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Vascular Dysfunction in Women with Recurrent Pregnancy Loss

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1. Introduction

Women have unique risk factors for cardiovascular diseases and cerebrovascular diseases such as pregnancy and hormone replacement therapy. Pregnancy provides an opportunity to reveal various cardiovascular disease risk factors and estimate a woman's lifetime risk because of its unique cardiovascular and metabolic stress.

The causes of recurrent pregnancy loss (RPL) are classified as genetic, anatomic, endocrinologic, immunologic, microbiologic, environmental, and further more (Kutteh, 1999; Christiansen et al., 2005). Several lines of study have suggested that certain coagulation abnormalities such as antiphospholipid antibodies or Factor V Leiden, the genetic defect underlying resistance to activated protein C, are causes of RPL (Kutteh, 1999).

New diagnostic methods have improved the clinical triage of RPL (Kutteh, 1999; Li, 1998). Transvaginal pulsed Doppler ultrasonography allows noninvasive evaluation of uterine circulation. The introduction of pulsed Doppler ultrasonography has provided noninvasive means for the evaluation of uterine impedance, and gives physiologic data, rather than anatomic information alone. It is known that resistance to uterine arterial blood flow is associated with poor obstetrical outcome such as preeclampsia and fetal growth restriction (Nakatsuka et al, 1999b; Nakatsuka et al, 2002; Takata et al, 200).

We have reported that impaired uterine perfusion is observed in a portion of women with RPL (Habara et al., 2002; Nakatsuka et al., 2003a, 2003b). Pulsed Doppler ultrasonography in the uterine artery may be useful in distinguishing women with RPL caused by vascular dysfunction from women with unexplained RPL (Habara et al., 2002). Furthermore, the plasma level of adrenomedullin, which is often associated with pathological processes of the vasculature (Hinson, 2000), is elevated in women with RPL (Nakatsuka et al., 2003a). However, vascular changes in women with RPL have not been fully elucidated.

Antiphospholipid antibody syndrome (APS), which is an autoimmune disease associated with coagulopathy, is a well-known cause of RPL (Nakatsuka et al., 2003b). Antiphospholipid antibodies refer to several groups of autoantibodies with specificity for a number of negatively-charged phospholipids such as cardiolipin, phosphatidylserine, and phosphatidylethanolamine, or phospholipid-binding glycoproteins such as β2 glycoprotein I

(β2GPI) and prothrombin. There are currently data supporting an association between various types of antiphospholipid antibodies and vascular diseases (Nayak & Komatireddy et al., 2002). Previous studies suggest that predominantly IgG and to lesser extent IgM isotype of antiphospholipid antibodies and lupus anticoagulant (LAC) are associated with arterial and venous thrombosis, thrombocytopenia, and livedo reticularis (Nayak & Komatireddy et al., 2002). Anti-cardiolipin and anti-β2GPI antibodies are elevated in patients with coronary artery disease. Anti-cardiolipin antibodies are also associated with typical chest pain, significant coronary artery stenosis on angiography and prediction of myocardial infarction (Sherer &Shoenfeld, 2003).

Premature atherosclerosis is a clinical feature of thrombotic patients with primary APS (Ames et al., 2009). Early data from the Italian Antiphospholipid Registry calculated a 2.5% patient/year incidence of recurrent thrombosis often fatal; a prospective Spanish study demonstrated that 5.2% of primary APS patients died of recurrent arterial occlusions; Italian longitudinal study showed a 5.2% patient/year mortality rate for recurrent arterial thrombosis and a Russian group recently reported a 17% 8-year vascular mortality for primary APS (Ames et al., 2009).

Polycystic ovary syndrome (PCOS) is one of the most common endocrinological disorders among reproductive-age women (Franks, 1995; Dunaif, 1997, The Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004). Using a combination of clinical, ultrasonographic, and biochemical criteria, the diagnosis of PCOS is usually reserved for those women who display one or more clinical symptoms including chronic anovulation, an ultrasonographical morphology of polycystic ovaries, inappropriate gonadotropin secretion, and hyperandrogenism (Franks, 1995; Dunaif, 1997). It is reported that women with PCOS have adverse pregnancy outcome including miscarriage (Abbott et al., 2002; Doldi et al., 1998; Glueck et al., 1999; Wang et al., 2001; Diejomaoh et al., 2003).

We and the other researchers demonstrated an impaired uterine perfusion in women with PCOS (Ajossa et al., 2002; Chekir C et al., 2005). Abnormal sex steroid hormones have been suggested as the cause for the elevated blood flow resistance in the uterine artery of women with PCOS (Zaidi et al., 1998). Furthermore, risk factors for cardiovascular disease including central obesity, hyperandrogenism, hyperinsulinemia, and dyslipidemia, which are commonly observed in women with PCOS, may lead to impairment of uterine perfusion and vascular dysfunction (Slowinska-Srzednicka et al., 1991; Legro ,2003; Sabuncu et al., 2001; Fenkci et al., 2003; Setji & Brown, 2007).

In the light of these studies, vascular dysfunction may be the key to the pathophysiology of pregnancy loss. This chapter reviews association between RPL and vascular dysfunction.

2. Impaired uterine arterial blood flow in women with RPL

Pregnancy loss in LPS-treated rats is associated with coagulopathy, decreased placental blood flow, and placental and fetal hypoxia. This impairment in uteroplacental hemodynamics in LPS-treated rats is linked to increased uterine artery resistance (Graham et al., 2011). In Human, peripheral vascular resistance in normal pregnancy decreases as early as 5 weeks of gestation (Robson, 1989). Resistance in uterine arterial blood flow also exhibits a progressive decrease after implantation while it increases in women with preeclampsia or fetal growth restriction (Steel et al., 1990). Pulsed Doppler velocimetry of

the uterine artery has been reported to predict preeclampsia, fetal growth restriction, or gestational diabetes (van den Elzen et al., 1995). However, predictive value of uterine arterial pulsed Doppler velocimetry in pregnancy loss is controversial (van den Elzen et al., 1993; Jauniaux, et al., 1994; Kurjak et al., 1994; Alcázar, 2000; Nakatsuka et al., 2003a)..

2.1 Pregnant women with RPL associated with antiphospholipid antibodies

We measured the resistance in the uterine arteries of 104 pregnant women with and without RPL at 4 to 5 weeks' gestation and evaluated association of autoantibodies including antiphospholipid antibodies (Nakatsuka et al., 2003a). In this study, uterine arterial pulsatility index (PI) in the RPL group was significantly higher than that in the control group (Figure 1). Women with antiphospholipid antibodies had an elevated PI in the uterine artery, which is prominent in women with RPL (Table 1). Coagulopathy and vascular dysfunction caused by antiphospholipid antibodies may impair uterine perfusion.
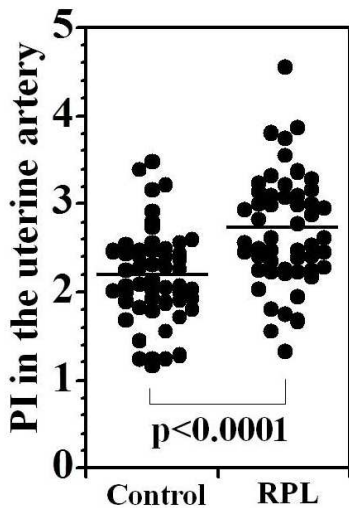

Fig. 1. Resistance in uterine arterial blood flow of women with recurrent pregnancy loss (Nakatsuka et al., 2003a).

