The role of mesenchymal stem cells in early programming of adipose tissue in the offspring of women with obesity

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Summary
Maternal obesity is a well-known risk factor for developing premature obesity, metabolic syndrome, cardiovascular disease and type 2 diabetes in the progeny. The development of white adipose tissue is a dynamic process that starts during prenatal life: fat depots laid down in utero are associated with the proportion of fat in children later on. How early this programming takes place is still unknown. However, recent evidence shows that mesenchymal stem cells (MSC), the embryonic adipocyte precursor cells, show signatures of the early setting of an adipogenic committed phenotype when exposed to maternal obesity. This review aims to present current findings on the cellular adaptations of MSCs from the offspring of women with obesity and how the metabolic environment of MSCs could affect the early commitment towards adipocytes. In conclusion, maternal obesity can induce early programming of fetal adipose tissue by conditioning MSCs. These cells have higher expression of adipogenic markers, altered insulin signalling and mitochondrial performance, compared to MSCs of neonates from lean pregnancies. Fetal MSCs imprinting by maternal obesity could help explain the increased risk of childhood obesity and development of further noncommunicable diseases.

KEYWORDS
adipogenesis, adipose tissue, fetal programming, mesenchymal stem cells, obesity, pregnancy

1 | INTRODUCTION

The incidence of obesity is increasing worldwide. More than 20% of women of reproductive age in middle and high-income countries are obese. This results in an increasing prevalence of overweight and obesity in pregnant women worldwide. Maternal obesity is a risk factor for maternal complications such as gestational diabetes, hypertension, preeclampsia and Caesarean section. Maternal obesity also affects the foetus, leading to several adverse outcomes in the offspring: stillbirth, congenital abnormalities, macrosomia and neonatal increased adiposity. It has been estimated that up to 41.7% of...
childhood overweight/obesity can be attributed to maternal overweight and obesity, making this a transgenerational problem.3

During maternal obesity, foetuses have increased access to nutrients, leading to fetal metabolic adaptations and increased adiposity.4 A high maternal BMI is associated with increased neonatal adiposity, hepatocellular lipid content, higher concentrations of inflammatory adipokines and metabolic mediators.7–9 Furthermore, neonates born to obese mothers are insulin resistant and prone to metabolic compromise.7 It has also been shown that excessive adipose tissue in these early stages of life results in obesity in the child.10 With this, childhood obesity is likely to extend into adulthood, which strongly predicts a lifetime of health problems, as it results in an acquired susceptibility to metabolic disease.10

An obesogenic intrauterine environment affects not only fetal adipose tissue but also adipose precursor cells, which are the mesenchymal stem cells (MSCs). MSCs are multipotent progenitor cells established during early development that commit and differentiate into mesenchymal tissue, such as adipocytes.11 In this review, we aim to evaluate how the obesogenic intrauterine environment could influence MSCs and explore the effect of maternal obesity on the metabolic state and specific adipogenic commitment of MSCs. The confirmation of a programming effect of adipose precursor cells exposed to an obesogenic intrauterine environment could be a major contribution to the current knowledge on programming the early onset obesity and chronic diseases. Understanding fetal adipogenesis in maternal obesity will increase our possibilities to prevent and intervene in infant obesity early in life.

