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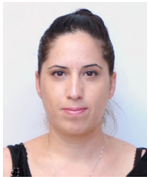
Preterm Birth Prevention: How Well Are We Really Doing? A Review of the Latest Literature

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Abstract Preterm birth is a global concern resulting in prematurity which is the leading cause of newborn death and long-term squeal in the survivors. In this review, we will summarize the data available to this date in regard to the causes, available interventions, and contemporary research for future applications.

Keywords Preterm birth · Cervical length · Prematurity

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Introduction

In 2010, approximately 15 million babies were born preterm worldwide based on an analysis published in the "Lancet." Although the majority of preterm births (PTB) occur in poor countries in south Asia and sub-Sahara Africa, USA is one of the 10 leading countries in preterm deliveries [1]. According to this estimation, India is ranked first in the number of PTB with approximately 3.5 million preterm deliveries that account for 13 % of all live births in India. The fact that in almost all countries PTB rates are increasing, and that prematurity is the leading cause of newborn death, with extreme inequalities in survival rates among low- and high-income settings, has led to publication of the global action report "Born too soon" [2]. This report was issued by the WHO and partners, and aimed to save 16 million lives by 2015. The survivors are at risk of neurodevelopmental impairments such as cerebral palsy, mental retardation, sensory impairments, minor neuromotor dysfunction, and behavioral sequelae. Serious morbidity also accompany the "late

preterm" (34–36 weeks) newborns that suffer from higher rates of temperature instability, respiratory distress, hypoglycemia, seizures, and kernicterus [3]. Prematurity was also suggested to have long-term influence on the risk for atherosclerosis, cardiovascular disease, and high blood pressure in adulthood [4, 5].

In this review, we aim to explore the contemporary available data on the causes of preterm birth, the interventions available to reduce preterm deliveries rates, and their use in current practice, and research for future applications.

Spontaneous Preterm Births

The main causes for spontaneous preterm birth (SPTB) are infection, spontaneous rupture of membranes, idiopathic contractions, multiple pregnancy, cervical dysfunction, antepartum hemorrhage, stress, and malnutrition [6]. Maternal risk factors such as smoking, alcohol consumption, low maternal BMI, advanced maternal age, and short interval between pregnancies have been identified. Yet, the causes for about half of preterm labor are unknown [7]. Many biological and genetic markers were assessed as predictors of PTB, while previous PTB and a short cervix measured by transvaginal ultrasonography are considered major risk factors for clinical practice [8].

Iatrogenic Preterm Births

More than a third of PTB are medically indicated for hypertensive diseases, diabetes, antepartum hemorrhage, intrauterine growth restriction, and non-reassuring fetal heart rate patterns [9]. The increasing rates of PTB during the last two decades were suggested to be related in part to more elective indications to reduce adverse fetal outcomes, increasing maternal age, and increasing rates of multiple gestations [10]. The rise in PTB in developed countries is primarily attributed to iatrogenic late PTB that account for up to 80 % of all PTB [11]. A study [12] that characterized delivery indications for late PTB in nearly 3.5 million deliveries in the United States during 2001 found that 23 % of the late PTB had no recorded indication for delivery. Those infants had higher mortality rates compared with those born after spontaneous delivery at similar gestational age.

In developing countries, that incur the highest burden in terms of absolute numbers, accurate data and medical records usually do not exist, and the rate of PTB is influenced by heterogeneous definitions and registration processes [13]. A cross-sectional study on the factors influencing perinatal mortality was carried out during 2010 in rural Mysore, India [14]. In this study, about a third of

preterm babies died, a rate that was attributed to higher vulnerability to infections and external environmental adversities. High perinatal mortality was also observed in mothers who were married and conceived young, had anemia, delivered at home, and suffered from placental complications. It was concluded that although the prevalence of perinatal mortality had declined, it could be further reduced by higher rates of hospital delivery and improved early neonatal care.

Preventing Preterm Births

Basic Care

While the risk of PTB is high for both rich and poor countries, there is a major survival gap due to lack of basic care in low-income countries. The provider-initiated PTB in those countries represents a relatively low proportion of PTB's where access to diagnostic tools is limited [15]. In low resource settings, significant progress can be made in preventing death with cost-effective interventions and improved health services before the intensive care is widely available [16]. The potential strategies, urgently needed to be globally researched, are basic interventions such as family planning, prevention, and management of sexually transmitted infections, malaria prevention, identification and treatment of pre-eclampsia, and reduction of physical workload [17].

