Prevention of Prematurity
Advances and Opportunities

Balaji Govindaswami, MBBS, MPH*, Priya Jegatheesan, MD, Matthew Nudelman, MD, Sudha Rani Narasimhan, MD, IBCLC

KEYWORDS

• Preterm birth prevention • Preterm prevention clinic • Progesterone • Cerclage • Aspirin • Clindamycin • Clotrimazole • Nifedipine

KEY POINTS

- Preterm birth (PTB) rate varies widely with significant racial and ethnic disparities. Causal mechanisms are ill understood, but phenotype and genotype provide insight into pathways for preventing PTB.
- Varied response to medical interventions is explicable by underlying pharmacogenomics. Prevention should focus on minimizing iatrogenic PTB and risk reduction, especially those with prior PTB.
- Current PTB prevention includes reduction of non-medically indicated delivery less than 39 weeks, smoking cessation, implementation of preterm prevention clinic and appropriate use of cerclage and medications (progesterone, antimicrobials, and nifedipine). Aspirin and oral magnesium are currently under study.
- Placental health requires optimal management of diseases in pregnancy, smoking cessation, omega 3 supplements if smoking continues during pregnancy, anti-platelet agents, and eliminating non-medically indicated uterine manipulation.
- Future preventive approaches should focus on better understanding of sociodemography, nutrition, dysbiosis, lifestyles, phenotype, risk factors, and underlying individual genetic, pharmacogenomics, and epigenetic variation.

INTRODUCTION

Preterm birth (PTB) occurs with a prevalence ranging from less than 5% to greater than 15% worldwide. The widespread variability is well emphasized in the United Nations/World Health Organization (WHO) report entitled "Born Too Soon."[1] All countries with PTB rates greater than 15% are in sub-Saharan Africa,[2] and PTB rates in African Americans have traditionally been significantly greater than for other ethnic and racial groups. In the United States, the rate increased for 14 consecutive years followed by a

Division of Neonatology, Pediatrics, Santa Clara Valley Medical Center: Hospital and Clinics, 751 South Bascom Avenue, San Jose, CA 95128, USA
* Corresponding author.
E-mail address: Balaji.Govindaswami@hhs.sccgov.org

Clin Perinatol 45 (2018) 579–595
https://doi.org/10.1016/j.clp.2018.05.013
perinatology.theclinics.com

decline for 7 consecutive years. Unfortunately, now US PTB rates have been increasing for 2 consecutive years to 9.84% in 2016.[3]

PREMATURITY PREVENTION AND INSIGHTS INTO CAUSE

Prevention of PTB has been attempted for several decades and in several settings with mixed success,[4–8] most likely related to the poorly understood heterogeneity of disease. Studies in the late 1990s showed some promise of interventions to prevent PTB with the publication of the injectable[9] and vaginal[10] progesterone trials. A population-based, multiethnic, cross-sectional study in 8 countries[11] over a 12-month period examined 60,058 births. Prevalence of PTB ranged from 8.2% in Muscat, Oman and Oxford, England to 16.6% in Seattle, Washington. Twelve PTB clusters were identified using phenotypes that included signs of presentation at hospital admission and a predefined conceptual framework. The distribution of clinical phenotypes in PTB across these multiethnic populations suggests that in 22% of these births, parturition started spontaneously and was unassociated with any of the phenotypes considered. A current genome-wide association study of 43,568 women with greater than 97% European ancestry demonstrates putative genetic and mechanistic insights into prematurity.[12] Six maternal genomic loci identified and replicated were robustly associated with gestational duration and contain genes whose established functions are consistent with a role in the timing of birth. Three of these loci are also associated with PTB with genome-wide significance. Furthermore, it is known that some of the variation in response to medications used in PTB prevention and treatment may be attributable to pharmacogenomic effects. Currently, greater than 50 genes are implicated in genomic biomarkers most commonly pertaining to polymorphisms in cytochrome p450 (CYP) enzyme metabolism. Polymorphisms in CYP enzymes are relatively common. For example, CYP2D6 is estimated to metabolize ~25% of drugs (including fluoxetine, metoprolol, codeine), and greater than 70 alleles have been identified in this highly polymorphic gene. As a result, CYP2D6 activity ranges widely even within populations, and up to 8% of European Americans may be identified as poor metabolizers.[13] Specific to 17-hydroxy progesterone caproate (17-OHPC) metabolism, Caritis and colleagues[14] examined plasma concentrations in 315 women at 25 to 28 weeks' gestation and grouped their 17-OHPC levels into quartiles. Women in the lowest quartile were significantly more likely to have recurrent PTB than those in the upper 3 quartiles (46% vs 29%; $P = .03$). Lowest PTB rates were seen when median 17-OHPC concentrations exceeded 6.4 ng/mL. Women in the second, third, or fourth quartiles had a 50% reduction in delivering preterm (hazard ratio: 0.48; 95% confidence interval [CI] 0.31–0.75; $P = .001$). Two specific pharmacogenomics studies have been performed to study the relationship between genotype and the response to 17-OHPC. Similarly, Nifedipine concentrations linked to CYP3A5 genotype are correlated with high clearance of Nifedipine and thus lower levels.[15] Women with high expression of CYP3A5 had less improvement in contraction frequency at several time points, including after the loading dose, at the steady state, and in the first hour after study dose.[16] No pharmacogenomics data are currently available for indomethacin or magnesium sulfate, although it is known that indomethacin is metabolized in the liver by polymorphic CYP2C9 and CYP2C19. Maternal and fetal genetic variance in several single nucleotide polymorphisms including CYP3A5 and CYP3A7*1E are associated with variation in neonatal respiratory outcomes, including need for surfactant and ventilator support. Thus, it has been surmised that genetic variation in betamethasone genes can be

associated with severity of respiratory morbidity.[17] In conclusion, these data suggest that genotype may influence response to commonly used therapies in PTB prevention and treatment.

CURRENT OPPORTUNITIES FOR PRETERM BIRTH PREVENTION

Several strategies exist to target PTB risk reduction and prevention. Included among these are nonmedically indicated PTB that might be an early target for studying practice-based variation. **Box 1** provides strategies for PTB prevention, which serves as an outline for this article.

