Brief Report

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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 (anticardiolipin antibodies/ACLA, lupus antikoagulans/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 off-spring, 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.[1] It is defined by the Body Mass Index (BMI). BMI is weight in kilograms divided by height in meters squared (kg/m²).[2] Obesity is associated with a broad spectrum of chronic diseases, as well as cardiovascular diseases, such as diabetes, dyslipidemia, insulin resistance and hyperglycemia[3-5] and degenerative joint disease, obstructive sleep apnea, gastro-esophageal reflux, non-alcoholic fatty liver and certain types of cancer.[6-8] It is a known fact that

obesity in pregnancy is increasing, rising from 3.2% in 1988 to 10.2% in 2002.[9]

Most of the comorbidities in obese patients can be explained by three "effects";[10] 1) the "mechanical" effect with an accumulation of visceral fat, leading to an increase of intra-abdominal pressure and i.e. activation of the Renin-angiotensin-aldosteron system (RAAS) with secondary hypertension, 2) the "metabolic effect" with peripheral insulin resistance and a systemic pro-inflammatory state and 3) the endothelial dysfunction with an imbalance of angiogenic factors. Endothelial dysfunction is known to be an early marker of atherosclerosis.[10]

This review will discuss obesity in pregnant women with Antiphospholipid Syndrome (APS) with focus on endothelial dysfunction as possible factor for adverse obstetric outcome in these women.

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.[11,12] Unfortunately this increased risk has also been described *in vitro* fertilization therapy.[13]

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).[14]

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.[16] 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/m^2 and 42.6% for women with a BMI ≥35 kg/m^2. 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.[18,19]

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).[9] 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.[21,22] 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 in 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.[25-29] The risk of thromboembolism is not surprisingly increased in obese preg-

nant women. Edwards. et al.[30] reported 683 obese women who were matched to 660 women of normal weight. The incidence of thromboembolism was 2.5% in the obese women, and only 0.6% in the control subjects.[30]

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 and 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 Erythematodes (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 coagulant is an immunoglobulin (usually IgG, IgM, or both) that binds to phospholipids and proteins associated with the cell membrane. Anti-cardiolipinanti bodies (ACLA) are acquired antibodies (IgG, IgM and/or IgA) that react against negatively charged cardiolipin. ß2-Glycoprotein-1 (ß2GP1) is present on the surface of trophoblastic cell membranes and has been added to the criteria in 2006.[37] The presence of aPl is not only essential for the diagnosis of APS, it leads to the thrombotic and obstetric manifestations *via* various pathways. APl 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.[38] In obstetric APS, aPL impair placentation, decreases throphoblast 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 the complement system (C3a und C5a) with consecutive thrombosis and pregnancy loss.[37] It has been suggested that local complement activation causes impaired throphoblast 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 (PGl2) 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[50] and is known to be an early marker of atherosclerosis.[10] Endothelial dysfunction results from endothelial cell injury and leads to endothelial cell activation

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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 vasodilatative,[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 derangement. By decreasing NO-bioavailability, ADMA activates processes, which are involved in atherogenesis, plaque progression, and plaque rupture.[61] 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 dimethyl-aminohydrolase (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 gestations 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.[83] Di Simone, et al, found out that aPL 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 (ETB), vascular smooth muscle cells, and fibroblasts (ETA and ETB), both of them triggering vasoconstriction, cell proliferation, inflammation, and fibrosis.[50,86] ET-1 decreases NO bioavailability, by decreasing NO production and by increasing NO degradation, thus leading to endothelial dysfunction.[50]

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.[87-95]

Obesity is associated with vasoconstrictor tone, mediated by ET-1.[96] A relationship of RAAS and ET-1 has been proposed.[94] Activation of the RAAS increases angiotensin II, leading to an increased activity of endothelin converting enzymes and enhanced ET-1 expression.[97]

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.[98]

ET-1 is also involved in the endothelial dysfunction in several autoimmune diseases.[99-103] Several studies found elevat-

ed titers of ET-1 in patients with SLE.[104,105] Ciołkiewicz, 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 least a 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 immunmodulatory 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.[123-128] 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 pregnancy[134,135] 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".[115] Its use during pregnancy has been reported being safe, although anti-TNF drugs are still classified by the FDA as 'pregnancy risk category B'.[115]

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 therapeutical 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 maternal 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 complications 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.

REFERENCES

1. WHO Consultation. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World health Organ Tech Rep Ser.* 2000; 894: i-253.

