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REVIEW

Molecular and Cellular Interactions between Mother and Fetus. Pregnancy as a Rejuvenating Factor

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Abstract—Aging is associated with a decline of various body functions, including ability to regenerate. Over recent decades, it has been demonstrated that some of these changes could be reversed in response to factors originating from a young organism, for example, fetal stem cells or "young blood" in models of heterochronic parabiosis. Pregnancy might be considered as parabiotic model of the interaction between two organisms of different age. In this work, we analyzed and summarized data on the effects of pregnancy on the maternal organism that confirm the hypothesis that pregnancy rejuvenates the mother's organism or slows its aging.

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Prevention or even reversal of aging have become topics of numerous studies. The discovery of rejuvenating factors, if they exist and are of chemical nature, would become a breaking point in solving many problems in gerontology. Scientists periodically report a discovery of such factors; however, careful examination of their data and technical details of these studies raise doubts if the discovered factors indeed possess rejuvenating properties. In particular, when the circulatory systems of two animals of different ages are connected in a heterochronic parabiotic model, the older partner undergoes rejuvenation [1]. Some recent studies aimed to identify the chemical factor that enters the older organism from the younger one suggested that this rejuvenating factor is GDF11, a differentiation growth factor that circulates in the common blood stream of parabiotic partners [2-4]. However, more detailed studies failed to unambiguously confirm that GDF11 is responsible for the rejuvenating effect [5-7].

The rejuvenating effect of pregnancy remains a subject for discussion. We find it promising to view pregnancy as a parabiotic system in which organisms of different age (young fetus and mature mother) are functionally connected and exchange factors that affect both, in either positive or negative manner. Pregnancy is a great burden for the maternal organism and carries a risk of numerous complications. Hence, for many years, both clinical medicine and academic research have concentrated mostly on negative effects of pregnancy on the mother's health. However, recent studies have shown that pregnancy might have positive effects on the physiological state of many organs and on maternal longevity in general, especially in the absence of pregnancy-accompanying complications. Some studies even discussed the "rejuvenating" effect of pregnancy on the maternal organism.

In this article, we review and analyze current data on the effect of pregnancy on aging.

REGENERATIVE CAPACITY DURING PREGNANCY

One of the main manifestations of aging is a diminished regenerative capacity of an organism. There is a body of evidence that pregnancy can reverse the process, at least in some organ systems.

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The regenerative capacity of liver (estimated from the rate of liver regeneration after removal of 2/3 of its volume) in 10-12-month-old mice was four times lower than in young (3-month-old) animals. In addition, the mortality after partial hepatectomy was higher in aged mice [8]. Aged animals had decreased blood-clotting ability due to the decline of liver synthetic functions. However, when old mice were in the third trimester of pregnancy, their rate of liver regeneration after hepatectomy was like that in young animals: in both young non-pregnant mice and aged pregnant mice, liver regenerated to its initial volume ~2 days after the surgery, while in old non-pregnant animals, liver volume remained less than 50% of the original one. Moreover, pregnancy decreased five-fold the post-surgery mortality in aged animals. The blood-clotting activity in aged pregnant mice was within the norm, which indicated that their liver not only regenerated to its initial volume, but restored its synthetic functions as well. Gielchinsky et al. [8] analyzed the mechanism of liver regeneration and found that in aged animals, pregnancy activated cell hypertrophy, whereas in young mice, liver regenerated mostly due to cell hyperplasia. Hepatocytes in aged pregnant mice increased their volume five-fold compared to liver cells in non-pregnant animals; less than 10% of these hepatocytes showed signs of activated proliferation. Hyperplasia was also activated after delivery in parous mice, which indicated that pregnancy shifts regenerative processes toward hypertrophy. These changes might be related to activation of the Akt/mTORC1 signaling pathway, since its inhibition blocks hypertrophy, while its activation stimulates the effects of pregnancy.