PRECONCEPTION STRATEGIES

Optimal Maternal Body Composition

It is known that extremes of body mass index (BMI, kg/m^2) increase the risk of PTB. Data from Poland[18] and 21 states in the United States[19] show PTB rates are increased with prepregnancy BMI less than 19.8 and in women with poor weight gain during pregnancy. These findings have been reiterated in more recent data from California, including almost a million live births.[20] Furthermore, this study also shows BMI greater

Box 1
Preterm birth prevention opportunity

Preconceptional and public health strategies

1. Optimal maternal body composition
2. Optimal IPI and exclusive breastfeeding
3. Tobacco avoidance and cessation, omega-3 supplements
4. Periodontal disease prevention
5. Dedicated PPC
6. Public health strategies

Minimize iatrogenic contributions to PTB

1. Judicious use of fertility treatment
2. Eliminate elective induction less than 39 weeks
3. Lower CS rates

Medical

1. Antiplatelet agents
2. Vaginal and injectable progesterone
3. Magnesium
4. Antimicrobials
5. Tocolytics
6. Ethanol, oxytocin receptor antagonists, Cox inhibitors
7. Nutritional supplements
8. Ongoing trials

Surgical

1. Cerclage
2. Pessary

than 30 is associated with increased risk of PTB with the highest risk of PTB less than 24 weeks in non-Hispanic white women followed by non-Hispanic black and then Hispanic women. Thus it is important to optimize maternal BMI before conception with lifestyle interventions, including diet and exercise, as a critical prevention strategy.

Optimal Interpregnancy Interval and Exclusive Breastfeeding

Interpregnancy interval (IPI), defined as the time between the birth of one child and conception of the next child, may affect pregnancy risk of adverse perinatal/neonatal outcomes. Based on information up to 2005, WHO recommended an optimal IPI to be at least 24 months to reduce risk of adverse maternal, perinatal, and infant outcomes.[21,22] Studies have shown that infants born after IPI less than 6 months had increased risk of adverse neonatal outcomes including PTB (odds ratio [OR] = 1.40, 95% CI 1.24–1.58), small for gestational age (OR = 1.26, 95% CI 1.18–1.33), and low birth weight (LBW) (OR = 1.61, 95% CI 1.39–1.86) when compared with IPI of 18 to 24 months.[22,23] However, controversies still exist. Recent studies from Perth, Australia and British Columbia, Canada, using matched controls, question the possible causal relationship between IPI and pregnancy risk.[24,25] The applicability of these studies in the US population require further validation. Data from several studies including in sub-Saharan Africa suggest long IPIs (60 months or more) are also associated with higher risk of adverse outcomes in maternal and infant health, including PTB.[26] Despite recommendations of optimal IPI, data from the 2015 National Vital Statistics Report and National Survey of Family Growth show 30% of women in the United States have IPIs less than 18 months.[27] The recommended optimal IPI is in alignment with the WHO's recommendation for breastfeeding duration of 2 years or more. Not only does breastfeeding provide infant benefit (including reductions in infections and improved long-term neurodevelopmental outcomes),[28–30] nursing mothers may also benefit from lactational amenorrhea for 6 months postdelivery if they continuously and exclusively breastfeed (feeding at least every 4 hours during the day and at least every 6 hours at night).[28,31] This method of contraception, although effective, is temporary. Thus, health care providers need to be proactive in following and counseling new mothers on the recommended IPI to reduce potential perinatal risks, including PTB.

Tobacco Avoidance and Cessation, Omega-3 Supplements

It has been recognized for decades that maternal cigarette smoking increases risk of PTB as well as LBW. Compared with women who continue to smoke, PTB risk is reduced in women who stop smoking in the first trimester of pregnancy. Data from 4876 women who delivered within 6 years of a 1988 US National Health Interview Survey showed that nonsmokers had a PTB rate of 5.9% versus 8.9% for smokers ($P = .003$).[32] More recently, data from Sweden (1999–2012) show tobacco use increases risk of extremely PTB. Although snuff use doubled the risk of medically indicated extremely PTB, smoking was associated with an increased risk of both medically indicated and spontaneous extremely PTB.[33] Other novel treatments like omega-3 supplementation have been shown to reduce PTB in smokers but not in nonsmokers.[34]

Periodontal Disease Prevention

A large prospective study from Birmingham, Alabama showed significant association between PTB and periodontitis between 21 and 24 weeks' gestation. In a group of high-risk women stratified by risk factors of either prior history of spontaneous PTB less than 35 weeks or BMI less than 19.8/bacterial vaginosis, a pilot intervention of scaling and dental root planing as a treatment intervention in women (85% African American) with periodontitis between 21 and 25 weeks' gestation reduced the risk

of PTB less than 35 weeks. The addition of Metronidazole to this intervention when compared with placebo, however, did not reduce risk of PTB less than 35 weeks.[35] More recently, it has been reiterated that periodontal treatment during pregnancy decreases risk of PTB.[36] Current evidence provides an interesting clinicopathologic correlate that the biome of the placenta is most similar to the maternal oral cavity.[37] More current and comprehensive reviews from India[38] and Africa[39] also suggest "the promotion of early detection and treatments of periodontal disease in young women before and during pregnancy will be beneficial, especially for women at risk."[38] However, more recent meta-analysis question the risk reduction in PTB less than 35 weeks in women treated for periodontal disease in pregnancy.[40]

Dedicated Preterm Prevention Clinic

In reviewing 6 randomized control trials (RCT), the effectiveness of PTB prevention educational programs in high-risk mothers showed no significant benefit in preventing death, LBW, or PTB rates. The only difference shown was an increase in the frequency of preterm labor diagnosis.[41]

Because the cause of spontaneous preterm labor is heterogeneous, inclusion criteria for women who should attend preterm prevention clinic (PPC) are important. Some have recommended excluding women with a multiple pregnancy, those with previous elective indicated PTB (due to preeclampsia, maternal reasons, intrauterine growth restriction), and those with previous intrauterine fetal demise without labor.[42] Utah Intermountain Health instituted a PPC with 3 visits wherein PTB risk assessment was done. Women were offered 17-OHPC as well as screened for bacterial vaginosis and urinary tract infection, and treated if positive. With this intervention, they showed fewer women enrolled in the PPC delivered before 37 weeks (49% vs 63% $P = .04$). The neonatal intensive care unit admission rate was the same, but neonatal morbidity, including intraventricular hemorrhage, sepsis, or death, was significantly lower in the PPC group (6% vs 16%, $P = .03$). More women in PPC received 17-OHPC (68.6% vs 39.1%, $P<.01$), but the use of progesterone was not associated with reduction of PTB.[43] In studying pregnant women's preferences and concerns[44] regarding PTB, 311 women completed a survey at median gestation of 32 weeks. If they were told that they were at increased risk for PTB, they preferred not to use PTB prevention methods, but chose close monitoring or nothing. They were most likely to follow use of 17-OHPC and least likely to follow recommendations for cerclage. They also report the women preferred to use sources other than their provider to seek information and learn about PTB, such as the Internet.