2. Gilmore J. Bodymass index and health. *Health Rep (Statistics Canada, Catalogue 82-003*). 1999; 11(1): 31-43.

3. Williams IL, Wheatcroft SB, Shah AM, Kearney MT. Obesity, atherosclerosis and the vascular endothelium: mechanisms of reduced nitric oxide bioavailability in obese humans. *Int J Obes Relat Metab Disord.* 2002; 26(6): 754-764.

4. Bakker W, Eringa EC, Sipkema P, van Hinsbergh VW. Endothelial dysfunction and diabetes: roles of hyperglycemia, impaired insulin signaling and obesity. *Cell Tissue Res.* 2009; 335(1): 165-189. doi: 10.1007/s00441-008-0685-6

5. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet.* 2005 16-22; 365): 1415-28

6. Catenacci VA, Hill JO, Wyatt HR. The obesity epidemic. *Clin Chest Med.* 2009; 30(3): 415-444.

7. Hu G, Tuomilehto J, Silventoinen K, Barengo NC, Peltonen M, Jousilahti P. The effects of physical activity and body mass index on cardiovascular, cancer and all-cause mortality among 47 212 middle-aged Finnish men and women. *Int J Obes (Lond).* 2005; 29(8): 894-902. doi: 10.1038/sj.ijo.0802870

8. Key TJ, Schatzkin A, Willett WC, Allen NE, Spencer EA, Travis RC. Diet, nutrition and the prevention of cancer. *Public Health Nutr.* 2004; 7: 187-200. doi: 10.1079/PHN2003588

9. Robinson HE, O'Connell CM, Joseph KS, McLeod NL. Maternal outcomes in pregnancies complicated by obesity. *Obstet Gynecol.* 2005; 106: 1357-1364.

10. Mauricio MD, Aldasoro M, Ortega J, Vila JM. Endothelial dysfunction in morbid obesity. *Curr Pharm Des.* 2013; 19(32): 5718-5729. doi: 10.2174/1381612811319320007

11. Lashen H, Fear K, Sturdee DW. Obesity is associated with increased risk of first trimester and recurrent miscarriage: matched case-control study. *Hum Reprod.* 2004; 19: 1644-1646. doi: 10.1093/humrep/deh277

12. Boots CE, Bernardi LA, Stephenson MD. Frequency of euploid miscarriage is increased in obese women with recurrent early pregnancy loss. *Fertil Steril.* 2014; 102: 455-459. doi: 10.1016/j.fertnstert.2014.05.005

13. Bellver J, Rossal LP, Bosch E, et al. Obesity and the risk of spontaneous abortion after oocyte donation. *Fertil Steril.* 2003; 79: 1136-1140. doi: 10.1016/S0015-0282(03)00176-6

14. Weiss JL, Malone FD, Emig D, et al. FASTER Research Consortium. Obesity obstetric complications and cesarean delivery rate-a population based screening study. *Am J Obstet Gynecol.* 2004; 190: 1091-1097.

15. Sheiner E, Levy A, Menes TS, Silverberg D, Katz M, Mazor M. Maternal obesity as an independent risk factor for caesarean delivery. *Paediatr Perinat Epidemiol.* 2004; 18: 196-201. doi: 10.1111/j.1365-3016.2004.00557.x

16. Sacks DA, Chen W. Estimating fetal weight in the management of macrosomia. *Obstet Gynecol Survey.* 2000; 55: 229-239.

17. Dietz PM, Callaghan WM, Morrow B, Cogswell ME. Population-based assessment of the risk of primary cesarean delivery due to excess pre-pregnancy weight among nulliparous women delivering term infants. *Matern Child Health J.* 2005; 9: 237-244. doi: 10.1007/s10995-005-0003-9

18. Perlow JH, Morgan MA. Massive maternal obesity and perioperative cesarean morbidity. *Am J Obstet Gynecol.* 1994; 170: 560-565.

19. Wall PD, Deucy EE, Glantz JC, Pressman EK. Vertical skin incisions and wound complications in the obese parturient. *Obstet Gynecol.* 2003; 102: 952-956.

20. Myles TD, Gooch J, Santolaya J. Obesity as an independent risk factor for infectious morbidity in patients who undergo cesarean delivery. *Obstet Gynecol.* 2002; 100: 959-964

21. Fretts RC. Etiology and prevention of stillbirth. *Am J Obstet Gynecol.* 2005; 193: 1923-1935.

22. Cedergren MI. Maternal morbid obesity and the risk of adverse pregnancy outcome. *Obstet Gynecol.* 2004; 103: 219-224.

