

Exercise during Pregnancy: Developmental Programming Effects and Future Directions in Humans

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ABSTRACT

Epidemiological studies show that low birth weight is associated with mortality from cardiovascular disease in adulthood, indicating that chronic diseases could be influenced by hormonal or metabolic insults encountered *in utero*. This concept, now known as the Developmental Origins of Health and Disease hypothesis, postulates that the intrauterine environment may alter the structure and function of the organs of the fetus as well as the expression of genes that impart an increased vulnerability to chronic diseases later in life. Lifestyle interventions initiated during the prenatal period are crucial as there is the potential to attenuate progression towards chronic diseases. However, how lifestyle interventions such as physical activity directly affect human offspring metabolism and the potential mechanisms involved in regulating metabolic balance at the cellular level are not known. The purpose of this review is to highlight the effects of exercise during pregnancy on offspring metabolic health and emphasize gaps in the current human literature and suggestions for future research.

Introduction

It is well established that a sedentary lifestyle is associated with an increased incidence of chronic diseases, such as type 2 diabetes, cancers, cardiovascular diseases, and comorbidities [1]. To reduce this burden, effective interventions need to be discerned and implemented. Physical activity is an accessible positive lifestyle habit that can contribute to weight loss, changes in body composition, and improved cardiorespiratory fitness [2–9]. Physical activity interventions have shown to be successful in increasing an individual's quality of life [10, 11] and continue to support the need for physical activity across all races, ethnicities, genders, and age groups. Once thought to be detrimental to the developing fetus, exercise is now recommended for most pregnant women [12]. The notion of increasing physical activity interventions in pregnancy is

gaining traction in that this period is a crucial timepoint to improve offspring outcomes.

In 1989, the epidemiologist David Barker coined the Developmental Origins of Health and Disease Hypothesis by linking small for gestational age infants with increased incidence of cardiovascular disease in adulthood [13]. This hypothesis postulates that if the fetus is exposed to unfavorable environmental conditions *in utero* and during the early stages of development, the fetus will undergo permanent metabolic adaptations that allow for survival in the unfavorable intrauterine environment. However, these adaptations may also lead to the development of diseases after birth [14]. Excess maternal weight gain and obesity during pregnancy have been known to contribute to poor fetal and maternal out-

comes related to risk factors/incidence for cardiometabolic disease [15] making pregnancy a potentially viable target for intervention. The cyclic nature of cardiometabolic diseases continuing from mother to child and the subsequent perpetuation of metabolic disease across generations marks a potentially dire need for interventions to halt this vicious cycle. Luckily, pregnancy has been identified to have the potential to be a “teachable moment” for mothers [16] due to the increased contact with healthcare providers and increased concern for the health of the fetus. The purpose of this review is to provide a synopsis on physical activity as a method of improving neonatal metabolic health. This review will begin with general guidelines on physical activity during pregnancy and a brief section on maternal responses. It will then turn its attention toward offspring responses to maternal physical activity that encompass changes in whole-body and cellular metabolism. Finally, potential areas of investigation for future research will be presented.

Exercise During Pregnancy

Physical activity recommendations

Pregnant women can benefit from physical activity to a similar extent as nonpregnant women [17], and various forms of physical activity have been deemed safe and appropriate during pregnancy [12, 17–19]. The American College of Obstetricians and Gynecologists (ACOG) currently recommends that women who begin their pregnancy with a “healthy lifestyle” (e. g., exercise, proper nutrition, nonsmoking) continue to maintain those healthy habits throughout their pregnancy [12]. Women not achieving “healthy lifestyle” habits should accordingly be encouraged to establish healthier habits and routines throughout the pre-pregnancy and pregnancy periods [12]. During pregnancy, 150 minutes of moderate intensity aerobic activity per week is recommended [12, 19]. Those who habitually engaged in vigorous intensity aerobic activity or who were physically active before pregnancy can continue their activities [12]. Consistent with recommendations from the American College of Sports Medicine (ACSM) [20], a combination of aerobic and resistance exercise appears to deliver benefits for both the mother and infant. This review will highlight beneficial changes with primarily aerobic exercise/physical activity.

