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Review

Pregnancy in the Era of the Environmental Crisis: Plastic and Pollution

Antonio Ragusa[1], Giulia Principi[2,*], Maria Matta[3]

[1]Department of Obstetrics and Gynecology, Campus Bio-Medico University Hospital Foundation Rome, 00128 Roma, Italy
[2]Department of Obstetrics and Gynaecology, University of Messina, 98122 Messina, Italy
[3]Harvey Medical and Surgery Course, University of Pavia, 27100 Pavia, Italy
*Correspondence: g.principi91@gmail.com (Giulia Principi)
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Abstract

Objective: The environmental crisis we are experiencing is becoming a more popular topic of expert discussion and analysis. Human activity and expansion on the planet are exacerbating climate change and global warming, this, together with the increase in plastic production, and general pollution, posing a threat to our resources, supplies, and survival. This research aims to review what is known about the association between pollution and pregnancy and sensitize experts to women's education towards healthier behaviors. **Mechanism**: We chose to focus on the effects of the environment on fetal development and maternal health, considering various studies that highlight the potential consequences of exposure to certain environmental stressors. The paper briefly illustrates the probable mechanisms that, starting from cellular and intracellular damage, determined above all by plastics, lead to chronic activation of the immune system in response to danger and, therefore, to epigenetic modifications at the base of diseases in adulthood. **Findings in Brief**: We describe the effects of the main pollutants on pregnancy, with particular attention to the role of plastic. Finally, we briefly outline some individual possible solutions to this complex problem. **Conclusions**: In the era of environmental crisis, becoming aware of the mechanisms behind biological damage resulting from exposure to certain pollutants and plastics, especially in a period as sensitive as pregnancy, should be the driving force behind a change of direction. As physicians, this means educating our patients and recommending individual solutions to reduce the impact of contaminants to provide the best possible environment for women's and children's health, especially during the delicate period of pregnancy; but the ultimate solution is to drastically reduce global plastic production and pollution, and to recycle the plastic that is needed anyway.

Keywords: pregnancy; placenta; pollution; plastic; disease mechanism; environmental

1. Introduction

Because of physiological changes in the mother's body and metabolism, as well as placental and embryo-fetal development, gestation is a very delicate period. Fetal growth and development during pregnancy are influenced by a variety of factors, including uteroplacental function, maternal age and diseases, cardiovascular function, nutrition, smoking and illicit drug use, and the presence of pathological conditions such as infections, aneuploidy, certain genetic conditions, etcetera. During this time, the organism is extremely sensitive to the effects of environmental contaminants such as medications, alcohol, and other potentially harmful exposures.

The mother represents the link between the fetus and the environment, delivering clues about what awaits outside. Because the materno-fetal unit is so intertwined, everything that affects the mother's physiology will have short- and long-term implications on the fetoplacental complex. Interactions with the surrounding environment and external chemicals can result in an alteration of the normal physiological equilibrium. It is difficult to propose a univocal tool to measure and state the harmful effects of various types of pollution on pregnant women because conditions vary greatly around the world. However, there is undeniable evidence of various effects that diverse types of environmental pollution can have on the mother, and thus the fetus.

The importance of epigenetics is becoming more apparent. Researchers believe that early-life exposure to environmental factors, particularly prenatal exposure, can cause long-term metabolic and physiological changes in the fetus, resulting in various degrees of vulnerability to chronic diseases. Epigenetics refers to heritable changes in gene expression without a modification in DNA sequence. It was first characterized as the interactions of genes with the environment that cause the phenotype to emerge, indicating a possible method by which environmental variables interact with intrinsic factors and influence gene regulation [1].

We must consider also that biological systems are difficult subjects to observe also in an experimental setting. The functional organization at the cellular and subcellular level can be grouped into three classes of processes: gene expression, metabolism, and cell signaling. It is of paramount importance to consider that cells are composed of a very large number and variety of components interacting in space and time and the dynamic functioning of cells is of a nonlinear nature. Finally, biological systems are subject to continuous change [2]. This change can be indeed also influenced by environmental pollutants.

2. Pollution and Pregnancy

To begin the reflection we would like to propose, it is important to recognize how pregnancy can be significantly influenced by the environment in which we live. Numerous correlations with various environmental contexts have been highlighted by researchers.

