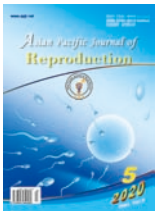

Review Article

Asian Pacific Journal of Reproduction

Journal homepage: www.apjr.net

doi: 10.4103/2305-0500.294663

Socioeconomic, biological and genetic factors influencing preterm birth

Pratibha Rathod[1], Trupti Patel[2], Ajesh Desai[3], Divya Chandel[1]✉

[1]*Department of Zoology, Biomedical Technology and Human Genetics, School of Sciences, Gujarat University, Ahmedabad, India*

[2]*Department of Integrative Biology, Vellore Institute of Technology, Vellore, India*

[3]*Obstetrics & Gynaecology Department, Superintendent, GMERS Medical College and Hospital, Sola, Ahmedabad, India*

ABSTRACT

The etiology of preterm birth is mostly underestimated in developing countries. Current presumptions are that both environmental and genetic factors contribute towards its onset and are responsible for the higher frequency of neonatal deaths. Despite there being considerable scientific data on preterm births across the world, the frequency of its occurrence and threat to the survival of neonates are alarming. It is important that variations among populations should be considered as the socioeconomic status, climatic zones and other genetic, as well as epidemiological factors vary, so as to draw definitive conclusions on the pathogenesis of preterm birth. Predictive biomarkers, prevention and optimum treatment strategies are still being discovered, but with well-designed studies and collaborative efforts, maternal and child healthcare can be prioritized. The purpose of this review is to understand the contributing factors of preterm birth as it is a critical issue and needs in-depth understanding with planned scientific studies to decrease the rate of preterm birth and complication related to it. Furthermore, the review enlists various factors linked to preterm birth *viz*., high maternal age, psychological state, environmental contaminants, infection, cervical length, addiction, cytokine interaction, preeclampsia, genetic composition, ethnicity, oxidative stress and microRNAs. We have summarized the status of preterm birth, its causes, and future line of work required to prevent mortality of mother and neonate that will help us design successful studies which aim to reduce preterm births effectively.

KEYWORDS: Preterm birth; Oxidative stress; Low birth weight; Inflammation; Genetic markers

1. Introduction

Preterm birth or premature birth is a condition that leads to the early parturition of the developing fetus, less than 37 weeks of gestation period. It is a public health issue that affects the mother and child health. It needs a major focus, due to its high prevalence as a long-standing disability in children and associated mortality and morbidity. The estimated global burden of preterm births in 2014 as analyzed by Saifon *et al*[1] using 1 241 data points and 107 countries was equated to 14.84 million live births. Preterm birth complications are the leading cause of death among children under 5 years of age, responsible for approximately 1 million deaths each year[2]. The impact of preterm birth has led to alarming statistics which shows that annually across 184 different countries preterm births range from 5% in several European countries up to 18% in some African countries[3]. Though the babies may survive the trauma of early birth, they suffer major health complications and lifelong disabilities, some of which are lung infections, poor vision, auditory problems and a certain amount of learning disabilities. South Asia and sub-Saharan Africa contribute more than 60% of the premature birth count of all global preterm deliveries[3].

Preterm birth can be categorized as: extreme preterm (<28 weeks), very preterm (28 to <32 weeks) and moderate to late preterm (32 to 37 weeks) based on the gestation period. It can be divided into two subtypes: (a) spontaneous preterm birth: initiation of spontaneous labor or induction of labor after preterm premature rupture of the membranes; and (b) preterm birth initiated by provider: initiation of labor or elective caesarean section before 37 weeks of complete

✉To whom correspondance may be addressed. E-mail: divya_chandel@yahoo.com

How to cite this article: Rathod P, Patel T, Desai A, Chandel D. Socioeconomic, biological and genetic factors influencing preterm birth. *Asian Pac J Reprod* 2020; 9(5): 215-222.

Article history: Received: 24 December 2019; Revision: 26 July 2020; Accepted: 20 August 2020; Available online: 12 September 2020

gestation by maternal or fetal indications (iatrogenic)[3]. Ample amount of work has been done so far in this field at different levels among different localities. However, the literature reviews which cover most of the affecting factors such as ethnicity, stress, socioeconomic condition, infections, environmental contaminants and genetic composition of the mother are difficult to find. Thus, in this review, we tried to include all the possible factors affecting early birth outcomes in the global ethnicities.

2. Social, physical, economic conditions and their relevance in preterm birth

The population's social and economic status contributes significantly to the causative frequency of preterm birth. One of the major issues in developing countries is poor hygiene and undernourished mother due to a low socioeconomic background, which is of utmost importance while taking into consideration the quality of child health. In the absence of full understanding regarding preterm causing factors, efforts to prevent preterm birth have focused on identifying risk factors which can be demographic data, body mass index of mother, past pregnancy history, biophysical markers (length of the cervix), and quantitative tests for biological fluids[4]. Ciancimino *et al*[5] did a retrospective case-control analysis to evaluate maternal-fetal outcomes in advanced maternal age among 1 347 pregnant women and concluded that advanced maternal age could be considered a significant risk factor for spontaneous abortions (*OR*=2.10, *P*=0.001) and preterm delivery (*OR*=69.84, *P*=0.001). Multiple pregnancies, second or third trimester bleeding and ethnicity have been associated with preterm birth most consistently. Early spontaneous premature delivery is more predictive of recurrence and is closely linked to subsequent spontaneous premature delivery[4,6]. The cervical length has also been associated most strongly and consistently with preterm birth[4]. Physical and psychosocial stress, as well as psychological abuse, including mild to severe depression, are found to be very high in socio-economically challenged population and have been linked with higher preterm birth rates[7–9]. Besides this, parental literacy, living in a violent and economically deprived neighbourhood, intimate partner violence or abuse from family and society, peri-pregnancy, spouse and in-law's harassment remain closely linked to multiple forms of poor obstetric outcomes[10].