The following are suggested minimum criteria of those in pregnancy who should be referred to a dedicated PTB prevention clinic:

- Systemic maternal disease associated with PTB
- Poorly controlled diabetes
- Chronic hypertension with associated renal or cardiac disease
- Fetal anomaly
- Fetal arrhythmia
- Certain types of isoimmunization (C, D, E, Kell)
- Monochorionic twins
- Triplets or greater
- Placenta accreta
- Mothers exposed to substance associated with PTB
- Severe or early intrauterine growth restriction
- History of cervical insufficiency

- History of spontaneous PTB
- Polyhydramnios greater than 30 cm
- Multiple CSs (3 or more)
- Recurrent loss (3 or more)
- History of preeclampsia

Preconceptional and Public Health Strategies

The overwhelming majority of Utah women in a prospective convenience sample studied in a state infant follow-up clinic (2010–2012) who had prior PTB were not educated on medical strategies to prevent future PTB,[45] thus providing opportunity for health promotion and PTB prevention through education in this very high-risk population. A variety of other effective public health approaches to PTB risk reduction have been explored in different populations. For example, an Ohio statewide collaborative consisting of 20 maternity hospitals achieved a 6.6% reduction in singleton births less than 32 weeks through greater progesterone access for at-risk pregnancies. Improved progesterone access was accomplished through expanding Medicaid eligibility, maintaining Medicaid coverage during pregnancy, improving communication, and adopting uniform data collection and efficient treatment protocols.[46] Similar examples are found in an Australian prospective population-based cohort study that found a 7.6% reduction in PTB within 1 year following implementation of a multifaceted PTB prevention program aimed at both health care practitioners and the general public, operating within the environment of a government-funded universal health care system.[47]

MINIMIZE IATROGENIC CONTRIBUTIONS TO PRETERM BIRTH

Judicious Use of Fertility Treatment

Between 1996 and 2014, the number of assisted reproductive technology (ART) procedures in the United States and the resultant births has nearly tripled. Although 17 reporting European nations had 81% of in vitro fertilization deliveries being singleton, the United States had a 72% comparable singleton rate. The 1.6% of US live births in 2014 who were ART-conceived had a singleton PTB rate of 13.2% and LBW rate of 8.9% compared with 9.7% PTB rate and 6.3% LBW rate of all singleton US births. Careful monitoring of rates of multiple embryo transfers and early single embryo transfer rates in addition to knowledge of infant outcomes can guide judicious use and evaluation of fertility treatment. The Centers for Disease Control and Prevention's National Center for Health Statistics plans to include information on the use of ART and non-ART treatments and birth outcomes from US birth certificate data year 2016.[48]

Eliminate Nonmedically Indicated Induction less than 39 weeks

Elimination of nonmedically indicated deliveries could potentially decrease PTB. Using a toolkit from California's Maternal Quality Care Collaborative, 26 hospitals in the "big 5" states (California, Florida, Illinois, New York, Texas) effectively reduced elective early-term deliveries (37–38 weeks) from 27.8% to 4.8%, an 83% decline within 1 year.[49]

Eliminate Nonmedically Indicated Cesarean Section Rates

Minimizing the primary cesarean section (CS) rate is the single best way to lower risk of repeated CS. Multiple CSs are associated with abnormal placentation, which can lead to increased risk of medically indicated CS and PTB. Cesarean scar pregnancies are associated with morbidly adherent placentas, which increase risk of PTB and have serious implications for maternal fertility.[50]

MEDICAL

Antiplatelet Agents

Multiple studies have evaluated the use of antiplatelet agents (low-dose aspirin–dipyridamole) to treat preeclampsia. A recent individual patient data (IPD) meta-analysis included 17 trials with 28,797 pregnant women at risk for pregnancy-induced hypertension showed a lower risk of PTB in those who received antiplatelet agents.[51] Currently, a multicenter RCT evaluating the efficacy of low-dose aspirin in preventing PTB in pregnant women with history of PTB is underway in The Netherlands and Australia.[52]

Vaginal and Injectable Progesterone

A matched sample comparison of intramuscular (IM) versus vaginal micronized progesterone for PTB prevention[53] studied 168 pregnant women at high risk of PTB randomized at 20 to 24 weeks' gestation to receive micronized progesterone tablets (200 mg) vaginally daily or 100 mg IM every 3 days: PTB rates were 20% and 27.5% in the vaginal and IM groups, respectively. The study concluded that although both therapies were nearly equally effective, vaginal progesterone had less undesirable side effects.

Progesterone in singletons

Vaginal progesterone 100 to 200 mg daily[54,55] and 250 mg weekly of IM 17-OHPC[9] have been used in women with singleton pregnancy at risk for PTB. Meta-analysis of RCTs has shown that progesterone decreases PTB risk at less than 37 weeks' gestation.[56–58] A recent network meta-analysis[58] of studies that evaluated progesterone, cerclage, and pessary as PTB risk-lowering treatment modalities showed progesterone is effective in lowering PTB risk less than 34 weeks' gestation (OR 0.44; 95% CI 0.22–0.79; low quality), less than 37 weeks' gestation (OR 0.58; 95% CI 0.41–0.79; moderate quality), and reducing neonatal death (OR 0.50; 95% CI 0.28–0.85; high quality). In subgroup analysis, vaginal progesterone was more effective than 17-OHPC in preventing PTB, and cerclage was effective in reducing PTB risk in those with short cervical length.

Progesterone in twin pregnancies

Even though multiple pregnancies account only for 1% to 2% of live births, they are overrepresented in PTB. Hence, numerous studies have evaluated the use of both 17-OHPC and vaginal progesterone use to reduce PTB risk in multiple pregnancies. IPD meta-analysis of 13 RCTs with 3768 women with twin pregnancies did not show a benefit in reduction of adverse perinatal outcome with the use of 17-OHPC.[59] However, in a subset of women with short cervical length less than 25 mm, the use of vaginal progesterone was associated with reduction in PTB. Another IPD meta-analysis of 6 trials with 447 asymptomatic women with twin pregnancies and short cervical length less than 25 mm showed that vaginal progesterone reduced the rate of PTB less than 33 weeks' gestation (OR 0.69, 95% CI 0.51–0.93, $P = .01$) and neonatal mortality and morbidity (respiratory distress syndrome, use of mechanical ventilation, birth weight <1500 g).[60] A recent network meta-analysis[61] comparing 17-OHPC, cerclage, and pessary did not show a significant benefit in reducing PTB with any of these interventions. However, a subgroup analysis showed that in women with short cervix vaginal progesterone was effective in reducing neonatal outcomes of very LBW and mechanical ventilation.

