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Systematic Review

Causes and Consequences of Preterm Birth: A Systematic Review

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ABSTRACT

To systematically review the potential causes and possible effects of preterm birth [<37 weeks gestational duration]. We searched PubMed, google scholar, clinicaltrials.gov and science direct for English language articles published from 2004 to march 2021. All kinds of study schemes were considered acceptable, comprising case –control, cohort studies, experimental and cross- sectional studies. Significant evidences indicate that social stress, elevated cadmium exposure, genomic variations, vitamin D deficiency, pre-conception hepatitis B infection, declined vaginal microbial community, intrauterine infection, reduction in cervical consistency index, strong exposure of creatinine corrected thallium, systemic autoimmune diseases, ozone, primary traffic air pollutants, road traffic noise, potential exposure of arsenic, HIV exposure, maternal thyroid dysfunction, maternal plasma protein level and COVID-19 exposure in pregnant females are the major risk factors for PTBs. Results of earlier investigations indicated prominent risk of insulin resistance, hypertension, neurological defects, heart failure, Chronic kidney disease, Lung function impairment, lower birth weight, thalamocortical system defects, cancer, altered cardiac phenotype and cardio metabolic diseases in survivors of preterm births. This review will help clinicians to isolate the fundamental etiology and to proactively identify, cope and improve outcomes of at-risk pregnancies.

INTRODUCTION

World Health Organization (WHO) suggested that birth before the end of gestational duration or fewer than 259 days since first day of women's last menstrual period (LMP) is preterm birth [1]. It affects approximately 12% of births [2]. Approximately 15 million babies with pre-term births (PTBs) born each year and 28% of child deaths at early age are related to prematurity [3]. At delivery and clinical presentation, PTBs are usually examined on the basis of gestational age [2]. An inverse relationship is found between risk of mortality and morbidity in infants and gestational age at delivery [4]. Various preterm risk factors have been identified by epidemiologic studies, such as smoking, reduced BMI, overweight pre-pregnancy BMI, short stature, physical and psychosocial stress and maternal age (<17 and >35 years) [1]. Results of earlier studies indicate a significant risk of stroke, cardiovascular mortality and hypertension in survivors of PTBs [5]. Moreover, the survivors of PTBs have increased risk of neurologic and developmental disabilities. Significant evidences are associated with intrauterine infection and/or inflammation to PTB [6]. From birth to mid adulthood two to three times risk factor for chronic kidney disease was observed in case of PTBs and extremely PTB (<28 weeks) respectively [7]. Prematurity can damage respiratory passage which ultimately cause obstructive lung diseases [8]. Recent studies described the incidence of germ cell tumor and AML in infancy[9] and cardio metabolic diseases in survivors of PTB [10]. To evaluate the risk of PTB in

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symptomatic females the most commonly used methods are the assessment of reduction in cervical length and fetal fibronectin [11]. Several other factors have also been associated with PTB including uteroplacental ischemia, mechanical over-distension of the uterus, infection chorioamnionitis and hemorrhage [12]. The bacterial community residing in lower genital tract of a female has crucial importance in neonatal and maternal health. Abnormalities of vaginal microbial community are frequently attributed with adverse reproductive health consequences, like PTB. Intrauterine infection is thought to be a prominent risk factor of preterm labor [13]. PTB and gestational age are complicated factors that affect both maternal and fetal genomes [14]. Cadmium, a ubiquitous lethal heavy metal, primarily gains enter into the body through smoking and food ingestion. Pregnant females have been found to accrue more cadmium as compared to non-pregnant women. Cadmium profoundly resides in placenta and adversely affects neonatal health. Several previous investigations have reported considerable associations between increased risk of preterm birth and prenatal cadmium exposure [15]. The high-risk factor for PTB in all autoimmune conditions was observed. Considering the rate of PTB population can achieve medical care and provide mechanistic understanding of obstetric problems [16]. During pregnancy higher levels of traffic noise and primary traffic non exhaust related PM2.5 are significant causes of still birth and PTB [17]. Recently it was described that HIV exposed unaffected infants experience very PTB and low birthweight more than HIV unexposed unaffected infants which ultimately contribute to severe morbidity such as respiratory, gastrointestinal, immune system and metabolic complications. These cases need advanced care and poses increased burden on health care system [18]. Another deadly effect of current pandemic of COVID-19 (SARS-CoV-2) is that it also elevates the risk of cesarean and PTB in pregnant females [19]. It is concluded from latest meta-analysis that to predict PTB no significant soluble biomarker from body fluid has yet been discovered. Moreover, may be possible biomarkers have low concentration or limited stability in blood that leave them unidentified [2]. Therefore, instant preventive measures are required to reduce the rate of PTB [4]. This review summarizes the possible effects caused by PTB and the potential reasons of the induction of PTB (Figure 1).

