WALKING RESTORES THE REPRODUCTIVE FUNCTION OF FEMALE RATS FROM REDUCED LITTERS, A CLASSICAL MODEL OF OBESITY

Elizete Rosa dos Santos

Especialista em Fisiologia Humana pela Universidade Estadual de Maringá - UEM; Técnica do laboratório de fisiologia do Departamento de Ciências Fisiológicas da Universidade Estadual de Maringá - UEM, Maringá (PR), Brasil.

Glaucia Midori Sakakima

Especialista em Fisiologia Humana pela Universidade Estadual de Maringá - UEM, Maringá (PR), Brasil.

Maria Montserrat Diaz Pedrosa

Mestrado e Doutorado em Ciências Biológicas - Biologia celular; Docente do Departamento de Ciências Fisiológicas da Universidade Estadual de Maringá - UEM, Maringá (PR), Brasil; E-mail: mmdpfurlan@uem.br.

ABSTRACT: As physical activity is a significant aid against obesity and its complications, this work was planned to assess the consequences of litter size reduction, a classical model of obesity, and treadmill walking on the reproductive function of adult female rats. Female rats were raised in reduced (three puppies, NR) or conventional (nine puppies, NC) litters during lactation, with free supply of chow after weaning. Some of the rats of each group were not exercised (sedentary, S) while some were subjected to treadmill walking (exercised, E). Litter size reduction increased biometric parameters (body weight, Lee index, weight/length ratio and adiposity) significantly ($p<0.05$, two-way ANOVA). Only one regular estrous cycle, a high number of cystic follicles (28) and irregular ovarian morphology were recorded in the sedentary rats (NR-S). These rats, when mated, did not procreate. Treadmill walking had a significant effect on most of the biometric parameters ($p<0.05$, two-way ANOVA). The exercised female rats (NR-E) had reproductive function similar to those of the NC groups: 14 regular estrous cycles, 16 puppies, and 16 cystic follicles. In the reduced-litter female rats, walking since early life preserved estrous rhythmicity and fertility, which were impaired in the sedentary reduced-litter females.

KEY WORDS: Exercise; Obesity; Reproduction.

CAMINHADA RESTAURA A FUNÇÃO REPRODUTIVA DE RATAS VINDAS DE NINHADAS REDUZIDAS, UM MODELO CLÁSSICO DE OBESIDADE

RESUMO: Como a atividade física é um auxiliar significativo contra a obesidade e suas complicações, este trabalho foi planejado para avaliar as consequências da redução da ninhada, um modelo clássico de obesidade, e da caminhada em esteira sobre a função reprodutiva de ratas adultas. As ratas foram criadas em ninhadas reduzidas (três filhotes, NR) ou convencionais (nove filhotes, NC) durante a lactação, com alimentação livre após o desmame. Algumas ratas de cada grupo não foram exercitadas (sedentárias, S), enquanto algumas foram submetidas a caminhada em esteira (exercitadas, E). A redução da ninhada aumentou significativamente ($p<0,05$, two-way ANOVA) os parâmetros biométricos (peso corporal, índice de Lee, relação peso/comprimento e adiposidade). Apenas um ciclo estral regular, um alto número de folículos císticos (28) e morfologia ovariana irregular foram registrados nas ratas sedentárias (NR-S). Essas ratas, quando acasaladas, não procriaram. A caminhada em esteira teve efeito significativo sobre muitos dos parâmetros biométricos ($p<0,05$, two-way ANOVA). As ratas exercitadas (NR-E) tiveram função reprodutiva similar àquelas dos grupos NC: 14 ciclos estrais regulares, 16 filhotes, e 16 folículos císticos. Nas ratas das ninhadas reduzidas, a caminhada desde antes da vida adulta preservou a ritmicidade estral e a fertilidade, que estavam corrompidas nas fêmeas sedentárias de ninhadas reduzidas.

PALAVRAS-CHAVE: Exercício; Obesidade; Reprodução.

