

Obesity in pregnancy: problems and potential solutions

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1. ABSTRACT

Recent years have witnessed an increase in the prevalence of maternal obesity during pregnancy in the United States and worldwide. Obese women have increased risks for gestational problems, such as diabetes, hypertension, and pre-eclampsia. Further, gestational obesity can adversely impact fetal growth and result in macrosomia, congenital abnormalities, and even fetal death. Measures must be taken to reduce maternal adiposity, as even a modest weight loss during pregnancy is beneficial for the health of mothers and fetus. Calorie restriction and moderate exercise are proven safe methods of stopping weight gain and/or inducing white-fat loss in these subjects. Additionally, therapeutic drugs that activate the AMP-activated protein kinase signaling pathway may be effective in ameliorating pathological conditions in obese patients. Finally, dietary supplementation with L-arginine or its effective precursor (L-citrulline) may be beneficial for managing overweight or obese gestating women by reducing white-fat accretion. Because of ethical concerns over human studies, animal models (e.g., sheep, pigs, baboons, rats, and mice) are warranted to test novel hypotheses with enormous biological significance and clinical applications.

2. INTRODUCTION

Overweight and obesity result from abnormal or excessive white fat accumulation in the body (1). The World Health Organization (2) and the National Institutes of Health (3) defined overweight as a body mass index (BMI, kg/m²) of 25 to 29.9, and obesity as a BMI of ≥ 30 . Further, obesity is characterized by BMI (kg/m²) into 3 classes: Class I (30-34.9), Class II (35-39.9), and Class III (≥ 40). Over the past few decades, obesity has become a troubling pandemic in developed nations and some developing countries (4,5). The obesity epidemic is not bound by societal factors, because adults and children from all groups of society are affected (5). The WHO estimated that nearly 1.6 billion adults worldwide are overweight and at least 400 million are obese (2,6). In the United States alone, 35% of adults are obese, and approximately two-thirds of the population is overweight (7). Similarly, in Australia, 16% of the adult population are obese and 49% are overweight (8). Obesity has been linked with multiple pathological conditions, such as insulin resistance, Type-2 diabetes, atherosclerosis, stroke, hypertension, and some types of cancer (including colon and breast cancers) (9). Consequently, obesity is claiming an increasing number of lives, and is a significant burden on the healthcare systems

of the world. In the United States alone, approximately 300,000 people die annually due to obesity related disease, and 6-8% of health care expenditures can be attributed to obesity. It is also disturbing that the current prevalence of Type-2 diabetes in China has reached nearly 10% for the adult population, which is even higher than that (6-7%) in the U.S. (10). The WHO (2,6) has declared that obesity is now so common that it is replacing the more traditional public healthcare concerns, including under-nutrition and infectious disease, as one of the most significant contributors to poor health.

The adverse effects of obesity may be more severe for women than for men and some of them could be sex-dependent (5). For example, obesity is associated with increased incidence of asthma in women but not in men (11). Further, women are more likely to be obese than men, as 34% of women are obese compared to 28% of men (12). Also, women are twice as likely as men to experience a major weight gain over a 10-year period. Additionally, women of reproductive age (25 to 34 years of age) have a greater risk of major weight gain as compared to either men of the same ages or older women (13). Between 1980 and 2004, the prevalence of obesity among women has doubled from 16.5% to around 33.2% (7,14).

Due to hormonal changes, women have 2 periods throughout their lives in which they are extremely susceptible to increased weight gains: pregnancy and menopause. Race plays a role in female obesity, as it has been determined that the problem of obesity is greatest in non-Hispanic black women (48.8%), as compared with Mexican-American (38.9%) and non-Hispanic white women (31.3%), according to the data of Centers for Disease Control and Prevention (5). Of particular interest is the vast number of women of reproductive age that are now becoming overweight (57%) or obese (30%) in the U.S. (5), compared with the previous values of 16.5-33.2% for the reported prevalence of obesity (15-19). This is particularly troubling for women, because pregnancy alone is a time of great stress on the body. Coupled with excess adipose tissue, the time during gestation could cause serious health consequences to the mother and the fetus.

