Chapter

Metabolic Syndrome and Pathogenesis of Obesity-Related Adverse Outcomes in Pregnancy

Motoi Sugimura

Abstract

Obese women with metabolic syndrome are at increased risk for cardio-thrombo-metabolic dysfunction that leads to pregnancy-related venous thromboembolism (VTE), hypertensive disorders of pregnancy (HDP), and gestational diabetes mellitus (GDM). Indeed, maternal death secondary to a pregnancy-related VTE has an enormous impact on the childbearing population. Recent research has provided evidence that elucidates the pathogenesis of adverse outcomes in obese pregnant women with metabolic syndrome. The chronic inflammation elicited by dysregulated infiltration of macrophages into adipose tissue and increased thrombin generation by inflammatory cytokines with activation of the tissue factor pathway may play important roles in the pathogenesis; however, a simple question has yet to be answered. Specifically, "why does prepregnancy obesity increase the risk of pregnancy-related VTE in association with a high estrogenic and prothrombogenic state?" The present review of the extant literature has focused on further understanding obesity-related adverse outcomes in pregnancy by elucidating the underlying pathogenesis of metabolic syndrome.

Keywords: obesity, metabolic syndrome, pregnancy-related venous thromboembolism, hypertensive disorders of pregnancy, gestational diabetes mellitus, inflammatory cytokines, thrombin formation, estrogen

1. Introduction

Epidemiologic studies in North America and Europe have shown that obesity increases the risk of venous thromboembolism (VTE) during pregnancy and the puerperium [1, 2], as well as postpartum hemorrhage [3]. Furthermore, women with prepregnancy obesity are also at increased risk of hypertensive disorders of pregnancy (HDP) [4, 5], including preeclampsia [6]. HDP is associated with placental abruption, which may lead to severe obstetric complications with disseminated intravascular coagulation (DIC) [7].

Recent research has shown that HDP and gestational diabetes mellitus (GDM) increase the risk of hypertension and diabetes mellitus (DM) later in life [8]. Conversely, maternal malnutrition during pregnancy because of inadequate dietary intake increases the risk of fetal growth restriction and low-birth-weight infants; it is increasingly evident that offspring are at increased risk of developing hypertension and DM as well [9]. Indeed, addressing nutrition and weight gain before pregnancy are an important part of perinatal care [10].

Thus, prepregnancy body weight and changes in weight gain during pregnancy may be indicators of maternal nutritional status, reflecting the balance between caloric intake and basal metabolism and exercise caloric expenditure [11].

Although hypertension and DM in obese patients with metabolic syndrome [12] are worrisome with respect to future health issues and increased mortality rate, pregnancy-related VTE has a greater and more direct impact on families among the childbearing population. Based on the annual report of the trends in maternal deaths and maternal mortality rates by cause of death from the Japan Ministry of Health, Labor, and Welfare in 2017 [13], the number of maternal deaths in Japan has decreased over time; however, 70% of maternal deaths are caused by hemorrhage, pulmonary embolism (including pulmonary thromboembolism and amniotic fluid embolism), and HDP. The percentage of maternal mortalities by cause of death has remained essentially unchanged over the past two decades, as shown in **Figure 1**. Increasing maternal age [14] due to changes in social lifestyle, advances in assisted reproductive medicine, and increased cesarean section rates may also be important factors in maternal deaths in Japan and developed countries worldwide [15]. Changes

