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Metabolic Roles of Fatty Acid Binding Protein 4 (FABP4) in Fetal and Maternal Health and Maintenance of Pregnancy in Women with Obesity: A Review

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Study Design A
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Literature Search F
Funds Collection G

AG 1 Magdalena Wierzchowska-Opoka
BE 2 Aleksandra Domańska
CE 2 Angelika Masiarz
DE 2 Natalia Olbrot
EF 2 Anna Oleszczuk

1 Chair and Department of Obstetrics and Perinatology, Medical University of Lublin, Lublin, Poland
2 Student's Scientific Association at the Chair and Department of Obstetrics and Perinatology, Medical University of Lublin, Lublin, Poland

Corresponding Authors: Magdalena Wierzchowska-Opoka, e-mail: magdaopoka11@gmail.com, Aleksandra Domańska, e-mail: aleksandradomanska0206@gmail.com

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The global obesity epidemic has seen a dramatic rise, with maternal obesity increasing from 20.9% to a projected 23.3% by 2030. In pregnancy, metabolic dysregulation linked to obesity and gestational diabetes mellitus (GDM) elevates risks for both mother and child, contributing to complications such as macrosomia, fetal growth restriction (FGR), preterm labor, and higher cesarean rates. Central to these processes is fatty acid-binding protein 4 (FABP4), a key regulator of lipid metabolism, vascular inflammation, and insulin sensitivity. FABP4, primarily expressed in adipose tissue and macrophages, plays a pivotal role in placental lipid transport and intracellular fatty acid handling, with elevated serum levels correlating with higher body mass index (BMI) and inflammatory states in obese individuals.

Emerging evidence highlights FABP4 as a potential biomarker for predicting metabolic complications, including GDM and pregnancy-induced hypertension, offering opportunities for early intervention.

This review underscores the critical role of FABP4 in obesity-related pregnancy complications, emphasizing its potential as both a biomarker and therapeutic target. Advancing research into FABP4's mechanisms and therapeutic applications could significantly improve outcomes for pregnant women with obesity, fostering healthier pregnancies and reducing long-term metabolic risks for mother and child.

This article reviews the metabolic roles of fatty acid binding protein 4 (FABP4) in fetal and maternal health and maintenance of pregnancy in women with obesity.

Keywords: Diabetes, Gestational • Fatty Acid-Binding Proteins • Obesity, Maternal • Pregnancy Complications

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Introduction

The global obesity epidemic has escalated significantly in recent decades, with the number of obese individuals worldwide surpassing 1 billion in 2022 [1]. Maternal obesity is also on the rise, estimated at 20.9% and projected to reach 23.3% by 2030 [2]. In a healthy pregnancy, a woman's body undergoes physiological changes to support fetal growth, but metabolic dysregulation can lead to complications affecting both mother and fetus [3]. Elevated triglycerides, cholesterol, and insulin resistance contribute to obesity, dyslipidemia, GDM, and metabolic syndrome, increasing the risk of cardiovascular disease for both mother and child [4]. Obesity and GDM, central to this study, are associated with adverse fetal outcomes, including macrosomia, fetal growth restriction, and low gestational age births [5-7]. Obstetric complications such as preterm labor, stillbirth, and higher cesarean rates are also linked to these conditions [5,8]. FABP4 (also known as adipocyte protein 2-aP2 or adipocyte fatty acid binding protein- AFABP) is a fatty acid-binding protein primarily found in adipose tissue and macrophages, involved in lipid metabolism, vascular inflammation, and insulin regulation [3,4,9]. Given FABP4's role in placental lipid transport, understanding its influence on obesity and pregnancy is essential. This article reviews the metabolic roles of fatty acid binding protein 4 (FABP4) in fetal and maternal health and maintenance of pregnancy in women with obesity.

FABP4 in Lipid Metabolism

FABPs are part of a versatile protein family associated with fatty acid metabolism. They are categorized into 12 types based on their tissue of origin. FABP4 is an intracellular chaperone secreted by white adipose tissue and macrophages [10]. It interacts with peroxisome proliferator-activated receptor-γ (PPAR-γ) and hormone-sensitive lipase (HSL) [11]. Its primary role within the cell is as a transporter protein, binding fatty acids that traverse the plasma membrane and facilitating their transport to cellular organelles (such as mitochondria) for lipid oxidation [10]. It also regulates enzyme activity in the cytosol and promotes lipid storage as cytoplasmic droplets. Additionally, FABP4 is involved in the regulation of inflammation, apoptosis, and endoplasmic reticulum stress. Importantly, it is proposed to deliver lipids to the endoplasmic reticulum, supporting membrane production and other signaling functions [12]. Clinical studies suggest that circulating FABP4 signals an elevated risk for metabolic diseases linked to obesity. In obesity, FABP4 synthesis is upregulated, resulting in elevated FABP4 levels in both tissues and the bloodstream [10]. FABP4 is significantly associated with conditions related to metabolic syndrome, obesity, diabetes, insulin resistance, and cardiovascular diseases, interacting with metabolic and inflammatory pathways within adipocytes and macrophages [11,13]. Several clinical studies have observed significant differences in serum FABP4 levels between males and females, potentially due to the greater amount of body fat typically present in females [14]. FABP4 concentrations have been shown to be strongly associated with BMI [15]. Visceral fat, in particular, exhibits a higher lipolytic activity compared to subcutaneous fat, and visceral obesity is known to increase oxidative stress [16]. This oxidative stress can alter the spatial structure of FABP4, causing it to preferentially bind saturated fatty acids instead of essential fatty acids like linoleic and α-linolenic acids. Under these conditions, FABP4 can act as an adipokine that induces an inflammatory response in endothelial cells, potentially accelerating the atherosclerotic process. Saito et al demonstrated that among patients monitored over a 12-year period, those with the highest serum FABP4 levels (>21.2 ng/mL) had a significantly increased risk of cardiovascular mortality. Circulating FABP4 may thus serve as a valuable biomarker for detecting preclinical stages of metabolic syndrome, particularly insulin resistance, within the general population [16]. Lv et al identified FABP4 as a reliable biomarker of aging in both humans and mice. FABP4 overexpression was found to accelerate senescence in human liver cell lines, while administration of a FABP4 inhibitor to older animals improved their metabolic profiles. FABP4 contributes to dyslipidemia by elevating proprotein convertase subtilisin/kexin 9 (PCSK9) levels, which leads to the degradation of the low-density lipoprotein receptor (LDLR). Notably, age-related downregulation of LDRL expression was reversed with FABP4 knockdown, suggesting a role for FABP4 in cholesterol utilization. Histological staining revealed substantial lipid accumulation in the livers of elderly mice, which was significantly reduced upon FABP4 knockdown. These findings suggest that FABP4 knockdown mitigates metabolic issues associated with aging and halts the aging process within the liver [17].