23. Davies GA, Maxwell C, McLeod L, et al. Society of Obstetricians and Gynaecologists of Canada. Obesity in pregnancy. *J Obstet Gynaecol Can.* 2010; 32(2): 165-173.

24. Alfaradhi MZ, Ozanne SE. Developmental programming in

response to maternal overnutrition. *Frontiers in Genetics*. 2011; 2(27). doi: 10.3389/fgene.2011.00027

25. Cedergren MI. Maternal morbid obesity and the risk of adverse pregnancy outcome. *Obstet Gynecol*. 2004; 103: 219-224.

26. Simmons R. Perinatal programming of obesity. *Exp Gerontol*. 2005; 40: 863-866.

27. Gillman MW, Rifas-Siman SL, Berkey CS, Field AE, Colditz GA. Maternal gestational diabetes, and adolescent obesity. *Pediatrics*. 2003; 111: E221-E226.

28. Himmelmann A, Himmelmann K, Svensson A, Hansson L. Glucose and insulin levels in young subjects with different maternal histories of hypertension: the Hypertension in Pregnancy Offspring Study. *J Int Med*. 1997; 241: 19-22. doi: 10.1046/j.1365-2796.1997.66890000.x

29. Catalano PM, Ehrenberg HM. The short- and longterm implications of maternal obesity on the mother and her offspring. *BJOG*. 2006; 113(10): 1126-1133.

30. Edwards LE, Hellerstedt WL, Alton IR, Story M, Himes JH. Pregnancy complications and birth outcomes in obese and normal-weight women: effects of gestational weight change. *Obstet Gynecol*. 1996; 87: 389-394.

31. Hotamisligil GS. Inflammation and metabolic disorders. *Nature*. 2006; 444 (7121): 860-867. doi: 10.1038/nature05485

32. Basu S, Haghiac M, Surace P, et al. Pregravid obesity associates with increased maternal endotoxemia and metabolic inflammation. *Obesity*. 2011; 19(3): 476-482.

33. Madan JC, Davis JM, Craig WY, et al. Maternal obesity and markers of inflammation in pregnancy. *Cytokine*. 2009; 47 (1): 61-64. doi: 10.1016/j.cyto.2009.05.004

34. Balistreri CR, Caruso C, Candore G. The role of adipose tissue and adipokines in obesity-related inflammatory diseases. *Mediators Inflamm*. 2010; 2010: 802078.

35. Challier JC, Basu S, Bintein T, et al. Obesity in pregnancy stimulates macrophage accumulation and inflammation in the placenta. *Placenta*. 2008; 29 (3): 274-281. doi: 10.1016/j.placenta.2007.12.010

36. X.Yan JF, Tong MJ, Zhu SP, Ford PW, Nathanielsz, Du M. Maternal obesity induces inflammation and adipogenesis in late gestation fetal sheep muscle. *Diabetes*. 2009; A85-A85.

37. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipide syndrome (APS). *J Thromb Haemost*. 2006; 4: 295-230. doi: 10.1111/j.1538-7836.2006.01753.x

38. Rand JH, Wu XX, Quinn AS, Taatjes DJ. The annexin A5-mediated pathogenic mechanism in the antiphospholipid syndrome: role in pregnancy losses and thrombosis. *Lupus*. 2010; 19(4): 460-469.

39. Girardi G, Berman J, Redecha P. Complement C5a receptors and neutrophils mediate fetal injury in the antiphospholipid syndrome. *J Clin Invest*. 2003; 112: 1644-1654.

40. Holers VM, Girardi G, Mo L. Complement C3 activation is required antiphospholipid antibody induced fetal loss. *J Exp Med*. 2002; 195: 211-220. doi: 10.1084/jem.200116116

41. Tedesco F, Narchi G, Radillo O, Meri S, Ferrone S, Betterle C. Susceptibility of human trophoblast to killing by human complement and the role of the complement regulatory proteins. *J Immunol*. 1993; 151(3): 1562-1570.

42. Salmon JE, Girardi G. The role of complement in the antiphospholipid syndrome. *Curr Dir Autoimmun*. 2004; 7: 133-148.

43. Gary T, Belaj K, Bruckenberger R, et al. Primary antiphospholipid antibody syndrome-one further aspect of thrombophilia in overweight and obese patients with venous thromboembolism. *Obesity (Silver Spring)*. 2013; 21(9).

