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Influence of magnetic iron oxide nanoparticles in reproductive efficiency of adult male rats

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Abstract

This study aimed to investigate the dose-dependent and time-dependent effect of magnetic iron oxide nanoparticles (MIONPs) on reproduction in male rats. Following their synthesis, the physicochemical properties of MIONPs were determined. Sixty-four adult male rats, aged 90 days were randomly assigned to control (C), orally administered with distilled water, and three treated groups, orally administered with 1, 5, 10 mg/kg/day of MIONPs solution (TL, TM, and TH groups, respectively), for 28 days. Each group was allocated to two subgroups, sacrificed after 14 and 28 days of treatment. After each period, the males were weighed and sacrificed. Decreased body weight and genital organ weights were shown in TM and TH groups, at both experimental periods, compared with control in a dose-dependent manner. The serum concentration of GnRH, FSH, LH, and testosterone increased in the TL group and decreased in TM and TH groups compared with control in a dose-dependent and time-dependent manner. At both periods, the lowest expression levels of pituitary FSHβ and LHβ genes and testicular *inh*-α and LHR genes were recorded in TM and TH groups, and the highest levels were expressed in the TL group. The testis sections of TL males, showed normal architecture, but those from TM and TH groups showed degenerative and necrotic changes, reduced germinal epithelium, vacuolation, and decreased number of spermatocytes apparent. It is concluded that a low dose of MIONPS has a beneficial effect, whereas moderate or high doses have pathological effects on male reproduction.

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Introduction

Nanotechnology studies control materials at the nanoscale, where properties change with changes in size, shape, density, aggregation, and surface area. Biology could be developed due to the developmental results in this field of science (1). Because of their biocompatibility and magnetic activity, iron oxide nanoparticles (MIONPs) are known as valuable agents for magnetic resonance imaging, drug delivery, magnetic hyperthermia, tissue engineering, cell separation, enzyme immobilization, bio-sensing, and protein purification (2). MIONPs are also utilized by many analytical procedures, including polymerase chain reaction (PCR), immunoassay, high performance liquid chromatography (HPLC), and liquid chromatography with tandem mass spectrometry (LC-MS-MS) (3). Moreover, MIONPs have been employed in water purification and remediation of environmental residues due to their low cost (4). MIONPs were recorded to be accumulated and transported mainly in the liver and spleen tissues in a size-dependent manner (5,6). Furthermore, the expression of genes involved in producing antioxidants, iron transporters, and the metabolism was detected when MIONPs were employed. In the study of Di Bona *et al.* (7), pregnant mice that were given multiple doses of MIONPs showed higher fetal deaths and iron distribution in the liver and placental

tissues. Auffan *et al.* (8) mentioned that various in vivo and in vitro investigations of several NPs revealed the creation of free radicals, indicating that the cellular dysfunction is primarily caused by oxidative damage. Also, similar creation has been shown by oral administration of AgNPs, which caused a toxic effect on blood (9). Propolis-MIONPs successfully rebalanced iron status by eliminating parasites and establishing iron availability (10). The fenton chemistry, which generates free radicals, may be triggered by overloading cells with MIONPs, resulting in harmful cellular effects (11). Although the cells have an antioxidant defense mechanism to intercept excess reactive oxygen species (ROS), if the biological systems fail to neutralize the excessive ROS, biomolecules such as proteins, DNA, and lipids will be oxidized (12).

Based on the initial findings, it was discovered that many of the changes detected in various tissues of exposed rats after MIONPS therapy was dosage-dependent. The present investigation examined the dose-dependent and time-dependent reproductive effect of MIONPs after repeated oral treatment to male rats for 28 days.

Materials and methods

Ethical approve and care

The animals were handled according to the international and national animal welfare standards (National Research Council's Gide for the Care and Use of Laboratory Animals, 8th ed., 2011).

Synthesis and characterization of MIONPs

MIONPs were synthesized and their physicochemical properties were characterized according to Salehizadeh *et al.* (13)

Experimental animals

In this experiment, adult male Wister rats were used, about 90 days old, with an average weight of about 174±5 g, which were obtained from the animal house of the College of Veterinary Medicine, University of Al-Qadisiyah. The experiment was carried out from 15 November 2020 to 30 August 2021. The animals were housed in well ventilated controlled conditions at about 12 hours of light and 12 hours of dark at 22 °C. The animals were allowed to acclimatize for 7 days before experimentation.