During lipolysis, as occurs during fasting, FABP4 binds free fatty acids (FFAs) in the cytoplasm, modifying the inhibitory effects of released lipids on lipolytic enzymes and facilitating their release from the cell. This process benefits survival by enabling distant tissues to use lipids as an energy source during periods of hunger. However, in modern contexts, where obesity is a prevalent issue and abundant adipose tissue often leads to uncontrolled lipolysis, FABP4 is continuously engaged. FFAs are crucial for both glucose- and non-glucose-induced insulin secretion. FFA-mediated stimulation of insulin secretion operates through activation of the free fatty acid receptor 1 (FFAR1) on β cells [18]. Notably, some researchers have identified FABP4, which is secreted by endothelial cells, as an essential factor in lipolysis-mediated insulin secretion. Since hyperinsulinemia contributes to insulin resistance, the facilitation of lipolysis-mediated insulin secretion by endothelial FABP4 could be detrimental to the health and function of β cells [19]. In addition, clinical studies have demonstrated a strong positive correlation

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between blood FABP4 levels and biochemical markers associated with GDM, such as insulin resistance, tumor necrosis factor-α (TNF), and interleukin-6 (IL-6). In a study using mice, treatment with the FABP4 inhibitor BMS309403 improved insulin and glucose tolerance, while also reducing TNF-α and IL-6 levels at the transcriptional level. Compared to untreated GDM mice, those treated with BMS309403 showed a marked reduction in macrophage infiltration into adipose tissue, underscoring the therapeutic potential of FABP4 inhibition in managing GDM [20]. Another study examined the levels of FABP4 and tumor necrosis factor receptors (TNFRs) in patients with type 1 (T1DM) and type 2 diabetes (T2DM). TNFR1 and TNFR2 are cell membrane receptors involved in inflammation and immune response. Both FABP4 and TNFR levels were significantly higher in patients with T2DM compared to those with T1DM. Positive correlations were observed between FABP4 levels and TNFR1 and TNFR2 concentrations in patients with both T1DM and T2DM; however, this association was more pronounced in those with T2DM. Given that insulin deficiency is the primary cause of T1DM, while insulin resistance underlies T2DM, this finding suggests that the stronger correlations in T2DM may indicate a particular link between FABP4 and insulin resistance. Collectively, these results support that circulating FABP4 is closely associated with soluble TNFRs in individuals with metabolic diseases, suggesting a connection between FABP4 and TNF bioactivity, which influences processes such as lipolysis, insulin resistance, and metaflammation [21]. In the previously mentioned study, Lv et al demonstrated that FABP4 knockdown significantly reduced age-related increases in insulin, fasting blood glucose, and homeostasis model assessment of insulin resistance (HOMA-IR) in mice. Moreover, FABP4 knockdown normalized elevated circulating pyruvate levels. At the metabolic level, this intervention altered age-related changes in genes associated with insulin resistance by enhancing glycolysis and reducing gluconeogenesis [17].

Although FABP4 is primarily concentrated in adipose tissue, recent studies have identified its expression in other cell types, including placental trophoblast cells. FABP4 plays a crucial role in modulating immune homeostasis, lipid metabolism, and fetal development by targeting the placenta throughout gestation [7]. Evidence suggests a positive correlation between maternal BMI and circulating FABP4 levels, particularly in individuals with a BMI exceeding 25 [22]. These findings emphasize the strong relationship between elevated FABP4 levels and pregnancy-associated adiposity, indicating that FABP4 may serve as a valuable predictor of the severity of maternal obesity [23]. FABP4's influence on the pathophysiology of insulin resistance may be mediated by its suppression of peroxisome proliferator-activated receptor gamma (PPARγ), a key regulator of insulin responsiveness [24,25]. FABP4 promotes the ubiquitination of PPARγ, leading to its degradation via the proteasome pathway [26]. Studies indicate that mice with PPARγ disruption in myeloid cells are more prone to diet-induced obesity and insulin resistance. In pregnant women with excessive gestational weight gain, FABP4's suppression of PPARγ in visceral fat may contribute to reduced insulin sensitivity [26,27].

FABP4 expression is primarily regulated by hormones. It is well documented that insulin promotes the uptake and storage of fatty acids in adipocytes by upregulating FABP4. Studies have shown that insulin signaling pathways, particularly through PI3K/Akt activation, increase FABP4 production [28-30]. Additionally, glucocorticoids like cortisol enhance FABP4 synthesis, linking metabolic processes to stress responses [31]. There is a strong association between inflammation and FABP4, especially in the context of obesity. Recent studies indicate that pro-inflammatory cytokines, such as TNF-α and IL-6, significantly upregulate FABP4 expression in adipose tissue. These cytokines activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, which in turn promotes FABP4 transcription, suggesting that FABP4 may play a role in the inflammatory mechanisms underlying insulin resistance and metabolic syndrome [32]. Diet is a crucial regulator of FABP4 expression. Levels of FABP4 have been shown to increase in response to high-fat diets, particularly those rich in saturated fatty acids. In contrast, polyunsaturated fatty acids, such as omega-3 fatty acids, appear to suppress FABP4 production. Supplementation with dietary omega-3 has been found to reduce FABP4 levels, possibly by modulating peroxisome proliferator-activated receptor (PPAR) signaling pathways [14]. This dietary influence underscores the importance of dietary choices in managing metabolic health. Epigenetic processes, including histone modifications and deoxyribonucleic acid (DNA) methylation, also regulate FABP4 expression [33]. Certain lifestyle factors, such as diet and exercise, can alter the epigenetic markers on the FABP4 gene, influencing its expression and related metabolic effects.

