Archives of Gynecology and Obstetrics (2019) 299:1261–1273
https://doi.org/10.1007/s00404-019-05095-y

MATERNAL-FETAL MEDICINE

Prevention of spontaneous preterm birth

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Received: 12 November 2018 / Accepted: 6 February 2019 / Published online: 14 February 2019

Abstract

Background It is estimated that globally, approximately 13 million preterm infants are born annually and a much higher number of pregnancies are characterized by threatening preterm birth.

Findings A proportional inverse correlation between gestational age at delivery and neonatal mortality has been observed which is more prevalent in countries without high standard neonatal care. The socioeconomic burden of preterm birth is enormous, as preterm neonates are particularly prone to severe morbidity that may expand up to adulthood. Several strategies have been proposed for the prevention of preterm birth which can be sub-stratified as primary (when these apply to the general population), secondary (when they target women at risk), and tertiary (optimizing neonatal outcomes when preterm birth cannot any longer be prevented). The aim of this review is to summarize the most important strategies.

Keywords Preterm birth · Prevention · Progesterone · Cerclage · Pessary · Smoking · Pregnancy

Introduction

It is estimated that annually, 13 million preterm infants are born [1]. The worldwide rates of preterm birth (PTB) vary with an estimated prevalence of 5% in some high-income countries (HICs) up to 25% in many low-and-middle-income countries (LMICs) according to data between 2005 and 2012 [2, 3]. Approximately 60% of preterm infants are born in south Asia and sub-Saharan Africa [4]. In Europe, the rates of PTB increased from 1996 to 2008 [4] and ranged from 4.9% in Lithuania to 11.2% in Greece in 2015 [5].

Preterm birth is associated with early neonatal morbidity such as temperature instability, respiratory distress, infections, apnoea, hypoglycaemia, seizures, jaundice, feeding difficulties, necrotizing enterocolitis, periventricular leukomalacia, and need for prolonged or repeat hospitalization [6]. The economic burden for the United States in terms of the medical and educational needs of the offspring exceeded 26.2 billion dollars in 2005 [1].

A proportional inverse correlation between gestational age at delivery and neonatal mortality has been observed, but depends also on the standard of neonatal care in different continents. Moderate prematurity between 32 and 36 weeks is more prevalent, and epidemiologic studies suggest that the rates still increase over time [1]. Despite advances in

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neonatal care, PTBs continue to be responsible for the majority of neonatal mortality both in HICs and LMICs [7].

In HICs, it is estimated that approximately 40–45% of preterm births are attributed to preterm labor; 25–40% follow preterm premature rupture of membranes (PPROM) [8]. Several factors are associated with spontaneous preterm birth (sPTB) and maternal age seems to be predominant. In a recent large cohort study that was based on 184,000 births, Fuchs et al. [9] performed a multivariate analysis to determine factors that increase the risk of sPTB. The authors reported on a U-shaped adjusted odds ratio (aOR) after stratification by maternal age, indicating an increased risk for women of 40 years and older (aOR 1.20, 95% CI 1.06–1.36). In contrast, the lowest risk for prematurity was found in the patient group of maternal age 30–34 with a nadir at 5.7%. Similar outcomes were also reported by Goisis et al. in their cohort study from Finnish population registers which included 124,098 children born between 1987 and 2000 [10]. The authors reported that the optimal outcomes in terms of the prevalence of low birthweight and preterm delivery were observed in maternal ages that ranged between 25 and 29 years. Women above 40 years had the highest risks (OR 1.20, 95% CI 1.04–1.39). Approximately one-third of PTBs are estimated iatrogenic due to maternal or fetal indications. Current data indicate that the prevalence of iatrogenic PTB is increasing in HICs [11]. Nevertheless, this may be beneficial, as studies report a sharp decline in neonatal mortality and morbidity among these infants [12, 13].

The pathophysiology that accompanies the spontaneous onset of preterm labor is heterogeneous and summarized by Romero et al. [14] in categories such as intraamniotic infection, decidual senescence, and breakdown of the maternal–fetal tolerance.

