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Spontaneous preterm labour that leads to preterm birth: An update and personal reflection

Ronald F. Lamont*

Department of Gynaecology and Obstetrics, University of Southern Denmark, Odense University Hospital, Odense, Denmark, and Division of Surgery, University College London, Northwick Park Institute for Medical Research Campus, London, UK

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ABSTRACT

Objective: The objective was to provide an update of progress made over time (including personal reflection) of our attempts to reduce the mortality and morbidity associated with spontaneous preterm labour that leads to preterm birth.
Methods: An experienced and evidence based approach was taken to provide an overview of progress made over a generation (~40 years) in our understanding of spontaneous preterm labour.
Results: It is evident that we have made significant progress in our understanding of the aetiology, the measurement of the burden, the basic science, systems biology and mechanical pathways of the preterm parturition syndrome. We have better ways of predicting, preventing and managing spontaneous preterm labour than existed a generation ago.
Conclusions: The profile of spontaneous preterm labour that leads to preterm birth, thanks to organisations such as the March of Dimes, WHO and PREBIC is much more evident than before. However, while we have come a long way, we must not be complacent, and clinicians and basic scientists must continue to work in harmony, while recruiting and encouraging young investigators to join the effort to improve survival and handicap in what is one of the Great Obstetric Syndromes.

1. Introduction

I gave my first lecture on preterm birth (PTB) around 1980 when I was a Trainee in Perinatal Medicine at the Institute of Obstetrics and Gynaecology, Hammersmith and Queen Charlotte's Hospitals in London, UK, the Regional Perinatal Referral Centre for the North West Thames Quadrant of London. My first 35 mm slide listed the current problems with the management of spontaneous preterm labour (sPTL) leading to PTB (Table 1). The comments to accompany the slides were that we do not know the aetiology of PTB; because we don't know the cause, we cannot predict it; because we cannot predict it, we cannot prevent it. Since we cannot prevent it, we have to manage it as it arises. As it arises, we have difficulty making the diagnosis. Even if we can make the diagnosis, we do not know whether or not we should interfere. If we do decide to interfere, we were unsure about the risks versus benefits of tocolytics, antepartum glucocorticoids or antibiotics. If we decide not to interfere or are unsuccessful interfering, we do not know the best way to deliver the preterm infant, and we still had difficulty at that time in the early 1980s persuading colleagues from other centres to send babies *in utero* to centres with neonatal intensive care unit (NICU) facilities. It could be argued that these comments ring true today, but I think that would be unfair. While we still have a great deal more to do, I think we have come a long way and know a great deal more now than we did then. This overview provides an update on how far we have come and what might be ahead of us in the future.

Abbreviations: BBV, Bacterial Vaginosis; CMP, Circulating Microparticle; COX, Cycloxygenase; CSAID, Cytokine Suppressive Anti-inflammatory Drugs; CST, Community State Types; ESPBC, European Spontaneous Pretrm Birth Congress; H_2O_2, Hydrogen Peroxide; IA, Intraamniotic; LDA, Low Dose Aspirin; MoD, March of Dimes; NICE, National Institute for Health and Care Excellence; NICU, Neonatal Intensive Care Unit; PG, Prostaglandin; PREBIC, Preterm Birth Internation Collaborative; PPROM, Preterm Prelabour Rupture of the Membranes; PTB, Preterm Birth; RCOG, Royal College of Obstetricians and Gynaecologists; TNF, Tumour Necrosis Factor; sPTL, Spontaneous Preterm Labour; WHO, World Health Organisation

* Corresponding author. Odense University Hospital, Department of Gynecology and Obstetrics, University of Southern Denmark, Institute of Clinical Research, Research Unit of Gynaecology and Obstetrics, Kløvervænget 10, 10th floor, 5000 Odense C, Denmark.
E-mail address: rlamont@health.sdu.dk.

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Table 1
Problems with the management of spontaneous preterm labour leading to preterm birth in 1980.

Aetiology
Prediction
Prevention
Diagnosis
Intervention
- *Tocolytics*
- *Steroids*
- *Antibiotics*
Mode of delivery
In utero transfer

2. Historical perspectives and timeline on how the profile of spontaneous preterm labour and preterm birth has changed

2.1. 1980s

In the early 1980s while I was undertaking my research for my doctorate thesis, like every young investigator, I was submitting abstracts to International Scientific Conferences for Poster or Oral Presentations on the subject of my thesis "The Role of Infection in the Aetiology of Spontaneous Early Preterm Birth". However, there were no Meetings or Conference Sections specifically for sPTL or PTB, so abstracts on the role of infection in the aetiology of PTB had to be submitted to the Section on "Labour" or the Section on "Infections in Pregnancy".

In 1987, an open label pilot study of 13 cases given an oxytocin receptor (OTR) antagonist as a tocolytic for the treatment of sPTL, which demonstrated efficacy without adverse effects was published [1]. The compound that Ferring Pharmaceuticals had discovered was a pure antagonist of OTRs and vasopressin V_{1a} receptors without any agonist effects. The compound had a much greater affinity for the vasopressin receptor than the OTR, so initially, the compound had been considered as a treatment of dysmenorrhoea. For reasons unknown, the compound was shelved until consideration was given to its potential role as a tocolytic.

