About 27 per cent of neonatal mortality has been reported to be related to complications of preterm birth (PTB) or delivery before 37 wk of gestation. In India, the incidence of PTB is about 21 per cent, which translates into 3.6 million births annually. This corresponds to 23.6 per cent of global annual PTB burden which is estimated to be 15 million.

PTB can be medically induced when there is an indication either related to the mother such as pre-eclampsia, eclampsia or foetus such as foetal distress. On the other hand, PTB can occur spontaneously due to multiple aetiologies such as uterine overdistension, as in multiple gestation, infection or inflammation. Other risk factors for PTB are poor maternal nutritional status as evident by low maternal body mass index, periodontal disease and racial disparity (as reported higher risk is seen in African American than European American). Increased levels of inflammatory cytokines, such as toll-like receptor 4 (TLR4), tumour necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), IL-6 have been reported in serum and/or amniotic fluid of women with spontaneous preterm labour (PTL). This review reports existing evidence on association of genetic variations in TNF-α, IL-1α, IL-1β, IL-6, IL-10 and TLR-4 with PTB.

Key words Cytokines - inflammation - polymorphism - preterm birth - spontaneous preterm labour

Preterm infants (i.e., born before <37 wk of gestation) are at increased risk of morbidity and mortality and long-term disabilities. Global prevalence of preterm birth (PTB) varies from 5 to 18 per cent. There are multiple aetiological causes and factors associated with PTB. Intrapartum infections are conventionally associated with PTB. However, maternal genotype modulates response to these infections. This review highlights the association of cytokine gene polymorphisms and their levels with PTB. Varying PTB rates across the different ethnic groups may be as a result of genetically mediated varying cytokines response to infections. Studies on genetic variations in tumour necrosis factor-alpha, interleukin-1 alpha (IL-1α), IL-1β, IL-6, IL-10 and toll-like receptor-4 genes and their association with PTB, have been reviewed. No single polymorphism of the studied genes was found to be associated with PTB. However, increased maternal levels of IL-1β and IL-6 and low levels of IL-10 have been found to be associated with PTB.

Cytokines and preterm birth

PTB and spontaneous PTL (PTL is defined as ‘regular contractions of the uterus resulting in changes in the cervix that start before 37 wk of pregnancy’) have been shown to be associated with infections such as bacterial vaginosis and chorioamnionitis. Infection leads to inflammation as evident by increased levels
of TLR4, TNF-α, IL-1 and IL-6 in the amniotic fluid. The release of pro-inflammatory cytokines is followed by leucocytosis which results in apoptosis, preterm premature rupture of membrane along with cervical ripening and onset of premature labour. Since specific genes regulate corresponding cytokines, genetic polymorphisms in mother have been investigated to assess their association with PTB\textsuperscript{12,13}.  

Inflammatory signalling is a highly complex pathway (Figure). This pathway can be modulated by external as well as the internal signals. The balance between pro-inflammatory and anti-inflammatory cytokines is crucial for implantation of the foetus, preparation of placenta and pregnancy outcome. While the T-helper 1 (Th1) cytokine is responsible for inflammation, the Th2 cytokine manages the anti-inflammation counter-regulatory pathway. The dominance of Th2 cytokine expression plays an important role in reducing inflammation and prevents allograft dismissal of the foetus\textsuperscript{14,15}.  

### Genetic factors

Familial and twin studies have reported that PTB is sometimes heritable\textsuperscript{16-19}. It has been observed that women with PTB have higher chances for recurrent PTB\textsuperscript{7}. There seems to be a genetic predisposition to the PTB. Therefore, it seems plausible that polymorphisms in maternal genes regulating cytokine expression are related to PTB\textsuperscript{17-19}. Tables I and II summarize the genes associated with inflammatory pathway and therefore, PTB\textsuperscript{20-46}. It has been reported that altered production of pro-inflammatory cytokines mainly IL-1β, TNF-α and interferon (IFN)-lambda at the maternal-foetal interface results in PTB. On the contrary, IL-10 downregulates the secretion as well as expression of pro-inflammatory cytokines by other cells\textsuperscript{47,48}. The present review focussed only on polymorphisms in the coding or promoter regions of genes listed in Tables I and II.