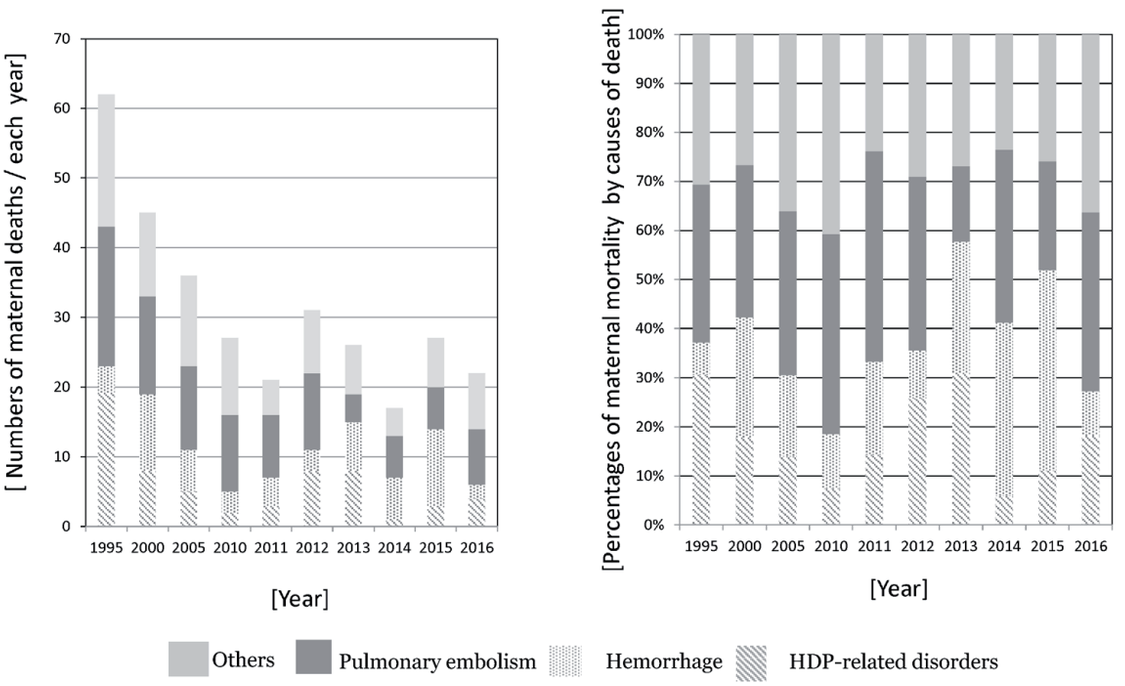

Figure 1.
Trends in maternal deaths and maternal mortality rates (per 100,000 total births) by causes of death in Japan.

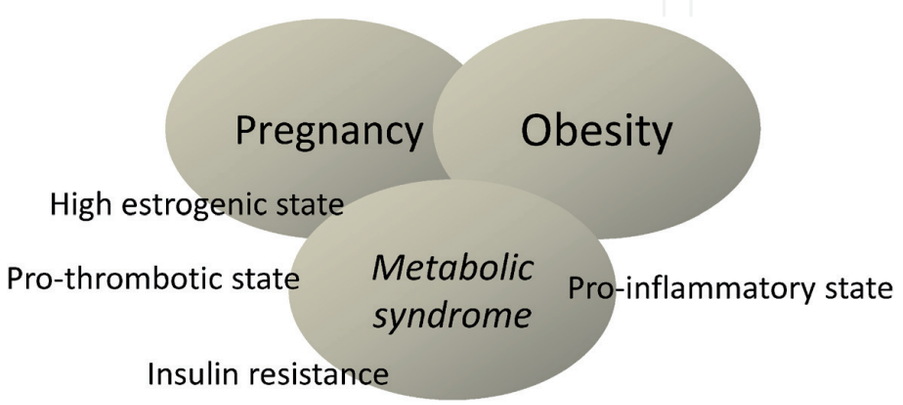

Figure 2.
Pathogenesis of obesity-related adverse outcomes in pregnancy with a similar background to metabolic syndrome. Key words are pro-inflammatory state with insulin resistance and a prothrombotic state with a high estrogenic state in obese pregnant women.

in dietary habits and a sedentary modern lifestyle are partly responsible for prepregnancy obesity, which is followed by obesity-related adverse outcomes in pregnancy.

A growing number of epidemiologic observations on obesity in pregnancy have linked basic research findings [16] with the pathogenesis of obesity-related adverse outcomes in pregnancy with a similar background to metabolic syndrome [12, 17], as shown in **Figure 2**.

2. Obesity-related adverse outcomes in pregnancy

2.1 Pathogenesis of obesity-related adverse outcomes in pregnancy with a background of metabolic syndrome

In recent years, visceral fat has been regarded as one of the endocrine organs [18]. Visceral fat plays an important role in the pathogenesis of local and systemic chronic inflammation in obese patients [19]. A large number of studies have demonstrated a relationship between obesity and the pathophysiology underlying metabolic syndrome, specifically involving dysfunction of adipocytes with reduced adiponectin and innate immune cells with subsequent production of inflammatory cytokines [16]. Inflammatory cytokines induce tissue factor (TF) and enhanced thrombin generation by up-regulation of TF expression on various types of cells (**Figure 3**). Enhanced thrombin generation consecutively leads to inflammation, thrombus formation, and vascular damage due to activation of the cell signaling system via protein-activated receptors (PARs) [20] with TF as a receptor [21]. The induction of cytokines and thrombin generation interacts with the crosstalk between coagulation and inflammation [22, 23].

Adipose tissue formed by adipocytes with fat accumulation increases the level of triglycerides and decreases the adiponectin level. The tissue also activates immunocompetent cells, such as macrophages and mast cells, which produce and release pro-inflammatory cytokines (TNF-α, IL-6, IFN-ϒ, and IL-1β) [24]. The induction of TF on the cell surface of adipocytes and macrophages accelerates the prothrombotic state accompanied by thrombin generation. With respect to the high estrogenic state in pregnancy, prothrombotic conditions are likely to be induced in obese women because of the additional effects of dietary, social, environmental, and genetic factors which increase the risk of pregnancy-related VTE, although the precise mechanisms are still uncertain.

