

# Smoking-Induced Changes in the Maternal Immune, Endocrine, and Metabolic Pathways and Their Impact on Fetal Growth: A Topical Review

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## Keywords

Pregnancy · Smoking · Fetal growth restriction · Immune system · Endocrine system · Metabolic system · Placenta

## Abstract

Perinatal maternal smoking exposure (PMSE) is one of the major environmental risk factors encountered by the fetus. PMSE is usually associated with adverse pregnancy outcomes that may manifest at different stages of life. Nevertheless, fetal growth restriction is the most common smoking-induced side effect. PMSE induces changes in the maternal multiple organ systems. These alterations may affect placental, which subsequently affects fetal growth. It is worthy to note, however, that the extent of maternal smoking-induced changes depends mainly on the maternal level of susceptibility. Hence, the perinatal pregnancy outcomes vary depending on the interaction between the triad: the maternal, fetal, and placental modifications, making it more complex. In this review, we try to unveil the effect of smoking-induced maternal changes on the maternal immune, endocrine, and metabolic pathways and their impact on fetal growth.

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## Introduction

There is no doubt that pregnancy and fetal growth are miracles that are taken for granted. Nevertheless, many factors may meddle with these miracles. During the past 40 years, many studies have shown that perinatal maternal smoking exposure (PMSE) restricts normal fetal growth. Fetal growth restriction (FGR) is a major cause of perinatal morbidity and mortality [1]. FGR is associated with increased risk of stillborn babies, premature birth, hypoxic brain injury, and intrauterine death in a subsequent pregnancy [2].

FGR is defined as fetal weight below 10th percentile adjusted for the gestational age and fetal sex, and affects up to 5–10% of pregnancies. Therefore, estimated fetal birth weight is a strong predictor of infant survival, and clearly FGR is of huge importance in obstetric practice. FGR can be classified into small for gestation age (SGA) and intrauterine growth restriction (IUGR). SGA fetuses are constitutionally small for normal biological factors as maternal ethnicity, parity, weight, and height [3]. On the other hand, IUGR fetuses are small due to pathological process that prevented them from achieving their growth potential [4]. Other classifications have been developed (e.g., <5th percentile, <3rd percentile) and customized fetal growth potential to replace the population-based cutoff.

Currently, there is consistent evidence regarding the causality between PMSE and both the FGR and the maternal various organ system changes. Yet, the mechanism is not fully understood.

In this report, we offer a topical review of PMSE and its influence on fetal growth, and other perinatal outcomes in an endeavor to clarify the aforementioned ambiguity. To our knowledge, this is the first review discussing the alterations in the maternal *immune, endocrine, and metabolic* systems induced by PMSE and their impact on *fetal growth*.

### Smoking Prevalence

In 2012, the World Health Organization announced that around 20–29% of women smoke and the majority of this population is in their childbearing period. In the USA and Canada, the prevalence rate is 17.8 and 33%, respectively. Most importantly, about 70% of them smoke during pregnancy until delivery [5]. In Spain, about 24.6% of Spanish women above the age of 16 smoke [6].

Additionally, maternal exposure to noncombustible nicotine-containing cigarettes (i.e., e-cigarettes) and nicotine replacement therapy have to be considered as PMSE; nevertheless, the prevalence rates are still not available [7].

### Cigarette Components

Cigarettes contain many toxic components, including nicotine, carbon monoxide (CO), cadmium (Cd), and polycyclic aromatic hydrocarbons. These toxic components may affect the fetus both directly as well as indirectly. The majority of these components can cross the placental barrier causing fetal injury. In addition, they may also affect placental development and decidualization. Nevertheless, it is uncertain which prenatal adverse effect is associated exactly with which component [8].

Several reports have documented that nicotine crosses the placenta. It has been detected in the fetal circulation and amniotic fluid at levels exceeding maternal serum concentrations by 15 and 54%, respectively, as well as placental tissues [9, 10]. Moreover, nicotine is known to be orally absorbed. Thus, the fetuses and neonates of smoking mothers are significantly exposed to nicotine during intrauterine and early neonatal life during breastfeeding [11].