44. Caldas CA, da Mota LM, de Carvalho JF. Obesity in primary antiphospholipid syndrome is associated with worse outcome. *Joint Bone Spine*. 2011; 78(3): 324-325.

45. Schiffrin EL. A critical review of the role of endothelial factors in the pathogenesis of hypertension. *J Cardiovasc Pharmacol*. 2001; 38 (Suppl 2): S3-S6.

46. Garg UC, Hassid A. Nitric-oxid-generating vasodilators and 8-bromo-cyclic guanosine monophosphate inhibit mitogenesis and proliferation of cultured rat vascular smooth muscle cells. *J Clin Invest*. 1989; 83: 1774-1777. doi: 10.1172/JCI114081

47. Radomski MW, Palmer RM, Moncada S. Endogenous nitric oxide inhibits human platelet adhesion to vascular endothelium. *Lancet*. 1987; 2: 1057-1058. doi: 10.1016/S0140-6736(87)91481-4

48. Zhang C. The role of inflammatory cytokines in endothelial dysfunction. *Basic Res Cardiol*. 2008; 103(56): 398-406. doi: 10.1007/s00395-008-0733-0

49. Palmer RH, Rees DD, Ashton DS, Moncada S. L-arginine is the physiological precursor for the formation of nitric oxide in endothelium-dependent relaxation. *Biochem Biophys Res Commun*. 1988;153(3): 1251-1256.

50. Iglarz M, Clozel M. Mechanisms of ET-1 induced endothelial dysfunction. *J Cardiovasc Pharmacol*. 2007; 50: 621-628.

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51. Ludmer PL, Selwyn AP, Shook TL, et al. Paradoxical vaso-constriction induced by acetylcholin in atheroslerotic coronary arteries. *N Engl J Med.* 1986; 315: 1046-1051.

52. Endemann DH, Schiffrin EL. Endothelial dysfunction. *J Am Soc Nephrol.* 2004; 15: 1983-1992.

53. Amiri F, Virdis A, Neves MF, et al. Endothelium-restricted over-expression of human endothelin-1 causes vascular remodeling and endothelial dysfunction. *Circulation.* 2004; 110: 2233-2240.

54. Montagnani M, Chen H, Barr VA, Quon MJ. Insulin-stimulated activation of eNOS is independent of Ca2+ but requires phosphorylation by Akt at Ser(1179). *J Biol Chem.* 2001; 276(32): 30392-30398.

55. Anderson EA, Hoffman RP, Balon TW, Sinkey CA, Mark AL. Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans. *J Clin Invest.* 1991; 87(6): 2246-2252.

56. Tack CJ, Schefman AE, Willems JL, Thien T, Lutterman JA, Smits P. Direct vasodilator effects of physiological hyperinsulin-aemia in human skeletal muscle. *Eur J Clin Invest.* 1996; 26(9): 772-778.

57. Feldman RD, Bierbrier GS. Insulin-mediated vasodilation: impairment with increased blood pressure and body mass. *Lancet.* 1993; 342(8873): 707-709.

58. Kim JA, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. *Circulation.* 2006; 113(15): 1888-904.

59. Clerk LH, Vincent MA, Jahn LA, Liu Z, Lindner JR, Barrett EJ. Obesity blunts insulin-mediated microvascular recruitment in human forearm muscle. *Diabetes.* 2006; 55(5): 1436-1442. doi: 10.2337/db05-1373

60. Reyes-Soffer G, Holleran S, Di Tullio MR, et al. Endothelial function in individuals with coronary artery disease with and without type 2 diabetes mellitus. *Metabolism.* 2010; 59(9): 1365-1371.

61. Cooke JP. Asymmetrical Dimetyhlarginine. The Über-Marker? Circulation. 2004; 109: 1813-1819.

62. Surdacki A, Martens-Lobenhoffer J, Wloch A, et al. Elevated plasma asymmetric dimethyl-L-arginine levels are linked to endothelial progenitor cell depletion and carotid atherosclerosis in rheumatoid arthritis. *Arthritis. Rheum.* 2007; 56: 809-819. doi: 10.1002/art.22424

63. Miyazaki P, Leone P, Calver A, et al. Endogenous nitric ox-

ide synthase inhibitor: a novel marker of atherosclerosis. *Circulation.* 1999; 99: 1141-1146. doi: 10.1161/01.CIR.99.9.1141

64. Stuhlinger MC, Abbasi F, Chu JW, et al. Relationship between insulin resistance and an endogenous nitric oxide synthase inhibitor. *JAMA.* 2002; 287: 1420-1426. doi: 10.1001/jama.287.11.1420

65. Boger RH, Bode-Borger SM, Szuba A, et al. Asymmetric dimethyl-arginine (ADMA): a novel risk factor for endothelial dysfunction: its role in hypercholesterinemia. *Circulation.* 1998; 98: 1842-1847.

