

Assessment of Toxicogenomic Risk Factors in Etiology of Preterm Delivery

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Abstract

Worldwide, preterm birth accounts for more than 60% of prenatal morbidity and mortality and is the leading cause of neonatal deaths. Globally, every year, around 13 million babies are born preterm, with rates being highest in the low and middle-income group. India is leading all the nations in PTD, as reported by WHO. PTD is considered as a major pregnancy complication. PTD continues to be a major clinical and public health problem and is regarded as a syndrome with multiple causes. Environmental stressors such as heavy metal, Organochlorine pesticides have a long history of widespread use all around the world. Because of high stability, extremely low biodegradability and long half life, these compounds are typically very persistent in the environment, and are known to accumulate in soil, food, blood, fatty tissue etc. Humans, being at the top of the food chain are most vulnerable to health effects as the level of the toxic chemicals is several folds higher through the process of bio-magnifications. The problem gets compounded in women because of increased adipose tissue in them and high liposolubility of these OCPs. Pesticide toxicity is of utmost concern during pregnancy as studies have revealed that mother and fetus are more vulnerable to their toxic effects. OCPs are metabolized by xenobiotic metabolizing enzymes such as CYP P450 and GSTs. Polymorphism in xenobiotic metabolizing genes may cause improper metabolism of xenobiotics which may cause high free radical generation, increased oxidative stress, improper cytokines release and also increased inflammation. OCPs levels are also correlated significantly with increased expression of COX-2 gene. The mechanisms underlying the etiology and onset of preterm birth is not clearly understood. Still more than 40-50% cases of preterm delivery are 'idiopathic'. So, it is very essential to assess the etiological factors and the mechanisms by which they result in preterm birth in order to make further research in targeted interventions to prevent preterm labor.

Keywords: Preterm delivery; Organochlorine pesticides; CYP gene polymorphism; GST gene polymorphism; Period of gestation; Inflammation; mRNA expression; Gene-environment interaction

Introduction

Preterm delivery

Preterm Delivery (PTD), period of gestation <37 weeks, is the largest cause of prenatal deaths, neonatal morbidities, mortality, and adult illness [1]. According to a WHO (2012) report, India tops the list of countries, with maximum number of preterm deliveries [2]. PTD complicates between 5-11% of all births and result in 70-80% of neonatal mortality and morbidity [3]. PTD affects approximately 5-7% of live births in developed countries, but its incidence is significantly higher in developing countries [4]. It is regarded as a syndrome with multiple causes. Preterm birth causes a range of neonatal morbidity like respiratory illness, infections, intraventricular hemorrhage, and necrotizing enterocolitis. The long term consequences like neurological disorders, cerebral palsy, developmental delay, hearing and vision impairment, retinopathy of prematurity, bronchopulmonary dysplasia and cognitive disorders, also prolonging monetary burden, emotional and stress related problems [4].

Etiology of PTD

The patho-physiology of preterm labor is not entirely clear, still 40-45% cases are idiopathic. It has been suggested the balance of reproductive hormones, such as progesterone, estrogen, infection, genetic factors, inflammation, and oxidative stress have an important role in PTD. Progesterone promotes the uterine quiescence activity. However, estrogen, may promote myometrial activation with increased receptivity to uterotonic agents by up-regulating membrane receptors and gap junctions. Therefore, it has been suggested that Endocrine Disruptor Chemicals (EDCs), especially those having estrogenic effect, may induce preterm labor [5,6]. The proposed mechanism of action of these exogenous substances is that it can alter function(s) of the endocrine system, alter the homeostasis of sex steroidal hormones and

thus cause adverse health effects. EDCs may mimic, block or modulate the synthesis, release, transport, metabolism and binding or elimination of steroidal hormones.

The presence of very small quantity of EDC in environment are potential enough to cause adverse health effects [7]. OCPs such as DDT and HCH may act as EDCs thus causes hormonal imbalance. Several studies have also reported that OCPs may increase the oxidative stress and the high oxidative stress causes the damage to macromolecules such as lipid, DNA, protein etc.

The reproductive effects due to persistent exposure of pesticides especially OCPs are a matter of worldwide concern. Although several studies have reported the reproductive effects of DDT in humans [6], there are very few studies about other OCPs such as β -HCH, aldrin, dieldrin, and endosulfan. Recently, studies from our laboratory have shown OCPs such as isomers of HCH, DDT, aldrin and its metabolites are one of the risk factors for adverse reproductive outcomes such as PTD, FGR, recurrent miscarriage, etc. [8-12].

Pesticides and its Association with Preterm Delivery

Pesticides are substances or mixture of substances intended for

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preventing, destroying, repelling or mitigating any pest. Pesticides have contributed greatly to the increase of yields in agriculture to fulfill the need of increasing population by controlling pests and also have been used in public health program for checking the insect-borne diseases such as malaria, dengue, encephalitis, filariasis.

OCPs are chemically stable, lipophilic in nature, and have a long half life and are very slowly degradable in nature. OCPs are still detected in ecosystem i.e., in water, soil, air, food items etc. and are biomagnified through food chain [13]. Increasing OCPs residues have been found in different human samples such as placental tissues, blood, amniotic fluid, semen, breast milk, etc. [8,12,14,15] and have wide range of acute and chronic health effects. The exposure to pesticides both occupationally and environmentally has been found to be associated with several human health related problems like hormone disruption, immune suppression, adverse reproductive outcomes, cancers, neurological disorder etc. [8,16,17].