The most recent hypothesis regarding the pathogenesis of HDP suggests that impaired trophoblastic invasion into the inner myometrial portion of the spiral arteries causes the vessels to retain musculoelastic properties, thereby inducing hypoperfusion and hypoxia [25]. The subsequent release of inflammatory cytokines [26] promotes the excess production of soluble fms-like tyrosine kinase 1 (sFLT1) [27], which binds to VEGF as a decoy instead of VEGFR. The cytokines may also enhance maternal inflammatory responses and systemic endothelial dysfunction, leading to maternal symptom [28]. The resulting inflammatory cytokines induce TF, which subsequently initiates the TF-dependent coagulation pathway as the receptor for coagulation factors VIIa/VII [29]. In a vicious cycle, activation of the coagulation system and thrombin formation in the placental intervillous space enhances the production of sFLT1s through G protein-coupled protease-activated receptors [30] and causes further ischemic damage to trophoblastic cells in a hypercoagulable state [31, 32], as shown in **Figure 4**.

As one of the current hypotheses of the pathogenesis in pregnancy-related VTE and HDP, these observations provide the probable relationship between the high estrogenic state of pregnancy and prothrombotic conditions caused by chronic

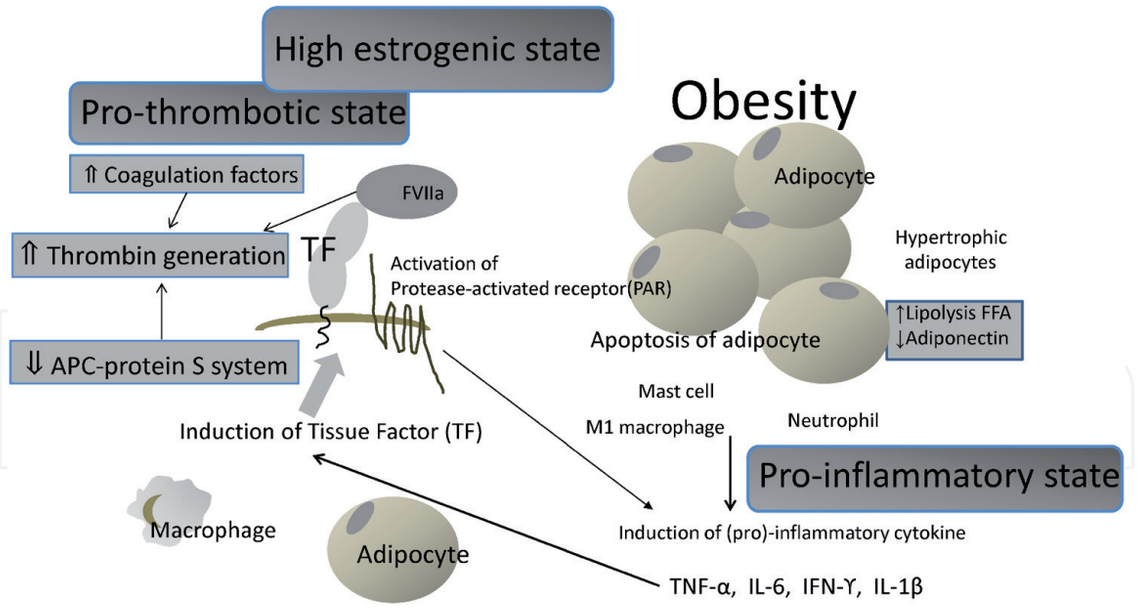

Figure 3.
Enhanced thrombin generation by tissue factor (TF) with activation of protease-activated receptor (PAR). The increased coagulation factors and reduced sensitivity to activated protein C in pregnancy accelerate the enhanced thrombin generation on tissue factor (TF) induced by (pro)-inflammatory cytokines (TNF-α, IL-6, IFN-ϒ, and IL-1β). The formed thrombin induces (pro)-inflammatory cytokines via activation of the protease-activated receptor (PAR).

inflammation due to the obesity with metabolic syndrome, although there is a lack of high-quality evidence (**Figure 5**).

2.2 Epidemiologic aspects of obesity-related adverse outcomes in pregnancy

Prepregnancy body mass index (BMI), weight changes during pregnancy, and perinatal prognosis are the epidemiologic aspects of obesity-related adverse outcomes in pregnancy.

Although various academic societies have recommended guidelines for optimal weight gain and nutrition during pregnancy, the basic concept for the management of maternal nutrition has changed over time based on epidemiologic data. From the view of adverse maternal outcomes in North America in the first half of the twentieth century, a weight gain of 9.1 kg throughout pregnancy was recommended to prevent HDP and operative deliveries, such as cesarean section and forceps deliveries, because of macrosomic fetuses.