Obesity in Pregnancy and its Metabolic Implications

Overweight and obesity have seen a notable increase in Europe in recent years, with incidence among women reaching 42.5% [34]. The latest global data indicate that 38.9 million pregnant women are overweight or obese, a burden that has significantly escalated over recent decades [35]. In 2018, the prevalence of overweight and obesity was 51.2%, with projections suggesting an alarming rise to 70% by 2030 [36]. The etiology of obesity can be divided into non-modifiable factors, which are relatively rare, and modifiable factors, which primarily account for the high obesity rates observed today. These modifiable factors include physical inactivity, excessive caloric intake, insufficient sleep, specific medications and medical conditions, and exposure to endocrine-disrupting chemicals

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[37]. Moreover, shifts in modern lifestyles and the widespread use of antimicrobial agents have reduced the diversity of the gastrointestinal microbiome across many populations in developed countries. Dysbiosis within the gut microbiome can lead to adverse effects, such as an imbalance between *Firmicutes* and *Bacteroidetes*, contributing to obesity and diabetes [38]. Maternal overweight and obesity are estimated to account for 23.9% of pregnancy complications [39]. Maternal obesity is a well-recognized risk factor for hypertensive disorders of pregnancy (HDP) [40]. Women with overweight and obesity are at a significantly higher risk of developing GDM and pregnancy-induced hypertension when compared to women of normal weight. Conversely, these risks were notably reduced among underweight women, while preeclampsia was observed to be more prevalent in women with overweight and obesity [41]. Similarly, GDM women with obesity demonstrated increased risks for macrosomia, cesarean delivery, gestational hypertension, and large-for-gestational-age (LGA) infants [42]. Hou et al revealed that ultrasound measurement of abdominal adipose tissue thickness could serve as a valuable predictor for GDM risk in pregnant women, independent of maternal BMI. A pooled analysis indicated that elevated abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) levels in early pregnancy are associated with a higher subsequent risk of GDM [43]. Despite these heightened risks, only approximately 10% of women who meet the BMI criteria for obesity develop preeclampsia (PE). It is hypothesized that obesity may contribute to the pathogenesis of preeclampsia. One investigation examined adipokine profiles unique to general adipose tissue, specifically adiponectin and leptin, among obese pregnant women with and without PE. In contrast to healthy pregnant women, obese pregnant women with PE were observed to have elevated leptin levels. Impaired cytotrophoblast migration and invasion of the uterine wall are among the earliest anomalies linked to PE, and elevated leptin levels have been associated with a reduction in cytotrophoblast proliferation. Adiponectin, on the other hand, enhances the production of vasodilator nitric oxide (NO) by stimulating endothelial nitric oxide synthase and exhibits anti-inflammatory effects through the inhibition of pro-inflammatory cytokine synthesis and release. The study found that obese pregnant women in the PE group were more likely to have lower adiponectin levels compared to those without PE [44].

In obese women, pregnancy brings about subtler metabolic changes alongside significant alterations in lipids and lipoproteins. Studies have shown that while gestational lipid metabolism changes occur in both lean and obese women, they are particularly pronounced in the latter. Between 16 and 36 weeks of gestation, all very-low-density lipoprotein (VLDL) particles rose by 1.5-3 standard deviations (SD), low-density lipoprotein (LDL) particles by 1-2 SD, and triglycerides by 2-3 SD, suggesting that these increases were 2-3 times greater in obese women than in controls [45]. Furthermore, obese women with GDM exhibit a distinct metabolomic profile compared to those without, including alterations in lipoproteins and their components in early and mid-pregnancy [46]. The composition of lipoproteins is known to influence cell membrane fluidity, and their phospholipid profile often mirrors that of in vivo plasma membranes. Protein activity and membrane composition, especially in hyperglycemia, are interlinked. Specific fatty acids, diglycerides (DG), and ceramides have been shown to activate serine kinases that impair insulin signaling, contributing to insulin resistance [46,47]. Another study linked GDM in obese women to elevated plasma concentrations of certain diglycerides [DG(32: 0)] and triglycerides [TG(48: 0), (50: 1), (50: 2)], containing fatty acids such as (16: 0), (16: 1), (18: 0), and (18: 1), aligning with increased de novo lipogenesis. Elevated levels of these lipogenesis-related lipids in pregnant women with obesity and GDM are also associated with higher measures of offspring adiposity [48]. As previously discussed, pregnancy-related obesity can impair glucose utilization and contribute to hypertensive complications. In one study, researchers examined the influence of glucose transporter type 4 (GLUT4) density, endothelial function, and vascular glucose uptake on agonist-induced vasoconstriction in the aortas of obese pregnant rats. The findings showed enhanced endothelium-independent vasoconstriction in the aortas of obese pregnant animals, which was notably diminished in the absence of glucose. Obesity significantly reduced GLUT4 expression in both maternal and fetal aortas, leading to increased vascular contractility during pregnancy. This heightened contractility was directly associated with glucose uptake by smooth muscle and inversely related to GLUT4 density [49]. Moreover, even with normal fasting and postprandial glucose levels, gestational weight gain (GWG) was negatively correlated with beta-cell function in a cohort of overweight or obese women. After adjusting for pre-pregnancy BMI, excessive GWG was associated with reduced insulin secretion sensitivity, likely due to the decline in insulin-sensitizing adipokine adiponectin and progressive insulin resistance with increased adiposity. High GWG can place added stress on already dysfunctional beta-cells, potentially compromising insulin secretion throughout pregnancy, particularly in metabolically predisposed pregnancies characterized by elevated adiposity. Even in the absence of GDM, excessive GWG was frequently linked to reduced beta-cell activity, which can elevate the long-term risk of developing T2DM [50]. Successful placental development and function in early pregnancy rely on proper trophoblast proliferation, differentiation, and fusion, processes that can be dysregulated in obese individuals. Recent research indicates that maternal obesity is associated with increased DNA damage in first-trimester villous cytotrophoblasts, and that DNA damage repair mechanisms may be insufficient to keep these cells in a proliferative state, thus leading to apoptosis [51,52]. Leonard et al found notable differences in immune and inflammatory