Pesticides (Global Scenario)

Approximately 5.6 billion pounds of pesticides are used worldwide. As a result, millions of people worldwide experience unintentional pesticide exposure each year. It has been suggested that 80% of all pesticides used in developed countries and two-thirds of the pesticides produced around the world are used in the USA, Canada and Japan. France and China are the fourth and fifth largest pesticide market respectively with annual consumption worth around US\$ 2Billion/year. Pesticide use in China is growing at the rate of five percent annually and it is projected to become the fourth largest consumer of pesticides within a decade. Globally herbicides are the leading pesticide of choice followed by insecticides and fungicides [18]. Biological monitoring studies indicate that pesticide exposure is widespread in pregnant women in New York City, Salinas Valley in California, the Netherlands, and Norway [19,20]. The amount of pesticides used internationally has risen fifty-fold since 1950. The recent study by [21,22] has reported the presence *p,p'*-DDE in 100% of the samples, with a median concentration of 19.7 ng/mL (4788.7 ng/g lipid), while *o,p'*-DDT was detected in 3 samples (4.3%). Further, they have reported that serum *p,p'*-DDE concentrations were associated with time of residence in the study area, personal hygiene after work, and body mass index in adjusted multivariable logistic regression models with tertiles of *p,p'*-DDE as the dependent variable. Interestingly, in the same study participants who did not take a daily bath after work showed an OR of 3 for the 2nd tertile and an OR of 6.3 for the 3rd tertile of exposure to *p,p'*-DDE. Results have also revealed high levels of exposure to *p,p'*-DDE which might be derived from a heavily polluted local environment and past occupational exposure.

Considering the higher percentage of body fat in women, the storage of these toxins is of great in them [23]. Owing to their xenoestrogenic nature, OCPs disturb the normal estrogen–progesterone balance, which is important in the maintaining the pregnancy [5,6,9,24]. Moreover, during pregnancy, concern over OCPs residue levels in maternal and cord blood becomes greater since studies have revealed that mother and fetus are more vulnerable to the toxic of these OCPs [9].

Pesticides and their Usage in India

Hexachlorocyclohexane (HCH)

HCH known as Benzene Hexachloride (BHC) is a synthetic chemical that exists in eight chemical forms called isomers. The different isomers are named according to the position of the hydrogen atoms in the structure of the chemical. One of these forms, gamma-

HCH (or γ -HCH, commonly called lindane), is produced and used as an insecticide on fruit, vegetables, and forest crops, and animals and animal premises. Moreover, it is also available as a prescription medicine (as cream, lotion, shampoo) to treat scabies (mites) and head louse in humans. γ -HCH alters the level of thyroid, pituitary and sex hormones in females and also suppresses follicle stimulating hormones and transforming growth factor β -1 stimulated progesterone production. It is also a potent carcinogen. Environmental Protection Agency (EPA) advises that level of γ -HCH in drinking water for adult humans should not be more than 0.0002 mg/litre, for lifetime. WHO recommended permissible levels of γ -HCH are 0.02 mg/mL in whole blood and 0.025 mg/L in serum samples. γ -HCH has also been found to inhibit Cytochrome P450 (CYP) enzyme level and Steroidogenic Acute Regulatory protein (StAR) expression in cultured rat granulosa cells [25]. StAR protein mediates the intra-mitochondrial transfer of cholesterol to the CYP450 enzyme and CYP450 enzyme catalyzes steroid hormone biosynthesis [26]. Impaired level of sex hormone may interfere with the normal pregnancy and can induce fetal abnormalities.

β -HCH is the most persistent isomer of HCH which constitutes 7-12% of technical HCH. β -HCH has been found to be a xenoestrogen in various *in vitro* and *in vivo* studies. β -HCH has negligible insecticidal activity but measurable estrogenic effect [27]. β -HCH increases uterine contraction frequency in a concentration-dependent manner in rats [28]. It may be the most toxicologically significant HCH isomer as evidenced by recent reports of its estrogenic effects in mammalian cells, laboratory animals and fish [29-31]. It has been reported that blood levels of β -HCH in ppb (ng/mL) range have the potential of producing estrogenic effects in mice [29]. β -HCH with mixture of other OCPs has the ability to generate an estrogenic microenvironment through Estrogen Receptor (ER α) activation [32]. It produces moderate uterotrophic effects in the rodent uterus [29]. Adverse effects of β -HCH were also seen in an *in vivo* rat bone marrow chromosomal aberration study [31]. These observations lend support to the role of β -HCH in reproductive toxicity and a possible association with preterm labor due to its estrogenicity.

Aldrin and dieldrin

Aldrin and dieldrin are structurally similar OCPs belonging to cyclodiene family and these pesticides are widely used in agriculture and public health program. Under most environmental conditions, aldrin is largely converted via biological and/or abiotic mechanisms to dieldrin, which is significantly more persistent. Because of low water solubility and tendency to bind strongly to soil both aldrin and dieldrin migrate downwards very slowly through soil or into surface or ground water [33].

Data regarding the health effects of dieldrin in humans come from either epidemiological reports of occupational exposure or case reports of accidental poisonings. The proliferative efficiency due to dieldrin at 10 μ M was 54.89% that of estradiol, suggesting high estrogenic potential of dieldrin. Earlier it has been reported aldrin and dieldrin are accumulated in the pregnant women on age and dietary habit basis [34].

Endosulfan

Endosulfan is sold as a mixture of two different forms of the same chemical (referred to as α - and β -endosulfan). It has been suggested that exposure to endosulfan is higher for people living near hazardous waste sites. Apart from occupational exposure which has resulted in many poisonings, residues in food and drinking water are widespread globally at sufficiently high levels to constitute a threat to human health [35]. Endosulfan contamination with adipose tissue, placental tissue and

umbilical cord blood, meaning that the unborn child is exposed, and then re-exposed on birth through breast milk-both exposures taking place at critical periods of development where estrogenic substances can have a profound life-long impact on new born [33].

Dichlorodiphenyl Trichloroethane (DDT)

DDT is a pesticide that was once widely used to control insects on agricultural crops and insects that carry diseases like malaria and typhus, but is now used in India to control malaria. Technical-grade DDT is a mixture of three forms, *p,p'*-DDT (60-80%), *o,p'*-DDT (15-21%), and *p,p'*-DDD (trace amounts). Most DDT in the environment is a result of past use. DDT still enters the environment because of its current use in other areas of the world. *p,p'*-DDE tends to persist for much longer in comparison to the parent compound and is considered a marker of past exposure to DDT.