INTRODUCTION

The prevalence of obesity in human populations has been increasing in the last decades. As the normal functioning of the reproductive axis depends on an appropriate energy balance, obesity, especially of the central (visceral, abdominal) type has a negative impact on the reproductive function of women (BREWER; BALEN, 2010). In overweight women, longer and more irregular menstrual cycles, premature puberty, higher incidence of polycystic ovary syndrome, higher indices of miscarriages and chronic anovulation were reported (BREWER; BALEN, 2010; LOMBARDI et al., 2012; LORDELO et al., 2007; McLEAN; WELLONS, 2012; MICHALAKIS et al., 2013). Lower concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), altered hypothalamic leptin signaling, hyperandrogenism, impairment of the hypothalamus-pituitary-adrenal axis and altered autonomic activity are among the identified mechanisms mediating the negative effects of obesity on reproductive function (BREWER; BALEN, 2010; LORDELO et al., 2007; MICHALAKIS et al., 2013; NAGAI; MORITANI, 2004; VILMANN et al., 2012).

The postnatal nutritional environment can contribute markedly to obesity (CASTELLANO et al., 2011; LEVIN, 2005; RODRIGUES et al., 2007; SPENCER, 2012). The mechanisms involved are not completely clear, but in rats they involve alterations in the hypothalamic circuitry controlling appetite, which is established between the end of gestation and weaning (CHEN et al., 2008; DAVIDOWA et al., 2003; HABBOUT et al., 2013).

Inadequate eating habits and physical inactivity are the environmental factors most acknowledged as significant for the human epidemic of obesity and its complications (FIMS, 1998; PHILLIPS, 2013; SHARMA et al., 2013); it follows that the basic treatment is based on the modification of eating habits and the practice of regular physical activity (BREWER; BALEN, 2010; FIMS, 1998; HENRIKSEN, 2002).

Physical exercise reprograms the homeostatic balance between energy intake and expenditure so as to decrease weight gain and adiposity (LEVIN; DUNN-MEYNELL, 2004). When physical activity is introduced early in life, it can permanently alter the development of the central pathways regulating energy homeostasis, thus antagonizing the actions of overeating on the brain development and making regular physical activity effective in the prevention and treatment of early obesity (NAGAI; MORITANI, 2004; PATTERSON et al., 2008; PATTERSON; LEVIN, 2008).

There is a large literature on the reproductive disturbances of obese women, and many arguments about the beneficial effects of exercise on obesity and its related impairments. Although obese humans have difficulty in complying to the practice of physical activity at the levels needed to decrease their adiposity (LEVIN, 2005), there are indications that weight losses of 5-10% are sufficient to improve hormonal profile, menstrual cycling and fertility in overweight and obese women (BREWER; BALEN, 2010). However, the type, amount and duration of the exercise necessary to improve the reproductive outcomes are not known (McLEAN; WELLONS, 2012). The practice of several types of physical activity is not adequate for overweight/obese people, but walking is a low-to-moderate type of exercise, which favors adhesion.

In rats, the reduction of the litter size is considered a classical model of overweight/obesity and increased adiposity (CHEN et al., 2008; HABBOUT et al., 2013; DUFF; SNELL, 1982), making it an ideal model to make systematic investigations about the relations between obesity, physical activity and reproductive function. In the present investigation, it was postulated that female rats coming from reduced litters could show alterations of reproductive function caused by early overfeeding, and that physical activity in the form of treadmill walking could reverse these alterations. The purpose was to assess parameters of the reproductive function of female rats from conventional or reduced litters, subjected or not to treadmill walking.

2 MATERIAL AND METHODS

2.1 ANIMALS

The rats were kept at the animal house of the Department of Physiological Sciences of the State University of Maringá, under controlled light/dark cycles (12 h light:12 h dark) and temperature (22±2ºC). The experimental protocols were approved by the Ethics Committee of the Institution (statement 015/2013).

The pregnant Wistar dams were housed in individual boxes, were they gave birth. The newborn litters were reorganized so that each dam had three or nine puppies, preferably females. The nine-puppies litters were the Conventional Litter group (NC) and the three-puppies litters were the Reduced Litter group (NR).

The puppies remained with their mothers until the age of 21 days (weaning), when the female puppies were put into collective plastic boxes with free access to water and chow (Nuvilab CR1®; Nuvital – Curitiba, PR, Brazil). The female rats from the NC and NR groups were subdivided into sedentary (S) and exercised (E), thus yielding four groups, NC-S, NC-E, NR-S and NR-E. The animals were kept for 140 days. The body weight of the rats was recorded each month. Body length was recorded at the day of the euthanasia.

The data of body weight and length were used to calculate the Lee index of the experimental groups. The Lee index is used as an indicative of adiposity in rats (BERNARDIS; PATTERSON, 1968; NERY et al., 2011), and is calculated by the formula [√body weight (g)/body length (cm)] x 1000. The weight/length ratio was also calculated.