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profiles, specifically IL-6 expression, in the fetal brains of offspring from obese women compared to those of normal-weight mothers exposed to lipopolysaccharide (LPS). Gene expression patterns linked to maternal obesity were associated with pathways involved in white matter damage. Embryo brains from overweight mothers exhibited elevated levels of neuroinflammatory markers activated by bacterial endotoxins via intrauterine LPS exposure. These expression profiles suggest that maternal obesity, in conjunction with intrauterine inflammation, can heighten the risk of embryonic white matter damage [53]. Pre-pregnancy obesity and overweight have adverse effects on both maternal and fetal health. Obesity is known to induce significant changes in gene expression in maternal peripheral blood mononuclear cells (PBMCs), yet little is understood about how pre-pregnancy obesity affects immune cell gene expression during pregnancy. Gurung et al examined the gene expression profiles of PBMCs at 12, 24, and 36 weeks of pregnancy in women with normal and elevated pre-pregnancy BMIs. At 12 weeks of gestation, PBMCs from obese women showed increased expression of IL-6, IL1-β, and chemokine ligands like CCL3, CCL4, CXCL2, and CXCL8. The study found that women with higher BMIs exhibited elevated levels of C-C chemokine ligands 3 and 4 (CCL3 and CCL4), known to alleviate steatohepatitis, diet-induced insulin resistance, and glucose intolerance upon suppression. There was a significant difference in inflammatory gene expression between women with higher BMIs and those of normal weight at 12 weeks of pregnancy. Additionally, the authors identified a correlation between human milk oligosaccharides (HMOs) and adipocyte-related gene expression, suggesting that maternal obesity can alter HMO composition through maternal cellular signaling and can even preprogram this composition prior to lactation [54].

Human epithelial cells in the uterine endometrium have been observed to express FABP4, initially identified in the placental labyrinth, particularly within endothelial cells [55,56]. Throughout gestation, FABP4 targets the placenta, playing a significant role in lipid metabolism, immune homeostasis, and fetal growth. FABP4 expression has also been detected in various placental immune cells, including macrophages, dendritic cells, and natural killer (NK) cells, which are essential in shaping the immune environment at the maternal-fetal interface [59]. Serum FABP4 concentration has been identified as a specific biomarker for cardiovascular diseases and metabolic syndromes, with elevated levels observed in patients with PCOS and endometriosis. During pregnancy, FABP4 levels fluctuate across different gestational stages. Elevated maternal FABP4 levels have been associated with preterm delivery, GDM, PE, maternal obesity, and miscarriage. Conversely, a deficiency in mid-gestational FABP4 can impair placental and decidual development, resulting in nutrient insufficiency. These findings suggest that circulating FABP4 could serve as a biomarker for a range of maternal and fetal disorders [23].

The Role of FABP4 in Maternal Health

The concept of metabolic syndrome encompasses a cluster of diseases and organic abnormalities, primarily involving cardiovascular risk factors such as dyslipidemia, hypertension, insulin resistance, and central obesity [58]. Numerous studies have demonstrated a positive correlation between the presence of these metabolic syndrome components and elevated plasma levels of FABP4, suggesting its potential as a promising biomarker for metabolic risk [59]. Furthermore, significant evidence links increased plasma FABP4 levels with obesity-related conditions, including polycystic ovary syndrome (PCOS) and diabetes. Given the positive associations between FABP4, obesity markers (such as BMI and body fat levels), and insulin resistance, it is highly plausible that FABP4 is also involved in the pathophysiology of GDM. Moreover, in patients with GDM, high serum levels of FABP4 during the early postpartum period may contribute to a greater risk of developing T2DM and metabolic syndrome in the future [60]. This protein has also been recognized as a reliable predictive biomarker for cardiovascular diseases owing to its significant role in the proliferation and migration of smooth muscle cells and angiogenesis [61]. In a 12-year prospective study of 721 individuals (302 men and 419 women), Saito et al concluded that elevated circulating levels of FABP4 can serve as a predictor of cardiovascular mortality in the general population [16]. In the field of ophthalmology, Ohguro et al found that intraocular levels of free fatty acids and FABP4 were markedly elevated in patients with proliferative diabetic retinopathy and other retinal vascular diseases [6]. Further evidence of FABP4's utility as a biomarker was highlighted in a cross-sectional study by Rodríguez-Calvo involving 389 participants. The study indicated that the risk of liver injury, including liver steatosis, and markers of inflammation such as AST, ALT, and GGTP, are positively associated with elevated levels of FABP4 in metabolic patients at heightened cardiometabolic risk, as confirmed by both linear and logistic regression analyses [62]. Collectively, these studies underscore that elevated plasma FABP4 levels are significantly associated with increased metabolic risk. This connection emphasizes the importance of understanding the underlying mechanisms and solidifies FABP4's role as a crucial biomarker for predicting future metabolic risk.

Currently, due to the potential adverse outcomes for both mother and baby, it is essential to identify biomarkers that can help detect women at an elevated risk of metabolic complications early in pregnancy. Beyond well-established molecules like leptin and adiponectin, newer adipokines such as FABP4 have shown undeniable links to the pathophysiology of GDM [60]. Recent meta-analyses highlight FABP4 as a particularly promising biomarker for predicting GDM. Early identification of women likely to develop GDM allows for timely intervention and tailored management strategies [63-65]. A study by Francis

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et al revealed that serum FABP4 levels during early and mid-pregnancy were significantly associated with a higher risk of GDM, compared to a control group of healthy pregnant women [66]. Similarly, Dong et al demonstrated a correlation between FABP4 levels and insulin resistance in GDM cases [65].

Elevated FABP4 levels may also serve as biomarkers for other pregnancy complications beyond GDM. In particular, Eastwood et al found that elevated FABP4 levels in the second trimester could predict the risk of hypertension and preeclampsia among women with GDM, with an odds ratio (OR) of 1.15 (95% CI: 1.00-1.27, *P*=0.045) [14]. This finding aligns with results from Li et al, which indicated an OR of 1.136 (95% CI: 1.003-1.286, *P*=0.045) [67]. These recent studies underscore the potential role of FABP4 in diagnosing metabolic complications during pregnancy, particularly in women with GDM. However, further research is warranted to deepen our understanding and refine the use of FABP4 as a diagnostic tool.