Progesterone pharmacogenomics

Whole-exome sequencing in pregnant women with a history of recurrent PTB shows key genetics differences in efficacy of 17-OHPC treatment between those who had success or lack thereof.[13] Success/nonsuccess was defined as either difference in gestational age at delivery between 17-OHPC-treated and untreated pregnancies

(success: delivered ≥3 weeks later with 17-OHPC) or success/nonsuccess based on reaching term (success: delivered at term with 17-OHPC).

Magnesium

RCTs in the 1990s investigating magnesium sulfate for PTB prevention have concluded it was ineffective.[62] Currently, maternal magnesium sulfate is used for its infant neuroprotective benefit in those at risk for preterm delivery. Oral magnesium sulfate is being studied for its potential in PTB prevention in an RCT in Brazil in women at risk for placental dysfunction.[63]

Antimicrobials

Multiple pathologic processes are involved in infection contributing to PTB. Although the molecular mechanisms are identified, there is a lack of consensus on effective antibiotics for bacterial vaginosis or related organisms, used early in pregnancy to reduce PTB.[64,65] Antibiotic treatment in women with preterm premature rupture of membranes (PPROM) <34 weeks has been associated with prolongation of pregnancy[66] but not in those with preterm labor. Early treatment of abnormal vaginal colonization with Clindamycin was associated with lower risk of PTB less than 37 weeks.[67] However, a meta-analysis of 17 trials using prophylactic antibiotics to prevent PTB did not show any benefit.[68,69] A meta-analysis of 2 trials (one was from a post hoc subgroup analysis) with 685 women showed treatment of asymptomatic vulvovaginal candidiasis significantly reduced PTB risk.[70] Although further discussion of antimicrobials is beyond the scope of this article, a recent comprehensive review of antibiotics and PTB is recommended reading.[69]

Tocolytics

Calcium channel blockers, mainly Nifedipine, are beneficial in postponement of birth by a mean of 4.38 days (95% CI 0.25–8.52) and a Cochrane review[71] showed reduction in PTB (relative risk [RR] 0.64, 95% CI 0.47–0.89). This short postponement demonstrated benefits in allowing opportunity for antenatal steroids and transfer to higher level of care. The review also recommends future trials to use blinding of the intervention and assessment of long-term childhood outcomes and costs.

Terbutaline for PTB prevention is not recommended, and its use should be limited to research settings because of several cases of maternal deaths and cardiovascular events in patients receiving terbutaline tocolysis.[72]

Cochrane Reviews of Nonbeneficial Interventions: Probiotics, Relaxation Therapy, Hydration Therapy, Magnesium Therapy, Oxytocin Receptor Antagonists, Cox Inhibitors, Ethanol

Several therapies are known to be ineffective in reducing the risk of PTB according to Cochrane reviews in the last decade,[73–79] although some ambitious new trials[52,63] are underway.

Nutritional Supplements

Vitamin C deficiency may lead to premature rupture of membrane (PROM). North Carolina women with total vitamin C intakes less than the 10th percentile preconceptionally had twice the risk of PTB associated with PROM (RR 2.2; 95% CI 1.1, 4.5). The elevated risk of PPROM was greatest for women with a low vitamin C intake during both preconception and in the second trimester.[80] In a secondary analysis of a double-masked, placebo RCT in low-risk nulliparous women (10,154 women randomized, outcome data available on 9968; 4992 vitamin group and 4976 placebo group)

administered 1000 mg vitamin C and 400 IU vitamin E or placebo daily from 9 to 16 weeks' gestation until delivery, no differences were noted in PTB attributable to PROM less than 37 and less than 35 weeks' gestation but were less frequent at less than 32 weeks' gestation (0.3% vs 0.6% adjusted OR 0.3–0.9).[81] The role of supplemental vitamin C in PPROM has shown some promise in an Iranian RCT that randomized 170 pregnant women with singleton pregnancy with history of PPROM to daily 100 mg vitamin C or placebo starting at 14 weeks' gestation.[82] It is unclear if this high-risk population in Iran was deficient in vitamin C. A current review[83] highlights other deficiencies of micronutrients such as zinc[84] and vitamin D in nutritionally deprived populations that may affect PTB rates. A Cochrane review inclusive of 3 trials involving 477 women suggest that vitamin D supplementation during pregnancy reduces the risk PTB (RR 0.36; 95% CI 0.14–0.93, moderate quality). The benefits of omega 3 supplementation in PTB reduction in smokers have been previously stated.[34]

In summary, these observations suggest the need to further understand nutritional deficiencies and their role in the variation of PTB prevalence, both endemic deficiencies and those peculiar to high-risk populations.

Ongoing Trials

Currently, multiple studies are underway comparing different treatments for PTB: vaginal progesterone versus cerclage versus pessary in pregnant women with short cervix[85]; progesterone versus pessary[86,87]; and pessary versus cerclage.[88] Studies evaluating novel treatments like low-dose aspirin and oral magnesium to decrease PTB are also underway.[52,63]

SURGICAL

Cerclage

A retrospective cohort study of 444 women who received 1 or 2 stitches during transvaginal cervical cerclage in PTB prevention did not show differences in PTB or pregnancy outcome, regardless of whether cerclage was indicated for prior history of PTB or cervical ultrasound changes.[89]

A systematic review of adjunctive therapies to cerclage in the prevention of PTB[90] identified 305 studies for review, of which only 12 studies compared use of adjunctive therapy with cerclage to cerclage alone. None of the 12 studies were prospective RCTs, and none of them demonstrated clear benefit of any adjunctive therapy used with cerclage or cerclage alone. In singletons, cerclage has been shown to reduce the risk of PTB in meta-analysis of 15 trials with 3490 pregnant women.[91] Subgroup analysis in a network meta-analysis showed cerclage was effective in reducing PTB risk in those with short cervical length[61] but not in all. In 2 separate meta-analyses, cerclage has not been shown to be effective in twin pregnancies.[61,92]

Pessary

A meta-analysis of 3 RCTs of cervical pessary in 1412 asymptomatic women with short cervix did not show a reduction in PTB or neonatal mortality or morbidity.[93]

Table 1 summarizes the most promising interventions to prevent PTB.