Another common object for studying regeneration and its decline with age is a skeletal muscle. The regeneration index in 20-month-old mice was almost 10 times lower than in 3-month-old mice [9]. The effects of pregnancy on skeletal muscles were like those observed in liver: pregnancy enhanced two-fold the regeneration of muscles in both aged (10-month-old) and young animals [9]. The number of satellite cells (muscle stem cells) did not differ between the groups, which indicates that deterioration of the regenerative functions was not due to the exhaustion of the pool of these cells. The decline in the regenerative capacity of muscle tissue with aging is believed to be related to changes in regulation, in particular, to inactivation of the Notch signaling pathway [10]. Pregnancy reverses these changes in aged animals and restores the activity of this pathway to the levels typical for young individuals. The effect of pregnancy on regeneration of damaged heart muscle has not been studied directly; however, retrospective analysis of the data from patients with cardiomyopathy showed that heart functions were restored spontaneously in 50% of pregnant women and those who had recently given birth – the highest positive outcome among all heart pathologies [11-13].

Another beneficial effect of pregnancy on the maternal organism is the protection of the central nervous system. Clinical studies on the effects of pregnancy on the development of multiple sclerosis found a reduction in the relapse rate during pregnancy [14, 15]. These results correlated with an observed decrease in the number and area of regions with active degradation of the brain white matter [16]. It has been shown that parous women have lower risk of multiple sclerosis than non-parous ones [17]; moreover, the protective effect of several pregnancies is cumulative [18]. Pregnant mice with multiple sclerosis induced by injection of lysolecithin into the spinal cord central canal had 50% fewer lesions and displayed considerable increase in the number of oligodendrocytes and remyelinated axons in the damaged area [19]. It was suggested that this phenomenon was partially because of prolactin, since injection of this hormone stimulated oligodendrocyte division in the zone of lesions.

PROPOSED MECHANISMS OF REGENERATIVE EFFECT OF PREGNANCY

There are several mechanisms that could explain the rejuvenating effects of pregnancy on the maternal organism. Most probably, these effects are related to a combination of several, or even all, factors described below. The suggested mechanisms could be divided into two groups: fetus-related and mother-related.

Fetus-derived regulatory signals. The rejuvenating effect of pregnancy might be explained by the donation of fetal cells capable to differentiate. The regenerative properties of stem cells are well known, and therapeutic effects of stem cells injection after brain, liver, or kidney damage have been well described [20, 21]. Some fetal cells enter the maternal circulation and tissues – a phenomenon known as microchimerism. Fetal cells could be found in the mother's blood and tissues several decades after pregnancy. Thus, cells bearing the Y chromosome were found in the blood of a woman that had given birth to her son 27 years before her blood was tested [22]. At present, there is no consensus on the mechanisms that would explain the effects of microchimeric cells on the maternal organism. Two main possibilities are discussed: the first one is regulatory interactions, and the second is direct differentiation of microchimeric cells into a type of cells required for the mother's regeneration. In the first case, a limited number of fetal cells act as coordinators of the regenerative process. For example, fetal cells are believed to regulate inflammatory response by downregulating TGF-β biosynthesis and by directing maternal regeneration toward scar-less fetal-like wound healing [23].

A direct contribution of microchimeric multipotent cells to regeneration has been demonstrated in a damaged heart model. Fetal cells actively migrated into the damaged area of the mother's heart, where they differentiated into

fully functional cardiomyocytes that contracted synchronously with surrounding cells. In the absence of damage, the number of fetal cells in the heart was 20-fold less [24].

Another study demonstrated the presence of microchimeric cells that showed elements of neuronal type differentiation in the brain of pregnant rats. The number of such cells was higher in animals with Parkinson's disease [25]. Similarly, the number of microchimeric cells in kidneys [26], liver [27], and lungs [28] increased after damaging of the organs.