	APA (-) (n=89)	APA (+) (n=15)	p value
Control (n=52)	2.19±0.54 * (52)	n.a. (0)	n.a.
Recurrent pregnancy loss (n=52)	2.51±0.52 * (37)	3.18±0.64 (15)	< 0.0003
Total (n=104)	2.32±0.55	3.18±0.64	< 0.0001

APA : Antiphospholipid antibodies,
n.a.: not available, Student's t-test* : p<0.007.
(Nakatsuka et al., 2003a).

Table 1. Antiphospholipid antibodies and pulsatility index in the uterine artery

Pregnancies complicated with hypertensive disorders and/or fetal growth restriction are known to be associated with a defective trophoblastic invasion. Antiphospholipid antibodies are known to interfere with syncytialization of the trophoblasts in early pregnancy and cause decidual vasculopathy, thrombosis, and placental infarction later in pregnancy. However, the elevation of uterine arterial PI that we observed is more likely to be associated with vascular dysfunction rather than impaired trophoblastic invasion. Trophoblastic invasion affects little on uterine arterial blood flow at 4-5 weeks of gestation because decrease in blood flow resistance in the uterine artery is very slow until 8 weeks of gestation (Dickey et al., 1995).

Pregnant women with antiphospholipid antibodies have vascular dysfunctions in the uterine artery although the prediction of adverse pregnancy outcome is not conclusive (Caruso et al, 1993; Venkat-Raman et al, 2001; Nakatsuka et al., 2003a).

Interestingly, the uterine arterial PI in RPL women without antiphospholipid antibodies is significantly higher than that in the control pregnant women even among women without antiphospholipid antibodies in our study (Nakatsuka et al., 2003a).

2.2 Non-pregnant women with unexplained RPL

Pulsed Doppler ultrasonography demonstrated blood flow changes in the uterus and ovaries during the menstrual cycle (Goswamy and Steptoe, 1988a; Chekir et al., 2005). The uterine arterial PI has been known to diminish progressively during the luteal phase, during which implantation occurs. Differences in uterine blood flow impedance between fertile and infertile women (Goswamy et al., 1988b; Steer et al., 1994). Based on studies from the IVF-ET programme, impedance of blood flow through the uterine arteries is a good indicator of the probability of subsequent pregnancy (Salle et al., 1998).

We investigated whether women with unexplained RPL have impaired uterine perfusion in the mid-luteal phase of non-conception cycles (Habara et al., 2002). The uterine arterial PI of 121 women including 49 women with unexplained RPL was measured by transvaginal pulsed Doppler ultrasonography. The uterine artery PI in RPL group (2.54±0.45, mean ±S.D.) was significantly higher than that in the control group (2.20±0.35). In the RPL group, the PI in the uterine artery of women with antinuclear antibodies (ANA) was significantly higher than that of women without ANA (Figure 2). There is no significant difference between the PI in the uterine artery of women with ANA and that of women without ANA in control group. Among women without ANA, the uterine artery PI in RPL group was also significantly higher than that in the control group.

Although ANA are not specific pathogens for pregnancy loss (Ogasawara, et al., 1996), women with positive ANA may have other autoimmune antibodies causing vasculopathy or coagulopathy. These pathological changes are likely to cause elevation of the uterine arterial blood flow resistance and lead to RPL, early onset preeclampsia, or fetal growth restriction. Although the apparent underlying pathophysiology of these cases was not elucidated, they may have subclinical vasculopathy, which was not diagnosed by routine screening tests for RPL.

2.3 Women with PCOS

Relatively high rate of pregnancy loss has been reported in women with PCOS. We performed a pulsed Doppler study on uterine arterial blood flow in 25 women with PCOS

and 45 control women with regular menstrual cycles (Chekir et al.,2005). Among the control group, the uterine arterial PI in the luteal phase was significantly lower than that in the follicular phase (Figure 3). Among women with PCOS, the uterine arterial PI in the luteal phase tended to be lower than that in the follicular phase. The PI in the uterine artery in women with PCOS was significantly higher than that for the control group both in the follicular phase and in the luteal phase. Among women with PCOS, women with amenorrhea had a significantly higher uterine arterial PI than that of women with oligomenorrhea.
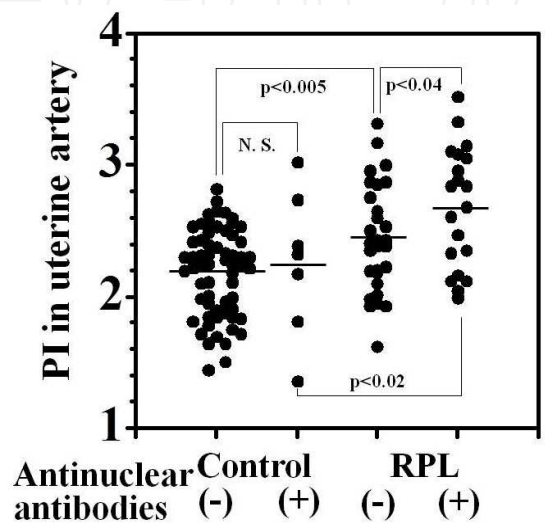

Fig. 2. Pulsatility index in the uterine artery of women with or without antinuclear antibodies in control or RPL group. Bars, Mean. Values are expressed as mean ±S.D. (Habara et al., 2002)
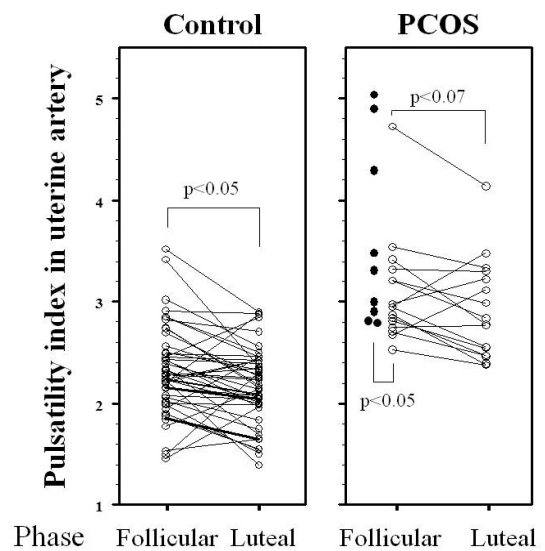

Fig. 3. Pulsatility index in the uterine artery in control women and women with PCOS. Left panel: Uterine arterial PI in control women. Data from control women during the follicular phase and the luteal phase are indicated by open circles. Right panel: Uterine arterial PI in women with PCOS. Data from women with amenorrhea during the follicular phase are indicated by closed circles. Data from women with oligomenorrhea during the follicular phase and the luteal phase are indicated by open circles (Chekir et al, 2005).

The uterine arterial PI was correlated with body mass index, luteinizing hormone /follicle-stimulating hormone ratio, or low-density lipoprotein-cholesterol (LDL-C)/high-density lipoprotein-cholesterol (HDL-C) ratio while it was inversely correlated with the HDL-C level.