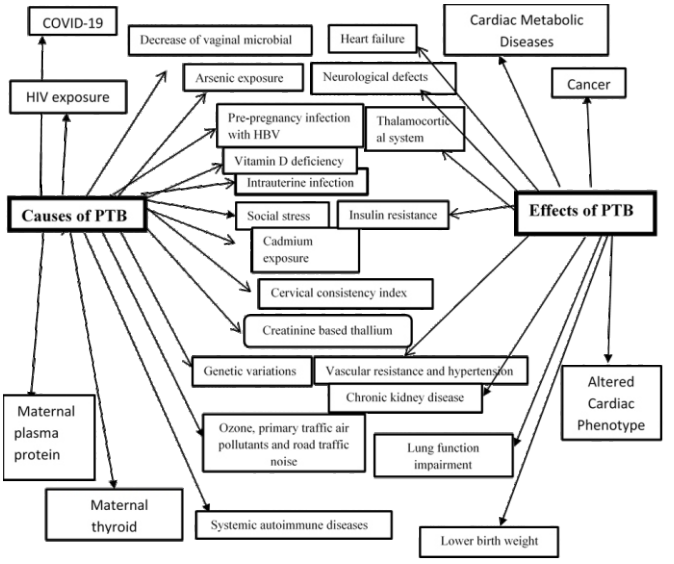

Figure 1: Flow sheet to summarize the effects and causes of PTB

METHODS

We searched PubMed, google scholar, clinicaltrials.gov and science direct for English language articles published from 2004 to March 2021. In all databases search items like: PTB OR preterm labor OR preterm delivery causes, reasons and effects on health were used. The search on electronic databases was conducted and unpublished studies were not included. All kinds of study schemes were considered acceptable, comprising case –control, cohort studies, experimental and cross- sectional studies. Type of studies in which women at high or low risk of PTBs were enrolled of any race, gestational age, parity, age or socioeconomic background were considered suitable to be included in this review. Moreover, information regarding the method of assessment of biological samples was also included. A data extraction form to confirm constancy and accuracy was created. A subset of 16 appropriate studies to pool causes of PTB and 10 eligible studies considering effects of PTB was collected. The following information was collected from each of the research article included in this review: design and objective, exclusion and inclusion criteria, features at baseline including race definition of the outcome phenotype, age of subject, number of participants in cases and controls studies, detail of sample collection and gestational age. All collected information was assembled in electronic datasheet.

RESULTS

The procedure of assortment, identification and addition of studies is illustrated in figure 1. Initially 1556 unduplicated references were searched out of which 455 were excluded due to irrelevant title and abstract. For full text reading, a total of 112 studies were chosen after careful selection. 91 articles were excluded due to various reasons. After

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careful screening 26 studies finally satisfied our criteria and reviewed thoroughly (Figure 2).

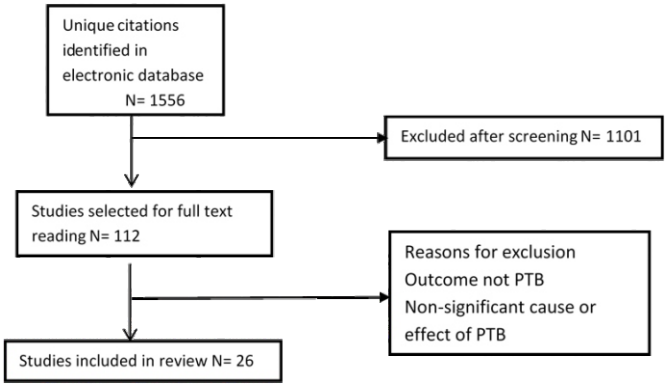

Figure 2: Identification and assortment flowchart of studies on effects and causes of preterm births

Causes of PTB

The association of Cadmium exposure and decreased gestational age was observed. Elevation in urinary Cadmium (µg/g creatinine) was associated with increased chance of PTB [13]. One study discovered the significant association of four loci EBF1, EEFSEC, AGTR2 and WNT4 with gestational period. It was analyzed that attachment of estrogen receptors was varied by WNT4. Deviation in EBF1, EEFSEC and AGTR2 depicted the strong link with preterm birth. Earlier studies have confirmed the function of these genes in maternal nutrition and uterine development [11]. Scientists described that high level of social stress predicts PTB. In logistic regression, controlling for anxiety, age and depression, the experience of difficulty in a closed relationship and a severe life incidence were the major factors predicting PTB [16]. In women, insufficiency of vitamin D greatly increase the risk of preterm birth. An inverse relation was observed in ethnic subgroups. Chances of PTB were enhanced by 4.05 times with plasma 25(OH)D concentrations of 0.03 µmol/L in mothers [17]. An independent association of hepatitis B virus in mothers with risk of developing PTB was noticed. In HBsAg positive and HBeAg negative women twenty six percent increased risk of PTB was observed. Twenty percent increased risk was in HBsAg and HBeAg positive women. Eighteen percent increased risk of PTB was in HBsAg positive and HBeAg negative women, whereas, thirty four percent higher risk of early PTB was in women positive for both HBsAg and HBeAg [20]. The vaginal microbiome richness and diversity in African American participants was examined. They observed the change during first and second trimester and concluded that decreased vaginal microbiome community leads to PTB [21]. It was experimentally confirmed that women with PTB experience high richness and variety of mollicutes occurrence. Maternal and neonatal health is highly influenced by bacterial community in lower genital tract. Seven community state types were detected by pyrosequencing [12]. Significant reduction in cervical consistency index (CCI) in women who labored at <37 weeks was noticed. They concluded that as compare to sonographic CL, CCI is better predictor of PTB [22]. Increased in gestational weight, multivitamin and iron supplementation, changes the Thallium concentration in maternal urine. Approximately three times higher creatinine corrected Tl concentration was related to 0.99-day reduction in gestational duration [23]. The trimester specific link between maternal arsenic contact and birth outcomes was checked. They determined a reduction in birth weight by 24.27g, decrease in birth length by 1.3 mm, and 25% increased risk of small gestational age by increasing the arsenic exposure in third trimester. They further reported that risk of small gestational age was factor particularly high for female infants [24]. During pregnancy exposure of high O3 level, and primary traffic air pollutants (nitrogen dioxides, nitrogen oxides, PM2.5 from traffic exhaust and traffic non-exhaust) and road traffic noise increase risk of PTB and stillbirth. High O3 level increase risk of PTB through oxidative stress and systemic inflammation [15]. The risk for PTB for all autoimmune rheumatic diseases was examined. Higher risk of PTB at early gestational age (<32 weeks) in women with systemic lupus erythematosus (SLE), systemic sclerosis (SSc), dermatomyositis and polymyositis (DM/PM) was noticed. However, at later gestational ages high risk of juvenile idiopathic arthritis (JIA) and rheumatoid arthritis (RA) was prominent [14]. Extreme PTB (<32 weeks) and low birthweight (<1500g) occurred more commonly among hospitalized neonates who were HIV exposed unaffected [18]. The link between adverse birth complications and maternal thyroid dysfunctionality was assessed. Pregnant females with free triiodothyronine (> 95th percentile) and low thyroid stimulating hormone (< 95th percentile) experienced the 4.02-fold higher risk of PTB. They also analyzed that high TSH and low FT3 faced 4.22 times greater risk of small gestational age [25]. It was analyzed that third trimester maternal plasma total protein increment was linked with 0.13 weeks gestational duration rise. Moreover, they also analyzed that the effect was stronger in pregnant female conceiving female fetus than those conceiving male fetus [26]. One study described that hospitalized pregnant females experienced cesarean, operational vaginal birth as well as PTB with symptomatic COVID-19(SAR-CoV-2)infection [27](Table 1).

