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Editorial

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 ηm (1×10^{-9} m) and 100 ηm (1×10^{-7} m) [1]; being smaller than visible light wavelengths (400–700 ηm), 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 (CeO_2NPs), and titanium dioxide NPs (TiO_2 NPs) [9]. A study on mice by Qi and colleagues has highlighted that CNTs overcome the fetal-placental barrier, mainly accumulating in the liver, lungs and heart of the fetus [10]. A further murine model by Fujitani *et al.* [11] has showed that CNTs possess teratogenicity at least under experimental conditions. Nanoscale iron is increasingly used into nutrient supplement since better-absorbed; however, high doses of (+) FeO NPs administered in a late stage of organogenesis are resulted more fetotoxic in mice than equivalent doses of (–) FeO NPs [12]. Ag NPs are currently being exploited into food packaging and for their antibacterial, antifungal and antiviral properties (Fig. 1). Once ingested or inhaled during pregnancy, they reach the placenta, increasing 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 indentation 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 germinal toxicity via extracellular signal-regulated kinases (ERK) pathway in female mice [30]. Prenatal exposure to Cu NPs triggers severe lung inflammation in dams and immunomodulatory aftermaths in offspring [31]. CeO_2 NPs are used in fuel additives, electronics and biomedical supplies; a lot of CeO_2 NPs applications imply their dispersion in the environment, with a consequent increase of polluting hazard. Both human cytotrophoblasts and syncytiotrophoblasts can internalize CeO_2 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 CeO_2 NPs during early pregnancy gives rise to placental dysfunctions, among which low-quality decidualization and abnormal recruitment of uterine natural killer cells [33]. TiO_2 NPs are currently exploited in sunscreens, cosmet-

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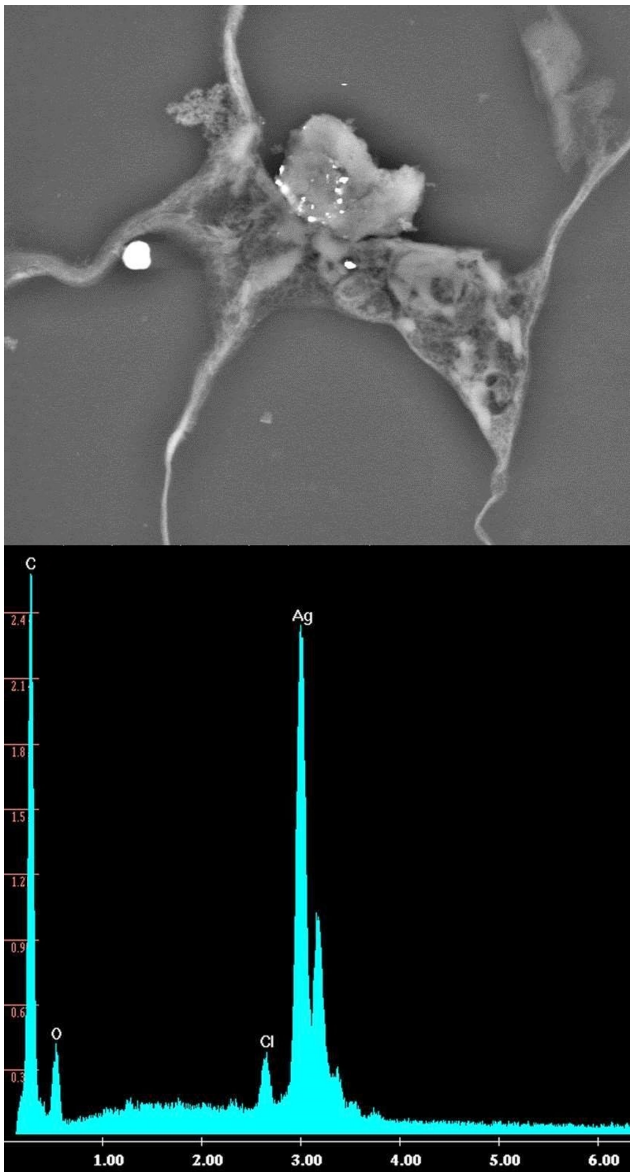

Fig. 1. Example of ESEM image with spherical Ag NPs from a human cellular substrate as confirmed by the Ag peak in the corresponding EDX spectrum [X axis: KeV; Y axis: counts $\times$ 10^3].

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 controls group (134 vs 129 ηg/mL, p-value = 0.039) [34]. A human maternofetal transfer of TiO_2 NPs during pregnancy have been previously demonstrated, as well as an increase in placental vascular resistance and an impairment in umbilical vascular reactivity due to TiO_2 NPs [35,36]. Maternal exposure to TiO_2 NPs during the periconception period 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, TiO2 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.

Ethics approval and consent to participate

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Conflict of interest

The author declares no conflict of interest. LR is serving as one of the Editorial Board members of this journal. We declare that LR 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 RG.

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