For women with uncomplicated pregnancies, fears of physical activity and exercise resulting in adverse outcomes have yet to be validated [21–24]. While these exercise recommendations have been in place for over a decade, the prevalence of active pregnant women is still alarmingly low. Among pregnant women, walking is the most frequently reported activity, usually occurring during the first trimester [25, 26]. Across the United States however, it is estimated that as few as 15.8% of women are physically active at the recommended level during pregnancy [27]. Only 21.5% of a cohort of healthy pregnant women in Ireland reported meeting the current ACOG recommendations of physical activity with 11.7% reporting no physical activity at all [28]. Studies across other countries report similar numbers [29–31]. Further, for those who do participate in structured physical activity during pregnancy, the intensity, frequency, and volume may not be at levels sufficient to incur the adaptations induced with an active lifestyle [32]. Aerobic exercise interventions have been found to minimize gestational

weight gain when combined with diet or with exercise alone [33]. However, a recent multi-site randomized clinical trial that managed to increase physical activity showed a modest effect between the intervention and control group (–1.59 kg) on total gestational weight gain [34] and did not prevent gestational diabetes in the mother [35]. Nonetheless, exercise has been shown to be protective against disorders such as preeclampsia and should be promoted due to several beneficial physiological adaptations [36–40].

Maternal responses during pregnancy

The scope of this article is offspring outcomes in response to maternal exercise; therefore, this review will briefly touch upon maternal adaptations. It should be noted that the effects of exercise on pregnant women has been reviewed extensively elsewhere [41–43]. During a healthy pregnancy, many physiological adaptations occur in the cardiovascular system to support adequate oxygen and nutrient supply to the fetus. Cardiac output is increased up until term by 30- to 50 percent due to both an increase in stroke volume and heart rate (HR) [44]. An additional increase in tidal volume is responsible for a 30- to 40 percent increase in minute ventilation in pregnancy. Although many of these changes would assume a rise in oxygen consumption, there is only a slight 15- to 20 percent increase, resulting in an increase in alveolar and arterial PaO₂ (partial pressure of oxygen) and a fall in PaCO₂ (partial pressure of carbon dioxide) levels [45]. These and other positive adaptations that occur with pregnancy are amplified with regular physical activity and exercise. Cardiovascular fitness, measured by maximal oxygen uptake (VO₂max), is rarely reported with pregnancy due to theoretical risk of fetal distress. However, there are instances where this has been performed in pregnancy [46]. As central responses (e. g. stroke volume, HR, cardiac output, etc.) do not differ significantly between pregnant and nonpregnant women during submaximal exercise [47], it seems that alterations in the periphery are at play.

Many of the peripheral cardiovascular changes seen in physically active mothers help to ensure the appropriate trafficking of nutrients to the developing fetus. Because the placenta is the central organ linking the fetus and the maternal environment, it is responsible for bridging the effects of external stimuli on maternal health status to the fetus. Placental growth is largely dictated through substrate availability and blood flow and is calculated as the product of substrate concentration measured in arterial blood and blood delivery to the placental bed, with a heavy focus on glucose [48–50]. With maternal exercise, blood flow is diverted from the placenta to exercising muscles and skin [51] which is proportional to the exercise intensity and muscle mass used [48]. After the cessation of exercise, blood flow quickly returns to normal [48]. Due to the invasive nature of measuring fetoplacental blood flow, exercise-induced blood redistribution has not been measured in humans. Animal data translated to humans, however, indicates blood flow redistribution associated with exercise intensities up to 95% VO₂max does not compromise the fetus. Repeated bouts of exercise at 95–100% VO₂max, however, are associated with negative effects on fetal growth confirming submaximal exercise does not compromise blood delivery to the fetus [43, 52–54].

Additionally, maternal exercise impacts placental gene expression to optimize fetal nutrient delivery and fetoplacental growth [55–57]. Those who performed strenuous exercise during preg-

nancy had increased T-type amino acid transporter 1 (*TAT1*), neutral amino acid transporter A (*ASCT1*), mitochondrial branched chain amino transferase (*mBCAT*), and glutamine synthetase (*GLUL*) placental expression indicating maternal exercise enhances amino acid transport pathways [58]. Genes associated with fatty acid metabolism are similarly altered with maternal exercise [59–61]. Mothers who met physical activity guidelines also showed improvements in the expression of genes involved in glucose transport as well as mammalian target of rapamycin (mTOR) and insulin signaling in the placenta, further highlighting the benefits of maternal exercise in the relationship between the maternal environment, placenta, and fetal environment [55]. Finally, reactive oxygen species (ROS) production in the placenta was also lowered with exercise suggesting improved oxygen metabolism [57]. All these beneficial adaptations are imparted in the offspring to ensure adequate growth.