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Study Country and year	Total participants	Gestational age	Sample	Cause of PTB	Method of analysis	Results
Yang et al., China, 2016 [13]	5364 pregnant females	NA	Urine	Cadmium exposure	Inductively coupled plasma mass spectrometry	OR=1.78; 95% CI: 1.45, 2.19 for all infants. 1.97; 95% CI: 1.46, 2.65 for boys. 1.67; 95% CI: 1.24, 2.25 for girls.
Zhang et al., England, 2017 [11]	PTB (n=3331) Term (n=37803) after Term(n=2434)	(37 to 42) Term, (<37 weeks) PTB, after term (>42 weeks)	Extracted DNA	Four loci (EBF1, EEFSEC, AGTR2, and WNT4)	Gene sequencing	Variants at the EBF1, EEFSEC, and AGTR2 loci cause PTB
Owen et al., UK, 2017 [16]	PTB (n=42) Term (n=73)	24-28 weeks	Pregnant women were interviewed	severe life incidence	ELISA	OR ¼15.6; 95%CI: 3.0 to 80.8
Tabatabaei et al., Canada, 2017 [17]	PTB (n=120) Term (n=360)	8-14 weeks	Plasma 25-hydroxy-vitamin D	Vitamin D deficiency	Liquid chromatography mass spectrometry	95% CI: 1.16, 14.12; P = 0.028
Jue Liu et al., China, 2017 [10]	489965 females	NA	Maternal serum	Pre-pregnancy infection with HBV	ELISA kits	HBsAg and HBeAg are associated with increased risk of PTB
Stout et al., USA, 2017 [21]	PTB (n=24) Term (n=53)	NA	Vaginal swabs	Decrease of vaginal microbial community	Sequencing of V1V3 region of the 16S rRNA gene	Increased vaginal microbiome instability was observed in PTB
Freitas et al., Canada, 2018 [12]	PTB (n= 46) Term (n=170)	11-16 weeks	Maternal vaginal swabs and maternal and infant blood	Intrauterine infection	PCR amplification and pyrosequencing	Women with PTB had higher richness of Lactobacillus crispatus dominated, Lactobacillus gasseri dominated, Lactobacillus iners dominated, Gardnerella vaginalis subgroup B or mix of species, G. vaginalis subgroup A dominated,G. vaginalis subgroup C dominated and Lactobacillus jensenii dominated.
Núria Baños et al., Spain, 2018 [22]	82 high PTB risk women	19-24 weeks	Sagittal view of cervix	Cervical Consistency Index	Image acquisition	For <37 weeks, AUC was 0.73 and 0.51. For < 34 weeks, AUC was 0.68 and 0.49
Jiang et al., China, 2018 [23]	7173 mother infant pair	NA	Urine	Creatinine-corrected Thallium	Inductively coupled plasma mass spectrometry	Tl concentrations higher than 0.80 mg/g cause PTB
Liu et a Liu et al., a al China, 2018 [24]	1390 pregnant females	Third trimester	Urine	Arsenic	Inductively coupled plasma mass spectrometry	increased risk by 25% (95% CI: 1.03-1.49)
Smith et al., 2020 [15]	total births =578238 PTB=33712	<37 weeks	birth certificate records	ozone, primary traffic air pollutants and road traffic noise	NA	For O3 exposure was (OR 1.1595%CI: 1.11, 1.18) For PM2.5 caused 3% rise in PTB.
Kolstad et al., USA, 2020 [14]	2481516 deliveries were assessed	20–36 weeks	birth certificate records	systemic autoimmune diseases	NA	SLE (RR 3.27, 95% CI 3.01–3.56), RA (RR 2.04, 95% CI 1.79–2.33), SSc (RR 3.74, 95% CI 2.51–5.58), JIA (RR 2.23, 95% CI 1.54–3.23), DM/PM (RR 5.26, 95% CI 3.12–8.89).
Anderson et al., South Africa, 2021[18]	466 HUU infants	24-37 weeks	Interviews; clinical assessments; electronic data and laboratory test results.	HIV exposed pregnant females	NA	P value 0.092 HUU 53(11%) HEU 70(15%)
	463 HEU infants	<37 weeks				P value 0.045 HUU 8 (2%) HEU 18(4%)
Yuan et al., China, 2021 [25]	11564 pregnant females	28-41 weeks	Maternal blood samples	Hypothyroidism	Electrochemilu-minescence immunoassays	OR: 1.56, 95% CI: 1.10–2.22
				Hyperthyroidism		OR: 2.41, 95% CI: 1.83–3.17
Xiong et al., China 2021 [26]	6860 pregnant females	3382 2nd trimesters 3478 3rd trimester females	Maternal blood samples	Maternal plasma protein	data from Tongji Maternal and Child Health Cohort (TMCHC) study	third-trimester MTP level, not the second-trimester MTP level, was inversely associated with the risk of PTB
Vousden et al., UK 2021 [19]	722 pregnant Females with COVID-19 symptoms	<37 weeks	Hospitals data from 1st March to 31 August 2020	COVID-19	NA	Iatrogenic preterm birth OR 11.43, (95% CI 5.07-25.75) Spontaneous preterm birth OR0.57(95% CI 0.32-1.01)