3. WEIGHT GAIN DURING PREGNANCY

Weight gain during pregnancy is normally credited to increases in both lean and fat tissues of the mother and fetus as well as to the production of amniotic fluid (20). Pregnancy outcomes are known to be associated with gestational weight gain and over time, the ideal weight gain during pregnancy has been occasionally questioned and revised. In the past, gestational weight gain guidelines were restrictive due to concerns about gestational hypertensive disorders, labor and delivery complications, and weight retention after parturition (21,22). More recent attention has been focused on preventing low birth-weight infants, and the current guidelines provide weight gain ranges depending on pre-pregnancy BMI (23,24). These guidelines were recommended by the US National Academy of Sciences Institute of Medicine (20) to decrease the prevalence of low birth-weight infants and prevent

conditions such as macrosomia, caesarean delivery, and post-partum weight retention associated with gaining too much weight during gestation (23,24). Current recommended gestational weight gain is 11.2 to 15.9 kg for women with a normal BMI, 6.8 to 11.2 kg for overweight women, and more than 6.8 kg for obese women (20). After establishing the IOM recommendations with cutoff limits for each pre-pregnancy BMI class, current research has largely focused on testing the significance of association between these guidelines and important clinical outcomes (25). The majority of these studies found that weight gains within the IOM's ranges were associated with a better pregnancy outcome than weight gains outside these ranges (18,19,26,27).

A higher percentage of mothers gain more weight during gestation than the IOM recommendation. For example, DeVader *et al.* (28) found that more than 60% of the 94,696 women surveyed gained more than recommended in the IOM guidelines. It is particularly disturbing that more than 42% of mothers gained over 16 kg. Also, Kiel *et al.* (22) reported that 46% of obese women gained more than 11.3 kg throughout gestation. Results of another study indicated that greater than 70% of obese women gained more than the recommended amount of weight for obese pregnant women, and 21% gained greater than 16 kg, which would be considered excessive even for women of normal pre-pregnancy weight (29). Further, Butte *et al.* (30) found that overweight and obese pregnant women have a net accrual of fat mass equal to about 8.4 kg, as opposed to 5.3 and 4.6 kg in women with a low and normal BMI, respectively. The fat depot is localized in the intra-abdominal area (31). Such an anatomical distribution of white fat may be of metabolic significance because fat deposited in this area is more correlated with disease later in life than white fat in other sites of the body (32). Collectively, excessive weight gain during gestation is especially problematic particularly in view of the fact approximately one half of women begin gestation as either overweight or obese (5) and obesity along with excess gestational weight gain can further compound their pregnancy complications. Therefore, great care needs to be taken to make sure that all women, regardless of BMI, should have weight gains in pregnancy closely monitored.

4. MATERNAL COMPLICATIONS OF GESTATIONAL OBESITY AND/OR EXCESS WEIGHT GAIN

Gaining too much weight during gestation has been shown in numerous studies to cause multiple problems, such as macrosomia, insulin resistance, gestational diabetes, hypertension, pre-eclampsia, deep vein thrombosis, coagulopathies, delivery complications, and post-partum complications (28). These problems adversely impact both mother and fetus (Figure 1).

4.1. Insulin resistance and gestation diabetes mellitus

Excess white-fat mass increases the risk of glucose intolerance (1). Even in moderately overweight subjects, the occurrence of gestational diabetes mellitus