3. Biomarkers for cardiovascular risk assessment in women with RPL

The introduction of pulsed Doppler ultrasonography has provided the means for the noninvasive evaluation of uterine impedance, thus providing physiologic data on hemodynamic abnormalities in early pregnancy failures. Are these vascular changes in women with PRL observed solely in the uterine artery? Biomarkers for cardiovascular risk assessment are substances that are released into the blood when the vasculature is damaged. Some biomarkers cause vascular dysfunction directly or indirectly. It may be worth measuring biomarkers for cardiovascular risk assessment in women with RPL.

3.1 Thrombomodulin

Thrombomodulin binds thrombin, changes thrombin conformation and allows thrombin to activate protein C, which inhibits coagulation and thrombin-activatable fibrinolysis inhibitor, which inhibits fibrinolysis. Increased serum thrombomodulin, cleaved products of cellular thrombomodulin, has been demonstrated previously in preeclampsia (Dusse et al., 2011). Endothelial thrombomodulin is known to be a major vasoprotective molecule. However, elevated serum thrombomodulin is also likely to be a response to vascular activation.

We measured serum levels of soluble thrombomodulin of 54 pregnant women at 4-8 weeks of gestation (Nakatsuka et al., 2004). Serum thrombomodulin was significantly elevated in women with antiphospholipid antibodies in RPL group compared with control women and with RPL women without antiphospholipid antibodies. Among women with APS, serum thrombomodulin in women who subsequently had a growth-restricted fetus had been significantly higher than that in women who subsequently had an appropriate-for-date fetus. Elevation of thrombomodulin is likely to indicate impaired uterine blood flow in women with RPL.

It is controversial whether the soluble thrombomodulin level is an independent risk factor for coronary heart disease (Wu, 2003; Huang et al., 2008; Karakas et al., 2011). However, anti-cardiolipin antibodies are reported to be important not only in the pathogenesis of mixed connective tissue disease (MCTD) but in the induction of endothelial cell causing elevation of soluble thrombomodulin, and may play crucial roles in the development of early atherosclerosis in MCTD (Soltesz, 2010). It is also known that development of atherosclerosis and elevation of soluble thrombomodulin in serum of systemic lupus erythematosus (SLE) patients with metabolic syndrome (Mok et al., 2010).

3.2 Adrenomedullin

Adrenomedullin, a 52-amino acids-ringed, structured peptide, mediates vasodilatory properties through the second messenger cyclic adenosine, 3,5-monophosphate (Jougasaki & Burnett, 2000). The main source of plasma adrenomedullin is considered to be vascular endothelial cells and vascular smooth muscle cells.

Adrenomedullin has interaction with various bioactive molecules including nitric oxide, prostaglandins, atrial natriuretic peptide, renin, aldosterone, norepinephrine, arginine vasopressin, endothelin-1, and adrenocorticotropic hormone (Jougasaki & Burnett, 2000). The plasma level of adrenomedullin is elevated in various diseases including hypertension, diabetes, cardiac failure, septic shock, or SLE, which are often associated with pathologic processes of the vasculature (Jougasaki & Burnett, 2000; Hinson et al., 2000).

We measured plasma levels of adrenomedullin of 100 pregnant women in the midluteal phase of a nonpregnant cycle (Nakatsuka et al., 2003b). We also measured the PI in the uterine arteries by transvaginal pulsed Doppler ultrasonography at the same time. The plasma level of adrenomedullin in women with RPL was significantly higher than that in control women. Uterine arterial PI of women with RPL was significantly higher than that in control women. Plasma level of adrenomedullin had a significant positive correlation with uterine arterial PI both in the control group (r=0.58, p < 0.001) and in the RPL group (r=0.78, p < 0.001) (Figure 4). Both plasma adrenomedullin concentration and uterine arterial PI were significantly high in women with antiphospholipid antibodies.
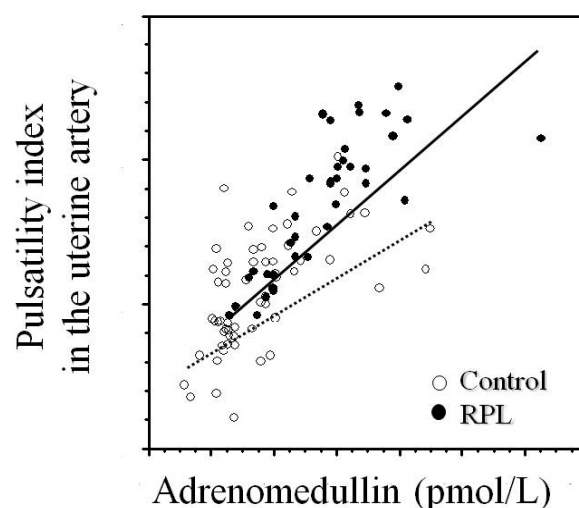

Fig. 4. Plasma adrenomedullin and uterine arterial pulsatility index.
A) Plasma adrenomedullin concentration and uterine arterial pulsatility index in control women. A significant positive correlation was determined by Pearson correlation coefficient (r =0.58, p<0.001). B) Plasma adrenomedullin concentration and uterine arterial pulsatility index in women with recurrent pregnancy loss. A significant positive correlation was determined by Pearson correlation coefficient (r =0.78,p <0.001). (Nakatsuka et al., 2003b)

Increased plasma adrenomedullin in women with RPL is likely to be a response to vascular damage and increased vascular tone. Plasma adrenomedullin levels observed in women with recurrent pregnancy loss were similar to the values reported in patients with hypertension, mitral stenosis, primary aldosteronism, or SLE (Nakatsuka et al., 2003b).

Although the pathophysiologic roles of adrenomedullin in RPL have not been fully elucidated, this peptide may serve as a biochemical marker to identify women with impaired uterine perfusion (Nakatsuka et al., 2003b; Ashraf et al., 2011) and also impaired systemic vasculatures.

3.3 The other markers associated with cardiovascular diseases

We have previously reported that there is no significant difference in serum nitric oxide metabolite level between control women and women with recurrent pregnancy loss (Habara et al., 2002). However, anti-cardiolipin antibodies induce nitric oxide and superoxide production from vascular vessels, resulting in enhanced local levels of plasma peroxynitrite (Alves & Grima, 2003), which is a powerful pro-oxidant molecule (Nakatsuka et al, 1999). These oxidative damages in the cardiovascular system may be involved in atherosclerosis.

PCOS has deserved major attention because it is linked to the same cluster of events that promote the metabolic syndrome. We have reported that women with PCOS had significantly higher total cholesterol, triglyceride, and β-lipoprotein levels than those of the control group. Significantly lower HDL-C, higher LDL-C, and consequently a higher LDL-C/HDL-C ratio were observed in women with PCOS as compared to those of the control women. Fasting serum insulin and homeostasis model assessment-R (HOMA-R), which are indexes of insulin resistance, in women with PCOS were significantly higher than those for the control group.

It has been reported that isolated adipocytes from women with PCOS express higher mRNA concentrations of some adipokines involved in cardiovascular risk and insulin resistance (Garruti et al., 2009). The actions of adipokines and adipocytokines on platelets and vascular smooth muscle cells, both of which are deeply involved in atherothrombosis, have been reported (Anfossi et al, 2010). Adipose tissue from individuals with central obesity synthesizes and releases increased amount of proinflammatory chemokines and cytokines, such as monocyte chemoattractant protein-1 (MCP-1), macrophage migration inhibitory factor (MIF), tumor necrosis factor-α (TNF-α), and interleukins, including interleukin-1β (IL-1β) and interleukin-6 (IL-6); procoagulant and proinflammatory mediators such as tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1); vasoactive substances such as angiotensinogen and endothelin-1 (ET-1); molecules involved in the pathogenesis of insulin resistance, such as TNF-α and resistin (Anfossi et al, 2010). Elevated levels of PAI-1, the major natural antifibrinolytic agent, are involved in atherothrombosis in women with PCOS (Ehrmann, 2005). Women with RPL, who are characterized as PCOS might be monitored by measuring these bioactive molecules to predict development of cardiovascular diseases.

