Obesity and Antiphospholipid Syndrome: A Particular Challenge in Pregnancy

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ABSTRACT

Obesity is associated with a broad spectrum of chronic diseases, as well as cardiovascular diseases, such as diabetes, dyslipidemia, insulin resistance and hyperglycemia. Obesity during pregnancy is of major concern due to the well-known risk factors for both the mother and the child. Complications in pregnancy include recurrent miscarriages, gestational diabetes, hypertensive disorders, thromboembolism, and stillbirth. Additionally, maternal obesity seems to have long-term consequences for offspring, predisposing or “programming” them to the development of metabolic disease in adulthood. Antiphospholipid syndrome (APS) is an autoimmune disease and is characterized by the presence of antiphospholipid antibodies (antiphospholipid antibodies/ACLA, lupus anticoagulans/LA and ß2-glycoprotein) in the maternal circulation. These antibodies are associated with arterial and/or venous thromboses and with adverse obstetric outcomes such as recurrent fetal loss, Preeclampsia (PE), Intrauterine growth restriction (IUGR) and Intrauterine fetal death (IUFD).

Obesity and APS are both chronic diseases with similar, even long-term consequences for mother and child; a co-occurrence of obesity and APS in pregnancy worsens the situation; the use of novel therapeutical tools should be therefore encouraged. A better understanding of the complex interactions between endothelial dysfunction and obesity and APS should be further investigated. Obese women with known APS should be counselled before conception not only about potential obstetrical complications as well as the long-term consequences for the offspring, but also about these important life-style modifications. This review will provide an overview of obesity and APS in pregnancy and will discuss endothelial dysfunction as mechanism for adverse obstetric outcome in these chronic diseases.

KEYWORDS: Obesity; Pregnancy; Antiphospholipid syndrome; Endothelial dysfunction.

ABBREVIATIONS: APS: Antiphospholipid syndrome; PE: Preeclampsia; IUGR: Intrauterine growth restriction; IUFD: Intrauterine fetal death; BMI: Body Mass Index; RAAS: Renin-angiotensin-aldosteron system; APS: Antiphospholipid syndrome; SLE: Systemic Lupus Erythematodes; PAPS: Primary APS; NO: Nitric Oxide; ET-1: Endothelin-1; EDHF: Endothelium-derived hyperpolarizing factor; NOS: Nitric Oxide Synthase; ADMA: Asymmetric dimethylarginine; DDAH: Dimethylarginine dimethyl-aminohydrolase; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic.

INTRODUCTION

Obesity is a multifactorial chronic disease, which is characterized by an accumulation of fat in the body. Obesity has dramatically increased in both developed and developing countries in recent times. It is defined by the Body Mass Index (BMI). BMI is weight in kilograms divided by height in meters squared (kg/m²). Obesity is associated with a broad spectrum of chronic diseases, as well as cardiovascular diseases, such as diabetes, dyslipidemia, insulin resistance and hyperglycemia and degenerative joint disease, obstructive sleep apnea, gastrointestinal reflux, non-alcoholic fatty liver and certain types of cancer.
OBESITY IN PREGNANCY

Obesity during pregnancy is of major concern due to the well-known risk factors for both the mother and the child.

Pregnancy complications may arise from early gestation on, such as the increased risk of spontaneous, even recurrent abortions. Lashen, et al. described an odds ratio for miscarriages of 1.2 (95% CI 1.01 to 1.45) for obese pregnant women, additionally the authors revealed an increased risk for recurrent miscarriages.11 Unfortunately this increased risk has also been described in vitro fertilization therapy.12

Gestational Diabetes is a classical and not surprising consequence of obesity in pregnancy. Weiss, et al. demonstrated in a cohort of 16, 102 women, that the odds ratio for obese women to develop gestational diabetes is 2.6 (95% CI 2.1 to 3.4) and for morbidly obese women is 4.0 (95% CI 3.1 to 5.2).13

Another complication is the increased risk of macrosomia. The likelihood of delivering an infant weighing more than 4000 g was 1.7 times (95% CI 1.4 to 2.0) greater for obese and 2.0 times (95% CI 1.5 to 2.3) greater for morbidly obese women. The odds of delivering an infant weighing more than 4500 g was 2.0 times (95% CI 1.4 to 3.0) and 2.4 times (95% CI 1.5 to 3.8) greater for obese and morbidly obese patients, respectively.14

One important consequence of macrosomia is shoulder dystocia, a rare, but severe complication.15 Although fetal macrosomia is a risk factor for shoulder dystocia, the absolute risk of a severe shoulder dystocia associated with permanent impairment, or death, remains low.15 When the sensitivity and specificity of ultrasound to predict a birth weight >4500 g are included, it is estimated that 3695 non-diabetic women would require caesarean section to prevent a single case of permanent brachial plexus injury due to shoulder dystocia.16

It is a common fact that the rate of caesarean sections as mode of delivery is higher in obese women. Dietz, et al.17 analyzed 24, 423 nulliparous women stratified by pre-pregnancy BMI and pregnancy complications. The caesarean section rate was 14.3% for women with a BMI b19.8 kg/m² and 42.6% for women with a BMI ≥35 kg/m². This significant increase might be due to the fact that the first stage of labour is more often prolonged in obese women.