2.2. 1990s

Never before having been involved in this area of research into PTB, in 1994, Ferring Pharmaceuticals who were taking the drug (atosiban Tractocile™) from the bench to the marketplace, organised a meeting of experts and opinion leaders in Cap Ferrat near Nice, France, to advise them on the key issues and how to conduct the appropriate clinical trials into sPTL. What followed was what Ferring referred to as the Cap-studies. This was a multinational, multicentre, double dummy, comparative controlled study that compared the effectiveness and safety of atosiban with conventional β_2-agonist therapy (ritodrine, salbutamol or terbutaline) for the treatment of sPTL. There was a pooled analysis of three prespecified subgroup reports produced by collaborative groups from eight different countries [2–4], culminating in the worldwide comparative trial of the vasopressin-OTR antagonist atosiban versus β_2-agonists, which remains the largest RCT of tocolytic therapy ever conducted [5]. Following the results, atosiban was licensed for use and was launched in Europe in 1999.

2.3. Noughties (2000s)

Along with the launch of atosiban, came support from Ferring Pharmaceuticals to increase awareness of sPTL and PTB and they sponsored the 1st, 2nd and 3rd International Preterm Labour Conferences, in Montreux, Switzerland in 2000, 2002 and 2004 respectively, the proceedings of which were published as Supplements to BJOG. Following the 3rd International Preterm Labour Conference, in Montreux, Switzerland in 2004, PREBIC (the **Pre**term **B**irth **I**nternational **C**ollaborative) which had been established some years earlier at a meeting in Aarhus in Denmark, held their first meeting nested under the auspices of the World Health Organization at their headquarters in Geneva, Switzerland supported also by the March of Dimes organisation. In 2006, a practical guide to setting up a preterm prevention clinic was published [6] and in 2009 the MoD published its "White Paper on Preterm Birth" [7], which addressed the global and regional toll of PTB.

2.4. Teenies (2010s)

By 2014 there were 23 special preterm clinics functioning in the in UK [8] albeit with inconsistencies between them, which was criticized [9]. In 2014, the 1st European Spontaneous Preterm Birth Congress (ESPBC) was held in Svendborg, Denmark, and in 2016 and 2018, the 2nd and 3rd were held in Gothenberg, Sweden, and Edinburgh, Scotland respectively. It is hoped and anticipated the 4th ESPBC will be held in The Netherlands in 2020. Currently, there are 52 systematic reviews in the Cochrane Database of Sytematic Reviews that pertain to sPTL and PTB including 19 on prediction and prevention, and 15 on treatment.

2.5. Raising the profile of the global burden of preterm birth

In the March of Dimes White Paper (2009) on PTB, WHO data indicated that the percentage rate of PTB varied from: i) $< 8\%$ in Europe (including Russia), Australia and New Zealand; ii) 8–8.9% in Central and South America; iii) 9–9.9% in Asia and iv) $\geq 10\%$ in North America and Africa [10], and that 10 countries, (that included the USA but no countries of Europe) accounted for 60% of the worlds PTBs by rank. In 2010, a population-based study comprising 9,376,252 singleton pregnancies, (conducted by the Euro-Peristat Scientific Committee) from 30 high-income countries (27 countries of Europe, plus Canada, Japan and USA), compared the variation in very early PTB rates. Of total births between 24 and 31 completed weeks of gestation, rates in Europe varied between 5.2% (Iceland) and 13.3% (Belgium) and in Canada, Japan and the USA rates were 8.2%, 6.7% and 12.2% respectively [11]. Later, data from the same source noted that these international rate variations, if not due to problems with reporting (which did not appear significant), suggested that a reduction in early delivery was achievable [12].

3. Basic science, systems biology, mechanistic pathways

3.1. The preterm parturition syndrome

About 40 years ago the aetiology of PTB was largely unknown and much of it was thought to be idiopathic. The idiopathic nature of sPTL leading to PTB was later questioned. In a study of 50 women consecutively admitted in sPTL with intact membranes who went on to have a PTB despite the use of tocolytics were evaluated comprehensively to seek a cause for the sPTL and PTB. The evaluation included: i) a detailed history; ii) a detailed physical examination; iii) fetal ultrasound examination; iv) amniocentesis for Gram stain microscopy, culture, and glucose determination; v) screen for sepsis (full blood count, urinalysis, and culture of urine and cervicovaginal sectretions); vi) screen for antiphospholipase syndrome; vii) placental histopathological examination and viii) urine toxicology screening. A number of possible cause for sPTL were identified (Table 2) and in 58% of cases, two or more causes could be identified, and only 4% could be considered to be truly idiopathic [13]. Clearly, while the final end common pathway may be the same, the aetiology of sPTL leading to PTB is multifactorial and this has been referred to as the "Preterm Parturition Syndrome" [14]. The last 30–40 years has also seen a greater understanding of these pathways, making better use of animal models to understand the structure and function of the cervix, placenta, myometrium, decidua,

Table 2
Contribution of causes of spontaneous preterm labour resulting in preterm birth [13].

Cause of Spontaneous Preterm Birth	Percentage Rate
Faulty Placentation	50%
Intrauterine infection	38%
Immunological Factors	30%
Cervical weakness	16%
Uterine factors	14%
Maternal factors	10%
Trauma or Surgery	8%
Fetal abnormalities	6%
Idiopathic	4%

and the extraplacental membranes [15].