4. Arterial stiffness in women with RPL

Impaired uterine arterial blood flow and elevated cardiovascular disease risk markers suggest that early changes of systemic vasculature may be progressing in women with RPL. These changes lead to athrosclerosis and atherothrombosis and may cause coronary heart disease and/or stroke.

4.1 Evaluation methods of arterial stiffness

Reductions in the elasticity of central arteries may act as a marker of early changes that predispose to the development of major vascular disease. Arterial stiffness has been known as a major contributory factor to cardiovascular morbidity and mortality in patients with hypertension. Independent studies have shown that central arterial stiffness is increased in older individuals and in those with coronary artery disease, myocardial infarction, heart failure, hypertension, stroke, diabetes mellitus, end-stage renal disease, hypercholesterolemia, and inflammation (Nichols, 2005).

There are various methods in evaluation of atherosclerosis. Intima media thickness (IMT) of carotid arteries is used to evaluate early atherosclerosis and the risk of associated cardiovascular disease (Burke, et al., 1995). The The ankle-brachial index (ABI) for each leg was calculated as the ratio of the systolic pressures in the leg and the systolic pressure of either the left or right arm. An ABI < 1.0 in either leg was considered abnormal, suggesting peripheral arterial disease; progressively lower ABI values indicate more severe obstruction (Sacks et al., 2002).

Pulse wave velocity (PWV) and the augmentation index (AI) are widely used as arterial stiffness indices. Recently, brachial-ankle PWV (baPWV) measurement can be performed easily by simultaneous oscillometric measurement of pulse waves in all four extremities. Brachial-ankle PWV was used as a substitute for aortic PWV because baPWV is known to be strongly correlated with aortic PWV (Matsui et al., 2004). PWV are known to be a marker of both the severity of vascular damage and the prognosis of atherosclerotic vascular diseases in patients with hypertension (Blacher et al., 1999), end-stage renal failure (London & Cohn, 2002), and diabetes (Yokoyama et al., 2003). Increased PWV is known to be an independent predictor of the prognosis in hypertension, including in subjects under anti-hypertensive medication (Laurent et al., 2001).

Carotid AI (cAI) was assessed by the proportion of the central pulse pressure resulting from peripheral arterial wave reflection. The AI is known to be an independent predictor of all-cause and cardiovascular mortality in end-stage renal failure patients (London et al., 2001). It has been also reported that increased AI is associated with the presence and severity of coronary artery disease, particularly in younger and middle-aged male patients (Weber et al., 2004). Although PWV and AI have been known to be useful indices of atherosclerotic vascular diseases, data in young females are scarce.

4.2 Women with PRL associated with antiphospholipid antibodies

Antiphospholipid antibodies is known to play a central role in both pregnancy loss and cardiovascular diseases (Mackworth-Young, 2004). Antiphospholipid antibodies is a risk factor for incident stroke, however, the evidence to support the role of antiphospholipid antibodies in recurrent stroke is conflicting (Brey, 2004). Neither anti-cardiolipin antibodies nor anti-β2GPI antibodies is reported to be associated with atherosclerosis in premenopausal women with APS and SLE, who have an increased prevalence of carotid and femoral plaque (Vlachoyiannopoulos et al., 2003). Furthermore, previous studies have paradoxically proposed a beneficial role for some antiphospholipid antibodies in atherosclerosis (Nicolo & Monestier, 2004).

We assessed arterial stiffness of 153 women with RPL and 66 healthy women with one or less pregnancy loss. It is reported that abnormal ABIs are more common in primary APS than in healthy controls (Baron et al., 2005). However, we did not observe significant difference in ABI value or incidence of abnormal ABI between RPL women with antiphospholipid antibodies and control women. More sensitive methods may be necessary to detect early changes of vascular system in younger patients with antiphospholipid antibodies.

Women with RPL had significantly higher baPWV than control women (Figure 5). Mean value of baPWV of RPL women with antiphospholipid antibodies is significantly higher than that in control women. None in control women or women with unexplained RPL

showed abnormal baPWV while five in RPL women with antiphospholipid antibodies showed abnormal baPWV (baPWV > 1,400 m/sec, American Heart Association Medical/Scientific Statement, 1993). Women with RPL had significantly higher cAI (22.5 ± 171.2 %) than control women (-67.3 ± 151.7 %) (p<0.0005). Mean value of cAI of women with unexplained RPL or that of RPL women with antiphospholipid antibodies is significantly higher than that in control women (Figure 6).
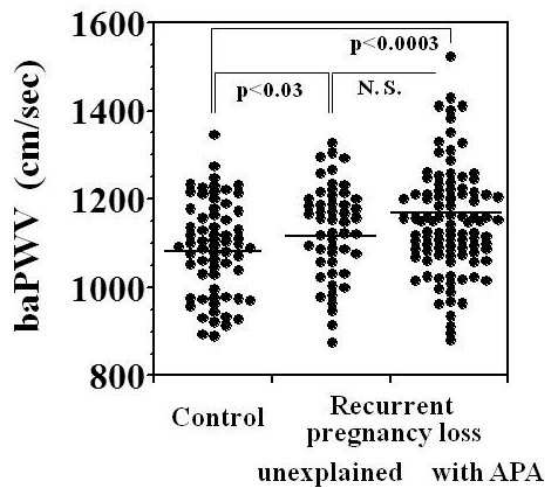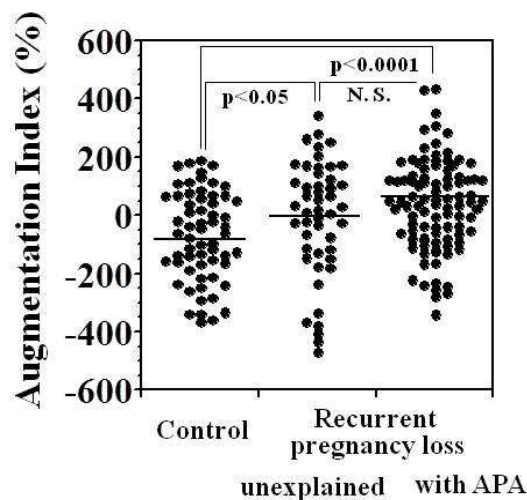

Fig. 5. baPWV of women with RPL

Fig. 6. cAI of women with RPL

4.3 Types of autoimmune antibodies and arterial stiffness in women with RPL

Antiphospholipid antibodies are a heterogeneous group of autoantibodies directed against phospholipid binding proteins, such as anti-cardiolipin antibodies, anti-β2GPI antibodies, and anti-phosphatidylserine/prothrombin antibodies, lupus anticoagulant, anti-phosphatidylserine antibodies and anti-phosphatidylethanolamine antibodies. Pathogenesis of antiphospholipid antibodies may vary depending on types and target phospholipid. There is an increasing interest in clinical significance of various types of antiphospholipid

antibodies to define the patient's risk of arterial and venous thrombosis (Galli et al., 2005) although it is inconclusive.