2.2 PHYSICAL ACTIVITY

Soon after weaning, the female rats were put into physical activity. This consisted of treadmill walking in a programmable treadmill (KT3000; Inbramed – Porto Alegre, RS, Brazil), in five sessions a week, at different days and times, excluding the periods of 10 a.m. to 16 p.m. and 18 p.m. to 06 a.m. For the first 20 days the female rats were adapted to the treadmill and to the activity, consisting of walking of increasing speed and/or duration. Since adaptation, each walking session lasted 30 minutes at the speed of 0.6 km/hr.

The compliance of the animals of the NC-E and NR-E groups to the physical activity was ranked as excellent, good or bad at each session. Excellent compliance was that in which the female rats walked during the whole session. The compliance was considered good when the animal walked during part of the session, demanding manual stimulation from the experimenter to continue. The compliance was considered bad when the rat stood still, without keeping up with the treadmill speed, during most of or the whole session, even with manual stimulation from the experimenter. Painful stimulation was not used to make the animals walk.

2.3 EVALUATION OF REPRODUCTIVE PARAMETERS

Since weaning, the rats were visually inspected daily for their vaginal opening. The day of the vaginal opening is considered the beginning of the sexual maturity of the female rat (CASTELLANO et al., 2011; GOLDMAN et al., 2000).

From 50 to 70 days of age, the rats had their estrous cycle assessed. For that purpose, a small amount of 0.9% saline solution was injected into the vagina with a Pasteur pipette and then removed. The epithelial cells collected were analyzed under light microscope to determine the phase of the estrous cycle: estrus, diestrus, metestrus or proestrus.

At the age of 70 days, three rats of each experimental group (NC-S, NC-E, NR-S and NR-E), when in proestrus (preovulatory period), were housed with a male rat for 24 hours. Next morning, when sperm was observed in the vaginal smear (indicating copulation) this was set as the first day of gestation. The mated NC-E and NR-E female rats continued to exercise normally. At the 18th day of gestation, they were transferred to individual boxes and physical activity was interrupted until the fourth day postpartum. The body weight of these mated rats was not recorded with those of the other rats of their groups.

2.4 TISSUE REMOVAL

The female rats were killed at the age of 140 days through deep anesthesia (sodium thiopental, 120 mg/kg body weight, intraperitoneal) after overnight fast. Visceral fat pads (retroperitoneal, periovarian, periuterine and mesenteric), brown adipose tissue and ovaries were removed and weighted. These data were expressed as relative weights (g/100 g body weight).

2.5 HISTOLOGY

Samples of ovaries were fixed in 10% formalin, dehydrated in increasing alcohol concentrations (70%, 80%, 90%, three times 100%), cleared in xylene and included in histologic paraffin. Afterwards the samples were sectioned in Leica RM2245 microtome (Leica Microsystems – Wetzlar, Germany) in semi-serial 5-6 μm-thick sections. The sections were stained with Hematoxolin-Eosin.

The morphological analyses were made from images captured through Nikon Eclipse E100 microscope coupled to Moticam 1000 camera with the aid of Image Pro Plus 4.0 image analyzer (Media Cybernetics – Rockville, MD, EUA). Four randomly selected ovarian sections, from four rats of each group, were analyzed for the presence of cystic follicles, according to descriptions in the literature (BRAWER et al., 1986; LARA et al., 2000).

2.6 STATISTICAL ANALYSIS

The means and standard deviations (SD) of the data sets were subjected to statistical treatment through two-way ANOVA (twANOVA) with Bonferroni post-test. P values below 0.05 were considered significant. The effects of litter size (NC against NR), exercise (groups -S against -E) or their interaction were taken into account. The statistical analyses were carried out with Prism 5.0 (GraphPad – San Diego, CA, EUA).

3 RESULTS

Table 1 shows the body weight of the four experimental groups from 30 to 120 days of age. Litter size had a significant effect on this parameter at almost every age recorded, in the sense that the female rats from the NR groups were heavier than those of the NC groups. Treadmill walking reduced significantly ($p<0.05$) the body weight at the age of 120 days of the NC-E group compared with its sedentary group (NC-S), but not of the NR-E compared with the NR-S ($p>0.05$).

Table 1. Body weight of female rats raised in reduced litters (NR) or conventional litters (NC), sedentary (S) or exercised (E).