Table 1: Studies that observed the main reasons for induction of PTB

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Effects of PTB

It was proved experimentally that children with PTB may face risk of type 2 diabetes mellitus as they have decreased insulin sensitivity as compare to controls. Premature children had an elevated acute insulin release [27]. Another study experimentally concluded that adult population which survived preterm birth may have future cardiovascular risk. It was found that high brachial and aortic blood pressure, thin and weak abdominal aorta and reduced peripheral skin blood flow is faced by preterm girls. High vascular resistance and increased blood pressure was experienced by preterm girls [28]. On Wechsler Scales of Intelligence, It was found that a full scale IQ of verbal IQ and performance IQ of children with PTB. After all psychometric tests they noticed the decrease of 6 to 14 points in preterm children than term controls. On the Clinical Evaluation of Language Fundamentals, 22% to 24% of preterm children scored abnormal (<70) than 2% to 4% of controls. More school services are required for preterm children in reading, writing and mathematics than controls [29]. The results of one study proved the disruption of cerebral development due to PTB. The cerebral grey and white matter defects and cognitive injuries are associated with PTB. Brain damage by PTB is linked with changed thalamic development. Decreased gestational age was linked with reduced volume in the thalamus, hippocampus, orbitofrontal lobe, posterior cingulate cortex, and centrum semiovale [30]. The strong association of heart failure (HF) with PTB (< 32 weeks) was described in one study. They found the inverse relation between gestational age and risk of HF. Adjusted frequency of relative risk of HF was 17.0 after extremely preterm birth and 3.58 after very preterm birth [31]. It was found that the association of 20-30% increased risk of CKD from birth to mid adulthood was present with PTB and extremely PTB (<28 weeks) respectively. Strongest association was found at ages 0-9 years and again at ages 10-19 and 20-43 years between PTB and CKD [7]. Prematurity was associated with lower Forced Vital Capacity /Forced Expiratory Flow (FEV1/FVC) and Forced Expiratory Volume 25–75% (FEF), indicating preterm birth may impair airway development, which suggests increasing vulnerability to obstructive lung diseases [8]. It was reported in one study that 141 different types of cancers in preterm neonates. The overall risk factor was increased for extremely preterm children. They also identified that the risk of germ cell tumor, retinoblastoma and acute myeloid leukemia was increased for preterm as compare to term. They noticed that germ cell tumor was diagnosed at younger age among preterm [32]. It was examined that the link of birth size and gestational age with patent ductus arteriosus with cardiac complications and bronchopulmonary dysplasia in neonates. Significant smaller width of right ventricles, smaller right atria and increased pulmonary vascular resistance than term neonates [33]. One study discussed that adult born preterm (average gestational age 29 weeks) higher oxygen consumption with significant rates of non-ATP-linked mitochondrial respiration. They also noticed the lower lung function in preterm adults as well [34] (Table 2).

Study Country and year	Participants with PTB	Effect of PTB	Gestational age	Results
Paul et al., New Zealand, 2004 [27]	22 children with term and 50 with PTB	Insulin resistance	32 weeks	insulin sensitivity decreased by; 14.2¬10-4 / minute / milliunit / lit (95%CI: 11.5 to 16.2);
Anna -Karin et al., Sweden, 2005 [28]	34 with and 32 with term birth	vascular resistance and hypertension	< 30 weeks	Increased blood pressure and resistance in the vascular tree and have future cardiovascular risk.
Mai Luu et al., Portland, 2009 [29]	375 Children with PTB	Neurological defects	23–34 weeks	PTB children have 6-14 IQ points less in all psychometric tests
Ball et al., UK, 2012 [30]	71 Children with PTB	Thalamocortical system defects	23- 35 weeks	Reduced thalamic volume, cortical volume, frontal and temporal lobe volume, hippocampus, and reduced parietal and occipital lobes. reduced fractional anisotropy in the corticospinal tracts and corpus callosum
Carr et al., Sweden, 2017 [31]	Out of 156879, 501 were with PTB	Heart failure	<28 weeks	17.0 (95%CI: 7.96 to 36.3)
			8 to 31 weeks	3.58 (95% CI: 1.57 to 8.14)
			32 to 36 weeks	1.36 (95% CI: 0.87 to 2.13)
Crump et al., USA, 2019 [7]	4186615 PTB	Chronic kidney disease	<37 weeks	1.94 (95% CI: 1.74 to 2.16)
			22-27 weeks	3.01 (95% CI: 1.67 to 5.45)
			28-33 weeks	2.22 (95% CI: 1.79 to 2.75)
			34-36 weeks	1.84 (95% CI: 1.62 to 2.08)
			37-38 weeks	1.30 (95% CI: 1.20 to 1.40)
			39-41 weeks	1.00 (95% CI)
			≥42 weeks)	0.98 (95% CI: 0.88 to 1.09)
He et al., 2020 [8]	3030 PTB	Lung function impairment	≤ 34 weeks	Lower FEV1/FVC and FEF25–75%. Indicating airway impairment
		Lower birth weight		Lower birth weight in boys was observed
Seppälä et al., Finland, 2020 [32]	12,222 PTB Diseased: n = 2,029 Controls n = 10,103	Cancer	early (<32)	n = 113 (OR 1.28, 95% CI: 1.06-1.57)
			late preterm (32-36)	n = 113 (OR 1.28, 95% CI: 1.06-1.57)

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			term (≥37 weeks)	n = 1,888 The risk of AML, retinoblastoma and germ cell tumors was increased among the preterm compared to term.
Mohlkert et al., Sweden, 2021[33]	176 PTB	altered cardiac phenotype	< 27 weeks	PTBs have smaller right atria, right ventricles with smaller widths, higher relative wall thickness and higher estimated pulmonary vascular resistance (PVR)
Kumari et al., UK, 2021[34]		Cardio metabolic disease	29 weeks	higher basal and non-ATP-linked mitochondrial respiration