3. Intrauterine inflammation and infection

Maternal infection and inflammation of intrauterine tissues induce responses to the developing fetal membranes, which has a significant role in triggering preterm delivery. The infections and colonization of the lower genital tract with pathogenic organisms lead to chorioamnionitis, which increases the risk of adverse outcome in preterms[11]. Romero *et al*[12] introduced the concept of preterm labor arising from pathological signalling alterations of components of parturition-pathway as opposed to full-term delivery resulting from physiological changes of such components. It pointed to the evidence indicating pathological processes like (1) intrauterine infection/inflammation; (2) cervical incompetence; (3) overdilation of the uterus; (4) abnormal allograft reaction; (5) any allergic reaction; (6) uterine ischemia; and (7) abnormality or imbalance in hormonal levels (progesterone or corticotrophin-releasing factor related) implicated in preterm parturition syndrome.

According to research carried out by Sebire[13], one of the main reasons behind the second-trimester miscarriage and preterm birth is the localized inflammation of the chorion and decidua, with or without amniotic inflammation. Hence, infection of the genitourinary tract is strongly associated with preterm delivery, resulting in early parturition. Surve *et al*[14] suggested that genitourinary tract infection with Group B Streptococcus, a Gram-positive pathogen correlated with premature rupture of amniotic membrane, causing chorioamnionitis that leads to preterm birth or intrauterine death of the fetus. As a result, Toll-like receptor-initiated pathways get activated[15], and proteins like antimicrobial peptides[16] and lipopolysaccharide-binding protein[17] are produced. Thus, a fetus develops the capacity to identify and react immunologically to invading microorganisms. However, the prominent and distinctive feature of intraamniotic immunity is the development of resistance mechanisms of a pro-inflammatory immune response to reduce fetal damage or prematurely expulsion from the uterus. Therefore, the dual-protection system by infection resistance and resilience to infection-induced immune activation prohibits damage to the developing fetus and avoids preterm births. Infection-related immunity is preferentially aimed at fighting extracellular microbial pathogens during gestation.

In spontaneous preterm birth, *Ureaplasma urealyticum* and *Mycoplasma hominis* cordblood infections (41.3% *vs.* 25.7%; *P*=0.007) were reported to be more frequent and strongly correlated with indicators of acute inflammation of the placenta[18]. Research done by Tellapragada *et al*[19] add a remarkable understanding on the role of asymptomatic infections such as transitional vaginal flora and vaginal inflammation on adverse pregnancy outcomes. In addition, a definite link between transitional vaginal flora and preterm birth in South Asian women has also been suggested (adjusted relative risk=2.75; 95% *CI*=1.4-5.1, *P*=0.002). Further, considering the importance of periodontitis and its negative effect on pregnancy, like preterm birth (adjusted relative risk=2.39; 95% *CI*=1.1-4.9, *P*=0.02) as well as low birth weight (adjusted relative risk=3.38; 95% *CI*=1.6-6.9, *P*=0.001), a need for routine screening, early diagnosis and treatment have been emphasized.

4. Oxidative stress, ethnic indications and environmental causes linked to preterm birth

4.1. Oxidative stress

Inflammation and oxidative stress are inter-related and are responsible for the causation of various human conditions. Oxidative stress is known to have a significant role in the pathogenesis of adverse pregnancy outcomes, including preterm birth. Overwhelming free radicals and the resulting oxidative stress affect the placental antioxidant capacity, which in turn adversely affects the placental efficiency and functioning, consequently compromising the quality of birth and fetal viability[20]. Many gestation-related problems, such as spontaneous abortions, low birth weight, embryopathies, preeclampsia, fetal growth restriction, intrauterine fetal death and preterm birth, are linked to oxidative stress. The most common reasons for the generation of oxidative stress are lack of proper nutrition and unfavourable environment, which may increase the susceptibility to adverse pregnancy outcomes. This outcome might occur due to impairment in the antioxidant resistance mechanisms and increment in reactive oxygen species levels, which changes cellular signalling adversely and damages cellular macromolecules even in the embryonic and placental cells[21].