FUTURE CONSIDERATIONS

Answering clinically important questions related to relatively rare outcomes or very small subgroup populations is difficult in a single RCT. Critical evaluation of evidence examining progesterone for the prevention of PTB shows studies of variable quality.[94] A cumulative meta-analysis showed that progesterone treatment benefit for the

Table 1
Summary of promising interventions to prevent preterm birth

Intervention	Detail	Effect RR (95% CI)	Reference
Progesterone: Singletons			
17-OHP 250 mg weekly	History of preterm delivery n = 463	PTB <37 wk 0.66 (0.54–0.81) PTB <35 wk 0.67 (0.48–0.93)	Meis et al,[9] 2003
Vaginal progesterone 100 mg daily	At risk for PTB n = 142	PTB <37 wk 0.48 (13.8% vs 28.5%) *P* = .03	da Fonseca,[10] 2003
Vaginal progesterone 200 mg daily	At risk for PTB n = 1228	PTB <35 wk 0.86 (0.61–1.22)	Norman,[55] 2012
Vaginal progesterone	Asymptomatic women with short cervix, IPDMA, 5 trials, n = 775	PTB <35 wk RR 0.66 (0.52–0.83) NNT 11	Romero,[56,57] 2012, 2016
Progesterone	Network meta-analysis in singletons, 10 trials, n = 2850	PTB <34 wk 0.44 (0.22–0.79) NNT 9	Jarde,[58] 2017 singletons
Progesterone: Multiples			
Vaginal progesterone	Network analysis in twins, 16 trials	BW <1500 g 0.71 (0.52–0.98) Mechanical ventilation 0.61 (0.45–0.82)	Jarde,[61] 2017 twins
Vaginal progesterone	Twins with short cervix, IPDMA, 13 trials, n = 3768	PTB <33 wk 0.69 (0.51–0.93)	Schui,[59] 2015; Romero,[60] 2017
Antiplatelet agents	At risk for preeclampsia, gestational hypertension, intrauterine growth restriction IPDMA 17 trials, n = 28,797	PTB <37 wk 0.93 (0.86–0.996) PTB <34 wk 0.86 (0.76–0.99)	van Vliet,[51] 2017
Antimicrobials			
Latency antibiotics	PPROM, 5 trials, n = 3226	Latency days 0.33 (0.17–0.5)	Hutzal,[66] 2008
Clindamycin	Asymptomatic bacterial vaginosis or abnormal vaginal fora <22 wk, 5 trials, n = 2346	PTB <37 wk 0.6 (0.42–0.86)	Lamont,[67] 2011
Clotrimazole	Asymptomatic vulvovaginal candidiasis, 2 trials, n = 685	PTB <37 wk 0.36 (0.17–0.75)	Roberts,[70] 2015
Cerclage	At high risk of PTB or ultrasound evidence of need for cerclage, 9 trials, n = 2415	PTB <34 wk 0.77 (0.66–0.89)	Alfrevic,[91] 2017

Abbreviation: IPDMA, individual participant data meta-analysis.

outcome PTB less than 37 weeks had a *P*<.01 in 1975. By 1985, the *P* value was less than .001 and by 2003 it was less than .0001. Another cumulative meta-analysis limited to just the highest quality trials showed significant benefit with OR 0.47; 95% CI 0.33, 0.66; *P*<.0001. Recently, a group of statisticians and scientists have suggested using a *P*<.005 as the threshold for statistical significance instead of *P*<.05 in an effort to increase the reproducibility of study results. Increasing the sample size and other methods of summarizing data such as using Bayesian factor instead

of *P* value have also been recommended. Future studies should consider such statistical methods to optimize the reproducibility of study results.[95] IPD meta-analyses have been helpful in answering clinical questions in smaller subgroup populations.[96,97] Such meta-analyses are possible when the studies have recorded all relevant outcomes with standardized definitions and the inclusion criteria have included subgroups of populations of interest. It is important for future trials to proactively consider including heterogeneous clinical subgroups, instead of having comprehensive exclusion criteria, to provide the opportunity for IPD meta-analysis to answer clinically important questions. Network meta-analysis evaluating comparative effectiveness of the different interventions provides an opportunity to identify the most effective interventions. It has been pointed out that several limitations in meta-analysis peculiar to nutrition research[98] merit consideration. It will be interesting to see how the future incorporates current nutritional trials such as Docosahexaenoic acid supplements to decrease the frequency of PTB less than 34 weeks using Bayesian adaptive randomization design[99] into novel meta-analytic frameworks in nutrition research. Integrating genomic factors with the phenotypic risk factors to identify the most effective treatment of each patient is essential to ensure successful clinical outcomes as highlighted by the Precision Medicine Initiative.[100]

Best Practices

What is the current practice?

Recognize higher risk of preterm birth as early as possible before or during pregnancy

Objective: To minimize risk of preterm birth, optimize management during preterm labor, and mitigate perinatal morbidity and mortality for both mother and infant

What changes in current practice are likely to improve outcomes?

Early recognition of risk factors for preterm birth and mitigation at the appropriate phase, be it before conception, during pregnancy, in preterm labor, or after preterm rupture of membrane

Major recommendations

Preconception strategies

I. Avoid BMI less than 19.8 or greater than 30
II. Optimal interpregnancy interval of 18 to 24 months and exclusive breastfeeding for $\geq$ 6 months
III. Tobacco avoidance and cessation, omega-3 supplements
IV. Periodontal disease prevention
V. Dedicated preterm prevention clinic for women with prior preterm birth

Minimize iatrogenic contributions to preterm birth

I. Judicious use of ART fertility treatment and limiting number of embryos transferred
II. Eliminate nonmedically indicated induction less than 39 weeks
III. Eliminate nonmedically indicated cesarean section rates

Medical

I. Vaginal progesterone/17-OHPC in singletons
   a. Decreases risk of PTB at less than 34, less than 37 weeks' gestation and neonatal death
   b. Vaginal progesterone was more effective than 17-OHPC in preventing PTB
II. Vaginal progesterone in twins
   a. Decreases risk of PTB at less than 33 weeks' gestation and neonatal mortality and morbidity in those with short cervical length less than 25 mm

Summary statement

Reexamine data for effectiveness of progesterone in preterm birth prevention and in high-risk subgroup populations. Long-term safety data on progesterone use for preterm birth prevention.

ACKNOWLEDGMENTS

This article is dedicated to all the great obstetricians who teach us so much and do so much for our women, children, and families. Special thanks to Drs James Byrne, Jin Chang-Yu, Iris Colon, Bonnie Dwyer, Matthew Garabedian, Kim Gregory, Andrea Jelks, Liza Kunz, Deborah Krakow, Anthony Ogundipe, and Neil Silverman.

