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Nanotechnology for Maternal Foetal Medicine

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Abstract

Last decade has seen a flourishing in the study of the properties of inorganic nanoparticles (NPs) for their application in medicine. Inorganic NPs behave as "artificial atoms" since their high density of electronic states -which controls many physical properties- can be extensively and easily tuned by adjusting composition, size, shape and surface state. Consequently, nanotechnology's ability to shape matter at the scale of biomolecules has opened the door to a new generation of diagnostics, imaging agents and drugs for detecting and treating disease. But perhaps even more important, nanotechnology is allowing to combine a series of advances into a single NP, creating nanosized objects that at the same time may contain drugs designed to kill tumoral cells or pathogenic invaders, together with targeting compounds designed to home-in on malignancies and target tissue, and be imaging agents designed to light up even the earliest stage of disease. Besides, it is becoming widely known that none of the existing single-modality treatments such as chemotherapy, radiotherapy, immunotherapy, gene therapy or thermotherapy can cure complex fatal diseases such as cancer or preeclampsia by itself. Consequently, a combination of treatments, such as combination of chemotherapy (combining more than one drug), chemotherapy and gene therapy, thermotherapy, radiotherapy or biotherapy, are being investigated for their synergistic effects that may dramatically improve outcomes and reduce the side effects of each single modality treatment. This is because therapeutic effects are designed to add up while side effects do not. In this context, NPs appear as ideal platforms for multimodal therapy in the special case of maternal fetal medicine where treatment for the mother and the foetus has to be differential

Keywords: Nanomedicine, Antioxidant Therapy, Cerium Oxide Nanocrystals, Nano-Obstetrics

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Introduction

Nanomedicine, the medical application of nanotechnology, is already providing a useful set of research tools and medical devices for researchers and clinicians, and more will come in the near future. As new drugs or active principles discovered from nature, from the highest mountain fungi to the deepest ocean protozoa, seem to have been exhausted, and the new designed drugs, immune therapy, stem cell therapy or genetic therapy are not yet fully working, nanotechnology and its application to medicine has emerged as a "disruptive technology", with great potential to contribute to improved treatments of different diseases by the generation of new diagnostic and therapeutic products, and by assisting other existing techniques (as for example delivering antibodies or as hyperthermia antennas). For instance, Nanoparticle (NP) conjugates can deliver simultaneously multiple therapeutic agents to a disease site in order to simultaneously attack multiple points in the pathways involved in complex diseases such as cancer. Also, some NPs are active by themselves while carrying at the same time imaging agents and therapeutic drugs enabling synergistic effects. Therefore, nanoconstructs can be designed in a way where the NP is at the service of the drug (e.g.: to transport it), or as an active principle where the coating is at the service of the NP to bring it to the target (e.g.: before a radiotherapy process) or both in a theranostics approach. In other words, the NP can be used as a scaffold and as an actuator. The outcome is a complex NP which is understood as a tool box for monitoring and manipulating biological states. In this platforms, different drugs, ligands and biomolecules can be combined (by absorption [1], loading [2], coordination bonding [3], entrapment [4], etc) and different tasks (delivery, heat, irradiate) can be performed [5].