4.2. Ethnic indications

Racial differences and genetic polymorphism have been directly related to preterm birth[22]. Urquia *et al*[23] analyzed the correlation between migratory patterns and adverse birth outcomes of over 30 million singleton births (from twenty-four research studies), and observed that black migrants (*OR*=1.62, 95% *CI*=1.30-2.03, *P*=0.0018) and Hispanics females (*OR*=1.35, 95% *CI*=1.10-1.66, *P*=0.0018) had reduced chances of giving low birth weight and preterm birth as compared to black women born in the United States (*OR*=1.89, 95% *CI*=1.64-2.19, *P*=0.0018). Asian migrants (*OR*=1.44, 95% *CI*=1.15-1.81, *P*=0.0018) were at higher risk than white migrants in general. Both native-born and migrant South-Central Asian along with Indian women, were at significant (*OR*=1.09, 95% *CI*=0.88-1.35, *P*=0.0018) chances of delivering preterm birth. Migrants from Asian ethnicity (*OR*=1.44, 95% *CI*=1.15-1.81, *P*=0.0018) were at higher risk than white migrants overall. South-Central Asian (*OR*=0.84, 95% *CI*=0.57-1.23, *P*<0.0001) women were at higher odds in both native-born and migrated, but the association was stronger in Europe (*OR*=0.99, 95% *CI*=0.79-1.25, *P*<0.0001). African ancestry (*OR*=0.78, 95% *CI*=0.60-1.01, *P*<0.0001) was found to be protective compared to European ancestry (*OR*=0.99, 95% *CI*=0.79-1.25, *P*<0.0001) in case of delivering earlier (preterm birth)[23,24]. Desai *et al*[25], in their study on a tribal group of Gujarat, India, observed that females with sickle-cell anaemia and other blood-related conditions had higher chances of stillbirths (*OR*=2.43, 95% *CI*=1.31–4.53, *P*<0.01), low birth weight (*OR*=2.99, 95% *CI*=2.03–4.41, *P*<0.01) and preterm births (*OR*=3.96, 95% *CI*=2.74–5.72, *P*<0.01) usually due to insufficient supply of oxygen and nutrients to the growing fetus as compared to normal pregnancies.

4.3. Environmental causes

The relation between environmental-gene interactions and birth outcomes are tremendously complex. A negative interaction leads to oxidative stress and mutations that may not be favourable to normal physiological processes, including pregnancy. Recent studies have shown that pregnant women's immediate surrounding has much impact on her health, along with other factors. Exposure to air pollution is more commonly found to be correlated with adverse pregnancy outcomes[26,27]. Like other environmental contaminants, smoking has a distinct and definite role in premature delivery. Smoking abstinence before pregnancy is linked with a significant improvement in birth outcomes as compared to smoking mothers (*P*<0.01). So, the data from a UK as well as Asian population study found that quitting smoking by the end of the first trimester did not make any difference in birth weight of babies as compared to non-smoking mothers but quitting after this period showed a significantly low birth weight of the infants (for Asian, *P*<0.05; for UK, *P*<0.01)[28]. Data from the United States also indicated that quitting smoking late in pregnancy increased the rate of preterm births (*OR*=1.70; 95% *CI*=1.60-1.80, *P*≤0.001) as compared to non-smoking mothers or quitting early in pregnancy (*OR*=1.20; 95% *CI*=1.02-1.40, *P*≤0.001)[29,30].

Bahreyni *et al*[31] first revealed that exposure to the mobile phone-induced electromagnetic field in the pregnant rats generate oxidative stress in both the mothers and their offspring tissues. However, the studies showing a similar effect of these radiations in human pregnancy are still lacking.

5. Various biological markers of preterm births

Biomarkers have a significant role in deciphering human condition and designing treatments to reduce diseased conditions, including preterm births. Biochemical and genetic markers in biological fluids (*e.g.*, blood, amniotic fluid, cervical mucus, vaginal secretions, serum/ plasma, saliva and urine) are used to determine biomarker values for predicting preterm birth[32]. Research carried out on the biological fluids till date reveals that fetal fibronectin levels in cervical or vaginal fluids have an evident connection with subsequent spontaneous preterm birth (relative risk=3.3, 95% *CI*=2.5-4.2) at >37 weeks[4].

5.1. Biochemical markers

High concentrations of fetal fibronectin in cervical-vaginal fluids suggest a strong correlation with spontaneous preterm birth and can be a highly relevant predictive indicator in preterm birth. However, in the opinion of Tripathi *et al*[33], phosphorylated insulin-like growth factor-binding protein holds more importance and reliability for predicting preterm delivery. Besides these, high levels of maternal serum alpha-fetoprotein is strongly associated with preterm birth (*OR*=8.7, 95% *CI*=7.1-10.7, *P*<0.01)[34]. For pregnant woman, regular analysis of plasma protein profiles is advised to be done at 10-15 weeks of gestation, as it is a significant (*P*<0.01) indication for having preterm birth later[35]. Fetal inflammatory response syndrome is a condition characterized by systemic inflammation and elevated levels of interleukin (IL) 6 in fetal plasma (>11 pg/mL) resulting in the preterm premature rupture of membranes, hence is a risk factor for spontaneous preterm birth, short-term perinatal morbidity and mortality[36]. Metabolic profiling of the mother in future can be an excellent diagnostic evaluator for detection of such complications. Compared to an invasive technique like amniocentesis, serum sample collection is preferable as it is safe for the fetus, and possible risks and harms with amniocentesis can also be avoided. Research by Virgiliou *et al*[37] offers clear evidence that metabolic profiling techniques may provide advantages in premature birth aetiology investigation. Consequently, diagnosis, treatment and prevention of early births can be managed. Generally, the second-trimester amniotic fluid and maternal blood serum metabolic content show the potential for the detection of biomarkers linked to fetal development and preterm delivery. In terms of the possible association between preterm birth and serum folate levels, several earlier reports have indicated the risk of premature delivery with a low serum folate level[38–40]. In contrast, research by Yamada *et al*[41] found that preterm birth, miscarriage, or growth of fetus were not correlated with the serum folate levels during the first trimester.