Another problem is the increased rate of especially postoperative complications in obese women, including blood loss >1000 ml, prolonged operative time, increased rate of postoperative wound infections and endometritis, and need for vertical skin incision.1819

Postoperative infections are even increased in those obese women who have elective caesarean sections with prophylactic antibiotics.20

Hypertensive disorders in pregnancy might also be due to maternal obesity. Robinson et al evaluated in their retrospective study over 15 years (1988-2002) an association of obesity and hypertensive disorders in pregnancy. The authors compared women whose weight was 55 to 75 kg with those whose weight was >90 kg. Compared with the normal weight group, the odds ratio of pregnancy induced hypertension for women with weight 90-120 kg (moderate obesity) was 2.38 (95% CI 2.24 to 2.52). The odds ratio for the group with women >120 kg (severe obesity) was 3.00 (95% CI 2.49 to 3.62). Severe forms of hypertensive disorders in pregnancy, such as preeclampsia and HELLP-Syndrome are also associated with obesity.

For the moderate obesity group the odds ratio of severe pregnancy induced hypertension, including HELLP syndrome, was 1.56 (95% CI 1.35 to 1.80) and for the severe obesity group was 2.34 (95% CI 1.59 to 3.46). These findings have been confirmed by others.14

Interestingly, the most prevalent risk factor for unexplained stillbirth is prepregnancy obesity.2122 The mechanisms suggested for increased still-birth risk in the obese woman might be a decreased ability to perceive a reduction in fetal movement, as well as hyperlipidemia leading to atherosclerosis affecting placental blood flow, and increased snoring and sleep apnea associated with oxygen desaturation and hypoxia.23

In addition, epidemiological evidence and data derived from animal models have demonstrated that maternal obesity has long-term consequences for offspring, predisposing or “programming” them to the development of metabolic disease in adulthood.24 More and more literature demonstrates that the utero environment is a predictor of future neonatal, child, and adult health.

Several studies describe an increased risk of obesity, diabetes mellitus and hypertension in the offspring.2529 The risk of thromboembolism is not surprisingly increased in obese preg-
OBESITY AND INFLAMMATION

In contrast to the “normal” inflammation, which has rather an acute character and is the response to injury or infection, the inflammation in obesity is chronic and is characterized by abnormal cytokine production, increased levels of adipokines such as CRP, IL-6, IL-18, TNFα, Angiotensin II, and leptin, as well as activation of inflammatory pathways.31 According to literature, maternal obesity is associated with metabolic inflammation, characterized by elevated adipose tissue and systemic proinflammatory cytokine levels and adipose tissue macrophage accumulation.32,33 These inflammatory processes are involved in vascular reactivity, thrombogenesis, angiogenesis, insulin sensitivity, and sympathetic nervous system.34 Additionally, these changes even affect the placenta, suggesting that maternal obesity exposes the fetus to an inflammatory environment during development.35 In animal models, maternal obesity has been shown to induce fetal inflammation which can result in promotion of adipogenesis and increased adiposity in offspring.36

ANTIPHOSPHOLIPID SYNDROME (APS)

The antiphospholipid syndrome (APS) is an autoimmune disease, which is defined by clinical and laboratory criteria.37 APS occurs isolated as primary APS or combined with other autoimmune diseases, such as Systemic Lupus Erythematoses (SLE) or Raynaud disease.37

The clinical manifestations might affect various organs and/or tissues; based on these manifestations one can divide between the thrombotic APS with the occurrence of arterial, venous or small-vessel thrombosis and the obstetric APS with a broad spectrum of pregnancy complications, including recurrent abortions, preeclampsia and placental insufficiency with consecutive intrauterine growth restriction, as well as otherwise unexplained intrauterine fetal death.