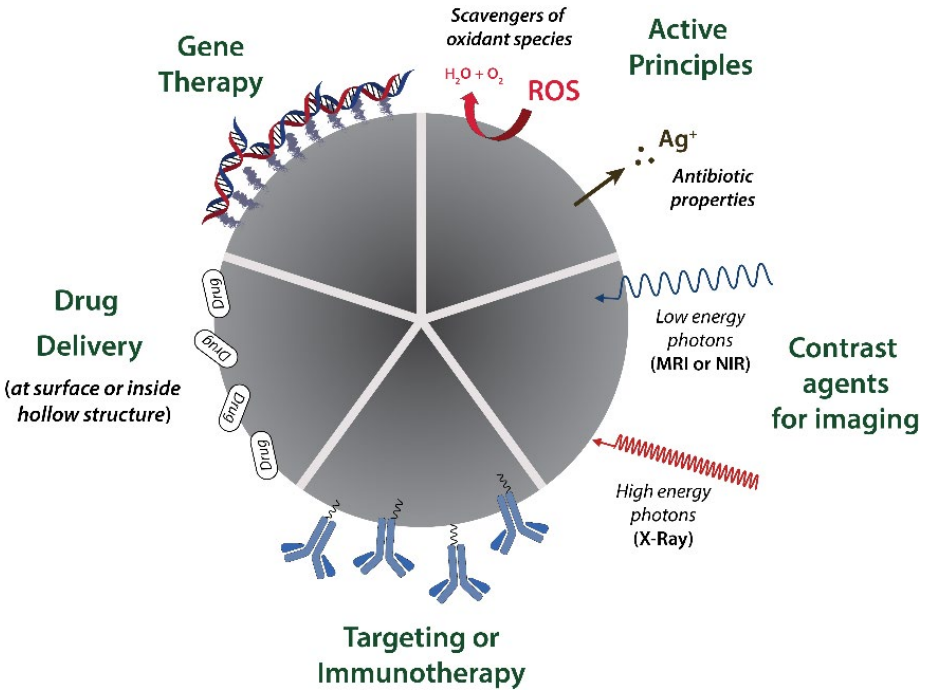

Figure 1: Representative schema of inorganic NPs multimodality

For that, NPs are unique to bring therapeutic and imaging agents to diseased tissue. NPs are ideal scaffolds to combine therapeutic agents (even several NPs may have therapeutic value per se, e.g. SiO_2NPs [6, 7] CeO_2NPs [8] and Fe_3O_4NPs [9]) and targeting agents (e.g. monoclonal antibodies, targeting peptides) and thus combine their pharmacokinetics profiles. In such cases, first, the NP conjugate reaches the target area and then, the monoclonal antibody locks it to its target. Second, these materials can be imaged with NIR or X-ray probes, or as in the case of Fe_3O_4NPs, can be detected by MRI, serving as diagnosis agent (note that normally tissue alterations occur before disease clearly manifest), enabling thus nanotheranostics platforms (Figure 1).

Thus, nanoscale drug delivery agents have been developed and exploited to enhance the delivery of drugs in the treatment of a number of diseases showing potential benefits in terms of pharmaceutical flexibility, selectivity, dose reduction and minimization of adverse effects [10]. Inorganic NPs can also be used as imaging and radiation contrast agents. Despite that the current knowledge on the subject is still scattered and too heterogeneous to deliver useful tools for society, many recent discoveries and advances preclude the inevitable success of nanomedicine, as far as the right strategies and methodologies are pursued. Thus, recent literature shows a larger than expected enhancement effect of radiotherapy when using AuNPs as contrast agents. This is thanks to the radioactiviation of the catalytic power of AuNPs in aqueous environments, assisting the production of free radical molecules which further damage tumoral cells [11]. Besides, NPs have been also designed not only to increase efficacy, but to improve efficiency by carrying antitumoral drugs away from the kidney avoiding severe side effects associated to treatment [3]. Also, Yeste et al., [12] showed recently a very specific targeting of dendritic cells on lymphatic nodes after i.v. administration with clear effects on inhibiting deleterious auto-immunity, while Xia et al. have developed inorganic nanocages to use them as drug delivery agents [2], and even more importantly, the Enhanced Permeability and Retention (EPR) effect which passively accumulates NPs in solid tumors [13] and in inflamed tissue due to vascular alterations, has been observed in humans recently [14] demonstrating that NP-based therapies can act as "precision medicine" for targeting disease areas while leaving healthy tissue intact. Similar effects have been observed in infections where the vascular permeability factor secreted by bacteria for tissue colonization and a defective lymphatic drain during inflammation, creates transient EPR effects [15] –so much used in nano-oncology. Indeed, already in 2005, synergetic effects of multiple drugs carried by a NP were described in a mouse model [16].

The therapeutic use of inorganic nanoparticles in humans is not entirely new. Traditionally, gold nanoparticles (Aurum Potabile) were administered for their supposed therapeutic benefits since the antiquity, initially in old India and then through the silk road up to Switzerland where was described by Paracelsus in the 17th century. In the same way, the use of silver nanoparticles (colloidal silver) as a disinfecting agent was already approved by the FDA more than 130 years ago [17]. Already in modern times, we continued with the medical use of gold salts, that when enter inside the body are reduced spontaneously into nanoparticles smaller than 5 nm and expelled by urine, have been used for the treatment of Rheumatoid arthritis (Auranofin, Ridaura®). Other uses of subnanometric inorganic material is Alum (Aluminum Sulfate, [18]), the most widespread adjuvant for vaccines. More recently, new NPs have been developed for therapeutic use, such as amorphous porous silicon dioxide (SiO_2) NPs intended as drug delivery platforms [6, 7, 19], where its degradation generates silicic acid, promoter of osteogenesis and proposed to treat osteoporosis; or magnetic iron oxides, as contrast agents for MRI (Resovist®, [20]), as hyperthermia agents for the treatment of cerebral neuroblastoma and glioblastoma (MagForce®), or as an injectable anti-anaemic drug in patients with fragile kidney (Feromuxytol®). And many others that are in clinical trials, notably, HfO_2 NPs, very similar chemically to the

anti-inflammatory radio-protector NPs of CeO_2 (Nanobiotix®).

In this context, it is not surprising that nanomedicine has been the focus of strong support as in the case of the European Technology Nanomedicine Platform (ETNP) or the United States Nanotechnology Characterization Laboratory (NCL) acknowledging the future importance of nanomedicine [21]. Similarly, in recent declarations, the 2016 Noble Prize on Chemistry Bernard Feringa was describing his achievements as "Such molecular machines can be developed in smart medicines that seek out disease or damage and deliver drugs to fight or fix it, and in smart materials, which can adapt in response to external triggers such as changes in light or temperature", underlying the potential huge impact nanomedicine will have in the coming future [22].