Table 2: Studies that observed the effects of preterm birth which manifest in early childhood and adulthood

DISCUSSION

To our knowledge, this is the first comprehensive review that summarize the potential causes and effects of PTB. Preterm birth is the commonest reason of death and disease in newborns, particularly in low-income countries [35]. Collectively greater than malaria, AIDS and tuberculosis, the largest contributor to neonatal mortality is premature birth [36]. Severe previous tragic events and significant social problems are experienced by women laboring prematurely. One of the dominating causes of PTB in women includes unstable microbiome community as indicated by the analysis of serial vaginal samples of pregnant women [21]. The particular channel of events leading to PTB are linked with the pro-inflammatory immune response against bacterial infection. The advanced culture independent gene amplification technology has estimated the proportion of infection related PTB to be higher than 50% [36]. The vaginal microbiota dominated by lactobacilli prevents the spread of bacterial pathogens. The vaginal pH ≥ 4.7 is the strong indicator of deficiency of lactobacilli. Therefore, to prevent at risk pregnancy, females should screen their vaginal pH [37, 38]. Most studies have reported that intrauterine infection ultimately leads to dermatitis, early onset sepsis, bronchopulmonary dysplasia, psychiatric disorders, long lasting neurodevelopmental disorders such as cerebral palsy, mental retardation, periventricular leukomalacia, retinopathy of Prematurity, respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage and fetal growth restriction [39-41]. Presence of hepatitis B viral DNA in placenta and trophoblast cells can predict the future link between maternal HBV infection and PTB, which ultimately leads to inflammatory reactions in placenta, a well-known contributor to PTB [20]. The presence of clinically important proteins, HBV surface antigen (HBsAg), HBV envelop antigen (HBsAg) and HBV core antigen (HBcAg) indicate infection. Out of this HBV surface antigen (HBsAg) is responsible for PTB [42]. Previous investigations have indicated that thallium exposure causes inflammation and oxidative stress. Which ultimately changes the mitochondrial functionality, increases the production of reactive oxygen species, results in peroxidation of liposomal membranes and disintegrates the membrane potential of mitochondria [23]. Thallium exposure during pregnancy decreases the gestational duration which ultimately leads to PTB [43, 44]. Vitamin D insufficiency is associated with a greater risk of preterm birth [17]. The action of activated form of vitamin D, 1, 25-dihydroxyvitamin D, is affected by decreased concentration of circulating 25(OH) D. which ultimately increases inflammatory reactions, immune system dysregulation and activate genes playing role in placental functions. These are some of the physiologic ways for the pathogenesis of preterm birth [45, 46]. Genomic variations at many loci are linked with gestational age and ultimately cause PTB through their formerly recognized roles in maternal nutrition, vascular control and uterine development [11]. In 3rd trimester maternal arsenic level have significant impact on birth outcomes [24]. Pregnancy is a period of vibrant growth. Sensitive windows of prenatal chemical exposure are established to ensure proper fetal growth. Arsenic can easily cross the placenta. The prenatal exposure to arsenic can impair fetal growth, cause spontaneous abortion and neonatal mortality [47]. Very preterm birth and low birth weight are more common in HIV exposed unaffected neonates. Low gestational age cause immature development of gastrointestinal, metabolic and respiratory and immune system. HIV exposure and additional complications poses amplified burden on health care system [18]. An autoimmune pregnant female experience greater risk of PTB but there is an inadequate understanding of the reasons behind these obstetric complications linked with these diseases. Many autoimmune diseases are linked with immune system dysfunction and vascular complications with ultimately cause obstetrics complications [14]. High ozone level increase risk of PTB through oxidative stress and systemic inflammation. The road traffic noise increase risk of PTB and stillbirth by causing hypertension [15]. Thyroid hormones are very essential for fetal growth as the fetal supply of thyroid hormone do not get started until 20 weeks of pregnancy so fetus depends entirely on maternal thyroid hormone supply. The Past studies indicated that maternal thyroid dysfunctionality in first and second trimester of pregnancy can cause dangerous outcomes like low birth weight and preterm birth [25]. Maternal protein status is

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crucial for newborn's health past studies depicted that mother with proper intake of protein diet faces very less risk for preterm birth. Protein play key role in protective mechanisms against infection and inflammatory responses are controlled by proteins. Ultimately protein deficiency causes infection and inflammatory responses [26]. In pregnant females with no obvious signs COVID-19 (SARS-CoV-2) virus may cause preterm labor. Its biological evidence is that female reproductive tract express angiotensin converting enzyme type 2 (ACE-2) receptor. Its expression is highly increased during mid to end of gestational period and provide vasodilatory effects stimulated by its products named angiotensin 1 to 7. Basically ACE-2 is the enzyme which COVID-19 uses to enter into cell and once it reaches the reproductive tract, it causes the decrease in vasodilation by down regulating the ACE-2 receptors which highly stimulate the vasoconstriction by angiotensin II and leads to stimulation of uterine contractions and ultimately causes preterm birth [19]. Newborns surviving preterm birth have significant chance of subsequently developing major health problem. One of the lethal outcomes of PTBs includes 3 to 17 times amplified risk myocardial infraction. Cardiomyocytes which play an important role in cardiac growth develop immaturely after PTB which ultimately lead to extra uterine conditions that affect normal cardiac functioning. Echocardiographic study showed delayed maturation of myocardium and left ventricular diastolic dysfunction in preterm infants [33]. Altered brain development is evidenced in preterm infants. Decreased cortical and gray matter volumes, evidenced by tissue segmentation causes neurodevelopmental and neurocognitive disabilities forecast by decreased cortical surface area. At 12 year of age delay in cognitive abilities are evidenced in preterm children as a result of which they continued to require numerous educational supports [29]. Gestational age of about 32 weeks or less causes the decrease in insulin sensitivity in children. Similar reduction in 24- or 32-weeks' gestation indicate the presence of specific time period during which insulin sensitivity is eternally changed. The reduction in diameter of abdominal aorta in spite of high pressure indicates the structural basis of difference which is due to ceased aortic development after PTB [27]. Most active fetal nephrogenesis take place during third trimester and PTB interrupts the kidney maturation which ultimately leads to advanced kidney disease and hypertension [7]. Extreme preterm neonates may face airways obstruction which cause them to be highly prone to asthma. First 1000 days of pregnancy are the crucial period for respiratory health. PTB may damage airway development which indirectly cause cardiovascular related risk factors. Previous studies have reported that birth weight is affected by prematurity and it is inversely associated by restrictive lung functions [8]. Preterm infants face high level of oxidative stress which along with causing retinopathy and dysplasia, is highly carcinogenic. One other reason for the association of preterm birth with cancer is that premature infants are excessively exposed to X-rays for diagnostic purposes during early life which is the potential risk factor for cancer [32]. Constrained fetal growth in uterus effects numerous organ systems which could raise the risk factor for hypertension and coronary heart diseases later in life [48, 49]. The developmental programming of blood pressure involved many central, vascular and renal regulation [50]. Towards the end of gestational period, the placental estrogen and progesterone elevates significantly [51]. The untimely delivery causes the abrupt ending of placental steroids. Previous studies have reported that abnormal retinal vascularization is due to irregular supply of estrogen [52]. During angiogenesis, a preterm cut in estrogen supply can hinder the expression of estrogen receptors, recent studies have paroposed its link with atherosclerosis [53].