Experimental design

Sixty-four mature male rats were equally assigned to control (C) and three treated groups (TL, TM, and TH). Control male rats were administered distilled water, whereas treated groups were administered 1, 5, 10 mg/kg/day of MIONPs solution for 28 days. Each group was subdivided to two subgroups, sacrificed after 14 and 28 days of treatment. After each treatment period, eight males from each subgroup were weighed and sacrificed. Relative genital organ weights (testis, epididymis, prostate, and seminal vesicle) were recorded. Blood samples were obtained for the assessment of serum hormone concentrations. Testicular samples were taken for histopathological examination. Pituitary and testicular tissue samples were obtained for molecular analysis to evaluate the expression levels of pituitary FSHβ and LHβ and testicular *inha* and LH receptors.

Body and genital organ weights

The animals were weighed before treatment (0 days) and at the end of each experimental period. Body weight gain after each period was calculated. Relative ovarian weight was calculated according to body weight (g/100 g BW).

Serum preparation and hormonal assay

Blood was collected, from the abdominal vein, in test tubes with a cap and allowed to clot (for 20 minutes), then serum was separated by centrifugation at (4000 rpm) for 10 minutes. The separated serum of each animal was subdivided nearly into 6 samples using appendroff tubes (0.5 ml) and kept in a deep freezer until use for assessment of the biochemical parameters (14). Serum GnRH, FSH, LH, and testosterone concentrations were assessed using the ELISA technique, according to the manufacturer's instructions (Ltd. Com, China and Shanghai Biological Co. Ltd, China).

Histopathological examination

According to Mescher (15), the dissected specimens from the testis of sacrificial males were prepared and stained with hematoxylin and eosin stains.

Total RNA extraction and evaluation of its purity

Total pituitary and testicular RNA extraction was performed using a TRIzol® reagent kit (Bioneer, Korea). A nanodrop spectrophotometer (THERMO. USA) was used to measure the quantity and purity of extracted RNA (Promega company, USA).

cDNA synthesis

Using the DNase I enzyme kit, the trace amounts of genomic DNA were removed from the eluted total RNA (accordingly to the procedure described by Promega company, USA). DNase-I treated total RNA samples were utilized in cDNA synthesis by employing AccuPower® RocktScript RT PreMix kit (Bioneer company, Korea).

qRT-PCR master mix preparation and analysis

The master mix was prepared using AccuPower™ Green Star Real-Time PCR kit depending on SYBER Green dye determination of gene amplification in Real-Time PCR system (Bioneer company, Korea). The levels of the relative quantification gene (fold change) Δ^{CT} Livak approach was used to test the obtained data of qRT-PCR for studied and housekeeping genes (16).

Statistical Analysis

Data analysis was performed using GraphPad Prism-Version 5 (SAS Institute, Inc., USA). Results were expressed as mean±standard deviation. One-way ANOVA was used with Newman- Keuls (17) to calculate the significant differences among means. P<0.05 is considered significant.

Results

Body weight changes

The result of body weight changes, clarified in table 1, revealed a significant decrease (P<0.05) of TH group males among experimental groups at both periods, whereas TM group males recorded higher body weight change (P<0.05) than TH group, but it was significantly lower (P<0.05) than control and TL groups, which showed no significant difference (P>0.05) between each other. When comparing the two periods, the control and TL groups showed a significant increase (P<0.05) at 28 day period than 14 day period, while no significant differences (P>0.05) were shown between the periods in the TM group. However, the TH group recorded a significant decline (P<0.05) in 28 day period compared with 14 day period.

Relative genital organ weights

At both of the studied periods, a significant decrease (P<0.05) in the testis, epididymis, prostate, and seminal vesicle relative weights has been shown in the TH group and TM groups as compared with the control group, whereas no significant change (P>0.05) was shown in TL group than the control. In comparison between the two periods, the relative genital organ weights of experimental groups, at 28 days period, recorded no significant differences (P>0.05) in comparison with 14 days period, but only prostate weight decreased significantly (P<0.05) at 28 days period than 14 days period (Table 1).

