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RESEARCH ARTICLE

Atrophy, Dystosia and Dysmorphic Feature of Mature Thyroid Follicle in 3rd Trimester of Pregnancy- A Disambiguate and Violation Effect of Smallest Size Nanosilver after Critical Penetration into Its Core

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Abstract

Background: Despite irregular shape and smallest size (2.75nm) silver nanoparticles have been showing up to mark positive response in form of several expandable applications like textile, war head, miscellaneous and cancer diagnostic with treating fields because of their significant coating ability and analyst agent nature in chemical reaction it also shows negative response as endocrine disruptor of vital endocrine glands in human body especially thyroid in 3rd trimester of pregnancy. I*n vivo* studies have demonstrated that these properties are also closely associated with devastative health effects while performing critical penetration into internal cell architecture of pregnant thyroid. There is extreme unavailability of relevant articles and information's in previous and present nano world on possible toxic effects of smallest size nanosilver on the mature thyroid follicle in 3rd trimester of pregnancy.

Methods: This script is an attempt to show off disrupted endocrine system functions and deviated cellular morphology in form of mature thyroid follicle disambiguatory effect which is associated with smallest silver nanoparticle critical penetration into it while performing experiment on pregnant Swiss Albino mice at 3rd trimester of pregnancy at a extreme lower dose (0.25 mg/kg b.w./500 ppm of AgNps in colloidal solution) serial oral application.(13 to 19 gestational age) Our aim was to intimate with the potential endocrine disrupting risks in 3rd trimester of pregnancy posed by smallest size nanosilver fresh colloidal solution.

Result: The smallest size silver nanoparticle alters the physiological activity of mature thyroid follicle along with histological features viewed in form of atresia, dystosia, atrophy and dysmorphology proved to be endocrine disruptor. 3rd trimester pregnant dissected thyroid released hormone (triiodothyronine, tetraiodothyroxine, thyroid stimulating hormone, thyro-calcitonin) analysis was done by using post hoc analysis (ANOVA and MANOVA) with p value <0.05 and found treated group hormone level depletes significantly from control group.

Conclusion-: A close and technical evaluation of these features suggests that the application of smallest size silver nanoparticle colloidal solution in sensitive period of 3rd trimester of pregnancy is an alarm which evokes endocrine disruptive risk in form of cellular toxicity to mature thyroid follicle is quite interesting and study oriented.

Keywords: **Smallest silver** nanoparticle; thyroid follicle disruptor; endocrine disambiguates; 3rd trimester of pregnancy; pregnant Swiss Albino mice; *in vivo* studies; primate vertebrate; mature thyroid follicle; fresh prepared AgNps colloidal solution

Introduction

Back 45 to 50 years history says, an eye attractive and emphasized upraise in the incidence and predominance of a several side effects on human body was reviewed by statistical and epidemiological survey. The developmental process and growth process have been featured by this survey, immunity and nervous system ailment, endocrine disruption and initiation of some vital but common diseases such as thyroid and prostate cancer, goiter and diabetes insipidus [1-3]. These diseases gradually increases and become epidemic when female workers and general public is exposed to infection spreading contaminants. Also these infections are virulent which lead human health to possible endocrine disruption effect. The debatable explanation is spread of infection. Lot of research works has been done till today on endocrine disruptive contaminants. The research says the virulent diseases occur due to spread of infections by these contaminants by altering hormonal and homeostatic systems [4-10]. The World Health Organization (WHO) in 2002 [11] end defined endocrine disruptive contaminants as an outward agent or mixture of