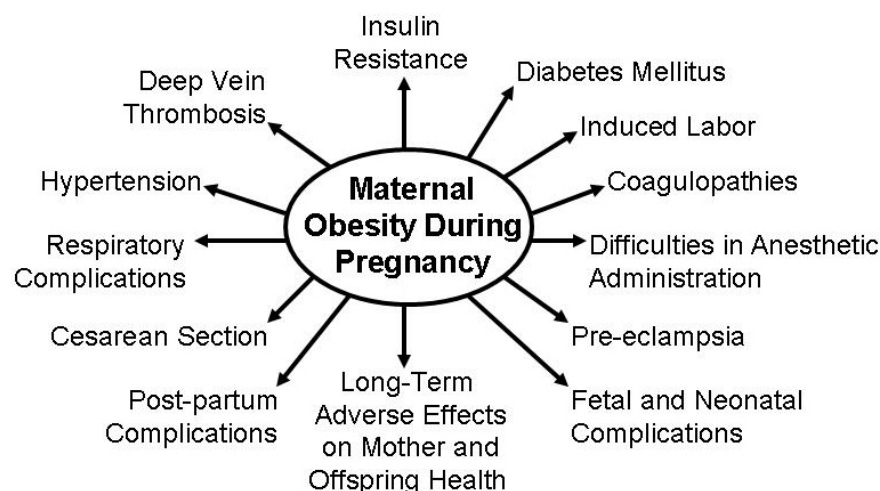


Figure 1. Multiple problems arising from maternal obesity during gestation. Excessive white adipose tissue in women negatively affects maternal and fetal health, pregnancy outcomes, and neonatal well-being. Maternal obesity also has long-term adverse effects on the health of both mother and offspring.

(GDM) is 1.8 to 6.5 times greater than in normal-weight subjects, while the incidence in obese subjects is 1.4-20 times higher (33). Pregnancy is already a time of insulin resistance even in the mother with a normal BMI, which may be a revolutionary mechanism to allow an adequate nutrient supply for the developing fetus. GDM is the result of an imbalance between pregnancy-induced insulin resistance (which is exacerbated by weight excess) and the inadequate compensatory secretion/action of insulin. Excess adipose tissue is a source of inflammatory cytokines and other metabolically active chemical mediators, such that obesity can be characterized by a state of low-grade chronic inflammation (34). Obese pregnant women have a higher concentration of C-reactive protein as well as higher fasting and postprandial concentrations of insulin in plasma than non-obese women. All of these factors lead to an increase in the incidence of GDM. Thus, the risk of GDM has been shown to increase with rising maternal BMI; overweight women have relative risk of 1.7, while obese women have a 3.6 times greater risk of GDM as compared to normal weight controls (35). Similarly, Schrauwers and Dekker (8) reported that overweight, obese, and morbidly obese women in gestation have a 6%, 8%, and 21.7% chance, respectively, of developing GDM as opposed to 1% for normal weight women. GDM is usually determined by an oral glucose tolerance test at week 24 of gestation, but in obese women, the condition can arise much sooner than that, and the condition remains unrecognized until it is too late for optimal management (36). GDM also predisposes a woman for type II diabetes mellitus later in life, and so proper therapy should be initiated as soon as possible to prevent future health risks associated with GDM.

4.2. Hypertension and pre-eclampsia

Excessive white fat also increases the prevalence of hypertension and toxemic syndromes during pregnancy (37). In obese women, the incidence of hypertension is increased by a factor of 2.2-21. Bhattacharya *et al.* (38) found a linear increase in gestational hypertension with

BMI, as well as an adjusted odds ratio of 3.1 for gestational hypertension in the morbidly obese. Gestational hypertension may be the result of decreased nitric oxide (a vasodilator) synthesis, and the bioavailability of this molecule in the vasculature is further reduced by obesity (39). A deficiency of NO can result in endothelial dysfunction and future cardiovascular disease (40).

Obesity, insulin resistance (such as in the form of GDM), and hypertriglyceridemia, along with endothelial dysfunction are all important factors in the pathogenesis of pre-eclampsia (41). Pre-eclampsia is a rapidly progressing condition that is manifested in maternal hypertension, oedema and proteinuria, and can result in death of the mother and fetus. Endothelial dysfunction reduces prostacyclin secretion and enhances peroxidase production that causes vasoconstriction and platelet aggregation. Of particular note, obesity has been identified as an independent and well-established risk factor for the development of pre-eclampsia (35,42,43). It is one of the major contributors to maternal morbidity and mortality worldwide, and has been associated with substantial health problems later in life (2). Large population studies have shown that obese women are two to three times more likely to develop pre-eclampsia than women of normal body weight (42,44). An increasing BMI results in an odds ratio of 7.2 for developing pre-eclampsia as opposed to normal BMI women (38). Even in studies which excluded women with GDM, obesity was still an independent risk factor for pre-eclampsia (45).