By the 1970s, at least 11.4 kg of weight gain during pregnancy was recommended to prevent spontaneous preterm births, fetal growth restriction, and adverse neonatal outcomes [33]. In the 1990s, the BMI classification was introduced as a means to establish optimal weight gain based on body weight and surface area. A weight gain of 11.5–16 kg was recommended in pregnant women with a normal prepregnancy BMI (19.8–26 kg/m^2) [17].

During pregnancy, it is preferable to increase caloric intake by approximately 390 kcal per day with small variations in addition to the daily caloric intake during non-pregnancy [34]. Insufficient calorie intake leads to increased proteolysis and the lack of nutrition for fetal growth. Strict limitation of weight gain during pregnancy may increase the risk of preterm birth and fetal growth restriction [33], which is why an 11–16 kg weight gain is recommended for women with a normal prepregnancy BMI in North America [35]. Maternal weight gain with excessive calorie intake increases the risk of dystocia with macrosomic fetuses. Recent research has also suggested that maternal obesity increases the risk of childhood obesity [36] and the risk of autism spectrum [37].

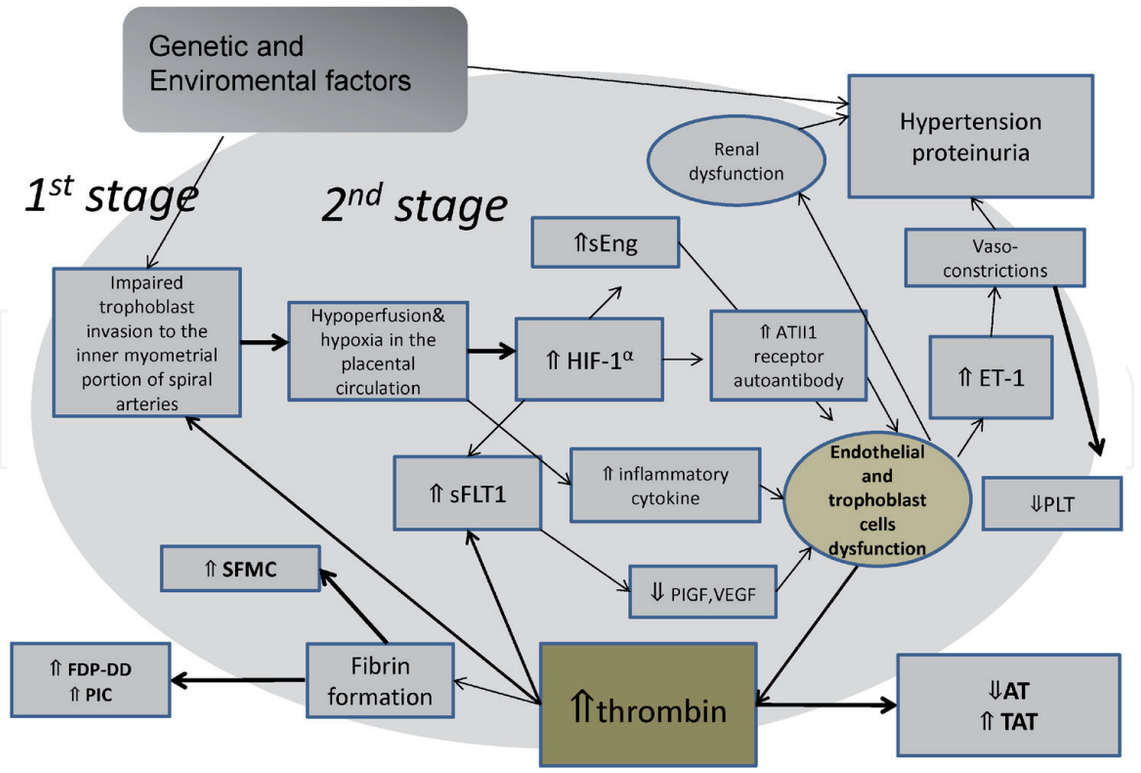

Figure 4.
Pathogenesis of hypertensive disorders of pregnancy (HDP). The important role of thrombin generation in the "two-stage disorder" theory for the pathogenesis of HDP. sEng: soluble endoglin, HIF-1α: hypoxia-induced factor, ET: endothelin, AT: angiotensin, sFLT1: soluble FLT1, PlGF: placental growth factor, VEGF: vascular endothelial growth factor, AT: antithrombin, TAT: thrombin-antithrombin complex, SFMC: soluble fibrin-monomer complex, PIC: plasmin-α 2-plasmin inhibitor complex.