Temperature by itself can have an impact on the duration of a human pregnancy and birth weight [3], a significant discovery considering the climate crisis and global warming. Even if the overall increase in temperature is disturbing in and of itself, it is also the cause of an increase in spontaneous combustion and forest fires, which has been linked to low birth weight, particularly in low and middle-income countries [4].

Global temperature resent by urbanization, which is also responsible for the negative health effects that follow from particulate matter (PM) being released into the air. PM is the total of all solid and liquid particles suspended in air, many of which are hazardous. The particle size ranges between 2.5 mm ($PM_{2.5}$) and 10 mm (PM_{10}) [5]. Preterm birth, low birth weight, and stillbirth have all been linked to $PM_{2.5}$. The risk assessment for preterm delivery, low birth weight, and stillbirth were considerably higher in exposed mothers: 11 times higher for preterm birth, 11 times higher for low birth weight, and 14 times higher for stillbirth [6–8]. It has been shown mothers who reside near congested areas are more likely to deliver children with low birth weight or small for gestational age (SGA) [9]. The study by Gat *et al*. [10] found that the more exposed the mothers were to air pollution, the higher the prevalence of pre-term rupture of membranes (PPROM). Moreover, $PM_{2.5}$ pre- and post-pregnancy exposures may contribute to an increased risk of gestational diabetes mellitus [11].

All these findings imply that increasingly common environmental exposures, such as air pollution and heat, exacerbated by climate change, are significantly associated with adverse pregnancy outcomes. Placental signaling to the fetus expresses pollution interference with fetal development and maternal physiology, leading to a particular impact on newborn weight and preterm births [12].

Poor air quality and temperature variations are not the only sources of contamination linked to increased urbanization and environmental damage. Studies have already proved how noise pollution can affect the cardiovascular system in humans [13], and now there is evidence that it can have consequences on the cardio-fetoplacental unit, contributing to an increased risk of severe early-onset preeclampsia [14].

Minamata Disease as Example of How Maternal Heavy Metal Poisoning Affects Fetal Well-Being

Even neurological development may be affected; there is already some evidence on the consequences of high concentrations of noxious agents in the ambient around the gestating mother, although more studies are needed. Cerebral palsy has been linked to contamination by the Minamata case of mercury-contaminated fish [15]. Similar effects have been reported in babies born to mothers exposed to lead and pesticides [16–18], while a possible link has been hypothesized between autism and maternal exposure to PM_{10} [19]. This reinforces evidence demonstrating that adverse health outcomes at birth are not always related to problems during labor and delivery, but that all events from conception to the end of gestation play a role in embryo-fetal development and the overall health of mother and baby [20].

3. The Role of Plastic

In the last century, the global production of plastic has grown exponentially reaching over 350 million tons per year produced all over the world. This greatly contributes to environmental pollution [21]. The recent Covid-19 pandemic has caused a peak in the production and consumption of discardable plastic, primarily for individual protection (masks, gloves, scrubs) and for the increase in home deliveries and home packages, increasing the waste of non-recyclable plastic [22]. Furthermore, unexpectedly and in the absence of any moral scruple, the large companies, which had recorded a reduction in the sales of fossil fuels, changed their production, producing more and more virgin plastic [23].

The Role of Microplastics

Microplastics (MP), which originated, above all, from the degradation of plastic in the environment, are recognized as particles of less than 5 mm [24]. They are found in water, which can be oceans or even lakes and rivers [25], soil [26], air [22], and in food [27], particularly in seafood [28,29], sea salt [30,31], and potable water [32,33].

The contamination from MP has been demonstrated from exposure after a prolonged period and even after one single exposure [34,35] and can be absorbed through 3 main pathways: ingestion, inhalation, and dermal contact [36]. The diameter is usually around 5–10 microns for penetration inside tissues [37].

The tiny particles can enter the human body in many ways, but the majority likely enter via ingestion or inhalation. Depending on its dimensions, it is hypothesized that it can spread through passive diffusion or active phagocytosis [38].

MP have been found originally in the gastrointestinal tract of sea animals [39], and scientists have now demonstrated cellular absorption and accumulation of micro-and nano plastic in organic tissues [40–43] and human blood [44].

Recent studies conducted on human samples showed MP presence in the placenta [37] and newborns [45], suggesting contamination since the earliest stages of life (Fig. 1). These findings are a worthy concern, and more studies are needed to investigate the direct consequences

on humans.