Earlier studies have reported that *p,p'*-DDT and/or *p,p'*-DDE in maternal, umbilical cord blood and serum are associated with PTD [5,6,36,37]. The most comprehensive assessment of the association between exposure to DDT and its metabolite included 2,380 women (361 of whom delivered at preterm) who had participated in the U.S. Collaborative Perinatal Project between 1959 and 1965 [5]. Furthermore, by using a logistic regression analysis of third-trimester maternal serum DDE concentrations, They have found that the odds increased steadily and significantly with increasing concentrations of serum DDE ($p < 0.0001$), with adjusted ORs of 2.5 (95% CI=1.5-4.2) when levels in serum were 45 to 59 μg of DDE/liter and 3.1 (95% CI=1.8-5.4) when levels in serum were $\geq 60 \mu\text{g}$ of DDE/liter. The same study failed to find a significant association between either third trimester maternal serum DDT concentrations or the ratios of maternal serum DDT levels to serum DDE levels. In contrast, a logistic regression analysis failed to detect an association between maternal serum concentrations of DDE or DDT or the DDT: DDE ratio among four hundred and twenty ($n=420$) women who had participated in the Child Health and Development Studies of the San Francisco Bay Area from 1959 to 1967 [38].

A case-control study [39] matched for potential confounding variables (maternal age, race, and pre-pregnancy body mass index) and analyzed other potential confounders in a group of New York women who gave birth between 1990 and 1993. They found no significant differences in first-trimester maternal serum DDE levels for women who delivered preterm ($n=20$) compared with those for

women who delivered at term ($n=20$). Saxena et al. [37] found elevated concentrations of three major isomers of DDT (including DDE), as well as lindane, aldrin, and HCB, in the blood and placentas of women who went into preterm labor (defined as labor during 12 to 32 weeks of gestation in the first study; preterm labor was not defined in the second study) compared with those in the blood and placentas of women who delivered at term ($p < 0.001$).

Likewise, a study of Israeli women who delivered preterm reported elevated maternal blood concentrations of the pesticides lindane, dieldrin, heptachlor, and several isomers of DDT, including DDE, at the time of delivery compared with the concentrations in women who delivered at term ($p < 0.02$) [36].

A study of births in Flix, Spain, of women exposed to extremely high levels of atmospheric pollution from an electrochemical plant found umbilical cord blood DDE concentrations that were three times higher for PTD ($n=4$) than for term births ($n=66$) ($p < 0.05$), but no significant differences in the concentrations of β -HCH were detected. A birth cohort study in Spain revealed an association between cord serum DDE levels (mean cord serum DDE, cases vs. controls, 2.40 vs. 0.80 $\mu\text{g/L}$, $p < 0.05$) [40]. A case-cohort study in Mexico City reported a non monotonic dose-response relationship between PTD and 1st trimester maternal serum DDE levels (3rd vs. 1st tertile, OR=1.7, 95% CI=0.8-3.3, p -trend=0.17) [6]. Further, they have also found a dose-response relationship between preterm birth and

1st trimester maternal serum β -HCH levels (3rd vs.1st tertile, OR=1.9, 95% CI 0.9–3.7, p -trend=0.08).

Newborns are exposed to these pesticides through placental transmission as well as breastfeeding [12,35]. In view of the reproductive toxicity of OCPs, their presence in pregnant women and subsequent transfer to the developing fetuses has the potential to hamper growth and development of the baby in the womb [5] have shown that the risk of Preterm Delivery (PTD) increases steadily with increasing concentration of serum DDE levels. Furthermore, [6] have also reported increased risk of PTD among women in the highest tertile of β -HCH values. OCPs are metabolized by Xenobiotic metabolizing enzymes which are divided into two phases, 'Phase I' enzymes, include Cytochrome P-450 and 'Phase II' enzymes mainly include Glutathione S-transferases (GSTs) [41-45]. Earlier studies have reported that polymorphism in xenobiotic metabolizing genes increases the risk of PTD [46,47]. A Review of studies on OCPs and its association with preterm delivery has been summarized in Table 1 and Figure 1.

Population/Ethnicity	Sample size	Cases/ Control	Findings of the study	Reference
Indian population	40	15/25	Higher levels of OCPs were found in PTD cases as compared to controls.	37
US population	2380	361/2019	The adjusted Odds Ratio (OR) of preterm birth increased steadily with increasing concentration of serum DDE. Further, they reported that DDE correlated with increased risk of PTD with the OR of 1.5 to 3.1 for DDE amounts of 15 $\mu\text{g/L}$ or more as compared to less than 15 $\mu\text{g/L}$.	5
USA	40	20/20	Median DDE 25 g/L serum Median DDE 1*3 g/L (cases).	39
Mexican population	233	100/133	Dose-response relationship between preterm birth and 1st trimester maternal serum DDE and β -HCH levels (3rd vs. 1st tertile, OR=1.7, 95% CI 0.8–3.3, p -trend=0.17) and (3rd vs. 1st tertile, OR=1.9, 95% CI 0.9–3.7, p -trend=0.08) respectively were reported.	6
Indian population	46	23/23	Maternal and cord blood levels of α -HCH, β -HCH, γ -HCH, total-HCH, <i>p,p'</i> DDE and <i>p,p'</i> DDT were found higher in preterm labor cases than term labor. However, a statistically significant relation was observed between preterm birth and β -HCH levels only.	9
Indian population	60	30/30	Higher levels of β -HCH, and α -endosulfan were observed in PTD cases as compared to controls.	10
European population	1322	-	Shortening of gestational age of -0.2 week per unit increase in <i>p,p'</i> -DDE concentration was observed.	17
San Francisco population	420	-	Binary logistic regression analysis failed to detect an association between preterm birth and maternal serum concentrations of DDE or DDT or the DDT:DDE ratio among 420 women who had participated in the Child Health and Development Studies of the San Francisco Bay Area from 1959 to 1967.	38
Indian population	307	157/151	After adjustment of the confounding factors education, baby weight, drinking water, residential area and maternal age the levels of α -HCH, γ -HCH, <i>p,p'</i> -DDEE in maternal blood and <i>o,p'</i> -DDT and <i>p,p'</i> -DDEE in cord blood of PTD cases as compared to term delivery.	85

Table 1: A review of studies on organochlorine pesticides levels and risk of PTD cases.