4.3. Deep vein thrombosis, coagulopathies and respiratory complications

Obese women are at greater risk for deep vein thrombosis, endometritis, postpartum hemorrhage, wound infections, urinary tract infections, and prolonged hospitalization associated with delivery complications (46). Pregnancy is a hypercoagulable state, associated with increases in the plasma concentrations of coagulations

factors, decreases in protein S, and inhibition of fibrinolysis, resulting in a 5-fold increase in risk for venous thrombosis (47,48). Obesity further increases the risk of thrombosis events by promoting venous stasis, increasing blood viscosity, and promoting activation of the coagulation cascade (41). White adipose tissue secretes numerous “adipokines”, including TNF- α , IL-6, and leptin (32). These peptides and non-peptide compounds, which are involved in cardiovascular homeostasis, can slow clot degradation and result in a furthered prothrombic state. Because obesity is characterized by an excess of white adipose tissue, circulating levels of chemical mediators produced by this tissue are elevated. This can place obese pregnant women at an increased risk for developing deep vein thrombosis, blood clots, and other thromboembolic complications.

Also of interest is the occurrence of respiratory complications in obese pregnant women. Excess weight causes a reduction in thoracic-wall compliance and increases airway resistance (37). Sleep-disordered breathing and snoring are fairly common in pregnancy, and women with higher BMI and increasing neck circumference during pregnancy have higher sleep apnea scores (49).

4.4. Delivery complications

Obesity in pregnancy can result in numerous delivery complications. It could be argued that these women have higher incidences of delivery complications due to underlying medical conditions associated with their weight. Callaway *et al.* (50) found that associations between increasing BMI and poor delivery outcomes were still present after adjustment for the presence of other conditions such as GDM. Several studies have evaluated the effect of obesity on preterm delivery, and most have concluded that the risk of preterm birth is not increased (41), and one study even found that the risk actually decreases in obese versus normal weight women (6.2% and 11.2%, respectively) (51). However, obese women are more likely than overweight and normal weight women to progress beyond term, but the difficulty in determining start of gestation in these women may mean that the phenomenon is an artefactual association (41). Obese women have a higher rate of induced labor and more cesarean sections than normal weight women. For example, adjusted mean odds ratios for cesarean section were 1.50, 2.02, and 2.54, respectively, for overweight, obese, and morbidly obese women (50). Bhattacharya *et al.* (38) also reported that the frequency of induced labor increased with rising BMI, such that a normal weight woman had an odds ratio of 0.8, while obese women were at 1.8. Further, both elective and emergency cesarean sections were increased in the morbidly obese group. Another study found that approximately one in two severely obese women were delivered by cesarean section and each one-unit increase in pregravid BMI increased the risk of a surgical delivery by 7% (52). Commonly reported reasons for surgical delivery included cephalopelvic disproportion, failed cervical dilatation, fetal distress, and risk of shoulder dystocia. Additionally, obesity in pregnancy is associated with more difficulties with anesthetic administration. Difficulties in

inserting epidural catheters include correct positioning of the patient, midline and epidural space identification, and dislodging the catheter (37). However, regional anesthesia seems to be the preference for obese women, as intubation of these women can be difficult, and a rapid desaturation and an increased risk of aspiration is associated with obese women during anesthesia (52).

4.5. Post-partum complications

Excessive weight gain during pregnancy and high prepregnancy weight are important predictors of long-term weight change and higher BMI later in life (41,53). Scholl *et al.* (54) found that excessive gestational weight gain resulted in a 12% increase in weight from prepregnancy at 6 months postpartum, and retained approximately 40% of that excess weight. This is in comparison to women who gained the recommended weight or who tended to weight only 5% more than prepregnancy weight postpartum. Further, women who have higher prepregnancy weights are at risk for substantial postpartum weight retention. For example, Soltani and Fraser (55) found that the majority of obese women were heavier 6 months postpartum than they were early in their pregnancy. Keeping an excessive weight places these women at greater risks for further complications in future pregnancies as well as higher risks for cardiovascular disease, type II diabetes, atherosclerosis, and the metabolic syndrome.

5. FETAL AND NEONATAL COMPLICATIONS

Maternal obesity is a risk for the high incidence of fetal distress, stillbirths, and neonatal deaths (24). A higher maternal BMI is associated with an increased odds ratio of meconium aspiration, fetal distress, and low Apgar score (56). Further, the Centre for Maternal and Child Enquiries (CAMCE) dataset indicated that almost one half of the stillbirth/neonatal deaths were associated with excess maternal weight (57). Huang *et al.* (58) reported that the factor most closely associated with unexplained fetal death was increased prepregnancy weight. Consistent with this finding is the fact that obesity was associated with a five-fold increase in the rate of stillbirths with histological placental dysfunction in the 1998-2001 Danish National Birth Cohort (59). The mechanism of fetal compromise has not been determined and likely involves a plethora of factors, including placental insufficiency, relative fetal hypoxia, and the dysfunction of fetal organs (60).

