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COMMENTARY

Environmental nanoparticles and placental research

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1 | INTRODUCTION

Nanoparticles (NP) (usually understood as in the range 1–100 nm) are, in principle, capable of intercellular barrier penetration as well as ingestion by cells, particularly phagocytes and transporting epithelia. Here we focus on particulate black carbon (BC) and nanoplastics.

Black carbon arises as a sooty paracrystalline insoluble product during combustion of wood, other plant material (including tobacco combustion products inhaled by smokers) or petroleum products in spaces with limited oxygen.[1] It is used as a stabiliser in tyre manufacture, paints and pigments and as a food colourant. Particulate material from vehicle emissions is classified by size; for example, $PM_{2.5}$ are NP <2.5 nm. Carbon NP are produced by design, too, for example as nanofibres or nanotubes. Routes of exposure are most likely to be via inhalation or ingestion. High exposures may occur as a result of vehicle emissions from nearby roads. Epidemiological studies have suggested associations between particulate air pollution (including $PM_{2.5}$) and hypertensive disorders of pregnancy, growth restriction and preterm birth, but are often confounded by the presence of other pollutants.[2]

Microplastics (around 1–100 mm) in the environment generally arise from pellets, packaging, personal protective equipment, textiles, tyres or fishing nets, either directly as a by-product of manufacturing or by mechanical, light-mediated or biological fragmentation and degradation.[3–5] They are already very widespread in soil and aquatic environments, and concentrations are rising. Microplastics break down into nanoplastic particles which are more difficult to detect and quantify, and more likely to become incorporated from air, water, soil or food into biological systems. In addition, primary nanoplastics are directly made for use in cosmetics, facial cleansing products, and air-blasting technologies. Data associating microplastics exposure with abnormal pregnancy outcomes have started to appear in the literature.[6]

Research is required to inform the updating of legislation to protect women as early as possible in their pregnancies, or ideally those planning a pregnancy. Within this context, epidemiology data supported by laboratory investigations are essential in understanding the placental transfer of NP and their impact on placental biological function and fetal development.

2 | HOW MIGHT NANOPARTICLES INTERACT WITH PLACENTAL TISSUES?

Nanoparticles in uterine or placental tissue compartments may cause adverse effects during pregnancy. Direct access of blood to the placental surface is limited during the first trimester,[7] but early pregnancy effects on uterine function such as decidualisation are pertinent.[8] From second trimester, particles might access the surface of chorionic villi, accumulate in the intervillous space, become incorporated into villous tissue or even cross the placenta to gain access to fetal blood and tissues. Human placental barrier thickness diminishes progressively over the course of pregnancy and in the third trimester may be only 3–4 μm, overlying fetal capillaries to form so-called vasculo-syncytial membranes. Ingestion of NP into syncytiotrophoblast may be via fluid phase pinocytosis, phagocytosis or endocytosis or via clathrin-coated vesicles for receptor-mediated uptake[9] (Figure 1). Where the syncytial epithelium suffers local damage, as always occurs even in normal pregnancy,