Thus, the field of actions of future nanostructures in medicine can be classified in diagnosis, imaging, drug delivery, hyperthermia and theranostics (simultaneous diagnosis and therapy) [23]. Personalised health care, rational drug design and targeted drug delivery are some of the proposed benefits of this nanomedicine-based approach to therapy.

Why Nanoparticles for Maternal Foetal Medicine

There are several main drives to address maternal-foetal conditions with nanotechnology. The application of NPs as platforms for targeted drug therapy in pregnancy-related conditions is extremely new and it represents an opportunity to improve maternal and foetal care. The initial approach is that foetus and mother may have different pharmacological needs and therapeutical responses, to primary and side effects, and that mother and child may share disease with different immune responses and defence strategies (even they have different genomes). Due to this, Maternal Foetal Medicine is an area with specific need for targeted delivery of different therapies. Importantly, the possibility to modify NPs physicochemical properties (size, shape, surface state, etc) enable targeting and theranostic approaches beyond the currently used small molecules, allowing, for example, to deliver drugs to the foetus but not the mother. This is well exemplified in the EPR effect, that accumulates passively NPs in the tumour area, or the altered biodistribution of drugs when attached to a NP, especially in the case of inflammation. In addition to the mother and the foetus, in between, there is the placenta, a highly dynamic and complex organ separating and linking at the same time the spaces between the mother and the developing foetus. The placenta develops from the same sperm and egg that gave development to the foetus and has two components: a maternal portion, the leafy chorion and a foetal or decidual basal portion. The health and function of the placenta, as a barrier and transporter organ, plays a vital role within the fields of perinatal health and maternal foetal medicine. Perturbation of placental function can limit transfer of necessary nutrients, reduce the removal of foetal waste, allow undesired passage of xenobiotics to the developing foetus, and alter placental metabolism. In addition, NPs uptake and transport at the placental barrier is an important consideration in the potential pharmacological treatment during pregnancy, either to avoid that the drug that the mother takes does not reach the foetus or reverse, that the drug for the foetus is protected and transported to the target sparing the mother.

In addition, an important factor limiting our ability to provide safe and effective therapies during major obstetric complications is the side toxicity of therapeutic agents. In this context, the versatility of the different nanostructures that can be prepared and their high loading capacity, allows to modify the biodistribution of molecules adsorbed onto the NPs and with that, reduce or avoid side effects. This also permits to control the total circulation times of the NP cargoes, and limits their action to a selected tissue or selected population of cells decreasing toxicity in the rest of the body.

This is even clearer in the case of obstetric complications, where considerations of the route of exposure, the physiological environment and biological interactions during the development of potential nanomedicines are crucial (Figure 2). To support the growing foetus the mother body undergo a series of physiologic modifications, such as the immune system adaptation and the increased respiration rate, blood volume, and cardiac output. This makes the distribution of NPs during pregnancy to be different than in a non-pregnant state as much as biodistribution is altered during the course of disease (cancer, inflammation, etc).

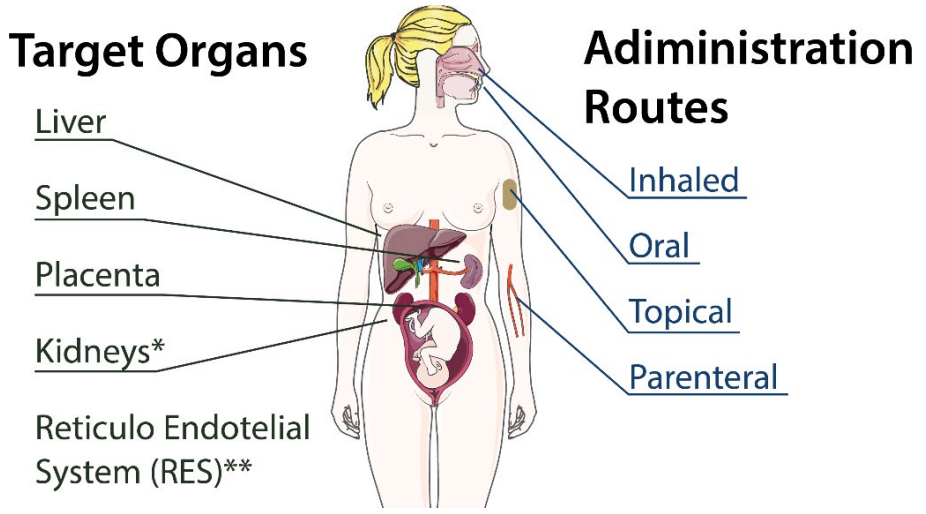

Figure 2: Portals of entry and expected biodistribution of inorganic NPs. *Small molecules and NPs (below 6 nm, the majority of current drugs) leak in-and-out from the blood vessels and are rapidly (in minutes) cleared mostly via the kidneys. **NPs larger than 100 nm are more antigenic, usually opsonized and detected in blood by cells of the RES (phagocytic cells such as monocytes)