Serum concentrations of hormones

At both of the studied periods, the serum concentrations of GnRH, FSH, LH, and testosterone of TH group male rats recorded the lowest mean value (P<0.05) among the experimental groups, followed by TM group male rats, as compared with control group male rats, whereas TL group male rats recorded the highest concentration (P<0.05). In comparison between the two studied periods, all groups showed no significant differences (P>0.05), except the GnRh level of the TL group revealed a significant increase (P<0.05) at 28 day period in comparison with 14 day period (Table 2).

Pituitary FSHβ and LHβ gene expression level

As illustrated in figure 1, both of the studied periods showed that the lowest expression levels (P<0.05) of pituitary FSHβ and LHβ genes were recorded in TM and TH group male rats among the experimental groups, whereas TL group male rats recorded increased expression level (P<0.05) than control group male rats. In comparison between the two studied periods, all experimental groups showed no significant differences (P>0.05).

Table 1: Effect of MIONPs on body weight and relative organ weight in adult male rats

Parameters		Periods	C	TL	TM	TH
Body weight change (g)		14 d	35.55±3.498 Ba	37.18±4.033 Ba	24.48±3.661 Ab	08.93±2.33 Ac
		28 d	71.37±3.127 Aa	76.37±4.188 Aa	22.74±2.890 Ab	- 6.33±2.41 Bc
Relative organ weight (g/100g BW)	Testes	14 d	1.56±0.190 Ab	2.38±0.197 Aa	1.04±0.091 Ac	0.88±0.093 Ad
	(g/100g)	28 d	1.66±0.169 Ab	2.27±0.181 Aa	0.97±0.082 Ac	0.61±0.087 Bd
	Epididymis	14 d	0.519±0.017 Ab	0.785±0.022 Ba	0.349±0.021 Ac	0.325±0.021 Ac
	(g/100g)	28 d	0.529±0.017 Ab	1.023±0.084 Aa	0.220±0.022 Bc	0.225±0.021 Bc
	Sem. Vesicle	14 d	3.18±0.139 Ab	3.81±0.099 Aa	2.41±0.192 Ac	1.87±0.093 Ad
	(g/100g)	28 d	3.23±0.1208 Ab	3.89±0.102 Aa	2.37±0.089 Ac	1.29±0.088 Bd
	Prostate	14 d	0.69±0.043 Ab	0.94±0.026 Aa	0.44±0.009 Ac	0.35±0.009 Ac
	(g/100g)	28 d	0.61±0.050 Ab	0.95±0.039 Aa	0.47±0.008 Ac	0.26±0.007 Bd

Data were presented as Mean±SD. Values with different small letters in the raw (between groups for each period) were significantly different (P<0.05). Different capital letters in the column (between periods for each group) were significantly different (P<0.05).

Testicular *inh*-α and LHR gene expression level

Significant elevation (P<0.05) of testicular *inha* and LHR gene expression levels have been shown in TL group males compared to control, whereas TM and TH group males recorded a significant decline (P<0.05) than the control group. These results were shown in both of the studied periods. In comparison between the two periods, all groups showed no significant differences (P>0.05) between the 14 and 28 days of the experiment (Figure 2).

Histopathological changes of testis

At both periods (day 14 and day 28) of the experiment, testis sections obtained from the TL group showed normal architecture (Figure 3) as that revealed by control sections

(Figure 3), as normal seminiferous tubule structure was indicated. Myoid cells surrounding the tubules, Sertoli cells, primary spermatocytes, secondary spermatocytes, and sperms in the lumen were evident. Histological sections of the testes obtained from TM and TH groups, at 14 days, showed degenerative changes and a reduced population of germinal epithelium (Figure 3). Moreover, vacuolation, necrosis, hyaline degeneration of spermatogonia, decreased number of spermatocytes, and hyperplasia of Sertoli cells were apparent. After 28 days of treatment, testicular sections revealed more histopathological changes represented by degeneration, and decreased primary and secondary spermatocytes. The testicular sections also showed deterioration of spermatogonia, Sertoli cells, and spermatocytes. Moreover, exfoliated cells and the absence of the sperms in the lumen were also recorded (Figure 4). Moreover, at 28 days, the TH group showed severely necrotic spermatogonia and Sertoli cells, loss of most primary and secondary spermatocytes, the presence of exfoliated cells and a lack of sperms in the lumen of seminiferous tubules.