### Toll-like receptor (TLR)

#### Location, function and regulation

TLR-4 gene is located on chromosome 9q33.1. Its alternative name is cluster of differentiation 284. TLR family has 13 distinctive proteins (TLR-1 to TLR-13). These are capable of recognizing microbial agents and initiating early immune response by activating various downstream pathways, such as transduction of nuclear-kappa β pathway which regulates expression of genes secreting pro-inflammatory cytokines\textsuperscript{49}.  

TLR-2 and TLR-4 genes have been extensively studied and their role has been identified in pathogen recognition and initiation of immune response. TLR4 regulates innate immune response during pregnancy and thus directly affects the duration of gestation. It is mainly expressed in human placenta\textsuperscript{50}.

#### TLR-4 pathway

It has been reported that most variations in TLR-4 are seen in the third exon\textsuperscript{50}. TLR-4 signal pathway includes enrolement of some signal transducer adapter proteins (MyD88, IRAK1/4 and TRAF6), rapid activation of intermediate kinases (RIP1, TAB2/3, TAK1 and IKK α/β) and phosphorylation/degradation of the chaperone protein (Iκβ)\textsuperscript{51}. Activation of immune system by endogenous and exogenous ligands such as heat shock proteins and bacterial lipopolysaccharides (LPS) is mediated through TLR-4. TLR-4 signalling activates the pro-inflammatory cytokines (IL-1, IL-6, IL-8) cascade which increases the level of prostaglandin (mostly PG-E and PG-F) and thus stimulates PTL causing PTB\textsuperscript{50}. TLR-4 is expressed by macrophages located in placental villi and in intermediate trophoblast of the placenta. Increased expression of TLR-4 was found in placentas of patients with chorioamnionitis\textsuperscript{50}, an independent risk factor for PTL. Hence, it is extrapolated that increased levels of TLR-4 may be associated with PTB. However, TLR4 expression has been studied in the placenta in vitro only\textsuperscript{50}. Corresponding serum levels have not been assessed.
| Gene  | Reference cited | Study design          | Population                                           | dbSNP | Gene position | Main findings                                                                                                                                 |
|-------|-----------------|-----------------------|------------------------------------------------------|-------|---------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| TLR-4 | Lorenz et al<sup>20</sup> | Case-control          | Finish, 94 mothers 74 premature birth (of whom, 62 were singletons and 12 were multiples). 20 Term birth term neonates-351 Preterm neonates (<35 wk; 282 were singletons and 158 were multiples) | rs4986790 | D299G         | No significant differences among different groups of mothers. In premature infants, the frequency of TLR-4 Asp/Gly or Gly/Gly was higher than term singleton (<0.02, 0.02, respectively) and preterm multiples (<0.03, <0.04, respectively). |
|       | Härtel et al<sup>21</sup> | Retrospective study   | Caucasian mothers=747 (of whom, 466 preterm and 181 term) | rs4986790 | D299G         | No association with TLR4 polymorphism                                                                                                           |
|       | Bitner et al<sup>22</sup> | Case-control study    | 121 mothers with preterm delivery 152 mothers with term delivery | rs4986790 | D299G         | No association                                                                                                                               |
| TNF-α | Drews-Piasecka <sup>et al</sup><sup>23</sup> | Case-control          | Polish Preterm=150 Term=150                          | rs361525 | -238GA genotype (<0.01) and -238A allele (<0.002) were found significant in PTB group. Mothers belonging to 28-32 wk group were having high frequency of -238GA (<0.01) and -238A allele. |
|       | Pu and Zeng<sup>24</sup> | Random                | Caucasian Term=46 Preterm=50                         | rs1800629 | Promoter      | In PTL, increased level of TNF-α in mRNA and maternal serum was seen in women carrying the GA and AA genotypes (<0.05).                          |
|       | Jones et al<sup>25</sup> | Cohort                | Non-Hispanic African American, 777 term and 230 preterm | rs361525 | Promoter      | Increased risk of PTB was found in women with TNF-α-238A/G or A/A genotype along with the nuget score ≥4 OR=2.6 (CI=1.2-5.8) P=0.02.              |
|       | Liang et al<sup>26</sup> | Case-control, hybrid design | Han Chinese Preterm=250 Term=247                     | rs1800629 | Promoter      | No association was found in between TNF-α (-308G/A) polymorphism and PTB                                                                    |
|       | Yilmaz et al<sup>27</sup> | Case-control study    | Turks Preterm=100 Term=101                           | rs1800629 | Promoter      | Relatively higher risk of PTB was seen in mother and foetus with A/A genotype. GA and AA genotypes were found associated in mother (<0.05) and neonates (<0.001) with term delivery; the incidence of PTL was increased in mother carrying GA genotype and foetus carrying the GG genotype (<0.01). |