Preventive strategies for sPTB can be sub-stratified as primary (when these apply to the general population), secondary (when they target women at risk), and tertiary (optimizing neonatal outcomes when PTB cannot any longer be prevented). The aim of the present review is to summarize these strategies. We consciously decided for the form of a narrative review and not for retrospective meta-analyses because of the heterogeneous quality of randomized controlled trials (RCTs) of studies dealing with PTB prevention, where the clinical skills, performance of procedures, audit, population, and compliance of patients vary significantly and would cause systematic reviews of poor quality.

Evidence-based interventions to reduce the incidence of sPTB

Primary prevention

Smoking cessation

Cigarette smoking has a dose-dependent relationship with PTB that may be partly attributed to the increased incidence of placental abruption, placenta previa, PPROM, and fetal growth restriction (FGR) [15–18]. A direct effect of cigarette smoking on sPTB has been suggested, because after adjusting for confounders, the incidence of PTB continues to increase among smoking pregnant women [5, 19, 20]. A European collaborative study found that smoking is more strongly related to PTB than to FGR [5]. Thereby, the level of smoke-free legislation correlated with lower PTB prevalence rates and that their data support greater implementation of smoke-free policies.

Decreasing the rates of multiple gestation in ART

The incidence of PTB is six-to-eight times more likely in multiple gestation. The increasing rates of assisted reproductive techniques (ART) during the last decades led to an increase of twin and high-order multiple pregnancies. The PTB rates are most probable due to overdistention and earlier cervical shortening [21]. Given the increased prevalence of maternal and fetal diseases in multiple gestation, selective embryo reduction has been previously adopted in clinical practice [22]. The need to practice this technique has been limited by current guidelines that aim to reduce the incidence of twin gestation and completely avoid the risk of high-order gestation in women that conceive with ART, by restricting the number of transferred embryos [23, 24].

Apart from twin and multiple gestations, also singleton pregnancies after ART have a higher incidence of PTB as demonstrated by a systematic review and meta-analysis [25].

Reducing occupational fatigue

Occupational fatigue is a major factor that increases the odds of PTB and should be, whenever possible diminished. A meta-analysis of 21 studies that included 146,457 women identified a high cumulative work fatigue score as the strongest work-related risk factor for preterm birth with an odds ratio (OR) of 1.63 and a [95% confidence interval (CI) of 1.33–1.98] [17]. Various occupational factors seem to influence the antenatal outcome and risk of PTB including the actual range of working hours, standing, lifting, and the amount of physical activity that is needed [26, 27]. In

addition, lack of social support, adverse child experiences, and a so-called allostatic load, which may even be epigenetically transferred, may induce PTB as shown in animal experiments and humans [28–30]. A primary prevention would be to avoid these stress factors.

Improving nutritional habits

Optimizing nutrition and maintaining a normal body-mass index (BMI) is essential to ensure improved pregnancy outcomes. It seems that improving dietary habits during the first and second trimesters of pregnancy may reduce the risk of PTB. The role of nutrition for the prevention of PTB has been underlined by Mikkelsen et al. who demonstrated that the adoption of a Mediterranean-type diet reduced the risk of PTB in a series of 35,530 women [31]. Parlapani et al. observed that a high adherence to a Mediterranean diet improved fetal growth and decreased the risk of developing necrotizing enterocolitis, bronchopulmonary dysplasia, and retinopathy of prematurity [32].

Two meta-analyses suggest that omega-3 fatty acid supplementation effectively reduces the risk of PTB either < 34 weeks by 58% [33] or for early PTB by 22% [34]. In contrast, in women with a history of PTB, its use did not prevent recurrent PTB.

Avoiding short interpregnancy intervals

Short interpregnancy intervals significantly increase the risk of adverse pregnancy outcomes and the incidence of PTB. The most prominent study is based on a cohort of 328,577 pregnancies in Denmark between 1994 and 2010 [33]. The authors observed that the interpregnancy interval had a U-shaped association with PTB and that women with an interval between 18 and 23 months had a lower risk of PTB. Whether a short interpregnancy interval (< 6 months) after dilatation and curettage translates in increased PTB rates are controversially discussed [34, 35].