66. Lundmann P, Erikson MJ, Stuhlinger M, et al. Mild-to-moderate hypertriglyceridemia in young men is associated with endothelial dysfunction and increased plasma concentrations of asymmetric dimethylarginine. *J Am Coll Cardiol.* 2001; 38: 111-116. doi: 10.1016/S0735-1097(01)01318-3

67. McDermott JR. Studies on the catabolism of NG-methylarginine, NG, N'G-dimetyhlarginine and NG.NG-dimethylarginine. *Biochem J.* 1976; 154: 179-184.

68. Murray-Rust J, Leiper J, McAlister M, et al. Structural insights into the hydrolysis of cellular nitric oxide synthase inhibitors by dimethylarginine dimethylaminohydrolase. *Nat Struct Biol.* 2001; 8(8): 679-683

69. Ito A, Tsao PS, Adimoolam S, Kimoto M, Ogawa T, Cooke JP. Novel mechanism for endothelial dysfunction: dysregulation of dimethylarginine dimethylaminohydrolase. *Circulation.* 1999; 99(24): 3092-3095. doi: 10.1161/01.CIR.99.24.3092

70. Fogarty RD, Abhary S, Javadiyan S, et al. Relationship between DDAH gene variants and serum ADMA level in individuals with type 1 diabetes. *J Diabetes Complications.* 2012; 26(3): 195-198. doi: 10.1016/j.jdiacomp.2012.03.022

71. Turiel M, Atzeni F, Tomasoni L, et al. Non invasive assessment of coronary flow reserve and ADMA levels: A case-control study of early rheumatoid arthritis patients. *Rheumatology (Oxford).* 2009; 48, 834-839. doi: 10.1093/rheumatology/kep082

72. Sandoo A, Dimitroulas T, van Zanten V, et al. Lack of association between asymmetric dimethylarginine and in vivo microvascular or macrovascular endothelial function in patients with rheumatoid arthritis. *Clin. Exp. Rheumatol.* 2012; 30: 388-396.

73. Atzeni F, Sarzi-Puttini P, Sitia S, et al. Coronary flow reserve and asymmetric dimethylarginine levels: New measurements for identifying subclinical atherosclerosis in patients with psoriatic arthritis. *J. Rheumatol.* 2011; 38: 1661-1664. doi: 10.3899/jrheum.100893

74. Sari I, Kebapcilar L, Alacacioglu A, et al. Increased levels of asymmetric dimethylarginine (ADMA) in patients with an-

kylosing spondylitis. *Intern. Med.* 2009; 48: 1363-1368. doi: 10.2169/internalmedicine.48.2193

75. Kemény-Beke Á, Gesztelyi R, Bodnár N, et al. Increased production of asymmetric dimethylarginine (ADMA) in ankylosing spondylitis: Association with other clinical and laboratory parameters. *Joint Bone Spine*. 2011; 78: 184-187.

76. Kiani AN, Mahoney JA, Petri M. Asymmetric dimethylarginine is a marker of poor prognosis and coronary calcium in systemic lupus erythematosus. *J Rheumatol.* 2007; 34: 1502-1505.

77. Bultink EM, Teerlink T, Heijst JA, Dijkmans BA, Voskuyl AE. Raised plasma levels of asymmetric dimethylarginine are associated with cardiovascular events, disease activity, and organ damage in patients with systemic lupus erythematosus. *Ann Rheum Dis.* 2005; 64: 1362-1365. doi: 10.1136/ard.2005.036137

78. Elmageed AM, Ahmed IK, Saleh BI, Ali SR. Exploring disease activity and cardiovascular events by raised serum asymmetric dimethyl arginine among systemic lupus erythematosus patients. *Egypt J Immunol.* 2001; 18: 43-49.

79. Fickling SA, Williams D, Vallance P, Nussey SS, Whitley GS. Plasma concentrations of asymmetric dimethylarginine, a natural inhibitor of nitric oxide synthesis in normal pregnancy and preeclampsia. *Lancet.* 1993; 342: 242-243.

