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Exercise as a therapeutic intervention to optimize fetal weight

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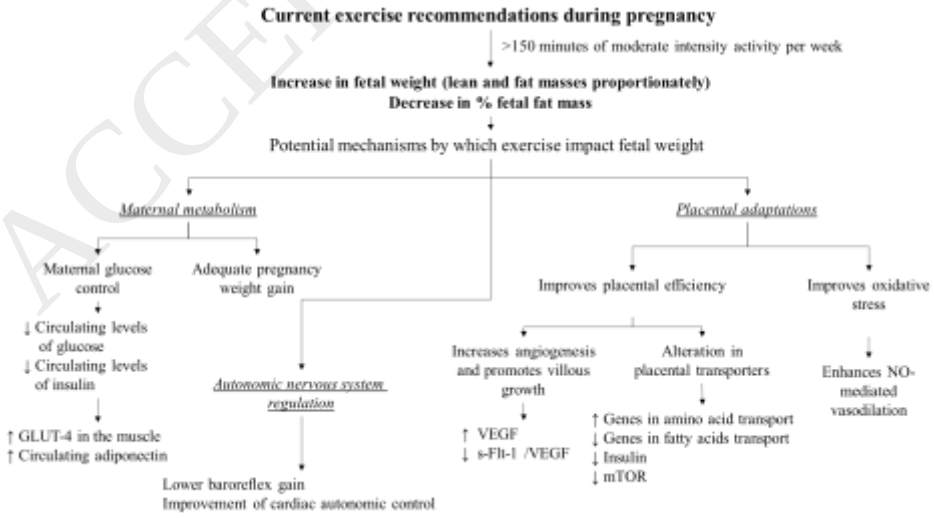
Graphical abstract



Abstract

The Developmental Origins of Health and Disease suggest the *in utero* environment programs offspring obesity and cardiovascular disease. Therefore, there is a need to implement safe therapeutic interventions that do not involve the intake of medications or biological products during pregnancy that can improve maternal and fetal health. Prenatal exercise is established to promote maternal and fetal health. It is generally recommended that women accumulate at least 150 minutes per week of moderate-intensity exercise. It has been demonstrated that prenatal exercise maintains healthy weight gain and improves maternal glucose control, maternal cardiac autonomic control, placental efficiency (increases angiogenesis, downregulates genes involved in fatty acid transport and insulin transport across the placenta, and upregulates genes involved in amino acid transport across the placenta), and oxidative stress. These adaptations following exercise improve maternal metabolism and provide adequate uteroplacental perfusion. In this review, we will focus on exercise as a therapeutic intervention to optimize fetal weight. It has been established that prenatal exercise does not increase the risk of having a small for gestational age baby. To the contrary, prenatal exercise has been associated with the prevention of excessive fat accumulation in the newborn and the maintenance of fetal muscle mass.

Abbreviations

BMI: Body mass index

CVD: Cardiovascular diseases

GLUT-4: Glucose transporter type 4

HR: Hazard ratio

LGA: Large for gestational age

mTOR: Mechanistic target of rapamycin

NO: Nitric oxide

SGA: Small for gestational age

SNA: Sympathetic nerve activity

s-Flt-1: Soluble fms-like tyrosine kinase-1

VEGF: Vascular endothelial growth factor

Keywords: Pregnancy; Exercise; Fetal weight.

1 Introduction

The Developmental Origins of Health and Disease suggest the *in utero* environment programs offspring obesity and cardiovascular disease [1, 2]. In order to support a healthy pregnancy, the maternal cardiovascular and metabolic systems undergo profound adaptations over the nine short months of pregnancy. This includes an increase in stroke volume (20-30%) and heart rate (15-25%) leading to an increase in cardiac output (30% [3]). In addition, there is a decrease in systemic vascular resistance due to increased vasodilation [4, 5] resulting in a slight decline in blood pressure reaching a nadir in the second trimester [6]. Moreover, mild insulin resistance [7] and dyslipidemia [8] are a hallmark feature of pregnancy. Combined, these maternal adaptations ensure adequate delivery of oxygen and nutrients to the fetus to maintain growth [9]. The magnitude of the cardiovascular, hormonal and metabolic adaptations that women undergo during pregnancy