Conclusions from the most recent summary comparing several systematic reviews

In 2018, Medley et al. published an overview of systematic Cochrane reviews about all kinds of interventions to prevent PTB [36]. There was clear evidence of benefit for primary prevention in specific populations based on four systematic reviews such as:

- midwife-led continuity models of care versus other models of care for all women;
- screening for lower genital tract infections for pregnant women less than 37 weeks and without signs of labor;
- bleeding or infection;
- zinc supplementation for pregnant women without systemic illness.

Secondary prevention

Secondary prevention aims at the early detection of patients at risk for PTB and an institution of treatment based on this diagnosis. The ultrasonographic assessment of cervical length (CL) with transvaginal sonography (TVS) at the second trimester of pregnancy has been already correlated with the risk of PTB both in singleton and in twin pregnancies [37, 38]. Several strategies have been introduced to help to limit the risk of PTB in these women with conflicting results concerning their efficacy [39].

Cervical pessary

Cervical pessaries have been reported as a potential strategy that may help limit the rates of PTB. Several models have been used, but the best investigated is a silicone-based pessary which was constructed as a negative reprint of the upper vaginal vault which surrounds the internal cervical os and performs a sacralisation of the cervix [40]. The use of this silicone Arabin pessary has been approved for the prevention of preterm birth in Europe (CE0482/EN ISO 13485:2003 Annexe/III of the Council Directive 93/42 EEC), an increasing number of countries and by the FDA as an investigational device exemption (IDE) for study use.

Cervical pessaries are minimally invasive, cost effective, and relatively easy to applicate. The success rates have been shown to increase with clinical experience indicating a learning curve [41]. They may act as mechanical barriers that promote cervical elongation and increase the uterocervical angle; it has been demonstrated by magnetic resonance imaging that the uterocervical angle is changed after pessary insertion and the cervix elongated [42].

Cervical elongation after pessary insertion has also been shown by transvaginal ultrasound (TVU) [43].

Singleton pregnancies In 2003, the first a case–control study based on TVU suggested that women with a short CL may benefit of the use of cervical pessary [44]. The first RCT by Goya et al. (the Pesario Cervical para EvitarPrematuridador PECEP trial) showed significant benefit in the reduction of PTB before 34 weeks (OR 0.18, 95% CI 0.08–0.37; $p < 0.0001$) in 385 women with a CL < 25 mm and a significant improvement of compound neonatal outcome. Results from further studies have been conflicting. The largest (multicontinental) RCT by Nicolaides et al. enrolled 932 women with singleton pregnancy and a CL < 25 mm between 20 and 24 weeks, but showed no significant reduction in sPTB < 34 weeks (OR 0.12; 95% CI 0.75–1.69; $p = 0.57$) [45]. The discrepancy with

the PECEP study might have been due to a difference in teaching and audit, the additional use of antibiotics in the treatment and vaginal progesterone in the control group, the lack of personal audit, experience, or the way of reassuring patients during surveillance [46]. A more recent RCT from Saccone et al. from one Italian center with experienced obstetricians could demonstrate significant benefit when a cervical pessary was applied between 18 and 24 weeks in women with a CL < 25 mm. The rate of PTB < 34 weeks was 7.3% in the pessary group and 15.3% in the control group with a between-group difference of − 8.0% (95% CI − 15.7% to − 0.4) and a relative risk (RR) of 0.48 (95% CI 0.24–0.95) [47]. Three additional RCTs had a high risk of bias, since they were underpowered or/and used pessaries not designed to prevent PTB [48–50] and should not be integrated into meta-analysis [40].

A recent retrospective cohort study stated that the combined treatment of Arabin cervical pessary and vaginal progesterone had lower rates of PTB < 34 weeks of gestation and prolonged gestation compared to women treated with vaginal progesterone alone [51].

There are two RCTs related to the use of cervical pessaries in patients who had already an episode of preterm contractions: The first study reported on a reduction of the admission rate and the rate of late PTB [52], and the second showed no significant effects. The differences again might depend on the clinical experience not to apply a pessary in patients with progressive dilatation, ongoing contractions, or first signs of amnioinfection [52, 53]. A retrospective observational study indicated that the use of the pessary in patients with a history of preterm premature rupture of membranes (PPROM) could be less successful [54].