Table (2): Effect of MIONP on serum concentrations of corticosteroid and reproductive hormones in adult male rats

Parameter	Periods	C	TL	TM	TH
GnRH (pg/mL)	14 d	68.33±5.351 Ab	87.22±5.723 Ba	42.34±4.388 Ac	36.32±2.177 Ad
	28 d	67.58±4.824 Ab	98.38±6.716 Aa	35.25±4.127 Bc	27.16±3.138 Bd
FSH (IU/L)	14 d	09.73±0.782 Ab	17.23±1.188 Aa	7.320±0.512 Ac	7.181±0.723 Ac
	28 d	10.35±0.906 Ab	17.88±1.396 Aa	5.140±0.473 Bc	5.445±0.834 Bc
LH (IU/L)	14 d	21.33±1.298 Ab	37.22±1.582 Aa	15.35±1.348 Ac	15.62±0.829 Ac
	28 d	20.51±1.562 Ab	37.73±1.677 Aa	15.17±1.071 Ac	10.43±1.037 Bd
Testosterone (ng/mL)	14 d	5.366±0.381 Ab	27.92±1.079 Aa	3.731±0.279 Ac	3.817±0.123 Ac
	28 d	5.621±0.209 Ab	29.02±1.028 Aa	3.925±0.228 Ac	1.794±0.098 Bd

Data were presented as Mean±SD. Values with different small letters in the raw (between groups for each period) were significantly different (P<0.05). Different capital letters in the column (between periods for each group) were significantly different (P<0.05).

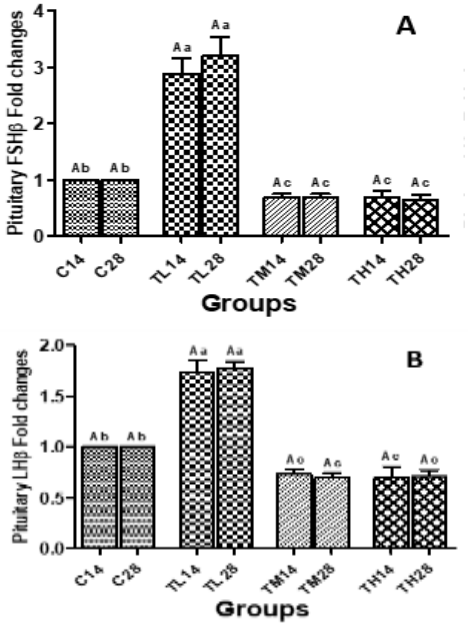

Figure 1: Pituitary FSHβ and LHβ gene expression levels (fold changes) in MIONPs treated male rats. Data were presented as Mean±SD. Different small letters denote significant differences (P<0.05) between groups for each period. Different capital letters denote significant differences (P<0.05) between periods for each group.

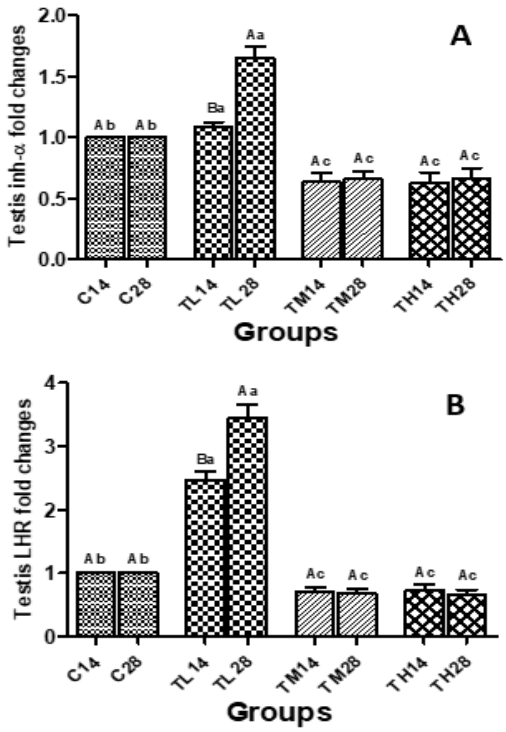

Figure 2: Testicular *inha* and LHR gene expression levels (fold changes) in MIONPs treated male rats.