have been hypothesized to unmask subclinical diseases (i.e. insulin resistance, endothelial dysfunction [10]). Women who do not tolerate these adaptations develop pregnancy complications including gestational diabetes, gestational hypertension and preeclampsia [11]. These findings have led to the suggestion that pregnancy is a stress test [12], which is predictive of the future development of cardiovascular and metabolic diseases later in life for the mother [10, 12]. Yet, the impact of diseases during pregnancy is not limited to the mother. Elevations in maternal blood pressure, and circulating glucose and lipids leads to suboptimal conditions *in utero*, affecting fetal growth at both ends of the spectrum. Babies born from pregnancies complicated by high blood pressure are likely to be born small for their gestational age (SGA)[13]. On the other hand, babies born from pregnancies complicated by elevated maternal glucose levels are likely to be born large for gestational age (LGA) [14]. Over the past 30 years, evidence derived from epidemiological studies have demonstrated that being born with a low birth weight is associated with the development of cardiovascular diseases (CVD) later in life [15-18]. Conversely, LGA infants have an increased risk of developing type 1 diabetes (odds ratio=1.43 [19]) and being overweight [20], while being born macrosomic (>4000 gr) is associated with a subsequent risk of being overweight during the adolescence and adulthood [21]. Unfortunately, approximately eight million women develop gestational diseases every year [22]. Therefore, there is a need to implement novel interventions during pregnancy that can improve maternal and fetal health. Prenatal exercise has been demonstrated to modify fetal weight, yet >85% of pregnant women fail to meet current guidelines; therefore, we propose that exercise is an underutilized therapeutic option to improve fetal body weight and composition. Since fetal weight is a surrogate of fetal wellbeing, in this review, we will focus on exercise as a therapeutic intervention to optimize fetal weight.

1.1 Birth weight as a surrogate for pregnancy outcomes

Birth weight is one of the most precisely recorded available data in epidemiology [23]. As such, the relationship between birth weight and birth weight categories [24] has been extensively studied and linked to critical birth outcomes. Low birthweight (<2500 gr) is strongly linked with infant mortality and is commonly used as a surrogate for infant survival [23]. Being born with a low birth weight is associated with the development of ischemic heart disease (hazard ratio [HR]= 1.94 [15, 25], insulin resistance [26], diabetes HR= 1.88 [25] and hypertension HR= 1.74 [18, 25] in adulthood. These findings were crucial in establishing the Developmental Origins of Health and Disease or Barker hypothesis, which stated that environmental factors early in development could produce permanent changes in fetal physiology, resulting in an increased risk of developing non-communicable diseases later in life. Interestingly, evidence has emerged suggesting the relationship between birth weight, and risk of glucose intolerance or obesity in later life follows a J-shaped relationship, with higher prevalence of these conditions at both low and high birth weights [27]. Thus, pregnancy-related complications could lead to an increase in CVD for the maternal and offspring dyad. CVD are the leading cause of mortality among non-communicable diseases [28], representing a major economic burden [29, 30]. Hence, it is important to consider that maintaining a healthy pregnancy must be a priority in order to decrease offspring's development of CVD. This should be even more important in countries where pregnancy-related complications are common [31].

1.2 The challenge of treating pregnant populations

An increasing body of evidence suggests that a healthy pregnancy is key to decrease the offspring's risk developing non-communicable diseases later in life, including CVD. Hence, in

order to detect those women at risk of developing a pregnancy complication, significant effort to increase the number of prenatal care visits have been taken into place [32]. Along with primary prevention care, there is a need to develop safe therapeutic interventions during pregnancy. It has been estimated that at least 50% of pregnant women take prescription medication during pregnancy in the United States [33]. However, given the ethical issues of conducting research in pregnant populations many drug safety studies specifically exclude pregnant women [34], and less than ten percent of available medications have assessed impact on birth defects [35]. Even alternative therapeutic approaches with supplements such as vitamin C and E to reduce the risk of preeclampsia, preterm birth or intrauterine growth restriction have been used as a possible intervention without any positive outcomes [36]. This may be due to the fact that the doses needed to mimic the antioxidant effect found in animal studies are sufficiently high, they may be deleterious for pregnant women [37]. Moreover, the unique cardiometabolic adaptations to pregnancy are known to alter the pharmacokinetic parameters of many medications [38]. In addition, research regarding placental drug transporter expression for many medications is insufficient.

