Preterm birth (PTB) is defined as a delivery that occurs before 37 wk gestational age. In the USA, the preterm delivery rate is 12-13 per cent; in Europe and other developed countries, reported rates are generally 5-9 per cent. PTB accounts for 75 per cent of perinatal mortality and it is the leading direct cause of prenatal and neonatal death, resulting in 3.1 million newborn deaths annually. Half of preterm infants have long-term morbidity such as severe childhood neurological disability. Preterm birth is a major contributor of infant mortality in India and constitutes 31 per cent of neonatal deaths.

The aetiology of PTB is multifactorial and complex and remains poorly understood, in fact, a precise mechanism cannot be established in most cases. There are many maternal or foetal characteristics that have been associated with preterm birth, including maternal demographic factors (age, socio-economic status activity, occupation, and sexual habits), genetic predisposition (familial factors and genetic mutation), nutritional status, pregnancy history, present pregnancy characteristics (diabetes mellitus, and hypertension/preeclampsia), infections, cervical dysfunction, foetal physiological stress (malformation, intrauterine growth restriction), placental abruption; uterine over distension (polyhydramnios or multifetal pregnancy). Environmental factors may also play a role in the pathogenesis of PTB. Persistent organic pollutants (POPs) are a group of toxic chemicals widely distributed in the environment which includes polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), polychlorinated biphenyls (PCBs), perfluorinated organic compounds (PFCs) and organochlorinated pesticides (OCPs) like \( p'p' \)-dichlorodiphenyldichloroethylene (\( p'p' \)-DDE), \( \beta \)-hexachlorocyclohexane (\( \beta \)-HCH) and \( o'p' \)-dichlorodiphenyldichloroethane (\( o'p' \)-DDD).

Many of these compounds have an effect on human female reproduction and their exposure seems to be associated to some gynaecological diseases such as endometriosis. Earlier studies have examined the role of environmental exposure to OCPs as a risk factor of PTB. OCPs are ubiquitous in the environment and living organisms, and widely used in the past decades for their versatility in industry and agriculture. Public Health Institutions of many developing countries still allow their use for malaria control. Previous studies revealed that human exposure to OCPs might occur through numerous routes of which food chain is an important pathway. Human exposure to OCPs is inevitable because of their ubiquitous presence in the environment. These pesticides tend to bioaccumulate in lipid-rich tissues because of their strong lipophilic nature and low degradation rates. Thus, OCPs have been found in different human tissues such as blood, placental tissue, amniotic fluid and secretions such as semen and breast milk. Porpora et al found a strong correlation between concentrations in the maternal and the foetal compartment for HCB (hexachlorobenzene) and \( p'p' \)-DDE for the group of the organochlorinated pesticides.

The role of environmental exposure to OCPs as a risk factor of PTB and the molecular changes involved in PTB may drive the biologic and pathologic processes that lead to disease. The OCPs may act as endocrine disruptor chemicals (EDCs) and these can also affect reproduction by induction of DNA damage and oxidative stress. There is evidence that free radical generation and oxidative stress cause an up-regulation of pro-inflammatory cytokine expression, which induces uterine contractions. Little is known about the molecular sequence of events that leads to the development of PTB. Intrauterine infection
and inflammation are considered the main aetiologic factors. It seems that the mechanisms are related to the activation of the innate immune system due to recognition of microorganisms by pattern-recognition receptors, e.g. toll-like receptors which lead to the release of inflammatory chemokines and cytokines such as interleukin 8 (IL-8), interleukin 1β (IL-1β) and tumour necrosis factor alpha (TNF-α). The release of endotoxins and pro-inflammatory cytokines induces the production of prostaglandins and other inflammatory mediators that stimulate uterine contractility.

The cyclooxygenase-2 (COX-2) enzyme is also involved in the synthesis of prostaglandins like PGE2 and PGF besides the increased expression of COX-2 gene, with subsequent elevated production of them could precede the onset of preterm labour. In this issue, in a case-control study Tyagi et al. investigated the levels of OCPs in maternal blood of women who had preterm delivery compared with women who had a gestation period of 37 wk or more. The authors analyzed the association of organochlorine pesticides levels with mRNA expression of TNF-α gene and gene-gene interaction between TNF-α and COX-2 genes in preterm birth. Significantly higher levels of β-HCH, p,p'-DDE and o,p'-DDD were observed in PTB cases as compared to controls. The other OCPs levels, although higher were not significantly different. Moreover, the mRNA expression of COX-2 and TNF-α genes were 3.13 and 2.31 folds higher in PTB cases, respectively in comparison with term delivery.

This study confirms the association between maternal serum concentration of OCPs and preterm labour, and also reports an increased mRNA expression of inflammatory pathway genes such as TNF-α and COX-2, which have not been correlated with OCPs levels in previous studies concerning preterm birth aetiology. Even if COX-2 and TNF-α cannot be considered as direct biomarkers for pesticide exposure, since these are involved in all inflammatory processes that contribute to the onset of PTB, a possible gene-environment interaction may occur. The association between OCPs with mRNA expression of TNF-α gene should be further investigated.

Several studies have shown that inflammatory-like processes caused by OCPs can interfere with the normal physiology of pregnancy. Mustafa et al. showed significantly higher levels of β-HCH, p,p'-DDE and o,p'-DDD with higher mRNA expression of COX-2 gene (3.27-fold higher) in PTB cases as compared with term labour controls.