In a healthy pregnancy, insulin sensitivity naturally decreases to accommodate the growing fetus's nutrient needs, allowing for increased glucose production. However, in pregnant women with metabolic disturbances, particularly those with metabolic syndrome and obesity, this balance is often disrupted. In GDM, the primary cause of insulin resistance is insufficient insulin production due to pancreatic β-cell dysfunction [20]. The immune response shifts significantly during pregnancy to maintain immunological harmony between mother and fetus, though often at a cost. This shift is reflected in elevated levels of inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-α, in maternal circulation [68]. FABP4, closely associated with adipocytes within adipose tissue, is particularly responsive during adipocyte differentiation [65]. It can also be expressed in macrophages, often through the activation of peroxisome proliferator-activated receptor γ (PPARγ) and sirtuin 3 (SIRT3), typically triggered by inflammatory stimuli. In GDM patients, inflammation is generally chronic and low-grade rather than acute [65]. FABP4 not only mediates PPARγ ligand delivery but also regulates the protein's level and activation [20]. Additionally, FABP4 facilitates the ubiquitination and proteasomal degradation of PPARγ. Consequently, preadipocytes lacking FABP4 display enhanced adipogenesis, suggesting that FABP4 modulates insulin responsiveness and adipogenesis by downregulating PPARγ [26]. Some studies even suggest that FABP4 exhibits insulinotropic potential similar to that of glucagon-like peptide-1 (GLP-1) [26]. Furthermore, elevated plasma FABP4 levels contribute to insulin resistance by inducing endoplasmic reticulum and oxidative stress [69]. High levels of FABP4 are often associated with visceral adiposity, including ectopic fat deposition in pancreatic islets, which can indicate an increased susceptibility to elevated insulin secretion in obese patients, particularly in pregnant women, as a means of maintaining glucose homeostasis [69]. Interestingly, a deficiency of FABP4 in macrophages has been shown to enhance PPARγ activity, which, while simplifying cholesterol efflux, results in reduced cholesterol levels [20]. Jin et al demonstrated that elevated serum FABP4 levels in early pregnancy could contribute to greater insulin resistance in later trimesters. FABP4 also impairs lipid trafficking and cellular response by altering the adipocytes' ability to absorb and retain free fatty acids, leading to increased insulin resistance and dyslipidemia, both of which are especially concerning during pregnancy [70].

Elevated plasma levels of FABP4 can significantly contribute to the severity of various complications during pregnancy. Notably, endothelial dysfunction, linked to increased FABP4 levels, is associated with a higher risk of preeclampsia [71]. Additionally, a moderately positive correlation has been observed between gestational weight gain and plasma FABP4 levels. In predictive models, FABP4 expression, alongside pre-pregnancy maternal weight and BMI, has emerged as a strong determinant of fetal birth weight [72]. It is also essential to highlight that women with GDM are at an elevated risk of premature membrane rupture and preterm birth [65]. A cohort study conducted by Li et al found that patients with elevated plasma FABP4 levels were more likely to develop hypertension and dyslipidemia. These patients were also more likely to require vascular intervention and had more severe peripheral artery disease compared to a control group with lower FABP4 levels [73]. Similarly, Zhao et al, in a multivariate analysis, confirmed the positive correlation between elevated serum FABP4 levels and the heightened risk of arteriosclerosis, relative to a control group [74]. However, the relationship between FABP4 levels and cardiovascular risk is complex. Dahlstrom et al found a 2.4-fold higher risk of cardiovascular disease in patients with lower FABP4 levels. These findings highlight discrepancies in previous studies, underscoring the need for further research to clarify the differences [75]. Additionally, a separate cohort study showed that even first-degree healthy relatives of obese or diabetic individuals had higher serum FABP4 levels than the general population [76]. In terms of diabetic retinopathy (DR), An et al demonstrated that high FABP4 levels in T2DM patients with mild non-proliferative DR could be predictive of the development of sight-threatening DR [77].

Potential Therapeutic Targets Involving FABP4

Due to the profound impact of FABP4 on metabolic health, developing effective strategies to lower its levels is essential. Given its correlation with components of metabolic syndrome, such as insulin resistance and diabetes, lifestyle interventions – particularly dietary changes and physical activity – are promising approaches. Spartano et al demonstrated the positive effects of a healthy lifestyle on preventing and treating

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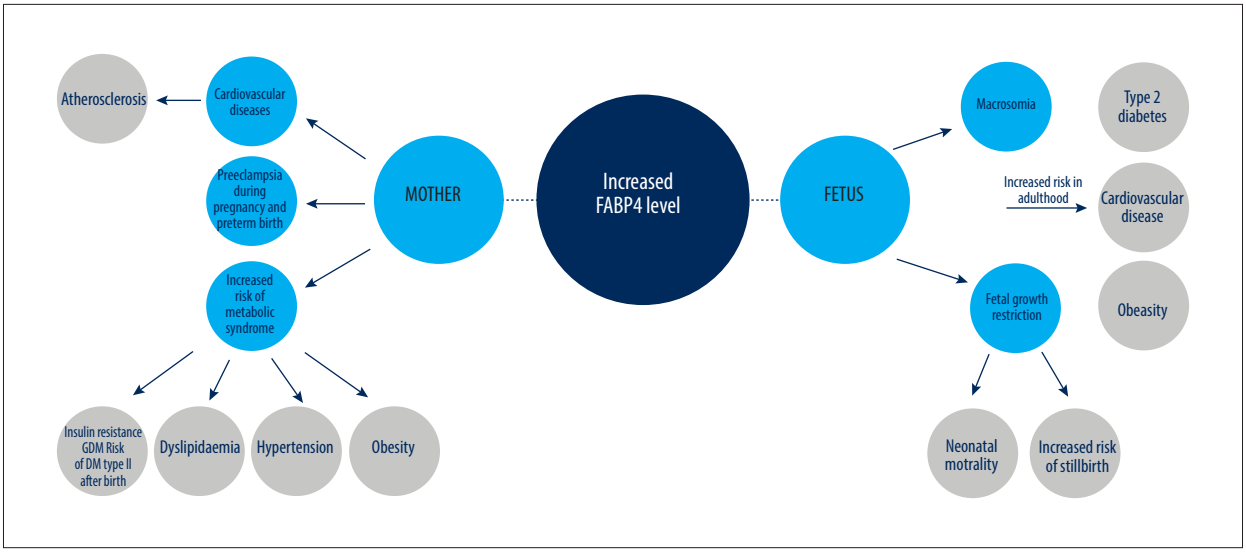