Twin pregnancies The pilot study from 2003 suggested for the first time that cervical pessaries can limit the odds of PTB among twin pregnancies with an ultrasonographically proven short CL [44]. The first published RCT in this field was the Dutch ProTWIN trial recruited unselected twin pregnancies (< 20 weeks) that were randomized to pessary versus expectant management [55]. The authors described that in monochorionic–monoamniotic twins, the risk of sPTB < 28 and < 32 weeks was significantly reduced when the 25th percentile of CL (38 mm) was used as a cut-off value. Similarly, a poor composite perinatal outcome that they described was reduced by 40% (RR 0.40, 95% CI 0.19–0.83). Within the entire study population, the Kaplan–Meier curves failed to denote a significant difference in pregnancy prolongation among women that had a pessary placed and controls. However, in a subgroup of women with a short CL < 38 mm mortality, up to discharge was 3% (2/78) versus 18% (10/55) and the rates of early preterm birth < 32 weeks and associated neonatal morbidity were significantly reduced as compared to expectant management.

In 2016, a further RCT was published by Goya et al. that recruited 137 pregnant women with a CL < 25 mm between 20 and 24 weeks who were allocated at a 1:1 ratio to cervical pessary or expectant management [56]. The authors reported a significant reduction with pessary use (RR 0.41; 95% CI 0.22–0.76). Similar results were published by Fox et al. in a short series that included 21 patients with cervical pessary and 63 matched controls [57]. Concurrently, Nicolaides et al. published a multicentre RCT that included 1.180 unselected twin pregnancies with a 1:1 allocation ratio, but did not find a significant reduction of sPTB< 34 weeks or any adverse outcomes, even not in a subgroup of 214 women that had a shortened CL (< 25 mm) [58]. However, the authors admitted that a high number of pessaries were removed too early and physicians had not been instructed [59]. A secondary per protocol analysis of the PRoTWIN trial confirmed that the pessary should not be removed until labor occurs [60]. Recently, van't Hooft et al. published the findings of a 3-year follow-up study of neurodevelopmental outcome of children from the ProTwin trial [61]. The authors observed that the cumulative risk of death and neurodevelopmental disability among these children was significantly reduced in the pessary group (OR 0.26; 95% CI 0.09–0.73). When compared to cervical pessary, evidence of cerclage or progestogens is poor and there are no other long-term results.

Supplemental progestogens

Singleton pregnancies The preventive effect of progestogens was already discussed by Papiernik-Berkhauer in 1970 and then by Keirse in 1990 [62, 63]. Progestogens have been used to reduce PTB in the form of the synthetic 17α-hydroxyprogesterone caproate administered weekly as 250 mg or the form of natural progesterone applied daily as vaginal suppositories or gel. Both substances have different half-time lives and different effects and should be separately analyzed.

Two randomized placebo-controlled trials from 2003 found that progesterone, administered as either weekly intramuscular injections of 250 mg of 17α-hydroxyprogesterone caproate or daily progesterone vaginal suppositories, reduced the rate of recurrent preterm delivery by about a third [64, 65]. Otherwise, the benefit of 17-OHPC is controversially discussed [66]. The still ongoing PROLONG trial is intended to investigate the use of 17-OHPC in high-risk pregnancies with the previous PTB.

The application of natural vaginal progesterone for the prevention of PTB has increased, since the publication by DaFonseca et al. [65]. However, this study failed to demonstrate a significant reduction in neonatal morbidity. Another multicenter RCT that was published in 2011 by Hassan et al. recruiting 465 women and a short CL < 25 mm who were allocated to progesterone gel and placebo suggested

that the risk of a delivery < 33 weeks was reduced by 45% [67]. Significant differences were also reported concerning the rates of sPTB 28 weeks, respiratory distress syndrome, and neonatal morbidity and mortality. This study was differently analyzed by statisticians of the FDA who 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 [68]. Thereafter, the OPPTIMUM trial investigated the long-term effect of vaginal progesterone versus placebo for the prevention of PTB until the age of 2 years and found neither significant benefits nor harms related to the post-neonatal outcome, neither a significant prolongation of pregnancy [69]. Therefore, the author Jane Norman concluded that a drug for which no differences could be determined after two years should at least require that patients are well-informed. Critics of this study were related to the inclusion criteria and allow compliance of only 60%. Meanwhile, Romero et al. have conducted three meta-analyses to repetitively underline the value of vaginal progesterone in asymptomatic singleton pregnancies with a short CL. The most recent one still found a significant reduction of PTB even when data from Norman et al. were integrated but no effect in normal weight, in obese women, not in black, 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 it was started between 22 and 25 weeks with a CL between 10 and 20 mm and it could not significantly reduce perinatal or neonatal mortality [70].