The lack of research in this area and the complexity of extrapolating results from animal studies to human populations have created the vicious cycle ‘no data, no prescription/ no prescription, no data’[39]; for pregnant women as a result warning labels posted on medications decreases the compliance to the medication and it further increases our knowledge gap [39]. Therefore, until trials establishing the safety and efficacy of medications have been conducted in pregnant women or international collaborative efforts to create networks with databases to analyze the risk of the use of medications during pregnancy; alternative therapeutic approaches that do not

involve the intake of medications or biological products are more feasible and acceptable during pregnancy.

2 Exercise as a therapeutic intervention

Extensive data from pediatric to adult populations indicate physical inactivity or too little exercise is a key risk factor for chronic disease development including obesity and diabetes [40]. In pregnancy, inactivity leads to increased gestational weight gain and decrements to maternal metabolism, which can adversely affect the *in utero* environment [41]. Excessive weight gain during pregnancy has been associated with LGA babies and macrosomia [42]. Macrosomic infants are at higher risk of delivery complications and are twice as likely to be classified as obese as children and into early adulthood [43].

Given the myriad of adverse health impacts, the *2011 American Heart Association Effectiveness-based Guidelines for the Prevention of Cardiovascular Disease in Women* lists physical inactivity as a risk factor, as strong as smoking, for the development of cardiovascular disease and associated sequela including obesity [44]. Among the strategies proposed to prevent CVD, exercise is the most effective [45]. The cardiovascular benefits from exercise are derived from: *a)* an increase in endothelium-dependent vasodilation following an increase in vascular concentrations of nitric oxide (NO) [46] and endothelium-dependent hyperpolarization [47]; *b)* a decrease in vasoconstrictor responses either by a reduction in plasma endothelin-1 concentrations [48], or a decrease in the expression of the angiotensin II receptor [49]; *c)* a modulation in the production/clearance of reactive oxygen species [49, 50]; *d)* a reduction in sympathetic outflow at rest or during conditions that increase sympatho-excitation [51]; and *e)* an enhancement of the arterial baroreflex sensitivity [52]. Taking into consideration the above-mentioned facts, the

American College of Sport Medicine proposed that a person should engage in moderate intensity aerobic activity for at least 150 min/week to delay premature mortality and reduce the risk of chronic diseases [53]. Since it has been established that the window of opportunity to prevent/treat the development of CVD later in life in offspring from complicated pregnancies is narrow [54], interventions starting during pregnancy may have a higher impact in their cardiovascular health than interventions in offspring born from complicated pregnancies.

2.1 Exercise during pregnancy

Prenatal exercise is established to promote maternal health by enhancing aerobic capacity [55], improving or maintaining maternal fitness [56], improving endothelium-dependent vasodilation [57, 58], decreasing the risk of developing preeclampsia [59], and maintaining healthy weight gain [60]. In addition, exercise is established to promote fetal health by preventing excessive fat accumulation in the newborn [61]. Therefore, guidelines around the world recommend that health care providers encourage pregnant women without contraindication to exercise to be physically active throughout pregnancy [62-65]. Regardless of the guidelines followed (i.e. United States, Canada, Australia, UK) [62-65], it is generally recommended that women accumulate at least 150 minutes per week of moderate-intensity exercise. Albeit the recommendations appear to be feasible, maternal adherence to these guidelines is low (between 9-15% [66, 67]). Engagement in physical activity prior to conception, and classification of underweight before pregnancy are strong determinants of increased adherence to the exercise guidelines during pregnancy [67]. Deterrents to adhering to prenatal exercise guidelines include physical discomfort and fatigue, fear of harming the fetus [68] and the influence of social norms [69]. Overall, pregnant women are less active and more sedentary than the general population. Indeed, most women are sedentary for >70% of the