Figure 1. Possible complications for the mother and fetus resulting from increased level of FABP4.

metabolic diseases, with physical activity improving insulin sensitivity and promoting a favorable adipokine profile [78]. Notably, changes in activity levels are significant predictors of FABP4 modifications. Among patients with increased anaerobic activity, FABP4 levels were significantly lower compared to those with reduced activity. This change coincided with reductions in BMI, improvements in insulin sensitivity, and decreased levels of low-density lipoprotein cholesterol and apolipoprotein B [79]. However, lifestyle changes alone may not always suffice, and pharmacological interventions are often necessary. Several drugs known for treating related metabolic conditions have shown efficacy in reducing FABP4 levels. Metformin, for example, enhances carnitine palmitoyltransferase I (CPT-1) expression and limits palmitate-induced lipid accumulation in macrophages by inhibiting FOXO1-induced FABP4 transcription, thus mitigating metabolic complications [80]. Angiotensin II receptor blockers (ARBs) are also effective, reducing serum FABP4 levels and blood pressure by 8-20%. This efficacy is largely attributed to telmisartan, which selectively antagonizes the angiotensin II type 1 receptor, reduces PPARγ phosphorylation, and regulates glucose and lipid metabolism by promoting glucose uptake and improving insulin sensitivity [81]. Dipeptidyl peptidase 4 (DPP-4) inhibitors, such as sitagliptin, have shown a 19.7% reduction in FABP4 levels and contribute to lowering glycated hemoglobin (HbA1c) levels over the long term [82]. Omega-3 fatty acid ethyl esters, particularly eicosatetraenoic-acid (EPA) and docosahexaenoic acid (DHA), also play a role in reducing triglycerides and plasma FABP4 levels, with sustained effects on FABP4 expression and secretion in adipocytes [85]. In addition to lifestyle changes and traditional pharmaceuticals, monoclonal antibodies targeting FABP4 are emerging as promising therapeutic agents. A monoclonal antibody CA33 has shown high specificity in reducing fat mass and improving glucose metabolism and insulin sensitivity in hyperinsulinemic-euglycemic clamp studies on obese mice with high FABP4 levels, while exhibiting no effect on FABP4-deficient mice [84]. Another well-studied FABP4 inhibitor, BMS309403, is highly effective in reducing inflammation in adipose tissues and restoring glucose-insulin balance by reducing macrophage infiltration. This treatment also promotes PPARγ activation and inhibits ferroptosis, lipid peroxidation, and oxidative stress, both in vivo and in vitro [20,85]. Since the development of BMS309403, other molecules, such as quinoxaline, aryl-quinoline, and niacin derivatives, have been synthesized, broadening the scope of FABP4-targeted therapies [86]. While these molecules show significant potential, further research is essential to enhance the efficacy of strategies aimed at reducing FABP4 plasma levels.

FABP4 is a well-recognized contributor to numerous metabolic complications, posing particular risks during pregnancy. To safeguard the health of both mother and child, it is crucial to reduce elevated FABP4 levels using available methods. Lowering FABP4 levels during pregnancy may help to mitigate or even prevent serious complications such as miscarriage, preeclampsia, GDM, and preterm birth. Emerging evidence also suggests that reducing FABP4 can prevent metabolic complications linked to metabolic disorders and inflammation, with protective benefits extending to both the mother and fetus, and potentially even across generations (**Figure 1**) [23,25].

The Role of FABP4 in Fetal Health and Development

Several studies have reported a correlation between elevated maternal FABP-4 levels and an increased risk of macrosomia in fetal development. Macrosomia is defined as a birth weight

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exceeding 4000 g [87]. In a case-control study involving 77 placental tissues and 77 cord blood samples, researchers found significantly increased mRNA expression of several molecules, including FABP4, in newborns with macrosomia [88]. However, in a separate study, Francis et al did not observe an association between FABP4 and neonatal anthropometric measures, including birth weight at delivery [89]. Obesity and diabetes also increase the risk of fetal macrosomia [7]. Scifres et al demonstrated that FABP4 expression was elevated in the placentas of pregnant women with obesity and diabetes compared to obese women without diabetes or those of normal weight [7]. Another study, including 28 healthy controls and 26 patients with GDM, found higher FABP4 levels in the umbilical cord blood of newborns from mothers with GDM, though without a significant correlation with birth weight [90]. Furthermore, Yang et al analyzed placental tissues from 17 955 women and confirmed a correlation between FABP4 and GDM, particularly noting higher FABP4 levels in male fetuses with macrosomia born to obese mothers with GDM [87]. Stanirowski et al examined patients with type 1 diabetes and GDM, showing a correlation between placental FABP4 levels and heavier birth weights in mothers with type 1 diabetes. Importantly, they identified that, among various lipid transport proteins, only lipoprotein lipase (LPL) and FABP4 were significant predictors of fetal birth weight [72]. Evidence also suggests that elevated maternal FABP4 can influence fetal development by increasing the risk of FGR, defined as the inability of a fetus to achieve its genetically determined growth and developmental potential due to placental dysfunction, affecting 5-10% of pregnancies [91]. Bolluk et al conducted a study involving 83 pregnant women, revealing significantly higher median maternal serum FABP-4 levels in FGR cases compared to controls. Additionally, FABP-4 levels were higher in pregnancies with abnormal Doppler flow patterns compared to those with normal flow patterns [91]. In a study testing 80 cord blood samples, Papathanasiou et al reported increased FABP4 levels in preterm newborns compared to full-term neonates and significantly higher levels in FGR (58.70 ng/ml) and low gestational age (LGA) groups (62.90 ng/ml) compared to the adequate gestational age (AGA) group [92]. Moreover, Assumpcao et al demonstrated elevated FABP4 mRNA levels in the placentas of pregnancies with FGR compared to normal pregnancies, hypothesizing that this could result from reduced maternal intake of long-chain polyunsaturated fatty acids (LC-PUFAs). They noted lower concentrations of arachidonic acid (AA), docosahexaenoic acid (DHA), and the DHA/ALA ratio in erythrocytes of both mother and newborn in FGR cases compared to normal pregnancies, potentially stimulating the mRNA expression of proteins involved in placental lipid transfer [93]. In a study on 36 twin pairs, Shrey-Petersen et al found that FABP levels were significantly higher in the smaller of discordant dichorionic (DC) twins, while no significant difference was observed between monochorionic (MC) twins [94].

