

Research Article

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Man vs Rat, vs Nanoparticle: Gold Nanoparticles as a Gentler Probe for Human Brain, Fertility / Embryo Treatments

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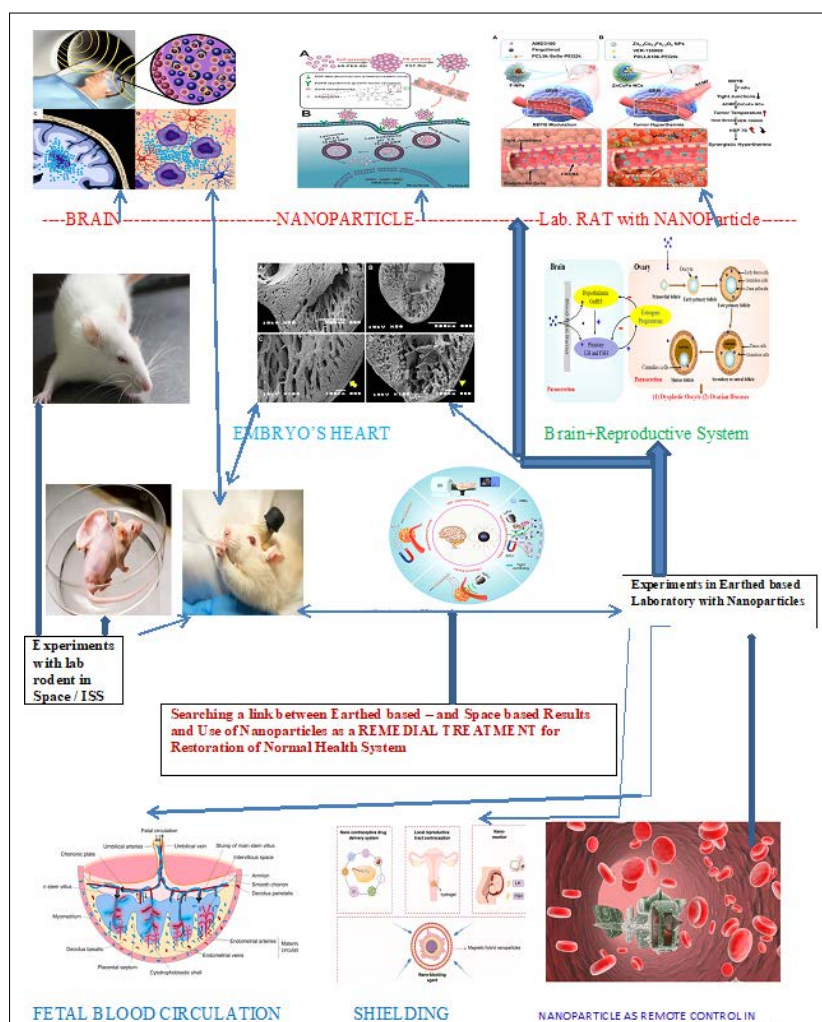
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ABSTRACT

Laboratory rats (or lab rodent) have physiological and genetic similarities to human. This suggests that results of observation, obtained from nano-particle based biomedical test, can be applicable to human. Detection of nano-particles and recent development of magnetic gold nano-particles offer the scientists as an invaluable tool for the brain-tumor treatment. Due to their nano level sizes and varieties of shapes these magnetic nano-particles have the capability to cross or pass through the blood-brain-barrier (BBB). Self-assembly, the uniqueness property of these nanoparticles, makes them a magical, gentler tool compared to other nanoparticles, for targeted drug delivery in brain-tumor treatment, as a contraceptive way to control reproduction but their ability to cross the BBB and brain-tumor targeting mechanism not yet fully known. The potential drawback of these magnetic nanoparticles is the disturbance or dis-balance in the sex hormones secretion leads to sufferings of dysplastic Oocyte and Overian diseases.

Due to the uniqueness of self-assembling property scientists are hopeful that mangetic nanoparticles will be capable to unlock the invisible secrets of the biological world.