Maternal obesity is a well-recognized risk factor for fetal macrosomia: birth weight greater than 4 kg. Multiple studies have shown strong associations between maternal obesity and macrosomia (44,45,60). In agreement, Bhattacharya *et al.* (38) found that macrosomia was more common in obese and morbidly obese groups with odds ratios of 1.9 and 2.1, respectively. Macrosomia can also cause its own set of complications. Fetal overgrowth brings about an increased risk of shoulder dystocia, birth injury, and neonatal death, which can further lead to delivery complications in the mother and an increased risk of perineal trauma, chorioamnionitis, or postpartum hemorrhage (61). The mechanism by which obesity affects neonatal birth weight is unclear. However, it is thought to

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include obesity-related insulin resistance, in which the elevated insulin levels signal for rapid fetal growth, and genetic factors (62). With the recent interest in the field of epigenetics and the developmental origins of health and disease hypothesis (Barker Hypothesis), much more knowledge will be learned as to the genetic mechanisms of how obesity affects fetal growth.

Maternal obesity is another significant risk factor for neonatal hypoglycemia (50) and congenital abnormalities (33,41). For example, adjusted mean odds ratios for low concentrations of glucose in plasma were 0.78, 2.57, and 7.14, respectively, for infants born to overweight, obese, and morbidly obese women (33). Additionally, data from the National Institute of Neurological and Communicative Disorders and Stroke showed an increase of major congenital abnormalities by 35% and 37.5%, respectively, in overweight and obese women (16). The most common abnormality seen is neural tube defects, specifically spina bifida. Odds ratios for neural tube defects range from 1.8 to 3 depending on the degree of maternal overweight (33). Because neural tube defects are typically associated with a deficiency of folic acid in the mother, it has been speculated that there is potentially a decrease in the absorption of dietary folic acid by obese women. However, these data are controversial (62). Other birth defects associated with maternal obesity are increased risks for omphalocele and cardiac dysfunction (63), cryptorchidism in male infants, and fluctuating dental asymmetry (an indicator of developmental destabilization) (64,65). Hendler *et al.* (66) reported that the rate of suboptimal visualization of fetal cardiac and craniofacial structures increased by 37% and 43% in obese women, respectively, when compared with normal-weight counterparts. Similar studies have shown that these affected structures include the heart, umbilical cord and spine, which are all known sites of obesity-related deformities (67).

6. OBESITY MANAGEMENT DURING PREGNANCY

6.1. Calorie restriction

Chronic negative balance between energy intake and expenditure always results in weight loss (1). Some experts believe that losing weight during pregnancy due to calorie restriction is inadvisable for women (37). However, Kiel *et al.* (22) reported that if greatly obese women lost 0 to 9 pounds, the risk of unfavorable pregnancy outcomes was minimal. Further, Artal *et al.* (68) found that birth weights were more likely to be in the normal range among infants born to obese women who either lost some weight or did not gain weight from the time of an obesity intervention to delivery. Importantly, such a management reduces the percentage of small and large for gestational age infants.

There is a scarcity of information regarding effects of obesity management either via calorie reduction or other means during pregnancy on both short-term and long-term maternal and fetal outcomes. Severe caloric restriction ($\geq 50\%$ calorie restriction) has been found to

increase ketonuria and ketonemia in pregnant women, which can lead to impaired mental development of the fetus (69). However, a 33% reduction in calorie intake has been recommended to control weight gain while not leading to ketosis (70). When energy intake is reduced, it is important that pregnant women be provided with adequate amounts of high-quality protein, vitamins, minerals from diets.