A lives saved tool (LiST) analysis [18] found that with universal coverage of selected interventions achieved, 84 % of preterm neonatal death could be prevented annually, with antenatal corticosteroids and Kangaroo Mother Care having the highest impact. The last two interventions, added to the recent shifts to more facility births in Africa and Asia, could have a high impact in a relatively short-time frame (Table 1).

Primary Prevention-Risk Factors Elimination

Smoking in pregnancy is related to PTB and low birth weight (LBW) among many other adverse pregnancy outcomes. Tobacco use among women has increased and expected to rise to 20 % by 2025, and although the prevalence declined in developed countries among higher income groups, it has remained static among the lowest income quarter [19]. A cochrane review of randomized controlled trials on smoking cessation interventions, found that interventions in pregnancy reduce the proportion of women who continue to smoke in late pregnancy, and reduce LBW and PTB [20]. Nicotine replacement therapy is the only pharmacotherapy that has been tested in

Table 1 Evidence-based intervention for preterm birth mortality and morbidity reduction

Intervention	Examples	Influence	References
Basic interventions	Family planning	84 % reduction in preterm mortality	[15, 16]
	Infection control		
	Prenatal care		
Primary interventions	Smoking cessation	Reduced LBW and PTB	[18]
Secondary prevention	Progesterone	Reduced PTB and perinatal mortality, singleton	[24]
	Cervical cerclage	Reduced PTB	[26]
		Singleton	
	Pessary	Reduced PTB	[29, 30]
		Singleton	
Tertiary interventions	Tocolytics	Delay PTB up to 48 h	[39–41]
	Antibiotics PPROM	Prolongation of pregnancy, reduced neonatal morbidity	[43, 45]

controlled trials during pregnancy without sufficient evidence in regard to effectiveness and safety [21].

Nutritional status during pregnancy has been associated with PTB, but there is little evidence to support nutritional counseling and supplements administration in order to reduce PTB rates. Yet, adequate nutritional status at the beginning of pregnancy and multi-vitamins supplements should still be encouraged since it was shown effective in reduction of the risk of small for gestational age babies and neural tube defects [22].

Asymptomatic bacteriuria has been associated with PTB and should be eradicated in order to reduce the risk of pyelonephritis in pregnancy [23], but treatment has failed to demonstrate reduction in PTB rates. Other health concerns that were shown to be related to PTB but treatment failed in reduction of PTB rates are bacterial vaginosis and periodontal disease [24, 25].

A recent case control study among rural women in India [26] found that mothers to LBW babies had significantly worse periodontal status. Periodontal disease demonstrated an adjusted OR of 2.85 for low birth rate and was suggested to be addressed as part of the antenatal preventive care among rural women in India.

Secondary Prevention

Progesterone for prevention of PTB in high-risk pregnant women has been advocated in many studies in recent years. It can be administered orally, vaginally, or intramuscularly. A systematic review of 36 randomized controlled trials [27] showed that progesterone was significantly superior to placebo in risk reduction for perinatal mortality, PTB less than 34 and 37 weeks, LBW, NICU admission, and prematurity morbidity, for women with prior PTB. Favorable significant results were also demonstrated for women with a short cervix identified on ultrasound. The optimal timing,

mode, and dose of administration have not been yet determined. Administration of daily vaginal progesterone gel to asymptomatic women with cervix length between 10 and 20 mm at 19–24 weeks of pregnancy was associated with a 45 % reduction in the rate of preterm delivery before 33 weeks and with improved neonatal outcomes [28]. It was shown that 11 women with a cervix shorter than 25 mm were needed to be treated with vaginal progesterone rather than with placebo in order to prevent 1 preterm birth before 33 weeks of pregnancy [29]. No difference was shown in progesterone treatment for multiple pregnancies. Increased doses of vaginal progesterone in twin pregnancies have also failed to prevent PTB in a recent randomized controlled multicenter trial [30]. Vaginal progesterone also showed benefit in PTB reduction in IVF single pregnancies regardless of the risk for PTB, but again, not for twin pregnancies [31]. A recent prospective trial assessed the efficacy and tolerability of vaginal compared with intramuscular progesterone initiated from 14 to 18 weeks of pregnancy in women with a history of PTB [32]. The researchers found that vaginal progesterone was significantly more effective in PTB reduction and NICU admissions, and had less adverse effects.