3.2. Gene-environmental interaction

We have long understood the interaction between exposure and susceptibility. Heavy smokers (maximal exposure) may not develop lung cancer (minimal susceptibility) yet non-smokers (minimal exposure) may develop lung cancer from passive smoking (maximal susceptibility). However, it took us many years to understand that it was not enough to know what organisms are in the vagina but that it was also important to know the host response to the microbial exposure. If the exposure is bacterial vaginosis (BV), and the susceptibility is a gene polymorphism at the TNF-alpha gene locus, women with BV but not the TNF-alpha polymorphism have a statistically significant 3.3-fold increase risk of PTB (95% CI = 1.8–5.9). Similarly women without BV but with the TNF-alpha polymorphism have a statistically significant 2.7-fold increase risk of PTB (95% CI = 1.8–4.5). However, if both BV and the TNF-alpha polymorphism were present, the risk of PTB was significantly increased > 10-fold (95% CI = 4.4–23) [16]. Accordingly, when a normal microbiota becomes abnormal, and the infective process begins with adhesion and invasion of the tissues, an inflammatory response develops that is genetically determined. The hope is that this genetic response will be appropriate, measured, and result in recovery and repair. However, sometimes the genetic response is hyper-responsive with tissue damage or hypo-responsive with overwhelming infection, both of which lead to perinatal mortality and morbidity with long-term lung and brain problems such as brochopulmonary dysplasia, periventular leucomalacia and cerebral palsy [17]. Although the biochemical mechanisms are unclear, another example of gene–environmental interaction, is the carriage of a gene deletion for dihydrofolate reductase which, in association with low folate intake, significantly increases the incidence of PTB and low birth weight [18].

3.3. Infection and inflammation

While the aetiology of sPTL and PTB is multifactorial, there is overwhelming evidence to link infection with PTB particularly at early gestations where neonatal morbidity and mortality is at its greatest. Recently, using culture-independent, molecular-based techniques, new information has emerged about the vaginal microbiome in health and disease [19]. These techniques have demonstrated that the genital tract microbiota is composed of different subtypes or community state types (CSTs) and show marked differences in diversity and relative abundance of dominant organisms [20].

3.4. Non-infectious inflammation

However, we now understand more about inflammation of non-infectious origin such as oxidative stress and the role of radical oxygen species [21]. In addition, among the most basic of defense responses to threat, whether in primitive organisms or in higher order species, are the responses to lack of nutrients and attack from a predator. Accordingly, many metabolic and immune response pathways, or nutrient-sensing and pathogen-sensing systems, together with the molecules and systems they comprise, have evolved in parallel and have been evolutionarily conserved throughout species. While the acute response has survival value, the chronic inflammatory response may explain the connection between PTB and metabolic disease in the form of obesity [22].

3.5. Vaginal eubiosis

These new developments in molecular-based, cultivation-independent techniques have led to a better understanding of vaginal eubiosis. The healthy human vagina is colonised by populations of lactic acid producing bacteria (mainly, but not exclusively from the genus *Lactobacilli*). By producing lactic acid, this microbiota maintains the vaginal pH < 4.5. At this acid pH, the growth of potentially pathogenic bacteria is suppressed. Using solely cultivation-dependent techniques, it is not possible to identify *Lactobacillus* spp beyond the genus level. That is to say, we know the organism is of the genus *Lactobacillus*, but we cannot comment on the species, and hence cannot comment on species-specific functions such as H_2O_2 or production of natural antimicrobials such as bacteriocins. This being the case, with over 250 species of *Lactobacilli* currently identified (mostly used in the food industry to manufacture yoghurts and milkshakes) it is not surprising that 25 years ago, some concluded that "no two women have the same vaginal lactobacilli" [23]. Using molecular-based, cultivation-dependent techniques we now know that this comment is wrong and that, worldwide, the eubiotic vaginal microbiota is colonised by one, or at the most two species of *Lactobacilli* from a shortlist of four [24]. These four species: *Lactobacillus crispatus, Lactobacillus gasseri, Lactobacillus iners* and *Lactobacillus jensenii* correspond to CSTs I, II III and V respectively [25]. A better understanding of the role of *Lactobacilli* might lead to improved development of new probiotics either alone or in combination with antibiotics to restore vaginal eubiosis [24,25].

3.6. Vaginal dysbiosis

Equally, a better understanding of vaginal dysbiosis may explain the relationship between vaginal dysbiosis and PTB, the different response to different antimicrobials and the different phenotypic outcomes. Cultivation-dependent techniques are unhelpful when dysbiosis is due to BV, because this is a quantitative rather than a qualitative diagnosis using the current Gold-standard of Nugent scoring of Gram stain microscopy [26]. Cultivation-independent molecular based techniques have also demonstrated that only 20% of organisms can be identified by culture and that in the vagina, there are previously unidentified and uncultivatable organisms of significance in BV (bacterial vaginosis associated bacterium [BVAB]-1, −2, −3). There are also previously under detected and hence underappreciated organisms like *Atopobium vaginae* that contribute to vaginal dysbiosis. Using molecular based techniques, it is likely that more than the two subgroups of dysbiosis described in CST IV [25], will be identified which might help to explain the different etiologies, microbiogy, responses to different antibiotics and phenotypic outcomes with vaginal dysbiosis [27,28]. The role of infection through structured polymicrobial biofilms involving *Gardnerella vaginalis* and other organisms is also an important contribution to our knowledge of the infection-related PTB [29,30].