6.2. Exercise

Lack of physical exercise increases the risk for excessive fat gain during pregnancy (71,72). Thus, exercise has been noted to be an effective treatment option in improving outcome of pregnancy. There are reports that exercise do not adversely affect birth weight and that vigorous exercise may even beneficially reduce birth weight of infants born to obese mothers by up to 400 grams (71). Interestingly, measures of physical activity have been observed to be reduced for some women during pregnancy, possibly due to the belief that all forms of exercise in pregnancy are contraindicated (72). However, exercise is now reviewed to be safe in pregnancy for both maternal and fetal well-being (24). One factor that may have implications for fetal development and health may be the type of exercise performed. For example, the risk of uterine contractions (and thereby adverse effects on the fetus) may be increased by lower-extremity exercise, whereas upper body exercise results in no uterine contractions (72). Compelling evidence shows that appropriate exercise of pregnant mothers can greatly benefit both maternal and fetal well-being.

6.3. Pharmacological intervention

One obesity management method that is of possible benefit is the use of pharmaceuticals to reduce weight. A potential enzyme target is AMP-activated protein kinase (AMPK). AMPK is considered a master switch, regulating key proteins in metabolic pathways known to control fatty acid and glucose oxidation in the liver and skeletal muscle, as well as lipolysis in adipocytes (73). Because skeletal muscle and adipose tissue are the main sites of energy utilization, finding ways to modulate AMPK activity in these tissues may play a significant role in energy homeostasis and lead to reduction of white fat. One currently available activator of AMPK is the experimental drug 5-aminoimidazole-4-carboxamide-1- β -D-ribofuranoside (AICAR). This synthetic substance is an adenosine analogue that can be absorbed into intact hepatocytes, adipocytes, and skeletal muscle. Once phosphorylated, AICAR mimics the effects of AMP on AMPK, thereby activating this regulatory protein (74). AICAR has been used in numerous studies involving diet-induced obese mice, genetically obese mice, and diabetic rats (75). Overall, a consistent observation from these studies of nonpregnant animals is that chronic AICAR administration has a strong anti-lipogenic effect by increasing expression of key factors that inhibit adipocyte differentiation (e.g., PPAR α , PPAR γ , and PGC-1 α). Further, AICAR suppressed fatty-acid uptake and promoted fatty-acid oxidation in white adipose tissue (76). This provides novel evidence that AICAR, through AMPK activation, can remodel white adipose tissue to function in reducing white fat. One negative effect observed, however,

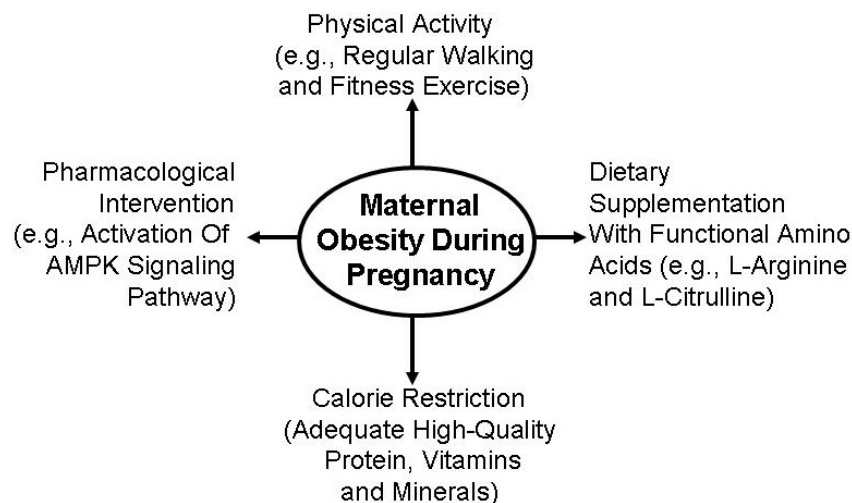


Figure 2. Means to ameliorate adverse effects of maternal obesity on pregnancy outcome. Excessive white adipose tissue in women contributes to multiple health problems for both mother and fetus. A combination of decreasing energy intake and increasing energy expenditure is an effective strategy to reduce obesity in pregnant women and improve pregnancy outcome.

is the alteration of the blood lipid profile in both normal and genetically obese mice. For example, Song *et al.* (74) found that in AICAR-treated obese rats, plasma levels of non-esterified fatty acids (NEFA) were increased, probably attributable to increased lipolysis in adipocytes. At present, little is known about long-term administration of AICAR on pregnancy outcome in obese animals or humans. In the future, tissue-specific and pathway-specific activators of AMPK could be developed to treat maternal obesity during gestation, while minimizing adverse effects on the blood lipid profile.