Effects of Maternal Exercise on Offspring

Anthropometrics

Infant birth weight allows for a crude measurement of newborn health and is an indicator of the fetal environment. Both low and high birth weights have been shown to be related to obesity, metabolic disease, and cardiovascular disease later in life [62–64]. The pregnancy field has outlined a clear U-shaped association between offspring birth weight and long-term metabolic complications [65]. Many of these have been outlined in epidemiological studies. For example, studies on famine in pregnancy concluded that infants exposed to conditions of malnutrition have reductions in glucose tolerance later in life [66]. In the case of maternal obesity, infants have increases in childhood body mass index (BMI), adiposity, and increased risk of diabetes as adults [67, 68]. Therefore, there is a need to fine tune this U-shaped association with lifestyle interventions, with one of the most prominent interventions being exercise.

Largely conflicting evidence exists for the support of structured maternal exercise affecting infant birth weight. Maternal exercise during pregnancy has been associated with increased infant lean mass compared to infants of sedentary mothers [69]. Other studies have shown that maternal exercise has been shown to be associated with a reduction in the upper quantiles of birth weight distributions [70, 71]. There are reports showing that maternal exercise may not affect infant weight at birth [72]; however, a recent study has shown that infants exposed to maternal exercise had increased adiposity at 7-years of age [69]. Finally, a recent meta-analysis conducted by Guillemette et al. concluded prenatal maternal exercise does not significantly impact infant birth weight nor fat mass nor large-for-gestational-age risk [73]. These studies highlight the continued need for more studies focused on maternal exercise and infant birth weight. Indeed, studies of regular aerobic exercisers and those who engage in vigorous physical activities, such as elite athletes, show that infants were born with lower birth weight [74, 75]. Thus, there might be a dose-response relationship between maternal exercise, again lending credence to the fine-tuned nature of maternal pregnancy outcomes and the U-shape

association that also exists in other aspects of pregnancy such as that in gestational weight gain [76].

Research on other forms of physical activity, such as non-structured leisure time physical activity (LTPA) has also been studied. Research has shown that LTPA does not increase the chance of a small for gestational age newborn [77]. At a minimum, adherence to physical activity guidelines has been shown to reduce risk of delivering large for gestational age newborn with no effect on delivering small for gestational age [71, 78–80]. LTPA is thought to normalize birth weight into a healthy range by normalizing maternal blood glucose, reducing maternal insulin resistance, and altering placental blood flow and nutrient delivery [32, 49, 81, 82]. While remaining cautious to not over-interpret these results, enough evidence of lasting benefits of LTPA during pregnancy exists to encourage larger, prospective studies to understand if prenatal interventions might be an effective way of preventing childhood obesity in humans.

With limited data on long-term outcomes of offspring to exercising mothers in humans, rodent studies may provide additional insights. In mice, maternal exercise improves offspring body composition [83, 84] or shows no effect [72, 85]. Interestingly, when fed a high-fat diet, offspring of trained mothers gained less weight and stored less fat compared to offspring of untrained mothers, which suggests a protective effect of exercise [72, 83]. While rodent findings may not be applicable in human research, due to factors such as uterine structure, length of gestation, size of litters, the idea of exercise as a protective measure to support a more favorable body composition is persuading.

Cardiovascular fitness

Aerobic fitness ($VO_2\max$) is the product of central cardiac output and the peripheral oxygen extractability of the working tissues [86]. Exercise training in non-pregnant cohorts increases aerobic fitness via coordinated adaptations of these central and peripheral components and the majority of work in this area has been substantiated in the animal literature. Prior data has shown that rodent offspring born to mothers who underwent aerobic exercise before and during pregnancy, have higher aerobic fitness [87] and physical activity levels [88] providing evidence that maternal exercise is capable of programming the offspring's cardiovascular system including cardiac output, macrovascular compliance, and skeletal muscle oxidative capacity. These are summarized in the subsequent paragraphs.

A hallmark adaptation of chronic exercise training is an increase in stroke volume and increased heart rate variability [89–93]. Although the effect of maternal exercise on offspring cardiovascular remodeling is not yet fully understood, exercise training has been shown to improve ejection fraction and left ventricular mass [94]. Exercise training also prevents obesity-induced impairments in cardiac output by attenuating pathological left ventricular hypertrophy and preserving the ejection fraction of adult rodent offspring [95]. While the mechanisms are not clear, studies have shown that maternal exercise epigenetically programs the offspring's cardiac transcriptome, increasing the expression and activity of genes involved in mitochondrial biogenesis [94, 96] – an important characteristic for many offspring peripheral adaptations.