Contd...
| Gene                          | Reference cited       | Study design       | Population                                      | dbSNP   | Gene position | Main findings                                                                                                                                 |
|-------------------------------|-----------------------|--------------------|-------------------------------------------------|---------|---------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Bitner and Kalinka\textsuperscript{28} |                       | Case-control       | Caucasian Preterm=32 Term=63                    | rs1800629 | Promoter      | No significant association was found between TNF-308G/A [OR=0.72 (CI=0.26-1.9)].                                                                |
| Heinzmann et al\textsuperscript{29} |                       | Case-control       | Caucasian, case (preterm)=121 Random control (term)=270 | rs1800629 | Promoter      | No association was reported -308G/A; $P=0.85$                                                                                                  |
| Harper et al\textsuperscript{30} | Cohort                |                    | American, total individuals=834                | rs1800629 | Promoter      | Women with TNF-α-308AA genotype were at higher risk of PTB [$P=0.03$; hazard ratio=1.74 (CI=1.04-2.9)] than women with -308 GA or GG genotype |
| Andalas et al\textsuperscript{31} | Case-control          |                    | Acehnese Term=40 Preterm=40                    | rs1800629 | Promoter      | No association                                                                                                                                  |
| Kalinka and Bitner\textsuperscript{32} |                       | Case-control       | Caucasian Preterm=63 Term=62                    | rs1800629 | Promoter      | No association                                                                                                                                  |
| Amory et al\textsuperscript{33} | Cohort                |                    | American; mother-infant pair=118               | rs1800629 | Promoter      | No association was reported between TNF-α (-308G/A) polymorphism and PTB.                                                                    |
| Jafarzadeh et al\textsuperscript{34} | Cross-sectional study |                   | Caucasian, case-64 mothers and neonates with preterm delivery. Control-71 mothers and neonates with term delivery | rs1800629 | Promoter      | No significant association was found in both maternal and foetal genotypes. GA genotype frequency in mother ($P=0.47$) and in infant ($P=0.40$) was not increased in PTB. |
| Speer et al\textsuperscript{35} | Case-control          |                    | Caucasian, 88 preterm mother-infant pair; 88 term mother-infant pair | rs1800629 | Promoter      | Individually, no association was found between TNF-α (308G/A) with PTB.                                                                    |
| Nuk et al\textsuperscript{36} | Case-control          |                    | European Preterm=106 Term=200                  | rs1800629 | Promoter      | Genotyping done in mother/child pair for TNF-α. No significant association was reported.                                                      |
| Moura et al\textsuperscript{37} | 2 case-control sets   |                    | Brazilian, first set Preterm=122 Term=101 Second set Preterm=82 Term=105 | rs1800629 | Promoter      | No association was found with PTB.                                                                                                             |
| Mattar et al\textsuperscript{38} | Cohort                |                    | Mixed population (Caucasian, mixed race, African women) Preterm=119 Term=139 | rs1800629 | Promoter      | No association was reported.                                                                                                                  |
| Menon et al\textsuperscript{39} | Meta-analysis         |                    | African-American, pooled data of 7 studies included 638 preterm and 1208 term individuals. | rs1800629 | Promoter      | No significant association was reported between TNF-α minor allele A and with increased expression of TNF-α OR=1.41 (CI=0.9-2.19).          |