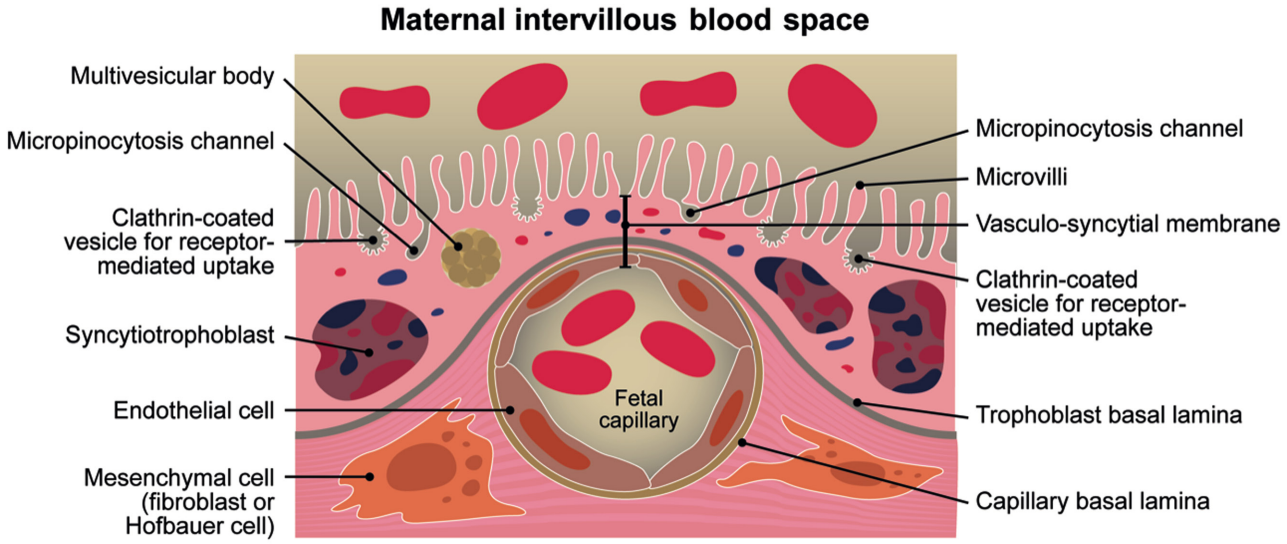

FIGURE 1 Diagram of a terminal villus of a human placenta showing the surface covered by microvilli at the base of which are clathrin-coated vesicles for receptor-mediated endocytosis and also macropinocytotic channels for fluid uptake, via which microparticles from the maternal blood in the intervillous space may also be ingested. Particulate matter would have to traverse the trophoblast and be discharged before penetrating both trophoblast and endothelial basal laminae plus the endothelium itself before entering the fetal circulation. Particles may also be taken up by mesenchymal cells rather than entering the fetal capillary. Precision is therefore crucial when characterising particle location in tissue, whether it be in the trophoblast, mesenchyme or endothelium as well as its position within the villous tree or chorionic plate.[16]

a paracellular route into the placental villous mesenchyme and potentially fetal circulation is available across the fibrinoid matrix, but this is limited to substances of relatively low molecular mass and is unlikely to be utilised by NPs. Intact syncytium has been reported to contain nanopores that connect the maternal blood space with the area between the syncytial basal surface and the basement membrane;[10] in principle these might offer a direct route of access for NPs (<10 nm) to the stroma.

Uptake of microparticles by the placenta and evidence for translocation to the fetus in both human and various animals have been reviewed.[11–13] In studies of other species, different barrier anatomy must be taken into account; the haemochorial placenta (seen in human, other primates, mouse, rat and rabbit) is unique in allowing direct access of blood-borne particles to trophoblast at the outer surface, though the number of tissue layers may vary. Accurate reporting of basic placental anatomy in the context of the particles detected is critical in assessing the barrier roles of different tissue layers and locations, optimising sampling protocols and evaluating the likelihood that NP might gain access to fetal tissues.[14–17]

3 | TECHNICAL ISSUES

Direct localisation in the tissue presents a technical challenge that is greater with plastic NP than with carbon NP can be seen by transmission electron microscopy, though it may be difficult to distinguish from other electron-dense inclusions. Density is difficult to quantify in 3D tissues, and microscopic approaches require morphometry to estimate quantity of NPs at whole organ level. Efficient internalisation of particles by Hofbauer cells – placental macrophages – has been documented in vitro. Presence of NPs in amniotic fluid or cord blood[18] can provide a high standard of evidence for transfer across the placenta but the inadvertent introduction of contaminating environmental NP during sample processing must be rigorously avoided. At present the route of transplacental transmission is unclear.[15,16] In some studies placental tissue was macerated, thus not allowing discrimination between fetal and maternal compartments or maternal blood retained in the intervillous space at delivery.[6,19,20] Another possible approach is to isolate specific single cell subpopulations from NP-exposed placentas for examination.

Studies of particulate matter in placental cells in vivo, in vitro and ex vivo show evidence of uptake by the syncytium.[13,15,16] Experimental approaches are useful in building hypotheses regarding mechanisms of functional impairment. These include oxidative stress and DNA damage, altered occurrence of Hofbauer cells, and effects on transport, metabolism, endocrine function, growth, vascular development, coagulation and complement activation, barrier integrity, inflammatory status, the renin-angiotensin system, intraplacental signalling including protein kinase A and altered release of signalling substances to the fetus.[12,13] Transfer within tissue, and more specifically across the placenta to fetal compartments, is affected by particle size, particle material, weathering, charge and surface composition, dose and gestational stage of the model.[13,21] Plastic NPs of varying size and surface charge have been tested in animals and in ex vivo dual perfusion studies in humans, where particles up to 240 nm were taken up by the placenta.[22]

Other studies suggest accumulation in the syncytium or in Hofbauer cells without further translocation.[13] Thus

an important component of the placenta's defence strategy involves ingestion and retention. The presence of particles in tissue, especially when this has been reported without quantification, does not justify an assumption that damage is occurring at a level that is consequential for pregnancy outcome. However, cell culture evidence has indicated cytotoxicity in trophoblast and BeWo cells, so the possibility that high levels of NP in syncytiotrophoblast could have a deleterious effect on placental function cannot be ignored.

4 | CONCLUSION

Exposure to high levels of air pollution and microplastics can have an adverse effect on the fetus,[23] possibly due to deterioration in placental endocrine, metabolic and immunological functions, and a range of effects have been shown in animal models including altered growth and protein expression. There is also evidence that nanoparticulate material may bind viruses and facilitate their entry into cells. Well-controlled epidemiological and experimental studies distinguishing direct and indirect effects of NP are now required as well as determining the timing (early or late) of exposures in pregnancy. More sophisticated 3D models of the human placental barrier are also required. Appropriate use of animal species will enable the possible longer-term impacts on offspring to be evaluated. In human, effects may alter after 11 weeks of gestation with the onset of maternal blood flow to the placenta. Most work to date on transplacental transfer has focused on solutes, and so methods for the quantification and accurate tracing of particles into and across the placental barrier need improving, including monitoring of location, accumulation and persistence in placental tissue, and metabolic and inflammatory adaptation.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and writing up of this commentary.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

ETHICS APPROVAL

None required.

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