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multiple infectious agents that alters functions of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or sub-populations [11,12]. Smallest nanosilver can be considered as endocrine disruptive contaminated agent. Endocrine disruptive contaminant are available in all parts of the world and in dense. Population and man exposure occurs via contamination of the environment through food, fresh water, fish and meat, or through contact with contaminated and affected environmental matrices, while occupational exposure can occur during the production, use and disposal of the aforementioned chemical substances [13,14]. General population and industrial worker can't avoid or escape from bad impact of endocrine disruptor contaminants, and the bad effects of theses endocrine disruptive contaminants on man body either knowingly or unknowingly exposure of these corrosive chemicals on hormone level is emphasized, so the effort should be done from grass root level in an urgency matter to discover the materials that can behave as endocrine disruptors and to study their molecular mechanisms of action. The Endocrine Disruptor Priority List (EDPL), developed as part of the European Union strategy for endocrine disruptor contaminants, represents a practical attempt to achieve a wider and more comprehensive knowledge of these substances. It provides a list and categorization of chemicals that are likely or suspected to be endocrine disruptor contaminants which also includes small size nanosilver [13,14]. Though several researches carried out in recent years, current knowledge of endocrine disruptor contaminants is still lacunae and most research into this growing problem has concentrated on a few groups of chemical substances such as small size silver nanoparticle colloidal solution, whereas data on a number of other nanomaterials that may act as endocrine disruptor contaminants is still scanty and incomplete [1]. Therefore, to adequately address the issue of endocrine disruptor contaminants, it is our belief that the first step should be to identify all the possible compounds that can interfere and disrupt the homeostasis and regulatory mechanisms of the endocrine system [15-18]. This provision is particularly urgent for those chemicals like poly vinyl coated (PVP) and sodium borohydried ($NaBH_4$) stabilized small size silver nanoparticle colloidal solution that have recently been used in workplaces and consumer products and whose toxicological profile has not yet been clearly and unequivocally defined. This is the case of small size silver nanoparticle's (AgNps). The International Organization for Standardization defines a silver nanoparticle as a small nano-object with all three external dimensions in the size range of approximately 1–100 nm [19]. Nanoparticle grouped into two types, engineered nanoparticle and incidental nanoparticle, engineered are those which are manufactured mechanically which also possess very specific nature and having unique compositions, and incidental nanoparticle, which is also called ultrafine particle these are nothing but byproduct of same manufacturing technique and these techniques are called combustion and vaporization which is ultimately produced by yielding and grinding processes and smaller and smallest silver nanoparticle which is a thyrotoxic agent in chronic penetrative procedure comes under incidental nanoparticle category [20]. Furthermore, because of their very small size, NPs can enter thyroid follicular cells directly by penetrating the cell membrane and may cause interference of important cell functions such as inflammation and disruption, atrophy, dystosia and dysmorphic feature of mature thyroid follicle even in 3rd trimester of pregnancy. The internal penetration of silver nanoparticle can occur in a variety of ways and particle size largely influences their endocytic processes and cellular uptake ability in mature thyroid follicle at 3rd trimester of pregnancy. With addition to this, several research reports have shown that silver nanoparticle size also affects their internal penetration in terms of efficiency to spread disruptive effects in mature follicle of thyroid [21,22]. By summarizing the findings of the *in vitro* and *in vivo* studies that have investigated the effects of silver nanoparticle on the endocrine system such as mature follicle of thyroid at 3rd trimester of pregnancy, this review aims to evaluate the potential role of smaller and smallest silver nanoparticle as endocrine disruptors which causes dystosia, atrophy and dysmorphic features of mature thyroid follicle at 3rd trimester of pregnancy. This study also focuses in particular on their molecular mechanisms of action and on the relationship between their physical and chemical properties and the induction of alterations in endocrine function of thyroid and proved to be endocrine disruptor.

Impact of Endocrine Disrupting silver NPs on Reproductive Health

Growth and luteinizing hormones play a vital role in boosting the development of the reproductive system and subsequently it guides the vital endocrine gland thyroid once developed in all trimester of pregnancy. For this reason, most of the experiments conducted on endocrine disruptor contaminants in the last three decades have focused its importance on reproductive health. Recently, several experiments conducted and the result shows potential toxic effects of smaller and smallest size silver nano particles on mature thyroid follicle at 3rd trimester of pregnancy, the results reported that smaller and smallest size silver nano particles poses risks to male and pregnant female thyroid gland by altering follicle maturation and growth hormone levels. It also causes atrophy, artesia and dysmorphic state of thyroid gland and mature thyroid follicle at 3rd trimester of pregnancy which becomes alarm to scientific world that never use silver products in microform in delayed stage of pregnancy (3rd trimester) in pregnant woman.