5.2. Genetic markers

In preterm births, plenty of studies have been conducted to find out related gene markers which alter the usual pathways and expressions of genes and ultimately lead to early deliveries. A review by Menon[42] has discussed the role of increased interleukins (IL-1β, IL-6, IL-8, IL-10), tumour necrosis factor-alpha (TNF-α), soluble TNF receptors (sTNFR1 and sTNFR2), and corticotrophin-releasing hormone in the amniotic fluid of premature babies. It is now well understood that due to infection and inflammation, prostaglandin producing chemokines, cytokines, inflammatory mediators and enzymes of matrix-degradation get released by the activation of inflammatory signalling pathways thus detaching the fetus earlier from the placenta[12,43–45]. Cytokines play a vital role in a reproductive process like ovarian cycle and maintenance of pregnancy as well. Moreover, disturbance in cytokine signalling is directly linked with adverse consequences of conception, such as miscarriage, preeclampsia, preterm labor and fetal brain injury[46].

In Hispanic population, the polymorphism (N680S) from asparagine to serine in the receptor of follicular stimulating hormone was found to be significantly (*OR*=2.52, 95% *CI*=1.20-5.33, *P*=0.02) associated with preterm birth[47], while the Chinese population, findings by He *et al*[48] suggest that polymorphisms of insulin-like growth factors and it's receptors at rs972936 (GA: *OR*=1.74, 95% *CI*=1.01-3.02 and GA/AA: *OR*=1.75, 95% *CI*=1.04-2.93; *P*=0.02) and rs2229765 (GA: *OR*=0.60, 95% *CI*=0.37-0.98 and GA/AA: *OR*=0.64, 95% *CI*=0.40-1.00; *P*=0.001) may change the maternal metabolic status which triggers the early birth. Allelic frequency of a single nucleotide variant from G>A at 12109 positions of renin was frequently found (*OR*=6.62, 95% *CI*=3.14–14.15, *P*<0.0000001) in mothers giving birth to preterm than the full term[49]. A polymorphism of major histocompatibility complex class I polypeptide related sequence A (rs2256318) may interfere with placental development and contribute to early birth (*OR*=6.97, 95% *CI*=2.34–20.74 for A/A, compared with G/G genotype, *P*=0.001)[50]. Research by Tiwari *et al*[51] provides crucial information on 6-base pair deletion of both the alleles of thymidine synthetase gene and associated hyper-homocysteinemia in vulnerability to low birth weight, preterm delivery and fetal death. It is observed that the key enzyme of folate metabolism, thymidylate synthase (TYMS) 14946bp del/del genotype increased the risk of preterm delivery (*OR*=2.801, 95% *CI*=1.433-5.472, *P*=0.002), indicating prognostic as well as the clinical significance of this genotype in preterm delivery.

Of the many polymorphisms and variants proposed in the contribution of preterm births, maternal methylenetetrahydrofolate reductase (*MTHFR*) gene could be a candidate gene for diagnosis. C677T polymorphism in *MTHFR* may be one of the candidate's prognostic variations to analyze the population-based variation of pregnancy cases predisposed to preterm delivery (*P*<0.001)[52]. However, in contradiction with this assertion, Resch *et al*[53] could not find a distinct association of *MTHFR* C677T gene polymorphism (*OR*=1.050, 95% *CI*=0.090-12.276, *P*=0.485) with preterm birth. In a study by Wang *et al*[54] involving a total of 12 single nucleotide polymorphisms of 11 genes involved in folate metabolism, none of the genotype distributions revealed any association with preterm birth. Also, none of the genotype distributions showed considerable significance even between full-term and preterm. Despite these findings, a meta-analysis by Wu *et al*[55] confirmed the affirmative association between *MTHFR* C677T polymorphism and preterm birth incidence risk, where the risk of preterm birth was observed under allele contrast (T *vs*. C, *OR*=1.36, 95% *CI*=1.02–1.81, *P*=0.034), homozygote (TT *vs*. CC, *OR*=1.70, 95% *CI*=1.07–2.68, *P*=0.024), and recessive genotypes (TT *vs*. CT+CC, *OR*=1.49,

95% *CI*=1.00–2.22, *P*=0.049). A study by Zhu *et al*[56] on *MTHFR* unveiled two polymorphisms within 3'-UTR rs1537515 and rs1537516, which increase the susceptibility of preterm birth (*OR*=0.65, 95% *CI*=0.47-0.91, *P*=0.012). Out of three frequencies (CC-homozygous normal; CT-heterozygous polymorphism; TT-homozygous mutant) of *MTHFR* C677T gene, the homozygous mutant - TT genotype may be contributing to the increased risk of premature delivery (*OR*=3.077, 95% *CI*=1.469-6.447, *P*=0.004)[57].

IL-6 with polymorphism G/C at 174 position was significantly lower (*P*<0.05) in mothers of preterm birth than a term birth. The presence of this polymorphism was protective against preterm birth in Turkish population[58]. Yin *et al*[59] pioneered in explaining IL-27 mediated excessive reaction to inflammation in the fetal membranes through various signalling pathways *viz*., JNK, PI3K or ERK contributing to fetal low gestation period (*P*<0.05). Andalas *et al*[60] did not find any association between IL-10 single nucleotide polymorphism (-1082 A/G) and spontaneous preterm birth in the Acehnese population. Likewise, research in the Brazilian population by Moura *et al*[61] also did not find the significance of this single nucleotide polymorphism alone. On the contrary, another study in Malaysia by Suki *et al*[62] showed a significant association of it along with the risk of preterm birth. Simhan *et al*[63] observed that women carrying an IL-6-174 C/C variant are more prone to give preterm births and showed the statistical significance of racial disparity between a white woman and African American women (*P*<0.001). A connection is found to exist between preterm birth and polymorphism in IL-4 in multiple pregnancies which might have contributed to increased expression of IL-4 in these individuals to show an effect.