Genetic Susceptibility to Preterm Delivery

Genomes are 99.9% identical in any two unrelated individual. Variation in individuals is brought due to differences in DNA sequences and structure. Specific sequences variation more than 1% which occurs in individual of any population is referred as polymorphisms. Commonly 10% or more is generally observed in any populations. A polymorphism may be functional or silent. In functional polymorphism stability, level of expression and catalytic function are altered in resulting protein. Functional polymorphisms have (1) SNPs in coding regions of genes resulting in amino acid substitutions, which may alter catalytic activity, enzyme stability, and/or substrate specificity (2) SNPs in the non-coding regulatory regions of genes, which affect their transcription and translation, and in turn the amount of protein expression (3) duplicated or multi-duplicated genes, resulting in higher gene product levels (4) completely or partially deleted genes, resulting in no gene product and (5) splice site variants that result in truncated or alternatively spliced protein products [48] presented Figure 2.

Women who deliver prematurely are at a greater risk of PTD during their subsequent pregnancies. A woman who herself was delivered preterm is more likely to experience spontaneous preterm labor and

preterm birth [4]. Several epidemiological evidences indicate that genetic factors play a significant role in the etiology of spontaneous PTD [49-51]. A number of candidate gene studies, almost exclusively using case-control design, have identified some genes that are associated with PTD [52-54]. CYP450-dependent monooxygenases such as *CYP1A1* and *CYP1B1* genes are major phase-I enzymes, while mu 1 (*GSTM1*) and theta 1 (*GSTT1*) are the major phase II enzymes, which are responsible for oxidative metabolism/ detoxification of xenobiotics such as OCPs [55-57]. In our previous studies, we have reported metabolic genes, such as *GSTM1*, *GSTT1*, are highly polymorphic in north Indian women and are genetic factors that confer susceptibility to preterm delivery [58].

CYP1A1 polymorphisms cause variation in activity of its enzymes, altering the metabolism of xenobiotics and steroidal hormones [59]. The polymorphism in *GSTM1* and *GSTT1* gene loci is caused by deletion which results in absence of enzyme activity, especially in individuals with null genotypes [60]. These oxidative stress-related genes such as *CYP450* and *GST* genes are good candidate preterm delivery susceptibility genes [46,47,61]. Xenobiotic metabolizing gene polymorphism may cause improper metabolism of OCPs and thus increased free radical generation which may lead to PTD.

Genes encoding enzymes that are involved in the bio-activation and detoxification of environmental chemicals have been reported to have various polymorphic forms. Polymorphism in xenobiotic metabolizing enzyme, e.g., in the CYP 450 and GST enzyme system, is suspected to influence susceptibility to other environmental factors, affecting the risk of PTD [46,62]. Xenobiotics are known to induce changes in the mRNA expression profile, as well as in the binding response to inflammatory pathway receptors which may lead to the development of patho-physiology of PTD.

Xenobiotic Metabolizing Enzymes and Risk of PTD

Phase I metabolizing enzymes (Cytochrome P 450 enzymes)

Human cytochrome P450 (abbreviated CYP, P450, CYP450 or infrequently as CYPs) is a diverse family of enzymes. Their ability to serve as terminal oxidase in steroid hormones [63] and xenobiotics metabolism [64]. These observations were followed by the identification of numerous cytochrome P450 enzymes [65]. Currently, around fifty seven human P450 genes (functional) and twenty nine pseudogenes (nonfunctional) have been identified [66]. Cytochromes P450 metabolize a plethora of both exogenous and endogenous compounds.

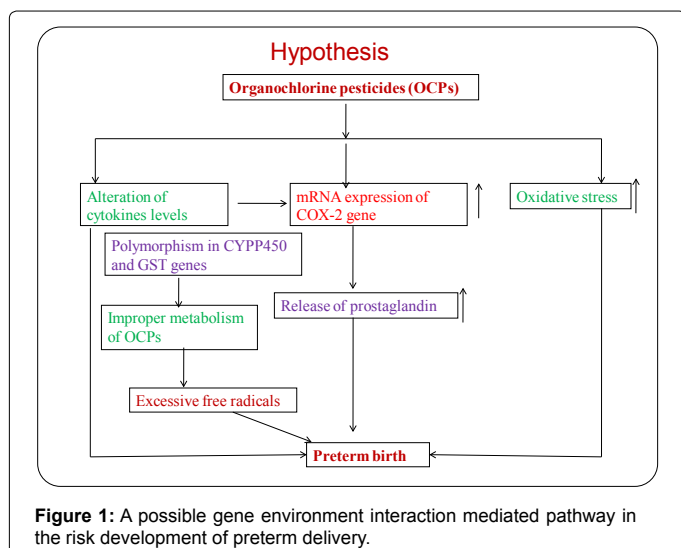


Figure 1: A possible gene environment interaction mediated pathway in the risk development of preterm delivery.