The laboratory criteria are defined by the presence antiphospholipid antibodies (aPL) in the maternal circulation. Lupus coagulants is an immunoglobulin (usually IgG, IgM, or both) that binds to phospholipids and proteins associated with the cell membrane. Anti-cardiolipin antibodies (ACLA) are acquired antibodies (IgG, IgM and/or IgA) that react against negatively charged cardiolipin. B2-Glycoprotein-1 (B2GP1) is present on the surface of trophoblastic cell membranes and has been added to the criteria in 2006.38 The presence of aPL is not only essential for the diagnosis of APS, it leads to the thrombotic and obstetric manifestations via various pathways. API activate platelets and endothelial cells, inhibit fibrinolysis and interfere with the protein C pathway in patients with thrombotic APS.

Another mechanism for thrombosis has been reported to be an involvement of a defective function of Annexin V, a plasma protein, which has an antithrombotic character.39 In obstetric APS, aPL impair placenta, decreases trophoblast proliferation and invasion. Complement activation is essential for both thrombotic and obstetric APS.39,40 The complement system is suppressed in normal pregnancy.36 In pregnancies with APS, aPL bind to trophoblast cells and activate complement system (C3a und C5a) with consecutive thrombosis and pregnancy loss. It has been suggested that local complement activation causes impaired trophoblast invasion and endothelial damage.41,42

Another interesting approach is the theory that the inflammatory status in obese patients might induce antibodies-production itself. Gary, et al. demonstrated in a retrospective study that Primary APS (PAPS) occurs more often in obese patients. Fibrinogen-levels increased with BMI, suggesting that an elevated inflammatory state in overweight and obese patients might be a reason for the increased PAPS occurrence.43

There are only a few authors who described obesity in APS-patients. Caldas, et al. compared obese and non-obese patients with primary APS. The obese PAPS-group had a higher frequency of adverse outcome as well as pulmonary embolism than the non-obese group. There was no difference in medication between the two groups.44

ENDOTHELIAL DYSFUNCTION

The vascular endothelium is responsible for vascular function by producing vasoconstrictive and vasodilatating substances, which modulate vascular tone, activity of inflammatory cells and angiogenesis. The endothelium plays a pivotal role in vascular homeostasis, controlling the tone of blood vessels via the secretion of relaxing factors such as Nitric Oxide (NO), Prostacyclin (PGI2) or Endothelium-derived hyperpolarizing factor (EDHF) and vasoconstrictive factors, including angiotensin II, Endothelin-1 (ET-1), and thromboxane A2. An imbalance of all these factors leads to an endothelial dysfunction.45

Nitric oxide (NO) is the main endothelium-derived relaxing factor, inflammation inhibitor, and suppressor of vascular smooth cell proliferation, platelet adhesion and tissue factor release.46,47 Therefore, it protects the vessels from atherosclerosis by an anti-inflammatory action, and inhibits the transformation of LDL, thrombus formation and smooth cell proliferation.48

Endothelial Nitric Oxide Synthase (NOS) converts the amino acid L-arginine into L-citrulline and NO.49 Endothelial dysfunction is known to be the result of a decrease in NO, it is an impaired vascular reactivity; it also describes a pro-inflammatory and pro-thrombotic state and is known to be an early marker of atherosclerosis.50 Endothelial dysfunction results from endothelial cell injury and leads to endothelial cell activation.
and inflammatory process. There are many trigger factors leading to endothelial cell injury, i.e., hypoxia and turbulent blood flow. It has been described in many cardiovascular and metabolic disorders, such as arterial hypertension, coronary heart disease, peripheral vascular disease and diabetes mellitus I and II and preeclampsia.51-53

The bioavailability of NO can be altered by pathways, such as DDAH-ADMA-NOS pathway, oxidative stress or several factors, such as insulin. Insulin stimulates NO production by activation of NOS.54 Although insulin is vasodilative,55-56 this effect might be altered in obese patients.57 However, insulin resistance is associated with a decreased NO bioavailability and impaired endothelial function.58-60

ASYMMETRIC DIMETHYLARGININE (ADMA)

Asymmetric dimethylarginine (ADMA) is an endogenous NOS inhibitor, which plays a key role in endothelial rearrangement. By decreasing NO-bioavailability, ADMA activates processes, which are involved in atherogenesis, plaque progression, and plaque rupture.51 A relationship of increased levels of ADMA and impaired endothelial function has been demonstrated. Associations of increased ADMA levels and high cardiovascular risk in hypertension, diabetes mellitus, insulin resistance, hypercholesterinemia, hypertriglyceridemia, hyperuricemia, obesity and hyperhomocysteinemia, as well as preeclampsia have been postulated.62-66

ADMA is eliminated via the urine or metabolized by the enzyme Dimethylarginine dimethylaminohydrolase (DDAH), by converting ADMA in L-citrulline and dimethylamine.67,68 Ito A, et al. have demonstrated that increased ADMA-levels in association with vascular disease and risk factors are mainly due to an decreased activity of DDAH.69