Cervical cerclage aims to reduce PTB by mechanical support to the cervix and can be considered in subgroups of women with a history of PTB. A Cochrane review [33] found that compared to no treatment, cerclage in women at high risk of recurrent PTB reduced the incidence of PTB without significant reduction in perinatal mortality or neonatal morbidity. It was also associated with higher rates of cesarean section. A meta-analysis of randomized trials [34] suggested that singleton pregnancies in women with prior PTB can be monitored with cervical length screening and consider the placement of cerclage for the women that develop a short cervix, instead of a routine history-indicated cerclage policy. Earlier research showed an increase in PTB associated with cerclage in twin pregnancies [35].

No trial compared vaginal progesterone and cerclage in PTB prevention. An indirect comparison [36] found no difference between either vaginal progesterone or cerclage in the prevention of PTB in women with a sonographic short cervix in the mid trimester, singleton gestation, and previous PTB. It was concluded that the optimal treatment should be personally considered.

Cervical pessary in pregnant women with cervical length of less than 25 mm demonstrated significant reduction in PTB before 34 weeks compared to expectant management in a randomized trial from Spain [37]. The latest Cochrane review [38] emphasized that there was a need for more research on pessaries since that was the only well-designed study on specific group of women. The ProTWIN trial failed to show reduction in poor neonatal outcomes with the use of prophylactic pessary in unselected women with multiple pregnancies, although in a subanalysis of women with less than 38 mm cervix length, extreme PTB was reduced with less frequent poor perinatal outcome [39].

The last 3 strategies (vaginal progesterone, cerclage, or cervical pessary) were compared in a study on cohorts of women with singleton pregnancies, prior PTB, and short cervix. No difference was found in neonatal morbidity and PTB rates in women with cervical length less than 25 mm. The optimal management requires direct comparisons in future studies [40].

Universal Screening of Cervical Length

The treatments suggested above raised the option of a universal screening of all pregnant women for cervical length, regardless of their obstetric history. It can potentially identify the asymptomatic women who are at higher risk for PTB due to short cervix, and to guide the management of women with prior PTB according to their current cervical status. This subject is still under debate. Berghella [41] claimed that due to effective interventions and the safe, available, and acceptable transvaginal ultrasound as a screening tool, a single measurement at the second trimester can be offered in all singleton pregnancies. Up to 5 % of the women are expected to present a cervix length of less than 20 mm and should be offered vaginal progesterone. Serial sonographic measurement is expected to identify a 25 mm or less cervix length in 40 % of the women with prior PTB, which can be offered cervical cerclage. Guidelines from the Society for maternal—fetal medicine summarized, that although a screening strategy could be viewed as reasonable, it could not yet be universally mandated [42]. This was further confirmed in the latest Cochrane review [43]. The lack of evidence to suggest universal screening might be due to missing trials on properly selected population and clear management protocols for specific groups that can help evaluate the effectiveness of such screening.

Tertiary Prevention

Tocolytic agents aim to inhibit myometrial contractions in an attempt to prevent delivery. Most of the agents were assessed by comparison to the first tocolytic agent, Ritodrine, and presented very little success in postponement of labor [44]. Their main role is to reduce neonatal risk associated with prematurity by allowing enough time for transfer the mother to tertiary center and administration of corticosteroids [45]. The agents in current practice are calcium channel blockers (CCB), betamimetics, magnesium sulfate, cyclooxygenase inhibitors, oxytocin receptor antagonists, and nitric oxide donors [46]. A systematic review and meta-analysis of 95 randomized controlled trials found that compared with placebo, prostaglandin inhibitors exhibited the highest probability of delayed delivery by 48 h, with no class superior to placebo in reducing neonatal respiratory distress syndrome. Prostaglandin inhibitors and CCB had the highest probability of delaying delivery and improving neonatal and maternal composite outcomes [47]. A recent expert opinion review claimed that based on efficacy and favorable side-effect profile, atosiban (oxytocin receptor antagonist) or nifedipine (CCB) should be used for initial tocolysis [48, 49]. In the case of PTB related to preterm premature rupture of membranes (PPROM), the use of tocolytic agents was not supported [50] due to increase in maternal chorioamnionitis without significant benefits to the infant.