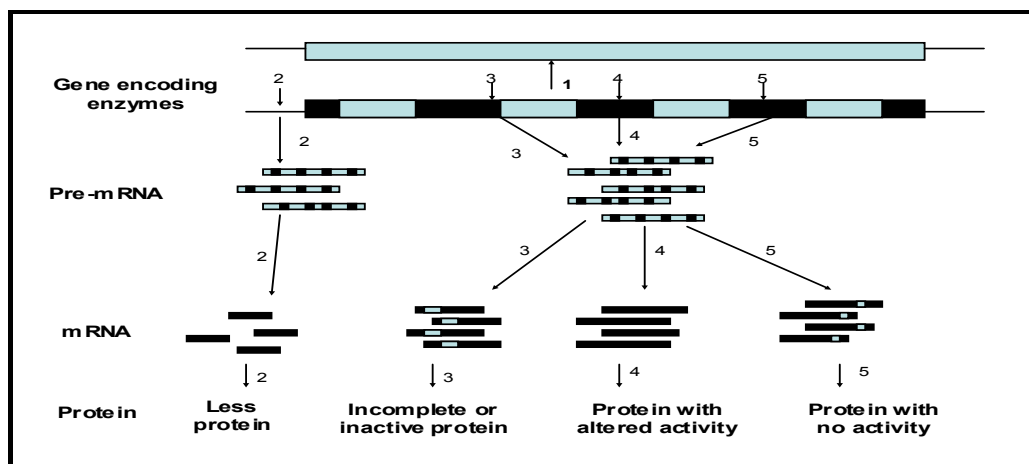


Figure 2: Schematic representation of different molecular mechanisms of genetic polymorphism.

Cytochrome P450 enzymes are heme-containing enzymes. The heme iron in cytochrome P450 is present in the ferric (Fe³⁺) state which reduces to the ferrous (Fe²⁺) state during ligands binding. Cytochrome P450 enzymes catalyze mono-oxygenation reaction in which one atom of oxygen is incorporated into a substrate (RH). General reaction catalyzed by cytochrome P450 enzymes is:-



The earliest P450s were believed to metabolize steroids (especially steroidal hormone) and fatty acids. The CYP450 enzymes mainly are classified into P450 families, namely CYP1, CYP2 and CYP3, CYP17 and CYP19 (a new family is also reported named as CYP4 and it is encoded in liver microsomes), the substrates of which include several fatty acids, eicosanoids and few xenobiotics. Due to the role of CYP450 enzymes in metabolism of several xenobiotics, carcinogens and endogenous hormones any variation in these genes might be associated with health risks. Polymorphisms in these family of genes is well known and leads to variations in enzyme activity hence these polymorphisms can be associated with increased risk of a number of human disorders including preterm delivery. Although this group of xenobiotic-metabolizing enzymes has been extensively studied in the fields of toxicology and pharmacology, their importance in the area of adverse reproductive outcomes needs to be explored. CYP genes polymorphism displays parallelism in racial, ethnical and geographical distribution and the ethnic-specific effect of CYP genes is well known. Indian population is a major distinct ethnic group representing 1/6 of the total world population.

Cytochrome P 450 1A1 (CYP1A1): *CYP1A1* is a major gene of CYP450 family; gene encoding *CYP1A1* enzyme has been localized at chromosome 15 and contains seven exons [66]. Complete gene spans 6311 base pairs [67]. Various studies have reported the *CYP1A1* is a candidate gene for preterm delivery [46,47]. *CYP1A1* also known as aryl hydrocarbon hydroxylase is an important member of cytochrome P450 enzyme family and expressed in various organs of our body including liver, placenta, kidney, etc. It is involved in the metabolism of relatively large flat structured aromatic hydrocarbons including dimethyl-benz- α -anthracene and nitrostyrene and a number of persistent organochlorines.

CYP1A1 gene coding region consists of four functional polymorphisms. *CYP1A1* m1 3801 T→C at the MSP1 site in the 3' untranslated region (rs4646903) located downstream of exon-7 [68]. It does not exert any effect on *CYP1A1* induction but possibly increases the microsomal enzymatic activity [69,70]. *CYP1A1* m2 2455 A→G transition leads to an amino-acid substitution of Ile462Val (rs1048943) in exon 7 [68] and is significantly associated with *CYP1A1* inducibility [69,70], *CYP1A1* m3,3205T→C located on 3' non coding region i.e., upstream of polyadenylation site in exon 7 and is reported to be African-American specific and *CYP1A1* m4, 2453 C→A, in exon 7 causing Thr461Asn (rs1799814) is located 2 bp upstream of m2 site. However, effect of this polymorphism on enzyme activity is not yet clearly elucidated. All four functional polymorphisms as mentioned above, allele frequency of *CYP1A1* m1 and *CYP1A1*m2 polymorphic variants are eight to eighteen times higher in Asian than in Caucasian population [71].

Polymorphic variants of *CYP1A1* enzyme when elicited by persistent organochlorine causes over expression of enzyme and has been shown to be associated with free radical generation resulting in oxidative stress. The high levels of free radicals may cause severe damage to crucial molecules which lead to PTD.

Phase II metabolizing enzymes (Glutathione S-transferases)

Phase II enzymes are involved in conjugation of phase-I products with glutathione making them hydrophilic, completing the detoxification cycle leading to excretion of metabolized compounds. Human GSTs (GST-EC 2.5.1.18) are ubiquitous multifunctional enzymes of phase II xenobiotic metabolizing enzymes family [27]. They are involved in the conjugation of phase I metabolites with glutathione, rendering the products more hydrophilic leading to their elimination. For this reason these enzymes are crucially involved in the protection of cellular macromolecules from free radical damage [72]. In Humans GSTs isoenzymes share upto 65% homology, and have been grouped into eight families based on sequence homology, designated as GSTA (alpha), GSTT (theta), GSTM (mu), GSTK (kappa), GSTO (omega), GSTP (pi), GSTS (sigma), and GSTZ (zeta) [73,74].

Two genes encode the cytosolic enzymes *GSTM1* (chromosome 1p13.3) and *GSTT1* (chromosome 22q11.2). These enzymes catalyze the addition (conjugation) of aliphatic aromatic heterocyclic radicals, epoxides, or arene oxides to glutathione. Epidemiological studies showed that *GSTM1* and *GSTT1* deficiency caused by homozygous deletion of the respective genes confers an increased risk of PTD [47]. Null genotypes of the *GSTM1* and *GSTT1* genes have been reported in approximately 50% and 20% of the Caucasian population and other racial groups, respectively [75,76].