REFERENCES

1. Howson CP, Kinney MV, Lawn JE, editors. Born too soon: the global action report on preterm birth. Geneva (Switzerland): March of Dimes, PMNCH, Save the Children, WHO; 2012.
2. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012;379(9832):2162–72.
3. Rossen LM, Osterman MJK, Hamilton BE, et al. Quarterly provisional estimates for selected birth indicators, 2015-Quarter 1, 2017. Available at: https://www.cdc.gov/nchs/data/vsrr/report004.pdf. Accessed September 18, 2017.
4. Goldenberg RL, Andrews WW. Intrauterine infection and why preterm prevention programs have failed. Am J Public Health 1996;86(6):781–3.
5. Goldenberg RL, Davis RO, Copper RL, et al. The Alabama preterm birth prevention project. Obstet Gynecol 1990;75(6):933–9.
6. Hobel CJ, Ross MG, Bemis RL, et al. The West Los Angeles preterm birth prevention project. I. Program impact on high-risk women. Am J Obstet Gynecol 1994;170(1 Pt 1):54–62.
7. Gomez-Olmedo M, Delgado-Rodriguez M, Bueno-Cavanillas A, et al. Prenatal care and prevention of preterm birth. A case-control study in southern Spain. Eur J Epidemiol 1996;12(1):37–44.
8. Holzman C, Paneth N. Preterm birth: from prediction to prevention. Am J Public Health 1998;88(2):183–4.
9. Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med 2003;348(24):2379–85.
10. da Fonseca EB, Damiao R, Nicholaides K. Prevention of preterm birth based on short cervix: progesterone. Semin Perinatol 2009;33(5):334–7.
11. Barros FC, Papageorghiou AT, Victora CG, et al. The distribution of clinical phenotypes of preterm birth syndrome: implications for prevention. JAMA Pediatr 2015;169(3):220–9.
12. Zhang G, Feenstra B, Bacelis J, et al. Genetic associations with gestational duration and spontaneous preterm birth. N Engl J Med 2017;377(12):1156–67.
13. Manuck TA, Watkins WS, Esplin MS, et al. Pharmacogenomics of 17-alpha hydroxyprogesterone caproate for recurrent preterm birth: a case-control study. BJOG 2018;125(3):343–50.
14. Caritis SN, Venkataramanan R, Thom E, et al. Relationship between 17-alpha hydroxyprogesterone caproate concentration and spontaneous preterm birth. Am J Obstet Gynecol 2014;210(2):128.e1-6.
15. Haas DM, Quinney SK, Clay JM, et al. Nifedipine pharmacokinetics are influenced by CYP3A5 genotype when used as a preterm labor tocolytic. Am J Perinatol 2013;30(4):275–81.
16. Haas DM, Quinney SK, McCormick CL, et al. A pilot study of the impact of genotype on nifedipine pharmacokinetics when used as a tocolytic. J Matern Fetal Neonatal Med 2012;25(4):419–23.

17. Haas DM, Dantzer J, Lehmann AS, et al. The impact of glucocorticoid polymorphisms on markers of neonatal respiratory disease after antenatal betamethasone administration. Am J Obstet Gynecol 2013;208(3):215.e1-6.
18. Omanwa K, Zimmer M, Tlolka J, et al. Is low pre-pregnancy body mass index a risk factor for preterm birth and low neonatal birth weight? Ginekol Pol 2006; 77(8):618–23 [in Polish].
19. Dietz PM, Callaghan WM, Cogswell ME, et al. Combined effects of prepregnancy body mass index and weight gain during pregnancy on the risk of preterm delivery. Epidemiology 2006;17(2):170–7.
20. Shaw GM, Wise PH, Mayo J, et al. Maternal prepregnancy body mass index and risk of spontaneous preterm birth. Paediatr Perinat Epidemiol 2014;28(4): 302–11.
21. Marston C. Research Technical Consultation and Scientific Review of Birth Spacing. Report of a WHO technical consultation on birth spacing: World Health Organization. 2005. Available at: http://apps.who.int/iris/bitstream/handle/10665/69855/WHO_RHR_07.1_eng.pdf?sequence=1&isAllowed=y. Accessed July 2, 2018.
22. Conde-Agudelo A, Rosas-Bermudez A, Kafury-Goeta AC. Birth spacing and risk of adverse perinatal outcomes: a meta-analysis. JAMA 2006;295(15): 1809–23.
23. Conde-Agudelo A, Belizan JM, Norton MH, et al. Effect of the interpregnancy interval on perinatal outcomes in Latin America. Obstet Gynecol 2005;106(2): 359–66.
24. Ball SJ, Pereira G, Jacoby P, et al. Re-evaluation of link between interpregnancy interval and adverse birth outcomes: retrospective cohort study matching two intervals per mother. BMJ 2014;349:g4333.
25. Hanley GE, Hutcheon JA, Kinniburgh BA, et al. Interpregnancy interval and adverse pregnancy outcomes: an analysis of successive pregnancies. Obstet Gynecol 2017;129(3):408–15.
26. Mahande MJ, Obure J. Effect of interpregnancy interval on adverse pregnancy outcomes in northern Tanzania: a registry-based retrospective cohort study. BMC Pregnancy Childbirth 2016;16(1):140.
27. Copen CE, Thoma ME, Kirmeyer S. Interpregnancy intervals in the United States: data from the birth certificate and the national survey of family growth. Natl Vital Stat Rep 2015;64(3):1–10.
28. Bar S, Milanaik R, Adesman A. Long-term neurodevelopmental benefits of breastfeeding. Curr Opin Pediatr 2016;28(4):559–66.
29. Kramer MS, Aboud F, Mironova E, et al. Breastfeeding and child cognitive development: new evidence from a large randomized trial. Arch Gen Psychiatry 2008; 65(5):578–84.
30. Belfort MB, Anderson PJ, Nowak VA, et al. Breast milk feeding, brain development, and neurocognitive outcomes: a 7-year longitudinal study in infants born at less than 30 weeks' gestation. J Pediatr 2016;177:133–9.e1.
31. Sridhar A, Salcedo J. Optimizing maternal and neonatal outcomes with postpartum contraception: impact on breastfeeding and birth spacing. Matern Health Neonatol Perinatol 2017;3:1.
32. Mainous AG 3rd, Hueston WJ. The effect of smoking cessation during pregnancy on preterm delivery and low birthweight. J Fam Pract 1994;38(3):262–6.
33. Dahlin S, Gunnerbeck A, Wikstrom AK, et al. Maternal tobacco use and extremely premature birth - a population-based cohort study. BJOG 2016; 123(12):1938–46.