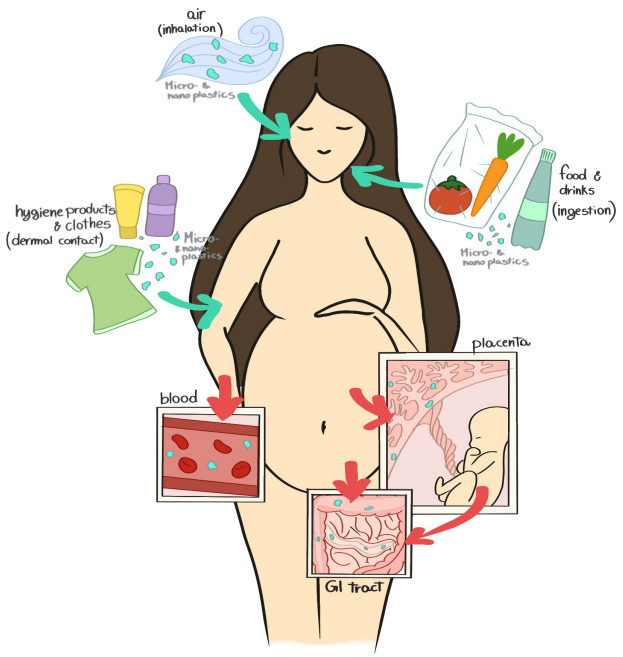

Fig. 1. Schematic representation of micro- and nanoplastic contamination by inhalation from air pollution, ingestion from food and drinks, particularly those in plastic wrapping or containers, and dermal contact from daily hygiene products and clothes. Consequent findings of MP in blood, inside the placenta, and in the gastrointestinal tract of the pregnant mother and fetus are also illustrated.

Are microplastics harmful? In animal models, various evidence of toxicity has been reported. They were found to interfere with energy production, lipid metabolism, increased oxidative stress, and neurotoxic responses [46]. Their presence has been associated with toxicological effects on cell cultures, causing apoptosis, inflammation, mitochondrial and lysosomal dysfunction, and genotoxicity [36]. Their interaction with the immune system appears to be disruptive, with alterations on a genetic level for the expression of genes involved in the immune response.

In mice models, MP can cause changes on a phenotypic level, in the expression of genes and epigenetics, as was demonstrated by brain abnormalities in mouse pups whose mothers were fed with plastic microparticles [47]. Cognitive capacity alterations were discovered, showing an alteration of RNA expression, and immunofluorescence was used to observe microplastic infiltrates in the brain of pups.

If microplastics in humans interact with placental cells and alter energy pathways as they do in animal models, there could be numerous concerning consequences [48].

4. Disease Mechanism and Cellular Damage

To understand how the environmental interactions that the fetus entertains during intrauterine life can influence events that take place far ahead in time, such as metabolic syndrome or diabetes, or heart disease, we must introduce the concept of developmental programming. Developmental programming refers to adaptation from an evolutionary perspective: at the individual level, it may confer a trade-off favoring short-term survival/reproductive fitness, at the long-term cost of disease susceptibility, particularly for complex, common disorders [49].

In cells, the response to danger (CDR) is a universal response to environmental threats or injuries. Once this response is activated, it ceases only when the stimulus that caused it is eliminated. But this cannot happen with plastic, since the body is unable to eliminate it definitively and completely, given the resistance of this material, which has recently appeared in the biological arena. The cell tends to treat this material as it treats any foreign body, of organic or inorganic origin, but in this case, it is faced with an indestructible product through the usual cellular mechanisms of recognition, lysis, and destruction. For this reason, given the persistence of the material, the cell undergoes alterations in the shape, structure, and function of some intracellular organelles. In particular mitochondria, assisted by the endoplasmic reticulum system, regulate CDR by monitoring and responding to physical, chemical, and microbial conditions in and around the cell. In this way, mitochondria link cellular health to environmental health.

In an interesting study, Deng *et al.* [41] used fluorescent and pristine polystyrene microplastic particles with two diameters (5 μm and 20 μm) to investigate the tissue distribution, accumulation, and tissue-specific health risk of MPs in mice. MPs accumulated in the liver, kidney, and gut, with a tissue-accumulation kinetics and distribution pattern that was strongly dependent on the MPs particle size. Analyses of multiple biochemical biomarkers and metabolomic profiles suggested that MPs exposure induced disturbance of energy and lipid metabolism as well as oxidative stress [41].