Glutathione S-transferase (*GSTM1*): Human GST mu family of enzymes (*GSTM*) are organized in a 100 kb gene cluster on chromosome 1p13.3 in the order: 5'-*GSTM4-GSTM1-GSTM5-GSTM3*-3' and are known to be highly polymorphic. *GSTM1* gene is ~6kb long with a total of 8 exons. *GSTM1* enzyme is located in the cytoplasm. *GSTM1* deletion can modify/affect an individual's susceptibility to xenobiotics and toxins as well as affect the toxicity and efficacy of certain drugs [77]. This gene has been of special interest in molecular epidemiological studies since up to half of individuals tested in Caucasian population were found to have homozygous gene deletion polymorphism of *GSTM1* which leads to the complete lack of the enzyme activity, which can vary from 30-70% depending upon ethnic group [78]. In Asian populations frequency of the null genotype is similar to Caucasians where as lower in African i.e., 30% [79].

The *GSTM1* genotype plays an essential role in detoxification metabolism as a phase II enzyme for metabolism of exogenous chemicals including Polycyclic Aromatic Hydrocarbons (PAHs) and chlorinated compounds [62,80]. Due to absence of *GSTM1* genotype DNA adduct level being increased. The effect increased tremendously when null genotypes persons were exposed to xenobiotics such PAHs, OCPs and leads to a high risk of toxicity which also increase the risk of toxicity [81,82].

Glutathione S-transferase (*GSTT1*): *GSTT1* and *GSTT2* is subfamily of human *GSTT1*, in which *GSTT1* produce homodimeric enzyme of 239 amino acids by single gene [60]. It is approximately 8 kb in length and includes 5 exons [83]. Like *GSTM1*, the *GSTT1* locus has a homozygous deleted allele, namely *GSTT1* deletion, resulting in the complete lack of enzyme activity [60]. The consequence of the null genotype is involved in reduced conjugation activity and, in most cases, an inability to efficiently eliminate electrophilic and reactive carcinogens [60]. The frequency of the *GSTT1* deletion varies among different ethnic group [84]. The prevalence of the *GSTT1* deletion is higher among Asians (20-40%) in comparison to Caucasians (10-20%). The *GSTT1* gene is located on chromosome number 22 (22q11.23). *GSTT1* is claimed to have an important role in adverse reproductive

outcomes via the mechanism of oxidative stress and gene environment interaction. *GSTT1* is mainly found in the erythrocyte, although low levels of expression have been reported in liver and lung (in ciliated cells at the alveolar/ bronchiolar junction).

The risk associated with gene deletion is difficult to predict since the enzymes may have both detoxification as well as toxification activities towards different industrial and environmental chemicals. *GSTT1* deletion genotype was a significant risk factor for increased sister chromatid exchange among workers exposed to benzene, thus suggesting that *GSTT1* is involved in detoxification of benzene. *GSTT1* deletion leads to an absence of enzymatic activity and it can be detrimental to pregnancy outcomes in the presence of cigarette smoke exposure [85] have shown that birth weight of newborns whose mothers had *GSTT1* deletion decreased with an increase in cord blood mercury level. OCPs are metabolized by Phase-I and Phase-II enzymatic system to nullify their toxic effects [55,56]. The risk of PTD associated with exposure to endogenous or exogenous substances such as OCPs thus may be modified by the genetic variations in individual metabolic detoxification activities. A Review of studies on xenobiotics metabolizing gene polymorphism and susceptibility to preterm delivery in the different population has been summarized in Table 2.

Gene Environment Interaction in Human Complex Disorder

Shared role of gene and environment is important risk factor for PTB and has remained largely unexplored. With the help of molecular biology tools and techniques we can deduce the role of environmental factors in preterm birth. This can result in major improvements in diagnosis and development of specific treatment strategies and targeted interventions like COX-2 inhibitor drugs for its prevention, as currently; there are no effective and safe strategies for the prevention of spontaneous preterm birth.

We all carry genetic variants that increase our susceptibility to a particular diseases and environmental exposure further increases the risk of diseases Figure 3.

The current scientific view is that neither genetics nor environment is solely responsible for producing individual variation, and that most of the diseases show gene–environment interaction [86]. GxE becomes the modern approach to explore the etiology of multifactorial complex diseases such as adverse reproductive outcomes. The GxE could be helpful in identifying the risk of disease by various means such as (1) It could help to stratify disease risks and differentiate interventions for achieving population health benefits, (2) It will identify new environmental risk factors for disease or help to confirm suspected environmental risk factors and (3) It could be helpful in understanding the disease occurrence in terms of natural history, severity, etiologic

heterogeneity, and targets for intervention at the population level. The advancement in genomic technologies and analytical techniques has facilitated major breakthrough in our understanding of the molecular details of normal biology and holds the promise of providing new insights into molecular mechanisms of a variety of toxicities and human disorders.

The field of gene-environment interaction as a whole is much more mature in the etiology of adverse reproductive outcomes [87]. The study of genetic variability may be helpful to understand biological responses to environmental toxicants with a focus on metabolizing enzymes and reproduction-related genes. Individuals in a heterogeneous population having differing alleles at a given genetic locus may have different levels of susceptibility to a particular disease. These individuals may also experience an interaction between environmental factors and the gene with polymorphisms that produces an even greater alteration in the level of susceptibility. Currently, the tools of molecular epidemiology are being used to probe the potential for enhanced susceptibility to disease due to variant genetic loci. Mechanisms by which genetic polymorphisms may contribute to a differential susceptibility to disease in different individuals are complex and not always well understood. Polymorphism has been identified in the genes encoding many enzymes involved in the bioactivation and detoxification of environmental chemicals.

A mutation may give rise to a bio-activating enzyme with increased activity or to a detoxifying enzyme with decreased activity; either scenario could increase susceptibility to various diseases [88].