Similarly, cotinine, the primary metabolite of nicotine, crosses the placenta [12]. It has been detected at increased levels in the cord blood of neonates of smokers compared to nonsmokers. In addition, cotinine level in serum concentration has been inversely related to the mean neonatal birth weight. Therefore, several studies have considered high cotinine serum concentrations to be predictive of nicotine exposure [13].

### Effect of Smoking on the Maternal Multiorgan System

#### *Immune System*

Normally, pregnancy causes physiological alterations in the maternal immune system to maintain pregnancy and prevent fetal rejection. Maternal immune system adaptations take place locally at the implantation site as well as in the peripheral circulation. Pregnancy is associated with leukocytosis, primarily increased circulation of neutrophils due to the pregnant state-induced stress [14]. Lymphocyte count decreases through the first and second trimesters and increases during the third trimester. During pregnancy, there is a shift from a T helper 1 (Th1) response to a T helper 2 (Th2) that functionally induces maternal tolerance [15]. In addition, the Th1/Th2 cytokine ratio in T cells of women during pregnancy was significantly decreased. In contrast, the Th1/Th2 ratio was elevated in women with adverse pregnancy outcomes as recurrent spontaneous abortions, indicating a marked shift towards Th1.

In contrast, PMSE may modulate the physiological maternal immune system alterations. PMSE leads to the increased influx of activated leukocytes and lower percentages of regulatory T cells [16]. Moreover, smoking during pregnancy may affect the balanced function between Th1 and Th2, leading to increased production of inflammatory Th1 cytokines, chemokines, and growth factors [17].

In the first trimester, the percentages of decidual inflammatory macrophages and NK cells were higher among smokers [18]. Also, Mian et al. [19] have proven that smoking alters NK cell cytotoxic ability leading to increased vulnerability of smoking mothers to infections. DeLoia demonstrated that PMSE causes an increase in the maternal lymphocytes (CD3+) and a decreased percentage of NK cells at 14–20 weeks of gestation in the maternal peripheral blood [20].

Furthermore, smoking leads to the activation and recruitment of inflammatory cells with subsequent release of cytokines IL-8 and IL-6 [21]. Similarly, it is proposed

that PMSE may result in an altered immune function through the induction of glucocorticoid hypersecretion and increased release of catecholamines, which both inhibit the maternal immune response.

These smoking-induced immune changes have been shown to be associated with unfavorable pregnancy outcomes including recurrent miscarriages, preterm labor, and FGR.

Surprisingly, PMSE has been shown to reduce the risk of preeclampsia (PE) by 32% in comparison to nonsmokers [22]. Furthermore, the meta-analysis results of 17 studies including approximately 1.8 million subjects where 62,000 patients developed PE revealed significant negative association between PMSE and the incidence of PE (RR = 0.67, 95% CI: 0.60–0.75) [23]. Yet, the biologic explanation of such association has not been established. Nevertheless, Llorba et al. [24] showed that PMSE had significantly higher circulating levels of the placental growth factor/soluble fms-like tyrosine kinase-1 ratio compared to nonsmokers, suggesting that PMSE affects placental angiogenesis. Furthermore, Jeyabalan et al. [25] and others are supporting this notion. Hence, it is reasonable to postulate that PMSE may lower the maternal risk of PE, yet has a negative influence on fetal weight.

#### *Hormone Release*

PMSE is associated with changes in the physiological maternal hormonal balance during pregnancy. In a previous study evaluating hormone balance between smoker and nonsmoker pregnant women, serum of smoking mothers showed significantly decreased levels of estradiol, sex hormone-binding globulin, and human chorionic gonadotropin compared to nonsmokers [26]. Placental samples showed lower concentrations of progesterone levels among smoking mothers [27]. Furthermore, maternal serum human placental lactogen,  $\beta$ -human chorionic gonadotropin, and placental growth hormone levels are negatively correlated with the number of cigarettes smoked per day [28]. Cord plasma concentrations of insulin-like growth factor-1 (IGF-1) and IGF-binding protein-3 were lower in fetuses of smoking mothers [29]. All these hormones interplay to ensure fetal growth; hence, any factor affecting the balanced cross talk may result in FGR through the increased risk of preterm labor and impaired placental function.