A threefold increase in risk of developing gestational diabetes has been implied with the use of 17-alpha-hydroxyprogesterone caproate; however, this has not been confirmed in subsequent studies [71–73].

The results of published RCTs concerning the effect of progestogens in pregnancy have been questioned and commented by Prior et al. in a recent meta-analysis [74]. The authors observed that trials that pre-registered their primary outcomes (which were considered as those with the lowest potential risk of bias) failed to show significant differences in terms of reported outcomes.

Twin pregnancies The majority of published RCTs that investigate the efficacy of progesterone in prolonging pregnancy fails to report significant differences compared to women that were managed expectantly [75, 76]. This observation is independent of the actual dose of the regimen that was used and of the actual CL [77, 78]. In a meta-analysis, Schuit et al. confirmed these findings and reported that vaginal progesterone cannot prolong the latency period, although the sub-group analysis of women with a short CL indicated that there might be evidence to support the use of vaginal progesterone to reduce poor neonatal outcome [79]. In 2017, Dodd et al. published a Cochrane systematic review that included 17 RCTs [80]. The authors concluded that the use of progesterone, either intramuscularly or vaginally applied, does not reduce the risk of PTB or improves neonatal outcomes. A meta-analysis of Romero et al. suggested some effect of vaginal progesterone in twin pregnancies [81]. However, the data were only caused, because the authors included a trial from Egypt which was neither placebo-controlled nor pre-registered and the results are, therefore, questioned.

Mothers who received progesterone for fertility treatment [82]. The actual [83] explanations why vaginal progesterone may work are related to accelerated cell proliferation and increased mutation that is caused by epigenetic changes.

Cervical cerclage

Cerclages have been used during the last 50 years as a mechanical tool to reduce PTB either prophylactically in patients with a history of PTB or later in women with a sonographically short CL. These indications are distinguished from emergency cerclage that is used for bulging membranes.

Several studies have investigated the actual efficacy of cervical cerclage in preventing recurrent preterm birth in women with a prior preterm birth/pregnancy loss. In an individual patient meta-analysis, Jorgensen et al. suggested that the use of cerclage effectively reduces the risk of pregnancy loss or neonatal death prior to discharge from the hospital [84]. Two main techniques have been described, the McDonald and the Shirodkar procedure. Although the latter permits the introduction of the stich in an upper cervical level, evidence does not support its superiority compared to the McDonald technique [85]. The introduction of a second cervical stich has been investigated by a meta-analysis that included six observational studies and suggested that this approach might reduce sPTB rates < 28 and < 34 weeks [86].

Transabdominal cerclage has been applied in patients with anatomical changes due to trachelectomy, several conisations, or in patients with previous failure of transvaginal cerclage with good success rate if the surgeons are experienced [87]. A cochrane review on cerclages in singleton pregnancies concludes that a cervical cerclage reduces PTB in women at risk of recurrent PTB without statistically significant reduction in perinatal mortality or neonatal morbidity and uncertain long-term impact on the baby, but increases cesarean delivery and that a decision on how to minimize the risk either because of poor history of a short or dilated cervix, should be 'individualized' [88].

Twin pregnancies A Cochrane review by Rafael et al. from 2015 was based on 5 prospective RCTs that included 122

twin pregnancies with cerclage [55, 73, 89]. The authors reported that there is no evidence to support the use of cerclage for the prevention of PTB and as a mean to reduce perinatal morbidity and mortality that is related to prematurity. An individual patient meta-analysis based on three trials confirmed these findings [90]. Therefore, the Society for Maternal–Fetal Medicine (SMFM) advised against the placement of a cerclage in women with short cervix and twin gestation [91].

Controversies within observational studies may be attributed to different operative skills and clinical surveillance. It can hardly be denied that the efficacy of both the vaginal and abdominal cerclage is highly dependent on the surgeon`s skills, and unfortunately, this has not sufficiently been considered or audited in published studies. Therefore, its implementation cannot be considered in inexperienced hands as the clinical risks, although rare can be devastating, as these include hemorrhage, sepsis, perinatal, neonatal, or even maternal death.