3.7. Molecular diagnostics

Currently there are four molecular diagnostic tests for the diagnosis of BV that are approved by the FDA for use in the USA [31], and two that have been licensed for use in Europe [32,33], one of which is common to both [32]. The bacterial species included and the sensitivities, specificities, positive and negative predictive values in those tests

Table 3
Bacterial species included in approved molecular diagnostic tests for bacterial vaginosis [31].

Organism	NuSwab	SureSwab	BD Max	BV MDL Panel
A. vaginae	X	X	X	X
G. vaginalis		X	X	X
Megasphaera (Type1,2 or spp)	X	X	X	X
BV associated bacteria (Type 1and/or 2)	X		X	X
Lactobacillus species	X	X	X	X

Table 4
Sensitivity, specificity, positive predictive and negative predictive values of approved molecular diagnostic tests for bacterial vaginosis [31].

Multiplex PCR Tests	Sensitivity	Specificity	PPV	NPV
NuSwab*	96.7%	92.2%	94%	95.6%
SureSwab*	–	–	–	–
BD MAX Vaginal Panel™	90.5%	85.5%	89%	87.7%
MDL BV Panel	99%	94%	94%	94%

approved by the FDA for use in the USA as molecular diagnostic tests for BV, are shown in Tables 3 and 4 respectively.

3.8. The genetics, epigenetics and pharmacogenetics of PTB

For at least 50 years, epidemiologists have appreciated the tendency to repeat gestational age and birth weight in successive births due to intrinsic factors, since complications during pregnancy, or other known risk factors which predispose to a similar pregnancy outcome, are unable to account for these events in successive births [34]. The genetic influence on duration of gestation and the risk of PTB has recently been elegantly reviewed [35]. Similarly, the role of pharmacogenetics of PTB to determine the optimal dose and likelihood of a successful response to prophylactic and therapeutic tocolytic agents based on maternal and/or fetal genotype, methylome, transcriptome has been reviewed. Along with this comes the possible application of nanotechnology to minimize fetal exposure while maximizing tissue-specific effects. Using specifically engineered liposomes designed for this purpose, these are encapsulated with tocolytic agents, to deliver directly to the myometrium while limiting fetal exposure [36–38]. We know that the epigenome and microbiome modulate perinatal and postnatal health and subsequent outcome. Intrauterine infection associated with PTB can alter gene expression and epigenetic programming as well as postnatal inflammatory responses in offspring. Epigenetic modifications of toll like receptors associated with exposure to intrauterine inflammation, as well as cross talk between the host epigenome and microbiome result in changes to the neonatal gut microbiome that modulates maturation of inflammatory pathways, and the neonatal immune system [39]. This effect of changes in the neonatal gut microbiome and modulation of the developing immune system can have long-term consequences of obesity, asthma, eczyma and atopic disease [40].

4. Prediction of preterm birth

In recent years, there have been significant advances in the development of biochemical, biophysical and microbiological markers of PTB such as fetal fibronectin, transvaginal ultrasound of cervical length and screening for vaginal dysbiosis mainly in the form of BV. The common factor between these screening tests is the poor sensitivity compared to the specificity. In other words, there are many false positives but negative tests usually indicate low risk of PTB. The use of fetal fibronectin testing is also dependent on the gestational age at sampling, whether testing is single or serial sampling, whether the patient is at high or low risk of PTB, and whether it is a singleton or multiple pregnancy. A recent advance has been the use of quantitative analysis of fetal fibronectin rather than categorical qualitative analysis [41]. While most investigators agree on a cut-off point of 25 mm for a definition of short cervix on transvaginal ultrasound, this differs between studies, as does the technique for measuring cervical length. Quantitative fetal fibronectin values alone and its synergistic effect when combined with cervical length has been proven in large prospective cohorts [42] and is now available as an app for widespread use [43].

Overall, the detection of BV in pregnancy is associated with a two fold increased risk of PTB but if detected before 20 weeks gestation is associated with a 5-fold risk and before 16 weeks, a 7-fold increased risk. Accordingly, the earlier in pregnancy that vaginal dysbiosis is detected, the greater is the risk of an adverse outcome. Even if the dysbiosis becomes eubiotic spontaneously or following successful treatment, there is still a much higher risk of an adverse outcome [44]. This suggests that the infective/inflammatory damage occurs early in pregnancy and persists.

4.1. Exosomes

The evolving field of circulating microparticle (CMP) biology shows promise for early detection of the risk of early PTB. Microparticles are membrane-bound nanovesicles that range in size from 50 to 300 nm and are shed by a wide variety of cell types. While nomenclature varies, microparticles of 50–100 nm are called exosomes that are increasingly recognized as important means of intercellular communication in physiological, pathophysiological and apoptotic circumstances. While the contents of exosomes differ between cell types and their expression, they can include nuclear, cytosolic and membrane proteins as well as lipids and RNA. The contents of exosomes hold information about the state of the cell type of origin at the time of expression and so represent a unique window in real time with respect to the activities of the cells, tissues and organs that might otherwise be too remote to sample. Since a high proportion of adverse pregnancy outcomes such as late miscarriage and PTB have their pathophysiological origins at the uteroplacental interface in early pregnancy, an understanding of protein signalling and the state of cell and tissue populations may be predictive of these adverse outcomes. Cantonwine et al. have demonstrated that they can capture, separate, extract and enrich exosomes that contain an informative, panel of exosome associated proteins at about 11 weeks gestation, which are able to predict PTB before 35 completed weeks of gestation [45].