Graphical Abstract



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Introduction

Man vs Rat

Human life is more precious. Any harmful effect on human body during a biomedical test may cause the end of life or longterm suffering. As an alternate laboratory rat (figure 1B) are considered as model organisms due to their (i) physiological and genetic similarities to human, (ii) manageable size, and (iii) well documented biology. Looking back into the history the earliest record was in the early 1800s but first use of rat in experiments started even earlier records dating back to 1850s. The first breakthrough was occurred in 1992 when Wister rat (figure 1A) was used for experimentation. Later Norway rats (Rottus Norvegicus) (figure 1C) became highly favorable in research because of its size and serving as an excellent model for studies involving neuroscience, toxicology and physiology. Not only that the benefits of using rats are:

- Rats are easily trainable and perfectly suited for psychological experiments specially for neural network;
- Medium sized rat typically weighing between 250-500 gm, measuring about 20-25 cm in body length with additional 18-25 cm tail which is the key species in biological and biomedical research;
- They (rats) reach sexual maturity around 6-8 weeks with a gestation period of approx. 21-23 days
- Female rat generally produces litters of 6-12 pups.
- The rat genomes are fully sequenced resulting which they are valuable resources for genetic studies / research.
- Their larger brain and complex behaviour render them ideal for research in particular for studying in various areas such as

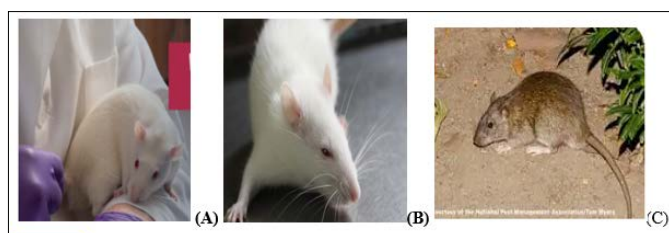


Figure 1: (A) Wister rat and (B) Laboratory rat (or Lab rodent) that have become the cornerstone of animal research due to their genetic and physiological similarities to human (Courtesy : Olena Kurashova/iStock), (C) Norway rat.

- Behavioral Science and and Psychology** - Learning, memory and addiction
- Stress Research** - Body's long term and short term reactions to stress, stress as a critical factor in health and diseases
- Endocrinology and Diabetes** - Study of Endocrinology, particularly streptocin-induced diabetic effects leading to critical insights into the disease's mechanism and treatments.
- Neurobiology and Neuroscience** - learning about brain's structure and function
- Genetic Research** - Comprehensive genetic informations, examining gene functions and disease mechanisms, complex traits and disease.
- Cancer Research** - Elucidating cancer biology, identifying carcinogens developing chemotherapy drug, hormone driven

cancers such as Breast Cancer and it treatment.

- Toxicology and Pharmacology** - Testing of safety and efficacy of drugs and chemicals before human exposures, determining hazard categorization, risk factors and safe exposure level.
- Rise in Population and Influences** - Preclinical knowledge

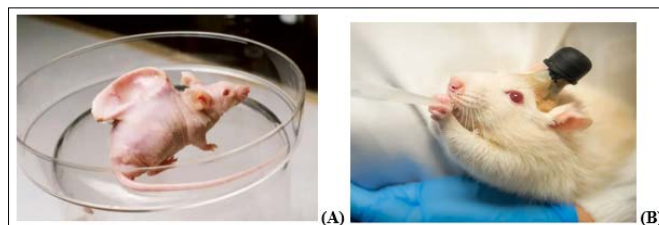


Figure 2: Shows (A) the Vacanti mouse with a human-ear-shaped piece of cartilage growing out of its back (Courtesy : Wikicommons under Fair Use) and (B) a laboratory rat with a brain implant used to record in vivo neuronal activity during a particular task (Courtesy: Anna Marchenkova via Wikicommons under CC BY 4.0)



Figure 3: Represents (A) an astronaut doing experiment using rat in International Space Station Lab and (B) used rat in the experiment with the cage (Credit : NASA)

Microgravity Effects on Rats and Applicable to Human

The Rodent (i.e. laboratory rat) are used to study the effect of neurology and psychology due to drug and diseases. NASA used lab. Rat to International Space Station (ISS) for experiment in microgravity , combined effect of microgravity & nanoparticles, remedial study of space borne effects using nano-technology. Most of the lab rats / mice are kept in a shoe-box sized cages (the space is about double) in order to see the effects / responses in an environment restricting house and also from natural behavior like burrowing, climbing or even standing up straight (figure 3).

The vacanti mouse or "Ear mouse" (having human ear shaped piece of cartilage showing out of its back of a lab mouse, shown in figure 2A) are one of the more bizzare and visually unsettling experiments used as rodent in 1902 onwards. A lab rat and vacanti mouse are used in experiment for multi-use studies. For example, a lab rat with a brain implant (see fig.2B) are used to record in vivo neuronal activity. NASA's different Rodent Research (RR) missions were to understand or gaining knowledge about :

- RR1 (2014)** - the effect of microgravity on rodent bone and muscle;
- RR2 (2015)** - how the space environment affect the musculoskeletal and neurological sustem;
- RR3 (2016)** - the treatment for skeletal muscle wasting and weakness exposed for staying in long time in space.
- RR8 (2018)** - exploring the physiology of aging and how age affects disease progression.