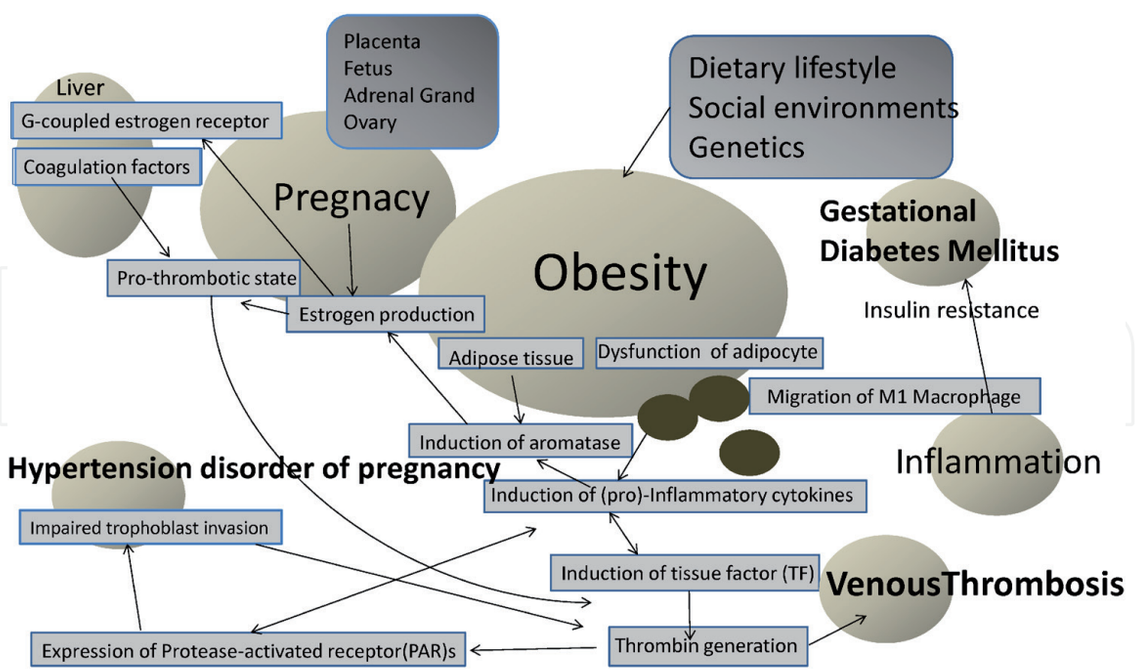

Figure 5.
Pathogenesis of obesity-related adverse outcomes in pregnancy. The critical role of the induction of pro-inflammatory cytokines by dysfunction of adipocytes with fat accumulation initiates the thrombin generation of tissue factor (TF) in various cells. The prothrombotic state with estrogen-induced hypercoagulability plays a role in the pathogenesis of venous thrombosis and hypertensive disorders of pregnancy.

The Institute of Medicine (IOM) guidelines in 2009 recommended that weight gain during pregnancy should be 0.3 kg/week for women who are overweight before pregnancy (25–29.9 kg/m^2) and 0.18 kg/week for women who are obese

(>30 kg/m^2) after the second trimester [38]. In addition, the IOM recommended an 11.3–15.8 kg weight gain during pregnancy for women with a normal prepregnancy BMI (18.5–24.9 kg/m^2), 6.8–11.3 kg for women who are overweight before pregnancy, and 4.9–9.0 kg for women who are obese before pregnancy. In 2015, the American College of Obstetricians and Gynecologists (ACOG) recommended a similar proposal in an ACOG Practice Bulletin [10]; however, it has been shown that women who are overweight and obese before pregnancy with inappropriate weight gain and loss during pregnancy are at increased risk for fetal growth restriction [39] due to pathologic placental changes [40].

In recent years, although underweight pregnant women with a prepregnancy BMI ≤18.5 kg/m^2 have a reduced risk of HDP compared with obese pregnant women, a decrease in newborn birth weight in underweight pregnant women is associated with future health problems [41]. With respect to fetal programming, future health issues in adulthood should focus on the relationship between an increased risk for essential hypertension and DM [42] and low birthweight infants. Barker's hypothesis in the 1980s [43] was based on epidemiologic observations of malnutrition during pregnancy in World War II and underweight children with an increased risk for hypertension (ischemic heart disease) and DM in adulthood.

Malnutrition is a significant problem in the developing countries. There is a relatively high prevalence of women of childbearing age who are obese worldwide [44]. During pregnancy, obesity with metabolic syndrome shares an underlying pathogenesis of cardio-thrombo-metabolic dysfunction and further worsens the health status. Specifically, pregnancy-related VTE and sudden maternal death have a greater impact [45] on the family and society compared with HDP and GDM.