Petri have reported that twenty years after diagnosis, SLE patients with lupus anticoagulant have a 50% chance of a venous thrombotic event and myocardial infarction occurs significantly more often (22%) in those with lupus anticoagulant (Petri, 2004). However, neither anti-cardiolipin nor lupus anticoagulant is associated with an increase of carotid IMT, carotid plaque, nor coronary calcium by helical CT, which are signs of subclinical atherosclerosis (Petri, 2004). In our study, we could not find any significant differences in baPWV or cAI between women with lupus anticoagulant and control women (Figure 7).
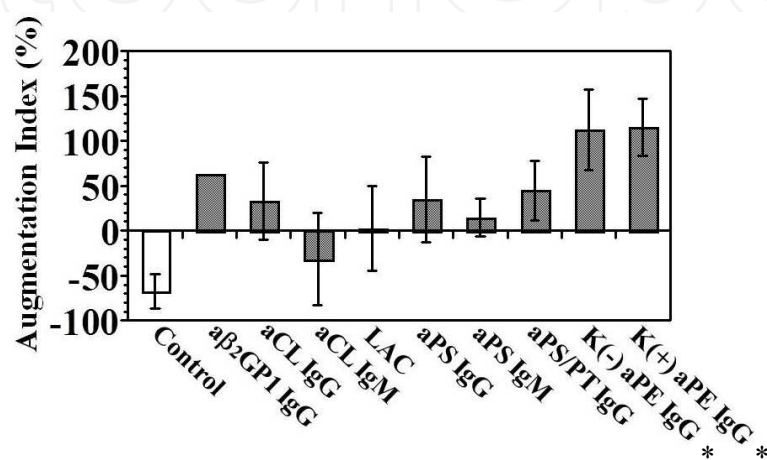
*:p<0.05 vs. Control, aβ2GPI: anti-β2GPI antibodies, aCL: anti-cardiolipin antibodies, LAC: lupus anticoagulant, aPS: anti-phosphatidylserine antibodies, aPS/PT: antibodies against phosphatidylserine/prothrombin complex, K(-)aPE: kininogen independent anti phosphatidylethanolamine antibodies, K(+)aPE: kininogen dependent anti-phosphatidylethanolamine antibodies

Fig. 7. cAI among women with various types of APA

There is some evidence that high anti-β2GPI antibodies can present a risk factor for atherosclerosis, but more epidemiological data are required in order to confirm whether the pro-atherogenic properties of anti-phospholipid antibodies signifies an independent risk factor for atherosclerosis and its complications. We observed that women with anti-β2GPI antibodies had high cAI. Unfortunately, we could not perform statistical analysis because women with anti-β2GPI antibodies were small population.

It has been reported that a significantly high prevalence of anti-phosphatidylserine IgG was found in stroke patients (57.7%) (Kahles et al., 2005). Anti-phosphatidylserine antibodies have a strong predictive value and association for arterial thrombosis (Lopez et al., 2004). Antibodies against phosphatidylserine/prothrombin complex have been reported to be closely associated with clinical features of APS rather than antibodies against prothrombin alone (Atsumi et al., 2004). However, there are no reports on atherosclerosis in women with these antibodies. We observed no significant association between anti-phosphatidylserine antibodies or antibodies against phosphatidylserine-prothrombin complex and arterial stiffness.

Recent studies have shown that some patients with unexplained thrombophilic disorders may have anti-phosphatidylethanolamine antibodies as the sole basis for their hypercoagulable

state (Sanmarco, et al., 2001). It is noteworthy that anti-phosphatidylethanolamine antibodies have been described as the sole antiphospholipid antibodies in patients with thrombotic diseases (Staub, et al., 1989; Karmochkine, et al., 1992; Berard, et al., 1996). However, there are little studies on association of anti-phosphatidylethanolamine antibodies and arterial stiffness or atherosclerosis.

We observed that cAI was significantly increased in RPL women with anti-phosphatidylethanolamine antibodies. Anti-phosphatidylethanolamine antibodies may be a risk factor for atherosclerosis in women with RPL. It has been reported that kininogen-dependent IgG anti-phosphatidylethanolamine antibodies markedly increases thrombin-induced platelet aggregation in vitro while kininogen independent IgG anti-phosphatidylethanolamine antibodies do not augment thrombin-induced platelet aggregation (Sugi et al, 1999). However, we observed that both two types of anti-phosphatidylethanolamine antibodies were associated with arterial stiffness.

Physical distribution of phosphatidylethanolamine is known to be at the blood-endothelium interface. The luminal phosphatidylethanolamine is a vulnerable to anti-phosphatidylethanolamine autoimmunity, which is consistent with the association between anti- phosphatidylethanolamine antibodies and elevated risk for idiopathic thrombosis (Zhixin et al., 2011).

Risk factors for atherosclerosis in SLE include traditional risk factors (mainly the Framingham risk factors). Moreover, specific antibodies to β2GPI; anticardiolipin antibodies; anti-oxidized low-density lipoprotein (oxLDL); and antibodies to heat shock proteins may be cardiovascular disease risk factors (Sherer et al., 2010). Immune complexes containing oxLDL, β2GPI, and/or CRP are known to be involved in atherosclerosis (Matsuura et al., 2006, Chekir et al, 2009). Autoantibodies to oxLDL/β2GPI complex were detected in SLE and APS patients, and were strongly associated with arterial thrombosis (Christodoulou et al., 2007). Further studies may help evaluating clinical usefullness of these autoimmune antibodies involving in progression of atherosclerosis in women RPL.

4.4 Women with PCOS

Previous study on arterial stiffness has shown that both baPWV and cAI are useful for risk stratification of hypertensive patients (Matsui et al., 2004). In this study, both of these indices are significantly correlated with age and systolic blood pressure and cAI is reported to be correlated with total cholesterol and LDL-C in hypertensive patients.

We have reported that women with PCOS in reproductive age have a significantly higher baPWV than that for the control women (Sasaki et al., 2011). Arterial stiffness evaluated using the baPWV and cAI in mildly-hypertensive women (systolic blood pressure ≥ 120 mmHg or diastolic blood pressure ≥ 90 mmHg) with PCOS was significantly higher than that in the control women or normotensive women with PCOS. Early changes in vascular function were detected in mildly-hypertensive women with PCOS.

4.5 Women with unexplained RPL

We observed that women with unexplained RPL showed increased baPWV and cAI in average as compared with control women (Figure 5, 6). Although ranges of these indices in

women with unexplained RPL and those in control women were overlapped, at least a portion of women with unexplained RPL showed increased baPWV and cAI. These observations suggest that antiphospholipid antibodies or endocrinological disorders may not be the sole cause for arterial stiffness in women with RPL. Vascular dysfunction caused by various factors may be involved in at least a portion of women with unexplained RPL.

A portion of women with unexplained RPL should be considered as a high risk group for atherosclerosis and cardiovascular diseases. Measurement of baPWV or AI is a promising technique to assess vascular dysfunction in women with RPL.

5. Possible cardiovascular diseases in pregnant women with RPL

In pregnant women with RPL, who have early changes of systemic vasculatures, may suffer vascular complications during pregnancy because of physiological hypercoagulability and hemodynamic changes associated with pregnancy.