Indirect and direct comparisons of cervical pessary, cerclage, and progesterone

Current research still focusses on the optimal treatment of pregnancies with a short cervix detected by transvaginal ultrasound. In 2013, Alfirevic et al. published the first retrospective study comparing cerclage, vaginal progesterone, and cervical pessary in patients at risk for PTB and a short CL and found that they were all efficacious in preventing PTB with some more benefits of the cervical pessary [92]. Conde-Agudelo et al. published an indirect comparison meta-analysis of vaginal progesterone versus cervical cerclage and found no clinically relevant differences [93] and a "network meta-analysis" which included 36 trials, suggested that progesterone seems to be better than cerclage and pessary [94]. However, there are several problems in these indirect comparisons. An open label multicenter RCT is currently recruiting patients to directly compare cervical cerclage, cervical pessary, and vaginal progesterone in women with a short cervix [95].

Some direct comparisons of two strategies have, meanwhile, been published as RCTs comparing vaginal progesterone and cervical pessary in singletons and in twins [96, 97]. The RCT in singleton pregnancies could not find a significant difference between cervical pessary and vaginal progesterone in reducing PTB < 34 weeks. More impressive results are the findings in twin pregnancies by Dang et al. [98, 99], where patients were randomized for cervical pessary or vaginal progesterone of 400 mg and a high compliance rate. The results are summarized in Table 1.

Possibly, there is a potential additive effect of either cerclage or cervical pessary as a mean that could potentially further decrease the risk in these women when combined with vaginal progesterone in singletons and convincing results in twins. Boelic et al. suggested that when the CL decreases < 15 mm with progesterone treatment the risk of sPTB rises significantly [100]. In a recent retrospective study, Enakprene investigated the effect of cerclage in singleton pregnancies with vaginal progesterone and progressive cervical shortening [101]. The authors observed that the addition of a cerclage prolonged the latency period by twofold and improved the neonatal composite morbidity and mortality. Nevertheless, their findings should be interpreted with caution, as the study series was subject to significant bias, since the decision to perform cerclage was solely based on physicians' preference.

Table 1 Selected significant results from the first direct comparison of Arabin-cervical pessary versus vaginal progesterone in twin pregnancies according to Dang et al. [99]

Outcome	Arabin pessary		Vag progesterone		RR (95% CI)
All women with a CL < 28 mm					
Delivery < 34 weeks	10/49	20.4%	16/34	44.0%	0.46 (0.24–0.89)
Delivery < 37 weeks	23/49	46.9%	26/36	72.2%	0.65 (0.45–0.93)
BW < 2500 g	50/98	51.0%	51/72	70.8%	0.72 (0.23–0.82)
Admission NICU	14/90	15.6%	28/63	44.4%	0.35 (0.11–0.49)
Respiratory distress syndrome	12/90	13.3%	21/63	33.3%	0.40 (0.14–0.69)
Neonatal sepsis	6/90	6.7%	33/285	23.8%	0.28 (0.08–0.63)
All women with a CL < 38 mm					
Delivery < 34 weeks	24/159	16.0%	35/150	22.0%	0.73 (0.45–1.17)
Delivery < 37 weeks	73/150	48,7%	91/159	60.7%	0.8 (0.65–0.83)
BW < 2500	143/300	47.7%	181/300	60.3%	0.79 (0.43–0.83)
Admission NICU	39/280	13.9%	66/285	23.2%	0.60 (0.35–0.83)
Respiratory distress syndrome	32/280	11.4%	51/285	17.9%	0.64 (0.37–0.95)
Neonatal sepsis	17/280	6.1%	33/285	11.6%	0.52 (0.27–0.9)

The authors defined the prevention of sPTB before 34 weeks as the primary endpoint, whereas secondary endpoints consisted of different maternal and neonatal complications

Recently, Wolnicki et al. [102] investigated the combined treatment of cerclage and Arabin pessary versus cerclage alone in singleton pregnancies with cervical shortening. Although there were no differences between the two study arms in the rates of preterm birth < 28, < 32, < 34, and < 37 weeks, the authors stated a significantly shorter admission time in the NICU as well as higher rates of birthweight in favor of the combined treatment arm. The lower incidence of neonatal infections following the additional pessary treatment might be the result of reduction in the stretching of the cervical cells and prevention of atypical interleukin production as an immunological barrier [103].