Material and Method

20 (10(C) +10 (Extreme lower dose 0.25mg/kg b.w./500ppm of AgNps in colloidal solution (T)) Pregnant Swiss albino mice from different genetically mutated breeding colony used in this research as experimental material weighing approximately 25-35 g from the animal house of Institute of Medical Sciences Banaras Hindu University, smallest size (2.75nm) Nano silver colloidal experimental stirring cool solution was prepared and orally feeded to experimental pregnant mice in repeated gavages form daily once at 9.00AM early morning by feeding needle and 2ml dispovan. At this particular time the pregnant mice had an average age of 45 to 55 days. Surrounding

temperature in animal house during the animal feeding was 20-24°C during the broad day light which is guided by an air conditioner. The 12 hours darkness and 12 hours light set in broad day lighting stage continued for such experiment. Hindustan liver food were mixed with tap water ad libitum and feed to pregnant animals. In this study, the animals were divided randomly into two group's one control group and another lower dose ppm (particle per million) treated group (0.25mg/kg b.w./500ppm of AgNps in colloidal solution). The control group consisted of 10 pregnant mice were tested in their daily 2ml of normal saline and tap water were fed for 15 days. (5 to 19 gestational age) The experimental group consisted of one treated group, consisting of 10 pregnant mice in which 0.25mg/kg b.w. 500ppm amounts of smallest size silver nano particles; colloidal solution was prepared in histology laboratory of Department of Anatomy IMS, BHU and sodium borohydried stabilizer with poly vinyl pyrollidone deaggregator. The minimum dose 0.25mg/kg b.w./500ppm of AgNps in colloidal solution, 15- day oral gavages fed through a feeding needle attached dispovan. All pregnant mice at the end of 19 gestational days, were dissected for mature thyroid under all aseptic precaution after giving deep ether/ chloroform anesthesia to pregnant from control and treated group and segregated the mature thyroid follicle and view it under sharp binocular microscope from NIKON company. Concentrations of thyroid hormones (T3 and T4) and TSH were measured by ELISA kit purchased from Trimurti Scientific chemicals and certain of each hormone were measured. Results by SPSS program and ANOVA and MANOVA test were analyzed. This script is an attempt to show off disrupted endocrine system functions and deviated cellular morphology in form of mature thyroid follicle disambiguatory effect which is associated with smallest silver nanoparticle (colloidal solution) critical penetration into it while performing experiment on pregnant Swiss Albino mice at 3rd trimester of pregnancy at a extreme lower dose (0.25 mg/kg b.w. and 500 ppm of AgNps in colloidal solution) serial oral application.(5 to 19 gestational age) In due course, to collect scientific data's on the disambiguatory effects of smallest size silver nanoparticle on targeted endocrine organs like pregnant thyroid, we critically go through detail data available in the literature regarding the endocrine effects of *in vivo* exposure to different smallest sizes of silver nanoparticle after serial oral application with extreme lower dose.

Result

Histomorphological alterations seen after fresh dissection

Histologically the fibrous capsule which covers thyroid showed moderate thinning and multiple calcified focuses in different regions. Septa which extend into the gland from the capsule found in dismorphic and atrophic state rather than viewing inflammatory state which normally maintains in pregnant stage that is 3rd trimester of pregnancy. The divide and redivide lobules which are formed by septa found in degenerated, loss of shape and in atrophic form. There is seen lack of aggregation of follicles in each lobule when examined under dissecting microscope and follicles are also found in traumatic stage. Follicular cells which rest on basement membrane are seen injured, loss of shape and dismorphic both on hyper extended magnified view (40x). The colloidal fluid which fills the cavity of the follicle is seen thin layer and non echoic with small size silver nanoparticle spread over all fluid matrix. Stroma which made up of delicate connective tissue in which there are numerous capillaries and lymphatic's seen are found in atrophic and degenerative stage (Figure 1).