One of the candidate gene responsible for preterm birth is the TNF-α). Polymorphism observed explicitly on the site of the promoter region of this gene has a higher chance of earlier premature rupture of the fetal membranes, which ultimately leads to spontaneous preterm birth[64]. Macones *et al*[64] observed that tumor necrosis factor-alpha gene-2 (TNF-2) at the -308 position, significantly increased the risk of spontaneous preterm birth (*OR*=2.7, 95% *CI*=1.7-4.5, *P*=0.04). Furthermore, they provided a preliminary proof that not only the genetic susceptibilities (*i.e*., TNF-α carriers) but the interaction with infection and inflammation of uterine or vaginal walls (*i.e*., bacterial vaginosis) also increases the risk of spontaneous preterm birth by many folds (*OR*=6.1, 95% *CI*=1.9-21.0, *P*=0.04). A meta-analysis by Aslebahar *et al*[65] reported that single nucleotide polymorphisms like TNF-α -308G>A [homozygote (*OR*=1.716, 95% *CI*=1.210-2.433, *P*=0.002) and the recessive (*OR*=1.554, 95% *CI*=1.100-2.196, *P*=0.012) models] and -238G>A (*OR*=1.554, 95% *CI*=1.100-2.196, *P*=0.012) located in the promoter region of TNF-α) gene are associated with recurrent pregnancy loss. Moreover, in Asians TNF-α -308G>A [homozygote (*OR*=2.190, 95% *CI*=1.465-3.274, *P*=0.001), the dominant (*OR*=1.642, 95% *CI*=1.269-2.125, *P*≤0.001) and the recessive (*OR*=1.456, 95% *CI*=1.039-2.040, *P*=0.029)] polymorphism was found more commonly than in the other population, which might indicate recurrent pregnancy loss also varies with genetic differences and ethnicity. This association was confirmed by Crider *et al*[66], who showed that TNF-α -308 allelic polymorphism was frequent in a significant proportion of mothers who parturiated preterm births. Many more such single nucleotide polymorphisms and other biochemical and metabolic markers have also been associated with preterm births, but with contrasting results. An elaborate confirmatory analysis on larger sample size is required to identify the underlying mechanisms which lead to premature birth.

6. miRNA and preterm birth

More than 1 880 miRNAs have been reported in humans, and most of them are expressed in the placenta, which is a crucial organ for embryonic and fetal development. There is increasing evidence on the role of microRNAs in various pregnancy-related complications, such as fetal growth restriction and preeclampsia. Fetal growth restriction refers to a condition in which the genetically determined potential growth of a fetus is stopped or decreased during pregnancy. Fetal growth restriction could be considered as a placental disorder, derived from deregulation in the invasion of trophoblasts with a characteristic tissue morphology that leads to uteroplacental insufficiency[67]. Preeclampsia is a multisystemic disease characterized by hypertension, proteinuria and other typical signs that can negatively affect the development of pregnancy. It is the most common complication of pregnancy and represents approximately one-third of preterm births. The data analysis by Laganà *et al*[68] supports a direct correlation between selective high/low expression microRNAs in the placenta and maternal serum markers with preeclampsia.

7. Conclusion

Preterm birth is undoubtedly a multifactorial condition, and there are plenty of factors which can lead to it along with the interaction between environmental factors and mother's internal health. Out of all risk factors, clinical conditions or phenotypical characters of the mother such as intrauterine infection and inflammation, maternal age, body mass index, previous bad obstetric outcome, stress (physiological and pscychological) and cervical incompetence are most significantly linked with preterm birth. The relationship between mother's genotype and having a preterm or subsequent

preterm birth or bad obstetric history also gives strong evidence for the occurrence of premature delivery or preterm birth morbidity or mortality. The interaction among the various factors are yet to be confirmed and therefore needs further research work. It is possible then that the finding of polymorphisms affecting preterm birth as well as some proven biomarkers may ultimately allow clinicians to identify pregnant mothers who are at risk for preterm delivery, so that prevention, proper guidelines and monitoring can be applied promptly.

Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

Pratibha Rathod carried out the literature review and drafted the manuscript. Trupti Patel helped to draft the manuscript and gave suggestions. Ajesh Desai gave the vision and suggestions regarding the importance of the study on preterm births in India. Divya Chandel conceived the study and helped to draft the manuscript.

References

[1] Saifon C, Joshua PV, Ann-Beth M, Pisake L, Max P, Daniel H, et al. Global, regional, and national estimates of levels of preterm birth in 2014: A systematic review and modelling analysis. *Lancet Glob Health* 2019; **7**: e37-e46.

[2] Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, et al. Global, regional, and national causes of under-5 mortality in 2000–2015: An updated systematic analysis with implications for the Sustainable Development Goals. *Lancet* 2016; **388**: 3027-3035.

[3] Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: A systematic analysis and implications. *Lancet* 2012; **379**: 2162-2172.

[4] Goldenberg RL, Iams JD, Mercer BM, Meis PJ, Moawad AH, Copper RL, et al. The preterm prediction study: the value of new *vs* standard risk factors in predicting early and all spontaneous preterm births. NICHD MFMU Network. *Am J Public Health* 1998; **88**: 233-238.

[5] Ciancimino L, Laganà AS, Chiofalo B, Granese R, Grasso R, Triolo O. Would it be too late? A retrospective case–control analysis to evaluate maternal–fetal outcomes in advanced maternal age. *Arch Gynecol Obstet* 2014; **290**: 1109-1114.