34. Kuper SG, Abramovici AR, Jauk VC, et al. The effect of omega-3 supplementation on pregnancy outcomes by smoking status. Am J Obstet Gynecol 2017;217(4):476.e1–6.
35. Jeffcoat MK, Hauth JC, Geurs NC, et al. Periodontal disease and preterm birth: results of a pilot intervention study. J Periodontol 2003;74(8):1214–8.
36. Novak T, Radnai M, Gorzo I, et al. Prevention of preterm delivery with periodontal treatment. Fetal Diagn Ther 2009;25(2):230–3.
37. Aagaard K, Ma J, Antony KM, et al. The placenta harbors a unique microbiome. Sci Transl Med 2014;6(237):237ra265.
38. Walia M, Saini N. Relationship between periodontal diseases and preterm birth: recent epidemiological and biological data. Int J Appl Basic Med Res 2015;5(1):2–6.
39. Teshome A, Yitayeh A. Relationship between periodontal disease and preterm low birth weight: systematic review. Pan Afr Med J 2016;24:215.
40. Iheozor-Ejiofor Z, Middleton P, Esposito M, et al. Treating periodontal disease for preventing adverse birth outcomes in pregnant women. Cochrane Database Syst Rev 2017;(6):CD005297.
41. Hueston WJ, Knox MA, Eilers G, et al. The effectiveness of preterm-birth prevention educational programs for high-risk women: a meta-analysis. Obstet Gynecol 1995;86(4 Pt 2):705–12.
42. Lamont RF. Setting up a preterm prevention clinic: a practical guide. BJOG 2006;113(Suppl 3):86–92.
43. Manuck TA, Henry E, Gibson J, et al. Pregnancy outcomes in a recurrent preterm birth prevention clinic. Am J Obstet Gynecol 2011;204(4):320.e1-6.
44. Ha V, McDonald SD. Pregnant women's preferences for and concerns about preterm birth prevention: a cross-sectional survey. BMC Pregnancy Childbirth 2017;17(1):49.
45. Clark EA, Esplin S, Torres L, et al. Prevention of recurrent preterm birth: role of the neonatal follow-up program. Matern Child Health J 2014;18(4):858–63.
46. Iams JD, Applegate MS, Marcotte MP, et al. A statewide progestogen promotion program in Ohio. Obstet Gynecol 2017;129(2):337–46.
47. Newnham JP, White SW, Meharry S, et al. Reducing preterm birth by a statewide multifaceted program: an implementation study. Am J Obstet Gynecol 2017;216(5):434–42.
48. Sunderam S, Kissin DM, Crawford SB, et al. Assisted reproductive technology surveillance - United States, 2014. MMWR Surveill Summ 2017;66(6):1–24.
49. Oshiro BT, Kowalewski L, Sappenfield W, et al. A multistate quality improvement program to decrease elective deliveries before 39 weeks of gestation. Obstet Gynecol 2013;121(5):1025–31.
50. Timor-Tritsch IE, Monteagudo A, Cali G, et al. Cesarean scar pregnancy is a precursor of morbidly adherent placenta. Ultrasound Obstet Gynecol 2014;44(3):346–53.
51. van Vliet EO, Askie LA, Mol BW, et al. Antiplatelet agents and the prevention of spontaneous preterm birth: a systematic review and meta-analysis. Obstet Gynecol 2017;129(2):327–36.
52. Visser L, de Boer MA, de Groot CJM, et al. Low dose aspirin in the prevention of recurrent spontaneous preterm labour - the APRIL study: a multicenter randomized placebo controlled trial. BMC Pregnancy Childbirth 2017;17(1):223.
53. El-Gharib MN, El-Hawary TM. Matched sample comparison of intramuscular versus vaginal micronized progesterone for prevention of preterm birth. J Matern Fetal Neonatal Med 2013;26(7):716–9.

54. da Fonseca EB, Bittar RE, Carvalho MH, et al. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol 2003;188(2):419–24.
55. Norman JE, Shennan A, Bennett P, et al. Trial protocol OPPTIMUM– does progesterone prophylaxis for the prevention of preterm labour improve outcome? BMC Pregnancy Childbirth 2012;12:79.
56. Romero R, Nicolaides K, Conde-Agudelo A, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. Am J Obstet Gynecol 2012; 206(2):124.e1-9.
57. Romero R, Nicolaides KH, Conde-Agudelo A, et al. Vaginal progesterone decreases preterm birth </= 34 weeks of gestation in women with a singleton pregnancy and a short cervix: an updated meta-analysis including data from the OPPTIMUM study. Ultrasound Obstet Gynecol 2016;48(3):308–17.
58. Jarde A, Lutsiv O, Park CK, et al. Effectiveness of progesterone, cerclage and pessary for preventing preterm birth in singleton pregnancies: a systematic review and network meta-analysis. BJOG 2017;124(8):1176–89.
59. Schuit E, Stock S, Rode L, et al. Effectiveness of progestogens to improve perinatal outcome in twin pregnancies: an individual participant data meta-analysis. BJOG 2015;122(1):27–37.
60. Romero R, Conde-Agudelo A, El-Refaie W, et al. Vaginal progesterone decreases preterm birth and neonatal morbidity and mortality in women with a twin gestation and a short cervix: an updated meta-analysis of individual patient data. Ultrasound Obstet Gynecol 2017;49(3):303–14.
61. Jarde A, Lutsiv O, Park CK, et al. Preterm birth prevention in twin pregnancies with progesterone, pessary, or cerclage: a systematic review and meta-analysis. BJOG 2017;124(8):1163–73.
62. Cox SM, Sherman ML, Leveno KJ. Randomized investigation of magnesium sulfate for prevention of preterm birth. Am J Obstet Gynecol 1990;163(3): 767–72.
63. Alves JG, de Araujo CA, Pontes IE, et al. The BRAzil MAGnesium (BRAMAG) trial: a randomized clinical trial of oral magnesium supplementation in pregnancy for the prevention of preterm birth and perinatal and maternal morbidity. BMC Pregnancy Childbirth 2014;14:222.
64. Oliver RS, Lamont RF. Infection and antibiotics in the acause, prediction and prevention of preterm birth. J Obstet Gynaecol 2013;33(8):768–75.
65. Ramsey PS, Lieman JM, Brumfield CG, et al. Chorioamnionitis increases neonatal morbidity in pregnancies complicated by preterm premature rupture of membranes. Am J Obstet Gynecol 2005;192(4):1162–6.
66. Hutzal CE, Boyle EM, Kenyon SL, et al. Use of antibiotics for the treatment of preterm parturition and prevention of neonatal morbidity: a metaanalysis. Am J Obstet Gynecol 2008;199(6):620.e1-8.
67. Lamont RF, Nhan-Chang CL, Sobel JD, et al. Treatment of abnormal vaginal flora in early pregnancy with clindamycin for the prevention of spontaneous preterm birth: a systematic review and metaanalysis. Am J Obstet Gynecol 2011;205(3): 177–90.
68. Simcox R, Sin WT, Seed PT, et al. Prophylactic antibiotics for the prevention of preterm birth in women at risk: a meta-analysis. Aust N Z J Obstet Gynaecol 2007;47(5):368–77.