CONCLUSION

By summarizing causes and effects of PTB, this review will help clinicians to overcome the major causes of birth mortalities and to improve the outcomes of at-risk pregnancies.

Conflicts of Interest

The authors declare no conflict of interest.

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REFERENCES

[1] Quinn JA, Munoz FM, Gonik B, Frau L, Cutland C, Mallett-Moore T, et al. Preterm birth: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016 Dec; 34(49): 6047-56. doi: 10.1016/j.vaccine.2016.03.045.

[2] Esplin MS. Overview of spontaneous preterm birth: a complex and multifactorial phenotype. Clinical Obstetrics and Gynecology. 2014 Sep; 57(3): 518-30. doi: 10.1097/GRF.0000000000000037.

[3] D'Silva AM, Hyett JA, Coorssen JR. Proteomic analysis of first trimester maternal serum to identify candidate biomarkers potentially predictive of spontaneous preterm birth. Journal of Proteomics. 2018 Apr; 178: 31-42. doi: 10.1016/j.jprot.2018.02.002.

[4] Frey HA and Klebanoff MA. The epidemiology, etiology, and costs of preterm birth. In: Seminars in Fetal and Neonatal Medicine 2016 Apr; 21(2): 68-73.

DOI: https://doi.org/10.54393/pjhs.v3i07.193

WB Saunders. doi: 10.1016/j.siny.2015.12.011.
[5] Carr H, Cnattingius S, Granath F, Ludvigsson JF, Edstedt Bonamy AK. Preterm birth and risk of heart failure up to early adulthood. Journal of the American College of Cardiology. 2017 May; 69(21): 2634-42. doi: 10.1016/j.jacc.2017.03.572.
[6] Lynch AM, Wagner BD, Deterding RR, Giclas PC, Gibbs RS, Janoff EN, et al. The relationship of circulating proteins in early pregnancy with preterm birth. American Journal of Obstetrics and Gynecology. 2016 Apr; 214(4): 517-e1. doi: 10.1016/j.ajog.2015.11.001.
[7] Crump C, Sundquist J, Winkleby MA, Sundquist K. Preterm birth and risk of chronic kidney disease from childhood into mid-adulthood: national cohort study. BMJ. 2019 May; 365: 1-10. doi: 10.1136/bmj.l1346.
[8] He B, Kwok MK, Au Yeung SL, Lin SL, Leung JY, Hui LL, et al. Birth weight and prematurity with lung function at~ 17.5 years: Children of 1997, birth cohort. Scientific Reports. 2020 Jan; 10(1): 1-2. doi: 10.1038/s41598-019-56086-7.
[9] Chiossi G, Saade GR, Sibai B, Berghella V. Using cervical length measurement for lower spontaneous preterm birth rates among women with threatened preterm labor. Obstetrics & Gynecology. 2018 Jul; 132(1): 102-6. doi: 10.1097/AOG.0000000000002695.
[10] Romero R, Espinoza J, Kusanovic JP, Gotsch F, Hassan S, Erez O, et al. The preterm parturition syndrome. BJOG: An International Journal of Obstetrics & Gynecology. 2006 Dec; 113: 17-42. doi: 10.1111/j.1471-0528.2006.01120.x.
[11] Zhang G, Feenstra B, Bacelis J, Liu X, Muglia LM, Juodakis J, et al. Genetic associations with gestational duration and spontaneous preterm birth. New England Journal of Medicine. 2017 Sep; 377(12): 1156-67. doi :10.1056/NEJMoa1612665.
[12] Freitas AC, Bocking A, Hill JE, Money DM. Increased richness and diversity of the vaginal microbiota and spontaneous preterm birth. Microbiome. 2018 Dec; 6(1): 1-5. doi: 10.1186/s40168-018-0502-8.
[13] Yang J, Huo W, Zhang B, Zheng T, Li Y, Pan X, et al. Maternal urinary cadmium concentrations in relation to preterm birth in the Healthy Baby Cohort Study in China. Environment International. 2016 Sep; 94: 300-6. doi: 10.1016/j.envint.2016.06.003.
[14] Kolstad KD, Mayo JA, Chung L, Chaichian Y, Kelly VM, Druzin M, et al. Preterm birth phenotypes in women with autoimmune rheumatic diseases: a population-based cohort study. BJOG: An International Journal of Obstetrics & Gynecology. 2020 Jan; 127(1): 70-8. doi: 10.1111/1471-0528.15970.
[15] Smith RB, Beevers SD, Gulliver J, Dajnak D, Fecht D, Blangiardo M, et al. Impacts of air pollution and noise on risk of preterm birth and stillbirth in London. Environment International. 2020 Jan; 134: 105290. doi: 10.1016/j.envint.2019.105290.
[16] Owen DJ, Wood L, Tomenson B, Creed F, Neilson JP. Social stress predicts preterm birth in twin pregnancies. Journal of Psychosomatic Obstetrics & Gynecology. 2017 Jan; 38(1): 63-72. doi: 10.1080/0167482X.2016.1235146.
[17] Tabatabaei N, Auger N, Herba CM, Wei S, Allard C, Fink GD, et al. Maternal vitamin D insufficiency early in pregnancy is associated with increased risk of preterm birth in ethnic minority women in Canada. The Journal of Nutrition. 2017 Jun; 147(6): 1145-51. doi: 10.3945/jn.116.241216.
[18] Anderson K, Kalk E, Madlala HP, Nyemba DC, Jacob N, Slogrove A, et al. Preterm birth and severe morbidity in hospitalized neonates who are HIV exposed and uninfected compared with HIV unexposed. AIDS. 2021 May; 35(6): 921-31. doi: 10.1097/QAD.0000000000002856.
[19] Vousden N, Bunch K, Morris E, Simpson N, Gale C, O'Brien P, et al. The incidence, characteristics and outcomes of pregnant women hospitalized with symptomatic and asymptomatic SARS-CoV-2 infection in the UK from March to September 2020: a national cohort study using the UK Obstetric Surveillance System (UKOSS). PloS one. 2021 May; 16(5): e0251123. doi: 10.1371/journal.pone.0251123.
[20] Liu J, Zhang S, Liu M, Wang Q, Shen H, Zhang Y. Maternal pre-pregnancy infection with hepatitis B virus and the risk of preterm birth: a population-based cohort study. The Lancet Global Health. 2017 Jun; 5(6): e624-32. doi: 10.1016/S2214-109X(17)30142-0.
[21] Stout MJ, Zhou Y, Wylie KM, Tarr PI, Macones GA, Tuuli MG. Early pregnancy vaginal microbiome trends and preterm birth. American Journal of Obstetrics and Gynecology. 2017 Sep; 217(3): 356-e1. doi: 10.1016/j.ajog.2017.05.030.
[22] Baños N, Julià C, Lorente N, Ferrero S, Cobo T, Gratacos E, et al. Mid-trimester cervical consistency index and cervical length to predict spontaneous preterm birth in a high-risk population. American Journal of Perinatology Reports. 2018 Jan; 8(01): e43-50. doi: 1055/s-0038-1636993.
[23] Jiang Y, Xia W, Zhang B, Pan X, Liu W, Jin S, et al. Predictors of thallium exposure and its relationship with preterm birth. Environmental Pollution. 2018 Feb; 233: 971-6. doi: 10.1016/j.envpol.2017.09.080.
[24] Liu H, Lu S, Zhang B, Xia W, Liu W, Peng Y, et al. Maternal arsenic exposure and birth outcomes: A birth cohort study in Wuhan, China. Environmental

