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Pregnancy, Exercise and Late Effects in the Offspring until Adult Age

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1 Abstract

Maternal exercise during pregnancy as one of the critical periods can have significant delayed effect in the offspring's fetal imprinting of future development until adult age; adequate and voluntary exercise is provided, not a forced one as a stress. Spontaneous physical activity of the offspring until adult age can be increased, and body composition, cardiac micro structure and reactivity (greater resistance to noxi), vasomotor function, glucose metabolism, insulin sensitivity along with related diseases (diabetes) can be positively influenced. Bone development and also the enhancement of brain function and learning sensitivity can be improved as revealed in a number of experimental model animal studies. Exercise during pregnancy was also shown to compensate in the offspring the detrimental effect of inadequate, e.g. high fat diets. Possibility of introducing significant modifications of the programming of the offspring's desirable development and health status by adequate and physiological maternal exercise during pregnancy was supported also by some observations in humans.

2 Keywords

Pregnancy; Exercise; Delayed Effects; Offspring; Adult Age; Physical Activity; Metabolic; Vascular; Brain Consequences

3 Abbreviations

PA – physical activity; Ex – exercise

4 Introduction

The level of physical activity (PA) and exercise (Ex) is an important environmental stimulus which has significant effect on a number of metabolic, humoral, functional, morphological, psychological and other characteristics of the organism which can manifest not only at present, but also as delayed consequences when implemented since the very beginning of life. Such effects depend on the character, intensity, frequency, duration of PA régimes and/or Ex, and the reaction and consequences can be also further modified by eventual adaptation to them when applied gradually and repeatedly during appropriate periods of time. Increased physical fitness, reduced adiposity along with reduced metabolic, musculoskeletal and psychological problems can result from adequate exercise, especially when applied during growth [1, 2]. On the other hand, sudden forced implementation of increased Ex can become a stress with undesirable results as revealed e.g. in experimental models [3, 4, 5].

Previous studies on the impact of Ex which modifies significantly energy balance and turnover showed also that the earlier such a stimulus is implemented and the longer it lasts, the more apparent are its manifestations; the adequacy of such a stimulus is essential, and should always have a character as related to the level of development of the organism when Ex is started to be implemented. Moreover, this effect can appear and has a special character when applied through the régime of PA of the pregnant mother [3-6].

Fetal origin hypothesis of morbidity [4, 5, 7, 8, 9] and metabolic imprinting by prenatal, perinatal and postnatal factors [6-10] concern also PA and Ex. Their impact can be transferred during pregnancy on the fetus due to physical activity régimes and reactive changes to them of the pregnant mother, and could manifest significantly in the offspring during its own postnatal period up to the adult age. The effect of PA is closely interrelated with the impact of nutrition manifesting energy balance and turnover, and the effects of these relationships can be mediated

and reflected also as delayed effects later in life. Changed nutrition of both, restricted and high fat diet during gestation can alter, along with low birth weight also physical activity [11].

Most important of the effects of adequate PA and Ex régimes during pregnancy are those which have more permanent character due to the intervention in the programming of the fetus under physiological conditions, in a way which can be considered positive for the development of health and overall fitness during later life up to adulthood. This has been supported by empirical and some practical observations, and has been studied both in humans and experimental models. Evidence-based prenatal exercise guidelines have been recommended to counsel healthy and adequately functionally well disposed pregnant women for appropriate and safe physical activity régimes [12].

5 Interrelationships between early nutrition related to physical activity

Most long-term data exist on the effect of maternal nutrition - energy intake related to its expenditure during pregnancy. Exposure to famine *in utero* and in early infancy during and shortly after WW2 resulted in more frequent obesity in young Dutch men; however, PA and energy expenditure later in life were not followed up [13]. Mother's undernutrition during pregnancy resulted in long-term shift of their offspring's nutrition and physical activity choices, i.e. preference for wheel running versus lever pressing for food [14]. Inequalities in nutrition - food restriction and/ or high-fat diet during gestation induced reduced birth weight, and altered also the level of PA in adult offspring [11].