2.3 Pregnancy-related VTE in the UK and North America

In Europe, especially in the United Kingdom, with a background of heritable thrombotic predisposition, medical journals have reported clinical cases of maternal deaths due to VTE since the 1860s [46, 47]. National policy in the UK has provided guidance to reduce maternal mortality from pregnancy-related VTE [45, 48]. Epidemiologic and clinical studies have focused on pregnancy-related VTE [49] and showed the relationship between VTE and prepregnant obesity in pregnant women [50]. Multivariate analysis of prepregnant obese patients compared with non-obese patients as controls demonstrated that the adjusted odds ratio (aOR) is 1.93 (95% CI, 1.10–3.39) for VTE in the moderately obese group and 4.32 (95% CI, 1.26–14.84) for VTE in the highly obese group, as shown in 2008 [49].

Studies focusing on prepregnancy BMI and immobilization in the hospital showed a further increased risk of VTE during pregnancy and postpartum [49]. The aOR for VTE in pregnant women with a prepregnancy BMI >25 kg/m^2 is 1.8 (95% CI, 1.3–2.4). During immobilization with bed rest, the aOR for VTE increases to 62.3 (95% CI, 11.5–337.6) in patients with a BMI >25 kg/m^2 [49]. The aOR for VTE in patients with a prepregnancy BMI >25 kg/m^2 is 2.4 (95% CI, 1.7–3.3) during the postpartum period. The aOR is 40.1 (95% CI, 8.0–201.5) in a similar condition [49]. These epidemiologic data have supported the guidelines for the prevention and reduction in the risk of pregnancy-related VTE in the UK [51, 52] and North America [53].

The Royal College of Obstetricians and Gynecologists published data in 2015 that indicated 60% of women who died of pulmonary thromboembolism (PE) between 2003 and 2008 were obese with a BMI ≥30 kg/m^2. The prevalence of obesity with a similar BMI at 16–44 years of age in the population was 20% in the UK [52]. Pregnancy is a risk factor for VTE, and the risk increases in proportion to the degree of obesity. Obese pregnant women had a higher aOR for PE

(aOR, 14.9; 95% CI, 3.0–74.8) than for deep vein thrombosis (DVT) (aOR, 4.4; 95% CI, 1.6–11.9). The risk for pregnancy-related VTE is minimal in overweight pregnant women who had a prepregnancy BMI of 25–29.9 kg/m^2; however, the guidance in the UK states that VTE risk in overweight women is extremely common, affecting nearly 50% in the childbearing population [52].

Obesity with a BMI of 3040 kg/m^2 alone is classified as a lower risk category for VTE according to the guidelines [52]. However, pregnant women with a BMI of 30–40 kg/m^2 are classified as having an intermediate risk if they have two or more additional risk factors, including elective cesarean section, prolonged labor (>24 h), and operative delivery. These risk factors are more likely encountered in daily clinical situations compared with a history of VTE.

The American College of Chest Physicians has also proposed similar guidelines to prevent pregnancy-associated VTE in obese pregnant women based on epidemiologic risk [51, 53]. Specifically, the American College of Chest Physicians showed that the occurrence of VTE is 3% among all women in the puerperium and the OR increases to >6 compared with women with a normal prepregnancy BMI if obese pregnant women with a prepregnancy BMI ≥30 kg/m^2 are combined with those with other risk factors in women undergoing emergency cesarean section [53].

Epidemiologic observations have suggested that obesity and pregnancy are related to the prothrombotic state. The pathophysiology of metabolic syndrome may, in part, provide insight into understanding the increased hypercoagulable status with obese women in pregnancy with a high estrogenic state.

2.4 Obesity and estrogen

Estrogens are a type of sex steroid hormone. The endogenous estrogens are classified into estrone (E1), estradiol (E2), estriol (E3), and esterol (E4) [54]. Estrogens were initially thought to be female hormones; however, it has recently been shown that estrogens are involved not only in female physiologic functions but also in male reproductive physiologic functions. Recent studies have explored the bioactivity of estrogen in the neuroendocrine [55], vascular [56], musculoskeletal [57], and immune systems. Estrogen is associated with the pathogenesis of infertility, obesity [58], osteoporosis, endometriosis [59], and various types of cancers [60]. Estrogen crosses the cell membrane and binds to estrogen receptor (ER) α and ERβ in the cell as a ligand and estrogen receptors (mERs) on the cell membrane as ligands. Then, estrogen regulates the expression of gene products by binding to a specific DNA sequence, the hormone response element [61].

In pregnancy, the placenta and fetal adrenal cortex are the main estrogen production sites. E3 is produced through the maternal liver, placenta, and fetal adrenal gland, although E2 is mainly produced by ovarian granulosa and capsular cells in women of reproductive age. By contrast, estrogen is produced in testicular stromal Sertoli cells in men [62]. The physiologic hormonal bioactivity is the highest in E2 and then decreases in the order of E1 and E3.

Epidemiologic observations have shown that obesity increases the risk of estrogen-dependent breast [63] and endometrial cancer [64].