Furthermore, oestrogens may promote myometrial activation with increased receptivity to uterotonic agents by upregulating membrane receptors and gap junctions. Therefore, EDCs, especially those that have oestrogenic effect, may induce preterm labour. Longnecker et al. have shown that DDT increases the risk of preterm delivery and the risk is proportional to DDT concentration. It seems that DDT affects the binding of progesterone to its receptor, inhibiting it and causing preterm birth.

Preterm labour continues to be a major clinical and public health challenge. There are well known risk factors of PTB as infections, cervical insufficiency, hormonal imbalance and genetic predisposition; the association of other risk factors like oxidative stress, environmental factors and gene-environment interaction with PTB needs further investigations. More in depth researches on the association of increased levels of OCPs and PTB are needed, in order to clarify the pathogenesis of some “idiopathic” preterm births and the possible interference of OCPs with hormonal activity in pregnancy.

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References
1. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet 2008; 371: 75-84.
2. Blencowe H, Cousens S, Oestergaard M, Chou D, Moller AB, Narwal R, et al. National, regional and worldwide estimates of preterm birth. Lancet 2012; 379 : 2162-72.
3. World Health Statistics 2006. Geneva: World Health Organization; 2006. Available from: http://www.who.int/gho/publications/world_health_statistic/whostat2006_erratareduce.pdf, accessed on June 28, 2015.

4. Porpora MG, Resta S, Fuggetta E, Storelli P, Megiorni F, Manganaro L, et al. Role of environmental organochlorinated pollutants in the development of endometriosis. Clin Exp Obstet Gynecol 2013; 40: 565-7.

5. Abballe A, Guarino M, Taggi F, Traina ME, Urbani E, Valentini S, et al. Maternal blood levels of persistent organic pollutants can be used to estimate in utero exposure. Ann Ist Super Sanita 2008; 44: 281-91.

6. Heilier JF, Nackers F, Verougstraete V, Tonglet R, Lison D, Donnez J. Increased dioxin-like compounds in the serum of women with peritoneal endometriosis and deep endometriotic (adenomyotic) nodules. Fertil Steril 2005; 84: 305-12.

7. Porpora MG, Medda E, Abballe A, Bolli S, De Angelis I, di Domenico A, et al. Endometriosis and organochlorinated environmental pollutants: a case-control study on Italian women of reproductive age. Environ Health Perspect 2009; 117: 1070-7.

8. Mrrema EJ, Rubino FM, Brambilla G, Moretto A, Tsatsakis AM, Colosio C. Persistent organochlorinated pesticides and mechanisms of their toxicity. Toxicology 2013; 307: 74-88.

9. Porpora MG, Lucchini R, Abballe A, Ingelido AM, Valentini S, Fuggetta E, et al. Placental transfer of persistent organic pollutants: a preliminary study on mother-newborn pairs. Int J Environ Res Public Health 2013; 10: 699-711.

10. Pathak R, Ahmed RS, Tripathi AK, Guleria K, Sharma CS, Makhijani SD, et al. Maternal and cord blood levels of organochlorine pesticides: association with preterm labor. Clin Biochem 2009; 42: 746-9.

11. Pathak R, Suke SG, Ahmed T, Ahmed RS, Tripathi AK, Guleria K, et al. Organochlorine pesticide residue levels and oxidative stress in preterm delivery cases. Hum Exp Toxicol 2010; 29: 351-8.

12. Menon R. Oxidative stress damage as a detrimental factor in preterm birth pathology. Front Immunol 2014; 5: 567.

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

14. Tyagi V, Mustafa MD, Sharma T, Banerjee BD, Ahmed RS, Tripathi AK, et al. Association of organochlorine pesticides with the mRNA expression of tumour necrosis factor-alpha (TNF-α) & cyclooxygenase-2 (COX-2) genes in idiopathic preterm birth. Indian J Med Res 2016; 143: 731-8.

15. Mustafa M, Garg N, Banerjee BD, Sharma T, Tyagi V, Dar SA, et al. Inflammatory-mediated pathway in association with organochlorine pesticides levels in the etiology of idiopathic preterm birth. Reprod Toxicol 2015; 57: 111-20.

16. Cioroiu M, Tarcau D, Mocanu R, Cucu-Man S, Nechita B, Luca M. Organochlorine pesticides in colostrums in case of normal and preterm labor (Iasi, Romania). Sci Total Environ 2010; 408: 2639-45.

17. Mustafa MD, Banerjee BD, Ahmed RS, Tripathi AK, Guleria K. Gene-environment interaction in preterm delivery with special reference to organochlorine pesticides. Mol Hum Reprod 2013; 19: 35-42.

18. Wood SL, Jarrell JJ, Swaby C, Chan S. Endocrine disruptors and spontaneous premature labor: a case control study. Environ Health 2007; 6: 35-40.

19. Siddiqui MKJ, Srivastava S, Srivastava SP, Mehrrota PK, Mathur N, Tandon I. Persistent chlorinated pesticides and intrauterine fetal growth retardation: possible association. Int Arch Occup Environ Health 2003; 76: 75-80.

20. Longnecker MP, Klebanoff MA, Zhou H, Brock JW. Association between maternal serum concentration of the DDT metabolite DDE and preterm and small-for-gestational-age babies at birth. Lancet 2001; 358: 110-4.