80. Holden DP, Fickling SA, Whitley GS, et al. Plasma concentrations of asymmetric dimethylarginine, a natural inhibitor of nitric oxid synthase, in normal pregnancy and preeclampsia. *Am J Obstet Gynecol*. 1998; 178: 551-556. doi: 10.1016/S0002-9378(98)70437-5

81. Petterson A, Hedner T, Milsom I. Increased circulating concentrations of asymmetric dimethyl arginine (ADMA), an endogenous inhibitor of nitric oxide synthesis, in preeclampsia. *Acta Obstet Gynecol Scand.* 1998; 77: 808-813.

82. Savvidou MD, Hingorani AD, Tsikas D, et al. Endothelial dysfunction and raised plasma concentrations of asymmetric dimethylarginine in pregnant women who subsequently develop preeclampsia. *Lancet.* 2003; 361: 1511-1517. doi: 10.1016/S0140-6736(03)13177-7

83. Cooke JP. NO and angiogenesis. *Atheroscel Suppl.* 2003; 4: 53-60.

84. Di Simone N, Di Nicuolo F, D'Ippolito S, et al. Antiphospholipid antibodies affect human endometrial angiogenesis. *Biol reprod.* 2010; 83: 212-219. doi: 10.1095/biolreprod.110.083410

85. Charakida M, Besler C, Batuca JR, et al. Vascular abnormalities, paraoxonase activity, and dysfunctional HDL in primary antiphospholipid syndrome. *JAMA.* 2009; 302: 1210-1217. doi: 10.1001/jama.2009.1346

86. Ames PR, Batuca JR, Ciampa A, Iannaccone L, Delgado Alves J. Clinical relevance of nitric oxide metabolites and nitrative stress in thrombotic primary antiphospholipid syndrome. *J Rheumatol.* 2010; 37: 2523-2530. doi: 10.3899/jrheum.100494

87. Yanagisawa M, Kurihara H, Kimura S, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature.* 1988; 332: 411-415. doi: 10.1038/332411a0

88. Best PJ, McKenna CJ, Hasdai D, et al. Chronic endothelin receptorantagonism preserves coronary endothelial function in experimental hypercholesterolemia. *Circulation.* 1999; 99: 1747-1175

89. Oliver FJ, de la Rubia G, Feener EP, et al. Stimulation of endothelin-1 gene expression by insulin in endothelial cells. *J Biol Chem.* 1991; 266: 23251-23256.

90. Andronico G, Mangano M, Ferrara L, et al, Cerasola G. In vivo relationship between insulin and endothelin role of insulin-resistance. *J Hum Hypertens.* 1997; 11: 63-66.

91. Schneider JG, Tilly N, Hierl T, et al. Elevated plasma endothelin-1 levels in diabetes mellitus. *Am J Hypertens.* 2002; 15: 967-972.

92. Alexander BT, Cockrell KL, Rinewalt AN, Herrington JN, Granger JP. Enhanced expression of preproendothelin mRNA during chronic angiotensin II hypertension. *Am J Physiol Regul Integr Comp Physiol.* 2001; 280: R1388-R1392.

93. Deng LY, Day R, Schiffrin EL. Localization of sites of enhanced expression of endothelin-1 in the kidney of DOCA-salt hypertensive rats. *J Am Soc Nephrol.* 1996; 7: 1158-1164.

94. Kassab S, Miller MT, Novak J, Reckelhoff J, Clower B, Granger JP. Endothelin-A receptor antagonism attenuates the hypertension and renal injury in Dahl salt-sensitive rats. *Hypertension.* 1998; 31: 397-402. doi: 10.1161/01.HYP.31.1.397

95. Schiffrin EL. Endothelin: a potential role in hypertension and vascular hypertrophy. *Hypertension.* 1995; 25: 1135-1143.

96. Weil BR, Westby CM, Van Guilder GP, Greiner JJ, Stauffer BL, DeSouza CA. Enhanced endothelin-1 system activity with overweight and obesity. *Am J Physiol Heart Circ Physiol.* 2011; 301(3): H689-H695.

97. Barton M, Carmona R, Ortmann J, Krieger JE, Traupe T. Obesity-associated activation of angiotensin and endothelin in the cardiovascular system. *Int J Biochem Cell Biol.* 2003; 35(6): 826-837.

98. Ou M, Dang Y, Mazzuca MQ, Basile R, Khalil RA. Adaptive regulation of endothelin receptor type-A and type-B in vascular smooth muscle cells during pregnancy in rats. *J Cell Physiol.*

2014; 229: 489-501.