In the past few years, several studies have been published that described positive effects of heterochronic parabiosis on the older partner. When the circulatory systems of two animals of different age were converged, this benefited the older animal. Parabiosis caused regeneration and, probably, rejuvenation of the heart [4], skeletal muscles [29], liver [30], and brain [31-33] and promoted myelination of the spinal cord [34]. A similar but less pronounced effect was induced by injecteion of blood from young animals. At present, it is believed that this effect is related to the "rejuvenating" regulatory factors that are "donated" to the aged organism by the young one. GDF11, which is supposedly one of these factors, has been extensively studied and discussed [2, 4, 35]. We believe that pregnancy can be considered as a specific form of parabiosis in which an aged organism (mother) is tightly joined to a young organism (fetus). Obviously, their bloodstreams do not mix together, but it does not exclude the possibility of the regulatory factor exchange.

Mother-derived regulatory signals. The mother can also be a source of rejuvenating factors. First, pregnancy activates production of "standard" female sex hormones, in particular estradiol. We have already discussed in detail the effect of female sex and female hormones on health and longevity [36]. In this article, we describe phenomena important for understanding the role of pregnancy in the modulation of lifespan. The life expectancy of women is 5-10 years longer than life expectancy of men [37]. Female mortality caused by almost any types of the diseases is lower than male mortality [37]; moreover, many diseases manifest themselves in women 5-10 years later than in men [38-43]. Most works in the field of gerontology suggest that women age more slowly than men. At least some of these differences are related to female sex hormones. Firstly, the "protective effect" against many diseases disappears after menopause, i.e. when production of female hormones decreases significantly [44-48]. Hormone replacement therapy protects women from certain disorders [49]. Moreover, estrogens directly protect organs from ischemic damage [45, 50-53]. Therefore, increased "femininity" caused by the elevated production of female sex hormones contributes to the total effect of pregnancy on rejuvenation.

False pregnancy can be induced by mating with an infertile male. It is typical for some animal species in which mating induces hormonal changes like those observed in early pregnancy (e.g. increased levels of progesterone [54]). False pregnancy induces hepatocyte hypertrophy typical for early pregnancy stages, but it is less pronounced at late pregnancy stages [8]. False pregnancy also activates muscle regeneration, like what happens in actual pregnancy [9]. It should be noted that injections of progesterone, one of the main pregnancy hormones, does not affect muscle regeneration. However, injections of another pregnancy hormone, prolactin, activate oligodendrocyte proliferation and promote regeneration of damaged myelin sheaths in multiple sclerosis models, an effect like one caused by pregnancy [19]. In this case, no fetal factors are involved because of the absence of a fetus.

The effects of pregnancy on the maternal organism are undoubtedly mediated by signaling cascades. It is not surprising that cascades associated with the protective effect of pregnancy are also associated with other protective mechanisms. Thus, protective effect of pregnancy on heart and liver is mediated by the Akt signaling pathway [8, 55]. The same signaling pathway is involved in a broad spectrum of regenerative and protective mechanisms, such as organ protection from ischemic damage [55] and tissue regeneration [56]. These processes involve changes in the activity of multiple regulatory proteins [55] whose roles in the development of various pathologies have been extensively described in numerous studies: eNOS [57], GSK-3β [58], VEGF [59], NF-κB [60], Nrf2 [61], mTOR [62], and Bcl2 [63]. The protective properties of the Akt signaling pathway are determined by its central role in regenerative process via regulating proliferation, migration, differentiation, and survival of mesenchymal stem and progenitor cells [56]. Moreover, mTOR directly regulates the aging rate and affects longevity; although the latter remains debatable, considering the number of complexes formed by mTOR [64-66]. Increased regeneration of muscles in aged pregnant animals is believed to be related to the reversal of age-related changes in the Notch signaling cascade [9], which is another major signaling pathway traditionally associated with embryonic development. Over recent years, the role of Notch signaling in aging and development of age-related disorders has been actively discussed [67].