Gene environment interaction and preterm delivery

Environmental factors and genetics both play a crucial role in determining complex traits like PTD, FGR as well as recurrent miscarriage [8,62,89]. In Korean woman during third trimester *CYP1A1*-1462V as well as *GSTM1* genotype and higher level of PM10 brings significant reduction in POG when causes PTD [62]. Report also shows that there is correlation between low level of exposure to benzene, shortened gestation period and polymorphisms with susceptible gene [46]. There is significant high risk of PTD in women, who smoke and carrying genotype *CYP1A1* along with *GSTT1* [90]. It has also been suggested that there is increased risk of disease like lung, prostate cancer due to exposure of harmful chemicals like OCP and GST null genotype interactions [17,91]. Recent study, from our laboratory has shown that the Gene environment interaction of *GSTM1/GSTT1* gene with OCPs decreased the period of gestation. Mustafa et al. [85] have shown relationship between β -HCH, dieldrin, and *GSTM1*, *CYP1A1m2* genotype which leads to reduction in the POG. In that study when *GSTM1* genotype absent, there is increasing level of β -HCH in maternal blood results in a significant interaction between β -HCH, dieldrin and *GSTM1*- and *CYP1A1m2* genotypes. In other words when the *GSTM1*

Genes	Population/ Ethnicity	Sample size	Cases/ Controls	Findings of the studies	Reference
<i>CYPP4501A1m1</i>	Korian Papulatin	235	117/118	No significant association was observed with PTD	62
<i>CYPP4501A1m2</i>	Korian Papulatin	235	117/118	No significant association was observed with PTD	62
<i>CYPP4501A1m1/m2</i>	Chinese population	542	302/240	<i>CYP1A1m1</i> was significantly associated with PTD	46
<i>CYPP4501A1m1</i>	Korian Papulatin	265	145/120	Significantly associated with PTD	62
<i>CYPP4501A1m2</i>	Korian Papulatin	265	145/120	No significant association was observed with PTD	62
<i>GSTM1/GTTT1</i>	Korian population	265	145/120	Significantly associated with <i>GSTM1</i> but not with <i>GSTT1</i>	62
<i>GSTM1/GSTT1</i>	American population	955		<i>GSTT1</i> was significantly associated with PTD	61
<i>CYP1A1</i>	Chinese population	-	198/524	<i>CYP1A1</i> and GSTs together, but not by any single genotype	22
<i>GSTT1</i>	Chinese population	-	198/524		
<i>GSTM1, GSTT1, CYP1A1, CYP1B1</i>	Indian population	307	151/157	<i>GSTM1/GSTT1</i> null, <i>CYP1B1</i> *2 mutant and <i>CYP1B1</i> *3 and <i>CYP1B1</i> *7 heterozygous genotype was significantly associated with PTD.	85

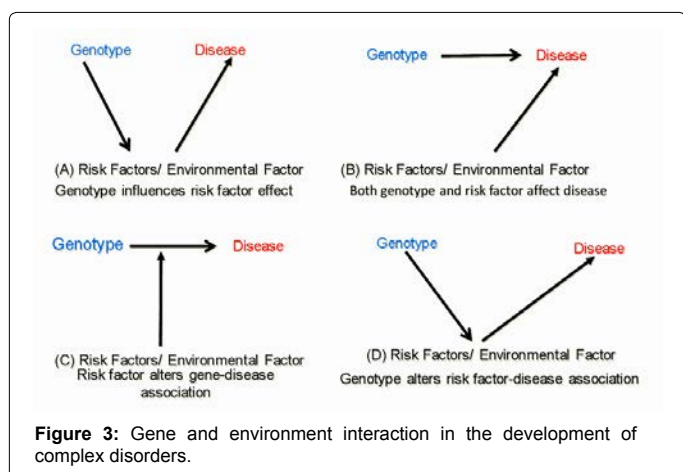
Table 2: A review of studies on xenobiotics metabolizing gene polymorphism and susceptibility to preterm delivery.

genotype was absent, increasing levels of β -HCH ($\geq 50^{\text{th}}$ percentile, \geq median values) in maternal blood resulted in an estimated 1.84 weeks (12 days, $p=0.003$) reduction in POG. A significant reduction of 1.11 weeks (8 days, $p=0.001$) was observed in POG when the interaction was made between dieldrin $\geq 50^{\text{th}}$ percentile in cord blood and *CYP1A1 m2* genotype.

Several studies suggest that gene-environment interactions, such as interactions between inflammatory gene alleles and bacterial infections also influence this disorder. Together, these studies imply that the etiology likely involves genetic as well as environmental factors in complex interactions. Gene environment interaction reflects the complex interaction between an individual genetic makeup and environment agents. This explains why some individuals have fairly low risk of developing diseases as a result of environmental insults while others are much more susceptible. A review of studies on Gene environment interaction and risk of preterm delivery in the different population has been summarized in the Table 3.

Correlation between OCPs Level, Inflammatory and Antioxidant Gene Expression

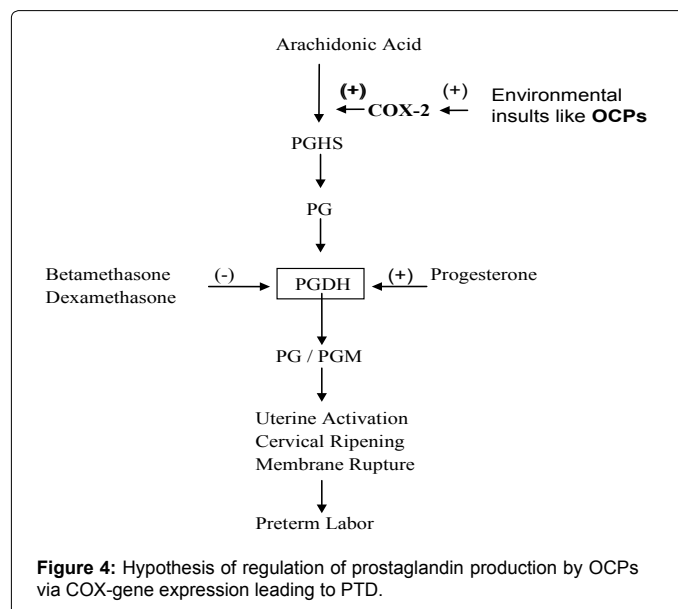
OCPs are reported to be associated with the mRNA expression of inflammatory and xenobiotic metabolizing genes [86] reported that *o,p'*-DDT dose dependently increases the COX-2 gene expression in *in-vitro* models. Similarly [87], also reported that environmental pollutants, like diesel particles, induces COX-2 gene expression which cause pulmonary inflammation and leads to conditions like asthma [88], have reported that diabetic rat models receiving Hyperbaric Oxygen (HBO) treatment have significantly increased levels of Reactive Oxygen Species (ROS) and decreased mRNA expression of Cu-Zn SOD and CAT gene, when compared to diabetic control group (without HBO treatment). Foreign chemicals like particulate matter have been reported to induce IL-6 secretion via Reactive Oxygen Species (ROS) dependent and ROS independent activation of COX-2/PGE₂ pathways