Age (days)	Body weight (g)			
	NC-S (n=9)	NC-E (n=9)	NR-S (n=8-10)	NR-E (n=8-9)
30*	78.40±8.80	70.90±3.72	86.80±15.08	89.00±8.97
60*	209.10±11.94	193.50±6.59	215.40±28.39	222.70±19.01
90	266.20±14.62	258.90±44.67	263.40±15.28	273.90±22.38
120#	286.60±21.39	257.70±19.30	287.60±18.33	291.30±31.73

Data shown as mean±SD.
*p<0.01 for litter size, twANOVA.
#p<0.05 for litter size/exercise interaction, twANOVA.

Litter size and treadmill walking had a significant effect on the Lee index (Table 2). Both exercised groups (NC-E and NR-E) had their Lee index significantly reduced when compared with their corresponding sedentary groups (NC-S and NR-S, respectively). The weight/length ratio (Table 2) was influenced by litter size and exercise in a fashion similar to the Lee index.

Table 2. Lee index and weight/length (WL) ratio of female rats raised in reduced litters (NR) or conventional litters (NC), sedentary (S) or exercised (E).

	NC-S (n=9)	NC-E (n=9)	NR-S (n=7)	NR-E (n=9)
Lee index*	288.00±8.77	274.70±4.15	298.70±9.04	288.60±10.27
WL ratio (g/cm)#	12.84±0.74	11.71±0.39	13.21±0.83	12.84±1.36

Data shown as mean±SD.
*$p<0.01$ for litter size and exercise, twANOVA.
#$p<0.05$ for litter size and exercise, twANOVA.

The compliance of the rats to the treadmill walking had high excellent score in both groups (72.81% in the NC-E and 85.14% in the NR-E). The bad compliance was low in both groups (2.11% in the NC-E and 1.35% in the NR-E).

Litter size reduction significantly increased the relative weight of the visceral adipose tissue, while exercise decreased it significantly (Table 3). Exercise significantly decreased the brown adipose tissue of the NR-E compared with the NR-S, resulting in values similar to the NC groups (Table 3).

The relative weight of the ovaries was statistically influenced by exercise, with the groups NC-E and NR-E showing values greater than their corresponding sedentary groups (NC-S and NR-S, respectively; Table 3).

Table 3. Relative weight of fat pads and ovaries of female rats raised in reduced litters (NR) or conventional litters (NC), sedentary (S) or exercised (E).

Relative weight (g/100 g body weight)	NC-S (n=9)	NC-E (n=7-9)	NR-S (n=6-10)	NR-E (n=6-9)
Visceral fat*	4.94±0.87	4.09±1.06	6.43±1.18	5.42±1.57
Brown adipose tissue#	0.08±0.01	0.07±0.02	0.09±0.01	0.07±0.01
Ovaries!	0.04±0.01	0.05±0.01	0.04±0.01	0.04±0.01

Data shown as mean±SD.
*$p<0.01$ for litter size and $p<0.05$ for exercise, twANOVA.
#$p<0.05$ for exercise, twANOVA.
!$p<0.05$ for litter size and exercise, twANOVA.

Vaginal opening took place at about 34 days of age in the NC-S (34.67±0.87 days n=9) and NR-S (34.29±1.11 days; n=7). There was a highly significant interaction of litter size and exercise on this parameter ($p<0.01$, twANOVA), so that the age of the vaginal opening in the NC-E (32.78±1.64 days, n=9) was decreased, while it was increased in the NR-E (37.13±2.03 days, n=8), compared with their sedentary groups.

With the data of the vaginal smears during the 20 days of follow-up of the estrous cycle, the number of regular cycles (those with estrus, diestrus, metestrus and proestrus, each lasting one day) was recorded. Nine female rats from each group were tested. Altogether, the female rats from the NC-S had 10 regular cycles; those of the NR-S had just one. Treadmill walking increased the total number of regular cycles in both groups: 16 in the NC-E and 14 in the NR-E (Table 4).

Table 4. Reproductive parameters of female rats raised in reduced litters (NR) or conventional litters (NC), sedentary (S) or exercised (E).

	NC-S	NC-E	NR-S	NR-E
Number of regular estrous cycles (n=9 per group)	10	16	1	14
Number of puppies (n=3 dams per group)	16	18	0	16

Of the three mated female rats of each group, those of the NC-S had an overall of 16 puppies, those of the NC-E had 18 puppies and those of the NR-E had 16 puppies. Each pregnant rat delivered 4-6 puppies. The mated female rats of NR-S did not get pregnant (Table 4).