99. Murdaca G, Colombo BA, Cagnati P, Gulli R, Spanò F, Puppo F. Endothelial Dysfunction in rheumatic autoimmune diseases. *Atherosclerosi*s. 2012; 224: 309-317.

100. Filep G, Bodolay E, Sipka S, Gyimesi E, Csipo I, Szegedi G. Plasma endothelin correlates with antiendothelial antibodies in patients with mixed connective tissue disease. *Circulation.* 1995; 92: 2969-2974. doi: 10.1161/01.CIR.92.10.2969

101. Yamada K, Miyauchi T, Suzuki N, et al. Significance of plasma endothelin-1 levels in patients with systemic sclerosis. *J Rheumatol.* 1992; 19: 1566.

102. Lima J, Fonollosa V, Fernandez-Cortijo J, et al. Platelet activation, endothelial cell dysfunction in the absence of anti-cardiolipin antibodies in systemic sclerosis. *J Rheumatol.* 1991; 18: 1833-1836.

103. Hashimoto Y, Ziff M, Hurd ER. Increased endothelial cell adherence, aggregation, and superoxide generation by neutrophils incubated in systemic lupus erythematosus and Felty's syndrome sera. *Arthritis Rheum.* 1982; 25: 1409-1418.

104. Ciołkiewicz M, Kuryliszyn-Moskal A, Klimiuk PA. Analysis of correlations between selected endothelial cell activation markers, disease activity, and nailfold capillaroscopy microvascular changes in systemic lupus erythematosus patients. *Clin Rheumatol.* 2010; 29: 175-180.

105. Kuryliszyn-Moskal A, Klimiuk PA, Ciolkiewicz M, Sierakowski S. Clinical significance of selected endothelial activation markers in patients with systemic lupus erythematosus. *J Rheumatol.* 2008; 35: 1307-131360.

106. Atsumi T, Khamashta MA, Haworth RS, et al. Arterial disease and thrombosis in the antiphospholipid syndrome: a pathogenic role for Endothelin-1. *Arthritis Rheum.* 1998; 41: 800-807.

107. Williams FM, Parmar K, Hughes GR, Hunt BJ. Systemic endothelial cell markers in primary antiphospholipid syndrome. *Thromb Haemoast.* 2000; 84: 742-74662.

108. de Souza AW, Silva NP, de Carvalho JF, D'Almeida V, Noguti MA, Sato EI. Impact of hypertension and hyperhomocysteinemia on arterial thrombosis in primary antiphospholipid syndrome. *Lupus.* 2007; 16: 782-787. doi: 10.1177/0961203307081847

109. Taylor RN, Varma M, Teng NN, Roberts JM. Women with preeclampsia have higher plasma endothelin levels than women with normal pregnancies. *J Clin Endocrinol Metab.* 1990; 71: 1675-1677. doi: 10.1210/jcem-71-6-1675

110. Baksu B, Davas I, Baksu A, Akyol A. Gulbaba G. Plasma nitric oxide, endothelin-1 and urinary nitric oxide and cyclic gu-

anosine monophosphate levels in hypertensive pregnant women. *Int J Gynaecol Obstet.* 2005; 90: 112-11742.

111. Nishikawa S, Miyamoto A, Yamamoto H, Ohshika H, Kudi R. The relationship between serum nitrate and endothelin-1 concentrations in preeclampsia. *Life Sci.* 2000; 67: 1447-1454. doi: 10.1016/S0024-3205(00)00736-0

112. Maltaris T, Scalera F, Schlembach D, et al. Increased uterine arterial pressure and contractility of perfuses swine uterus after treatment with serum from preeclamptic women and endothelin-1. *Clin Sci.* 2005; 109: 209-215. doi: 10.1042/CS20040340

113. Schummers L, Hutcheon JA, Bodnar LM, Lieberman E, Himes KP. Risk of adverse pregnancy outcomes by prepregnancy body mass index: a population-based study to inform prepregnancy weight loss counseling. *Obstet Gynecol.* 2015; 125(1): 133-143.