Tertiary prevention: tocolysis and corticosteroids

Tocolytic therapy has been adopted during the last decades to limit the rates of PTB. Although tocolysis may temporarily reduce contractions, it does not treat the underlying pathophysiology that acts as a stimulus initiating the process of parturition. This is why tocolytic therapy has not been adopted as a mean of PTB prevention but rather as a method that permits a prolongation of gestation for at least 48 h, so that the effect of corticosteroids may reach its peak, thus reducing neonatal morbidity and increasing survival in sPTBs [104].

Maintenance tocolysis has been investigated in observational studies and proven to be ineffective; therefore, it is unanimously rejected by most published guidelines. Thereby, oral nifedipine failed to prolong pregnancy when maintenance dose was administered in women with preterm contractions between 24 and 34 weeks of gestation [105–107]. Similar negative results were reported for progesterone in women with contractions [108, 109]. Data concerning the effect of maintenance tocolysis with atosiban remain limited as only one study investigated the effect of this treatment and reported a mean difference of 5 days (32.6 versus 27.6 days in control group) when atosiban was continuously administered in a titrated dose of 30 mg/min until the completion of 36 weeks of pregnancy [110]. Nevertheless, infant outcomes were reported to be similar among the two groups.

Unspecific interventions

Diagnosis and treatment of genital tract infection

Lower genital tract infections predispose women to PTB [111, 112]. Ureaplasma and mycoplasma infections seem to be significantly more prevalent among women with sPTB than among controls. Positive swabs seem to be associated with neonatal systemic inflammatory response syndrome and bronchopulmonary dysplasia.

Some studies could not show a reduction in PTB after treatment of asymptomatic vaginal or cervical colonization and a certain microbiome [113], but the data are conflicting [114]. Only one meta-analysis which was based on 10 studies that recruited 3696 pregnant women with bacterial vaginosis suggested a significant reduction PTB rates after antibiotic treatment (OR 0.42; 95% CI 0.27–0.67) [115]. On the other hand, a meta-analysis that evaluated the effect of prophylactic antibiotic administration in women with abnormal vaginal swabs, in women with a history of the previous sPTB and in those with positive fetal fibronectin test, failed to observe a significant effect to reduce sPTB < 37 weeks (RR 1.03 95% CI 0.86–1.24) [116]. Given this information, the decision to screen and treat for genital tract infection remains at the physician's preference. There is no consensus yet mainly because antibiotics may have harmful short- and long-term effects on mothers and their offspring [117].

Treatment of periodontal disease

Several studies suggested that periodontal disease may be a predisposing factor for preterm birth. The rationale behind this association is based on the action of bacterial pathogens and inflammatory cytokines that are released from the mother's mouth cavity periodontal infection is not a direct cause of PTB, but rather a marker that designates a predisposition towards the induction of an excessive local or systemic inflammatory response to bacterial infections. Based on this assumption, it is believed that these women tend to hyperrespond to vaginal infections, thus producing an abundance of inflammatory cytokines that ultimately lead to preterm labor or rupture of membranes [118]. Nevertheless, data on the use of mouth rinse are conflicting [119, 120] and good oral health is desirable, so that periodontal disease should be treated as a component of good dental hygiene.

Bed rest and hospitalization

Bed rest has been traditionally considered as the optimal life style change to reduce the risk of PTB. However, to date, there is no evidence to support this policy [121]. Current recommendations support that routine physical activity is recommended in pregnant women with a history of a PTB [122]. Recently, it has even been shown that in asymptomatic singleton pregnancies with short CL, performing exercise ≥ 2 days a week for ≥ 20 min each day was associated with a non-significant reduction in PTB < 37 weeks by 32% [123].