The observation of the histological sections revealed the presence of developing and/or mature follicles in all the groups, as well as the presence of corpora lutea (Figure 1). However, hyperemic blood vessels and altered ovarian stroma were seen in the NR-S (Figure 1C). Cystic follicles were also observed in all the groups. The number of cystic follicles was 19 in the NC-S, 20 in the NC-E, 28 in the NR-S and 16 in the NR-E.

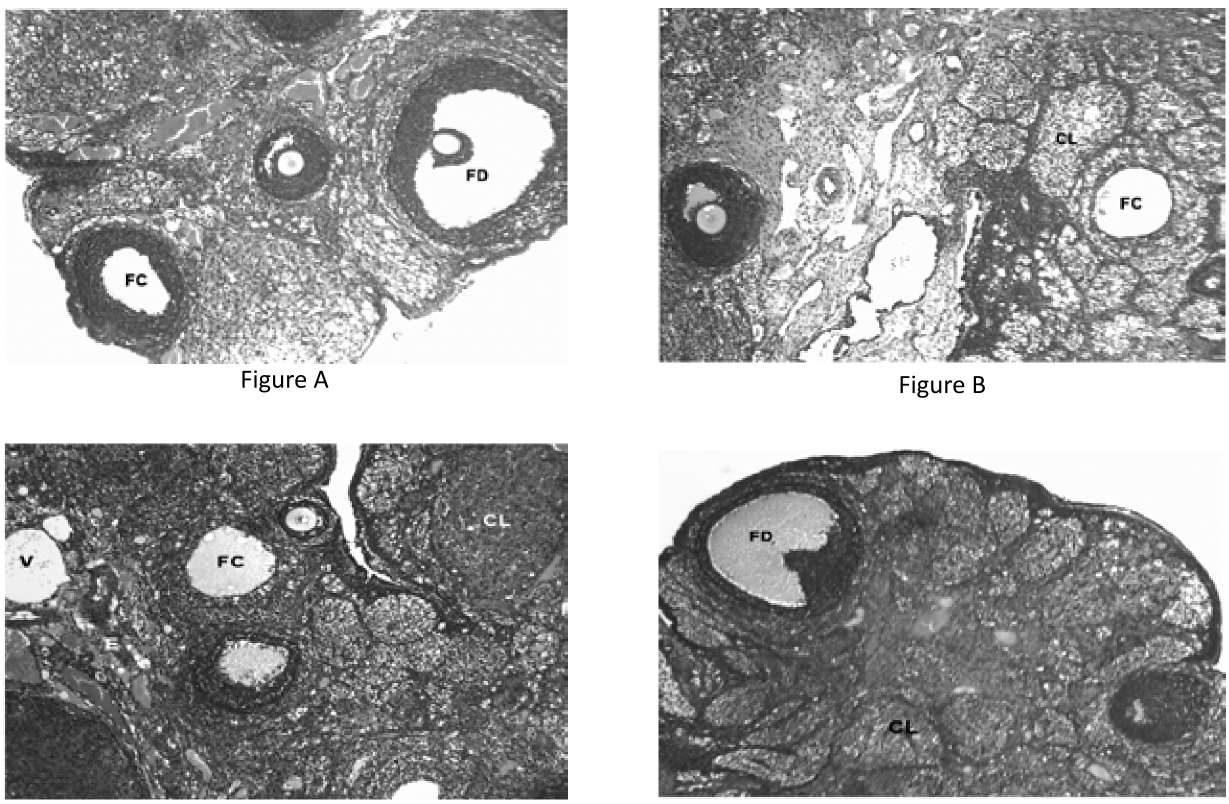

Figure 1. Histological sections of ovaries from female rats raised in reduced litters (NR) or conventional litters (NC), sedentary (S) or exercised (E). A) NC-S; B) NC-E; C) NR-S; D) NR-E. CL: corpus luteum; V: blood vessel; FC: cystic follicle; E: ovarian stroma; FD: developing follicle. H.E. 4X.

4 DISCUSSION

The biometric pattern corresponded to that commonly described in this obesity model (RODRIGUES et al., 2007; DUFF; SNELL, 1982; GOMES et al., 2012; RODRIGUES et al., 2009), with the Reduced Litter groups (NR) exhibiting higher body weight, Lee index, weight/length ratio and greater adiposity than the Conventional Litter (NC) groups. Exercise was capable of significantly reducing body weight of the NC-E, but not of the NR-E, although Lee index, weight/length ratio, visceral and brown adipose tissues were decreased by treadmill walking in both exercised groups. The increased relative weight of the ovaries in the exercised groups may be a reflection of their reduced adiposity compared with the sedentary groups.