Another study showed that maternal administration of polystyrene nanoplastic in mice during gestation and lactating periods altered the functioning of neural cell compositions and brain histology in progeny. Furthermore, polystyrene nanoplastic induced molecular and functional defects also in cultured neural cells *in vitro*. The abnormal brain development caused by exposure to high concentrations of polystyrene nanoplastic results in neurophysiological and cognitive deficits in a gender-specific manner [47].

The effects of plastic are very important, especially on the central nervous system. Adult offspring of female mice (L-DE-71 F1) exhibit short- and long-term deficient social recognition, reduced sociability, and increased repetitive behavior when they were exposed to the Polybrominated diphenyl ethers. Ultimately, exposure to Polybrominated

diphenyl ethers, during intrauterine development produces neurochemical, olfactory, and behavioral processes that are relevant and very similar to those of autism spectrum disorders (ASD) in humans. These effects can reprogram early neurological development within central memory and social networks [50]. Importantly, autism spectrum disorders prevalence in humans has dramatically increased in recent years [51,52].

Oral administration of monodispersed polystyrene causes damage to the visceral organs in mice. The main toxicities are the damage to the liver function and the lipid metabolism abnormality. Chronic exposure to monodispersed polystyrene significantly increases plasma glucose levels and ROS levels but does not influence plasma insulin secretion. Ultimately oral administration of monodispersed polystyrene increases ROS, liver triglycerides and determines the accumulation of cholesterol in mice [53]. A schematic summary of the various effects consequent from microplastic presence in mice offspring is illustrated in Fig. 2.

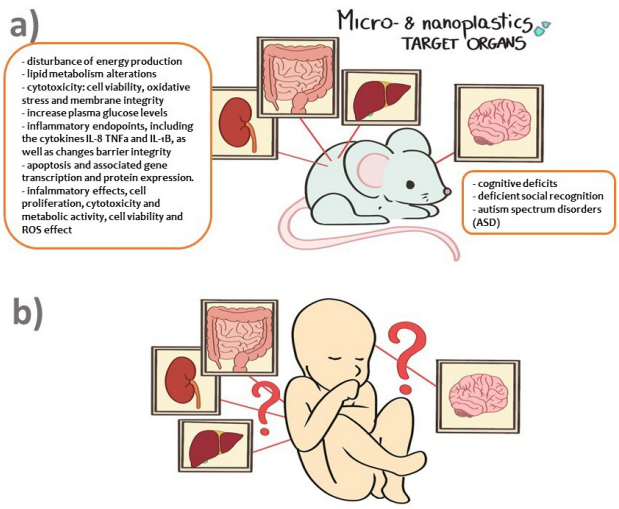

Fig. 2. Micro- and nanoplastics: target organs in progeny esposed during gestation. (a) Schematic illustration of effects of microplastic in mice born from mothers exposed to microplastics during pregnancy. (b) The possible effects on human newborns are yet to be confirmed.

Electron Microscopy and Microplastics

Scanning electron microscopy analysis shows that plant cells, subjected to intense stress, in this case dehydration, undergo phenomena of induced death had unambiguous morphological features of autophagic cell death, including an increase in vacuole size, degradation of organelles, and collapse of the tonoplast and the plasma membrane, especially affecting the endoplasmic reticulum and mitochondria [54]. The cause of the damage to the endoplasmic reticulum and mitochondria and ERMCSs may be different (dehydration, plastic, heat, etc.) but, likely, the effects on the morphology and endocellular function are monotonous and similar in all living beings, it is an evolutionarily conserved response [55].

The endoplasmic reticulum and mitochondria are in close contact through the endoplasmic reticulum–mitochondria contact sites (ERMCSs) [56]. ERMCSs regulate various biological processes, including lipid transfer, calcium homeostasis, autophagy, and mitochondrial dynamics. The dysfunction of ERMCS is closely associated with various diseases, neurodegenerative, cardiovascular, obesity, etc. [57,58].

When the placental cells come into contact with the plastic material they activate a mechanism aimed at eliminating the material itself, failing to eliminate the plastic material, the cells remain chronically in a state of pathological activation (CRD) which through chronic activation of the immune system, leads to a modification in the shape and function of cellular organelles and to changes in epigenetic expressiveness, which will ultimately lead to the development of diseases in the future (Fig. 3).