4.2. Vaginal microbiome

With new information about the vaginal microbiota from molecular based techniques, we may be able to relate the vaginal microbiome to adverse outcomes of pregnancy such as PTB. In this issue of the journal we have presented a systematic review of this possibility [46]. As you can read, the evidence is evolving but the studies are heterogeneous and some are of poor quality. While the conclusions differ, 3-studies showed no relationship and 6-studies showed a relationship between the vaginal microbiome and PTB. In general, the former studies were published a few years ago and the latter in more recent years suggesting that either improved technology is providing better information. Alternatively, this may be due to a better understanding of the role of *L. iners* in vaginal eubiosis and dysbiosis [47,48] and how it pertains to PTB. If possible, it might be informative to re-analyse earlier studies with special attention to the role of *L.iners* and whether this would alter their results.

5. Prevention of preterm birth

As stated in Section 2.4, in the UK and many other countries, preterm prevention clinics have been set up, though not necessarily with consistent practices between clinics. Some clinics even pride themselves in carrying out no interventions and claim to successfully reduce the rate of PTB by preventing poorly evidence based preventative measures.

5.1. General measures

These may be long-term or short-term. In the long-term, sociobiological variables related to PTB such as age, weight, height, parity, and socio-economic status will take a generation or more to change but they should not be ignored. In recent times, we have also seen a welcome response from our fertility specialist colleagues to reduce the rate of twins and higher order births associated with medically assisted reproduction techniques and ovulation induction. In the short-term, cessation of smoking in pregnancy will halve the incidence of PTB in this group, and steps should be taken to provide support for individuals to reduce or curtail substance abuse. Lifestyle changes aimed at reducing work-related stress, particularly in primiparae [49], or other forms of stress such as domestic violence, may reduce the rate of PTB.

5.2. Nutritional supplementation

Low maternal weight and low BMI are associated with PTB, and pre-pregnancy BMI is a strong predictor of PTB. Nutritional supplementation in pregnancy with marine n-3 fatty acids reduces the rate of PTB and increases birth weight [50]. The offspring of women with low maternal folate status during second trimester of pregnancy with a daily intake of < 500 μg is associated with an increased risk of sPTL and PTB. By 6-months postpartum, 20% of women remain folate deficient and this is aggravated by a short inter-pregnancy interval which is another factor associated with PTB. Accordingly, folate supplementation in pregnancy may also reduce the rate of PTB.

5.3. Progesterone

Convinced by Marc Keirse's systematic review and meta-analysis in 1990, I introduced into my clinical practice the use of weekly intramuscular injections of 17-a-hydroxyprogesterone (17P) in women at high risk of PTB. My "experienced based medicine" convinced me that this was the right thing to do and I was subsequently reassured by the randomised controlled trials of Meis et al. and de Fonseca et al. in 2003, and the commentaries and systematic reviews/meta-analyses that followed [51]. Doubt was expressed about the use in twin pregnancy, long-term effects on the infant, the use of systemic 17P versus micronized vaginal progesterone (taking into consideration commercial availability). The debate continues with publication of the OPPTIMUM Study [52], which showed no benefit, yet ACOG recommends that progesterone supplementation should still be used (restricted to) women with a singleton pregnancy and a previous history of sPTL and PTB and the RCOG and NICE in the UK have not yet changed their existing guidelines to incorporate the OPPTIMUM Study.

5.4. Mechanical prevention of PTB

For many years, the only mechanical option to prevent PTB was cervical cerclage and opinions were polarised. Currently, options for mechanical prevention of PTB include cerclage and pessary. Cervical cerclage is beneficial in women with singleton pregnancies who have: ii) a weak cervix based on previous second trimester painless cervical dilatation leading to recurrent late miscarriage or early PTBs or ii) a history of early sPTL and PTB and a short cervix on second trimester transvaginal ultrasound scan of cervical length. For women with multiple gestations, the benefit of a cerclage remains uncertain, and further research is needed [53]. The choice of surgical technique and suture material, together with their effects on the vaginal microbiome [48] and the use of routine ultrasound screening of cervical length requires further research [54]. Equally, while vaginal pessary has also been used for mechanical prevention of PTB in various populations, to date, the results have been contradictory and further randomised controlled trials are necessary before routine use can be recommended compared to cervical cerclage and progesterone [55].

