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Pollution and the risk of premature birth – the current state of knowledge

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ABSTRACT

The potentially dangerous substances present in the geographical area where the pregnant woman works must be well known to healthcare professionals, starting with the family doctor, who is in the front line of prevention, and continuing with all the other specialists. Environmental factors, acting individually or cumulatively, have important effects on human reproduction. With all the recognized progress of modern obstetrics, with the wide use of new technologies in diagnosis, but also with the improvement of the therapeutic arsenal, the percentage of premature newborns has remained constant during the last decades.

Studies over the past two decades have shown that preconceptional and prenatal exposure to toxic, environmental agents has a profound and lasting effect on reproductive health. We analyzed the literature to find out the current state of knowledge in the field of the influence of pollution on the risk of premature birth.

The study of literature (environmental hygiene, ecology, toxicology, occupational medicine, obstetrics-gynecology, etc.) shows clear causal relationships between certain environmental factors and the risk of premature birth, while for several substances the results are inconclusive.

Keywords: pollution, premature birth, environmental contaminants, inflammatory cytokines

INTRODUCTION

The potentially dangerous substances present in the geographical area where the pregnant woman works must be well known to healthcare professionals, starting with the family doctor, who is in the front line of prevention, and continuing with all the other specialists. Periodic information and the interdisciplinary approach of specialists in the environment, agriculture, water and forests and the sanitary field are imperious. The involvement of local decision-makers and organizers is essential to ensure a healthy environment, in which human health is preserved on long term (1).

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Environmental factors, acting individually or cumulatively, have important effects on human reproduction: there are studies that have shown their involvement in reproductive failure (abortion or infertility), premature birth or low birth weight newborns, consequences in neurological and psycho-emotional development (attention deficit syndromes, autism). With all the recognized progress of modern obstetrics, with the wide use of new technologies in diagnosis, but also with the improvement of the therapeutic arsenal, the percentage of premature newborns has remained constant during the last decades, not being able to fall below 11-12% even in technologically developed countries. The costs of immediate and long-term care are enormous, hence the natural tendency to look for predictable factors and obviously solutions to reduce this rate of neonatal morbidity (2).

Undoubtedly, the great technological development of the last decades has brought innumerable advantages to the industrial and agricultural environment, with an unprecedented economic development, but with diverse and still insufficiently known side effects. The USA is one of the countries with high technological development, an increased rate of pollution, but also with great concerns in the field of their effects and possibilities for action. For this reason, the Centers for Disease Control (CDC) provides regular reports on pollution levels and its effects on human health. These reports are based on extensive studies on pollutants (from air, soil, water). Demonstration of the effects of the contaminated is based on their concentrations in amniotic fluid, umbilical cord blood or placenta, during pregnancy and/ or at birth. Those values that have statistically significant variations between pregnant women who give birth prematurely and those who give birth at term are considered.

Studies over the past two decades have shown that preconceptional and prenatal exposure to toxic, environmental agents has a profound and lasting effect on reproductive health. We analyzed the literature to find out the current state of knowledge in the field of the influence of pollution on the risk of premature birth (3).

Exposure to chemicals and metals in air, water, soil, food, and other products is ubiquitous. Virtually every pregnant woman is exposed to at least 43 chemicals during pregnancy. These chemicals can cross the placenta, and in some cases (methyl-mercury) can accumulate in fetal tissues, resulting in a higher fetal exposure than the mother. Prenatal exposure to pollutants is correlated with various consequences on health, and exposure of an individual at any time in life can have repercussions on the reproductive health. The tissues, organs and systems involved in human reproduction are particularly active, and are therefore extremely susceptible to changes in equilibrium in dangerous situations (4).

Today it is generally accepted that food strongly influences the health of the population and the biological evolution of the individual, so that food issues are among the most stringent national and international study topics.

The big problem at the international level is that many chemicals, which are part of widely used materials, including cleaning and personal care products, have not been tested on long term for their influence on human health and the environment.

