vaginal progesterone seems to reduce prematurity rates below 36 weeks in a screening population of white mothers only when the treatment starts between 20 and 24 weeks and with a CL between 10 and 20 mm [31]. Up to now, no positive long-term effect could be demonstrated after 2 years. It seems to have no benefit to prolong pregnancies after a period of preterm contractions and in risk patients without cervical shortening. Meta-analyses still demonstrate conflicting results dependent on quality criteria

used for selection. All apart one single RCT showed no benefit in unselected or selected (short CL) twin pregnancies. In the most recent meta-analysis positive results were only based on this RCT, which was not registered nor placebo controlled and therefore does not meet the British selection criteria for meta-analysis by Prior et al. [16].

A cerclage is (only) indicated in singleton pregnancies with previous sPTB and a combined cervical shortening in the current pregnancy. Nevertheless, the short- and long-term outcome could not be improved, whereas maternal complications may be increased. A prophylactic cervical cerclage should not be indicated in twin pregnancies even not when they have a short CL. Emergency cerclage remains an indication after individual counseling.

The effect of a *cervical pessary* in singleton pregnancy seems to be more pronounced in studies where a few investigators with increasing experience have treated and followed the patients at risk for preterm birth. Mainly in twin pregnancies, pessary treatment seems to be promising compared to other treatment options of secondary prevention when the therapy is started at early stages of precocious cervical ripening. There are several trials in progress comparing different treatment options in specific subgroups.

For a successful therapy with vaginal progesterone, communicative skills and audit of the patients' compliance are prerequisite. For cerclage and pessary treatment, clinical experience related to technique of operation or insertion, clinical surveillance and mode and timing of removal should not be neglected as an essential factor contributing to a successful or unsuccessful strategy. Therefore, these patients should be treated by experienced obstetricians within preterm birth clinics and surveillance protocols should be available.

Apart from strict methodological selection criteria for RCTs and meta-analyses the consideration of good clinical practice and standard outcome (CROWN) criteria including long-term outcome seem all necessary to avoid further research waste [104, 105].

The US initiative PROMPT including many RCTs from different countries comparing secondary prevention strategies for sPTB may widen our horizon by a large international collaboration and may better convince clinicians, health care politicians and funders: "Whether we can all speak with one voice, only time will tell" [65].

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Conflict of Interest

The authors declare that they have no conflict of interest.

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