As described above, apoptotic cell death of adipocytes in adipose tissue by overstored fat in obese patients induces the migration of macrophages to the tissues [19, 65]. Consequently, chronic inflammation caused by pro-inflammatory cytokines, such as TNFα and IL-8, leads to activation of the NF-κB signaling system and increased aromatase activity in various cells, including adipocytes, thus resulting in estrogen production [66]. Although the abnormal regulation of aromatase activity in adipose stromal cells in response to various inflammatory mediators involves a complex signaling pathway, visceral fat, which contributes to obesity,

plays an important role in the local and systematic production of estrogen [67]. The enhanced production of estrogen can be associated with the upregulated production of coagulation factors that may lead to the induction of a prothrombotic state.

2.5 Estrogen and prothrombotic state

As described above, it is widely accepted that the risk of VTE is increased during pregnancy and the puerperium. The hypercoagulable state with elevated maternal estrogen levels during pregnancy is, in part, one of the explanations for the pathogenesis, although the mechanism has not been fully elucidated.

Maternal estrogen levels during pregnancy increase enormously over the course of pregnancy, reaching concentrations approximately 100–500 times higher than non-pregnant levels [68]. Ninety percent of urinary estrogens are the conjugated form of E3, which has a 500- to 1000-fold higher concentration compared with non-pregnant women. The rapid increase in maternal estrogen levels is mainly due to the enhanced production of estrogen from the ovaries until the seventh week of gestation. Thereafter, the main origin of estrogen production shifts from the ovary to the fetal placental tissues [69].

LDL cholesterol is the main source of dehydroepiandrosterone sulfate (DHEA-S) in the fetal adrenal gland [69]. The 16α-hydroxylase converts a part of DHEA-S to 16OH-DHEA-S in the fetal liver, and the sulfatase and aromatase in the placenta convert the substrates to E2 and E3, which is followed by the secretion of E2 and E3 into the maternal blood [70]. Therefore, the fetal placental system gives rise to higher estrogen status, especially at the end of pregnancy.

By contrast, the high estrogen levels in pregnancy show abrupt reductions during the postpartum period because of the delivery of the placenta and fetus; the placenta is the main organ of estrogen production. Epidemiologic observations demonstrate that the risk of developing VTE during the puerperium is the highest within 1 week after delivery and then the risk of VTE decreases gradually 2 weeks after delivery. From the intrapartum to the postpartum period, the high levels of inflammatory cytokines associated with the onset of labor change dramatically [71]. Because of the changes in the levels of coagulation factors, endothelial injury, and stasis of blood flow [72], which are related to the onset of VTE, it is difficult to evaluate how estrogen-related coagulation factors are involved in the pathogenesis of VTE.

In 1961 [73], a patient with oral contraceptive (OC)-related VTE presented after taking an OC. Initially, the pathogenesis of VTE was understood to be simply due to dehydration caused by vomiting after taking the OC. Recently, upregulated production of coagulation factors by ethinyl E2 (EE2), a synthetic E2 that is less metabolized in the digestive system, is seen as a potential cause of VTE [74]. There is a significant correlation between the amount of EE2 contained in OCs and the increased risk of developing a VTE in an estrogen-dependent manner, which has led to the development of OCs containing ultra-low-dose estrogen (<50 μg) [75].

The current formulation of combined OCs (COCs) is a fourth-generation COC, which is defined as those containing a new type of progestin. However, different risks of VTE have been presented in COCs with different types of progestins instead of a low-dose estrogen (<50 μg) [76].

Some reports have suggested significant differences between second-generation COCs and third-generation COCs in the level of various coagulation factors [77]. These reports have speculated that the different progestins in COCs may be associated with the increased risk of OC-related VTE because of changes in coagulation. Prothrombin and factor VII levels are significantly increased in third-generation COCs compared with that of second-generation COCs. Furthermore,

the activated protein C resistance by the aPTT method and the endogenous thrombin potential (ETP) method has been shown to be greater in third-generation COCs compared with that of second-generation COCs. These observations may indicate the probable relationship between female hormones and a thrombophilic tendency [77].

The second- and third-generation COCs have a different type of synthetic progestin. Although the mechanisms are not fully understood and are controversial [78], some studies have indicated that a small statistical difference exists in the risk of developing VTE [76].

Interestingly, unlike EE2, the endogenous estrogen 17β-E2 is rapidly metabolized by 17β dehydroxysteroid dehydrogenase [79] to E1 with less estrogenic activity. A COC containing a low dose of 17β-E2 has a relatively little effect on changes in the levels of coagulation factors [80]. Therefore, a COC containing 17β-E2 has been approved in Europe as a novel COC [81].

However, it is unclear how much of the endogenous estrogen (E2 and E3) in pregnant women magnifies the risk of pregnancy-related VTE compared with that of non-pregnant women. The changes in coagulation factors by female hormones do not provide strong evidence with the understanding of the mechanisms in the developing of VTE so far.