day [66] (compared to 55% for non-pregnant adults [70]) and become increasingly sedentary with gestation [71]. High levels of sedentary behaviour during pregnancy is associated with increased gestational weight gain [41] and is linked to reduced glucose tolerance, elevated cholesterol and systemic inflammation during pregnancy [72, 73]. Importantly, these adaptations may influence the developing fetus by increasing their adipose tissue deposition. However, a survey regarding the use of the guidelines recommendations in pregnant populations, distributed to health care providers in Canada (n=195), showed that 50% of the respondents were unaware of what were the best practices towards exercise prescription during pregnancy [74]. Similarly, Bauer *et al.*[75], in a convenience sample of 93 health care providers in Michigan USA (physicians, doctors of osteopathy and certified nurse midwives) found that even though 99% of them believed that exercise during pregnancy is beneficial, only 64% of them were aware of the American College of Obstetricians and Gynecologist guidelines to prescribe exercise during pregnancy. Thus, there is a need to decrease the barriers to physical activity among pregnant women [68] and health care providers [74]. Since one of the barriers is fear of harming of the fetus by negatively impacting fetal growth, we will focus on the effects of exercise during pregnancy on birth weight. It is important to note that the impact of exercise during pregnancy on fetal weight and fetal body composition may be influenced by the exercise intensity, volume, duration and when exercise was initiated (i.e. pre-pregnancy, 1st, 2nd or 3rd trimester).

2.1.1 Exercise and small for gestational age newborns

In non-pregnant individuals, exercise is known to induce a reduction in visceral blood flow to meet the metabolic demand of the working muscles [76]. Early studies in pregnant women suggested high volumes of exercise may limit fetal growth and increase the risk of having a small

for gestational age (<10th percentile for gestational age) or low birth weight baby [77-79]. It was hypothesized that during exercise there is an acute reduction in the oxygen and nutrient delivery to the placenta and the fetus, with a subsequent decrease in fetal body weight. As such, the impact of exercise on uterine blood flow during pregnancy has been extensively studied. Conflictive data derived from animal studies have demonstrated that exercise did not lead to a reduction in uterine blood flow [80-83], while other authors demonstrated the opposite [84-86]. However, it is important to note that when authors noted a reduction in uterine flow, this was proportional to the intensity of exercise [85], and it was compensated by an increase in oxygen extraction [84, 87] and hemoconcentration [87], together, these data suggests that fetal oxygenation is maintained even in response to acute reductions in uterine blood flow. Data derived from human populations, although limited has not demonstrated an adverse impact of prenatal exercise on maternal or fetal health [88-91]. This hypothesis is supported by a recent meta-analysis suggesting that although structured prenatal exercise reduced fetal weight by 30.6 g (p=0.002) the risk of having a SGA baby was not increased [92].

2.1.2 Exercise and large for gestational age newborns

The maternal intrauterine environment is the critical determinant of fetal growth. An increasing body of evidence has demonstrated a strong association between increased maternal pre-pregnancy weight, excessive gestational weight gain and gestational diabetes, with increased infant birth weight and adiposity, and elevated body mass index (BMI) in childhood [93-95]. Although excessive fetal growth is often associated with maternal diabetes, up to eighty per cent of macrosomic infants are born to mothers who are normoglycemic [96]. Interventions targeting improvements in the intrauterine environment (e.g., improved insulin resistance, optimized

gestational weight gain) such as exercise require significant resources; however, factors including timing of the intervention and quantity of gestational weight gain, have a strong influence on birth weight [92, 97]. In fact, women who followed a structured prenatal exercise intervention during pregnancy had a 31% decrease in the odds of delivering a baby who was large at birth [92]. Exercise was associated with a reduction in maternal weight gain by 1.06 kg. Remarkably, exercise reduced gestational weight gain in women with gestational diabetes (-2.18 kg; p=0.004) but not in obese or overweight women (-0.3g; p=0.47) [92]. The discrepancy in the results can be attributed to a lower compliance to the exercise protocol and the small number of studies in the overweight/obese population. Thus, evidence suggests that exercise is associated with adequate pregnancy weight gain and reduced risk of having a LGA baby.

2.2 *The impact of exercise on fetal body composition*

Fetal body composition (fat and lean mass) is affected by maternal exercise differently depending on exercise intensity, volume and timing during pregnancy.