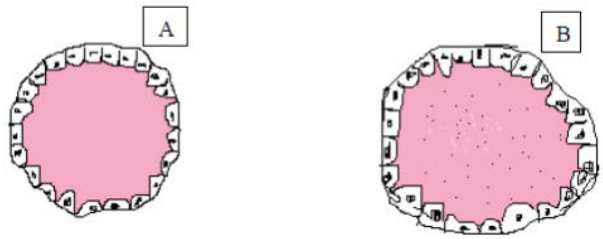

Figure 1: (A) Normal thyroid follicle. (B) Dismorphic thyroid follicle treated with small size AgNps colloidal solution.

View of Histological alterations of follicular cells

Follicular cells found atrophic, irregular, vary in shape and size with degenerative and dismorphic because of traumatized and injured with sharp edged horny tiny small size silver nanoparticle. Depending on the level of their activity usually follicular cells are found cuboidal in our study such type of feature histologically assessed in control group. Colloidal fluid also found moderate amount in follicular cell cavity in control group. When inactive or in resting stage the cells are usually seen flat or squamous type and follicle usually found distended with abundant colloidal fluid, more or less similar histological feature observed in control group. When the cells are highly active they become columnar and colloidal fluid is found scanty more or less similar feature is observed in treated group (0.25mg kg b.w. /500 ppm AgNps in colloidal solution) but found in degenerative and dismorphic state though seen in hypertrophic state. (Thyroid in 3rd trimester of pregnancy) In our study different follicle showed different level of activity histologically.

View of Histological alterations of Para follicular cells(C-Cells)

The Para follicular cells which are also called clear cells or light cells are also seen in atrophic, dysmorphic and in degenerated state in treated group whereas control group cells found absolutely normal and healthy. The control group cells are found polyhedral with oval eccentric nuclei. They are found in lie state between the follicular cells and their basement membrane. They may however, lie between adjoining follicular cells; but they do not reach the lumen. They also found lie in the connective tissue between the follicles and arranged in groups. This presentation is viewed in control group. Whereas treated group showed loss of shape and size, loss of formal histological structure. Also the cells from treated group showed atrophic, dystosia and dysmorphic features.

Transmission electron microscopic view of follicular cells

In TEM view control group follicular cells shows the presence of normal and healthy apical microvilli, abundant granular endoplasmic reticulum and a prominent supra nuclear Golgi complex, Lysosome, microtubules and microfilaments. The apical part of cell contains many secretory vacuoles which are seen normal and healthy in treated group where as in treated group shows same structures in atrophy, dystosia and dysmorphic stage in 10lakh time magnified TEM view.

Transmission electron microscopic view of Para follicular cells or C-cells

In TEM view control group Para follicular cells shows the presence of normal and healthy well developed granular endoplasmic reticulum, Golgi complexes, numerous mitochondria and membrane bound secretory granules. The apical part of cell contains many secretory vacuoles. All these structures are seen in normal and healthy stage in control group where as in treated group shows same structures in atrophy, dystosia and dysmorphic stage in 2lakhs to 10lakh time magnified TEM view (Figure 2).

Figure 2: (A) Ultra structure of a follicular cell of the control group mouse thyroid gland. (B) Ultra structure of a follicular cell of the treated group mouse thyroid gland which is found shrunken and weak and irregular outer border when compared with control group.

Effects of small size silver nanoparticles on hormonal secretion of Follicular and Para follicular cells