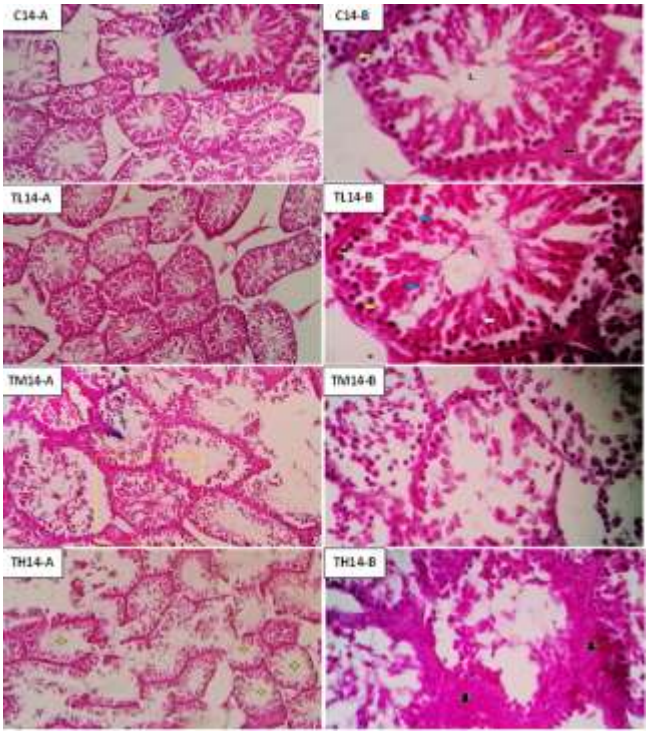

Figure 3: Photomicrograph of testis sections from control (C), MIONP (1 mg) treated (TL), MIONP (5 mg) treated (TM), and MIONP (10 mg) treated (TH) male rats at day 14 of the experiment. C14-A and C14-B: show normal seminiferous tubules with germinal epithelium (GE), and some of the seminiferous tubules contain few sperms in the lumen (L), and Leydig cells were indicated (black arrow). H&E, 100X and 400 X. TL14-A and TL14-B: show normal seminiferous tubule structure. The Myoid cells (black arrow) surround the tubules, Sertoli cells (blue arrows), primary spermatocytes (yellow arrow), secondary spermatocytes (white arrow), and sperms in the lumen (L). H&E, 100X and 400X. TM14-A and TM14-B: show severely degenerated seminiferous tubules (yellow box) with few spermatocytes and Sertoli cells. H&E, 100X. and 400X. TH14-A and TH14-B: show severely degenerated seminiferous tubules, degeneration of spermatogonia, few spermatocytes, central edema, and hyperplasia of interstitial tissue (black arrows). H&E, 100X and 400X.