In women who did not exercise regularly, a moderate-intensity exercise-training program starting from the first trimester increased fetal birth weight and lean mass with a decrease in the percentage of fat mass [98]. Whereas in women who exercise regularly before pregnancy (run/aerobic exercise program), a moderate-intensity exercise training program starting from the first trimester was associated with a reduction in birth weight and fat mass [78]. Clapp *et al.* [99], found that in women who exercised regularly, and were enrolled in a moderate-intensity exercise-training program; changing from high volume (60 min/day/5 days a week) to low volume activity (20 min/day/5 days a week) at the second half of pregnancy was associated with an increase in fetal birth weight with proportional increases in fat and lean masses. Furthermore, when a

moderate intensity exercise program is started at the second half of pregnancy, birth weight and lean mass were reduced with no changes in fat mass or bone mineral density [100]. Moderate intensity physical activity (measured by accelerometry [GT3X+, ActiGraph]) during the second trimester was associated with a reduction in birth weight and fat mass; whereas moderate intensity physical activity during the third trimester was associated with an increased lean mass (with no changes in birth weight) [61]. In previously sedentary women, starting a vigorous exercise-training program during the second trimester did not affect birth weight [101]. Results from Bisson *et al*. [61], showed that vigorous physical activity (measured by accelerometry [GT3X+, ActiGraph]) during the second trimester were associated with reduced birth weight, fat mass and bone mineral density. Finally, in a cohort of 826 pregnant women that completed a Pregnancy Physical Activity Questionnaire, Harrod *et al*. [102], found that during late pregnancy, higher energy expenditure was associated with lower neonatal fat mass. These results suggest that *a)* the impact of exercise on fetal composition seems to be determined by the activity status of the mother before pregnancy, which is also associated with her pre-pregnancy BMI and with fetal body composition. *b)* Even if there was a reduction in birth weight, exercise was not associated with babies born SGA; and *c)* exercise during pregnancy is associated with a decrease in fetal fat mass. This is important, since it has been established that the percentage of body fat in neonates is correlated with the percentage of body fat in 9-year old children [103]. Moreover, childhood adiposity has been associated with decreased insulin sensitivity [104]. Therefore, it has been hypothesized that exercise during pregnancy is important because it could have the ability to modify fat mass, potentially reducing children's risk of developing cardiometabolic diseases later in life.

3 Mechanisms associated with the cardiometabolic adaptations following exercise during pregnancy that lead to changes in fetal growth

3.1 Metabolism and glucose control during pregnancy

Maternal metabolism is a critical determinant of fetal growth [105]. Mild insulin resistance is a hallmark feature of pregnancy which serves to sustain adequate nutrition to the fetus [106]. However, even in the absence of gestational diabetes, increased maternal insulin resistance is strongly correlated to fat mass at birth [105, 107]. In addition, pregnancy is associated with an increase in maternal fat deposition [108], followed by an increase in adipose tissue inflammation [109], and subsequently an increased cytokine production [110] .This increase in cytokine production is known to exacerbate insulin resistance [111]. Moreover, it has been determined that conditions such as diabetes or obesity during pregnancy can increase the placental expression of GLUT-1 and System A activity [112]. These findings suggest that alterations in glucose metabolism are associated with changes in placental nutrient transfer leading to an increase in fetal weight and fat mass [112], which is associated with increased fat mass and body fat percentage at birth as well. These data are supported by Hamilton *et al.* [113], who demonstrated that greater maternal insulin resistance later in pregnancy, independent of maternal glucose tolerance and parental BMI, was associated with increased infant weight gain and adiposity at one year of age.

It has been demonstrated that acute and regular weight-bearing exercise decreases circulating glucose and insulin concentrations in healthy pregnant women [114, 115]. Interventions that target a reduction in insulin resistance in the mother may be a mechanism to prevent excessive fat accumulation and/or body mass in the offspring. A recent systematic review evaluating the combined effect of life style interventions (education, diet, exercise and self-monitoring of blood

glucose) in the treatment of gestational diabetes, showed that these interventions were associated with a reduction in the risk of being born LGA, the incidence of macrosomia, and decreased neonatal fat mass [116].

The mechanisms by which exercise enhances maternal metabolism are thought to result from *a)* increasing the expression of glucose transporter type 4 (GLUT-4) at the cell surface in the muscle [117, 118]; *b)* increasing adiponectin levels and improving cytokine levels [119]; and *c)* improving oxidative stress [119].