linking air pollution particles to the inflammatory response in airway epithelium [89]. Similarly pesticides being an environmental persistent pollutant may induce prostaglandin production by altering COX-2 gene expression and result in preterm labor (Figure 4). It has been reported that differential expression of CYP3A gene on chronic exposure to *p,p'*-DDE and dieldrin but the mechanisms is not yet clear. In mammals *p,p'*-DDE and dieldrin have been shown to induce CYP3A expression by activation of the constitutive androstane receptor and nuclear receptors in mammals [90]. Further, they have suggested that steroid hormones regulate the expression of CYPs. By changing activation of steroid receptors *p,p'*-DDE and dieldrin molecule the CYP expression role of *p,p'*-DDE and dieldrin mainly estrogen and anti androgenic so possibly it acted on steroid level [91].

DDT and DDE increased PGF2 α secretion from endometrial cells. Treatment of endometrial cells with PCBs was also followed by an increase of PGF2 α secretion [92]. On the other side, DDT and DDE decreased PGE2 secretion from endometrial cells. The opposite effect of DDT and its metabolite on PGF2 α and PGE2 secretion disturbs the ratio of these prostaglandins. The increase of PGF2 α secretion and concomitant decline of PGE2 release may elicit an increase of myometrial contraction on one hand and to accelerate luteal regression on the other hand. It should be noted that PCBs may also disturb the ratio of PGF2 to PGE2 secreted from endometrial cells, but without influence on PGE2 secretion [92]. The effect of DDT on prostaglandin synthesis in reproductive system in mammals has not been investigated yet.

Prostaglandin plays key role in development of PTD as it is known inflammatory marker. Increased prostaglandin in early stage of pregnancy may increase the early uterine activation, cervical ripening,



Population/Ethnicity	Sample size	Cases/ Controls	Findings of the study	Reference
Korean population	265	145/120	Exposure to high levels of PM10 during the third trimester in the presence of <i>GSTM1</i> null genotype is significantly associated with the risk of PTD.	62
Chinese population	542	302/240	A significant decrease in POG was reported among mothers exposed with benzene and <i>CYP1A1 AA-GSTT1</i> absent.	75
Chinese population	-	-	Significant joint association of maternal smoking and <i>CYP1A1 (Aa/aa)</i> and <i>GSTT1</i> null genotype, increases the risk of preterm birth by 5.8 times.	48
Indian population	307	157/151	The interaction between high OCPs levels and polymorphism in <i>CYP1A1m2</i> and <i>GSTM1</i> null genotypes may magnify the risk of PTD.	85

Table 3: A review of studies on gene environment interaction and risk of preterm delivery.

membrane rupture and finally the early delivery. Progesterone is given to such pregnant women to delay the period of gestation. β -methasone is given when the women in under early pregnancy labor to inhibit the COX-2 gene expression as well as lung maturation of the fetus. PG is synthesized from arachidonic acid under the control of COX-2 gene. Studies have shown that OCPs effect the COX-2 gene expression in dose dependently manner. Therefore, high OCPs level may increase the prostaglandin synthesis and ultimately PTD.

Future Prospects and Research Needs

The problem of multiple chemical exposures is not confined to India. People throughout the world are exposed to similar or even worse conditions of environmental contamination. Besides, the rate of PTD remains high throughout the world and most cases PTD occurring in general population cannot be readily explained by any of the known or suspected risk factor. It will be therefore interesting to ascertain whether genetic susceptibility to pesticides increases the risk of PTD and such gene environment interaction studies would help to shed light on the patho-physiology of PTD, possibly leading to better strategies for preventive diagnosis and treatment.

Our review stresses generation of epidemiological data and establishment of relative risk/relationship between the incidence of preterm births and mother's exposure to pesticides, with special reference to organochlorine pesticides. This review will lead to the identification of specific expression profiles of genes viz. molecular signature, which will help in understanding the mechanism of pesticide induced toxicity in preterm birth. This will help us to extend these molecular expression profiles to screen individuals who are occupationally exposed to pesticides such as farmers, pesticide formulators, sprayers, etc.

One of the major challenges of exploring mechanism and treatment of complex diseases is that neither environment nor purely genetic factors can fully explain the observed estimate of disease incidence and progression. To correctly estimation of risk we must measure genetics and environment together in the same studies. In the present review we have found that the Gene Environment interaction between xenobiotic metabolizing gene and levels of OCPs may lead to reduction the POG of pregnant women. This review provides the platform to use the recent advance in human genomics which make possible to study more than ten thousand gene simultaneously by micro array and evaluate their interaction with environmental factors/stressors. For this review, last ten years article based on environmental pollutant, genetic polymorphism in xenobiotics metabolizing genes, Gene-environment interaction and risk of adverse reproductive outcomes especially preterm birth were extensively searched. Further, most of the articles were searched through PubMed, Scopus Authors search, Google Scholar search tools etc.

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