A clear example is in the case of intrauterine inflammation which can increase maternofoetal transfer of NPs in a size-dependent manner. This maternofoetal transfer of NPs is a critical issue in designing theranostic NPs for in vivo applications during pregnancy. Recent studies have reported that certain NPs can cross the placental barrier in healthy pregnant animals depending on the size and surface modification of the nanoparticles and the developmental stages of the foetuses. This has also been shown in the study of Tian et al., [24] where the intrauterine inflammation enhanced the maternofoetal transfer of AuNPs in the late gestation stage of murine pregnancy in a size-dependent manner. Using AuNPs with diameters of 3 nm (Au3), 13 nm (Au13) and 32 nm (Au32) it was observed that the accumulation of Au3 and Au13 NPs in the foetuses was significantly increased in intrauterine inflammatory mice compared with healthy control mice: the concentration of Au3 was much higher than Au13 in foetal tissues of intrauterine inflammatory mice. In contrast, Au32 NPs could not cross the placental barrier either in healthy or in intrauterine inflammatory mice. The structural and functional abnormalities of the placenta under intrauterine inflammation is hypothesized to be the potential mechanism of the increased maternofoetal transfer of the small-sized NPs on the pathological conditions described [24].

Evolution of NPs in biological media

Despite the tremendous potential of nanomedicine and hundreds of millions (if not billions) poured from funding institutions, it could be acknowledged that little progress has been made towards matching expectations. Thus few years ago, in 2012, Nature Reviews Drug Discovery was already wondering if the wave of nanomedicine was cresting [25], and Bayer announced that when they tried to replicate results of 67 studies involving nanomedicine published in academic journals, nearly two-thirds failed [26], which is in part attributed to poorly described nanomaterials along with the lack of publication of negative results in the scientific community. Also in Nature Nanotechnology, editor in chief Ai Li Chun required that works with NPs in biological context should present better (and properly) characterized NPs, and at the same time, Prof. Harald Krug, after analysing about 10.000 nanotoxicology papers, did find serious problems in the state and purity of the employed NPs [27]. And again, most recently, Derek Lowe's commentary on drug discovery and the pharma industry in the Science Magazine Blog, commenting on the Nature Materials paper Analysis of Nanoparticles Delivery to tumours [28, 29], recognized it again: "Working out that delivery and pharmacokinetics aspects of these things [NPs] was already known to be a challenge, but it's proven to be even more of one than anybody thought".

Therefore, it is clear that one of the factors limiting NP application in medicine in general is the needed to properly understand and describe their physico-chemical behaviour in biological media and inside the body. Thus, while the scientific community keeps on trying new nanosized constructs in animal models looking for therapeutic efficacy, little progress is done towards proper knowledge of the full exposure process, and if very promising results have been observed in these referred cases, it will not be possible to master nanomedicine without a proper knowledge of the physical and chemical evolution of NPs inside living bodies [27]. Thus, whichever the NP intended effect, it has to be correlated with how the NP interact, evolve and is transformed during its exposure to the mother's body, during Administration, Distribution, Metabolization and Excretion (ADME), how inside the body the placental barrier discriminate and filters NPs and how this biodistribution is altered during the course of the targeted disease. Moreover, due to interactions between NPs and components from the biological medium, NPs are known to suffer different type of alterations. This includes, loss of colloidal stability [30], protein adsorption [31-33] and dissolution [34, 35]. The question is to understand how an evolving size, shape and surface state, depending on portal of entry, determines the final fate of NPs inside the mother and the foetus during treatment.

Once NPs have been synthesized, they have to be stabilized and dispersed in the biological media of interest. Small NPs show high surface energies what increases instability with decreasing size since atoms at the surface of a NP are quite unsettled: They do not benefit from the protection of the crystal in highly coordinated bulk atoms, nor they dispose the high mobility and vibration frequency of small molecular species to dissipate energy. Therefore it is advised that the surface of a NP is passivated before they are used in reactive environments, such as the biological ones. Thus, conjugation, initially used to passivate and stabilize NPs, can also be used as an interface for functionalization, providing the chemical and biological moieties that will determine behavior and fate of the NPs inside the body. This can also be used to trap drugs in the NP coating layer, as much as binding them to that layer, directly or via linkers. At the same time targeting moieties as antibodies or aptamers are easily absorbed onto NPs. Clearly, once a molecule is bound to a NP, its fate and biodistribution is determined by the NP physicochemical features rather than the drug. Thus, nanocarriers can strongly contribute to modifications on pharmacokinetics and biodistribution of numerous active principles, by driving them through different pathways, depending on morphological, surface state and the physicochemical properties of the nanocarrier. In fact, this, adding other chemical moieties to the drug, has been a traditional way to alter drug pharmacokinetics in both ways, their biodistribution and their in-body metabolization, what determines dosing (concentration and time) parameters in the different organs. This can be clearly seen in the different platinum (three generations), cortisone (five generations), benzodiazepines (four generations) and many other families of pharmacological compounds and their different generations.