69. Lamont RF. Advances in the prevention of infection-related preterm birth. Front Immunol 2015;6:566.
70. Roberts CL, Algert CS, Rickard KL, et al. Treatment of vaginal candidiasis for the prevention of preterm birth: a systematic review and meta-analysis. Syst Rev 2015;4:31.
71. Flenady V, Wojcieszek AM, Papatsonis DN, et al. Calcium channel blockers for inhibiting preterm labour and birth. Cochrane Database Syst Rev 2014;(6):CD002255.
72. Gaudet LM, Singh K, Weeks L, et al. Effectiveness of terbutaline pump for the prevention of preterm birth. A systematic review and meta-analysis. PLoS One 2012;7(2):e31679.
73. Othman M, Neilson JP, Alfirevic Z. Probiotics for preventing preterm labour. Cochrane Database Syst Rev 2007;(1):CD005941.
74. Khianman B, Pattanittum P, Thinkhamrop J, et al. Relaxation therapy for preventing and treating preterm labour. Cochrane Database Syst Rev 2012;(8):CD007426.
75. Stan CM, Boulvain M, Pfister R, et al. Hydration for treatment of preterm labour. Cochrane Database Syst Rev 2013;(11):CD003096.
76. Han S, Crowther CA, Moore V. Magnesium maintenance therapy for preventing preterm birth after threatened preterm labour. Cochrane Database Syst Rev 2013;(5):CD000940.
77. Reinebrant HE, Pileggi-Castro C, Romero CL, et al. Cyclo-oxygenase (COX) inhibitors for treating preterm labour. Cochrane Database Syst Rev 2015;(6):CD001992.
78. Haas DM, Morgan AM, Deans SJ, et al. Ethanol for preventing preterm birth in threatened preterm labor. Cochrane Database Syst Rev 2015;(11):CD011445.
79. Flenady V, Reinebrant HE, Liley HG, et al. Oxytocin receptor antagonists for inhibiting preterm labour. Cochrane Database Syst Rev 2014;(6):CD004452.
80. Siega-Riz AM, Promislow JH, Savitz DA, et al. Vitamin C intake and the risk of preterm delivery. Am J Obstet Gynecol 2003;189(2):519–25.
81. Hauth JC, Clifton RG, Roberts JM, et al. Vitamin C and E supplementation to prevent spontaneous preterm birth: a randomized controlled trial. Obstet Gynecol 2010;116(3):653–8.
82. Ghomian N, Hafizi L, Takhti Z. The role of vitamin C in prevention of preterm premature rupture of membranes. Iran Red Crescent Med J 2013;15(2):113–6.
83. Gernand AD, Schulze KJ, Stewart CP, et al. Micronutrient deficiencies in pregnancy worldwide: health effects and prevention. Nat Rev Endocrinol 2016;12(5):274–89.
84. Ota E, Mori R, Middleton P, et al. Zinc supplementation for improving pregnancy and infant outcome. Cochrane Database Syst Rev 2015;(2):CD000230.
85. Hezelgrave NL, Watson HA, Ridout A, et al. Rationale and design of SuPPoRT: a multi-centre randomised controlled trial to compare three treatments: cervical cerclage, cervical pessary and vaginal progesterone, for the prevention of preterm birth in women who develop a short cervix. BMC Pregnancy Childbirth 2016;16(1):358.
86. van Zijl MD, Koullali B, Naaktgeboren CA, et al. Pessary or progesterone to prevent preterm delivery in women with short cervical length: the Quadruple P randomised controlled trial. BMC Pregnancy Childbirth 2017;17(1):284.
87. Cabrera-Garcia L, Cruz-Melguizo S, Ruiz-Antoran B, et al. Evaluation of two treatment strategies for the prevention of preterm birth in women identified as at risk by ultrasound (PESAPRO Trial): study protocol for a randomized controlled trial. Trials 2015;16:427.
88. Koullali B, van Kempen LEM, van Zijl MD, et al. A multi-centre, non-inferiority, randomised controlled trial to compare a cervical pessary with a cervical

cerclage in the prevention of preterm delivery in women with short cervical length and a history of preterm birth - PC study. BMC Pregnancy Childbirth 2017;17(1):215.
89. Giraldo-Isaza MA, Fried GP, Hegarty SE, et al. Comparison of 2 stitches vs 1 stitch for transvaginal cervical cerclage for preterm birth prevention. Am J Obstet Gynecol 2013;208(3):209.e1-9.
90. Defranco EA, Valent AM, Newman T, et al. Adjunctive therapies to cerclage for the prevention of preterm birth: a systematic review. Obstet Gynecol Int 2013; 2013:528158.
91. Alfirevic Z, Stampalija T, Medley N. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. Cochrane Database Syst Rev 2017;(6):CD008991.
92. Rafael TJ, Berghella V, Alfirevic Z. Cervical stitch (cerclage) for preventing preterm birth in multiple pregnancy. Cochrane Database Syst Rev 2014;(9):CD009166.
93. Jin XH, Li D, Huang LL. Cervical pessary for prevention of preterm birth: a meta-analysis. Sci Rep 2017;7:42560.
94. Coomarasamy A, Thangaratinam S, Gee H, et al. Progesterone for the prevention of preterm birth: a critical evaluation of evidence. Eur J Obstet Gynecol Reprod Biol 2006;129(2):111–8.
95. Benjamin DJ, Berger J, Johannesson M, et al. Redefine statistical significance. Nature Human Behaviour 2018;2:6–10.
96. Berghella V. The power of meta-analysis to address an important clinical question in obstetrics. Am J Obstet Gynecol 2017;216(4):379.e1–4.
97. Broekhuijsen K, Bernardes T, van Baaren GJ, et al. Relevance of individual participant data meta-analysis for studies in obstetrics: delivery versus expectant monitoring for hypertensive disorders of pregnancy. Eur J Obstet Gynecol Reprod Biol 2015;191:80–3.
98. Barnard ND, Willett WC, Ding EL. The misuse of meta-analysis in nutrition research. JAMA 2017;318(15):1435–6.
99. Carlson SE, Gajewski BJ, Valentine CJ, et al. Assessment of DHA on reducing early preterm birth: the ADORE randomized controlled trial protocol. BMC Pregnancy Childbirth 2017;17(1):62.
100. Dzau VJ, Ginsburg GS. Realizing the full potential of precision medicine in health and health care. JAMA 2016;316(16):1659–60.