Although indirect, aerobic exercise generally improves cardiac function by decreasing afterload via structural and functional changes that increase vascular compliance [97–99]. Maternal exercise has been shown to improve endothelium-dependent vasodilation in porcine offspring at birth, but this effect was blunted in the presence of N^G-nitro-L-arginine methyl ester (L-NAME), a nitric oxide synthase inhibitor, suggesting increased nitric oxide bioavailability is responsible for this improvement [100]. However, follow-up studies indicated the effects of maternal exercise on offspring endothelium are transient and no longer evident in the months following birth in either healthy [101] or high-fat fed swine offspring [102]. Furthermore, endothelium-independent relaxation in the adult offspring exposed to maternal exercise was reduced, suggesting maternal exercise may accelerate the age-related decline in smooth muscle compliance [101]. In rodents, maternal exercise did not alter the offspring's endothelial-dependent or -independent relaxation in the months following delivery [103]. Similarly, Boonpatrawong et al. reported that maternal exercise alone had no effect on offspring vascular function but was protective against maternal obesity and high fat post-weaning diet. Interestingly, aerobic exercise improved nitric oxide bioavailability in the offspring fed the Western diet, despite the groups having similar levels of nitric oxide synthase expression. The authors determined maternal exercise improved aortic one-carbon metabolism, which could have indirectly improved nitric oxide bioavailability by reducing the uncoupling of nitric oxide synthase in the mice fed the high fat diet [104]. Finally, Li et al., observed that maternal exercise reduced smooth muscle vasoconstriction responses to norepinephrine and Bay K8644 (a Ca²⁺ channel agonist) of offspring born to spontaneous hypertensive mother rats. DNA bisulfite sequencing revealed maternal exercise increased methylation of the calcium voltage-gated channel subunit α -1C (*Cacna1c*) promoter, preventing it from being upregulated during the programmed hypertension [105]. Taken together, these data suggest maternal exercise can serve a protective role in vascular function, but this protection is only evident with gestational obesity and/or postnatal insults (e. g., high-fat diet).

Despite extensive work being conducted in animal models, it is still unclear if these results can be translated to humans. Limited data stems from a recent pilot study revealing moderate-intensity aerobic exercise in healthy pregnant women reduced the carotid intima-media thickness in offspring, suggesting improved vascular compliance [106]. Furthermore, there have been few studies to track the effectiveness of maternal exercise on cardiac function in humans. May et al. determined maternal aerobic exercise reduces fetal heart rate and increases heart rate variability at 36 weeks of gestation [107]. Follow-up analysis by this group revealed the increase in heart rate variability was retained one month following delivery, providing evidence of a lasting cardiovascular phenotype [108]. Whether or not these other mechanisms, such as the nitric oxide system, are at play in humans remains to be discovered.

Skeletal muscle oxidative capacity

The peripheral component, oxygen extractability (A-VO₂), of working skeletal muscle increases with aerobic training via increases in capillary density and mitochondrial biogenesis [109–111]. Like cardiovascular changes, most of this work has been shown using ani-

mal models. Liu et al. was the first to establish a programming effect of maternal exercise on the oxidative capacity of rodent skeletal muscle. They and others [87] noted that exercise prior to and during pregnancy did not alter skeletal muscle capillary density but did increase markers of mitochondrial biogenesis including mitochondrial density and the enzymatic activity of citrate synthase and cytochrome C oxidase in the offspring [112]. Further, Siti et al. reported that maternal exercise in rodents increased the enzymatic activity of electron transport system complexes II and III, reduced substrate-specific H₂O₂ production, and increased ADP-stimulated respiration rates in offspring skeletal muscle [113]. Peroxisomal proliferator-activated receptor γ coactivator-1 α (PGC-1 α) has been termed the “master regulator” of mitochondrial biogenesis and plays a key role in several exercise-induced adaptations [114–117]. Therefore, it can be proposed that maternal exercise could epigenetically modify the PGC-1 α gene (*Ppargc1a*), to ‘prime’ PGC-1 α expression in the offspring skeletal muscle. Son et al. provided the first evidence that exercise alone reduced the methylation status of the offspring's skeletal muscle *Ppargc1a* promoter, increasing the expression of PGC-1 α . Importantly, the authors noted several other markers of mitochondrial biogenesis and oxidative capacity increased, including increased VO₂max, proportion of oxidative muscle fiber (higher IIa/lower IIx), mitochondrial DNA (mtDNA) content, and markers of mitochondrial fission/fusion [87]. Taken together, there is accumulating evidence in rodents to suggest maternal exercise enhances the oxidative capacity of the skeletal muscle of offspring via intrinsic changes in the mitochondrial phenotype. However, due to the invasive and longitudinal nature of these studies, these results have yet to be substantiated in humans.