2 | OVERVIEW OF ADIPOSE TISSUE IN NORMAL WEIGHT AND OBESITY

Adipose tissue is a crucial regulator of energy homeostasis, with a principal role in lipid storage, but responding to external signals for buffering, synthesizing and secreting a wide range of endocrine products to regulate whole-body metabolism.12 Adipose tissue consists of adipocytes, surrounded by loose connective tissue. It is highly vascularized and innervated and contains macrophages, fibroblasts and adipocyte precursor cells, amongst others.13 Adipocytes take up free fatty acids and glucose to convert them into triglycerides (TG), the optimal way for lipid storage in mammals; the process is known as lipogenesis.14,15 This process protects the body from possible lipotoxicity in other organs.16 Uptake of free fatty acids into the adipocyte occurs via both passive diffusion and a protein-mediated mechanism (fatty acid-binding and transport proteins such as CD36 and FABP4/aP2).17 In parallel, the influx of glucose into the adipocyte is mainly regulated by the insulin receptor, the activation of which leads to translocation of glucose transporter protein 4 (GLUT4) to the cell membrane, promoting glucose uptake.18 Both fatty acids and glucose are essential substrates for cell metabolism, promoting TG synthesis and storage.15,19 The process of fat mobilization is known as lipolysis, where several neuroendocrine signals, such as norepinephrine and insulin, initiate the process of TG breakdown for body energy expenditure.20 The adipocyte machinery relies on glycolysis and mitochondrial oxidative phosphorylation as the main ATP-producing pathways to obtain energy and perform all adipocyte functions.21 Altogether, in normal weight conditions, adipocytes respond to systemic signals to either store or mobilize nutrients as needed by the organism, and a healthy and regulated balance between nutrient uptake and metabolism contributes to the adipocyte system to work (Figure 1). Adipose tissue is not only crucial for lipid storage, but this tissue also communicates with other organs through adipokines such as leptin, adiponectin, tumour necrosis factor-alpha (TNFα), interleukin-6 (IL-6), IL-8, IL-1β and monocyte chemoattractant protein 1 (MCP1).22 These molecules are known to intervene directly with metabolic balance, emphasizing the role of adipose tissue in regulating body energy homeostasis.23

Overnutrition leads to increased storage of nutrients and less nutrient mobilization, insulin resistance and adipocyte dysfunction, resulting from the combination of adipocyte cellular stress, hypertrophy and hypoxia.24 This adipocyte dysfunction is associated with mitochondrial dysregulation and adipose tissue inflammation: overnutrition supplies excess of electrons to the respiratory chain, while lack of physical activity and low ATP demand favours a high proton motive force with a low respiratory rate, leading to mitochondrial superoxide formation.25,26 Thus, in obesity, high levels of oxidative stress lead to cellular damage in adipocytes.27 Studies have also reported systemic oxidative stress.28 Obesity is also associated with low levels of generalized inflammation.29 This inflammation is induced by the adipocyte secretome, with increased secretion of pro-inflammatory cytokines such as TNFα, IL-6, IL-8 or MCP-1, and a decrease in the anti-inflammatory adipokine adiponectin.29 Inflammation has detrimental effects on insulin secretion, sensitivity and lipid metabolism, resulting in insulin resistance, where there is no response nor translocation of GLUT4, corresponding with obesity and later metabolic syndrome (Figure 1). Thus, obesity is a low-grade inflammatory state of the whole body, also referred to as meta-inflammation.30 It is now known that insulin resistance, secretion of proinflammatory adipokines and oxidative stress are hallmarks in dysfunctional adipocytes and are also found in children with obesity.31

3 | MESENCHYMAL STEM CELLS AND ADIPOGENESIS

During early development, the first totipotent stem cell proliferates and establishes the blastocyst, from which pluripotent stem cells arise.32 Consequently, these stem cells commit to specific cell lineages to eventually differentiate and form the numerous tissues and organs of the body.32 MSCs are multipotent cells capable of renewing themselves through cell division and differentiating into mesenchymal tissue, such as adipocytes.11