Developmental programmings of metabolic disorders in the offspring of obese mothers were discussed, with regard to the elucidation of mechanisms underlying altered obesity risk in the offspring [15]. Intrauterine origin of adult morbidity due to fetal programming was considered to be influenced by various changes of internal milieu of the mother, e.g. modification of its acidity which change the frequency of heart rate of the fetus and its movements in the womb [16].

Fetal growth restriction due to reduced food intake reduced physical activity and energy expenditure, and increased obesity in female, not male offspring mice [17]. Diet with decreased percent of protein fed to rat mothers during weaning decreased in the offspring slightly body weight and fatness along with increased economy of following growth (expressed as g diet /g body weight increase), increased spontaneous PA level in running wheels and reduced experimental cardiac necrosis and mortality after isoprenaline application in adult age [6,18,19]. Early interventions including fetal one concerning energy balance and turnover has appeared to be significant for adult health and sensitivity to noxi.

6 Effect of exercise during pregnancy in humans

PA during pregnancy has been considered especially from the point of view of the influence on health risks of the mother and offspring. Observations in the mother and the outcome of pregnancy revealed mostly beneficial effects of an adequate PA régimes during pregnancy, depending on their character and in-

tensity. Significant changes of birth weight gain and subcutaneous fat distribution due to PA appeared during second half of pregnancy [21]. Pregnant women who continued in endurance Ex gave birth to children with significantly lower birth weight, lower ponderal indexes, smaller fetoplacental weight ratios and lower skinfold thicknesses ; crown-heel lengths and head circumferences were not influenced [22,23]. Interruption or reduction in preconceptional Ex increased birth weight and skinfolds of newborns [23]. However, consequence of PA interventions during pregnancy in later life were not reported, or only those manifested e.g. at the age of 18- 24 months only [24].

The adequacy of Ex during normal pregnancy has to be carefully specified and defined; moderate regular Ex does not have an adverse effect on the neurodevelopment of the child and motor skills up to 18 months of age [25]. Aerobic Ex training has been determined as safe and efficacious throughout pregnancy, but other characters of physical training (circuit and resistance) have been studied only more recently [26]. The effect of Ex during pregnancy of women spending at least 20 min three times per week, at minimum intensity of 55 % of their maximal aerobic capacity on newborn's brain was considered to give insight on fetal neuroplasticity [27].

The amount, range and type of PA which was performed before becoming pregnant were followed in Polish women; in addition, comparisons were made between the infant and newborn status using the APGAR scale with the amount of PA performed by the mother. There were decidedly low PA levels observed in pregnant women compared to those before becoming pregnant. Interventions have to be targeted to test the hypothesis and attempt to identify the most appropriate levels for intensity, duration and frequency of PA and Ex during pregnancy which are considered to have also a direct relationship on the method of delivery and health of the newborn [28].

Most studies on the effect of PA and Ex during fetal period concern those manifested in the offspring after birth, or in very young subjects), but fewer also for those in later life up to the adult age. However, a study in the offspring of mothers who remained physically active during pregnancy displayed more positive academic performance at the age of 6-18 years [29] revealing benefits of the continuing maternal PA practice (however, the contribution of additional possible factors were not analyzed). Higher birth weight, smoking status and low physical activity during pregnancy were also associated with obesity in the offspring at the age of 8 years [30].

In humans it has been hardly possible to follow up separately, without interference of other factors, the effect of PA and Ex during normal pregnancy, in the offspring later in life. Studies of the long-term influence of PA and Ex during pregnancy have been therefore mostly conducted in experimental models with animals, mostly laboratory.

7 Late effects of PA and Ex during pregnancy in experimental animal models

Offspring of mice mothers which had access to spontaneous PA in running wheels during pregnancy displayed lifelong propensity for higher PA as compared to offspring of inactive mothers,

along with slightly higher weight at birth. Body weight and composition later in life when they had no possibility to use running cages no differences were found [31]. However, in other comparably arranged experiments the differences between the offspring of mice using running wheels or inactive ones during pregnancy were not found; the same concerned body composition. At the level of the individual, correlation analyses revealed some statistically significant relationships between maternal and offspring Ex levels, likely reflecting previously known heritability estimates for such similar PA [32].