5.5. Antibiotics

Since we have become aware that infection is a major cause of sPTL and PTB, and vaginal dysbiosis in the form of BV is predictive of PTB, it is understandable that the use of antibiotics for the prevention of infection-related PTB has been explored [27]. However, the heterogeneity of studies demonstrated the problems of using the wrong antibiotics (those not active against BV or BV-related organisms) for the wrong indication (women not at risk of infection-relayed PTB) at the wrong time in pregnancy (too late) before sufficient knowledge was available to guide choice. The systematic reviews and meta-analyses that tried to sort out the confusion, contributed to further confusion by a blunderbuss approach without focus and led to a perception that antibiotics are unable to prevent PTB under any circumstances. The Cochrane systematic review regularly cited to support this view [56] is an update that potentiates the faults of previous versions. The first step in carrying out a systematic review is to construct a focused research question that is highly specific with respect to PICO (**P**opulation, **I**ntervention, **C**omparator [if appropriate] and **O**utcome) [57], otherwise the search results will be too voluminous and complex to form meaningful conclusions. This is what happened with the Cochrane systematic review [56], which carries the title "Antibiotics for treating bacterial vaginosis in pregnancy (Review)", with no mention of PTB in the title or search. The review was 123 pages long, included 21 trials and carried out 57 different analyses ("the Heinz Review") only about 13 of which had any connection with PTB. The review also included studies in which the risk of PTB was previous PTB without stipulating whether this previous PTB was elective/spontaneous, and if spontaneous, related to an infection and hence a risk of subsequent infection-related PTB. In contrast, a more focused review of the use of clindamycin, before 22 completed weeks of gestation, in women with objective evidence of vaginal dysbiosis in the form of BV demonstrated a statistically significant 80% reduction in the rate of late miscarriage and a 40% reduction in the rate of PTB with additional important benefits with respect to secondary outcomes [27,28].

5.5.1. PREMEVA study

The recently published PREMEVA1 study [58] has also raised concerns with respect to the contribution it makes to this discussion. This study was presented in abstract form in 2013 at the 34th Annual Meeting of the Society for Materno-Fetal Medicine Meeting, New Orleans, USA [59], yet, for such a large, seemingly well conducted study, it has taken nearly 6-years from presentation to publication. The results of the study are counterintuitive to robust evidence that clindamycin used before 22 weeks gestation in women with objective evidence of BV is effective in reducing the risk of infection-related PTB [27,28]. Experts in the field were convinced that this was due to errors in the diagnosis of BV and this was confirmed when a PREMEVA1 co-author confirmed their worries about the quality of BV diagnosis (personal communication). A colleague and I were informed that because of this concern, the submission would be delayed until molecular diagnostic methods of BV could be applied to the DNA on secretions on Gram stained slides. This is also suboptimal, and has not as yet occurred. For training, the protocol recognized that Nugent scoring of BV using Gram stain microscopy was rare in France and training for the 149 laboratories that participated was by video, technical brochure and training slides yet no supporting details were given. For quality control, the protocol planned to recheck just over 1% of the total number of slides. This is in contrast to a high quality study that checked 100% of abnormal and 10% of normal Gram stains (overall 30%) [28]. Nugent scoring should be done at ×1000 magnification using oil immersion yet there are concerns and that the PREMEVA1 study used ×100 magnification without oil immersion. In my view and those of others, this study should not be used to guide practice yet this has already happened [60] before publication of full data, which has been criticised [61].

5.6. Anti-inflammatory agents

The potential for adding cytokine suppressive anti-inflammatory drugs (CSAIDs) to antibiotics shows promise and this has been comprehensively reviewed elsewhere [62]. In the ovine model, intraamniotic (IA) administration of a single dose of CSAID suppressed the lipopolysaccharide-induced IA inflammatory response with few fetal effects [63]. Several animal model studies have shown additional benefit of co-treatment with antibiotics and anti-inflammatory drugs. In rhesus monkeys, following IA inoculation of *Ureaplasma parvum*, azithromycin plus dexamethasone and indomethacin was able to prolong pregnancy and prevent severe fetal lung injury [64]. Similarly, in rhesus monkeys, to determine whether treatment with ampicillin plus dexamethasone plus indomethacin (AMP/DEX/INDO) delayed PTB following sPTL induced by IA inoculation with Group B streptococcus, ampicillin alone eradicated Group B streptococcus, but uterine activity, amniotic fluid cytokines, prostaglandins (PG), and matrix metalloproteinase-9 remained elevated. In contrast, the combination of AMP/DEX/INDO suppressed interleukin-1β, TNF-α, PGE_2, and $PGF_{2\alpha}$ but did not alter matrix metalloproteinase expression or chorioamnionitis. The combination of AMP/DEX/INDO suppressed inflammation and significantly prolonged pregnancy [65].

5.7. Probiotics

Now that we know more about the species-specific roles of different *Lactobacilli*, with respect to the production of lactic acid (see Section 3.5), the ratio of different L- and D-isomers of lactic acid, whether the lactic acid molecules produced are protonated (neutrally charged) or dissociated (anions that have given up a H^+ ion) [66], and whether or not they produce antibacterial compounds like bacteriocins or H_2O_2, we may be better able to help develop more effective probiotics that may be used as well as, or in place of antibiotics. A higher percentage of strains of *L. crispatus* compared to strains of *L. iners* provide these species-specific benefits, so probiotics based on *L. crispatus* [67] may prove more efficient at inducing eubiosis than probiotics based on other species of *Lactobacilli.* A potential role for the use of probiotics for the prevention of PTB has been suggested [68].

5.8. Low-dose aspirin

Low-dose aspirin (LDA) has been studied for the prevention of preeclampsia and intrauterine fetal growth restriction. There have also been suggestions that LDA may decrease the rate of PTB, though speculation is that this is due to a decrease in medically indicated PTB. LDA has anti-inflammatory properties and inhibits platelet aggregation through cyclo-oxygenase inhibition. This may affect both the inflammatory and uteroplacental ischemia pathways of PTB, leading to a reduction in contractility and inflammation and subsequent reduction in the rate of sPTL and PTB. In a secondary analysis of a randomised, placebo-controlled trial of LDA for the prevention of preeclampsia in low-risk nulliparae [69], after adjusting for clinically relevant variables, there was a significant reduction in in the rate of sPTL and PTB before 34 completed weeks of gestation in the LDA group (adjusted odds ratio, 0.46; 95% confidence interval = 0.23–0.89). This new potentially therapeutic option for the prevention of PTB merits further investigation.