3.2 Autonomic nervous system regulation

Over the course of a healthy pregnancy, the cardiovascular system experiences rapid adaptations to guarantee adequate uteroplacental perfusion [120]. A decrease in blood pressure and total peripheral resistance along with an increase in resting sympathetic nerve activity (SNA) is observed during healthy pregnancy [121-125]. These changes are known to provide appropriate oxygen and nutrient delivery to the growing fetus [120], thus alterations in SNA could affect fetal growth. However, the role of the autonomic nervous system on blood pressure regulation during pregnancy is not well understood. The discrepancy between an increase in SNA and a decrease in total peripheral resistance suggests that there is a concomitant reduction in vascular transduction resulting in maintenance of blood pressure [122]. These data are supported by the fact that during pregnancy, there is a progressive regression of the uterine sympathetic nerves [126]. Therefore, any perturbation to the normative blunting of vascular transduction during pregnancy could lead to a decrease in blood flow to the uterus with a concomitant decrease in fetal weight.

The baroreflex is a mechanism regulating acute changes in blood pressure. It has been established that sympathetic baroreflex gain decreases [121, 128, 129] while cardiac baroreflex

sensitivity increases or remains the same during pregnancy [121, 130]. Changes in cardiac baroreflex sensitivity are associated with increased cardiac parasympathetic activity [131-134], while changes in the sympathetic baroreflex gain have been speculated to be related to progesterone changes [135]. These data suggest that during pregnancy baroreflex it is blunted and offset, making women at a higher risk of presyncope or syncope [127].

Exercise is known to improve cardiac parasympathetic activity, decrease muscle SNA and improve baroreflex function in non-pregnant populations [136]. Within the context of pregnancy, Carpenter *et al.* [137], showed that pregnant women who attended weekly exercise classes had lower baroreceptor sensitivity compared to control women. Moreover, May *et al*. [138], found that in active pregnant women (self-reported of compliance to The American College of Obstetrician and Gynecologist guidelines [63]) there is an improvement in cardiac autonomic control by an increase in parasympathetic activity in the second trimester of pregnancy. It is important to note that one of the studies did not find differences among the groups regarding fetal weight [137], while the other did not report this outcome [138]. Given the profound changes in blood pressure regulation during pregnancy, it appears that the autonomic changes observed following chronic exercise during pregnancy guarantee adequate tissue perfusion. The impact of the changes of autonomic nervous activity following chronic exercise during pregnancy on fetal weight, requires further investigation.

3.3 Placental adaptations

Many factors can determine the ability of the placenta to maintain adequate nutrient delivery to the fetus (i.e. total area of syncytiotrophoblast, protein expression of nutrient transporters, blood flow [139, 140]). Near-term fetal weight is correlated to placental weight [140]. Placental

efficiency, which is defined as grams of birth weight per gram of placenta [141], is considered a surrogate of fetal growth. Although placental efficiency is genetically determined, changes in the environment can also modify placental efficiency [140]. Exercise is known to either increase [98, 99, 142, 143] or decrease the size of the placenta without changes in fetal weight [57, 144], suggesting that exercise increases placental efficiency. The variability of results could be explained by when exercise was initiated (i.e. pre-pregnancy vs. 1st, 2nd or 3rd trimester) Interventions initiated during the first trimester [98, 99, 142, 143] demonstrated an increase in placental size. Suggesting placental angiogenesis could have been affected. Whereas, exercise interventions initiated during the second trimester could improve oxidative stress and NO modulation [144].

Studies examining the impact of exercise on placental function have demonstrated an impact through multiple mechanistic pathways (i.e. angiogenesis, and oxidative stress). Alterations in the vasculature or structure of the placenta, and/or the transport systems within the placenta are associated with changes in its efficiency. Immunohistochemistry studies carried out in placentas from women who exercise during their pregnancies illustrated an increase in villous growth [98, 99, 142, 143] and an increase in proliferation activity in cytotrophoblast cells as well as endothelial and stromal cells [142]. In addition, it has been suggested that exercise induces placental angiogenesis. For instance, Gilbert *et al*. [57], identified that voluntary wheel running before and during pregnancy increased placental expression of heat shock proteins-27,-60,-90 in Sprague-Dawley dams. These heat shock proteins are involved in stimulating vascular endothelial growth factor [VEGF] production [145], and enable NO production [146]. Interestingly, the authors found that exercise increased serum vascular endothelial growth factor [VEGF] with a reduction in the balance of soluble fms-like tyrosine kinase-1 (s-Flt-1)/ VEGF suggesting that exercise enhanced angiogenesis balance in these dams. Interestingly, in an animal model of a complicated pregnancy

(ischemia-induced hypertension) it was demonstrated that voluntary wheel running increased endothelial tubule formation [147].