Challenges in low- and middle-income countries

Within the last two centuries, governments and health care commissions have tried to improve global human health through declarations and charters such as the *International Sanitary Conference* in 1851, the *Declaration of Alma Ata* in 1978, the *Commission on social determinants of heal*th in 2005, and the *Agenda 2030 for sustainable development* in 2015 [124]. While most efforts on prevention of sPTB come from high-income countries, many LMIC have to deal with more challenging conditions. Poorly developed public institutions, limited funding and a relatively low number of skilled staff compounded by contextual factors such as corruption and patronage may lead to adverse and unpredictable neonatal outcomes.

Unfortunately, many LMIC have failed to promote modernisation in health care administration [125]. Consequently, there may be a kind of public/private collaboration, supported in part by external aid agencies. These conditions may be met in well-equipped hospitals, but are often absent in lower level facilities, such as second-level hospitals and primary health care centers, where most of the deliveries occur in these countries [126].

It has been recognized that the lack of awareness and education of stakeholders outside the health care sector, as well as the socioeconomic burden in LMI countries have made it difficult to understand the dimensions and necessary actions for any kind of prevention of sPTB. The recognition of a risk for sPTB is bound to regular pregnancy controls and cervical examinations which is frequently not guaranteed. But also, tertiary approaches such as maternal transport to a perinatal center or the application of antenatal corticosteroids (ACS) for women at high risk of sPTB are frequently not possible and, therefore, have failed to reduce neonatal morbidity and mortality in LMIC. Althabe et al. [127] even reported that ACS did not significantly reduce neonatal mortality for < 5th centile infants, while it was associated with an overall 12% increase in neonatal deaths compared to the control group. A further trial by Berrueta et al. [128] described an overall utilization rate of ACS among pregnant women of < 5th centile babies, ranging from 44% in Argentina to 2% in Kenya. Among preterm new-borns born in hospitals, only 9% of the new-borns < 5th centile received ACS.

These findings should stimulate policy makers, researchers, and health care providers to implement basic population-based pregnancy controls at regular intervals, relevant frameworks, and strategies to improve perinatal care in LMIC and we encourage them to focus on primary and secondary prevention to improve the outcome of pregnancies at risk for sPTB.

Summary and recommendations

- Risk factors for preterm birth may be classified as non-modifiable or modifiable. Identification of risk factors for preterm delivery before conception or early in pregnancy may provide an opportunity for primary prevention. However, most preterm births occur among women with no obvious risk factors and the number of effective interventions is limited.
- In the majority of cases, obstetric medicine has not yet significantly reduced PTB. Nevertheless, neonatal intensive care could optimize perinatal and neonatal outcomes in HICs. Tertiary preventive tools such as administering antenatal corticosteroids and transferring risk patients to a tertiary care center have also contributed to a better outcome of these children.
- For asymptomatic women with a previous PTB and a singleton pregnancy, transvaginal ultrasound is mandatory, and in case of cervical shortening, secondary preventive strategies such as a cervical cerclage, vaginal progesterone, or cervical pessary may be indicated. Vaginal progesterone and cervical pessary may both have a place in patients with cervical shortening without a history of PTB.
- In twin pregnancies, cervical cerclage and vaginal progesterone have up to now failed to show convincing results, but the evidence of a cervical pessary seems promising.
- Women with vaginal progesterone treatment that have progressive cervical shortening are at risk of delivering preterm; however, the addition of cervical cerclage or the use of pessary may both have a beneficial effect in these patients.
- There is insufficient evidence to support the use of bed rest; on the contrary, daily physical activity should be supported among women at risk of sPTB.
- Utilizing strategies to prevent multiple gestations resulting from assisted reproduction should decrease the number of preterm births related to multiple gestations.
- Women with periodontal disease are at increased risk of preterm delivery. Periodontal disease should be treated as a component of good dental hygiene, but there are inadequate data to suggest a treatment for prevention of PTB.
- An interpregnancy interval of more than six months may reduce the risk of PTB.

Author contributions GD: project development. MG: manuscript writing. VP: manuscript writing. LC: project development. IK: data

collection, manuscript writing and revising. AA: project development. BA: manuscript writing and revising.

Funding The authors did not receive funding for the present work.

Compliance with ethical standards

Conflict of interest Birgit Arabin has a direct ownership interest in a company that designed, produces and now distributes the Arabin pessary. The company is privately held and the profit is used to support the Clara Angela Foundation. The remaining authors report no conflicts of interest.

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