6. Management of SPTL

6.1. Case study of In utero transfer

I stated in the introduction that, in the early 1980s, persuading colleagues to send babies *in utero* to centres with NICU facilities was difficult on some occasions. Sadly, I remember a case at the Hammersmith Hospital in 1980, when we were contacted by a Hospital on the outskirts of London, UK, about a case of triplets at 28 weeks who needed elective PTB because of fulminating pre-eclampsia, to see if we had NICU cots for the triplets. We had the capacity and suggested they transferred the babies to us *in utero* for delivery in our unit, but the referring hospital team was resistant to "giving up their triplets". We even offered their obstetric team access to our operating theatres to come with the patient and do the caesarean section on our site, and if the babies needed NICU care we would keep them, and if not, send them back with the team to the referral hospital (better to send healthy neonates back through London traffic to the referral hospital than sick neonates to the Tertiary Referral Centre). They declined and delivered the triplets themselves, two of whom weighed ~900g and one weighed ~700g, one of which went to another referral centre in London and two came to us at the Hammersmith Hospital. Only one triplet (Anita) survived and spent 3-months on our NICU, during which time, I got to know her very well, and she never weighed more than her case notes. I still wonder, had the triplets had been transferred *in utero* to us, whether Anita's siblings would have survived with her. Soon after this, we demonstrated that *in utero* transfer was associated with a much lower morbidity and mortality than neonatal transfer [70] and this is now almost universally accepted, although NICU cots are not always available locally.

6.2. Tocolytics

The principal reasons for using tocolytics is to delay delivery long enough to: i) administer a full course of antepartum glucocorticoids and ii) arrange transfer to a centre with NICU facilities, both of which have been shown to be associated with a reduced incidence of neonatal mortality and morbidity. As a very junior doctor, we were using bed-rest, opiates, IV fluids (which has some scientific logic, through suppression of vasopressin production and subsequently, less stimulation of V_{1a} myometrial receptors) β_1-agonists and alcohol to treat sPTL. Currently, β_2-agonists are still used worldwide but less than before, magnesium sulphate as a tocolytic has been discredited, and there is increasing recourse to using no tocolytics, or reverting to PG-synthetase inhibitors (like indomethacin) and calcium channel blockers (like nifedipine). For further information on the safety and efficacy of tocolytics, the reader is referred to a recent comprehensive review [71].

6.2.1. Oxytocin receptor antagonists

In 1999, atosiban was launched in Europe and is widely used globally though not in the USA, or Australia (from where, strangely, the Cochrane Review on these agents originates). Atosiban, a vasopressin/OTR antagonist (though marketed as an oxtocin receptor antagonist to emphasise the utero-specificity of the agent) is an important addition to the reactive response to sPTL (rather than the proactive approach of prevention), which on unbiased and critical review of the evidence is as efficacious if not better than any other group of tocolytics. It also has placebo level side effects and so it is also safer for mother and baby than any other group of tocolytics. Nevertheless, there remains resistance to its use, even in licenced regions of the world, partly due to cost and opposition to Big Pharma. The perfect tocolytic that is universally efficacious and has no feto-maternal adverse effects does not exist, but the search continues. There have been trials on β_3-agonists, $PGF_{2\alpha}$ inhibitors, cyclo-oxygenase (COX)-2 inhibitors, simvastatin and new, more selective oxytocin receptor antagonists that can be administered orally [71].

6.3. Management of sPTL around the limits of viability

For babies born between 23 and 26 completed weeks of gestation, the 1-year survival rate increases by 3% for each day of gestation gained, so that delay of delivery by one week over this gestational age range, increases 1-year survival by ~20%. Accordingly, there are some who feel that, around the limits of viability (24 completed weeks of gestation) there is a case to be made to use combination therapy involving antepartum glucocorticoids, antibiotics and combined tocolytic therapy in an "all or nothing" approach. The risk: benefit analysis of such combination therapy around the limits of viability has not been widely investigated. However I am aware of one study in which, using very strict entry criteria, such a therapeutic cocktail of interventions (metronidazole, cefuroxime, terbutaline, sulindac and antepartum glucocorticoids) demonstrated significant neonatal benefit, primarily by prolonging gestation [72] albeit that this was in Sweden which has one of the lowest perinatal mortality rates in the world.

7. Future research

For some novel thoughts on future PTB research, the reader is directed to the research proceedings of the 13th annual PTB international collaborative (PREBIC) meeting in Galveston in 2017 [73]. With new information from molecular based techniques such as, *inter alia*, genomics, transcriptomics, proteomics, metabolomics, microbiomics, metagenomics, epigenomics, methylomics, and virulomics, investigators will have to become familiar with the handling of "Big Data" with the help of bioinformatics and computational statisticians, be it for Registry Data, Independent Patient Data Analysis or reanalysis of data from previous studies. Similarly, some form of Register for biobanking with linked databases would be extremely helpful for future research and PREBIC have already started this process.