Another important aspect is the dichotomy between the continuous technological development, the increase of the degree of civilization and implicitly of intervention on the environment, on the one hand, and the disadvantaged areas, with more precarious, more exposed socio-economic development, on the other hand. An important chapter is occupational exposure to chemically toxic compounds. Hazardous metabolite concentrations of organophosphorus pesticides and phytate are more common in people who encounter these substances at work than in the general population. This exposure should be strictly forbidden to women who are preparing for a pregnancy or who are already pregnant.

EXPOSURE TO ENVIRONMENTAL CONTAMINANTS AND THE RISK OF PREMATURE BIRTH

Premature birth is defined as the spontaneous termination of the pregnancy before 37 weeks of amenorrhea (SA). Thus, according to the WHO, any newborn who is born after 24 weeks of amenorrhea, but before 37 SA is called premature, prematurity having different degrees, which will affect the immediate prognosis, but also the long-term prognosis of the conception product.

Over time, it has been observed that in some areas there are even higher rates of prematurity, combined with malformations or associated diseases. On closer inspection, it was found that in these areas there were important factors of air, soil, or water pollution, respectively of agri-food products, with which women in different phases of the reproductive period, and especially pregnant women, came into contact. Exposure immediately before or during puberty - the period of maximum development of the reproductive organs - is another important association (3).

Preventing premature birth is not an easy task. In essence, premature birth is a phenomenon that occurs before the planned time, not being a disease, a diagnosis itself. There are several ways to reach this end. Prevention on any of them requires deci-

phering the intimate, molecular mechanisms, requiring a special scientific effort, an optimal interdisciplinary collaboration, in order to substantiate the clinical intervention protocols.

Synthetically, several pathogenic processes can be outlined that result in premature spontaneous birth: premature activation of the fetal hypothalamic-pituitary-adrenal (HPA) axis (with the onset of premature labor), an exaggerated inflammatory response at the decidual level (possibly following an infectious process with varied localization), decidual hemorrhage, and uterine overdistension. These processes can be initiated long before the actual onset of premature labor or premature rupture of membranes. However, deciphering the mechanism of preterm birth individually is difficult because demonstrating the involvement of the risk factor (s) is difficult and sometimes, risk factors seem not to exist. There is no animal study model for premature birth, superimposable on premature birth in the human species.

At the maternal-fetal interface (at the decidual level) there is a special richness of cells involved in immunological mechanisms, which have as main role the tolerance of fetal semiallograft, but which are involved among others in determining labor (activation of specific subsets of lymphocytes). The placental barrier can respond when proinflammatory factors with a specific tissue response increase in the maternal circulation (myometrium, fetal membranes, cervix). Primum movens in the process of triggering labor seems to be primarily the first phase of inflammation. Subsequently, other local cells will synthesize and release prostaglandins, oxytocin, and extracellular matrix metalloproteinases, which will activate myometrial contractility or cause degradation of the structure of the fundamental substance of the cervix or cause rupture of membranes.

Recent studies are looking for answers regarding the effect of the following contaminants in reproduction: persistent organic pollutants (POPs) (trichlorophenol, pentachlorophenol, mirex and some ingredients of the Agent Orange - 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid); non-persistent pesticides (phenylphenol, acetochlor, alachlor, metolachlor, N,N-Diethyl-meta-toluamide, carbamate-carbofuran and propoxur insecticides and pyrethroid insecticides); contaminants of drinking water (perchlorate), as well as other environmental contaminants: phenols, triclosan, parabens, volatile organic compounds - such as xylene and dibromo-methane, acrylamide.

Persistent organic pollutants

Persistent organic pollutants are suspected to be involved in the etiology of premature birth. These include chlorinated organic pesticides - dichloro-diphenyl-trichloroethane (DDT) and hexachlorobenzene (HCB), polychlorinated biphenyls (PCBs), dioxin, perfluorinated compounds (perfluorooctanoic acid - PFOA and perfluorooctanesulfonic acid (PFOS) and more recently introduced polybrominated diphenyl ethers (PBDEs) (5).