Interfacing the as-synthesized NPs with biological media is not always straight forward. The chemical environment desirable for inorganic NPs and the one desirable for cells and biomolecules may be quite different and certainly, in many approaches, obviously incompatible. Thus the NP surface, once it has been generated, has to be modified in order to be inserted efficiently into the biological machinery. The requirements are controlled colloidal stability (avoiding aggregation, sedimentation and stickiness), controlled interaction with proteins in plasma (formation of a Protein Corona), controlled (no) immunogenicity, controlled chemical reactivity and controlled integrity of the material for its expulsion or destruction after use.

As the features of the core of NPs are determined by the needed physical-chemical properties, the pharmacological properties are adjusted by the NP surface engineering. As said, once being brought into contact with a medium, NPs experience surface modifications (aggregation, protein adsorption, and chemical transformation, loose of atoms – dissolution) due to interactions between them and components from that biological medium. More than one of these processes can happen at the same time and there might also be a competition between them. In fact, it is common to observe that NPs become unstable in the biological media and that they corrode while aggregate and are coated by proteins, and then precipitate. Similarly, corrosion increases the ions concentration leading to aggregation [36], while aggregation, via total surface area reduction, reduces corrosion. Importantly, small modifications on the nature of the conjugate have a strong influence on conjugate interactions, protein corona formation, aggregation, degradation, and consequently different biological behavior and fate [37]. For example, inside the body, pores smaller

than 1 nm have been reported in tight junctions on certain continuous capillaries (including blood-brain barrier, placenta and testis barrier) while continuous capillaries (muscle, lung, skin) have pores of about 6 nm allowing small drugs to flood the body (carpet bombing). Fenestrated capillaries (intestine, some endocrine and exocrine glands) have pores up to 50–60 nm, usually closed by a diaphragm. Finally, discontinuous capillaries (liver, spleen, bone marrow) have pores between 100–1000 nm, which allow the passage of macromolecules between plasma and interstitium. Thus, small molecules (below 6 nm, the majority of current drugs) leak in-and-out from the blood vessels and are rapidly (in minutes) cleared mostly via the kidneys, while the passive transport of macromolecules (and consequently NPs) through these porous is negligible and they tend to accumulate in liver and spleen. It is worth noting here that blood vessel permeability changes during the course of disease, such as in the case of inflammation and cancer. In cancer, the rapid growth of tumors results in leaky vessels surrounding them. These fenestrated vessels allow macromolecules and NPs to reach and permeate through the tumor. In addition, the NPs are retained due to the lack of a functional lymphatic system. This effect, EPR, is widely reported in the literature [13, 38] and has been exploited to passively accumulate nanocarriers in tumors [39]. Besides, during inflammation, the blood vessels around the tissue becomes permeable to allow macrophages translocation. In all cases, surface modifications allow the modification of this size-dependent fate, for example, by making small NPs recognizable by the immune system [40] or stealth the large ones by means of chemical surface modification, such as pegylation or PVP coating.

Thus, subtle alteration of the NP state may have critical consequences on NP behavior and performance [31, 37]. Therefore, in recent years, it has become evident that it is necessary to systematically and accurately define particle characteristics not only in order to understand their potential effects to biological systems but also to ensure that results are reproducible. For example, several studies showed that the methods used for samples preparation had an impact on the NPs stability and consequently on the results of the tests. These synthesis differences affected how the NPs evolve and transform in biological media. Among the major NP transformations, the following are the most common:

Aggregation: Regarding aggregation, the loss of colloidal stability has a dramatic effect on the abilities of NPs to travel through the body. Unless that intra-site (e.g. intratumoral) injections are foreseen, good dispersing NPs are needed. There are several factors that cause the aggregation of colloidal NPs, for instance, initial concentration of NPs and ionic strength of the medium, which is well described in the DLVO theory for colloidal stability [41, 42]. In these cases, the aggregation detected here is due to the charge screening effect of salts or charge carriers present in biological media which causes a compression of the electrolytic double layer and a decrease in interparticle repulsion [43]. Therefore, unless steric repulsion is provided to the NP surface, it has been observed that NPs tend to agglomerate/aggregate after relatively short incubation times in different buffers and biological media. It has to be noticed that no aggregation occurs in media with high protein concentration like serum, despite the fact that they are highly saline fluids. Here, the stability of NPs is maintained thanks to the formation of a Protein Corona. In this case, the stabilizing mechanism changes from electrostatic to steric, and then the charge screening becomes irrelevant. The competition between aggregation induced by high ionic concentration and stabilization by protein absorption is well correlated to the relative amounts of both (ions and proteins) in the media and can be controlled by the addition sequence [33]. Evidently, the special properties of NPs are lost if they aggregate. Therefore, in too many cases, the loss of colloidal stability, aggregation and sedimentation are behind the lack of (or unexpected) biological responses [44, 45].