ADMA-levels are also elevated in obese patients, as well as in patients with metabolic syndrome. Hypercholesterinemia leads to a decrease of DDAH-activity with consecutive elevated ADMA-levels and endothelial dysfunction.70 Additionally, polymorphisms in the DDAH-1 and 2 genes have been associated with ADMA-levels in diabetes.71

In autoimmune diseases, such as APS and SLE, anti-endothelial cells antibodies including aPL lead to endothelial cell injury, apoptosis and endothelial dysfunction. Several studies have found higher levels of ADMA in patients with autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis.71-75

Kiani, et al. showed in their study, that elevated ADMA-levels are associated with markers of poor prognosis in patients with SLE.76 Other authors proposed according to their results, higher ADMA-levels as independent risk factor for disease activity and poor prognosis.77,78

Several studies observed elevated ADMA concentrations in maternal circulation in women with preeclampsia.79-81 Savvidou, et al. reported that elevated ADMA-levels actually preceded preeclampsia, suggesting a possible preeclampsia screening parameter.82 ADMA concentrations increased at 23-25 weeks of gestation in women who developed late preeclampsia. The authors also found elevated titers of ADMA in pregnancies with pathologic uterine Doppler, including pregnancies with intrauterine growth restriction. These findings suggest a possible association with a pathologic placental perfusion.

Additionally ADMA serves as an antiangiogenic factor and high levels of ADMA affect negatively angiogenesis in pregnancy and preeclampsia.30 Di Simone, et al, found out that aPRL are able to decrease endometrial endothelial cell angiogenesis. Beside complement activation, this mechanism might explain the defective placentation in pregnancies with adverse obstetric outcome in pregnancies with APS.84

ENDOTHELIN-1

ET-1, the most potent vasoconstrictor known;85 its overall action is to increase blood pressure and vascular tone. ET-1 acts by binding to two receptors: ETA and ETB, which are located on endothelial cells (ET) vascular smooth muscle cells, and fibroblasts (ETA and ETB), both of them triggering vasoconstriction, cell proliferation, inflammation, and fibrosis.86 ET-1 decreases NO bioavailability, by decreasing NO production and by increasing NO degradation, thus leading to endothelial dysfunction.80

Amiri, et al. showed that the over-expression of ET-1 causes a decrease in NO and endothelial dysfunction.53 ET-1 is involved in endothelial dysfunction in several pathologic situations, such as atherosclerosis, diabetes mellitus and pulmonary arterial hypertension.87-89

Obesity is associated with vasoconstrictor tone, mediated by ET-1.90 A relationship of RAAS and ET-1 has been proposed.91 Activation of the RAAS increases angiotensin II, leading to an increased activity of endothelin converting enzymes and enhanced ET-1 expression.92

Normal pregnancy is associated with systemic vasodilation, decreased vascular contraction, resulting in a decrease of vascular resistance; partly due to increased release of endothelium-derived vasodilator substance, such as NO. Therefore reduced NO production/availability might lead to increased blood pressure and vascular resistance. The role of ET-1 receptor subtypes in the regulation of vascular function during pregnancy is unclear. A recent study found out, that the adaptive vasodilatation in pregnancy might be due to a down regulation of ET-1 receptors.93

ET-1 is also involved in the endothelial dysfunction in several autoimmune diseases.94-96 Several studies found elevat-
ed titers of ET-1 in patients with SLE.104,105 Ciółkiewicz, et al. found significantly increased concentrations of ET-1 in patients with active SLE.104 In another study the authors postulated a correlation between enhanced ET-1 levels and Lupus disease activity, measured by SLEDAI score.105

Atsumi, et al. found increased levels of ET-1 in patients with arterial thrombosis, but not in venous thrombosis, suggesting that ET-1 induced by antiphospholipid antibodies might play an important role in altering arterial tone, leading even to occlusion.106

Other authors did not find increased ET-1 concentrations in patients with APS.107,108 Williams, et al. presumed that one reason might be the anti-inflammatory effect of the patient’s medication, such as salicylates.