Among the organochlorine pesticides, dichloro-diphenyl-trichloroethane (DDT) is a pesticide whose use has been very limited in recent decades, but which unfortunately continues to be interesting today by polluting water and agro-zootechnical products. Its metabolites in the human body are dichlorodiphenyldichloroethylene and dichlorodiphenyldichloroethane. These metabolites are found in significantly increased amounts in the placenta and umbilical cord, but not in maternal blood at birth in mothers who give birth prematurely. In contrast, the levels of these metabolites are higher from the beginning of the third trimester in the maternal blood of those who give birth prematurely, and the risk of premature birth seems to be directly proportional to the degree of contamination (dose-dependent effect). Extensive studies conducted in communities with a degree of contamination report similar results (USA: New York, San Francisco, Mexico City, Greenland, Spain, Poland, Italy). Another organochlorine pesticide is hexachlorobenzene, whose use is recommended to be greatly reduced. In countries where this recommendation is complied with, however, there is still a risk of contamination by contaminated fish (Spain, USA) (6).

Polychlorinated biphenyls are a large group (over 200) of organic chemical compounds with various uses, which can contaminate water and fish, but are also found in the air near contaminated areas. They are not water soluble and accumulate slowly in the human body. They seem to be involved in carcinogenesis, but also in premature birth. An important effect is due to their presence in breast milk.

Dioxins are compounds that arrive unintentionally in the environment, as a result of industrial processes (paper bleaching, drinking water disinfection, waste incineration). The risks to humans are due to the consumption of contaminated food (meat, dairy products, fish).

Special information on this substance could be drawn from population studies in Seveso (Italy), where an industrial accident occurred in 1976, which led to the elimination of large amounts of dioxin. The risk of premature birth increased in this area by 20-50%. More recent studies have also shown the mechanism by which dioxin metabolites act at the placental level, namely the increase of proinflammatory factors (proinflammatory cy-

tokines interleukin 1, TNF alpha and prostaglandin E2), to the detriment of anti-inflammatory ones (interleukin 10) (6).

Perfluorinated chemicals are part of solutions for treating clothing and textiles (carpets), being able to remove stains (repel oils and greases). They are also found in the composition of food packaging or containers. These compounds are not biodegradable in soil or water. Thus, exposure occurs through the consumption of contaminated water or food, ingestion of household dust or inhalation. Despite all efforts to reduce the use of these compounds, their use is still widespread and the exposure significant. Studies in the US, Denmark, Norway, and Canada have shown that when exposure levels are high, the rate of premature births is high (8).

Non-persistent pesticides

Non-persistent pesticides forcedly entered into agricultural use worldwide (because they have replaced older, persistent products) and have been relatively little studied in terms of their impact on human health. Exposure may be through ingestion of food, contact with contaminated surfaces or inhalation of the product. Exposure to organo-phosphorus compounds (dolichyl phosphate, chlorpyrifos, maltion, etc.) leads to decreases in cholinesterase levels, a phenomenon that has been observed in both maternal blood and umbilical cord at birth, directly correlating with the risk of premature birth (9-11).

Atrazine, a widely used herbicide because it does not bioaccumulate, has a long half-life and can contaminate water. A study in France observed an increase in the incidence of premature births in areas with water thus contaminated, but without statistical significance, while a more recent study in the US confirms the risk, but also gives it statistical significance.

Contaminated drinking water

Contaminated drinking water has been extensively studied in terms of the effect on premature birth. Disinfection of drinking water with chlorinated products is widespread. This chlorination is possibly dangerous due to the resulting compounds. Very few studies in literature conclude any risk associated with premature birth. In contrast, the accidental presence of chlorinated or brominated contaminants (unrelated to the disinfection process) appears to suggest a higher risk of premature birth (the presence of trichloroacetic acid in early pregnancy is a biomarker of prolonged exposure to chlorinated compounds).

Chlorinated solvents (trichlorethylene and tetrachlorethylene) have also been the subject of numerous studies. They are used for degreasing metals, but also in industrial laundries. No increased risk of preterm birth was observed (12).