Substrate metabolism

The increased prevalence of sedentary lifestyles and Western-style diets has led to a parallel rise in metabolic diseases including type 2 diabetes, metabolic syndrome, and cardiovascular disease. A distinctive feature of these diseases is disordered substrate metabolism and the eventual ectopic deposition of substrates and excessive spillover of metabolites [118]. These aspects have significant relevance to the pregnancy field as well [119]. Generally, exercise interventions that aim to improve aspects of substrate handling is concomitant with enhancements in mitochondrial content/function to resolve the perturbations in metabolic stress. Due to the robust changes in the skeletal muscle mitochondrial phenotype elicited by maternal exercise as described in the section above, there is a vested interest in determining whether it can protect the offspring from metabolic dysfunction and disease in the current obesogenic environment.

Thus far, several investigations have determined maternal exercise can reduce the offspring's susceptibility to metabolic diseases by rescuing glucose intolerance, hyperlipidemia, endocrine dysregulation, and global oxidative stress in offspring born to mothers with obesity or that were fed a high-fat diet during pregnancy [115, 120–125]. These have been shown in models of rodent exercise where mice were trained preconception and in combination of preconception and during pregnancy. Data suggests maternal exercise acts on tissues responsible for regulating whole-body metabolism including the skeletal muscle, liver, and pancreas.

The skeletal muscle is responsible for 70–80 % of postprandial glucose disposal, thus development of skeletal muscle insulin resistance is a key tenant in the pathogenesis of type 2 diabetes [126]. Carter et al. was the first to show maternal exercise improves *ex vivo* glucose uptake in the skeletal muscle, but not adipose tissue of the rat offspring [127]. Although the exact mechanisms have yet to be elucidated, data suggests maternal exercise relieves skeletal muscle *Ppargc1a* promoter hypermethylation, induced by maternal high-fat diet, which was associated with elevations in the mRNA expression of glucose transporter 4 (*Glut4*), cytochrome *c* (*Cyt c*), and cytochrome *c* oxidase subunit 4 (*Cox4*) [115]. Furthermore, a recent study indicated maternal exercise protects the offspring's oxidative capacity by rescuing their mitochondria phenotype and fiber type distribution. The authors determined maternal exercise was responsible for demethylating the *Ppargc1a* promoter and increasing PGC-1 α expression, in contrast to the repression evident with a maternal sedentary lifestyle and high-fat gestational diet [87]. Taken together, maternal exercise improves the substrate handling of the offspring skeletal muscle and offers protection from certain disruptions associated with maternal obesity and Western-style gestational diets. However, Quiclet et. al found that maternal exercise did not rescue the glucose tolerance in rat offspring fed a high fat/high sucrose diet. *In situ* mitochondrial respiration assays revealed maternal exercise improved substrate affinity (K_m) for palmitoyl-CoA and pyruvate in sedentary, chow-fed offspring, but not in mice fed a high-fat/high-sucrose diet [83]. Therefore, it is still unclear if maternal exercise can protect the offspring skeletal muscle from postnatal dietary insults. Moreover, no investigations have been done to determine if these results can be translated to humans.

In coordination with the skeletal muscle, liver metabolism and pancreatic β -cell function plays an obligatory role in regulating whole body metabolic health and therefore has been investigated in the context of maternal exercise. Stanford et al. recently determined maternal exercise improved glucose tolerance in mice born to mothers fed a standard chow or high-fat diet [120]. Interestingly, their *ex vivo* experiments revealed no effect of maternal exercise on the skeletal muscle, but instead a robust remodeling of the hepatic insulin sensitivity and glucose production phenotype. Although the mechanisms have yet to be elucidated, studies from the same group show evidence of hepatic mitochondrial biogenesis in the offspring born to mothers who exercised. Although attention has been centered on determining the effect of maternal obesity and gestational diabetes on offspring β -cell function [128–131], Zheng et al. was the first to show that the combination of pre-gestational paternal exercise and pre- and during-gestational exercise preserved β -cell mass, size, and islet morphology in offspring born to parents fed a high-fat diet [132].