TLR, toll-like receptor; OR, odds ratio; CI, confidence interval; PTB, preterm birth; PTL, preterm labour; TNF-α, tumour necrosis factor-alpha; dbSNP, single nucleotide polymorphism database
### Table II. Pooled data for the association of interleukin (IL)-1, interleukin-6 and interleukin-10 polymorphisms with preterm birth in different populations

| Gene | Study design      | Population                                      | dbSNP       | Gene position | Main findings                                                                                                                                                                                                 | Reference cited |
|------|-------------------|-------------------------------------------------|-------------|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| IL-6 | Retrospective study | Caucasian Mothers = 747 (out of whom, 466 preterm and 181 term) | rs1800795   | Promoter      | IL-6GG genotype frequency was high in mothers with preterm very low birth weight infants. Preterm mothers reported less expression of IL-6 -174C allele.                                                      | Härtel et al\(^21\) |
| IL-1 | Case-control study | Turks Preterm = 100 Term = 101                  | rs17561     | Promoter      | Minor allele of +4845T polymorphism increases the incidence of PTB in both mother (P<0.001) and foetus (P<0.001).                                                                                           | Yilmaz et al\(^27\) |
| IL-6 | Case-control      | Caucasian Preterm = 32 Term = 63                | rs1800795   | Promoter      | No significant association was reported between IL-6 -174G/C [OR = 0.77 (CI = 0.27-2.1)] and PTB.                                                                                                             | Bitner and Kalinka\(^28\) |
| IL-6 | Cohort            | American, total individuals = 834              | rs1800795   | Promoter      | No association was found with IL-6 -174G/C and PTB.                                                                                                                                                    | Harper et al\(^29\) |
| IL-1 | Case-control      | Caucasian                                      | rs1143634   | Exon 5        | No association                                                                                                                                          | Kalinka and Bitner\(^32\) |
| IL-6 | Case-control      | Caucasian, 88 preterm mother-infant pair; 88 term mother-infant pair | rs1800795   | Promoter      | IL-1RN*2 was found to be associated with increased risk of PTB. IL-1RN*2 along with IL-6 -174G allele increased the risk of PTB.                                                                                | Speer et al\(^5\) |
| IL-10| Case-control      | European Preterm = 106 Term = 200              | rs1800896   | Promoter      | Genotyping done in mother/child pair for -1082 and -819. No significant association was reported.                                                                                                         | Nuk et al\(^36\) |
| IL-6 | Case-control      | Brazilian, first set Preterm = 122 Term = 101  | rs1800795   | Promoter      | No association was found with PTB                                                                                                                   | Moura et al\(^37\) |
| IL-10| Case-control      | Second set Preterm = 82 Term = 105             | rs1800896   | Promoter      | No association was found with PTB.                                                                                                                  | Mattar et al\(^38\) |
| IL-6 | Cohort            | Mixed population (Caucasian, mixed race, African women) Term = 119 Preterm = 139 | rs1800795   | Promoter      | No association was reported.                                                                                                                        |                 |
| IL-10| Cohort            |                                                  | rs1800896   | Promoter      | No association was reported.                                                                                                                        |                 |