In humans, adipose tissue develops by the 14th week of gestation, when aggregates of MSCs condense next to primitive blood vessels. These MSCs proliferate and differentiate into preadipocytes.33 Finally, preadipocytes acquire lipid droplets and endocrine capacity
During the first step, MSCs are activated by transforming growth factor-beta (TGF-β)/bone morphogenic protein (BMP), wingless-type MMTV integration site (Wnt), Hedgehogs (Hh), Notch and fibroblast growth factors (FGFs), including superoxide anion (O₂⁻), hydrogen peroxide (H₂O₂), hydroxyl radical (‘OH) and hydroxyl ion (OH⁻). ROS promote essential cell functions, including proliferation, differentiation and apoptosis. Unphysiological levels of ROS react readily with a variety of chemical structures such as proteins, lipids, sugars and nucleic acids, leading to oxidative damage. Therefore, ROS levels are regulated by antioxidant enzymes and radical scavengers, such as superoxide dismutase, peroxidases and glutathione, among others. ROS have been shown to be essential in adipocyte lineage commitment: increased mitochondrial biogenesis and activity, which are associated with increased levels of ROS, are a prerequisite for MSC differentiation into mature adipocytes. For instance, differentiation of adipose-derived stem cells (ASC) and mouse embryonic 10T1/2 cells is dependent on ROS and oxidative stress status. Moreover, it has been determined that ROS generation from mitochondrial complex III is a causal factor for the adipogenic commitment of bone marrow MSC and that inhibiting mitochondrial respiration significantly suppresses adipogenic differentiation. Furthermore, exogenous application of H₂O₂ may induce and augment adipocyte differentiation and cell cycle progression of 313-L1 mouse preadipocytes. ROS are indeed known to trigger several pathways that set up the transcriptional machinery, including Wnt, Hg and Forkhead Box O (FoxO) signalling cascades, towards PPARγ activation and adipogenic commitment.
Evidence shows that fetal adipogenesis can be programmed by maternal obesity. High glucose levels and lipids in the maternal circulation are transported across the placenta, inducing hyperglycemia and hyperlipidemia in the developing fetus. In addition, the placental function is regulated by maternal signals, such as maternal nutritional state, metabolic changes, endocrine mediators and growth factors, which will determine the placental function and, therefore, fetal development. Many of these signals are influenced by maternal obesity. Clinical studies show that neonates born from mothers with obesity have increased neonatal adiposity and adiposity markers such as higher concentrations of umbilical cord leptin, interleukin 6 (IL-6) and insulin-like growth factor 1 (IGF-1). Furthermore, epidemiological studies have shown that neonates from obese mothers are insulin resistant and prone to metabolic compromise.

Studies on fetal adipose tissue from obese pregnancies are limited to animal models and show that fetal development is vulnerable to changes in nutrition during early and late third trimester of gestation, with high fetal growth and fat deposition. Data suggested that offspring from mothers with obesity show increased fetal adiposity, with a higher fat mass and hypertrophy of adipocytes in both sheep and mice. Also, at this time, regulatory set points in the brain, neuronal-metabolic feedback loops and mitochondrial function may be impacted in rodents. Offspring from obese high-fat diet-induced rats and ewes accumulate excessive fat mass associated with upregulation of lipogenic genes, increased fatty acid and glucose transporters and increased expression of enzymes mediating fatty acid biosynthesis in adipose depots. Other animal studies showed upregulation of PPARγ, C/EBP, zinc finger protein 423 (Zfp423), leptin and other lipogenic gene expression together with adipocyte hypertrophy in offspring of obese mothers.

Epigenetic mechanisms participate in the regulation of fetal adipogenesis: a decreased methylation of C/EBP and Zfp423 promoter and enhanced adipogenesis are present in fetal adipose tissue from high-fat diet dams. It has also been shown that maternal obesity in animals can lead to a metabolic syndrome-like phenotype through epigenetic modifications of the genes encoding higher expression of leptin and lower levels of adiponectin in adipose tissue of the offspring. The outcome of adipose tissue programming is vastly stereotypic, proposing common underlying mechanisms: offspring develops altered metabolic features such as insulin resistance, obesity, immunity disorders and endothelial dysfunction. How early this programming takes place is unknown.

5 | MESENCHYAL STEM CELLS FROM NEONATES OF WOMEN WITH MATERNAL OBESITY

As indicated above, growing evidence indicates that increased fat mass in offspring from obese animals occurs in prenatal life, suggesting that prenatal adipocyte development may differ in fetuses of obese versus lean mothers. Studying adipocyte progenitor cells and their in vitro development into adipocytes could shed light on potential aberrant adipocyte development in the offspring of obese women. The human umbilical cord is an easily accessible and noninvasive source of MSCs, also exempt from ethical debate. MSCs from umbilical cords are easy to isolate and culture. MSCs have a multi-potent differentiation potential towards the mesodermal lineage and are adipocyte precursor cells. Therefore MSCs obtained from umbilical sources could provide an efficient model for studying fetal adipose tissue.