The changes in various markers of coagulation and fibrinolysis during the postpartum period of pregnancy have shown a significant increase in the levels of fibrinogen, FV, FVII, FVIII, and FX after pregnancy compared with that of non-pregnancy [82].

Focusing on the inhibitory coagulation factor, protein S, which acts as a coenzyme in the activated protein C system, is significantly reduced during pregnancy [83]. In fact, 17β estradiol acts on ER-mediated suppression of the protein Sα gene (PROS1) mRNA and antigen production in a hepatocellular carcinoma-derived cultured cell line (HepG2) in an *in vitro* experimental system [84]. The experiment in a cultured cell line suggests that the increased estrogen during pregnancy can suppress protein S production. In addition, a report describes that a decrease in free protein S level due to an increase in C4b-binding protein during pregnancy is also associated with a decrease in protein S during pregnancy [85]. The changes in the various coagulation-fibrinolysis-related factors quickly return to the prepregnancy state during the postpartum period.

To confirm the hypothesis that the maternal high estrogenic conditions in pregnancy are related to the onset of the pregnancy-related VTE, previous research provided data on the changes in thrombin generation in an experiment with animals treated with exogenous estrogen [86] and the *ex vivo* determinants of thrombin potential reflecting prothrombotic conditions in pregnant women [87].

A variety of thrombin generation tests for evaluating the hypercoagulable state have been proposed for clinical samples derived from patients [88]. An *ex vivo* clotting assay has been the classical method, such as the aPTT and PT methods [88]. These clotting time assays initiate the coagulation reaction by adding a coagulation-inducing substance, thromboplastin, into sample plasma and estimate the thrombin activity based on the fibrin clot formation time.

By contrast, as an alternative standardized method to evaluate the production of thrombin, the thrombin generation test by the endogenous thrombin potential (ETP)-based method was presented [89]. In this method, the extrinsic coagulation cascade is activated in the presence of calcium ions by adding standardized phospholipids containing recombinant tissue factor into samples. The amount of thrombin generated is calculated from continuous measurement of the changes in fluorescence emission (or coloring) of the synthetic substrate. The activity measured over time and integrated is defined as ETP.

In aPTT- and PT-based methods, by measuring the time to fibrin clot formation, these reactions terminate at the time of clot formation; however, thrombin continues to be formed after the termination of clot formation and the activity is maintained in the fibrin clot as the trapped form in α-2 macroglobulin. Compared with the thrombin activity measured by the PT-based method, the activity by the ETP-based method can reveal the approximate value of coagulation ability in *ex vivo* samples [89].

An animal experiment has shown that thrombin generation is upregulated in high estrogenic conditions [86]. The ETP-based assay detected changes in thrombin generation in non-pregnant rats treated with exogenous estrogen compared to controls to examine the direct effect of estrogen on the thrombin generation. A peak of ETP was observed on day 21 of administration compared to the control group. ETP in the administration group showed a significant increase as compared to that of the control group and returned to a similar level as the control group. By contrast, the conventional method did not show a difference in coagulation ability between the rats treated with estrogen and control. This animal experiment may simply indicate that estrogen induces a hypercoagulable state [86].

Other studies have demonstrated changes in thrombin generation, which is measured by an ETP-based method because the conventional method detects a small difference between thrombin generation in pregnant and non-pregnant women. Those studies showed that thrombin generation is significantly enhanced in late pregnancy and on day 1 postpartum compared to non-pregnancy. This observation indicates more directly that the hypercoagulable state can be induced during pregnancy and the puerperium [87].

The prothrombotic state is regulated by the balance between coagulation and inhibitory factors. This concept has focused on the resistance to the inhibitory regulation of thrombin generation by activated protein C (APC) in studies of OC users [77, 90] because the reduced activity of APC can be associated with an increase in the risk of pregnancy-related VTE.

Like the COC studies, a clinical case report [91] and previous research have shown a significant decrease in sensitivity to APC [87] during the postpartum period. Decreased sensitivity to APC during pregnancy in clinical samples is partially dependent on reduced protein S levels; however, it is difficult to conclude that resistance to APC in pregnancy and the puerperium is associated with the development of pregnancy-related VTE. Although the phenomena of APC resistance may be relevant [87], the sample size measured in the study is too small to judge the impact of the mechanisms in VTE during pregnancy and the puerperium.

3. Conclusions

Epidemiologic observations have demonstrated that prepregnant obese women with underlying mechanisms of metabolic syndrome are at increased risk of pregnancy-related adverse outcomes of VTE, HDP, and GDM. Above all, maternal death by pregnancy-related VTE has an impact of great magnitude in the childbearing population. The mechanisms underlying the pathogenesis of VTE remain poorly understood although the overlapping connections among obesity, high estrogen levels, and prothrombotic status are essential keys for expanding knowledge.

Conflict of interest

The authors declare no conflicts of interest.

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