Atmospheric pollutants

Atmospheric pollutants are gaseous compounds and small particles, in which suspension and small aggregates of transition metal oxides, ammonium nitrate and sulfur salts, as well as other toxic substances can be found. Particle toxicity is given by their concentration, composition, and size. Small particles, between 2.5 and 10 microns, are released from natural sources and may include microbiological components. Once inhaled, the particles can be eliminated or, on the contrary, stored in the ciliated epithelium of the tracheobronchial apparatus. Small particles, below 2.5 microns, are related to fuel emissions. These small particles are easier to store deep in the lungs, from where they enter the circulatory system or various organs, and can induce systemic inflammation. Inflammation in the uterus may thus be related to direct proinflammatory stimulation or oxidative stress. The phenomenon of inflammatory cascade has been demonstrated both in vitro and in vivo (13). The mechanism by which inhaled pollutants determine local pulmonary, but also systemic response, with localization in different target organs, has been proven. After exposure to particles, both in vitro and in vivo, the following can be met: airway inflammation, monocyte and macrophage recruitment, cytokine release and T cell activation, as well as cytotoxic effects including apoptosis, genotoxic effect, necrosis, generation of oxygen free radicals and thrombosis. Thus, the inflammation cascade is activated, achieving a generalized inflammatory response (14-18).

Metals and metal oxides (vanadium, nickel, lead) contribute to the toxicity of inhaled particles. It has been shown that phagocytosis of metal oxides by alveolar macrophages stimulates the release of IL1beta; this in turn activates the platelet-derived growth factor receptor (PDGFR), which plays an important role in the proliferation of other cytokine-releasing cells.

Transition metals have been shown to have a genotoxic effect in vitro because they cause DNA breaks. Interestingly, most small particles induce two types of cellular response: when toxic particles come from the soil, they induce cytotoxicity, while those that come from burning fuels produce a pro-inflammatory effect. The effects of PM10 appear to be more harmful than those of PM 2.5 (19).

Particularly interesting is the fact that endotoxins released from the cell wall of Gram-negative bacteria can be found in the suspension of polluting particles. They activate helper T cells, which will secrete cytokines (TNF alpha, IL-6, IL-8, IL-12). Most

endotoxins are found in the insoluble fraction of polluting particles. In vitro studies also detected elevated concentrations of E-selectin in the researched cells, which is involved in the adhesion and recruitment of monocytes. E-selectin is synthesized and released by endothelial cells in response to increased cytokine release, being considered an important factor in airway inflammation. It turns out that not only the size of the inhaled particles is important, but especially their composition (if endotoxins are also contained, the toxic effect will be more marked) (20-22).

Most studies have focused on the potential influences of ozone, small particles (below 2.5 or below 10 microns PM 2.5 and PM 10), carbon monoxide (CO), nitrogen oxides (NOX) and sulfur dioxide. Two very recent studies revealed the association of premature birth with exposure to SO2 and PM 2.5. A study conducted by the US Department of Health concluded that exposure to tobacco smoke (especially for active pregnant smokers) is directly related to the increased risk of premature birth.

Aromatic hydrocarbons and volatile organic compounds have long been in the spotlight of researchers, especially for congested urban areas with high levels of air pollution. Several studies show increased concentrations of aromatic hydrocarbons in umbilical cord blood in premature infants compared to full-term infants. Benzene also appears to be involved in the pathogenesis of preterm birth.

Air pollutants resulting from hydraulic fracturing used to extract shale gas appear to be involved in the risk of premature birth (23).

Other environmental contaminants

The information must be separated between contamination by occupational exposure or in everyday life. The following metals were studied: lead, cadmium, arsenic, mercury.

Lead is a major contaminant, because it is released from fossil and non-fossil fuels, so it can be inhaled, but can also be ingested (lead from pipes, ceramic objects, etc.). The effect of increasing the rate of premature births is real and is dose dependent (USA, Mexico, China, Iran, Spain). Exposure is important from the beginning of pregnancy, and the levels of lead detected in premature placentas is high compared to those at term. Cadmium contamination data are contradictory and inconclusive. Arsenic does not seem to be correlated with the risk of premature birth. Mercury, which must be considered due to the risk of ingestion of contaminated fish or seafood, may be involved in premature births before 35 weeks (24-26).

