Nanoparticles and pregnancy: from benchside to the community

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According to the International Union of Pure and Applied Chemistry (IUPAC), ultrafine particles or nanoparticles (NPs) are particles of matter of any shape with dimensions between 1 μm (1 × 10⁻⁹ m) and 100 μm (1 × 10⁻⁷ m) [1]; being smaller than visible light wavelengths (400–700 μm), NPs cannot be observed with common optical microscope, demanding the use of an environmental scanning electron microscope (ESEM), possibly coupled to an energy dispersive X-ray (EDX) spectroscope for elemental microanalysis [2]. By virtue of this, NPs dispersions in transparent media are in turn transparent; moreover, they easily pass through common filters, and the separation from liquids needs nanofiltration techniques [3]. NPs can be of both natural and artificial origin: natural ones derive from many cosmological, geological and meteorological processes, while artificial ones are man made by means of combustion processes [3]. An ultra-specialized branch of nanotechnology is precisely focused on the realization of NPs with specific properties, while nanotoxicology studies the toxicity of these NPs on the living beings [4]. Of the possible hazards, inhalation and ingestion appear to present the most concern, because of the high NPs surface-to-volume ratio, which makes them highly catalytic or reactive [3]. In addition, they can receive a coating from phospholipid bilayers, pass through cell membranes, and to aggregate together [5]; obviously, a fetus body is more sensitive to environmental disruptors than an adult [6–8].

As of 2013 the USA Environmental Protection Agency was testing the safety of the following NPs: carbon nanotubes (CNTs), iron oxide NPs (FeO NPs), silver NPs (Ag NPs), copper NPs (Cu NPs), cerium dioxide NPs (CeO₂ NPs), and titanium dioxide NPs (TiO₂ NPs) [9]. A study on mice by Qi and colleagues has showed that placental transfer of Ag NPs causes increased the expression of pregnancy-relevant inflammatory cytokines, and inducing immunological dysfunction in pregnant mice [13]. Prenatal exposure to Ag NPs can compromise postnatal development of neonatal rats, especially the pulmonary, reproductive, immune and neuronal functions [14–23]; moreover, they show toxicity on endometrial receptivity in female mice [24]. ESEM investigations have showed that placental transfer of Ag NPs causes induction of nuclei, clumped chromatin, pyknotic nuclei and focal necrosis; therefore, further studies of genotoxicity have been recommended [25]. Vidmar and colleagues have proved Ag NPs translocation in an ex vivo human placenta perfusion model [26], while Gatti et al. [27] have found Ag NPs in the human fetal brain of an unexplained stillbirth suggesting a possible pathogenetic role. Cu NPs are used as preservatives in pressure treated lumber and in some paints or coatings. Oral exposure of pregnant mice to Cu NPs causes liver disorders in fetuses [28,29]; moreover, they show evident genotoxicity via extracellular signal-regulated kinases (ERK) pathway in female mice [30]. Prenatal exposure to Cu NPs triggers severe lung inflammation in dams and immunomodulatory afterbirths in offspring [31]. CeO₂ NPs are used in fuel additives, electronics and biomedical supplies; a lot of CeO₂ NPs applications imply their dispersion in the environment, with a consequent increase of polluting hazard. Both human cytotoxicologists have showed that CeO₂ NPs applications induce internalization CeO₂ NPs, which influence trophoblastic metabolic activity in a dose and time dependency, induce caspase activation, a lactate dehydrogenase release, and disturb secretion of pregnancy-relevant hormones [32]. In a murine model, maternal exposure to CeO₂ NPs during early pregnancy gives rise to placental dysfunctions, among which low-quality decidualization and abnormal recruitment of uterine natural killer cells [33]. TiO₂ NPs are currently exploited in sunscreens, cosmetic...
Fig. 1. Example of ESEM image with spherical Ag NPs from a human cellular substrate as confirmed by the Ag peak in the corresponding EDX spectrum [X axis: KeV; Y axis: counts \( \times 10^3 \)].

ics, paints and coatings; they also find application into removing contaminants from drinking water. Recent research from the northern China, performed under TiO\(_2\) NPs mining exposure, has put in correlation the maternal blood Ti concentration with low birth weight (LBW) risk. A total of 45 females who gave birth to LBW babies (cases) and 352 females with no LBW newborns (controls) have been compared; interestingly, median total blood Ti concentration in the cases group was significantly higher than in the control group (134 vs 129 ng/mL, \( p \)-value = 0.039) [34]. A human maternofetal transfer of TiO\(_2\) NPs during pregnancy has been also correlated with a higher risk of neural tube defects in human offspring [37]. In mice, TiO\(_2\) NPs exposure in pregnancy significantly affects the placental development, most likely by dysregulating proliferation, vascularization and apoptosis [38–40]. In addition, TiO\(_2\) NPs exposure alters mice ovary resulting in hypofertility [41,42]. In conclusion, all these preliminary data suggest to protect pregnant women from high exposures of NPs, and stimulate new research inside this pioneering field in the interest of the whole community.

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