Gestational exercise of swine mothers was revealed as a potent stimulus for programming vascular smooth muscle relaxation in adult offspring. Ex training for the finite duration of mother decreased in adult offspring vascular smooth muscle responsiveness to an exogenous nitric oxide donor, i.e. vasomotor function of adult offspring can be thus programmed by mother's exercise during pregnancy [33]. However, other experiments using Sprague Dawley rats showed that maternal wheel running during pregnancy did not significantly modify behavior or vascular function in adult offspring, i.e. vasorelaxation response to acetylcholin or sodium nitroprusside [34]. Significant effect of maternal Ex (1 hour of daily running on a running carpet at the speed 20m/min.) was found in Sprague Dawley rats during the whole period of pregnancy. Number of fibers and capillaries, capillary/fibre ratio were increased, and diffusion distance reduced in the heart, i.e. these parameters of the heart development were significantly changed in the offspring of exercised rats at the age of 110 days, positively with regard to function. This prenatal impact was further positively increased by similar Ex during postnatal life in other groups up to 110 days; the character of changes indicated that Ex impact during pregnancy was more important [6,35,36]. This effect on heart microstructure was confirmed along with aerobic power [35]. Negative effect of isoprenaline application on the development of experimental cardiac necrosis and mortality in adult offspring of rat mothers exercised during pregnancy was significantly less harmful as compared to the offspring of control mothers [37].

The effect of strenuous Ex at the level of 70, 80, 90 percent of VO₂ max was followed in the offspring of rat mothers exercised during pregnancy: weight of heart, capillary/fibre ratio in newborn rats and their VO₂ max at the age of 90 days were assessed. The body weight was reduced – was less in mostly Ex offspring, capillary/fibre ratio was different compared to control inactive group. The effect of Ex was shown to depend of the relative work load applied to the mother, which was particularly marked at high work loads [38].

Moderate Ex during pregnancy can change also musculoskeletal system and body composition in the offspring, i.e. Alter bone and adiposity in a gender-specific way [39]. The positive effects of preconceptual training comparing groups of female mice with or without voluntary Ex in running wheels were revealed in significant changes of bone gene expressions, in particular to-

wards osteogenic remodelling markers [40].

8 Metabolic consequences of exercise during pregnancy in the offspring

Glucose metabolism in skeletal muscle and fat of weanling rats was significantly influenced by modest voluntary Ex (running wheels) of mothers during pregnancy; maternal exercise appeared to decrease the metabolic risk induced by maternal obesity improving insulin/glucose metabolism, with more apparent effect in male than female offspring [41].

Preliminary evidence on the effect of voluntary Ex during pregnancy was found in the offspring compared with offspring of sedentary mice at the age of 8 weeks, when following at similar age of two generations. Small, but broad generation- and sex-specific effects of Ex ancestry were observed for body mass, fat and muscle mass, serum insulin, glucose tolerance and muscle gene expression (mRNA levels for multiple genes, especially those related to metabolic genes), which varied with regard to first and second generation of mice followed up [42].

Long-term glucose homeostasis in the offspring of mothers Ex during pregnancy was shown to be also influenced. Blood glucose concentrations were reduced to lower values in response to an intraperitoneal insulin tolerance test for both male and female adult offspring of parents with access to running wheels. Male offspring from exercised mice showed increased percent of lean body mass along with decreased fat mass percent compared with male offspring from sedentary dams; in females no differences were found [43].

The comparison of the offspring of Ex and sedentary Sprague-Dawley rat mothers showed that intrauterine environment can influence insulin sensitivity in mature age. Adult female offspring born to Ex mothers had enhanced glucose disposal during glucose tolerance testing as well as increased glucose infusion rates and whole body glucose turnover rates during hyperinsulinemic - euglycemic clamp testing compared with offspring from sedentary dams. Offspring of exercised dams had also, compared to offspring of sedentary dams, decreased insulin levels and hepatic glucose production during the clamp procedure, and increased glucose uptake in skeletal muscle, along with decreased heart glucose uptake in response to insulin infusion during the clamp procedure. Apparently Ex during pregnancy enhances offspring's insulin sensitivity and improves glucose homeostasis, which can decrease offspring susceptibility to insulin-resistant related diseases such as type-2 diabetes mellitus [44].