To summarize, maternal exercise has been shown to improve cardiovascular function, skeletal muscle oxidative capacity, and whole-body substrate metabolism partly as a result of tissue-specific improvements in skeletal muscle, liver, and pancreatic phenotypes. It is believed that epigenetic modifications underpin these improvements, specifically in genes that affect mitochondrial outcomes of these tissues. Unfortunately, most of these findings are derived from animal studies and thus, it is still unclear if these results can be translated to humans. These specific types of studies

are wrought with challenges in human cohorts due to the invasiveness of tissue sampling procedures. Often, human studies are limited to the presence/absence of metabolites or hormones in cord blood and tissue. Thus, there is a need to identify new avenues for future studies that explore the transmission and signaling behind maternal and fetal health and disease in the context of human tissues and metabolism.

Recommendations for Future Studies

Intrauterine microenvironment

Previously, exercise has been shown to induce robust changes in circulating factors that affect the tissue's microenvironment. To date, the most studied exercise “factors” are the cytokines released from skeletal muscle, termed myokines. There are presently 600 skeletal muscle myokine species that have been identified [133], and targeted approaches aim to understand the effects of myokines in remodeling skeletal muscle metabolism. For example, interleukin 6, brain-derived neurotrophic factor, and interleukin 15 have been shown to 1) be secreted from skeletal muscle [134–136], 2) increase in circulation following exercise [134, 135, 137–139], and 3) independently improve mitochondrial density and/or function [140–142]. Importantly, these myokines help mediate the skeletal muscle-to-organ crosstalk and therefore may play a role in fetal programming resulting from maternal exercise, depending on their permeability through the placental-blood barrier. Recently, the novel myokine and adipokine known as apelin has been shown to mediate several of the skeletal muscle phenotype changes that occur in mice offspring born to mothers who exercised during pregnancy [87]. In this study, maternal exercise increased levels of apelin, which subsequently increases mitochondrial biogenesis and oxidative capacity in the offspring. Like apelin, other undiscovered myokines and/or adipokines, which are now termed “exerkines” in the field when they are secreted in response to exercise, may be signaling from mother to infant and lend support to the notion of maternal exercise improving offspring metabolic health.

Maternal donation of mtDNA

Mitochondria are originally descendent from endosymbiotic bacterium and this derivation from symbiotic ancestors allows the maintenance of their own genome (mtDNA) [143, 144]. mtDNA consists of a DNA ring of approximately 16570 nucleotides and contains 37 genes [145] but is responsible for transcription of 13 essential electron transport chain (ETC) proteins, 2 rRNAs, and 22 tRNAs [143]. The remainder of the nearly 1200 proteins that make up mitochondria require nuclear transcription and subsequent import into appropriate mitochondrial compartments resulting in a finely tuned coordination between mtDNA and nuclear DNA.

Unlike the nuclear genome, mtDNA is inherited strictly through a maternal inheritance pattern in eukaryotes where only the oocyte contributes mtDNA to the offspring [141]. Several mechanisms are recognized for the elimination of paternal mtDNA from the embryo and include a genetic bottleneck, autophagy post-fertilization, ubiquitin-protease pathways, and altered paternal mitochondrial transcription factor A (TFAM) expression [146]. In addition, while exclusive maternal donation of mitochondria and

mtDNA is generally acknowledged, a few, exceptional cases of biparental inheritance of mtDNA in humans exist [147]. This lack of recombination of mtDNA and its unique inheritance pattern thus allows for an accumulation of transmitted mutations which can lead to severe diseases in the offspring.

When maternal obesity was studied across three generations of mice, its effects could be tracked across all three generations alongside mitochondrial changes in morphology, bioenergetics, and dynamics [116]. The first generation of female offspring (F1) showed peripheral insulin resistance, increased intramuscular lipid content, mitochondrial dysfunction, and impaired mitochondrial dynamics in skeletal muscle. Oocyte mitochondria from the F1 mice also showed deranged morphology, reduced mtDNA copy number, and impaired mitochondrial dynamics. These were also apparent in the subsequent two generations. This propagation of mitochondrial impairments across generations is not restricted to skeletal muscle. A follow-up study by this group showed that maternal obesity in mice results in transgenerational cardiac mitochondrial deficiencies as well [148]. Elegant *in vitro* fertilization studies from another group have shown that the oocyte at the time of fertilization is susceptible to the intrauterine environment [149]. Whether or not this is generating changes in mtDNA or some nuclear aspect remains to be discovered and is the central crux to understanding the inheritability of the mitochondrial phenotype. Nonetheless, the initial insult is presently thought to stem from changes in oocyte mitochondria, particularly issues with mitophagy in the oocyte [150], that propagate to mitochondria that are present in all tissues/organs. Finally, it is not certain in rodents or humans if exercise is protective in rescuing a deleterious mitochondrial phenotype that is seen in maternal obesity. With new evidence of transmission of mitochondrial impairment and as mtDNA codes for critical bioenergetic genes, any potent approaches of improving mitochondrial health could lead to substantial advancements of offspring health.