The above-described mechanisms of the regenerative effects of pregnancy on the maternal organism are not mutually exclusive. For example, heterochronic parabiosis significantly activates regeneration of muscles in aged animals. Joining the circulatory systems of a pregnant young female and an aged animal doubles the effect, similarly to pregnancy-induced activation of muscle regeneration in aged and young females [9]. This suggests that activation of muscle regeneration in an animal sharing blood with a young pregnant female is caused not only by regulatory juvenile factors from the young animal's blood, but also by additional contribution of pregnancy-associated factors.

A major question remains: what exactly is the contribution of each of the factors to the rejuvenating effect of pregnancy on the maternal organism? The answers to this question will allow to develop clinical approaches for protection of pregnant women and health improvement in the human population in general.

EFFECTS OF PREGNANCY ON LONGEVITY

The discussion of pregnancy effects on the maternal organism would be incomplete without analysis of the longevity of parous animals.

Ecology and gerontology often describe the phenomenon of inverse correlation between reproductive potential and longevity: the higher the reproductive activity, the shorter the expected lifespan. Based on these observations, in 1997 Kirkwood proposed his disposable soma theory [68], which considered ecological and evolutionary strategies for the distribution of resources between reproductive functions and somatic maintenance in an organism. Undoubtedly, this theory is not absolute and can be applied primarily to analysis of reproductive types and strategies, but not of individual subjects within a species. Nevertheless, a body of evidence indicates that this model can be used for comparing populations of the same species [69, 70]. Moreover, several studies suggest that the disposal soma theory can be applied to humans as well. Retrospective analysis of the longevity in eunuchs at the Korean Royal Court (more than 80 peoples within the period from the XIV to XX centuries) showed that their average lifespan exceeded the lifespan of common people by 14-19 years [71]. Genealogical studies of English aristocracy found that childless women lived longer than those with children [72]. On the other hand, statistical studies of human populations produced the opposite results: analysis of 15,000 twins revealed that the lifespan of twins with children (both men and women) was longer than of their childless brothers or sisters [73].

Unfortunately, these studies have many flaws that prevent extrapolation of the results to the whole population. Thus, we cannot ignore the effects of decreased testosterone production in castrates or social help from children to their aged parents. Such studies do not distinguish between disease-caused infertility and conscious refusal to have children.

Genealogical statistics helps to partially circumvent these obstacles, since for certain human populations it is very detailed and based on large samples. For obvious reasons, these studies mostly consider childbirth in women. First, the number of children can be estimated with a high degree of reliability for women; second, the maternal organism undergoes considerably more significant physiological changes during reproduction; third, because of menopause, there is a possibility to compare the lifespans of women who lived beyond their reproductive period, which excludes the inverse effect of longevity on the possibility to conceive more children.

Retrospective analyses of various human populations that involved up to 10,000 people (Sami [74], Amish [75], inhabitants of Quebec [76], Utah [77], and Wales [78]) and a time from XVII century to our days result in the same conclusion: late age of the last childbirth positively correlates with longer lifespan [79]; large number of children (above 10-14) or their absence decrease longevity; the age of the first pregnancy does affect longevity.

The results of these works, as well as of any correlational studies, do not reflect direct dependence between the studied phenomena. For example, correlation between the age of birth of the last child and maternal longevity can reflect the reverse cause-and-effect relation: the healthier the mother is and the slower is her aging, the later she can give a birth to her last child. Nevertheless, despite ambiguous interpretation, the above-described facts are important for understanding the relations between pregnancy, health, and longevity in women.

POSSIBLE EVOLUTIONARY REASONS FOR REJUVENATING EFFECT OF PREGNANCY

To understand the phenomenon of the rejuvenating effect of pregnancy, we will discuss evolutionary processes that might underlie it. There are two ecological reproductive strategies – the *K* and the *r* strategies [80]. The *r* strategy involves high fertility, low probability of survival in the offspring, short in time pregnancy, and thus, rapid replacement of one generation with another. Typical representatives of animals with the *r* strategy among mammals are most rodents. The *K* strategy, on the contrary, implies reduced number of offspring with increased parental investment, slow maturing, low mortality, high longevity, and slow generation replacement. Animals with the *K* strategy are usually large mammals, such as humans, tigers, elephants, and whales. It is important to note that longevity in the *r* strategy animals is a subject of negative evolutionary pressure aimed to ease the competition between parents and their progeny. This pressure hardly exists for the *K* strategy animals: low number of individuals, fertility, and long maturing period relieve the competition between the generations and "allow" them to have longer lifespans or even to live beyond their reproductive periods (as in animals with menopause).