5.1 Venous thromboembolism (VTE)

Thrombophilia is a risk factor for venous thromboembolism (VTE) in pregnancy because of the hypercoagulability of pregnancy, which is further increased in the presence of thrombophilia. Vascular reactivity, which is believed to be increased during pregnancy, may also compound the risk.

Pregnant women are at increased risk of venous thromboembolism (VTE). Estimated incidence of VTE during pregnancy is about 1 event per 1000 pregnancies (Chauleur et al., 2007). Despite this low incidence, thromboembolic complications occurring during pregnancy and post-partum remain a major cause of maternal death. Although pregnant women have a higher risk of developing thromboembolic complications than non-pregnant women, treating all pregnant women to prevent these events is not recommended.

A scoring system for VTE risk in pregnant women (Chauleur et al., 2007) includes antiphospholipid antibodies and reproductive history of one stillbirth or at least three recurrent miscarriages, which are clinical features of women with APS (Bobba et al., 2007).

5.2 Coronary heart disease and stroke in pregnancy

The risk of acute myocardial infarction is known to be approximately 3 to 4 times higher in pregnancy. The incidence of pregnancy-related acute myocardial infarction is in the broad range of 3 to 10 per 100 000 deliveries that has been reported previously (James et al., 2006). Hypertension (odds ratio (OR) 21.7), thrombophilia including history of thrombosis and APS (OR 22.3), diabetes mellitus (OR 3.6), smoking (OR 8.4), transfusion (OR 5.1), postpartum infection (OR 3.2), and age 30 years and older remain as significant risk factors for pregnancy-related acute myocardial infarction in the multivariable analysis (James et al., 2006). The odds of acute myocardial infarction are 30-fold higher for women aged 40 years and older than for women 20 years of age.

Thrombophilia, gestational diabetes mellitus associated with PCOS, or age 30 years and older may increase the risk further in women with RPL.

There are few data on the risk of stroke in relation to the full range of outcomes of pregnancy (spontaneous or induced abortion, stillbirth, and live birth) (Kittner & Stern, 1996). One of the most important risks factors for stroke is advanced maternal age, which suggests arterial stiffness and atherosclerosis may affect on the incidence of stroke (Bushnell, 2008). The majority (48%) of pregnancy-related strokes occur in the postpartum period, versus 41% at delivery, and 11% antepartum (James et al., 2005). The Baltimore Washington Cooperative Young Stroke Study found that stroke rate was not increased in pregnant compared with nonpregnant women, but during the postpartum period, there was a fivefold increased risk of ischemic stroke (Kittner et al., 1996). Risk factors found to be associated with pregnancy-related stroke in the most recent analysis include thrombophilia (OR 16.0) and lupus (OR 15.2) (James et al., 2005). Preeclampsia and gestational hypertension, which are sometimes observed in women with RPL even during treatments, increase the risk of stroke during pregnancy as a result of severe hypertension and disturbed cerebral autoregulation.

6. Reproductive history and cardiovascular disease risk later in life

Adverse reproductive history and complications during pregnancy in women with RPL should to be considered as cardiovascular risk factors later in life. Physiological hypercoagulability, hemodynamic changes, and metabolic syndrome during pregnancy may provoke pregnancy complications including pregnancy loss, preeclampsia, placental abruption, preterm birth, or birth of an infant small for gestational age, or gestational diabetes mellitus in women with subclinical thrombophilia such as antiphospholipid antibodies or Factor V Leiden and/or subclinical endcrinological abnormalities such or PCOS. They could be considered a "failed stress test," possibly unmasking early or preexisting endothelial dysfunction and vascular or metabolic disease (Mosca, 2011).

6.1 Parity

Endothelial function is improved and asymmetrical dimethylarginine, an endogenous nitric oxide synthase inhibitor, decreased during pregnancy, both of which would be expected to slow the progression of atherosclerosis. In contrast, childbirth modified cardiovascular risk factors, most notably a redistribution of body fat to a phenotype characterized by increased abdominal adiposity and marked reductions in HDL-C and apoA-I.

There is an emerging body of literature examining the association between parity and cardiovascular disease. After adjustment for age, obesity, and family history of diabetes, increased parity was associated with a significantly increased risk of both non insulin dependent diabetes mellitus (NIDDM) (OR 1.16 per pregnancy) and impaired glucose tolerance (OR 1.10 per pregnancy) (Kritz-Silverstein et al., 1989).

Most of the studies on the association between parity and coronary heart disease have included only women. However, comparisons between men and women distinguish whether the mechanisms for the association between parity and atherosclerosis involve biological processes related to pregnancy or socioeconomic or lifestyle factors that are related to family size and child-rearing. It has been reported that increasing parity is associated with carotid atherosclerosis in women but not in men among a population with at least one risk factor for cardiovascular disease (Lawlor et al., 2003; Skilton et al., 2009; Skilton et al., 2010).

Lifestyle risk factors associated with child-rearing lead to obesity and result in increased coronary heart diseass in both sexes but biological responses of pregnancy may have additional adverse effects in women (Lawlor et al., 2003).

It is suggested that the association between childbirth and concurrent changes in IMT may be independent of traditional cardiovascular risk factors (Skilton et al., 2010). However, another study described no association between parity and either IMT or presence of plaques after adjustment for age in a population based cohort of 746 Finnish women (Kharazmi et al., 2007). The causality of the link between parity and early atherosclerosis is not concluded.

6.2 Pregnancy loss

Women who suffered one or more pregnancy losses have had pregnancies of shorter duration than usual and consequently they have received less/shorter estrogen exposure during pregnancy. The protective effect of estrogen, therefore, is potentially less than in the case of a full-term pregnancy (Kleijn & Schouw, 1999). However, it is more likely that cardiovascular disease risk in women with history of RPL may reflect common determinants, such as thrombophilic genetic defects, antiphospholipid antibodies, and endocrinological or metabolic disorders.

Women with subclinical cardiovascular disease could have a higher risk of pregnancy loss and cardiovascular events later in life. There have been various reports on association between pregnancy loss and coronary heart disease risk or pregnancy loss and stroke risk, which are inconclusive (de Kleijn & Schouw, 1999; La Vecchia et al., 1987; Smith et al, 2001).

It has been reported that a history of any spontaneous loss of early pregnancy before the first live birth was associated with an increased risk of ischemic heart diseases (Smith et al., 2003). The association was independent of maternal age at the time of first birth, height, socioeconomic deprivation, essential hypertension, and complications during the first pregnancy. By contrast, there was no association between therapeutic abortion and subsequent risk of ischemic heart diseases. Women who had experienced at least one spontaneous or induced abortion had either increased or similar risk of coronary heart disease than women who had never had an abortion (Bertuccioa et al., 2007).

There is a report describing that abortions, either spontaneous or induced, are not related to myocardial infarction risk, although underreporting cannot be excluded, because some women do not realize that early abortion may have occurred and because induced abortion may not be reported (Bertuccioa et al., 2007).