5.1 | Increased adipogenesis in neonates of women with obesity

Different studies have been performed on MSCs from Wharton jelly in the umbilical cords of obese and lean pregnant women. Laffaldano et al. (2013) showed that MSCs from neonates born from obese mothers have a higher expression of adipogenic genes, such as PPARγ and FABP4/aP2, compared to MSCs from lean mothers, suggesting a higher adipogenic potential in MSCs of neonates from mothers with obesity. Recently, it has been demonstrated that during adipogenic induction, these cells have higher lipid accumulation, consistent with hypertrophy. A particular commitment towards adipocyte lineage in MSCs from neonates of obese mothers has been attributed to the downregulation of the Wnt signalling pathway. More specifically, Boyle et al. (2016) demonstrated that umbilical cord MSCs from mothers with obesity were predisposed to differentiate towards adipogenic, rather than myogenic tissue in vitro. This was due to the downregulation of the Wnt/β-catenin pathway. Downregulation of Wnt/β-catenin pathway is associated with lower translocation of β-catenin to the nucleus, an inhibitory signal for muscle formation. The low levels of β-catenin also indirectly promote adipogenesis of these cells by reactivating PPARγ and C/EBPα. Similarly, Chen et al. (2016) suggested that umbilical cord MSCs from neonates from mothers with obesity have a lower osteogenic potential and an increased potential towards adipocyte in vitro differentiation. This was associated with an increased induction of PPARγ and adipocyte protein 2 (FABP4/aP2) gene expression. An impaired bone formation is associated with fat accumulation and loss of bone density, and could be explained by a deficient Wnt signalling leading to decreased osteogenesis and reconstitution by adipose tissue. Together, these data indicate that an obese environment could promote a shift in MSC commitment towards adipocyte differentiation. This suggests that progenitor cells can determine their lineage commitment according to external signals.

Furthermore, recent studies showed that lipid accumulation in Wharton Jelly MSCs correlates to metabolic features in neonates, suggesting that phenotypical characteristics of MSCs do translate to the clinical outcome of the child. This means that early metabolic dysregulations may establish the adipocyte pool and programme long-term effects: this has been associated with adiposity gain (Figure 2).
Insulin signalling is necessary for glucose and lipid metabolic balance in cells. During early differentiation of MSCs, insulin is also required to activate PPARγ and mitochondria, leading to healthy preadipocyte that will proliferate. Final adipocytes express PPARγ, together with lipogenesis markers and adipokines. Obese pregnancies: fetal mesenchymal stem cells present a decreased insulin signalling and increased induction of adipogenesis through a stronger downregulation of Wnt. Metabolic activity is decreased. Final adipocytes show higher PPARγ expression, together with altered fatty acid metabolism, mitochondrial dysfunction and senescence markers. Wnt, wingless-type MMTV integration site. PPARγ, peroxisome proliferator-activated receptor-gamma. GLUT4, glucose transporter 4. FABP4/aP2, fatty acid-binding protein 4. LPL, lipoprotein lipase. ROS, reactive oxygen species.

5.2 | Insulin in MSC-adipocytes from neonates of women with obesity

Insulin signalling is necessary for glucose and lipid metabolic balance in cells. During early differentiation of MSCs, insulin is also required to activate PPARγ, C/EBPs and thus adipogenesis. Upon insulin binding, the insulin receptor triggers the downstream signalling cascades involving phosphoinositide 3-kinase (PI3K)/Akt, MAPK, ERK1/2 and inhibits AMPK. Insulin signalling works as a strictly regulated mechanism, and a minor disruptive activity of downstream pathways could lead to perturbations in metabolism. Disruptive signalling is often the result of inflammation, hyperglycemia, lipotoxicity and ER-mitochondrial stress. Women with obesity often enter pregnancy with pre-existing glucose intolerance and insulin resistance, which intensifies with advancing gestation and are often transferred to the foetus. Therefore, a state of hyperglycemia and insulin resistance is characteristic in obese mothers and their foetuses, which could also programme metabolic activity during adipocyte differentiation. There appears to be a downregulation of nutrient-sensing pathways in in vitro adipocyte-differentiated MSCs from offspring born to mothers with obesity, particularly with lower AMPK, MAPK and PI3K-AKT transcription. Downregulation of these pathways related to insulin signalling is known to alter insulin sensitivity, with lack of GLUT4 membrane translocation and fatty acid oxidation. MSCs from the offspring of women with obesity have no response from Akt to insulin stimulation, concluding insulin resistance. Moreover, they show impaired cytoskeleton protein expression that could attempt to decrease GLUT4 transport to the membrane, in response to hyperglycemia. Whether this is a cause or a consequence of insulin resistance is yet to be studied. It is also reported that MSC from offspring of mothers with obesity show hypermethylation of lysophospholipases regulated by insulin. Together, these results suggest that umbilical cord-derived MSCs of neonates from mothers with obesity may have an altered insulin receptor signalling, related to lower insulin sensitivity and impaired glucose and lipid metabolism.