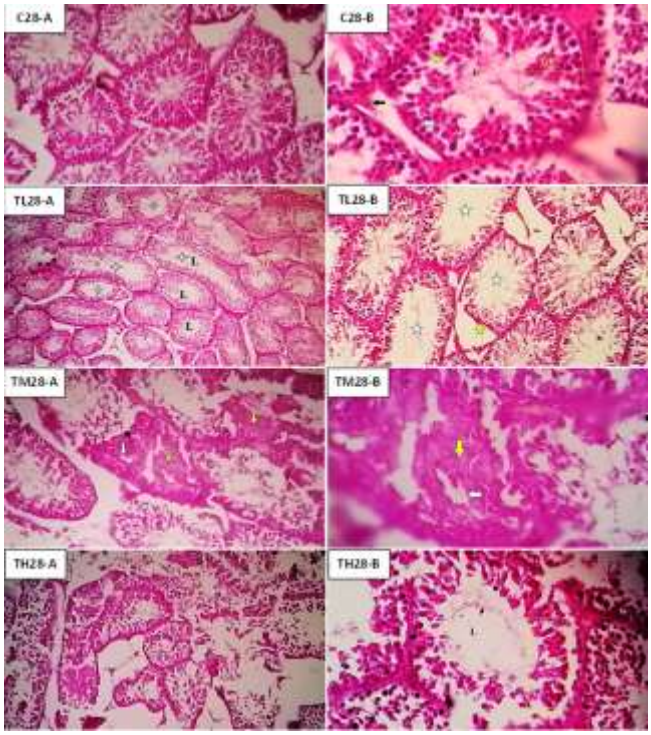

Figure 4: Photomicrograph of testis sections from control (C), MIONP (1 mg) treated (TL), MIONP (5 mg) treated (TM), and MIONP (10 mg) treated (TH) male rats at day 28 of the experiment. C28-A and C28-B: show normal seminiferous tubules with germinal epithelium (GE), and some of the seminiferous tubules contain few sperms in the lumen (L), and Leydig cells were indicated (black arrow). H&E, 100X and 400 X. TL28-A and TL28-B: show normal seminiferous tubule structure with Myoid cells (black arrow) surrounding the tubules, Sertoli cells (blue arrows), primary spermatocytes (yellow arrow), secondary spermatocytes (white arrow), and sperms in the lumen (L). H&E, 100X and 400X. TM28-A and TM28-B: show vacuolation (white arrow), necrosis, hyaline degeneration of spermatogonia, the lake of spermatocytes, and central edema (yellow arrow). H&E, 100X. and 400X. TH28-A and TH28-B: show severe destruction of a group of seminiferous tubules, exfoliated cells (yellow box), and no sperms in the lumen (L). H&E, 100X and 400X.

Discussion

The stabilizing activity of MIONPs on cell membranes, which protected the cells and improved many organ functions, could have contributed to the weight gain in the TL group. It could also be linked to the stimulatory role of MIONPs on protein synthesis. The biosynthetic rate of structural and functional proteins may be improved by increased ribosome production and enhanced protein and DNA biosynthesis (18). Furthermore, the stimulatory action of MIONPs may provide more transporters and enzymes, which could improve the activities of many body cells (18).

The cellular degradation of MIONPs is thought to be similar to ferritin degradation (19). After degradation, there is an overabundance of iron that must be regulated by the clearance processes (20). Because NP poisoning causes cellular antioxidant defense capacity overloading, decreased body weight gain in TM and TH groups could be linked to increased oxidative stress. According to Park *et al.* (21), body weight increase in male mice treated with MIONPs was

dose-dependently reduced. While iron is necessary for numerous metabolic functions, increased iron can be toxic, which can have an impact on physiologic activities. MIONPs, on the other hand are harmless and even beneficial in several trials (22,23).

Despite the increase in body weight gain in the TL group, the relative weights of the genital organs also increased. At the same time, although the weight of the TM and TH groups decreased, the relative weights of genital organs also decreased. These results were parallel with the results of reproductive hormones, as the levels of LH, FSH, and testosterone increased in male rats of the TL group and decreased in TM and TH groups compared to the control. Through this, it can be suggested that the increase or decrease is due to the increase or decrease of reproductive hormones, particularly testosterone. This improvement in reproductive organ weights recorded in the TL group could be attributed to the improvement of the pituitary-gonadal axis (24) by enhancement of pituitary gonadotropin and testicular testosterone secretion.

The reported reproductive improvement in the TL group and reproductive toxicity in TM and TH groups were accompanied by hormonal changes from pituitary and testis sources. Orchestrated results have been shown in the present study regarding the serum levels of FSH, LH, and testosterone, the expression levels of pituitary FSHβ, LHβ and testicular *inha* and LH receptor genes, and histological findings. In TL group male rats, the increased levels of FSH, LH, and testosterone were accompanied by increased expression levels of pituitary FSHβ, LHβ and testicular *inh*-α and LH receptor genes. In contrast, the results of the TM and TH groups were opposite to those of the TL group.

The administration of 1mg of MIONPs /kg BW (TL group) to male rats markedly enhanced the production of reproductive hormones. As a result, the importance of endogenous antioxidants in preventing oxidative damage caused by MIONPs has been highlighted. On the other hand, MIONPs may normalize testicular function by increasing the spermatogenic success rate and density of sperms inside the lumen of the seminiferous tubules, as evidenced by the apparent improvement in the histological structure of the testes observed in this study. FSH and testosterone levels were higher in TL group male rats, indicating a preference for reproductive activity. The reduction of oxidative stress and the regulation of lipid components were found to be crucial variables in enhancing fertility (25). Moreover, exposure to many environmental toxins may harm fertility (26,27). High doses of MIONPs may be a hazardous inducer of male infertility, according to the present findings, which might be due to a direct influence on spermatogenesis or indirectly through higher centers in the brain.