Protein Corona formation: Ionic strength, pH and biological macromolecules alter the NP characteristics and potentially the biological effects of these nanomaterials. For example, that the presence of proteins in the medium affected the entry and intracellular localization of NPs in cells, and thus modulated their potential toxicity, was already described in 2004 [46]. In fact, the formation of a protein corona on top of the NP surface has been observed to control biodistribution, uptake and biological response, transforming them from innocuous to toxic, or reverse. The protein corona is a layer of proteins that associate with the NP surface, and it is the analogue of the interaction of serum components with medical implants. This protein corona can be soft or hard. Soft means that the proteins on it are in equilibrium and exchange with proteins in the media. Hard refers to the formation of a stable monolayer of proteins that do not detach anymore from the NP surface. Normally, at short times a soft protein corona is formed and, in some cases, it evolves towards a hard one as described by the Vroman effect [47]. This protein corona' formation is time and NP functionalization dependent. Remarkably, surface properties of NPs are found to play a very significant role in determining the NPs behavior with proteins in different environments. Indeed once the corona is hardened [48], it is the protein corona what actually the cell "sees" [49].

Oxidation, Corrosion, Dissolution: it is well-known that some NPs can dissolve in certain dispersing media [35, 50, 51]. The extent of their dissolution depends not only on their intrinsic properties such as size and shape, but also on characteristics of the surroundings, including pH and ionic strength, as well as the presence of organic matter, mainly proteins [52, 53]. For example, iron oxide NPs dissolve in vivo and this phenomenon is used to deliver iron ions in the case of ferropenic anemia and kidney compromised patients (as in the case of Feromuxytol, Feraheme®; Amag Pharmaceuticals, Waltham, MA). Thus, while small NPs can be preserved for a long time in solution in the appropriate conditions, they may also be prone to degradation (oxidative and non-oxidative dissolution) in physiological media. Indeed, it is said that is below ca. 30 nm in diameter where the small NP core cannot support the high energy surface [54] and tends to dissolution in non saturating conditions. The driving force behind NP dissolution mainly depends on the solubility of the constituent ions in a given environment and their concentration gradients in solution. This phenomenon, accelerated at the nanoscale, is referred to as the Gibbs-Thomson effect, and in NPs manifested as Ostwald ripening, where precipitates dissolve or grow due to concentration gradients of reacting species [55]. This has strong consequences, not only on the metabolization and expulsion of NPs from the body, but also on its regulation, since if they are permanent, they may be regulated as a device, like and implant, while if they are metabolized and expulsed, they may be regulated as a drug.

Thus, it is in this scenario, where all these above described factors must be assessed and taken into account, where the potential benefits of nanotechnology in Maternal Fetal Medicine and NP-mediated treatments for obstetric conditions have to be properly developed for the benefit of patients.

NPs at work in Maternal Foetal Medicine

Despite the benefits that can entail the use of NPs as platforms for multimodal therapy in Maternal Foetal Medicine, examples in the literature are still scarce and disperse. Currently, several experimental nanomaterial based approaches are being investigated as a safer

and less invasive alternative to standard diagnostic and therapeutic techniques for the management of several traditionally „'surgical' reproductive diseases that we try to review below, classified in their use as diagnostic agents, application in gynaecologic oncology and in other obstetric complications either as carriers or therapeutic agents or both.

NPs used in diagnosis and imaging

One of the NP most commonly used since decades as Magnetic Resonance Imaging contrast agent is Fe_3O_4NPs [56]. The feasibility of their use for the detection of experimentally induced endometriosis was evaluated in the study of Lee et al [57]. Endometriosis is a common condition, affecting 6–10% of women from premenarche to postmenopause [58]. In the above mentioned study of Lee et al., [57] endometriosis was surgically induced in rats by transplanting an autologous fragment of uterine tissue onto the inner surface of the abdominal wall, the posterior surface of the uterine body and the arterial cascades of the small intestines adjacent to mesenteric blood vessels. MRI using Gadolinium with DTPA (diethylenetriaminepentacetate), the molecular complex of the already commercialized Gadopentetic acid as MRI contrast agent, and Fe_3O_4NPs was performed for the evaluation of the ectopic uterine tissue. The use of Fe_3O_4NPs was proved to give higher and better signal in all animal groups used, while it bears a lower toxicity than gadolinium compounds.