RR9 (2019) - examining the effect of microgravity on blood vessels, in the brain, eye and on cartilage loss in joints.

RR10(2020) - how bone tissue affected by microgravity jointly and difference with that of on Earth induced by oxidation stress and radiation.

RR11,12 - vascular miRNA response and adoption to microgravity and antibody produced and immune memory.

RR14,15 - how microgravity affects on human body's internal clock and biological circadian rhythm, i.e. affects on colon, heart, lungs, liver, kidney and hypothalamus, change in daily clock affected behavior.

RR 16,17 - physiology of aging in response to microgravity and biological age of the onset of disease progression.

RR18 - microgravity affects in visual function i.e. vascular system of the retina and its potential treatment.

RR19 - signalling pathways and breakdown of muscles and bones

RR20-22 - studying the change in reproduction system - whether temporary or permanent, fertility issue, cardiovascular and musculoskeletal deconditioning, effects on normal aging on Earth i.e. searching a link between aging and gravity at molecular level.

RR23 - affects on vision i.e. structure and function of the associated arteries, veins and lymphatic vessel, shed light on eye condition and eye disease on Earth, effects on weightlessness time.

Rodent Researches in ISS provide the scientists to search for finding a mechanism how to handle the possible effects on human body due to microgravity or weightlessness, that are observed in lab rats, in the environment of the Earth. Based on the above experiments it is confirmed that whole human body parts from eye, brain, muscle, bone to blood-cells including immunity, reproductive system are affected by microgravity. Two significant treatments of body parts i.e. brain and reproductive system are discussed in this paper.

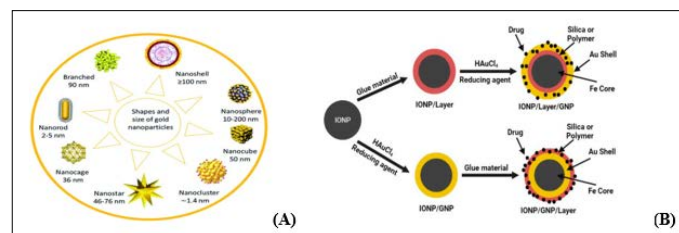


Figure 4: Represents (A) various shapes and sizes of gold-plasmon-resonance nanoparticles (adopted from ref. Mobed et al. [1] and (B) schematic diagram showing the schemes of synthesizing magnetic gold nanoparticles with intermediate layer (adopted from ref. Elmi et al [2])

Gold Nano-Particles and Magnetic Nanoparticles

The prefix term “Nano” means ranging between 1 and 100nm and particles having sizes within this range are called nanoparticles. In fact, nanoparticles in natural environment are the result of physical, chemical and biological activities [1, 3]. According to our present knowledge the nanoparticles are capable to enter cells, causing structural and functional disruption via intercellular oxidative stress or producing reactive oxygen. Not only that, several nanoparticles have the ability to cross the blood-brains, blood-testis and placental barriers. Gold nanoparticles have a variety of sizes and forms ranging from 1nm to 8µm and various shapes including nano-rods, nano-shells, nano-cubes, nano-cages, etc (figure 4A) [4]. These particles have a unique properties

through combination of chemical, physical, optical and electrical capabilities that make a novel platform useful in various sectors including medicines.

Magnetic gold nanoparticles (mAuNPs) (figure 4B) are recently developed magnetic nanoparticles have high magnetic moments and surface-area to volume ratio that makes them inevitable aids for hyperthermia therapy and targeted drug delivery [5]. In addition, these magnetic particles offer the scientists as an inevitable probes of high contrast agent for magnetic resonance imaging (MRI) particularly in the field of sensitivity of bio-sensors and diagnostic tools. These magnetic nanoparticles, in general, are typically fabricated from pure metals such as Fe, Co, Ni and some rare earth metals or a mixture of metals and polymers. Note that, in the case of magnetic gold nanoparticles they are basically a hybrid metallic nanocomposites i.e. bimetallic core-shell structure in which iron (Fe), cobalt (Co) or nickel (Ni) as magnetic core while gold (Au), platinum (Pt) or silver (Ag) as the plasmonic shell (figure 4B) [2].