[6] Mercer BM, Goldenberg RL, Moawad AH, Meis PJ, Iams JD, Das AF, et al. The preterm prediction study: Effect of gestational age and cause of preterm birth on subsequent obstetric outcome. *Am J Obstet Gynecol* 1999; **181**: 1216-1221.

[7] Barnes DL, Adair LS, Popkin BM. Women's physical activity and pregnancy outcome: A longitudinal analysis from the Philippines. *Int J Epidemiol* 1991; **20**: 162-172.

[8] Austin MP, Leader L. Maternal stress and obstetric and infant outcomes: Epidemiological findings and neuroendocrine mechanisms. *Aust N Z J Obstet Gynaecol* 2000; **40**: 331-337.

[9] Rao D, Kumar S, Mohanraj R, Frey S, Manhart LE, Kaysen DL. The impact of domestic violence and depressive symptoms on preterm birth in South India. *Soc Psychiatry Psychiatr Epidemiol* 2016; **51**: 225-232.

[10] Silverman JG, Balaiah D, Ritter J, Dasgupta A, Boyce SC, Decker MR, et al. Maternal morbidity associated with violence and maltreatment from husbands and in-laws: Findings from Indian slum communities. *Reprod Health* 2016; **13**: 109.

[11] Seliga-Siwecka JP, Kornacka MK. Neonatal outcome of preterm infants born to mothers with abnormal genital tract colonization and chorioamnionitis: A cohort study. *Early Hum Dev* 2013; **89**: 271-275.

[12] Romero R, Espinoza J, Kusanovic JP, Gotsch F, Hassan S, Erez O, et al. The preterm parturition syndrome. *BJOG–Int J Obstet Gynecol* 2006; **113**: 17-42.

[13] Sebire NJ. Choriodecidual inflammatory syndrome (CoDIS) is the leading, and under recognized, cause of early preterm delivery and second trimester miscarriage. *Med Hypotheses* 2001; **56**: 497-500.

[14] Surve MV, Anil A, Kamath KG, Bhutda S, Sthanam LK, Pradhan A, et al. Membrane vesicles of group B streptococcus disrupt feto-maternal barrier leading to preterm birth. *PLoS Pathogens* 2016; **12**: e1005816.

[15] Abrahams VM. Pattern recognition at the maternal-fetal interface. *Immunol Invest* 2008; **37**: 427-447.

[16] Yoshio H, Tollin M, Gudmundsson GH, Lagercrantz H, Jörnvall H, Marchini G, et al. Antimicrobial polypeptides of human vernix caseosa and amniotic fluid: Implications for newborn innate defense. *Pediatr Res* 2003; **53**: 211-216.

[17] Roos T, Martin TR, Ruzinski JT, Leturcq DJ, Hillier SL, Patton DL, et al. Lipopolysaccharide binding protein and soluble CD14 receptor protein in amniotic fluid and cord blood in patients at term. *Am J Obstet Gynecol* 1997; **177**: 1230-1237.

[18] Goldenberg RL, Andrews WW, Goepfert AR, Faye-Petersen O, Cliver SP, Carlo WA, et al. The Alabama preterm birth study: Umbilical cord blood *Ureaplasma urealyticum* and *Mycoplasma hominis* cultures in very preterm newborn infants. *Am J Obstet Gynecol* 2008; **198**: 43.e1-43.e5.

[19] Tellapragada C, Eshwara VK, Bhat P, Acharya S, Kamath A, Bhat S, et al. Risk factors for preterm birth and low birth weight among pregnant Indian women: A hospital-based prospective study. *J Prev Med Public Health* 2016; **49**: 165-175.

[20] Sultana Z, Maiti K, Aitken J, Morris J, Dedman L, Smith R. Oxidative stress, placental ageing-related pathologies and adverse pregnancy outcomes. *Am J Reprod Immunol* 2017; **77**: e12653.

[21] Al-Gubory KH, Fowler PA, Garrel C. The roles of cellular reactive oxygen species, oxidative stress and antioxidants in pregnancy outcomes. *Int J Biochem Cell Biol* 2010; **42**: 1634-1650.

[22]Esplin MS. Preterm birth: A review of genetic factors and future directions for genetic study. *Obstet Gynecol Surv* 2006; **61**: 800-806.

[23]Urquia ML, Glazier RH, Blondel B, Zeitlin J, Gissler M, Macfarlane A, et al. International migration and adverse birth outcomes: Role of ethnicity, region of origin and destination. *J Epidemiol Commun Health* 2010; **64**: 243-251.

[24]De Andrade Ramos BR, Mendes ND, Tanikawa AA, Amador MA, dos Santos NP, dos Santos SE, et al. Ancestry informative markers and selected single nucleotide polymorphisms in immunoregulatory genes on preterm labor and preterm premature rupture of membranes: A case-control study. *BMC Pregnancy Childb* 2016; **16**: 30.

[25]Desai G, Anand A, Shah P, Shah S, Dave K, Bhatt H, et al. Sickle cell disease and pregnancy outcomes: A study of the community-based hospital in a tribal block of Gujarat, India. *J Health Popul Nutr* 2017; **36**: 3.

[26]Liu S, Krewski D, Shi Y, Chen Y, Burnett RT. Association between gaseous ambient air pollutants and adverse pregnancy outcomes in Vancouver, Canada. *Environ Health Perspect* 2003; **111**: 1773-1778.