As a whole, these data indicate that even a light-moderate physical activity can have a positive impact on body weight and adiposity. Discrepancies in the effect of exercise in litters of different sizes are found in other investigations. Body weight and fat weight loss in exercised rats from reduced litters were observed in other studies (LEVIN; DUNN-MEYNELL, 2004; GOMES et al., 2012), while opposite modifications of body weight in exercised rats from small and large litters, compared with their sedentary groups, were reported (NERY et al., 2011). Obviously, the gender, frequency and degree of compliance to physical activity, as well as the type of exercise, can influence the magnitude and direction of the results obtained. It should be stressed that the exercised groups of this study had excellent compliance, above 70-80%, to treadmill walking.

Studies report pubertal precocity in overweight or obese female rats and women (LORDELO et al., 2007; MICHALAKIS et al., 2013; VILMANN et al., 2012; CASTELLANO et al., 2011; MARTINEZ et al., 2010; VITALLE et al., 2003). This was not seen with the NR-S in this study. However, the NR-E showed a significant delay of sexual maturation (from 34 to 37 days), while the NC-E had sexual maturation reduced from 34 to 32 days, so that there was a highly significant interaction of litter size and exercise over this parameter. In women, it is reported that physical exercise is linked to reduced levels of leptin, with consequent delay of sexual maturation (MEIRA et al., 2009). The results of the present study indicate that other mechanisms acting on the hypothalamus-pituitary-ovaries axis may be involved, as expected considering the complexity of the neural and hormonal pathways involved in the reproductive function.

The influence caused by litter size and physical activity on the reproductive function of the NR female rats was surprising. Of the nine NR-S females, just one regular estrous cycle was recorded, the mated females did not have puppies, their ovaries had an irregular appearance and the number of cystic follicles was high, 28. Cystic follicles are frequently devoid of oocytes, show a large antral cavity, thin and/or irregularly shaped granulosa layer and normal or enlarged tecal layer (LARA et al., 2000). Together with the general appearance of the ovaries, the large number of cystic follicles could be a morphologic correlate of the infertility of the NR-S female rats: none of the three mated females had puppies. On the other hand, physical activity increased the number of regular estrous cycles of the NR-E (14 cycles) to values similar to those of the Conventional Litter groups (10 in the NC-S and 16 in the NC-E). In addition, the mated NR-E female rats had 16 puppies, a number not different from those of the NC-S (16 puppies) and NC-E (18 puppies); the number of cystic follicles in the NR-E, 16, was also similar to those of the Conventional Litter groups (19 in the NC-S and 20 in the NC-E), and the ovarian morphology was similar to these groups as well.

Walking is a physical activity whose energy expenditure, for most of its range of speeds and most body weights, is considered of light to moderate intensity (McARDLE et al., 2011). In addition, it can have a recreational character, because it does not demand any equipment, instructor, or specific setting. These features favor compliance and therefore the fulfillment of the primary goals in overweight/obese individuals, which is body weight and adipose mass reduction.

The results of the present investigation show that treadmill walking starting early in life had a marked beneficial effect on biometric parameters of female rats raised in small litters. In addition, although the number of mated females in each group was small, the data on the reproductive function were meaningful: the number of regular estrous cycles, of puppies and of cystic follicles in the NR-E remained within the range of the Conventional Litter groups, while the female rats from the NR-S had rupture of the estrous cycling, infertility, greater incidence of cystic follicles and morphologic alterations in the ovaries.

These data are relevant because they demonstrate that, regardless of the mechanisms, which most likely involve the hypothalamic circuitry of the reproductive axis, light physical activity can preserve the reproductive function in situations in which it is commonly compromised. Future, more sophisticated investigations shall indicate the specific mechanisms by which litter size reduction and exercise influence the reproductive function.

5 CONCLUDING REMARKS

Litter size reduction had a significant effect on biometric parameters and adiposity of female rats, as well as on their reproductive function. Many of these effects were reversed by treadmill walking since early life, so that Lee index, weight/length ratio and fat pads were diminished, and the number of regular estrous cycles, ovarian cystic follicles and the number of puppies delivered were restored to the levels of female rats raised in conventionally-sized litters.

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