The ORACLE trials established the routine use of antibiotics in PPROM. Daily administration of erythromycin was associated with prolongation of pregnancy and health benefits for the newborn [51] without reduction in perinatal mortality, and the little effect at the age of 7 as was demonstrated in a long-term follow up [52, 53]. Administration of a similar protocol in women with intact membranes and spontaneous PTB was not recommended and was associated with an increased risk of functional impairment at 7 years of age [54].

Minimizing Iatrogenic PTB

Multiple gestations are associated with many obstetrical complications and PTB. It is estimated that about two-thirds of the increase in twin birth rate in the last three decades is likely associated with assisted reproductive technology (ART) and other infertility treatments [55]. Efforts are made to implement a policy of elective single

embryo transfer (eSET) when suitable [56]. Contemporary data suggest that SET is associated with lower rates of multiple pregnancies, and a policy of repeated SET may minimize the risk of multiple pregnancies in ART treatments without substantially reducing the likelihood of live birth rate [57].

Another share of PTB that needs to be explored is iatrogenic late PTB. A study on 2693 late preterm deliveries [58] found that 32.3 % were iatrogenic and more than a half of them were delivered for non-evidence-based (NEB) indications such as chronic hypertension or mild cholestasis. Women with NEB deliveries were more likely to be older, carry twins, have private insurance or have a second complicating factor. The authors highlighted that NEB does not equal not indicated, and that the main problem is the lack of supported evidence and clear guidelines. Another call for review of the indications for late PTB from a Canadian retrospective cohort revealed a 25.2 % rate of singleton deliveries for NEB indications. Those deliveries were less likely if the patients were delivered by their own doctor or their doctor's practice partner [59]. A survey among ACOG fellows implied that many obstetricians underestimate long-term neurodevelopmental outcomes among infants born late preterm [60].

Finally, an analysis of the trends in 39 countries, with very high human developmental index (VHHDI) with good quality data, aimed to estimate the potential reduction in PTB if current evidence-based interventions were implemented [61]. It was found that if all VHHDI countries presented an annual reduction rate as Sweden and the Netherlands, then rates would diminish by less than 5 % on average by 2015. The study was constrained by insufficient data regarding specific interventions and few studies on the impact of simple interventions such as maternal infections control in low-income countries. The existing data analysis predicted 0.01 % rate reduction due to smoking cessation, 0.06 % to decreasing multiple embryo transfer during ART, 0.15 % due to cervical cerclage, 0.01 % with progesterone supplementation, and 0.29 % rate reduction due to reduction of non-medically indicated labor induction or cesarean delivery. The authors called for research with appropriate classification for better diagnosis and risk stratification, followed by novel prevention interventions in order to improve the low rate reduction of PTB predicted in their analysis.

Future Perspectives

As demonstrated above, the current interventions for PTB prevention are limited. Novel research in basic science aims to understand the underlying mechanisms in hope for better treatment and risk stratification.

Research in mice models suggested that Trp53 deletion was related to changes in the deciduae that predisposed it to PTB due to oxidative stress [62]. Moreover, PTB was reduced in model mice that were treated with rapamycin and progesterone which were aimed and inhibiting proteins in the signaling pathway [63]. Studies on the human genome [64, 65] found that polymorphisms of genes in the complement, coagulation, and oxytocin pathways were related to PTB in affected families. A linkage study in Finnish families also demonstrated the role of fetal genome in genetic predisposition to spontaneous PTB [66].

Summary

The current interventions display a humble success in the prevention of PTB. Basic care interventions can impact mortality and morbidity rates substantially in poorer countries. Efforts should focus on the learning and standardization of the indications for iatrogenic deliveries and research of the pathophysiology of PTB. Novel gene studies hold a future promise for revelation of the causes and effectors of PTB that will hopefully allow better care in high-risk patients.

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