The role of exercise on placental function has been recently studied. Pregnant woman who follow the exercise guidelines during their second trimester had altered placental gene expression. [148]. Interestingly, genes involved in transporting fatty acids across the placenta, insulin and mechanistic target of rapamycin (mTOR) signaling pathways were downregulated, whereas genes involved in amino acid transport to the fetus were upregulated [148]. Thus, physical activity during pregnancy is associated with the regulation of genes involved in fetal growth and energy consumption.

Regarding oxidative stress, it has been determined that exercise decreases the production of reactive oxygen species in the placenta, with a subsequent increase in placental NO production, and protein expression of endothelial nitric oxide synthase [144]. It can be hypothesized that improvements in the reactive oxygen species balance towards an increase in NO could augment placental perfusion and oxygen/nutrient exchange by an increase in endothelium-mediated vasodilation in the uterine arteries, and therefore it would improve fetal weight. However, more research is needed, to determine the role of exercise on endothelium-mediated vasodilation in the uterine arteries.

4 Limitations and future directions

The vast majority of evidence presented in this review supports the concept of exercise as a therapeutic intervention during pregnancy to improve fetal body composition without increasing the risk of having a SGA or LGA infant. However, the variability of the findings could be attributed to different exercise training paradigms, aerobic exercise training being the primary paradigm. In

addition, the ideal frequency, intensity, time and type of exercise that pregnant women should perform in order to prevent cardiometabolic complications that would lead to an increase risk of fatal CVD for both mother and child is unknown. Hence, more research is needed regarding other types of exercise (high intensity interval training, yoga, cross-fit) and its safety during pregnancy. This is important since it has been established that women with complicated pregnancies are at higher risk of developing CVD later in life. Moreover, offspring born from complicated pregnancies are also at higher risk of developing CVD later in life. Rice *et al.* [149], found that 23% of children born form women who had gestational diabetes in addition to gestational hypertension or preeclampsia were hypertensive by ten years of age. Therefore, exercise during pregnancy could be use a therapeutic approach to treat pregnancy complications, but more importantly, its use during pregnancy may prevent the development of CVD later in life to their offspring. We must consider that interventions during pregnancy target two different populations, therefore, they are highly cost-effective in ameliorating the burden of CVD for both mother and offspring.

There is a critical gap in our understanding of how increased placental efficiency would modify drugs or drugs metabolites' transport across the placenta. Animal models of exercise training during pregnancy would allow us to better understand how placental function is increased by exercise, and therefore, develop guidelines to modify dosing of medications that cross the placental barrier in active pregnant women.

Finally, There are some contraindications for exercise during pregnancy (i.e. preeclampsia, restrictive lung disease, placenta previa after 26 weeks of gestation [150]). Interestingly, exercise decreases a plethora of risk factors associated with the development of preeclampsia. In fact, a recent meta-analysis suggests that increasing levels of physical activity before and early during

pregnancy could prevent the development of preeclampsia [59, 151]. Thus, more research is needed in order to determine the role of exercise in preventing pregnancy complications to improve lifelong fetal health.

Conclusions

It is now established that exercise for pregnant women is safe and beneficial for both mother and fetus. National and International guidelines encourage women who do not have any contraindications to exercise to begin or continue moderate-intensity exercise during pregnancy to achieve health benefits (Figure 1). It has been suggested that preventative measures (such as exercise) which positively influence placental development and decrease systemic inflammatory responses, oxidative stress and endothelial dysfunction prior to or during early pregnancy are warranted in high risk women such as women with overweight or obesity, and women with gestational diabetes. Adopting healthy life-styles during pregnancy such as exercise will decrease excessive fat deposition in the fetus, and could potentially ameliorate the burden of CVD later in life for both the mother and the fetus.

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Declaration of interest

The authors declare no conflict of interest.

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Figure 1. Potential mechanisms by which exercise impact fetal weight.

Summary flow chart representing the potential mechanisms by which exercise during pregnancy will impact fetal weight. GLUT-4: Glucose transporter type 4; mTOR: Mechanistic target of rapamycin; s-Flt-1: Soluble fms-like tyrosine kinase-1; VEGF: Vascular endothelial growth factor.