114. Segovia SA, Vickers MH, Gray C, Reynolds CM. Maternal obesity, inflammation, and development programming. *Biomed Res Int.* 2014; 2014: 418975. doi: 10.1155/2014/418975

115. Alijotas-Reig J. Treatment of refractory obstetric antiphospholipid syndrome: the state of the art and new trends in the therapeutic management. *Lupus.* 2013; 22: 6-17

116. Sawhney N, Patel MK, Schachter M, Hughes AD. Inhibition of proliferation by heparin and expression of p53 in cultured human vascular smooth muscle cells. *J Hum Hypertens.* 1997; 11: 611-614.

117. Kohno M, Yokokawa K, Yasunari K, et al. Heparin inhibits human coronary artery smooth muscle cell migration. *Metabolism.* 1998; 47: 1065-1069. doi: 1016/S0026-0495(98)90279-7

118. Dilley RJ, Nataatmadja MI. Heparin inhibits mesenteric vascular hypertrophy in angiotensin II-infusion hypertension in rats. *Cardiovasc Res.* 1998; 38: 247-255.

119. Ragazzi E, Chinellato A. Heparin: Pharmacological potentials from atherosclerosis to asthma. *Gen Pharmacol.* 1995; 26: 697-701.

120. Shulman AG. Heparin and atherosclerosis: An investigative report on the treatment of atherosclerosis. *Biomed Pharmacother*. 1990; 44: 303-306.

121. Engelberg H. Heparin and atherosclerosis. A review of old and recent findings. *Am Heart J.* 1980; 99: 359-372.

122. Vasdev S, Prabhakaran V, Sampson CA. Heparin lowers blood pressure and vascular calcium uptake in hypertensive rats. *Scand J Clin Lab Invest.* 1991; 51: 321-327.

123. Susic D, Mandal AK, Kentera D. Heparin lowers the blood

pressure in hypertensive rats. *Hypertension.* 1982; 4: 681-685.

124. Imai T.Heparin has an inhibitory effect on endothelin-1 synthesis and release by endothelial cells. *Hypertension.* 1993; 21: 353-358.

125. Imai T, Hirata Y, Marumoand F. Heparin inhibits endothelin-1 and proto-oncogene c-fos gene expression in cultured bovine endothelial cells. *J Cardiovasc Pharmacol.* 1993; 22(Suppl 8): S49-S52.

126. Castellot JJ Jr. Inhibition of vascular smooth muscle cell growth by endothelial cell-derived heparin. Possible role of a platelet endoglycosidase. *J Biol Chem.* 1982; 257: 11256-11260.

127. Yokokawa K. Heparin suppresses endothelin-1 peptide and mRNA expression in cultured endothelial cells of spontaneously hypertensive rats. *J Am Soc Nephrol.* 1994; 4: 1683-1689.

128. Yokokawa K. Effect of heparin on endothelin-1 production by cultured human endothelial cells. *J Cardiovasc Pharmacol.* 1993; 22(Suppl 8): S46-S48.

129. Kuwahara-Watanabe K, Hidai C, Ikeda H, et al. Heparin regulates transcription of endothelin-1 gene in endothelial cells. *J Vasc. Res.* 2005; 42: 183-189.

130. Agapitov A, Haynes WG. Role of endothelin in cardiovascular disease. *JRAAS.* 2002; 3: 1-15. doi: 10.3317/jraas.2002.001

131. Clouthier DE, Hosoda K, Richardson JA, et al. Cranial and cardiac neural crest defects in endothelin-A receptor-deficient mice. *Development.* 1998; 125: 813-824.

132. George EM, Granger JP. Endothelin: Key mediator o hypertension in preeclampsia. *Am J Hypertens.* 2001; 24: 964-969. doi: 10.1038/ajh.2011.99

133. Kingman M, Ruggiero R, Torres F. Ambrisentan, an endothelial receptor A-selective endothelin receptor antagonist, for the treatment of pulmonary arterial hypertension. *Expert Opin Pharmacother.* 2009; 10: 1847-1858. doi: 10.1517/14656560903061275

134. Taniguchi T, Muramatsu I. Pharmacological knockout of endothelin ET (A) receptors. *Life Sci.* 2003; 74: 405-409. doi: 10.1016/j.lfs.2003.09.027

135. Paradis A, Zhang L. Role of endothelin in uteroplacental circulation and fetal vascular function. Role of endothelin in uteroplacental circulation and fetal vascular function. 2013; 11: 594-605.

136. Spinelli FR, Di Franco M, Metere A, et al. Decrease of asymmetric dimethyl arginine after anti-TNF therapy in patients with rheumatoid arthritis. *Drug Dev Res.* 2014; 75(Suppl 1):

S67-S69. doi: 10.1002/ddr.21200