Large molecule phthalate esters (diethylhexylphthalate) are widely used in the modern world, entering the composition of polyvinyl, but also in cosmetics (lotions, nail polish, car interiors, polyvinyl shower curtains, wallpaper, linoleum, medical devices etc.). Small molecule phthalates (dibutyl phthalate, diethyl phthalate) are used as solvents and plasticizers, found in varnishes, perfumes, lotions, cosmetics, packaging. Exposure is due to ingestion of contaminated water or food, but also from the daily use of cosmetics. The metabolites of these compounds are found in 99% of the urine samples of the population in the USA. Phthalates are considered endocrine disruptors, with implications in human reproduction. Two recent large studies have shown opposite results on the risk of preterm birth, which requires the undergoing of larger studies to investigate these influences (27,28).

Bisphenol A (BPA) is part of polycarbonate plastics and epoxy resins (which are used in the production of food packaging), as well as in the inner linings of canned foods. The level of metabolites found in urine is impressive – over 92% of the samples are positive (2008, USA). It is found in significant quantities in wastewater, drinking water, air, dust. Because it has a weak estrogen-like action, it is considered to have major implications for human reproductive health. A very recent study suggests a statistically significant link between bisphenol A exposure and preterm birth. The possible mechanism of action for both phthalates and BPA appears to be the induction of a pro-inflammatory activity and an increase in oxidative stress (they are found in significant amounts in both the placenta and the amniotic fluid). However, what is particularly significant is that when the target population (respectively pregnant women) becomes aware of the possible negative effects of these products and encourages a decrease in exposure to them (consumption of fresh, unpackaged, uncanned food, reasonable reduction of exposure to cosmetics for personal or household use, the use of gloves and protective masks when cleaning etc.), urinary levels of the metabolites of these compounds decrease greatly - which is an easily correctable but high impact factor in the pregnancy (29).

INFLAMMATORY CYTOKINES AND PREMATURE BIRTH – HYPOTHESES REGARDING THE INFLUENCE OF ENVIRONMENTAL FACTORS

Mediators of term labor in the human species belong to the family of proinflammatory cytokines. For this reason, at least in theory, any inflammatory response, even in the absence of an infectious process, can induce the onset of preterm labor, regardless of gestational age or degree of fetal maturation. This kind of inflammatory response, with implications in triggering uterine contractions, however,

has no other pathological resonance on the two organisms (maternal and fetal). On the other hand, if such an inflammatory process becomes chronic, as is the case in choriodecidual infections, the conditions for initiating a premature labor or premature rupture of the membranes are met again.

Experimental studies, but also clinical studies show that, in the presence or absence of an infectious process, mediators of inflammation such as interleukin 1-beta (IL1-b), tissue necrosis factor alpha (TNF-a), interleukin -6 (IL-6) and interleukin 10 (IL-10), can trigger premature labor.

Intra-amniotic instillation of IL-1b in non-human primates results in increased uterine contractile activity. IL-1b also mediates myometrial activation after inoculation of bacteria into the choriodecidual space in an experimental model in non-human primates. Il1 b is considered a key mediator in the degradation of extracellular matrix support in fetal membranes, inducing their rupture. Il-6 and TNF-α are pro-inflammatory cytokines involved in systemic inflammation, and in literature there is a link between elevated serum levels of IL6, but also TNF-α and premature birth. Regarding IL-10, its elevated levels are negatively correlated with the risk of premature birth.

The cellular source of these cytokines is represented by the choriodecidual space, inside the maternal-fetal interface, which is a real target area of action for exogenous factors such as infections, but also air pollutants or other possible triggers of inflammation. At the level of this microenvironment, there is an enrichment with leukocyte subpopulations, which can enter the cascade of cytokine secretion, which will have as final response either the premature onset of labor or the premature rupture of membranes.

COUNSELING DURING PREGNANCY REGARDING EXPOSURE TO TOXIC SUBSTANCES

At the time of the first pregnancy visit, exposure to toxic substances may have already occurred and the influences on organogenesis may have already begun. However, as much data as possible on specific types of exposure to toxic, occupational agents (both maternal and paternal or environmental) should be obtained. The visit is also an opportunity to provide as much information as possible about pregnancy hygiene and potentially toxic factors to avoid (at home, at work or in the family environment). Whenever a specific factor is identified, the patient can be referred to the occupational medicine specialist or the environmental health specialist in the targeted area can be contacted. In any case, careful anamnesis and proper monitoring of pregnancy can lead to strong impacts (we should remember that many such observations, from fetal death in utero, malformation syndromes or numerous miscarriages have led over time to the identification of dangerous toxic agents).