Umbilical cord-derived mesenchymal stem cells

Human trials examining the effects of maternal exercise on offspring have primarily measured body composition and epigenetic outcomes in placental biospecimens such as umbilical cord and cord blood. Although much has been gained from rodent models, several discrepancies exist including a gestational period that is significantly shorter than humans as well as differences in placental physiology including estrogen synthesis/release [151], miRNA profile [152], expression of cell surface markers for trophoblast invasion [153], and accumulation of diet-specific metabolites [154]. Thus, it remains unclear if rodent findings can be translated to humans.

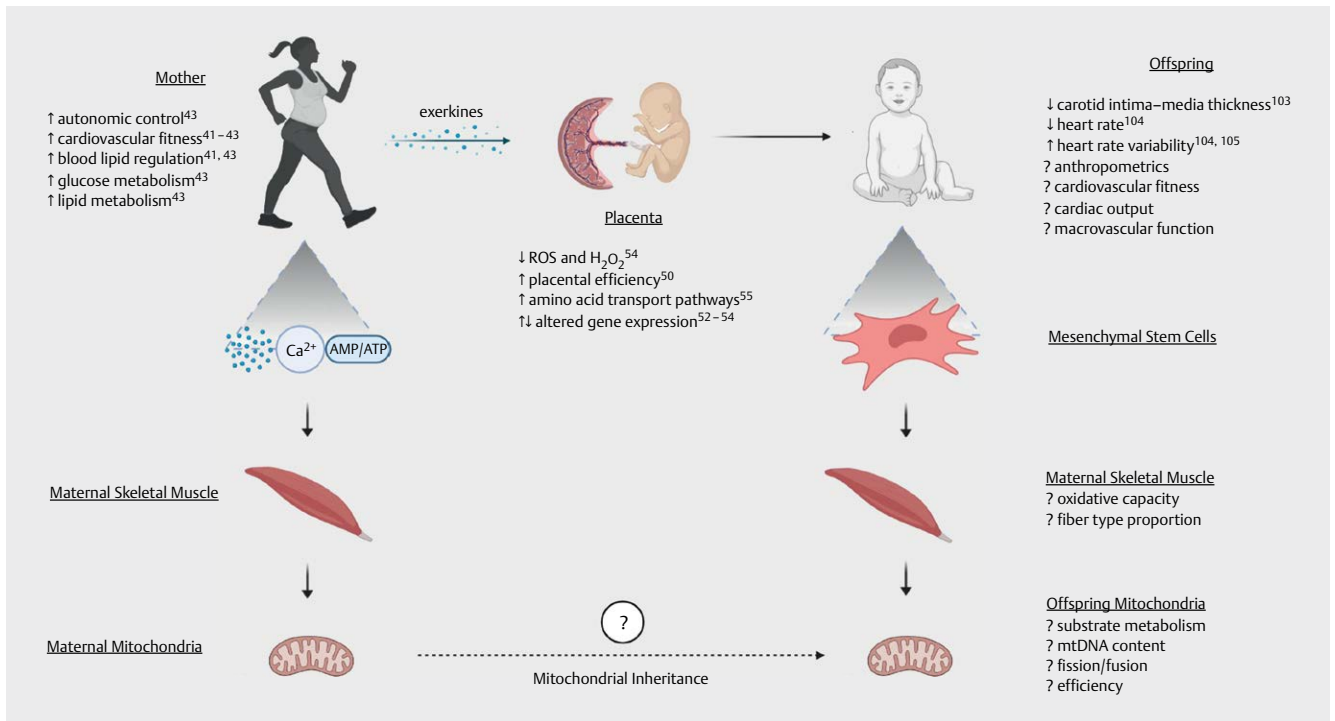
Non-invasive means to examine the effects of maternal exercise on offspring skeletal muscle metabolism need to be implemented in humans. Primary human skeletal muscle cells (SKMcs) have been used to investigate cell-autonomous mechanisms that underly the effects of lifestyle interventions including exercise [155], as well as the pathophysiology of diseases including diabetes [156], obesity [157, 158], and peripheral arterial disease [148]. For example, SKMcs derived from exercise-trained subjects retain the hallmark adaptations seen *in vivo* including, elevations in lipid handling capacity [159, 160], oxidative capacity [155], and insulin sensitivity [161]. Thus, it is believed the phenotype expressed *in vitro* is the