Contd...
| Gene  | Study design  | Population                           | dbSNP  | Gene position | Main findings                                                                                                                                                                                                 | Reference cited |
|-------|---------------|--------------------------------------|--------|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| IL-1  | Cohort        | Caucasian                            | rs1800587       | Promoter      | Increased risk was reported in women carrying IL-1α -889T rare/minor allele $P=0.01$, OR = 2.5 (CI = 1.3-4.6).                                                                                               | Sata et al40    |
|       |               | Term = 74                           | rs17561       | Promoter      | Increased risk was reported in women carrying IL-1α +4845T allele $P=0.01$, OR = 2.4 (CI = 1.2-4.2).                                                                                                        |                 |
|       |               | Preterm = 341                       |            |               | Haplotypic association showed that IL-1α TT ($P<0.001$) was significantly higher in mother with PTB and IL-1α CG was higher in term mothers ($P<0.001$).                                                  |                 |
| IL-1  | Case-control  | Caucasian                            | rs16944       | Promoter      | No association was found between IL-1β-511C/T $P=0.47$; OR = 1.3 (CI = 0.7-2.3).                                                                                                                          | Schmid et al41   |
|       |               | Term = 100                          | rs1143634     | Exon 5        | IL-1β (+3953C/T was found associated $P=0.04$; OR = 0.6 (CI = 0.3-1.0)                                                                                                                                   | Hollegaard et al42 |
| IL-1  | Case-control  | Danish Caucasian, 117 singleton      | rs16944       | Promoter      | Increased risk was found in women carrying the -857C>T (rare allele T) along with IL-1β CC [OR = 3.1 (1.0-10.3)] and IL-1β TT [OR = 6.4 (CI = 1.3-60.5)] of IL-1β-31T/C and IL-1β-511 C/T, respectively. |                 |
|       |               | pregnant women; 62 with PTB and 55  | rs1143627     | Promoter      |                                                                                               |                 |
|       |               | control                              |            |               |                                                                                               |                 |
| IL-1  | Case-control  | Japanese                            | rs1143634     | Promoter      | No association was found.                                                                                                                             | Sugita et al43   |
|       |               | Term = 71                           | rs17561       | Promoter      |                                                                                               |                 |
|       |               | Preterm = 57                        | rs1143627     | Promoter      |                                                                                               |                 |
|       |               |                                       | rs16944       | Promoter      |                                                                                               |                 |
| IL-6  | Case-control  | 559 preterm and 559 term mothers    | rs1800796     | Promoter      | No association was found.                                                                                                                             |                 |
| IL-1  | Case-control  | European-descent and non-European-admixed population, 1165 PTB 3830 term | rs17561       | Promoter      | Increased risk was found in women with CT genotype of IL-1α-889C/T $P=0.002$; OR = 1.7 (1.24-2.46) and IL-1α +4845C/T $P=0.003$; OR = 1.5 (1.1-1.9). | Pandey and Awasthi44 |
|       |               |                                       | rs1143627     | Promoter      |                                                                                               |                 |
|       |               |                                       | rs16944       | Promoter      |                                                                                               |                 |
|       |               |                                       | rs1800587     | Promoter      |                                                                                               |                 |
| IL-10 | Prospective   | European, total individuals = 1616 pregnant women | rs1800896     | Promoter      | No association was reported.                                                                                                                             | Stonek et al46   |
|       | cohort        |                                       |            |               |                                                                                               |                 |

OR, odds ratio; CI, confidence interval; PTB, preterm birth; dbSNP, single nucleotide polymorphism database; TNF-α, tumour necrosis factor-alpha
Polymorphism of TLR-4 gene

TLR-4 is located on long arm of chromosome 9. The polymorphic site rs4986790 is present on position 896. This A/G transition causes substitution of amino acid aspartic acid by glycine at position of 299 (i.e. Asp299Gly). This polymorphism has also been found to be associated with increased risk of severe disease due to respiratory syncytial virus and Gram-negative bacterial infection in children. Thus, it can be hypothesized that substitution of aspartic acid by glycine in TLR-4 gene at position 299 can exaggerate the chances of infection and thus inflammation during pregnancy leading to PTB.

Many studies were conducted to determine the association of TLR-4 and PTB. Table I summarizes the studies of TLR4 and PTB. Lorenz et al. reported significant association of PTB with TLR4Asp299Gly in infants but not in mothers and this was supported by other studies also. On the contrary, other groups reported increased expression of TLR-4 in chorioamnionitis membranes of patients with histologic chorioamnionitis regardless of their gestational status and in mothers with PTL, respectively. Equivocal results have been found for the association of polymorphism of TLR-4 gene and PTB.

Tumour necrosis factor-alpha (TNF-α)

Location, function and regulation

TNF-α is located on chromosome 6p21.3. It is a pro-inflammatory cytokine, which promotes the production of collagen-degrading matrix metalloproteinases, and suppresses biosynthesis of tissue inhibitors of metalloproteinases. The metalloproteinases act on foetal membrane collagen resulting in loss of tensile strength. It also impairs the progesterone stimulating receptor B thus blocking the progesterone release. Both these actions promote onset of PTL.