6.3 Recurrent pregnancy loss

In women 50–74 years of age who had experienced pregnancy, history of pregnancy loss tended to be associated with a higher risk of myocardial infarction (age-adjusted OR 2.1), and the risk increased significantly with the number of pregnancy loss (age-adjusted OR 1.4) (Kharazmi et al., 2010). This result suggests that women who experience RPL are likely to be at an increased risk of vascular disease later in life. Spontaneous RPL (>3) is associated with about five times higher risk of myocardial infarction after full adjustment (Kharazmi et al.,

2011). Women who experience spontaneous pregnancy loss are at a substantially higher risk of myocardial infarction later in life. Although women who had history of RPL (>3) tended to have a higher risk of stroke (adjusted OR 1.43), associations between RPL and cerebrovascular events including stroke are also inconclusive.

Several studies have shown associations between acquired and inherited thrombophilias and both spontaneous loss of early pregnancy and ischemic heart disease (Smith et al., 2003). High homocysteine levels in early pregnancy are another risk factor for pregnancy loss and preecclampsia (Dodds, et al., 2008). Elevated levels of homocysteine in the bloodstream can irritate the blood vessels, which may eventually lead to hardening of the arteries, stroke or heart attack.

Miscarriage can sometimes lead to infections which may also have some links with cardiovascular diseases (Kharazmi et al., 2011). For instance, chlamydia infection has been found to be associated with occurrence of miscarriage and also with atherogenesis. Inflammation and infection as known risk factors for cardiovascular diseases might be the underlying mechanisms that explain the association between miscarriage and cardiovascular disease.

It is possible that the cause of pregnancy loss is related to hemodynamic factors, such as preeclampsia, and therefore to cardiovascular risk or disease (de Kleijn & Schouw, 1999). This means that the causal relationship could be reversed: women with a cardiovascular disease risk could have a higher risk of pregnancy loss. Occult cardiovascular, microvascular, or haemostatic dysfunction result in pregnancy complications during reproductive years and in overt cardiovascular disease later in life (Smith et al., 2003).

6.4 Still birth

Stillbirth is known to be associated with an increased risk of death from coronary heart disease, all circulatory and renal causes (Calderon-Margalit et al., 2007). A history of stillbirth is reported to be associated with an increased age-adjusted risk of plaque (OR 3.43), but it lost its statistical significance in the fully adjusted model (Kharazmi et al., 2007). Recent study have reported that each stillbirth increased the risk of myocardial infarction 2.32 times after adjustment for age, smoking, alcohol consumption, body mass index, waist to hip ratio, physical activity, education, number of pregnancies, hypertension, hyperlipidaemia and diabetes mellitus (Kharazmi et al., 2011). Stillbirth is a strong sex-specific predictor for myocardial infarction and thus should be considered as important indicators for cardiovascular risk factors monitoring and preventive measures (Kharazmi et al., 2011).

7. Complications in women with RPL and cardiovascular diseases

Pregnancy complications such as preeclampsia, placental abruption, preterm birth, or birth of an infant small for gestational age, or gestational diabetes mellitus are characteristic in women with RPL. Women with RPL are also at increased risk for recurrent episode of major depressive disorder. These complications may be associated with vascular dysfunction in women with RPL.

7.1 Preeclampsia

Preeclampsia affects about 5–8% of all first pregnancies and is a major cause of maternal and fetal morbidity and mortality worldwide. Preeclampsia is associated with vascular dysfunction manifesting hypertension (Nakatsuka et al., 2002) and one of common complications observed in women with RPL even during treatment. We have reported that uterine, orbital, and brachial circulations are impaired in women with preeclampsia (Takata et al., 2002). Several studies focused on an attenuated vasodilatory response in large blood vessels by evaluating flow-mediated dilatation or venous occlusion plethysmography (Spaana et al., 2010). One study evaluated microvascular function several years after preeclampsia, observing a lower response to both endothelium-dependent and independent vasodilatation using laser Doppler imaging of the forearm 20 years after preeclampsia (Ramsay et al. 2003).

One of the most common risk factors for stroke in pregnancy, particularly postpartum, is preeclampsia/eclampsia (Bushnell & Chireau, 2011). A history of preeclampsia during pregnancy lead to an increased risk of stroke later in life (Bellamy et al, 2007). Biomarkers of endothelial dysfunction such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are known to be elevated in women preeclampsia. Women with a history of preeclampsia are more likely to have higher insulin levels compared to controls.

Although the symptoms of preeclampsia typically regress within a few days post partum, impaired vascular dilatation is still present several years after preeclampsia, suggesting persistent endothelial dysfunction, which may contribute to the development of cardiovascular disease in these women (Spaana et al., 2010). A recent large meta-analysis found that women with a history of preeclampsia have approximately double the risk for subsequent ischemic heart disease, stroke, and venous thromboembolic events over the 5 to 15 years after pregnancy (Moska, 2011). Preeclampsia, particularly in association with preterm delivery, has been identified as a risk factor for myocardial infarction and mortality from cardiovascular disease later in life (James et al., 2006).

As described in the meta-analysis and other longitudinal studies, hypertension is the risk factor for cerebrovascular disease that women with a history of preeclampsia and gestational hypertension are most likely to develop (Bellamy et al, 2007).

7.2 Anxiety and depression

Other factors, which are prevalent among women with RPL and may make special contributions to cardiovascular disease risk, include anxiety, depression, and other psychosocial risk factors (Blackmore et al., 2011).

Anxiety, which is often observed in women with RPL, is also suggested to be an independent predictor of adverse cardiovascular events (Olafiranye et al., 2011). Individuals with high levels of anxiety are at increased risk of coronary heart disease, congestive heart failure, stroke, fatal ventricular arrhythmias, and sudden cardiac death. Anxiety following a major cardiac event can impede recovery, and is associated with a higher morbidity and mortality.

Risk for an episode of major depressive disorder among miscarrying women in the 6 months following loss is compared with the 6-month risk among community women who

have not been pregnant in the preceding year (Neugebauer et al., 1997). Among miscarrying women, 10.9% experience an episode of major depressive disorder, compared with 4.3% of community women. The overall relative risk (RR) for an episode of major depressive disorder for miscarrying women is 2.5 and is substantially higher for childless women (RR 5.0) than for women with children (RR 1.3).

Midlife women are particularly vulnerable to depressive mood; the changing hormonal milieu during the menopausal transition contributes to increased prevalence of depressive symptoms and to the worsening of the cardiovascular disease profile (Janssen et al., 2011). Among miscarrying women with a history of major depressive disorder, 54% experience a recurrence later in life.

Symptoms of depression and major depressive disorder have been identified as potential risk factors for coronary heart disease (Janssen et al., 2011). Longitudinal studies have consistently shown that persons with high levels of depressive symptoms, or with a history of major depressive disorders, are more likely to have clinical coronary events than persons without depression. Major depression and depressive symptoms are associated with cardiovascular disease, but the impact of depression on early atherogenesis is less well known (Janssen et al., 2011). Anxiety and/or depression may be a risk factor for cardiovascular diseases in women with RPL.

8. Vascular dysfunction in children of women with PRL

Previous studies suggested that the atherogenic process in humans has already started during fetal development (Napoli et al, 1997). Intrauterine exposure to maternal atherosclerotic risk factors may increases the susceptibility to atherosclerosis in adult life (Alkemade et al., 2007). In a morphometric postmortem analysis of atherosclerosis in fetuses and children (Fate of Early Lesions in Children Study), it is demonstrated that specifically maternal hypercholesterolemia is associated with a higher incidence of atherosclerotic lesions during the fetal period and a faster progression of these atherosclerotic lesions after birth even under conditions of normocholesterolemia in the offspring (Napoli et al, 1999).