6.4. Supplementation with functional amino acids

Instead of using drugs, nutrients, particularly amino acids, may play a significant role in prevention and treatment of obese subjects during pregnancy, as reported for nonpregnant animals (77). As precursors for the synthesis of physiologically important substances, amino acids have versatile roles in the maintenance of whole-body homeostasis (78). Of particular interest, L-arginine, L-cysteine, and glycine are substrates for the generation of NO, CO, and H₂S (gaseous signaling molecules) in cells, respectively (79,80), whereas taurine is a potent antioxidant (78). Because obese or diabetic subjects often have vascular dysfunction (40), modulating the arginine-NO (a major vasodilator) pathway may be a promising therapeutic means for the management of overweight or obese women before and during pregnancy (81,82). Notably, dietary supplementation with L-arginine has been reported to reduce obesity in Zucker diabetic fatty rats (a Type-2 diabetic animal model) (83,84), diet-induced obese rats (85,86), growing-finishing pigs (97-99), and obese humans with Type-2 diabetes (90). Besides increasing cAMP concentrations (77) and activating the mTOR signaling pathway (91-93) in insulin-sensitive tissues, L-arginine acts in many of the same ways as AICAR, such as increasing the activities of AMPK and other proteins that stimulate fat and glucose oxidation (83,94). Additionally, Jobgen *et al.* (86) found that high fat feeding to diet-induced obese rats

altered gene expression in white adipose tissue, including decreases in mRNA levels for AMPK and antioxidative proteins, whereas arginine supplementation attenuated these adverse affects. Furthermore, arginine enhances mitochondrial biogenesis and the development of brown adipose tissue (77), which plays an important role in oxidizing fatty acids and glucose in animals (1). Enteral or parenteral administration of L-arginine or its effective precursor (L-citrulline) is safe and effective in increasing circulating levels of arginine in both mother and fetus (95-97). Therefore, we propose that supplementation with L-arginine or L-citrulline could result in beneficial effects on improving pregnancy outcomes in overweight or obese mammals (including women, pigs, sheep, and rats). Future research is warranted to test this novel and exciting hypothesis.

7. CONCLUDING REMARKS AND PERSPECTIVES

The current obesity epidemic is the major public health problem worldwide, which adversely affects an increasing number of pregnant women. Growing evidence shows that maternal obesity negatively impacts fetal growth and development as well as postnatal metabolism and health in offspring. However, little is known about effects of maternal obesity before and during gestation on the post-partum health of mothers. Likewise, there are no standard guidelines for the weight management of obese pregnant women to optimize maternal and fetal health. In addition to exercise and AMPK activators, attractive strategies to improve pregnancy outcome in obese mothers could include a global reduction of energy intake and dietary supplementation with L-arginine (Figure 2). These nutritional means can enhance the mobilization of maternal fat store, ameliorate oxidative stress, and improve the metabolic profile in the conceptus. Because of ethical concerns over human studies, animal models, which include sheep (98-102), pigs (103), baboons (104) and

rodents (86,75), play an important role in developing safe and effective means to treat obesity in gestating women.

8. ACKNOWLEDGEMENTS

This work was supported, in part, by grants from National Institutes of Health (1R21 HD049449), the USDA National Institute of Food and Agriculture (2008-35206-18762, 2008-35206-18764, 2008-35203-19120 and 2009-35206-05211), Texas AgriLife Research (H-8200), National Natural Science Foundation of China (u0731001, 30810103902 and 30928018), the National Basic Research Program of China (No.2004CB117503), and the Thousand-People-Talent program at China Agricultural University. The authors thank Ms. Frances Mutscher and Mr. Gregory Fritz for assistance in manuscript preparation.

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Abbreviations: AICAR, 5-aminoimidazole-4-carboxamide-1- β -D-ribofuranoside; AMPK, AMP-activated protein kinase; BMI, body mass index; GDM, gestation diabetes mellitus; IOM, Institute of Medicine; NEFA, non-esterified fatty acids

Key Words: Obesity, Brown Adipose Tissue, Metabolism, Uncoupling Protein, Adipocyte, Arginine, Nitric Oxide, Thermogenesis, Review

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