Uniqueness of Self-Assembly of Gold Nanoparticles

Self-assembly is a process in which individual units of nano-material associate with themselves spontaneously into a defined and organized structure or larger units with minimum external direction. Simply, it is autonomous organisation of components into pattern or structure without human intervention i.e. a spontaneous and reversible process that brings together randomly moving nanoparticles in a definite geometry [6]. The importance of this self-assembly of nanomaterials is that at present it is considered for nano-structuring and nano-fabrication because of its simplicity, versatility, spontaneity such that it offers a promising source of low cost and high yield in drug delivery, self-assembling materials as block copolymers, as magnetic nanochains i.e. a new class of magneto responsive and super-paramagnetic nano structures with highly anisotropic shapes (chain like) suitable for magnetic drug delivery under low and super low frequency alternating magnetic field [7-9].

Treatment of Brain Tumor

Brain tumors are the life threatening diseases of central nervous system. Glioblastoma (GBM) is a grade IV astrocytoma, and the most common but difficult brain tumor to treat [10]. Secondly, even though it detected earlier, still the median survival rate for patient is only 12 – 15 months [11]. Our present knowledge shows the standard treatment of GBM involves surgery and radiation with concurrent and adjuvant chemotherapy. In case of surgery the bulk of a GBM tumor is to be removed and then for remain portion chemotherapy and radiotherapy are applied into the patient's brain for restoration. In this phase, blood-brain-barrier (BBB) offers another challenge to the treatment of GBM tumors for overall survival.

Figure 5 shows the localized hyperthermia effect (also known as thermotherapy) used in brain tumor treatment through the application of an alternating magnetic field. When a magnetic field is applied to the target area, the effectiveness (i.e. strength) of the hyperthermic treatment depends on the (i) strength of alternating magnetic field (AMF), (ii) the size and the concentration of the magnetic nanoparticles and (iii) the time duration of the applied field to the tumor region [12].

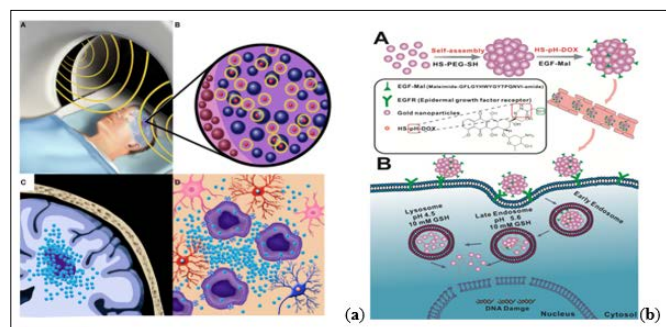


Figure 5: Schematic diagram showing (a) local hyperthermia treatment of a patient with malignant brain tumor through magnetic nanoparticles (for details see the text of reference and adopted from ref [12]); and (b) the schematic design of the self-assembly of gold nanoparticles which is used active targeting in brain tumor (through EPR effect (for details see the text of ref.Feng et al 2017 ; adopted from ref [13])

The use of the uniqueness of self-assembly of gold nanoparticles in brain tumors and also in blood –brain-barrier (BBB) (see figure 6a) are shown in figure 5b and 6a, respectively. In this case nanoparticles with tunable sizes and surfaces that accumulate in affected brain tumors via EPR effect and active targeting [12, 14]. The size of the nanoparticles are < 20nm so that they are able to pass the BBB and be excreted [15-17]. For self-assembled nano-structure the responsive sizes are 95.4 nm spherical. For nano-assembly of iron oxide, nano-clusters and gold nanoparticles with the size range 205 nm are sensitive to pH (i.e. enzymes and changes in pH) and matrix metalloproteinases in tumor microenvironment [18].

Figure 6a indicates the possible mechanism of crossing the blood-brain-barrier (BBB) through assembly based ways for lab rodent. Although it is hypothesized in a simple approach that the self-assembled gold nanoparticles / spheres via cross linking with dithiol-polyethelene glycol (HS-PEG-SH) are capable :

- to take advantage of disrupted BBB in the brain tumor
- as a targeted drug delivery platform for enhanced brain tumor treatment
- to increase the nanoparticle retention in the tumor tissue via passive targeting effect [19].

This means that the assembling approaches of gold nanoparticles with different sizes and shapes can be considered as an effective and feasible targeting strategy for brain tumor treatment. In fact, this assembling approaches based on sizes and shapes are known but their ability to cross the blood-brain-barrier (BBB) and brain tumor targeting mechanism not yet fully known.