Similarly, Girardi et al., [59] conjugated the anti-complement C3 vector to Fe3O4NPs to develop a MRI-based method for non-invasive detection of complement activation in placenta and foetal brain in vivo in utero. Using this method, it was found that the anti-complement C3 conjugated Fe_3O_4NPs not only increased contrast, but also the anti complement bind the nanostructure preferentially within the inflamed placenta and foetal brain cortical tissue. Using two mouse models of pregnancy complications (a model for obstetrics antiphospholipid syndrome (APS) and a model of preterm birth (PTB), they also found that detection of C3 deposition in the placenta in the APS model was associated with placental insufficiency characterised by increased oxidative stress, decreased vascular endothelial growth factor and placental growth factor levels, and intrauterine growth restriction, in an example of a theranostic NP-based platform.

NP used for Gynecologic Oncology

Gynecological cancers such as endometrial, ovarian, cervical and vulvar are rare when compared to the most common lung or colon cancers. However, they occur, and also during pregnancy, threating life of both mother and child. All the knowledge generated in nano-oncology [60] during the last decades can be potentially be applied to them. As previously said, none of the existing single-modality treatments used to cure cancer are entirely efficient. Moreover, current anticancer therapies (including chemotherapy, radiotherapy, surgery, hormone therapy, immunotherapy, photodynamic therapy, and targeted therapies) are not effective for tumour resistance prevention and treatment [5, 61]. Hence, multimodal treatments are being investigated for the possible synergistic effects of the combination of different therapies and the lack of resistangenesis of multimodal approaches. In such cases, NPs are especially suited to combine in a unique platform different tumour treatment modalities. Importantly, in this area, the combination of nab (albumin nanoparticles)-paclitaxel with the antitumoral drug Nedaplation (NDP) for the treatment of patients with late-stage, recurrent, or meta-static cervical cancer appears to be active and tolerable. The use of this combination is presented in the recent work of Li et al., [62] (phase 2 study), where nab-paclitaxel and NDP were used for the treatment of patients with cervical cancer. A total of 27 patients were included in the study. Out of them, 26 patients completed a total of 92 cycles of chemotherapy, with an average of 3.4 cycles per patient. The response rate was 50.0% (13 out of 26 patients), the overall survival rate was 16.6 months and the progression-free survival was 9.1 months (95% confidence interval, 2.4-15.8 months). These results show values higher when therapies are combined, than the use of Nab-paclitaxel and NDP alone, respectively.

NPs used in drug delivery for different obstetric conditions

Since their firsts description in the 60s [63], liposomes have gained attention as drug delivery vehicles. As nanosized lipid bilayers, they are highly biocompatibile, nonimmunogenic, they can encapsulated a wide array of drugs and enhance their solubility. In maternal foetal medicine, they have been used to deliver insulin factor to improve foetal weight in cases of fetal growth restriction [64]. In that work, the authors used targeted liposomes to efficiently deliver cargoes of carboxyfluorescein and insulin-like growth factor 2 to the mouse placenta. Tumor-homing peptide sequences CGKRK and iRGD were used as the targeting agents to selectively bind the liposomes to the placental surface. This peptide-coated liposomal NPs intravenously injected into pregnant mice accumulated within the mouse placenta, whereas control NPs exhibited reduced binding and/or fetal transfer. In turn, Insuline-like growth factor 2 significantly increased mean placental weight when administered to healthy animals and significantly improved fetal weight distribution in a well-characterized model of fetal growth restriction. Thus, these data provide proof of principle for targeted delivery of drugs to the placenta and provide a novel platform for the development of placenta-specific therapeutics. Dendrimers have been another material in the nanoscale largely used for drug delivery since their synthetic developments in the late 1970s. They consist on repetitive branched molecules that can be synthesized with controlled sizes and functionalities in the nano regime, useful for delivery of associated therapeutic molecules. As example, Polyamidoamine PAMAM dendrimers have been employed for siRNA delivery to regulate placental soluble fms-like tyrosine kinase 1 (sFlt1) in the works of Maynard et al., [65] and Yu et al [66]. sFlt1, an antagonist of the Vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), is upregulated in preeclampsia (PE), leading to increased systemic levels of sFlt1 that fall after delivery. The works of Maynard [65] and Yu [66] suggested that siRNA-sFlt1-PAMAM effectively decreased sFlt1 secretion and improved pregnancy outcomes in a preeclamptic rat model, which may provide a new therapeutic strategy for PE.