[27]Poirier A, Dodds L, Dummer T, Rainham D, Maguire B, Johnson M. Maternal exposure to air pollution and adverse birth outcomes in Halifax, Nova Scotia. *J Occup Environ Med* 2015; **57**: 1291-1298.

[28]Yan J, Groothuis PA. Timing of prenatal smoking cessation or reduction and infant birth weight: Evidence from the United Kingdom Millennium Cohort Study. *Matern Child Health J* 2015; **19**: 447-458.

[29]Blatt K, Moore E, Chen A, Van Hook J, De Franco EA. Association of reported trimester-specific smoking cessation and fetal growth restriction. *Obstet Gynecol* 2015; **125**: 1452-1459.

[30]Moore E, Blatt K, Chen A, Van Hook J, DeFranco EA. Relationship of trimester-specific smoking patterns and risk of preterm birth. *Am J Obstet Gynecol* 2016; **215**: 109.e1-e6.

[31]Bahreyni Toossi MH, Sadeghnia HR, Mohammad Mahdizadeh Feyzabadi M, Hosseini M, Hedayati M, Mosallanejad R, et al. Exposure to mobile phone (900–1800 MHz) during pregnancy: Tissue oxidative stress after childbirth. *J Matern–Fetal Neonatal Med* 2018; **31**: 1298-1303.

[32]Goldenberg RL, Goepfert AR, Ramsey PS. Biochemical markers for the prediction of preterm birth. *Am J Obstet Gynecol* 2005; **192**: 36-46.

[33]Tripathi R, Tyagi S, Mala YM, Singh N, Pandey NB, Yadav P. Comparison of rapid bedside tests for phosphorylated insulin-like growth factor-binding protein 1 and fetal fibronectin to predict preterm birth. *Int J Gynecol Obstet* 2016; **135**: 47-50.

[34]Waller DK, Lustig LS, Cunningham GC, Feuchtbaum LB, Hook EB. The association between maternal serum alpha-fetoprotein and preterm birth, small for gestational age infants, preeclampsia, and placental complications. *Obstet Gynecol* 1996; **88**: 816-822.

[35]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. *Am J Obstet Gynecol* 2016; **214**: 517.e1-e23.

[36]Vitale SG, Marilli I, Rapisarda AM, Rossetti D, Belluomo G, Iapichino V, et al. Cellular and biochemical mechanisms, risk factors and management of preterm birth: State of the art. *Minerva Ginecol* 2014; **66**(6): 589-595.

[37]Virgiliou C, Gika HG, Witting M, Bletsou AA, Athanasiadis A, Zafrakas M, et al. Amniotic fluid and maternal serum metabolic signatures in the second trimester associated with preterm delivery. *J Proteome Res* 2017; **16**: 898-910.

[38]Vollset SE, Refsum H, Irgens LM, Emblem BM, Tverdal A, Gjessing HK, et al. Plasma total homocysteine, pregnancy complications, and adverse pregnancy outcomes: The Hordaland Homocysteine Study. *Am J Clin Nutr* 2000; **71**: 962-968.

[39]El-Khairy L, Vollset SE, Refsum H, Ueland PM. Plasma total cysteine, pregnancy complications, and adverse pregnancy outcomes: The Hordaland Homocysteine Study. *Am J Clin Nutr* 2003; **77**: 467-472.

[40]Siega-Riz AM, Savitz DA, Zeisel SH, Thorp JM, Herring A. Second trimester folate status and preterm birth. *Am J Obstet Gynecol* 2004; **191**: 1851-1857.

[41]Yamada T, Morikawa M, Yamada T, Kishi R, Sengoku K, Endo T, et al. First-trimester serum folate levels and subsequent risk of abortion and preterm birth among Japanese women with singleton pregnancies. *Arch Gynecol Obstet* 2013; **287**: 9-14.

[42]Menon R. Spontaneous preterm birth, a clinical dilemma: Etiologic, pathophysiologic and genetic heterogeneities and racial disparity. *Acta Obstet Gynecol Scand* 2008; **87**: 590-600.

[43]Menon R, Fortunato SJ. Infection and the role of inflammation in preterm premature rupture of the membranes. *Best Pract Res Clin Obstet Gynaecol* 2007; **21**: 467-478.

[44]Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet* 2008; **371**: 75-84.

[45]Agrawal V, Hirsch E. Intrauterine infection and preterm labor. *Semin Fetal Neonatal Med* 2012; **17**: 12-19.

[46]Orsi NM, Tribe RM. Cytokine networks and the regulation of uterine function in pregnancy and parturition. *J Neuroendocrinol* 2008; **20**: 462-469.

[47]Dominguez-Lopez P, Diaz-Cueto L, Arechavaleta-Velasco M, Caldiño-Soto F, Ulloa-Aguirre A, Arechavaleta-Velasco F. The follicle-stimulating hormone receptor Asn680Ser polymorphism is associated with preterm birth in Hispanic women. *J Matern–Fetal Neonatal Med* 2018; **31**: 580-585.

[48]He JR, Lai YM, Liu HH, Liu GJ, Li WD, Fan XJ, et al. Maternal IGF 1 and IGF 1R polymorphisms and the risk of spontaneous preterm birth. *J Clin Lab Anal* 2017; **31**: e22125.