It is important to note that hyperinsulinemia and hyperglycemia from the mother to the foetus may impact many other insulin-sensitive metabolic organs, such as fetal liver, pancreas and muscle, which externally contributes to the increased neonatal adiposity and risk of metabolic disbalance in the future. Clinical observations show that increased maternal BMI is linked with fetal macrosomia and enhanced adiposity. Altogether, this strongly suggests that programming of adaptive responses to conditions such as elevated glucose, lipids and hyperinsulinemia in utero could promote higher adipose tissue formation, with the characteristic neonatal macrosomia. With altered insulin sensitivity it is suspected that the final mature adipocyte could be programmed to become hyperproliferative and prone to dysfunction.

5.3 | Mitochondrial dysfunction in MSC from neonates of women with obesity

Mitochondria are pivotal in coordinating energy production with nutritional cues. Glycolysis and mitochondrial oxidative
phosphorylation are the main ATP-producing pathways by which cells obtain energy to drive their biological functions. In response to changes in energy demand and supply, the organism adapts by adjusting its capacity and ATP production efficiency. MSCs are characterized for being highly glycolytic, while during differentiation of MSCs towards adipocytes, oxidative phosphorylation by mitochondria is an important contributor to ATP production and metabolic reprogramming. In mature adipocytes, apart from ATP production, healthy mitochondria are contributors to the metabolic balance due to their role in fatty acid oxidation and energetic demand for adipokine production. In fat depots of patients with obesity, the mitochondrial membrane potential and the activities of respiratory chain complexes are reduced. Such mitochondrial dysfunction leads to oxidative stress, cell death, inflammation and metabolic dysfunction. Next to this, in fat depots of patients with obesity, the antioxidant defence mechanisms are also decreased. High levels of oxidative stress and the simultaneous decline of antioxidant defence lead to cellular damage, which is a primary cause of adipose tissue inflammation.

MSCs from umbilical cords of neonates from women with obesity show less efficient mitochondrial respiration compared to MSCs of neonates from lean mothers: the electron transport chain is impaired and maximal respiration is lower in MSCs of newborns from women with obesity. This suggests early signatures of mitochondrial dysfunction, oxidative stress and metabolic disruption in the MSCs from umbilical cords of obese women. Baker et al. (2017) characterized mitochondrial gene expression of adipocytes differentiated from umbilical cord MSCs. This study showed upregulation of the mitochondrial respiratory chain but downregulation of mitochondrial biogenesis, mitophagy and fusion/fission in MSCs from newborns of women with obesity as compared to the MSCs from neonates of lean women. Altered mitochondrial electron transport machinery is considered a major ROS generator, suggesting increased ROS production in MSCs from neonates from obese mothers as compared to neonates to lean mothers.

Although ROS production in MSCs from neonates of obese versus lean mothers has not been determined, oxidative stress is known to be related to premature ageing, and MSCs of neonates from women with maternal obesity show higher p53, p21 and senescence associated βIgalactosidase (SAβGal): markers of cell senescence signalling. This indicates an ageing phenotype of MSCs from offspring of mothers with obesity (Figure 2). In addition, studies by Capobianco et al. (2016) reported reduced stress response proteins in these cells, suggesting a different oxidative stress response in MSCs from neonates from mothers with obesity. Further studies should thus measure the levels of ROS in MSCs from neonates from mothers with obesity. It has not been determined whether the altered mitochondrial function in early precursor cells are maintained in mature adipocytes in postnatal life.