Among other nanomaterials employed, it can be mentioned the use of chitosan-DNA NPs for in vitro and in utero gene delivery in mice [67]. In this study, the feasibility of the transfer of reporter gene (GFP) using chitosan as a transfer vehicle was evaluated. Results showed that although amniotic fluid decreased in vitro transfection efficiency, in vivo transfection of this chitosan-DNA NPs by amniotic injection achieved short-term transgene expression in foetus' lung and intestine. The in utero delivery of chitosan-DNA resulted in postnatal gene expression, showing promising applications for non-viral gene transfer in animal models of foetal gene therapy. In another work, engineered bacterial-derived nanospheres (EnGeneIC Delivery Vehicles (EDVs)) were prepared to actively target epidermal growth factor receptors (EGRF), which are abundantly expressed in human placenta [68]. In this work, the EDVs were also loaded with doxorubicin and tested to overcome existing limitations in the medical management of ectopic pregnancy and trophoblastic diseases. Specifically, the authors aimed to determine whether these EGRF-targeting EDVs loaded with the chemotherapeutic doxorubicin could regress placental cells in vitro, ex vivo, and in vivo. Results showed that those EDVs may be a novel nanoparticle treatment for ectopic pregnancy and other disorders of

trophoblast growth.

NPs as therapeutic agents

NPs as antibiotics. Dendrimers have also emerged as topical microbicides to treat vaginal infections. The study of Wang et al., [69] explored the in vitro and in vivo antimicrobial activity of PAMAM dendrimers, and the associated mechanism. Interestingly, topical cervical application of the neutral charged G4-PAMAM-OH dendrimer and amino-terminated, positively charged, G4-PAMAM-NH2 dendrimer showed potential to treat the Escherichia coli induced ascending uterine infection in guinea pig model of chorioamnionitis. Amniotic fluid collected from different gestational sacs of infected guinea pigs posttreatment showed absence of E. coli growth in the cultures plated with that dendrimer. Tumor necrosis factor (TNFα) and interleukin (IL-6 and IL-1β) levels in placenta of the G_4-PAMAM-OH treated animals were comparable to those in healthy animals while these were notably high in infected animals.

Inorganic NPs: The case of Cerium Oxide Nanoparticles (CeO_2NPs). Recently, CeO_2NPs have caught considerable attention as a potential therapeutic tool in the prevention and treatment of oxidative stress related diseases. They display minimal toxicity to normal tissues and provide protection from various forms of excess of Reactive Oxygen Species (ROS) in the case of inflammation.Those features can be used for the benefit of the patients in maternofoetal medicine. This interest relies on the expected properties of this nanomaterial to catalytically (does not get consumed) scavenge most of the ROS due to its multi enzyme mimetic activities resembling mechanism of SOD [70-72], catalase [73, 74] and peroxidase [75], becoming inert at healthy physiological ROS levels [76]. The beneficial effects of CeO_2NPs treatment have been reported in the fields of neurology [77], diabetes [78], retinal diseases [75, 79], liver cirrhosis [8], oncology [70, 80] and cardiology [81, 82], among others. With time (weeks), CeO2NPs are degraded into safe Ce^{3+} ions and expulsed via urinary track [83].

In maternalfoetal medicine, it is suggested that free radicals play an important role in the pathogenesis of endometriosis, among other complications, such as preeclampsia. In the sutdy of Chaudhury et al., [84] it has been observed that CeO_2NPs mitigated the endometrial lesions induced in mice model by decreasing oxidative stress and inhibiting angiogenesis. Moreover, CeO_2NPs protected endometriosis related adverse effects on the oocytes, which is critical for successful pregnancy.

Organic NPs: Curcumin. The study of Behroozi et al., [85] investigated the effects of intraperitoneal administration of nanocurcumin on ischemia-reperfusion injury in ovaries, which often causes an acute lower abdominal pain in women known as ovarian torsion. In this study healthy female Wistar rats, laparotomy induced rats, and ischemia induced rats were compared. Results showed that nanocurcumin treated animals experienced significantly improved development of ischemia and reperfusion tissue injury compared to non-treated ones. Thus, intraperitoneal administration of nanocurcumin can also be helpful in minimizing ischemia-reperfusion injury in ovarian tissue exposed to ischemia.

Conclusion

As described in this review, nanoparticulate materials have been under intense research and exploited to enhance the delivery of drugs in the treatment of a number of diseases, used as therapeutic agents by themselves and/or used as imaging agents, demonstrating that NP-based therapies can act as "precision medicine" for targeting specific sites of interest in maternofoetal medicine while leaving healthy tissue intact. These materials showed potential benefits in terms of pharmaceutical flexibility, selectivity, dose reduction, and minimization of adverse effects. In addition, we have been reviewed several experimental nanomaterial based approaches, which are being investigated as a safer and less invasive alternatives to standard diagnostic and therapeutic techniques for the management of diseases in maternofoetal medicine. However, to effectively design, produce and monitor the biological work of NPs, and finally unleash nanomedicine potential in maternofoetal medicine, the proper knowledge of the NPs physico-chemical state at all times of its evolution inside living bodies is needed. This knowledge comprises among others the colloidal stability, vicinity interactions, chemical transformations-as corrosion-, association with plasma proteins (protein corona), interaction with components of the immune system, and all the traditional ADME studies (administration, distribution, metabolization, and excretion of drugs from the body) but adapted to the unique NP specificities.

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