Polymorphism of TNF-α

Increased level of TNF-α was linked with various reproductive diseases such as frequent spontaneous abortions, pre-eclampsia, infections or endometriosis. Elevated levels of TNF-α can change the delicate equilibrium between the anti-inflammatory and pro-inflammatory cytokines and thus induce PTB. Till date, two polymorphisms, -238G/A and -308G/A, present on promoter region have been studied. Table I lists the studies which analyzed the association of TNF-α and PTB. The TNF-α-238 G allele was reported to be associated with high transcriptional activity. Significant association of TNF-α (-308G/A) polymorphism has been reported with PTB. Interaction between infection, stress, obesity and TNF-α (-308G/A) polymorphism has also been reported, and all of these increase the risk of PTB. However, in contradiction to these studies, negative or no associations were also reported. A meta-analysis which included all studies from 1990 to 2005 found no association between TNF-α (-308G/A) and PTB (odds ratio=1.41; 95% confidence interval=0.90-2.19). Hence, association of polymorphisms of TNF-α with PTB is equivocal till date.

Interleukin-1 (IL-1)

Location, function and regulation

The IL-1 gene is located on long arm of chromosome 2 (2q14). IL-1 is a pro-inflammatory cytokine. Its secretion is controlled by IL-1 gene which has two subunits, IL-1α and IL-1β. On the same chromosome, IL-1 receptor antagonist (IL-1RA) gene is also located which is a competitive inhibitor of IL-1β. IL-1β is the most investigated candidate gene of the pro-inflammatory cytokine family. The activity of pro-inflammatory IL-1β is counterbalanced by the action of IL-1RA which inhibits the binding of circulating IL-1β to cell surface receptors. Therefore, IL-1RA helps in terminating the acute inflammation response but gets activated late during the course of an inflammatory event.

Polymorphisms in IL-1 gene complex

There are many reported polymorphisms and microsatellites in the IL-1 gene complex, and the most studied polymorphisms are summarized in Table II. The promoter site of IL-1α consists of two polymorphisms; +4845G/T and -899C/T. IL-1β consists of three polymorphisms, namely, -31T/C, -511C/T and +3954C/T. Studies have reported a microsatellite in intron 2 of the IL-1RA gene which results in variation in transcriptional activity. This polymorphism results in five alleles. The most common allele is allele 2 (IL1RN*2) with the recurrence of 4-26 per cent, whereas alleles 3, 4 and 5 are in <5 per cent of population. Allele 2 has been associated with various chronic inflammatory conditions. IL-1RA polymorphism appears to affect both IL-1 and IL-1RA expression. The T allele of a polymorphism at position 31 (IL1B-31T) is in a transcriptional start site and is likewise connected with a decrease in IL-1β production. This may be a consequence of the underlying
link between IL1RN*2 and IL1β-31T. Carriers of rare alleles of IL-1β polymorphisms (IL-1β -511T and -31C) have shown higher levels of IL-1RA than individuals with wild-type IL-1β genotypes62-73.

IL-1β has consistently been associated with increased risk of spontaneous preterm delivery. A study conducted on European population by Puchner et al74 reported that with a unit increase in IL-1β level in women, there was 7.2 times increased risk of PTB. Thus, it may serve as predictive marker of PTB.

In a case-control study conducted on European and Japanese population, significant association was found between IL-1 (+4845G/T) and PTB. Others reported the significant association of IL-1β (+3953/3954) with enhanced production of IL-1β41,66. On the contrary, inconsistent results were reported in case of IL-1β (-511C/T) and IL-1β (-31C/T) polymorphisms. Various studies have reported inconsistent association of different polymorphisms of IL-1α and β with PTB. However, increased IL-1β levels are found consistently associated with PTB.