Follicular cells secrete two hormones that influence the rate of metabolism. Iodine is an essential constituent of these hormones. One hormone containing three atoms of iodine in each molecule is called triiodothyronine or T3. The second hormone containing four atoms of iodine in each molecule is called tetraiodothyronine, T4, or Thyroxine. T3 is much more active than T4. In control group follicular cell when biochemical analysis performed normal level T3 and T4 was found. The activity of follicular cell is influenced by the thyroid stimulating hormone (TSH or thyrotropin) produced by the hypophysis cerebri. There is some evidence to indicate that their activity may also increased by stimulation. In control group thyroid tissue and follicular cells same thing observed. Synthesis and release of thyroid hormone takes place in two phases. In the first phase thyroglobulin (a glycoprotein) is synthesized by granular endoplasmic reticulum and is packed into secretory vacuoles in the Golgi complex. The vacuole travel to the luminal surface where they release thyroglobulin into the follicular cavity by exocytosis. Here the thyroglobulin combines with iodine to form colloid. Colloid is iodinated thyroglobulin. In the second phase particles of colloid are taken back into cell by endocytosis. Within the cell the iodinated thyroglobulin is acted upon by enzymes (present in lysosomes) releasing hormones T3 and T4 which pass basally through the cell and are released into blood. Hormone produced in the thyroid gland is mainly T4 (output of T3 being less than 10%). In the liver, the kidneys (and some other tissues) T4 is converted to T3 by removal of one iodine molecule. T3 and

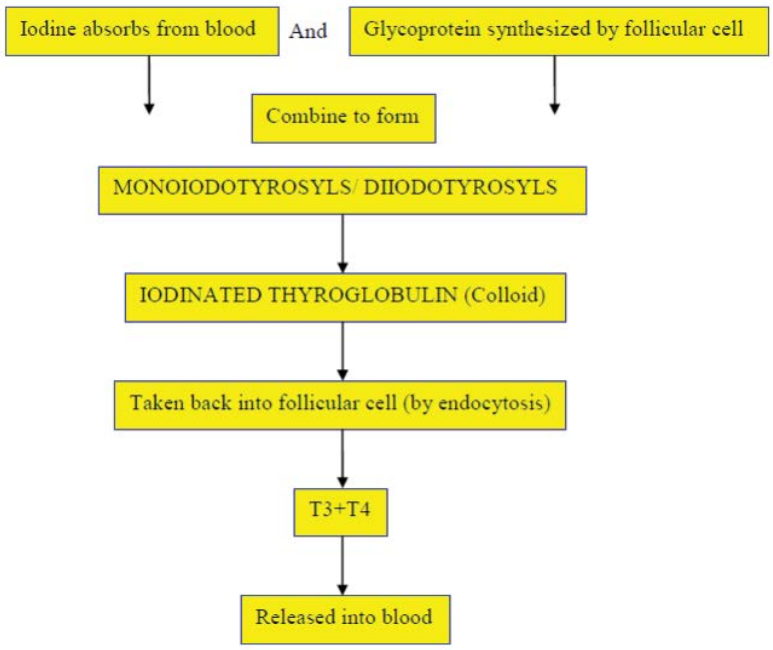

Figure 3: Showing normal mechanism of hormone secretion from follicular cells.

T4 circulating in the blood are bound to a protein (thyroxin binding globulin, TBG). The bound form of hormone is not active. In control group nothing is found abnormal or disturbed in the above explained mechanism (Figure 3). The rate of synthesis of thyroglobulin is found decreased in first phase in treated group follicular cells. But in treated group (0.25 mg/kg b.w. /500 ppm AgNps in colloidal solution) exocytosis and endocytosis mechanism is found blocked and hampered in second phase. The rate of the exocytosis and endocytosis activity is found decreased in treated group follicular cells (Table 1).

Para follicular cells or C-cells secrete hormone thyro-calcitonin. This hormone has an action opposite to that of the parathyroid hormone on calcium metabolism. This hormone comes into play when serum calcium level is high. It tends to lower the calcium level by suppressing release of calcium ions from bone. This is achieved by suppressing bone resorption by osteoclast. In control group thyro-calcitonin level is found normal whereas in treated group thyro-calcitonin level is found depleted from normal level.