DOI: https://doi.org/10.54393/pjhs.v3i07.193

Pollution. 2018 May; 236: 817-23. doi: 10.1016/j.envpol.2018.02.012.
[25] Yuan X, Wang J, Gao Y, Wang H, Yu B. Impact of maternal thyroid hormone in late pregnancy on adverse birth outcomes: A retrospective cohort study in China. Endocrine Journal. 2021 Mar; 68(3): 317-28. doi: 10.1507/endocrj.EJ20-0377.
[26] Xiong T, Wu Y, Huang L, Chen X, Zhang Y, Zhong C, et al. Association between the maternal protein nutrition status during pregnancy and the risk of preterm birth. Maternal & Child Nutrition. 2021 Jan; 17(1): e13043. doi: 10.1111/mcn.13043.
[27] Hofman PL, Regan F, Jackson WE, Jefferies C, Knight DB, Robinson EM, et al. Premature birth and later insulin resistance. New England Journal of Medicine. 2004 Nov; 351(21): 2179-86. doi: 10.1056/NEJ Moa0 42275.
[28] Bonamy AK, Bendito AN, Martin H, Andolf E, Sedin G, Norman M. Preterm birth contributes to increased vascular resistance and higher blood pressure in adolescent girls. Pediatric Research. 2005 Nov; 58(5): 845-9. doi :10.1203/01.PDR.0000181373.29290.80.
[29] Luu TM, Ment LR, Schneider KC, Katz KH, Allan WC, Vohr BR. Lasting effects of preterm birth and neonatal brain hemorrhage at 12 years of age. Pediatrics. 2009 Mar; 123(3): 1037-44. doi: 10.1542/peds.2008-1162.
[30] Ball G, Boardman JP, Rueckert D, Aljabar P, Arichi T, Merchant N, et al. The effect of preterm birth on thalamic and cortical development. Cerebral Cortex. 2012 May; 22(5): 1016-24. doi: 10.1093/cercor/bhr176.
[31] Carr H, Cnattingius S, Granath F, Ludvigsson JF, Edstedt Bonamy AK. Preterm birth and risk of heart failure up to early adulthood. Journal of the American College of Cardiology. 2017 May; 69(21): 2634-42. doi: 10.1016/j.jacc.2017.03.572.
[32] Seppälä LK, Vettenranta K, Leinonen MK, Tommiska V, Madanat-Harjuoja LM. Preterm birth, neonatal therapies and the risk of childhood cancer. International Journal of Cancer. 2021 May; 148(9): 2139-47. doi: 10.1002/ijc.33376.
[33] Mohlkert LA, Hallberg J, Broberg O, Sjöberg G, Rydberg A, Liuba P, et al. Right Heart Structure, Geometry and Function Assessed by Echocardiography in 6-Year-Old Children Born Extremely Preterm-A Population-Based Cohort Study. Journal of Clinical Medicine. 2020 Dec; 10(1): 122. doi: 10.3390/jcm10010122.
[34] Kumari S, Barton GP, Goss KN. Increased mitochondrial oxygen consumption in adult survivors of preterm birth. Pediatric Research. 2021 Dec; 90(6): 1147-52. doi: 10.1038/s41390-021-01387-9.
[35] Rahman ML, Kile ML, Rodrigues EG, Valeri L, Raj A, Mazumdar M, et al. Prenatal arsenic exposure, child marriage, and pregnancy weight gain: Associations with preterm birth in Bangladesh. Environment International. 2018 Mar; 112: 23-32. doi: 10.1016/j.envint.2017.12.004.
[36] Witkin SS. The vaginal microbiome, vaginal anti-microbial defense mechanisms and the clinical challenge of reducing infection-related preterm birth. BJOG: An International Journal of Obstetrics & Gynecology. 2015 Jan; 122(2): 213-8. doi: 10.1111/1471-0528.13115.
[37] Saling E, Schreiber M, Al-Taie T. A simple, efficient and inexpensive program for preventing prematurity. Journal of Perinatal Medicine. 2005 Jun; 29(3): 199-211. doi: 10.1515/JPM.2001.029.
[38] Krauss-Silva L, Almada-Horta A, Alves MB, Camacho KG, Moreira ME, Braga A. Basic vaginal pH, bacterial vaginosis and aerobic vaginitis: prevalence in early pregnancy and risk of spontaneous preterm delivery, a prospective study in a low socioeconomic and multiethnic South American population. BMC Pregnancy and Childbirth. 2014 Dec; 14(1): 1-10. doi :10.1186/1471-2393-14-107.