Transplacental Transfer of Fatty Acids and FABP4

Lipids are fundamental to fetal growth and development [7,88]. However, the exact mechanisms of lipid transport across the placenta remain incompletely understood [88]. Most free fatty acids (FFAs) circulating in maternal blood are bound to triglycerides, lipoproteins, albumin, VLDL, or chylomicrons [56]. These FFAs are subsequently released by the action of lipoprotein and endothelial lipases [72,95], facilitating their availability for placental transfer. Transport across the trophoblastic microvillous membrane can occur through diffusion or by binding to specific proteins, including fatty acid transport proteins (FATPs), fatty acid translocase (FAT/CD36), plasma membrane fatty acid-binding protein (FABPpm), and fatty acid-binding proteins (FABPs) [7,93]. Furthermore, maternal fatty acids that successfully cross the placenta activate nuclear transcription factors such as PPARs, liver X receptor (LXR), retinoid X receptor (RXR), and sterol regulatory element-binding protein 1 (SREBP-1) – which regulate lipid metabolism, placental lipogenesis, and the production of human chorionic gonadotropin (hCG) [95]. PPARs and hypoxic conditions additionally increase the expression of specific FABPs and fatty acid transport proteins [56,88]. In trophoblastic tissue, only FABP1, FABP3, FABP4, FABP5, and FABP7 have been identified [76]. Makkar et al investigated FABP4 expression in a mouse model, revealing its presence in the placental labyrinthine layer and maternal decidua. Previous research has indicated that FABP4, alongside FABP1, FABP3, FABP5, and FABPpm, is a predominant form expressed in human placental trophoblasts [56]. FABPs also play a regulatory role in fatty acid metabolism, influencing processes such as β-oxidation, eicosanoid synthesis, re-esterification into phospholipids and triglycerides, elongation, desaturation, release into fetal circulation, and placental tissue metabolism [91,93]. FFAs serve critical functions in cellular energy production, gene expression regulation, cell signaling, membrane synthesis, and storage. Interestingly, FFAs are also involved in angiogenesis within human placental trophoblast cells, mediated by molecules such as vascular endothelial growth factor (VEGF), angiopoietin-like protein 4 (ANGPTL4), FABPs, and eicosanoids. Insufficient placental angiogenesis or impaired trophoblast invasion of the maternal decidua and uterine spiral arterioles can lead to structural and functional placental deficiencies. These deficiencies can result in complications, including preeclampsia, FGR, spontaneous abortion, and other adverse effects on fetal growth and development [95].

Long-Term Consequences for Offspring

Fetal programming is a well-established paradigm that underscores the profound influence of the intrauterine environment on epigenetic modifications, gene expression, and metabolic

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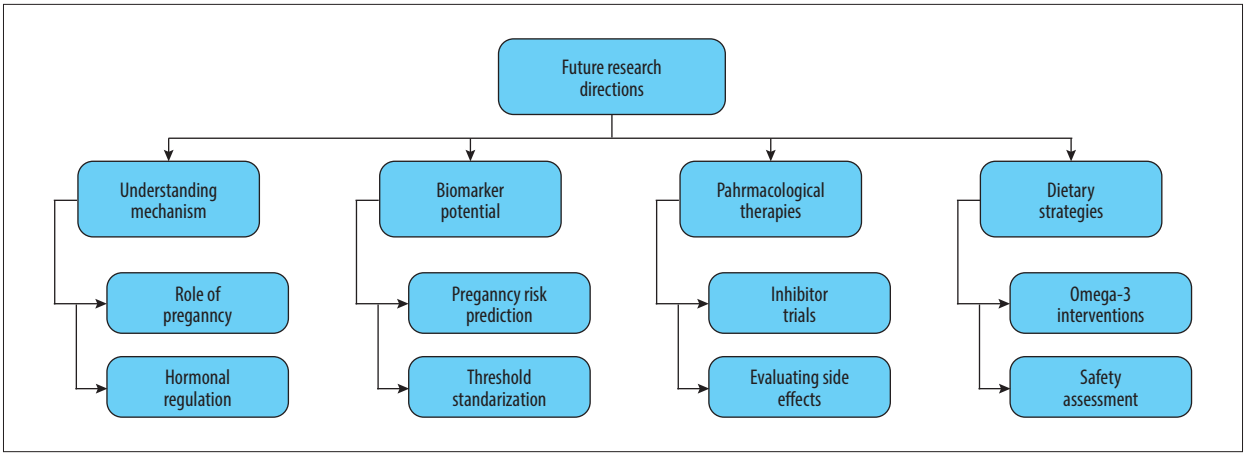

Figure 2. Future research directions.

signaling pathways [92,96]. During prenatal development, the fetus has heightened susceptibility to maternal and placental factors, which critically shape its physiological trajectory. It is well documented that these mechanisms can predispose offspring to a spectrum of metabolic disorders, including an elevated risk of obesity, type 2 diabetes, and metabolic syndrome. Fetal growth restriction (FGR) frequently arises as a consequence of placental insufficiency, which can stem from maternal complications such as preeclampsia or hypertension, as well as from inadequate maternal nutrition during gestation. This insufficiency is often linked to dysregulated nitric oxide synthesis, leading to compromised vascular endothelial integrity and an increased propensity for hypertension in later life [97]. Notably, studies have identified a correlation between elevated levels of fatty acid-binding protein 4 (FABP4) and markers of adiposity, suggesting a potential mechanistic link to heightened metabolic disease susceptibility [92,94,96]. The long-term ramifications of FGR extend beyond perinatal morbidity and mortality, encompassing an increased risk of adult-onset cardiovascular disease and other chronic conditions [93,98]. Empirical evidence suggests that both intrauterine growth restriction and excessive birth weight independently contribute to a heightened susceptibility to obesity, cardiovascular pathology, and type 2 diabetes in adulthood [88,92,99]. Moreover, elevated maternal FABP4 levels have been observed in cases of gestational diabetes, which can predispose offspring to macrosomia and its associated complications [7,72]. In summary, adverse health outcomes in offspring can arise as a consequence of fetal programming or perinatal complications linked to aberrant FABP4 expression, underscoring the intricate interplay between intrauterine conditions and long-term metabolic health.