Plastic waste, for instance, now exceeds 83 billion pounds/year. In the 1980s, 5–10% of children lived with a chronic disease. As of 2018, 40% of children, 50% of adolescents, 60% of adults under 65, and 90% of adults over 65 are living with a chronic disease [59].

The pathogenetic mechanism, briefly described in the previous lines, might explain the epidemic of chronic, noncommunicable diseases (NCD) which afflicts human beings in a worsening and progressive way in recent decades.

Among the contributing causes of NCDs, we must not only consider tobacco use, physical inactivity, use of alcohol, and unhealthy diets [60] but also environmental pollution and above all plastics.

The endoplasmic reticulum and mitochondria and ERMCSs alteration could be in fact at the base of many chronic diseases and the imprinting given by the interference of microplastics could be determinant for their expression [59].

More studies are needed to give more precise answers and determine the implications that microplastic can have on human development. However, their presence alone should be enough to make us reconsider the way we consume polluting products such as plastics, and act towards a more sustainable lifestyle, both for the planet's survival and ourselves'.

5. Individual and Partial Solutions to a Global Problem

Health professionals, and women, should pay attention to recent studies and learn how to communicate these information to women, to incorporate them into health plans. Physicians can play a more active role in educating and pressuring elected officials in charge of public policy to take meaningful actions to address the climate crisis.

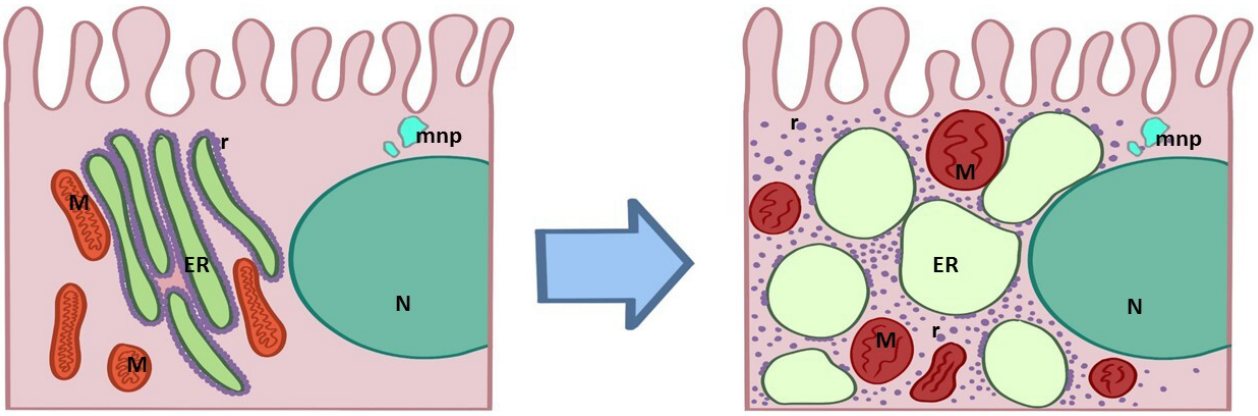

Fig. 3. Schematic illustration of the syncytiotrophoblast in section, depicting normal physiological morphology of organelles on the left, and organelles degeneration on the right, due to severe stress. The stress of the endoplasmic reticulum and mitochondria are thought to cause swelling of both ER and mitochondria as well as ribosomal dispersion in the cytoplasm. Stress could be a consequence of non-degradable micro/nanoplastic contamination, causing perpetual activation of CDR response, degeneration of organelles, and eventually inhibition of their function in cellular metabolism. ER, endoplasmic reticulum; M, mitochondria; N, nucleus; mnp, micro-nano-plastic; r, ribosomes.

A study conducted by Nieuwenhuijsen *et al.* [61] highlights the associations between pregnancy outcomes and the exposome. It proposes to examine a variety of environmental exposures at the same time during key life stages to gain a comprehensive understanding of their impact on human health. The most consistent statistically significant relationships were seen between greater green space exposure, increased birth weight, and a reduced risk of term low birth weight [61].

Human physical and mental health advantages from access to urban green places. Less air pollution exposure, reduced stress, greater social contact, physical activity, and overall enhanced general health outcomes, and lower mortality risk are just a few of the benefits. Green space also helps to mitigate and respond to climate change by sequestering carbon and providing local cooling benefits [62].

