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COMMENT

Appropriate exercise might have some benefits for both mothers and their babies via epigenesis

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Maternal factors beyond genes on offspring

Historically, the phenomenon of the maternal-to-zygotic transition was observed in the Dutch Hunger Winter. In the winter during World War II, the population, including pregnant women, suffered from severe hunger because of a shortage of food due to transportation disruptions by the Nazis. During this period, the total calories of the delivered food ranged from 580 kcal/day to 1000 kcal/day. There were ~40,000 low-weight newborn babies during this period. After these babies grew, many developed diabetes mellites, hypertension, cardiovascular disease, and microalbuminuria, although calorie restriction usually decreases the incidence of these diseases [1]. Moreover, a high incidence of these diseases was observed in the third generation. This phenomenon strongly suggests that some mechanism by which maternal environmental factors transmit to offspring exists [1]. Later, many studies revealed that this phenomenon was caused by epigenesis (Fig. 1), which can be mainly explained by maternal germline histone methylation [2]. This finding indicated that some maternal factors, such as nutrition, beyond the central dogma regulated by genes, are important for offspring health.

Factors that can cause epigenetic changes have been evaluated. Most of them were nutritional factors because original findings indicated that nutritional factors are obviously important. Exercise and aging seem to be some important candidates (Fig. 1), although evidence about the relationship between epigenesis and these factors is limited at this point [3, 4]. In a previous study, the exercise treated to participants was a 6-month supervised exercise intervention consisting of mainly endurance exercise (one session of 1-h spinning class and two sessions of 1-h aerobic class per week) [5]. But, how hard and how long exercise could cause epidemic effect had remained unclear [6].

Epigenesis and hypertension, including vascular function

The original findings related to the Dutch Hunger Winter included an increase in the incidence of hypertension in subsequent generations. Therefore, epigenesis related to hypertension has been investigated [7]. Hypertension can be caused by many gene expression abnormalities related to the renin-angiotensin-aldosterone (RAS) system, ionic balances, and so on. DNA methylation has been reported in the Atgr1alpha, Argr1beta, and Ace-1 genes, which are related to the RAS system in animal models. Histone modification of Ace1 was also reported (Fig. 1) [7, 8]. DNA methylation has also been reported in ADD1, SCNN1A, and SCNN1B, which are related to ionic balances [8]. In terms of the relationship between vascular function and epigenesis, the available information is limited. DNA methylation in ESR1 in the uterine artery, which is related to vasodilation, was reported. Histon modification in NOS3 (also known as eNOS) in cell lines was reported (Fig. 1) [8]. However, vascular function itself was not evaluated in these reports. Therefore, the relationship between epigenesis and vascular function remains unclear. Moreover, the stimulator of epigenesis was only nutritional standard methods.

Effect of maternal exercise on both the mother herself and her offspring

Exercise has been reported to be an important modifiable factor for health. Exercise ameliorates hypertension,

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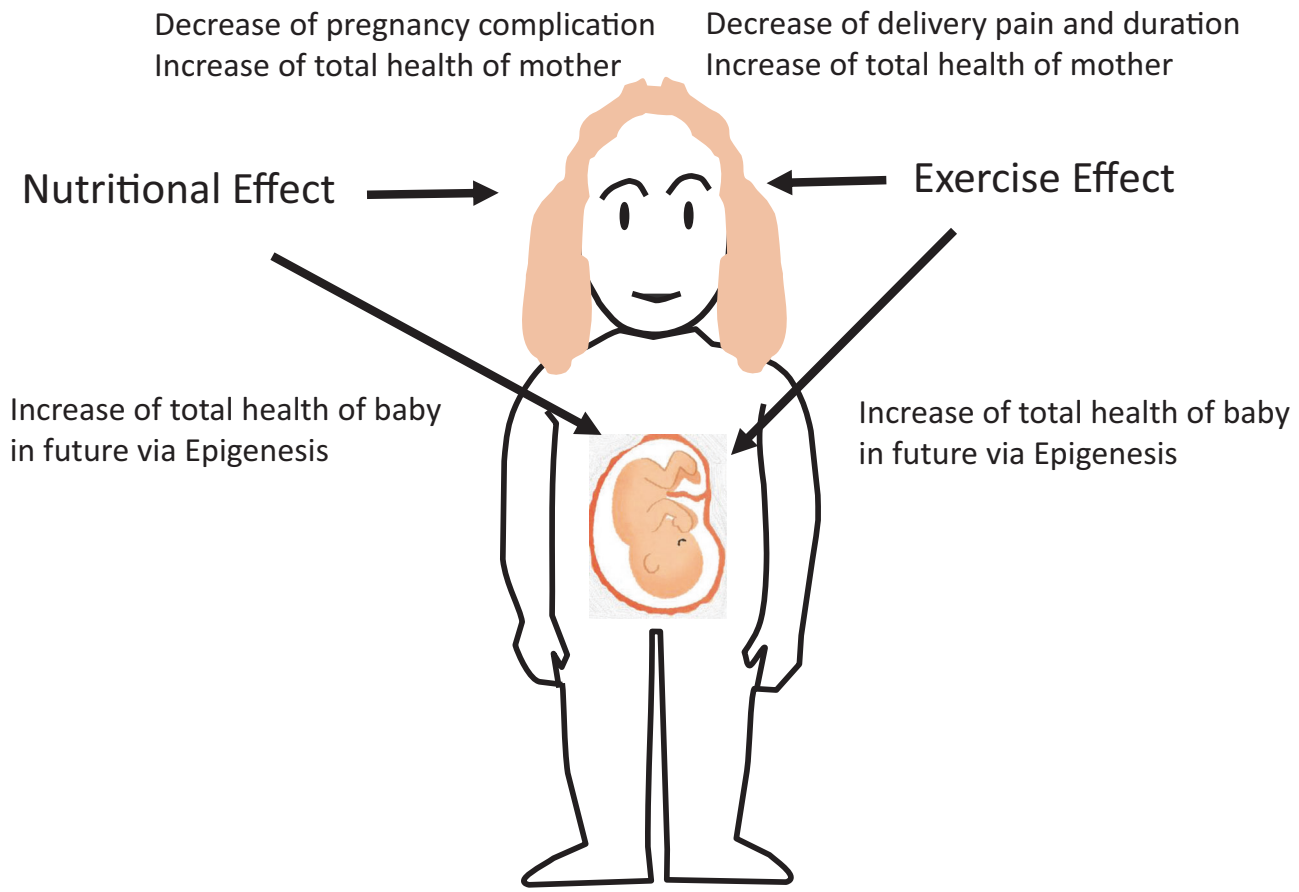
Graphical Opinion