Iaffaldano et al. (2018) also showed that glycolysis is less efficient in fetal MSCs isolated from the umbilical cord of women with obesity than in those isolated from control women. These findings suggest maternal obesity can alter the glycolytic machinery with a less efficient response to the energy demand. Furthermore, it has been established that low ATP production has been associated with increased accumulation of intracellular TGs in mouse preadipocytes. Whether this could be an adaptive response of the developing foetus to the excessive nutrient supply is still unknown.

Genomic studies in adipocytes differentiated from umbilical cord MSCs show that maternal free fatty acids (FFA) and neonatal adiposity are associated with upregulation of mitochondrial electron transport genes, but downregulation of mitochondrial biogenesis genes, including EP300, CREBBP and PPARG. This is consistent with lower mitochondrial abundance. In similar studies, epigenetic analysis show hypermethylation of genes of the fatty acid oxidation machinery and differently expressed miR-138-3p and miR-222-3p, which upregulate genes engaged with lipid metabolism and stress response. Overexpression of miR-138-3p and miR-222-3p has been found in subcutaneous and visceral adipose tissues from obese adults associated with the chronic inflammatory environment. These results suggest that energetic adaptation during gestation may enable the foetus to survive in an aversive energetic environmental condition by reprogramming mitochondrial function for adaptive responses (Figure 2).

6 CONCLUDING REMARKS

Maternal obesity is known to create an adverse intrauterine environment that can lead to fetal adaptation. Maternal obesity programmes several developmental pathways, including fetal adipogenesis. The potentiation of adipogenesis in early life may trigger the later development of obesity. During a lean pregnancy, adipocyte precursor cells in the foetus express high mesenchymal stem cell markers, maintained in a committed but undifferentiated state, limiting the differentiation towards adipocytes. In an obese pregnancy, however, MSCs have an increased differentiation potential towards adipocytes, which may help to explain the progressive increase in fat mass of the offspring of women with obesity. It is still unclear if this is a protective mechanism from the foetus to the mother's nutritional overload.

The increased adipogenic potential of MSCs from umbilical cords of neonates from mothers with obesity raises several questions: could maternal obesity lead to increased adipogenesis in other mesodermal tissues, such as bone and muscle? Could this result in a decreased differentiation towards muscle, bone and cartilage cells? In this respect, it is important to note that obesity is a condition associated to a disturbed muscle and bone physiology, together with higher intramuscular fat deposition and osteoporosis. This suggests that proper development of these tissues may also be disturbed in uterus. Also, this raises the question of whether other stem cell lineages could be compromised: are ectodermal and endodermal lineages altered by maternal obesity? These questions remain unclear and are necessary to answer in future research of early embryonic cell programming.

It appears that the insulin pathway as well as mitochondrial activity are different in MSCs from neonates born to mothers with obesity,
and this could contribute to the early commitment towards adipocytes and, with this, increased adipogenesis of its precursor pool. Whether it would lead to dysfunctional adipocytes in the neonate is a question that remains, and more follow-up studies are needed. However, these progenitor cells can determine their lineage commitment according to external signals. Premature signatures in early progenitor cells from neonates exposed to maternal obesity may indicate that the problem starts with the early first totipotent cell exposed to this adverse intra-uterine environment. This could be the main reason why interventions, such as nutrition and exercise during mid and late gestation, have concluded no beneficial effects over the altered anthropometric and metabolic parameters in these neonates—it may be too late.90

Stem cells are abundant during early life and carry specific prenatal signatures. We suggest that they may be proposed as potential performers of the developmental programming of obesity and metabolic diseases. Although studies on maternal obesity and fetal outcomes have been performed for many decades, the current knowledge of the altered phenotype of this progenitor cells can be an interesting instrument to understand the mechanisms by which the high nutrient supply in early progenitor cells may lead to adipocyte imprinting. The knowledge on this early imprinting of precursor cells shows that there is an urgent need to focus on preventive strategies targeted to preconceptional and early days of pregnancy. This may provide an opportunity to break the rising cycle of obesity and the concomitant noncommunicable diseases.

AUTHOR CONTRIBUTIONS

SB contributed to the investigation, conceptualization, analysis of the information and writing this manuscript. PC, MF and TP contributed to conceptualization and editing. SB prepared figures. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests to declare.

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