[49]Rodríguez-Sánchez IP, Suárez-Caro S, Rivas-Solís F, Delgado-Enciso I, Sánchez-Chaparro MM, Gómez-Govea MA, et al. Association of the polymorphism 12109g> A from the *REN* gene as a risk factor for preterm birth. *J Renin–Angio–Aldo Syst* 2016; **17**: 1-6.

[50]Song J, Li J, Liu H, Gan Y, Sun Y, Yu M, et al. A genetic variant in the placenta-derived MHC class I chain-related gene A increases the risk of preterm birth in a Chinese population. *Hum Genet* 2017; **136**: 1375-1384.

[51]Tiwari D, Das CR, Bose PD, Bose S. Associative role of TYMS 6bp del polymorphism and resulting hyperhomocysteinemia in the pathogenesis of preterm delivery and associated complications: A study from Northeast India. *Gene* 2017; **627**: 129-136.

[52]Tiwari D, Bose PD, Das S, Das CR, Datta R, Bose S. *MTHFR* (C677T) polymorphism and PR (PROGINS) mutation as genetic factors for preterm delivery, fetal death and low birth weight: A Northeast Indian population-based study. *Meta Gene* 2015; **3**: 31-42.

[53]Resch B, Gallistl S, Kutschera J, Mannhalter C, Muntean W, Mueller WD. Thrombophilic polymorphisms–factor V Leiden, prothrombin G20210A, and methylenetetrahydrofolate reductase C677T mutations–and preterm birth. *Wien Klin Wochenschr* 2004; **116**: 622-626.

[54]Wang BJ, Liu MJ, Wang Y, Dai JR, Tao JY, Wang SN, et al. Association between SNPs in genes involved in folate metabolism and preterm birth risk. *Genet Mol Res* 2015; **14**: 850-859.

[55]Wu H, Zhu P, Geng X, Liu Z, Cui L, Gao Z, et al. Genetic polymorphism of *MTHFR* C677T with preterm birth and low birth weight susceptibility: A meta-analysis. *Arch Gynecol Obstet* 2017; **295**: 1105-1118.

[56]Zhu Q, Chen Y, Dai J, Wang B, Liu M, Wang Y, et al. Methylenetetrahydrofolate reductase polymorphisms at 3'-untranslated region are associated with susceptibility to preterm birth. *Transl Pediatr* 2015; **4**: 57-62.

[57]Nan Y, Li H. *MTHFR* genetic polymorphism increases the risk of preterm delivery. *Int J Clin Exp Pathol* 2015; **8**: 7397-7402.

[58]Karaka NM, Ecevit AN, Yalçın Y, Özdemir B, Verdi H, Tekindal MA, et al. Effect of maternal and neonatal interleukin-6-174 G/C polymorphism on preterm birth and neonatal morbidity. *J Matern Fetal Neonatal Med* 2017; **23**: 1-7.

[59]Yin N, Wang H, Zhang H, Ge H, Tan B, Yuan Y, et al. IL-27 induces a pro-inflammatory response in human fetal membranes mediating preterm birth. *Int Immunopharmacol* 2017; **50**: 361-369.

[60]Andalas M, Hakimi M, Nurdiati DS, Astuti I, Ichsan I, Wahyuniati N, et al. Lack of association between the 1082 (A/G) IL-10 polymorphism (rs1800896) and spontaneous preterm birth in the Indonesian Acehnese population. *Polish Ann Med* 2017; **24**: 209-213.

[61]Moura E, Mattar R, de Souza E, Torloni MR, Gonçalves-Primo A, Daher S. Inflammatory cytokine gene polymorphisms and spontaneous preterm birth. *J Reprod Immunol* 2009; **80**: 115-121.

[62]Suki SZ, Omar SZ, Mohamed Z. Association study of interleukin 10-1082 G/A polymorphism and interleukin-10 levels with occurrence of spontaneous preterm birth in a tri-ethnic Malaysian population. *Public Health Genom* 2015; **18**: 27.

[63]Simhan HN, Krohn MA, Roberts JM, Zeevi A, Caritis SN. Interleukin-6 promoter 174 polymorphism and spontaneous preterm birth. *Am J Obstet Gynecol* 2003; **189**: 915-918.

[64]Macones GA, Parry S, Elkousy M, Clothier B, Ural SH, Strauss III JF. A polymorphism in the promoter region of TNF and bacterial vaginosis: preliminary evidence of gene-environment interaction in the etiology of spontaneous preterm birth *Am J Obstet Gynecol* 2004; **190**: 1504-1508.

[65]Aslebahar F, Neamatzadeh H, Meibodi B, Karimi-Zarchi M, Tabatabaei RS, Noori-Shadkam M, et al. Association of tumor necrosis factor-α (TNF-α)-308G> A and-238G> A polymorphisms with recurrent pregnancy loss risk: A meta-analysis. *Int J Fertil Steril* 2019; **12**: 284-292.

[66]Crider KS, Whitehead N, Buus RM. Genetic variation associated with preterm birth: A Hu GE review. *Genet Med* 2005; **7**: 593-604.

[67]Chiofalo B, Laganà AS, Vaiarelli A, La Rosa VL, Rossetti D, Palmara V, et al. Do miRNAs play a role in fetal growth restriction? A fresh look to a busy corner. *Biomed Res Int* 2017; **2017**: Article ID: 6073167. doi: 10.1155/2017/6073167.

[68]Lagana AS, Vitale SG, Sapia F, Valenti G, Corrado F, Padula F, et al. miRNA expression for early diagnosis of preeclampsia onset: Hope or hype? *J Matern Fetal Neonatal Med* 2018; **31**: 817-821.