Discussion

The results of the corrosive and hazardous histomorphological effect of extreme smaller dose and size of silver nanoparticles on thyroid tissue indicate that histomorphologically the fibrous capsule which covers thyroid showed moderate thinning and multiple calcified focuses in different regions. Septa show dismorphic and atrophic state rather than viewing inflammatory state. The lobules found in degenerated, loss of shape and in atrophic form in treated group. There is seen lack of aggregation of follicles in each lobule when examined under dissecting microscope and follicles are also found in traumatic stage. Follicular cells which rest on basement membrane are seen injured, loss of shape and dismorphic both on hyper extended magnified view (40x). The colloidal fluid which fills the cavity of the follicle is seen thin layer and non echoic with small size silver nanoparticle spread over all fluid matrix. This type of findings indicates silver nanoparticles at extreme lower dose and size (2.5mg/kg b.w. / 500ppm) caused a significant increase in deleterious effects in histomorphology in thyroid gland when injected in body through repeated oral gavages. The results of histology of follicular cells indicate, Follicular cells found in atrophic, irregular, vary in shape and size with degenerative and dismorphic state because of traumatized and injured with sharp edged horny tiny small size silver nanoparticle. Follicular cells are found cuboidal in control group whereas in treated group it is found in altered state from cubiodal shape. Colloidal fluid also found moderate amount in follicular cell cavity in control group. When inactive or in resting stage the cells are usually seen flat or squamous type and follicle usually found distended with abundant colloidal fluid, more or less similar histological feature observed in control group. When the cells are highly active they become columnar and colloidal fluid is found scanty more or less similar feature is observed in treated group (0.25mg kg b.w. /500 ppm AgNps in colloidal solution) but found in degenerative and dismorphic state though seen in hypertrophic state. (Thyroid in 3rd trimester of pregnancy) Different follicle showed different level of activity histologically. The Para follicular cells which are also called clear cells or light cells are also seen in atrophic, dysmorphic and in degenerated state in treated group whereas control group cells found absolutely normal and healthy. The control group cells are found polyhedral with oval eccentric nuclei. They are found in lie state between the follicular cells and their basement membrane. They may however, lie between adjoining follicular cells; but they do not reach the lumen. They also found lie in the connective tissue between the follicles and arranged in groups. This presentation is viewed in control group. Whereas treated group showed loss of shape and size, loss of formal histological structure. Also the cells from treated group showed atrophic, dystosia and dysmorphic features. In TEM view control group follicular cells shows the presence of normal and healthy apical microvilli, abundant granular endoplasmic reticulum and a prominent supra nuclear Golgi complex, Lysosome, microtubules and microfilaments. The apical part of cell contains many secretory vacuoles which are seen normal and healthy in treated group where as in treated group shows same structures in atrophy, dystosia and dysmorphic stage in 10lakh time magnified TEM view. In TEM view control group Para follicular cells shows the presence of normal and healthy well developed granular endoplasmic reticulum, Golgi complexes, numerous mitochondria and membrane bound secretory

Groups Enzymes	Control	0.25mg/kg b.w./ 500ppm treated group
T3	106.3 ± 1.2	104.3 ± 1.01
T4	1.3 ± 0.15	1.02 ± 0.12
Thyro-calcitonin	0.14 ± 0.007	0.12 ± 0.01
TSH	0.15 ± 0.008	0.13 ± 0.01

(P≤0.05). Data as "Mean ± SD "are

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Table 1: Serum concentrations of thyroid hormones, thyroid stimulating hormone and thyro-calcitonin in the control group and the treated group receiving small size silver nanoparticles in AgNps in colloidal solution.