Multiple studies have found elevated levels of ET-1 in women with preeclampsia, some of these studies indicate that the level of circulating ET-1 correlates with the severity of the disease symptoms.109-111 However, ET-1 serves as a marker for endothelial dysfunction in preeclampsia, but also as predictor in women who develop preeclampsia.109-111

**MANAGEMENT**

A prepregnancy weight loss should be the first and simplest way for a better maternal and neonatal outcome. A recent study demonstrated that even small differences in prepregnancy BMI (10%) are associated with less than 10% lower risk of preeclampsia, gestational diabetes, indicated preterm delivery, macrosomia, and stillbirth. In contrast, larger differences in prepregnancy BMI (20-30% differences in BMI) were necessary for significant reduced risks of cesarean delivery, shoulder dystocia, neonatal intensive care unit stay 48 hours or longer, and in-hospital newborn mortality.112,113 Unfortunately, many patients tend to maintain prepregnancy lifestyle habits throughout pregnancy; To reduce adverse obstetric outcome and negative long-term complications, especially in the off-spring, certain nutritional interventions as anti-inflammatory strategy, such as Eicosapentaenoic Acid (EPA) and Docosahexaenoic (DHA), Taurine and Curcumin are another important possibility. These dietary interventions are particularly to minimize complications in the fetal/neonatal development.114 Bariatric surgery is the most appropriate strategy to lose weight when others fail.10

The basic treatment of APS in pregnancy is low-dose-aspirin and low-molecular-weight-heparin. The efficacy of corticosteroids remains uncertain; its use is discouraged solely for the treatment of APS.

Alijotas, et al. formed the term “refractory obstetric antiphospholipid syndrome” and described several treatment options for cases with adverse obstetric outcome despite therapy, which consisted i.e. of intravenous-immunoglobulins (IVIG), corticosteroids, antimalarias, TNF-targeted therapies or other immunomodulatory agents such as pentoxifylline.115

Heparin has a variety of actions including anticoagulant activity and inhibitory actions on vascular smooth muscle cell proliferation and migration, as well as anti-inflammatory effects.116-118 It is also known that heparin acts as an endogenous antiatherosclerotic factor,118-120 and chronic use of heparin shows a blood pressure-lowering effect in hypertensive patients and experimental animals.121,122 In endothelial cells, ET-1 has been shown to be suppressed by heparin in cultured bovine endothelial cells.123-126 Kuwahara-Watanabe, et al. demonstrated in their study that heparin suppressed ET-1 gene expression at the transcription level.129

ET-1 is responsible for endothelial dysfunction; therefore it serves as a possible therapeutic target in several diseases.130 ET receptor antagonists as treatment for preeclampsia has also been discussed several studies.131,132 Generally, the treatment with all endothelin receptor antagonists, such as sitaxentan, ambrisentan, atrasentan is contraindicated in pregnancy because the use of ETA receptor antagonists during pregnancy has proven to cause birth defects and embryonic lethality in mice.131,133 ETA receptor antagonists might be used in later pregnancy134,135 for treatment of preeclampsia.

Tumor-necrosis-factor-alpha (TNF-alpha) is known to be jointly responsible for aPL-related placental injury and consecutive miscarriage. Anti-TNF-alpha drugs, such as infliximab, etanercept and adalimumab are used for the treatment of certain rheumatic, digestive and cutaneous immune-mediated diseases. Anti-TNF-agents are also thought being used in cases of so-called “refractory obstetric APS”.134 Its use during pregnancy has been reported being safe, although anti-TNF drugs are still classified by the FDA as ‘pregnancy risk category B’.135

According to literature tumor-necrosis-factor inhibits enzymatic degradation of ADMA; therefore anti-TNF agents could restore physiological level of ADMA. Spinelli, et al. treated 33 patients with rheumatoid arthritis for 3 months either with etanercept or with adalimumab. They demonstrated a significant decrease of ADMA-levels.136 Therefore, anti-TNF-drugs as possible treatment for cases of especially refractory obstetric antiphospholipid syndrome should be further investigated.

**CONCLUSION**

Obesity and antiphospholipid syndrome (APS) are both chronic diseases with similar, even long-term consequences for mother and child. Both diseases are associated with adverse obstetric outcome; a co-occurrence of obesity and APS in pregnancy worsens the situation; the use of novel therapeutic tools should be therefore encouraged. The NO-pathway and inflammation are among the key mechanisms likely involved in the endothelial dysfunction in both conditions. A better understanding of the complex interactions between endothelial dysfunction and obesity and APS should be further investigated. Goals of treat-
ment in obesity and APS in pregnancy are to improve the mater-

nal and fetal/neonatal outcome. However, pre-pregnancy weight

loss, as well as changes in life-style are feasible methods, which

might prevent or delay the onset of endothelial dysfunction;

therefore obese women with known APS should be counselled

before conception not only about potential obstetrical complica-

tions as well as the long-term consequences for the off-spring,

but also about these important life-style modifications.

CONFLICTS OF INTEREST

The author declares that this article content has no conflicts of

interest.

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