Effects of Magnetic Nanoparticles on Female Reproductive System
In the previous section it is mentioned that the magnetic nanoparticles (MNPs) may cross or circumvent the blood-brain-barrier (BBB) and accumulate in the CNS [20]. One of the harmful impacts from such stimulation of CNS is the disruption of hormones secretion. Different regulated neuro-hormones such as gonadotropin-releasing hormone (GnRH), follicle stimulated

hormone (FSH) and Luteinizing hormone (LH), secreted by hypothalamus and pituitary, play a significant roles in the aspect of positive and negative feed back regulation during Oogenesis i.e. an indirect affects of MNPs on Oogenesis and Ovarian health through disturbing the balance of sex hormones [21, 22].

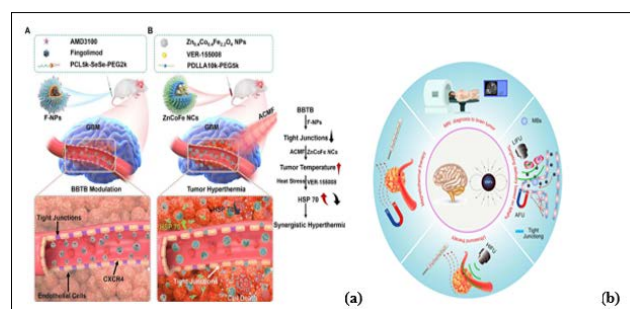


Figure 6: (a) Schematic diagram showing magnetic apoptotic hyperthermia for glioblastoma therapy in which (A) construction of AF-nanoparticles and reduction of barrier function in brain tumor barrier (BTB), and (B) delivery of anti-tumor drugs for highly effective magnetic apoptotic hyperthermia. For details see the text of the reference Wu et al 2023; adopted from ref. Wu et al [19]; copyright : Elsevier 2023), (b) Overview of various treatments of brain tumor using magnetic nanoparticles (adopted from ref. [23]).

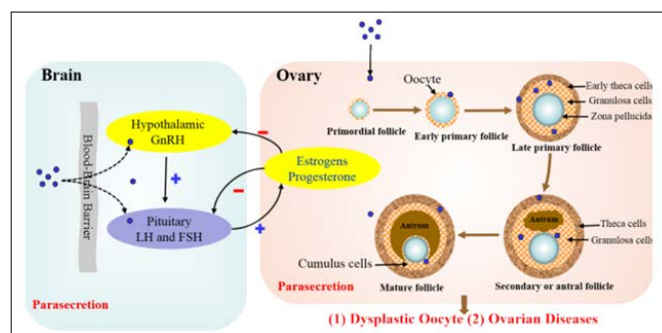


Figure 7: Schematic diagram showing effects of nanoparticles on hormone secretion on hypothalamus-pituitary (left) and on the ovary regarding disbalance in hormone secretion. For details see the text. (adopted from ref. [23]).

Disturbance in the secretion of sex hormones by nanoparticles occurs in two ways:

- **Inside the Brain** - in this case the nanoparticles cross or pass through the BBB and reach into the hypothalamus and also the secretory cells of the pituitary, resulting which an altering appears in the secretion of GnRH, LH and FSH (left side of figure 7).
- **In Ovaries** - after entering inside the ovaries through circulation the nanoparticles accumulate in theca cells and granulosa cells via the primary follicle (right side of figure 7). As a result, it affects steroidogenesis and this parasecretion situation thus eventually leads to sufferings of dysplastic Oocyte and Ovarian diseases [24].

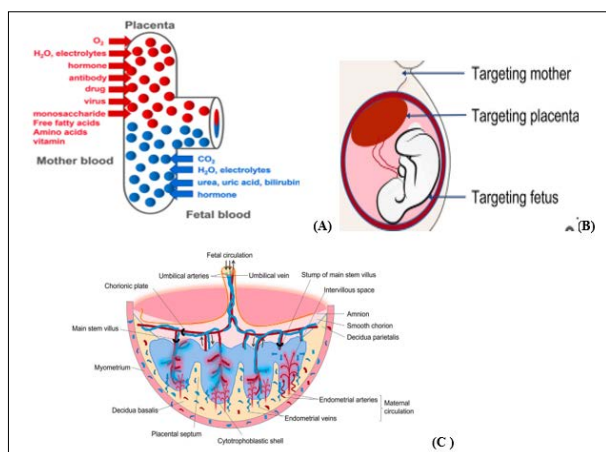


Figure 8: Schematic diagram representing (A) material exchange between mother and fetus, (B) placental targeted drug delivery and nanoparticles applied in pregnancy. Note that the nanoparticle mediated controlled drug and gene delivery specifically targeted to placenta may provide novel avenues for treating placental dysfunction without potential side effects., and (C) the view of a transverse section through a full-term placenta. (for details see the text of reference Jiang et al 2022 adopted from ref [24])