8.1 Perinatal arterial ischemic stroke (PAS)

Perinatal arterial ischemic stroke (PAS), defined as a thromboembolic event occurring before age 28 days, is an increasingly recognized cause of neurological disabilities such as cerebral palsy, epilepsy, and cognitive abnormalities (Lee et al., 2005). PAS occurs at a frequency of 1/1600 to 1/5000 live births (Chabriera et al., 2010). Previous fetal loss, first pregnancy, primiparity, twin-gestation, cesarean and traumatic delivery, neonatal distress, male sex and premature rupture of membranes in PAS were statistically more common than in the general population (Chabriera et al., 2010).

PAS may result from thrombosis of intracranial vessels or from embolism from another site such as extracranial vessels, heart, umbilical vein, or placenta (Nelson, 2007). Although the site of origin is usually not clearly established, it is suspected that the fetal side of the placenta may often be the source. In addition to cerebral infarction, thrombosis in other sites, including kidney, heart, aorta, and limb arteries, is more common in neonates than at other times in childhood.

Antiphospholipid antibodies in women RPL may pass from mother to child via the placenta, can alter the placenta itself and may be a risk for PAS. The inherited thrombophilias both in mothers and fetuses may cause RPL and PAS in neonates (Nelson, 2007). It seems likely that maternal and perhaps infant thrombophilias can lead to complications of pregnancy, such as RPL, preeclampsia, placental abruption, placental vasculopathy, and fetal growth restriction, which are in turn risk factors for neonatal encephalopathy, stroke, or cerebral palsy (Nelson, 2007).

8.2 Genetic risk factors

Complications of pregnancy such as preeclampsia, which are observed in untreated and treated women with PRL, link to low birth weight. Previous studies have shown an association between an individual's birth weight and his or her subsequent risk of ischemic heart disease, hypertension, and diabetes mellitus (Hübinettea et al., 2001). Barker and colleagues have postulated that fetal adaptation to inadequate intrauterine nutrition, due to poor maternal diet or placental dysfunction, results in physiological programming of a "thrifty phenotype", which increases the risk of hypertension and ischemic heart disease in later life (Barker et al., 1989).

An alternative hypothesis is that common genetic factors predispose to fetal growth restriction, preterm birth, and ischemic heart diseases. Common genetic risk factors might explain the link between birthweight and risk of ischemic heart disease in both the mother and the child (Smith et al., 2001). A genetic link would be consistent with the much stronger association between birthweight and ischemic heart disease in the mother (11-fold) (Smith et al., 2001) than in the offspring (1.5–2.0-fold) (Barker et al., 1989). Maternal genes might modulate fetal growth both by affecting the intrauterine environment, for instance by effects on uterine blood flow, and by inheritance of genes from the mother that regulate fetal growth directly.

Epidemiological studies also provide evidence for common genetic links. Fathers of low-birthweight babies are at increased risk of coronary heart disease, hypertension, and diabetes (Smith et al., 2001). Children and their mothers, who experienced RPL, may have common genetic factors linked to cardiovascular diseases.

9. Treatment of pregnancy loss and prevention of cardiovascular diseases

Currently, low-dose aspirin treatment is used as an effective therapy for women with RPL associated with anti-phospholipid antibodies (Coulam et al., 1997). It has been reported that low-dose aspirin is effective in improving implantation and pregnancy rates in the IVF programme (Rubinstein et al., 1999). Two trials demonstrated that women without hereditary thrombophilia and at least three unexplained consecutive losses randomized to prophylactic low molecular weight heparin had higher live birth rates than those assigned to placebo or no treatment (Bates, 2010).

Antiphospholipid antibodies are more common in patients with thrombosis but a causal association is unproven and the clinical relevance of transient or low titer antiphospholipid antibodies remains uncertain (Lim et al., 2006). In patients with APS, moderate-intensity warfarin is effective for preventing recurrent venous thrombosis and perhaps also arterial thrombosis. Aspirin appears to be as effective as moderate-intensity warfarin for preventing

recurrent stroke in patients with prior stroke and a single positive test result for antiphospholipid antibody. Many patients with myocardial infarction and antiphospholipid antibodies are treated by warfarin.

The relationship between preeclampsia and stroke involves shared risk factors for both disorders, including chronic endothelial dysfunction and increased risk for long-term hypertension following preeclampsia, one of the major risk factors for stroke (Bushnell & Chireau, 2010). Thrombophilic conditions and Vitamin D deficiency (Grant, 2009) has emerged as an important potentially modifiable risk factor for both preeclampsia and stroke. These overlaps provide insights into underlying pathophysiology and potential preventive strategies for both preeclampsia and stroke. For example, aspirin or Vitamin D may prevent both disorders.

Early changes in vascular function are detected in mildly-hypertensive women with PCOS (Sasaki et al., 2011). All women diagnosed with PCOS are not likely to share the same cardiovascular risk profiles and increased mortality and morbidity rates from cardiovascular disease in the PCOS population. However, lifestyle intervention such as diet and exercise should be the first-line of treatment in women with PCOS, particularly if they are hypertensive or overweight.

It is unlikely to treat all young women with aspirin following the occurrence of PRL without any other risk factors. Pharmacological therapies for hypertension, insulin resistance, or dyslipidemia are also available but should be tailored on an individual basis. It is important to evaluate arterial stiffness to identify women at early risk of cardiovascular disease and stroke and ultimately assess the risks and benefits of various prevention approaches.

10. Conclusion

Women who experienced RPL are at a substantially higher risk of vascular dysfunction, which leads to coronary heart disease, stroke, or VTE later in life. Reproductive history of obstetrical complications associated with RPL such as preeclampsia, premature delivery, fetal growth restriction, placental abruption, and gestational diabetes mellitus could be considered a "failed stress test," possibly unmasking early or preexisting vascular dysfunction and vascular or metabolic diseases. Therefore, these women should be carefully monitored and controlled. Healthcare professionals who meet women for the first time later in their lives should take a careful and detailed history of RPL and characteristic pregnancy complications.

Further studies will provide more information on association between PRL and vascular dysfunction, effective treatment for both women with PRL and their fetuses.

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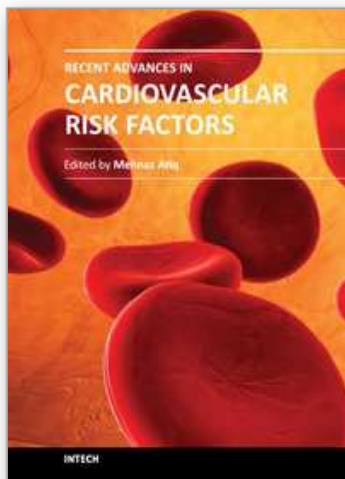
Among the non-communicable diseases, cardiovascular disorders are the leading cause of morbidity and mortality in both the developed and the developing countries. The spectrum of risk factors is wide and their understanding is imperative to prevent the first and recurrent episodes of myocardial infarction, stroke or peripheral vascular disease which may prove fatal or disabling. This book has tried to present an update on risk factors incorporating new research which has thrown more light on the existing knowledge. It has also tried to highlight regional diversity addressing such issues. It will hopefully be resourceful to the cardiologists, general practitioners, family physicians, researchers, graduate students committed to cardiovascular risk prevention.

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