[39] Mi Lee S, Romero R, Lee KA, Jin Yang H, Joon Oh K, Park CW, et al. The frequency and risk factors of funisitis and histologic chorioamnionitis in pregnant women at term who delivered after the spontaneous onset of labor. The Journal of Maternal-Fetal & Neonatal Medicine. 2011 Jan; 24(1): 37-42. doi: 10.3109/14767058.2010.482622.
[40] Scholaske L, Buss C, Wadhwa PD, Entringer S. Acculturation and interleukin (IL)-6 concentrations across pregnancy among Mexican American women. Brain, Behavior, and Immunity. 2018 Oct; 73: 731-5. doi: 10.1016/j.bbi.2018.08.005.
[41] Dammann O, Brinkhaus MJ, Bartels DB, Dördelmann M, Dressler F, Kerk J, et al. Immaturity, perinatal inflammation, and retinopathy of prematurity: a multi-hit hypothesis. Early Human Development. 2009 May; 85(5): 325-9. doi: 10.1016/j.earlhumdev.2008.12.010.
[42] Elefsiniotis I, Tsoumakas K, Vezali E, Glynou I, Drakoulis N, Saroglou G. Spontaneous preterm birth in women with chronic hepatitis B virus infection. International Journal of Gynecology & Obstetrics. 2010 Sep; 110(3): 241-4. doi: 10.1016/j.ijgo.2010.04.020.
[43] Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. New England Journal of

DOI: https://doi.org/10.54393/pjhs.v3i07.193

Medicine. 2008 Jul 3; 359(1): 61-73. doi: 10.1056/NEJMra0708473.

[44] Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. Bulletin of the World Health Organization. 2010 Jan; 88: 31-8. doi: 10.2471/BLT.08.062554.

[45] Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science. 2006 Mar; 311(5768): 1770-3. doi: 10.1126/science.1123933.

[46] Evans KN, Nguyen L, Chan J, Innes BA, Bulmer JN, Kilby MD, et al. Effects of 25-hydroxyvitamin D3 and 1, 25-dihydroxyvitamin D3 on cytokine production by human decidual cells. Biology of reproduction. 2006 Dec; 75(6): 816-22. doi: 10.1095/biolreprod.106.054056.

[47] Selevan SG, Kimmel CA, Mendola P. Identifying critical windows of exposure for children's health. Environmental health perspectives. 2000 Jun; 108(suppl 3): 451-5. doi: 10.1289/ehp.00108s3451.

[48] Kistner A, Jacobson L, Jacobson SH, Svensson E, Hellström A. Low gestational age associated with abnormal retinal vascularization and increased blood pressure in adult women. Pediatric Research. 2002 Jun; 51(6): 675-80. doi: 10.1203/00006450-200206000-00003.

[49] Norman M and Martin H. Preterm birth attenuates association between low birth weight and endothelial dysfunction. Circulation. 2003 Aug; 108(8): 996-1001. doi: 10.1161/01.CIR.0000085069.09770.3D.

[50] Gluckman PD and Hanson MA. Developmental origins of disease paradigm: a mechanistic and evolutionary perspective. Pediatric Research. 2004 Sep; 56(3): 311-7. doi: 10.1203/01.PDR.0000135998.08025.FB.

[51] Kaijser M, Jacobsen G, Granath F, Cnattingius S, Ekbom A. Maternal age, anthropometrics and pregnancy oestriol. Paediatric and Perinatal Epidemiology. 2002 Apr; 16(2): 149-53. doi :10.1046/j.1365-3016.2002.00397.x.

[52] Sedin G, Bergquist C, Lindgren PG. Ovarian hyper stimulation syndrome in preterm infants. Pediatric research. 1985 Jun; 19(6): 548-52. doi: 10.1203/00006450-198506000-00009.

[53] Dong C, Yoon W, Goldschmidt-Clermont PJ. DNA methylation and atherosclerosis. The Journal of Nutrition. 2002 Aug; 132(8): 2406S-9S. doi: 10.1093/jn/132.8.2406S.