These findings support the theory that iron regulates gonadal function, hormone release, proliferation, and apoptosis (28). Iron is required for various cellular activities, including reproductive functions, as iron is vital for regulating spermatogenesis and spermatozoa differentiation, as well as the local regulation of gonadal function. Because developing male germ cells go through numerous mitotic divisions and need iron for DNA synthesis and cell expansion, especially mitochondriogenesis, spermatogenesis is an iron-dependent process (29). Excess of iron, on the other hand, is poisonous to cells. Free iron ions are poisonous and can catalyze various harmful processes in cells and tissues. Varzeghani *et al.* (30) found that high doses of MIONPs (300 mg/Kg/day) reduced sperm quality and male reproductive performance.

Conclusion

It could be concluded that a low dose of MIONPS has a beneficial effect, whereas moderate or high doses of MIONPS have pathological effects on male reproduction.

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Conflict of interest

No conflict of interest was found.

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تأثير الجسيمات النانوية من أكسيد الحديد المغناطيسي في الكفاءة التكاثرية لذكور الجرذان الناضجة

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الخلاصة

تهدف هذه الدراسة التحري عن تأثير الجسيمات النانوية لأوكسيد الحديد مع تقدم الوقت وزيادة الجرعة على الفعالية التكاثرية لذكور الجرذان. بعد التصنيع، تم تحديد الصفات الكيميائية والفيزيائية للجسيمات النانوية. تم توزيع ٦٤ جرذا ذكرا بالغا بعمر ٩٠ يوما على مجموعة سيطرة، جرعت الماء المقطر، وثلاث مجموعات معاملة، جرعت محلول الجسيمات النانوية لأوكسيد الحديد بالجرع ١ و ٥ و ١٠ ملغم/ كغم من وزن الجسم (مجموعة المعاملة بالجرعة الواطئة، والجرعة المتوسطة والجرعة العالية على التوالي) لمدة ٢٨ يوما. قسمت كل مجموعة الى مجموعتين ثانويتين، تمت التضحية بهما بعد ١٤ و ٢٨ يوما من المعاملة. سجلت النتائج انخفاضا في وزن الجسم والوزن النسبي للأعضاء التكاثرية في مجموعة المعاملة بالجرعة المتوسطة والعالية، في كلتا مرحلتي التجربة، بالمقارنة مع السيطرة باعتماد الوقت. انخفضت مستويات الهرمون المحرر لمحرضات القند والهرمون محفز الجريب والهرمون المصفر والتستوستيرون في مجموعة المعاملة بالجرعة المنخفضة وارتفعت في مجموعة المعاملة بالجرعة المتوسطة والجرعة العالية بالمقارنة مع السيطرة باعتماد الوقت وزيادة الجرعة. في كلتا مرحلتي التجربة، أدنى مستوى لتعبير جينات FSHβ و LHβ في النخامية و جينات *inha* ومستقبلات الهرمون المصفر في الخصى قد تم تسجيله في مجموعة المعاملة بالجرعة المتوسطة والجرعة العالية وأعلى مستوى تم تسجيله في مجموعة المعاملة بالجرعة المنخفضة. أظهرت مقاطع الخصى النسجية معالم طبيعية في مجموعة المعاملة بالجرعة المنخفضة بينما تلك المأخوذة من مجموعة المعاملة بالجرعة المتوسطة والجرعة العالية أظهرت تغيرات تحطمية وتنكسية وانخفاض الظهارة الجرثومية وتفكك نسجي وانخفاض أعداد الخلايا النطفية. يستنتج أن التراكيز الواطئة من جسيمات أوكسيد الحديد النانوية لها تأثيرات ايجابية بينما تؤدي التراكيز المتوسطة والعالية الى تأثيرات مرضية في الأعضاء التكاثرية لذكور الجرذان.