Counseling during pregnancy gives special weight to dietary recommendations. Pregnant and lactating women, but also those who want a pregnancy should be advised to eat well-washed fruits and vegetables from safe sources, seeds, grains, and whole grains daily, and to avoid fast food, processed or preserved products whenever possible. Fish is particularly important for the neurological development of the fetus, but the risk of mercury contamination of large ocean fish (shark, swordfish, king mackerel, etc.) should not be neglected (30).

It is also advisable for pregnant women to avoid excessive exposure to products containing phthalates and parabens in large quantities (cosmetics, environmental perfumes, various household hygiene solutions, plastic containers etc.).

At the individual level, the pollution of the environment from air, water, soil cannot be influenced, at this point the role of the decisional political factors and of the specialists from the system being the one that intervenes. What civil society can do, influenced by specialists in environmental and health issues, is to increase the pressure on economic factors to ensure a healthy environment. No chemical should be approved for widespread use if there are no studies on its influences on the environment and human health (31).

A relatively little studied chapter in Romania, but present in literature, the implication of pollution on reproductive health can answer, if properly explored, some questions about the possible causes and interrelationships between environmental changes and health. All the articles in literature converge on the need to create comprehensive, prospective, controlled studies that can better correlate and integrate pollutants and their influences on the condition of the mother, fetus, but also the evolution of pregnancy at different moments. It is desirable that this kind of concern, deeply interdisciplinary, materializes in the Romanian scientific space. Only in this way, coming with concrete results, will it be possible to sound the alarm, to act targeted and efficient, for the benefit of our patients, but also of our entire society.

CONCLUSIONS

The study of literature (environmental hygiene, ecology, toxicology, occupational medicine, obstetrics-gynecology etc.) shows clear causal relationships between certain environmental factors and the risk of premature birth, while for several substances the results are inconclusive.

For persistent organic pollutants, there is strong evidence of exposure to elevated DDT levels and premature birth (especially in studies using biomarkers of exposure). Also considered dangerous: polybrominated diphenyl esters and toluene (organic solvent). For other pesticides, especially the organochlorine ones, the results are inconclusive.

For drinking water contaminants, the results published so far are inconclusive.

For air pollutants, there is a strong correlation between sulfur dioxide exposures, small particles (less than 2.5 microns), particles resulting from hydraulic fracturing and PAH and premature birth, while for nitrogen compounds and ozone the results they are inconclusive.

For metals and metalloids, the correlation of premature birth with exposure to high doses of lead is strong, while exposure to low doses of lead, cadmium, arsenic, and mercury remains unspecified.

Other contaminants from the environment: phthalates, BPAA, organophosphorus pesticides and atrazine have still been insufficiently studied, and the studies so far do not allow any conclusions to be drawn.

Cigarette smoke and ethylene oxide are risk factors in premature birth.

A pregnant woman who lives in the vicinity of a power plant or shale gas exploitation area has an increased risk of premature birth.

Climate changes, associated with air pollution, through exposure to extreme heat or cold are risk factors for premature birth and/ or low birth weight.

Reviewing the current international literature, there are some inconsistencies and limitations of the studies presented. Obviously, interdisciplinarity is the key word for progress in this field, which is at the border of several specialties, each of great importance: ecology, environmental pollution, agronomy, medicine.

In addition to the family doctor who cares for the pregnant woman or the woman who is preparing for a pregnancy, the obstetrician may perform an anamnesis related to the pollutants to which there is a potential exposure. The woman can encounter these pollutants at home, at work or by exposure in the natural (recreational) environment. Identifying a risk factor allows information on avoidance (e.g., renouncing work) or reduction of exposure. These are opportunities to provide educational information on hazardous pollutants and minimize their effects.

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