granules. The apical part of cell contains many secretory vacuoles. All these structures are seen in normal and healthy stage in control group where as in treated group shows same structures in atrophy, dystosia and dysmorphic stage in 2lakhs to 10lakh time magnified TEM view. The results of the effect of extreme small size (2.75nm) and dose (0.25 mg/kg b.w. /500ppm) amounts of silver nanoparticles on thyroid hormone levels indicate that silver nanoparticles at extreme low dose (0.25 mg/kg b.w. /500ppm) caused a significant decrease in the concentration of the hormone T3,T4, TSH and Thyro-calcitonin. Monitoring of thyroid hormones T3, T4, TSH and Thyro-calcitonin and damaged thyroid follicular and Para-follicular cells release the hormone is significantly decreased (Table 1). It may decrease due to the detrimental and destructive effects of extreme small size silver nanoparticles on cells of the mature thyroid at 3rd trimester of pregnancy. Obstruction of the follicular and Para-follicular cells also cause decreased hormone level from same. It is probably due to the destruction of follicular and Para-follicular cells and blockage of the secretory cells resting on the basement membrane. T3, T4, TSH and Thyro-calcitonin concentrations decreased. Decreased T3, T4, TSH and Thyro-calcitonin levels may decrease due to decreased anabolism or catabolism in it [23]. Looks changes in thyroid hormones levels due to the effects of extreme small size silver nanoparticles at extreme low dose on thyroid hormones and due to its important role in the metabolic activity of the tissue and that metabolic activity is found lowered in treated group. Follicular cell and Para-follicular cells resting membrane stability and integrity are essential functions of the thyroid gland [24]. According to the physicochemical properties of extreme small size silver nanoparticles have been stabilized over time and will cause thyroid malfunction. Many studies have been done on the physiochemical characteristics of extreme small size nanoparticles .For example, research showed that the extreme small size nanoparticle has severe toxic effects on Oyster fish and Danio Rario in water and eco system [25]. Physico-chemical properties of extreme small size silver nanoparticles cause depletion of vigor and vitality of follicular and Para-follicular cells and reduce the proliferation of cells causing atrophy, dystosia and degenerative changes [26,27]. In this study we observed that the extreme small size silver nanoparticles significantly decreased serum concentrations of T3, T4, TSH and Thyro-calcitonin. It is possible that these nanoparticles could be through augmentation of pituitary endocrine actions - affect the hypothalamus, which may be due to its indirect effect decreases T3, T4, TSH and Thyro-calcitonin level. All thyroid hormone levels were found depleted, this is probably due to destruction of thyroid tissue follicular and Para-follicular cells .Destruction of thyroid tissue, peak levels of extreme small size silver nanoparticles in the blood, also accentuates depletion of T3, T4, TSH and Thyro-calcitonin level and thyroid tissue is found damaged. The existing research has shown that the low level TSH release will also lead to decrease BMR (Basal Metabolic Rate) [28]. Extreme small size silver nanoparticles are likely to have degenerative impact on mature thyroid hormone level at 3rd trimester of pregnancy with deplete secretion of TSH and release, which in turn leads to a significant alteration of the basal metabolic rate [24].

Conclusion

Because of depletion and variation of the results of this existing research study can be concluded that extreme small size silver nanoparticles have size and dose-dependent effects on mature thyroid gland of the body at 3rd trimester of pregnancy is so that at extreme low dose and extreme small size silver nanoparticle in colloidal form is proved to be toxic at penetrative mode into the core of the said organ and damaging effects on the thyroid gland activity and inhibits its activity at last phase of pregnant condition. A disambiguate and violation effect of smallest size nano silver (2.75 nm) after critical penetration into core of mature thyroid follicle at 3rd trimester of pregnancy is hence forth proved as a new research discovery after this experiment in repeated oral gavages intake mode.

Declarations

Ethical approval and consent to participate

All procedures performed in studies involving animal participants were in accordance with the ethical standards of the institutional and/or national research committee and its later amendments or comparable ethical standards. The studies were performed with the approval of the Central Animal Ethical Committee of the Banaras Hindu University Varanasi (No. /Dean /2014 /CAEC / 614).

Consent for publication

All authors read the final manuscript and approved manuscript for publication.

Competing interests

There is no competing of interest in opinion between 1st author and 2nd author also with corresponding author.

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Authors' contributions

Pani JP designed the study, performed the experiments and participated in manuscript drafting, Pani JP carried out the histological and biochemical analyses and performed *in vitro* experiments; Pani S recruited animals, and collected the animal dissection data, Pani JP and Pani S revised the manuscript, Pani JP provided some theoretical and experimental guidance for the design and performing the biochemical analysis, Pani JP and Pani S participated in results discussion, data analyses and manuscript drafting. All authors read and approved the final manuscript.

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