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Editorial

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Parity and Maternal Cardiovascular Disease

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Metabolic Changes in Normal Pregnancy

Insulin resistance and hyperinsulinemia are observed during a normal pregnancy and are most common in the third trimester due to hormonal changes including elevations in human placental lactogen, progesterone, cortisol, and estradiol. Placenta expresses several proinflammatory cytokines; pregnancy is a state of low-grade inflammation, which may also contribute to the development of insulin resistance in a normal pregnancy[1].

Serum triglyceride (TG) and low-density lipoprotein-cholesterol (LDL-C) decrease in the first 8 weeks of pregnancy then gradually rise throughout pregnancy, peaking at delivery. TG increases by 200%–300% during normal pregnancy, while LDL-C increases by 40%. Following delivery, TG and LDL-C levels return to pre-pregnancy levels by 6 and 8–16 weeks after delivery, respectively[2]. During early pregnancy, insulin sensitivity increases and glucose decreases, due to increased glucose uptake by the fetus/placenta. Insulin sensitivity decreases as pregnancy progresses and serum insulin levels increase by over 60% in the third trimester; postprandial glucose levels also rise. Glucose levels and insulin requirements rapidly return to pre-pregnancy levels within 72 hours after delivery in a normal pregnancy[3]. A decrease in systemic vascular resistance occurs during pregnancy, leading to a drop in both systolic and diastolic blood pressure in early pregnancy, slowly rising back to pre-pregnancy levels throughout the third trimester. Blood pressure returns to pre-pregnancy levels within 2 weeks after delivery[4]. Pregnancy and childbirth are life events that greatly impact the maternal blood vessels.

Parity and Risk of Maternal Cardiovascular Disease

Recently, a meta-analysis of cohort studies to assess quantitatively the association between parity and cardiovascular disease (CVD) risk was performed[5]. Ten cohort studies including about three million participants from the US, European countries and China were included. A significant association between parity and CVD risk was observed while comparing parity with nulliparity, with a relative risk of 1.14 (95% CI, 1.09–1.18; P=0.002). However, the association between parity and metabolic risk factors remained unknown.

In the current issue, Egawa *et al.* reported that the prevalence of arteriosclerotic CVD (ASCVD) was highest in Japanese women with three or more children, using the data from 32,000 women aged ≥ 50 years obtained from the Tohoku Medical Megabank database[6]. Compared with nulliparous women, those who had a higher number of children had a higher body mass index (BMI), increased waist circumference, increased weight change from age 20 years, and higher blood pressure. As the number of children increased, so did the prevalence of hypertension and type 2 diabetes, and the rate of such diseases was highest in the group with three or more children. Blood glucose and TG were highest, and high-density lipoprotein-cholesterol was lowest in the group with three or more children. To my knowledge, this study is the first to show unfavorable effects of multiparity on metabolic risk factors such as atherogenic dyslipidemia and elevated blood pressure and plasma glucose. Further, the authors demonstrated the possibility that multiparity is a significant risk for ASCVD independent of obesity by using the heatmap analysis. However, it still remains unknown how multiparity induces obesity, metabolic disorders, and ASCVD. The information after pregnancy such as

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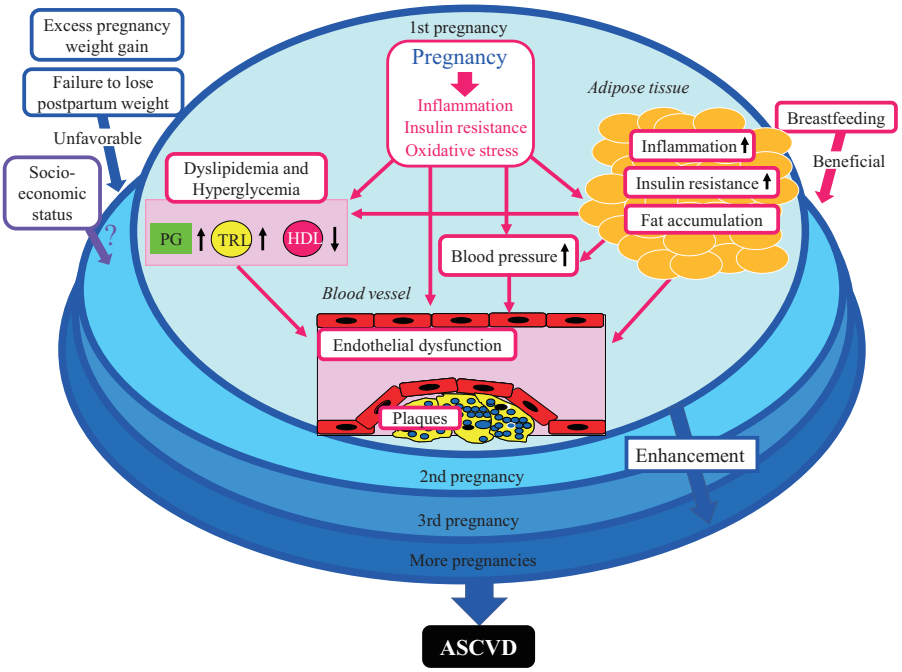

Fig. 1. Possible underlying mechanisms of ASCVD development due to multiparity

ASCVD, arteriosclerotic cardiovascular disease; HDL, high-density lipoprotein; PG, plasma glucose; TRL, triglyceride-rich lipoprotein.

socio-economic status, breastfeeding, miscarriage, and stillbirth is necessary to elucidate the association between multiparity and ASCVD risk.

Although the association of multiparity with the ASCVD risk factors remains largely unknown, I personally speculate possible underlying mechanisms for the development of ASCVD due to multiparity as shown in **Fig. 1**. Pregnancy induces systemic inflammation, insulin resistance, and oxidative stress leading to elevation of inflammatory cytokines, insulin resistance, and fat accumulation in adipose tissue. Pregnancy itself and altered adipocytes due to pregnancy induce atherogenic dyslipidemia and elevate blood pressure and plasma glucose, resulting in vascular damage such as endothelial dysfunction. A recent study showed that greater parity was associated with higher levels of adipokines such as resistin and leptin[7], suggesting altered adipocytes due to repeated pregnancies.

Perinatal weight changes, excess pregnancy weight gain, and failure to lose postpartum weight have been suggested to crucially influence long-term obesity and obesity-related illnesses such as CVD[8]. Although the factors which determine excess pregnancy weight gain and failure to lose postpartum weight remain largely unknown, breastfeeding has beneficial effects on preventing postpartum abdominal obesity[9], and multiparity is associated with higher pre-pregnancy BMI[10].

Multiparity has been reported to induce endothelial dysfunction by increasing oxidative stress[11]. Furthermore, a significant association of multiparity with carotid plaque and intima media thickness was observed[12]. The cumulative effect of metabolic and adipokines abnormalities (metabolic memory), endothelial dysfunction, and atherosclerotic plaques (vascular memory), due to repeated pregnancy, may be involved in the development of ASCVD.

Conflicts of Interest

None.

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