With regard to metabolic health, the effect of Ex before and during pregnancy can compensate positively e.g. the effect of inadequate diet fed to male offspring of mothers with different PA. Ex (swimming) of mothers during pregnancy prevents negative effect of high fat diet inducing obesity in adult mouse; this could be important for succeeding generations as well [45].

Offspring of chow-fed diet dams who trained in running wheels before and during gestation had improved glucose tolerance beginning at 8 weeks of age and continuing throughout the 1st year of life, and at 52 weeks of age had significantly lower serum insulin concentrations and percent body fat compared to other groups (sedentary with different diets). High-fat feeding of

sedentary dams resulted in impaired glucose tolerance, increased serum insulin concentrations, and increased percent body fat in the offspring. Apparently, maternal Ex before and during gestation compensated and ameliorated the detrimental effect of a maternal high fat diet on the metabolic profile of the offspring [46]. Central leptin sensitivity and signalling in adult offspring of dams fed high-fat diet during pregnancy and lactation can be improved by Ex also during early weaning period, through the effects on hypothalamic neuropeptide and receptor mRNA expression [47].

9 Exercise effects on brain function of the offspring

Maternal running during pregnancy has also been suggested to exert beneficial effects on brain functions of the offspring. Experiments in the offspring of rats exercised during pregnancy revealed significant increase in the expression of leptin receptor in prepubertal male rat offspring (not in prepubertal female pups), enhanced hippocampal cell survival and improved learning memory capability in prepubertal and adult male pups, as compared to control group without pregnant mother's Ex. These results showed that maternal Ex during pregnancy may regulate spacial plasticity in the hippocampus of the offspring by increasing the expression of leptin secreted from adipose tissue, which has positive effects on learning, memory and synaptic plasticity [48].

Ex of pregnant rat mother enhanced also cognitive functions (habituation behavior and spatial learning) in the offspring, and increased brain-derived neurotrophic factor levels and cell numbers in the hippocampal formation of the offspring [49]. Maternal swimming during pregnancy increased mitochondrial mass and membrane potential suggesting mitochondriogenesis in cerebellum and parietal cortex of pups, i.e. neurometabolic programming in the offspring by Ex during fetal period [50]. However, forced maternal Ex at high intensity had a negative effect on the neurogenic niche development in postnatal offspring – reduction of cell proliferation in the postnatal dentate gyrus of mouse offspring [3]. Testing of object recognition memory and following the increase c-FOS- positive cells expression in peripheral cortex, suggested that ex during pregnancy may enhance also brain function of the male offspring of exercised mothers ($\sim 0.76 \pm 0.09$ km) per night in the running wheel [51].

10 Conclusions

Selected long-term studies of the effect maternal Ex during pregnancy on their offspring later in their life revealed significant changes of a number of characteristics, starting with the level of spontaneous PA. These follow-ups have not given always identical results, depending on Ex character : spontaneous, voluntary in running wheels and/or induced on running carpet, swimming etc., then, also intensity and duration of mother's Ex, species of experimental animals, character of delayed changes, age of the offspring when consequences were assessed, including total duration of experiments, etc. was not always identical and comparable. Effect of Ex in females of many species was complicated with regard to the changes of PA during estruous cycle, so results

were not always apparent, or only males were used for experiments. Delayed consequences concerning level of spontaneous PA, morphological, metabolic and functional characteristics, brain function and morphology were found in the offspring prevalingly positive. When Ex has been adequately implemented, resulting changes appear to be desirable, indicating important physiological effect of maternal Ex during pregnancy on later functional development of their offspring's organism, its fitness and health prognosis until adult age.

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