"Shinrin-yoku" (SY) or "forest bathing" is a traditional Japanese practice of immersing oneself in nature while mindfully using all five senses; it appears to be associated with beneficial effects on the immune system function (increase in natural killer cells/cancer prevention); the cardiovascular system (hypertension/coronary artery disease); the respiratory system (allergies and respiratory disease); depression and anxiety (mood disorders and stress); mental relaxation (attention-deficit/hyperactivity disorder) and human feelings of "awe" (increase in gratitude and selflessness) [63]. After the practice, patients reported lower concentrations of cortisol, lower pulse rate, lower blood pressure as well as greater parasympathetic nerve activity, and lower sympathetic nerve activity than in city environments [64]. Various studies suggested that even just the essential oils from plants can stimulate the immunological function of our organisms [65,66], which is fundamental for fetal and maternal wellbeing. Women should be therefore encouraged to "forest bathe" as frequently as they can.

Another habit to introduce that can be beneficial in decreasing pollution exposure around women is reducing plastic consumption. To witness the effectiveness of a plastic-free environment, a group of children was offered an alternative to plastic, limiting almost zero their exposure, and the results after one month showed a significant decrease in *plastic* concentration in urine, as opposed to the control group [67].

We can therefore assume that the concentration of plastic in our bodies is reversible: the less plastic we are exposed to, the less will stay in our tissues. What everyone can do individually, and particularly women during pregnancy, in this sense is use organic alternatives to plastic for everyday use, buy products that are in carton packages rather than plastic ones, buy clothes made of natural materials rather than synthetic, drink tap water and avoid water in plastic bottles, avoid the use of plastic utensils, increase recycling, and educate their children and partners to do the same.

Alimentation and mindfulness can also play a role. In Barcelona, a group of scientists conducted a randomized trial, that showed that treating pregnant individuals at high risk for SGA with a structured Mediterranean diet or with mindfulness-based stress reduction, compared with usual care, significantly reduced the percentage of newborns with a birth weight below the 10th percentile [68]. Due to important study limitations, these findings should be considered preliminary and require replication, as well as assessment in additional patient populations, but what is certain is the negative impact that intensive farming for food production can have on the environment. Being more conscious and attentive to product choices, prioritizing food with a smaller carbon footprint, and from establishment closer to the con-

sumer can be beneficial for the environment and personal health. These measures can help counterbalance the negative effects that inevitable exposure from living in a polluted environment can cause.

Curing alimentation and reducing ingestion of food contaminated by microplastic and other pollutants can improve wellbeing and diminish the negative effects of such contamination, whilst practices of mindfulness, adequately combined with forest baths, can help reduce their stress and cortisol levels and boost immunity. because as someone has already said, to solve the environmental crisis, we need to upgrade not just our technology, but also our collective imagination, and we absolutely owe this to future generations.

6. Conclusions

The data presented so far both on the climate crisis, environmental pollution, and its effects on human health are not reassuring and suggest the need for immediate action. Our organism and the expression of our genetic inheritance are conditioned by the environment.

The relationship between a person and the environment is extremely complicated, and it can change genetic expressivity throughout life. Epigenetics modification could even be transferred to the next generations. Functional systems of the organism develop from open-loop systems without feedback control into closed systems controlled by a feedback mechanism [69]. This delicate mechanism is extremely adaptable and can be altered at any time, but it is especially sensitive during the perinatal period. For our sake and the sake of the planet, it is therefore critical to implement strategies that promote a healthy environment that can be passed from intrauterine life down to children after birth.

We must remember that we are the first to suffer the consequences of our actions. The harm we inflict on the planet is directly reflected on us. More than 2000 new chemicals are released into the environment every year and only 1% of these are properly tested for safety [70]. We must change this if we want to guarantee a future for the new generations.

Even in the era of environmental crisis, we are not impotent in the face of the discovery of pollution inside our bodies and our children's. There are individual solutions that we can implement to reduce the impact of contaminants in the environment and thus inside us. As physicians, we should educate and recommend these solutions to provide the best environment possible for women and babies' health, especially during the sensitive time of pregnancy; but the ultimate solution is to drastically reduce global plastic production, and pollution, and recycle the plastic that is nevertheless needed.

Author Contributions

AR conceived the presented idea and developed the theory. AR, GP and MM wrote the manuscript and corrected the English. MM created the original drawings. All authors contributed to the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. AR is serving as one of the Guest editors of this journal. We declare that AR had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to MSA.

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