result of lasting metabolic programming which occurs *in vivo*. Therefore, it is plausible to suggest that the metabolic programming in SKMcs results from extrinsic changes in the tissue microenvironment, similar to what may be occurring in the intrauterine environment. Performing invasive measures such as muscle biopsies in young infants and children is impractical, making it difficult to understand the tissue-specific effects of maternal programming unique to exercise training. To test these hypotheses, researchers must identify a primary cell niche that can be noninvasively obtained and exists beyond the placental-blood barrier.

Recently, blood and umbilical cord-derived mesenchymal stem cells (MSCs) have gained attention in regenerative medicine because of their ability to differentiate into several cell types including chondrocytes, adipocytes, and skeletal myocytes [162]. Importantly, MSCs are of fetal origin and thus, a mesodermal stem cell lineage that contributes to the fetal development of several peripheral tissues and are the primary stem cell lineage responsible for fetal myogenesis as well as postnatal skeletal muscle growth and repair. Therefore, MSCs also offer the potential to gain insight into the metabolic phenotype of the developing skeletal muscle at birth and possibly how it will be maintained into adulthood. Recently, Boyle et al. indicated that MSCs from offspring born to obese mothers have lower rates of fat oxidation and elevated rates of lipid deposition [163]. These same MSCs were differentiated into an adipogenic phenotype and measured for the quantity of fat stored in these cells. Interestingly, this fat storage phenotype was shown to correlate positively with infant fat mass, which is direct support for translating this model to the phenotype of the infant. Interestingly, when stratified by oxidation rates, offspring with low MSC oxidation rates had higher adiposity and fasting plasma insulin levels *in vivo*, providing evidence that maternal obesity has lasting negative implications for the metabolic phenotype of the infant [164]. Although maternal physical activity has been shown to have a beneficial effect on rodent offspring, it has yet to be determined whether this is evident in humans and elicited primarily by the intrauterine environment. Thus, MSCs may bridge the gap for future investigations into this area and may be used as an *in vitro* model for myogenic outcomes but also for exploring the inheritance of the maternal mitochondrial phenotype.

Conclusion

The aim of the present review was to examine the current knowledge in the field of exercise in pregnancy as it relates to the mother and developing fetus and identify gaps in the literature (summarized in ► **Fig. 1**). Animal studies have outlined several mechanisms through which the metabolic health of offspring is improved through maternal exercise and have established inheritance of metabolic impairments that track across multiple generations. Through these studies, mitochondria seem to be key organelles in the progression of metabolic health across generations. Exerkines may be a new research area of understanding how maternal exercise may signal changes to the developing fetus. In addition, MSCs present themselves as a potential and relevant model to gain insight into this cellular and metabolic programming of offspring. With these models, exercise scientists may soon have the necessary tools to



► **Fig. 1** The physiological effects of exercise during pregnancy on maternal and infant outcomes. Maternal exercise promotes increases in cytosolic and intracellular calcium (Ca^{2+}) concentrations, and increases AMP/ATP ratio, which may result in signaling skeletal muscle (SKM) contraction and cell signaling. Both subsequent SKM and SKM mitochondrial adaptations to maternal exercise during pregnancy are not yet clearly defined. In addition, exerkine release (blue dots) into maternal blood results in subsequent placental exposure to these molecules. While placental adaptations to maternal exercise are still thoroughly unknown, exerkines could pass the placental barrier and mediate changes in infant outcomes. Epigenetic programming of the offspring's metabolic health is suggested to occur with maternal exercise, and mesenchymal stem cells (MSCs) are proposed to be a primary cell model for highlighting the infant's potential skeletal muscle and mitochondrial adaptations. In addition, due to the maternal donation of mitochondria, the potential role of exercise training as a means of improving offspring mitochondrial health warrants further investigation. Question marks identify all of these areas that are currently gaps in the literature and open to future research directions. This figure was created using BioRender.com.

explore the advantageous mechanisms in humans that exercise elicits from mother to offspring. There is a dire need to translate these findings to human cohorts as exercise during pregnancy maybe be a viable nonpharmacological strategy for prevention of metabolic diseases at the earliest timepoint – while in the womb.

Conflict of Interest

The authors have nothing to disclose. The authors confirm that the manuscript was built based on the IJSM ethical standards [165].

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