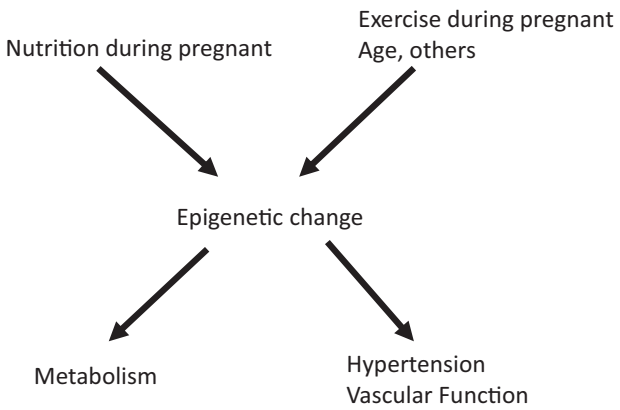


Fig. 1 Epigenetic changes linked maternal environmental factors to metabolism and vascular function in the next generation. Nutritional factors in pregnant women can affect the next generation via epigenetic changes in germline DNA. The relationship between nutritional factors and metabolism has been revealed. The relationship between nutritional environmental factors and hypertension has been reported. Exercise, age and other factors have been evaluated as stimulators of epigenetic changes. At this point, the relationship between exercise and vascular function in the next generation has not been confirmed

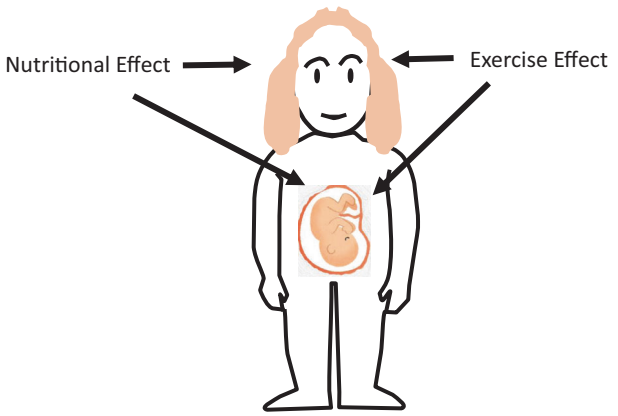


Fig. 2 Effects of nutrition and exercise on both mothers and their babies. Maternal nutrition effects can contribute to mothers' health to appropriate growth in their babies and to the health of their babies in the future. Maternal exercise can also have effects on the future health of both mothers and their babies. As traditionally recommended for pregnant women, healthy foods and appropriate exercise may have some benefits on both mothers and their babies

although hypertension patients should pay attention to their blood pressure during exercise. Exercise decreases the incidence of proteinuria [9] and has a protective effect on the prevention of renal dysfunction [10]. Recently, exercise has been revealed to have favorable effects on the immune system, mental health, and cancer prevention in addition to physical conditions [11]. In terms of pregnant women, doctors have been concerned that exercise might increase complications during pregnancy. However, recent studies, including some intervention studies [12], have shown that exercise during pregnancy has favorable effects, such as a decrease in delivery time and delivery pain, without an increase in eclampsia or pregnancy hypertension [13]. Whether exercise during pregnancy has a beneficial effect on babies is a future research direction.

In this issue, Meiling et al. reported that maternal exercise caused epigenetic changes in the Atgr1alpha gene, resulting in enhanced vascular function in offspring using hypertensive rat models [14]. The upregulation of Agtr1a gene promoter methylation status was confirmed in the mesenteric arteries of 3-month-old male offspring of spontaneously hypertensive rats (SHRs) and Wister-Kyoto (WKY) pregnant rats treated with exercise therapy. As a phenotype in the next generations, maternal exercise significantly reduced resting blood pressure and cardiovascular reactivity. Moreover, the effects of ANGII-AT1R on both blood pressure and vasoconstriction in the offspring of SHRs and WKY rats were attenuated by maternal exercise. These findings indicate that maternal exercise may have favorable effects on the incidence of hypertension and the vasocontraction response.

Of course, these findings should be interpreted with caution. The rats' exercise treatment was a 60 min swimming program 6 days per week, which means a maximal aerobic velocity of ~60%. Obviously, this strength of exercise is not tolerable for human pregnant women. At this point, it is unknown how much exercise could cause epigenetic changes in human offspring. Moreover, exercise overload might increase complications during pregnancy. With such religious care, healthy foods and appropriate exercise might have some benefits for both mothers and their babies (Fig. 2), although traditional recommendations for pregnant women have supported this message.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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