**Interleukin-6 (IL-6)**

**Location, function and regulation**

Gene for IL-6 is located on 7q21 and commonly known as IL-6, IFN β-2 or rarely as hybridoma growth factor or hepatocytes-stimulating factor or B-cell stimulatory factor-2. IL-6 is a pro-inflammatory cytokine causing induction of T-lymphocytes, C-reactive protein synthesis and B-cell differentiation. It is widely expressed in the decidual tissue, placenta, foetal membrane and amniotic fluid. It mainly functions in embryo implantation and placental development, as well as in the immune adaptations, which are required for continuing pregnancy79. IL-6 production is stimulated by various factors, namely, IL-1, TNF-α and LPS. Increased levels of IL-6 are found in unexplained infertility, recurrent miscarriage, pre-eclampsia and preterm delivery. Altered systemic IL-6 trans-signalling in women can lead to recurrent miscarriage. IL-6 inhibits the generation of CD4+ T regulatory cells required for pregnancy tolerance37,43,76-78.

**Polymorphism in IL-6 gene**

At position -174 in the IL-6 gene, C>G substitution (i.e. Cytosine to Guanine) causes higher transcriptional activity in response to IL-1 and LPS stimuli. A polymorphism at the -174 position (G/C) in the promoter region of the IL-6 gene results in decreased cytokine production and therefore, decreased risk of PTB37.

Table II shows the polymorphisms of IL-6 and their association with PTB. Sugita et al83 reported a significant association of IL-6 (-6572 G/C) in PTB in the Japanese population. Moura et al74 found strong evidence for the association of IL-6 (-174G/C) with the PTB in the European population. Menon et al79 compared amniotic fluid concentrations of IL-6 in cases of PTB and term births and found significant association (P=0.003). On the contrary, Kalinka and Bitner85 reported no association between IL-6 (-174G/C) and PTB but found an increased incidence of PTB with combined GG+GC genotype. Harper et al80 carried out a study on 834 women with high risk of PTB and assessed the IL-6 (-174 G/C) polymorphisms but was unable to detect any association with PTB. A study by Karakaş et al80 found this polymorphism protective against PTB, while others reported that maternal IL-6 (-174G/C) polymorphism was associated with chorioamnionitis81,83.

Inconsistent results were found for the association of IL-6 polymorphism with PTB. However, increased IL-6 levels have been reported in chorioamnionitis45,84,85 which in turn leads to PTB. Further translation research in this area may be able to identify therapeutic agents to prevent PTB.

**Interleukin-10 (IL-10)**

**Location, function and regulation**

The IL-10 gene is located on chromosome 1q31-1q32. It is also known as cytokine synthesis inhibitory factor or T-cell growth factor inhibitor. IL-10 is an anti-inflammatory cytokine produced mainly by monocytes and to a lesser extent by lymphocytes. Being pleiotropic in nature, it modulates both immune regulation and inflammation. It reduces Th1 cytokines by reducing the MHC class II antigens on macrophages and thus enhances B-cell survival, proliferation and antibody production. IL-10 can hinder NF-kappa B activity, which is a key mediator of the JAK-STAT signalling pathway86.

**Polymorphism in IL-10 gene**

Table II summarizes the studied polymorphisms and their outcome in PTB. Polymorphisms located at the promoter region of IL-10 gene are -1082G/A, -819C/T and -592C/A. Studies conducted on Caucasian population found polymorphism (rs1800896) associated with PTB46,87. Moura et al87 conducted
two independent studies on Brazilian population and found no association between polymorphisms (IL-10-1082G/C, IL-10-819C/T and IL-10-592C/A) and PTB. Similar findings were reported by other studies also.32,34,35,36,37,44,47

Thus, IL-10 was not consistently found to be associated with PTB. However, low levels of IL-10 were reported to be associated with PTB.47,48,84,85,88,89

Conclusion

Since PTB rate has remained almost static over the past few years in the developed countries, researchers are now looking into possible genetic aetiology. The concept of involvement of cytokines-stimulating prostaglandin production resulting in PTB has been widely accepted. Many studies have been conducted in different populations to find out the association of TLR-4, IL-1α, IL-1β, IL-6 and IL-10 gene polymorphisms with PTB, yet the results are inconclusive. This can be due to differences in the ethnic groups studied or the influence of environmental factors. Further genome-wide differences in the ethnic groups studied or the influence of environmental factors. Further genome-wide and gene expression studies are needed that are also capable of assessing interactions with infections and environment. Accurate prediction of risk of PTB by molecular methods may help in planning appropriate antenatal care in women at risk.

Conflicts of Interest: None.

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