Future Directions

It is hypothesized that, through its association with inflammatory processes and lipid metabolism, FABP4 plays a role in GDM and other metabolic disorders [65,100], making FABP4 a promising therapeutic target. The potential for FABP4 to serve as a biomarker in predicting GDM risk in pregnant women is under consideration. Studies indicate that women with GDM exhibit significantly elevated serum FABP4 levels compared to healthy women [20,59,65,101,102], with this increase particularly pronounced in the second and third trimesters of pregnancy [103]. However, these are currently theoretical concepts, which would require the development of methods to measure FABP4 in larger cohort studies before practical application. Defining precise FABP4 threshold values that correlate with specific pathological states would also be essential [23,64]. Beyond the mother's metabolic disorders, the impact of FABP4 on placental and fetal development should also be explored. Further studies could clarify whether FABP4 might also be predictive of long-term metabolic complications in offspring (**Figure 2**) [23,104].

Various approaches to modulate FABP4 levels through pharmacological and non-pharmacological means are currently under investigation. Among the pharmacological methods, the most promising is the use of FABP4 inhibitors, such as BMS309403, which block the binding of FABP4 to fatty acids [105]. Studies in animal models have shown that BMS309403 can reduce blood glucose levels and improve lipid metabolism, thereby alleviating diabetic symptoms. Additionally, the therapy led to a decrease in pro-inflammatory cytokines, including TNF-α and IL-6, suggesting an anti-inflammatory benefit of BMS309403 [20,65,106]. In a study involving mice on a high-fat diet, BMS309403 administration resulted in up to a 50% reduction in atherosclerosis symptoms, indicating potential for treating other metabolic disorders like atherosclerosis [93,94]. Unfortunately, despite its efficacy, adverse effects associated with BMS309403 therapy have been observed, including impaired cardiac contractility, which presents a major limitation and risk in its use. Thus, further studies are needed to assess the safety of long-term use, especially in pregnant women and

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individuals with cardiovascular diseases [107]. A non-pharmacological approach to modulating FABP4 levels includes dietary interventions. In one study, the administration of omega-3 fatty acid ethyl esters over 4 weeks significantly reduced FABP4 levels in dyslipidemic patients. The acids included EPA and DHA, and it is speculated that this reduction in FABP4 expression was due to decreased expression of the PPARγ2 and C/EBPα genes, which regulate adipocyte differentiation [83]. This line of research offers an innovative non-pharmacological strategy for regulating FABP4 levels, potentially avoiding the adverse effects associated with pharmacological inhibitors like BMS309403 [107].

A primary focus for future research may be elucidating the mechanisms of FABP4 action across various pathological states, especially during pregnancy. Our current understanding of the specific tissues contributing to elevated FABP4 levels during pregnancy remains notably limited. Additionally, it is crucial to thoroughly investigate how the complex hormonal changes occurring in a pregnant woman's body influence FABP4 expression. Given these uncertainties, it remains unclear whether elevated FABP4 levels are causative or a consequence of metabolic disorders, such as GDM [102]. Notably, many studies have relied on animal models, with limited data on the impact of these therapies in humans. Thus, further clinical studies are essential to evaluate the safety and efficacy of these therapies in pregnant women, as well as their potential impact on the fetus [23,65]. Research on FABP4 as a potential biomarker for GDM must also be expanded to assess its clinical relevance through larger cohort studies. Currently, no standardized FABP4 threshold values exist for diagnosing GDM or other metabolic syndromes influenced by FABP4 [64]. Investigating whether FABP4 levels could predict other pregnancy complications, such as preeclampsia, would be important for the diagnosis and treatment of these conditions, which often carry long-term health implications for both mother and child [108,109]. A promising direction for future investigation is the development of therapies aimed at modulating FABP4 levels. FABP4 inhibitors, such as BMS309403, have shown initial efficacy in animal models [65]. However, further clinical trials are necessary to evaluate these therapies' efficacy and safety in humans, particularly concerning long-term maternal and fetal health effects. As early reports indicate cardiovascular adverse effects with these therapies, it is vital to assess their suitability for use during pregnancy, especially given the sensitive nature of this period [94]. Moreover, non-pharmacological strategies for FABP4 modulation require further exploration. There is evidence that administering omega-3 fatty acids, including EPA and DHA, can reduce FABP4 levels in dyslipidemic patients, suggesting dietary interventions as an effective means of regulating FABP4. Future research should assess the safety and efficacy of this approach specifically in pregnant women [83].

Conclusions

Our analysis shows the critical role of FABP4 in regulating metabolic processes in pregnant women with obesity. FABP4 is essential for intracellular fatty acid transport, participating in lipid oxidation and fat storage in adipocytes. Research indicates that excess body fat and inflammation contribute to elevated serum FABP4 concentrations in women with higher BMI. Due to its functions, FABP4 is gaining attention as a potential biomarker for predicting metabolic complications in obese pregnant women. Its serum levels could serve as an early indicator of patients at risk for gestational diabetes and pregnancy-induced hypertension, enabling early intervention to reduce risk and improve health outcomes for both mother and child. The therapeutic potential of FABP4 in managing obesity-related pregnancy complications is also under investigation. Pharmacotherapy targeting FABP4 reduction is being considered, with promising benefits for enhancing insulin sensitivity, reducing inflammation, and modulating lipid metabolism. FABP4 inhibitors, such as BMS309403, have shown encouraging results, improving glucose balance and reducing hypertension risk. Additionally, dietary interventions, such as omega-3 fatty acid ethyl esters (eg, EPA and DHA), may complement therapy by preventing metabolic complications and supporting fetal health. Further research into FABP4 would deepen our understanding of its mechanisms and support the development of effective therapeutic strategies. Utilizing FABP4 as a biomarker and therapeutic target could substantially enhance healthcare quality for pregnant women, improving prevention of complications and optimizing pregnancy outcomes.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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