Historically, PTB was considered to be a single entity, but while the final end common pathway may be the same, the aetiology is multifactorial and hence the title, "preterm parturition syndrome". In future we should be breaking down PTB into its various phenotypes according to aetiology [74] or presentation such as: i) elective PTB; ii) preterm prelabour rupture of the membranes (PPROM); iii) preterm stillbirth; iv) sPTL with intact membranes and no bleeding and v) sPTL with bleeding and intact membranes, as these may have different aetiologies, different management regimens and different neonatal outcomes with respect to mortality and morbidity.

I hear and read in lectures and publications that BV in pregnancy is associated with a 2-fold increased risk of PTB. Overall, this is true, but includes studies in which screening took place as late as 32 weeks gestation by which time, pregnancies that resulted in other adverse outcomes like late miscarriage or very early PTB have been missed. Pregnant women with vaginal dysbiosis due to BV before 20 weeks of gestation, have a 5-fold increased risk of late miscarriage or PTB before 34 completed weeks of gestation [75] and a 7-fold increased risk if BV is detected before 16 weeks [76].

Equally, with respect to infection-related PTB, it is not enough to consider only vaginal dysbiosis but we should also address whether infection-related PTB is due to the presence of dysbiosis or the absence of eubiosis including the important role of *Lactobacillus iners,* which has a foot in both camps. Whether the vaginal microbiota is eubiotic or dysbiotic is important, but we must also consider what milieu this microbiota creates in the vagina and lower genital tract with respect to numerical dominance, relative abundance, diversity and virulence factors. Conversely, the milieu created by the microbiota may contain beneficial antimicrobial compounds such as bacteriocins, H_2O_2, and lactic acid. Eubiotic *Lactobacillus* species differ in their ability to produce these antimicrobials, and the antimicrobial properties are also influenced by what species produce which ratio of D- or L-lactic acid isomers, whether the lactic acid isomer is pronated (the neutrally charged intact molecule) or the dissociated negatively charged anion that has given up its H^+ ion. Having accepted that different vaginal microbiota produce a different vaginal milieu we also have to consider the host response to this combination of microbiota and milieu. Let us assume that there are five sub-types of vaginal microbiota (A, B, C, D, E), four types of vaginal milieu associated with these microbiota (α, β, γ, δ) and three types of host response to the different microbiota and milieu (X, Y, Z). Different combinations of microbiota, milieu and host response may combine to result in different phenotypic outcomes from normal term birth to PPROM to preterm stillbirth (Table 5).

Table 5
Phenotypic outcome according to the vaginal microbiome, vaginal milieu and host response.

Microbiome	Milieu	Host response	Phenotypic outcome
A	α	Z	Normal term birth
B	δ	X	Preterm stillbirth
C	β	Y	PPROM
D	γ	Z	Early sPTL with bleeding
E	β	Y	Early sPTL without bleeding

8. Conclusions

PTB remains the major cause of neonatal mortality and morbidity. This distinction used to apply only to high-income countries but now applies worldwide. A generation ago in London UK, a woman in sPTL at 28 weeks gestation at the Regional referral centre would be sedated with opiods, given a cup of tea and placed in a darkened room for the baby "to take its chance". It was only after a few babies at that gestation were found still alive in a bedpan in the sluice room some 3–4-h later, that PTB at that gestational age was taken seriously and we requested neonatal paediatricians to attend the birth. From a time when no conference had a designated section for sPTL and PTB, we now have a live Reference Textbook of sPTL and PTB with 160+ stand-alone chapters about to be launched (Table 6).

Contribution to authorship

The author confirms being the sole contributor of this work and

Table 6
Reference Textbook on Spontaneous Preterm Labour and Preterm Birth (2019)

Section Editors	Section Subjects	
• Dr Elizabeth Bonney (USA) • Prof GianCarlo Di Renzo (Italy) • Dr Cynthia Gyamfi-Bannerman (USA) • Prof Hans Helmer (Austria) • Prof Bo Jacobsson (Sweden) • Prof Mark Johnson (UK) • Prof Jan Stener Jörgensen (Denmark) • Prof Jeff Keelan (Australia) • Prof Ram Menon (USA) • Prof Indira Mysorekar (USA) • Prof Andy Shennan (UK) • Prof Nanbert Zhong (China/USA)	• Importance of PTB • Sociobiological Aspects of PTB • Genetics of PTB • Mechanisms of SPTL • Etiology of PTB • Prediction of PTB • Prevention of PTB • Management of SPTL & PTB • Evidence Based Approach to the Problem of PTB • Future Issues" Policy, Funding, Research • Ethical, Legal and Community Aspects of PTB • Pathological Pathways of PTB with Integrated Omics • International Preventions and Interventions for PTB • Immunology of PTB • Nutritional Aspects of PTB	
Editor-in-Chief: Prof Ronnie Lamont	rlamont@health.sdu.dk	160 Chapters

approved it for publication.

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In the past, the author has advised or given lectures on conferences organised or supported by Glaxo-Smith-Klein, Sanofi-Synthelabo and Ferring Pharmaceuticals pertaining to PTB in general and tocolytics in particular. Currently R.F.L is and has been a member of an Independent Drug Monitoring Committee for randomised controlled trials of tocolytic agents.

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Appendix A. Supplementary data

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