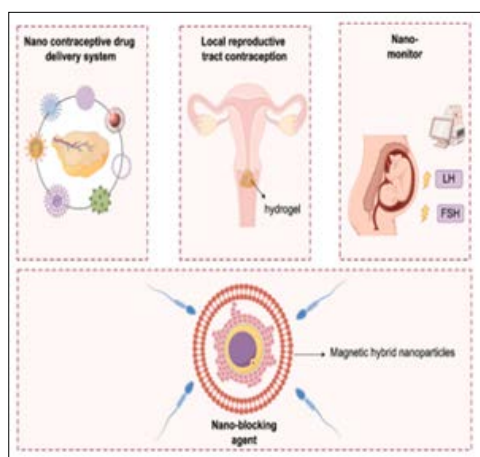


Figure 9: Illustrations of nano material used in contraception and fertility control in the cases of (1) delivery of contraceptive drugs (2) modulation of motility (3) implementation of localized contraception method (4) Monitoring of reproductive states (adopted from ref. Jiang et al [24])

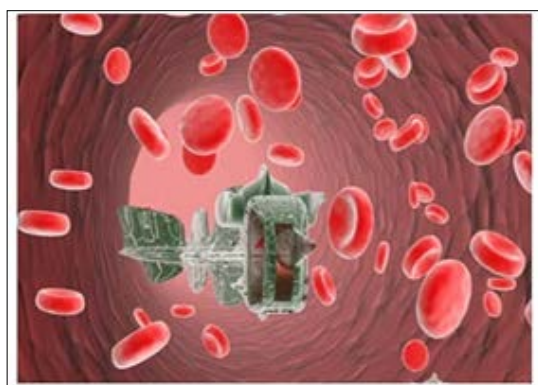


Figure 10: Artist's impression of a future medical nano-robot to be used in the blood stream (Credit : Christian Darkin/Alamy)

Conclusion

Magnetic nanoparticles (MNPs) are considered as the latest and most suitable tool as nano-carrier for the delivery of brain-tumor drugs because of their unique properties like self-assembling and capabilities of easy penetrating the blood-brain barrier compared to other nano-particles. Using the potential of these nano-particles scientists have developed the techniques of magnetic targeting, magnetic thermal therapy (through optimization) for the diagnosis and treatment of brain-tumor focusing on their efficacy in the delivery of anti-brain-tumor drug based on magnetic targeting and low intensity [21]. The current advances in the clinical applications of MNPs for the treatment of brain-tumor (shown in fig.6(b), the placental dysfunction treatment (shown in figure 8).

Oogenesis (or ovum production) is the process of development from oogonia to a mature egg inside ovarian follicles. According to the natural physiological process, so called Follicular atresia covers (i) follicle development, (ii) follicle maturation and (iii) ovulation in female body. During this process regulated hormone secretion like estrogen, GnRH, gonadotropic hormones, growth hormones are essential for healthy follicle atresia system. Nano-particle's ability to cross the blood-brain-barrier and its accumulation in the central nervous system (CNS) raises a harmful potentiality in impacting the disruption of hormone secretion. This disturbance in the balance of sex hormone secretion gives rise difficulty in maintaining the Oogenesis and ovarian health. Not only that, this parasecretion eventually leads to dysplastic Oocyte and ovarian diseases.

Contraception and fertility control is the otherside of the hopeful potential of magnetic nanoparticles. Not only that, beyond this contraception the nanoparticles can also be used in (a) delivery of contraceptive drugs, (b) modulation of sperm motility and functionality (c) implementation of localized contraception method (i.e. blocking agent) and (d) monitoring the reproductive status, etc (figure 9) [22].

Scientists are hopeful that magnetic nanoparticles may become a magical probe (figure 10) to go inside the blood cell for investigating the realistic scenarios to uncover the secrets of biological world [25].

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Data availability Statement

No new data is generated.

Competing Interest

The Author declares no competing authority.

Ethical Interest

Not applicable

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