Childbirth (or compensation of its negative consequences) might be evolutionarily rewarded by increase in longevity. However, this phenomenon manifests itself differently in animals with different reproductive strategies. First, in animals with the *r* strategy, increased longevity of the elder generation will heighten intraspecies competition. Second, additional pregnancy at later age will give more advantages to animals with the *K* strategy, but not to

those with the *r* strategy, because in the latter case it will be more beneficial to let the younger generation reproduce using the same resources but avoiding negative consequences of late pregnancy. Despite these negative effects, animals with the *K* strategy will benefit by allowing an older, but "trusted" (i.e. already parous) subjects to reproduce, since the younger generation takes a long time to mature and to reach reproductive age. Also, increased longevity of the elder generation might be beneficial in *K* strategy animals even if they do not reproduce. For example, postmenopausal females can take care of other's offspring or protect youngsters from predators (for example, the so-called "grannies" in groups of killer whales [81]). Animals with the *r* strategy do not usually demonstrate such complex social behavior and receive no benefits from the presence of older individuals in the population. All these facts lead to the conclusion that increased longevity of "reproductively validated" organisms are more beneficial for animals with the *K* strategy than for animals with the *r* strategy, for whom the populational value of a single subject is insignificant.

These theoretical considerations have high practical significance. Unlike humans, mice and rats use the *r* strategy of reproduction. It puts significant limitations on the already complicated extrapolation of results obtained in these animals to humans. It is probable that experiments in dogs or other available laboratory animals with the *K* strategy will be more reliable for such extrapolations of results.

In all previous issues of *Biochemistry (Moscow)* dedicated to phenoptosis, we aimed to reveal fundamental rather than particular processes that happen between birth and death and determine the quality of life in this period. We emphasize the word "quality", since aging can be accelerated by numerous diseases (although this is not the case when some "not serious" diseases activate the immune system, and this activation counteracts the effects of further, more serious illnesses that could speed aging and initiate death). However, it is extremely difficult to understand which diseases exacerbate aging. Moreover, we are trying to answer the question if aging could be decelerated (in the ideal case, reversed) by developing strategies that would affect the course of these diseases. In our previous works, we discussed the ambiguities in the definition of causes of death [82], analyzed the role of mitochondria in death and diseases [83, 84], and estimated the role of sexes in susceptibility to diseases [36]. Here, we attempted to prove the commonly accepted role of pregnancy as a rejuvenating factor. This role seems obvious if we ignore the complications that occur when preexisting pathologies in the maternal organism are exacerbated by pregnancy and can result in death. All studies of aging, as well as anti-aging strategies have the same flaw – they lack exact definition of aging. Even longevity cannot serve as an indicator of the aging rate, since it is impossible to determine for how long an organism has been "young" or "old". These considerations are important, because health and life quality and productivity depend on the "youthfulness" of an organism. Humankind is interested in prolonging years of youth and maturity, but not in adding more time to old age. Rejuvenation studies do not decipher the "rejuvenating" effect per se; they only describe restoration of organismal functions to their "young" state. We are aware that the use of the term "rejuvenation" for the described pregnancy-related phenomena can raise many questions, as well as other studies on aging and rejuvenation. Nevertheless, putting in good order factors associated with aging and its modulation will make it possible one day to understand exact mechanisms of aging and to find ways to affect this process. If we believe that pregnancy "rejuvenates" an organism, then studies of its effects on aging will give a unique opportunity to observe (at least partially) the functioning of the aging machinery within a short time period with the desired process of returning to the young state.

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