Moreover, nicotine, the major component in cigarettes, has a substantial impact on maternal hormones. Nicotine exerts its effects through direct stimulation of acetylcholine receptors, releasing vasoactive catecholamines (i.e., norepinephrine, epinephrine). Also, nicot-

tine receptor activation leads to the release of acetylcholine, dopamine, serotonin, growth hormone and adrenocorticotrophic hormone, and glutamate (Fig. 1) [30]. All these hormones significantly affect fetal growth [31].

#### *Maternal Metabolism*

Pregnancy induces significant adjustments in the maternal glucose and lipid metabolism mainly due to the placental hormones. In turn, these changes in the maternal metabolism substantially affect fetal growth.

As expected, PMSE also modulates alterations in the maternal metabolism. Smoking is associated with higher serum levels of cholesterol, triglyceride, and lower concentrations of high-density lipoprotein cholesterol. PMSE also enhances platelet aggregation, reduces the dispensability of blood vessel walls, and induces both prothrombotic and proinflammatory state, leading to placental vascular malfunction. Several reports have confirmed a strong association between smoking and the incidence of diabetes and impairing insulin sensitivity, which may affect the metabolism and growth of the fetus [32]. Hence, any disturbance in this delicate balance between the metabolism and hormones may lead to FGR and placental function impairment.

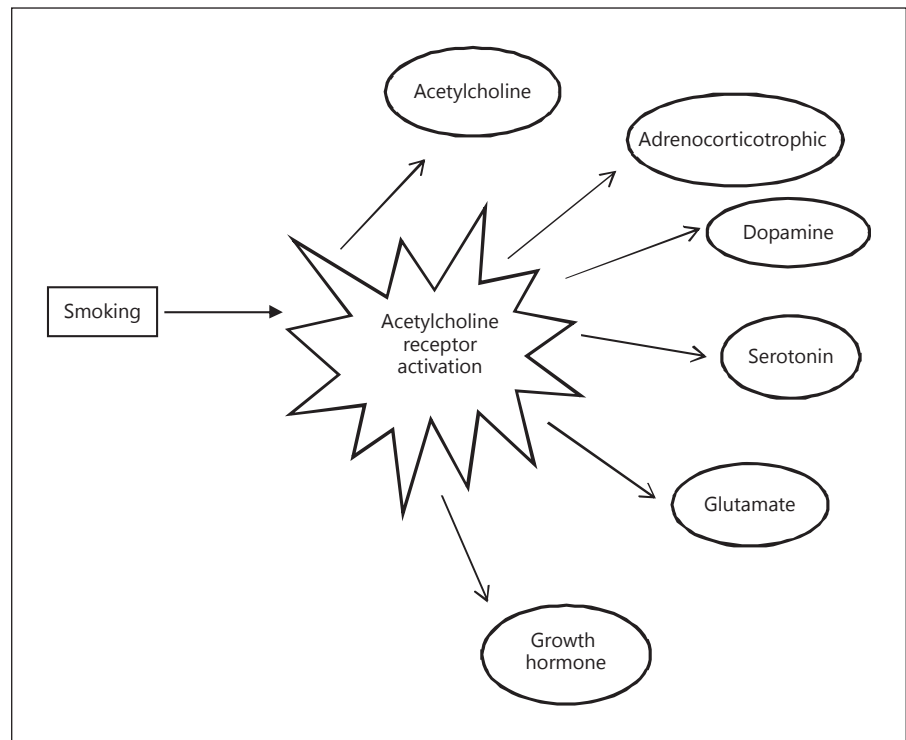
### **Effect of Smoking on Fetal Growth**

#### *Fetal Growth*

The gestational age at which FGR is diagnosed has a major impact on the pregnancy outcome. Figueras and Gardosi [33] classified FGR into early- and late-onset FGR. Their results have shown that early-onset FGR is an early embryonic event before 32 weeks of gestation and represents 20–30% of all FGRs. Late-onset FGR occurs after 32 weeks of gestation and is most frequently associated with abnormal cerebroplacental ratio values [34]. Bar and colleagues [35] suggested that late-onset FGR may represent a different pathophysiologic condition, as differences in placental pathology were noted between early- and late-onset FGR groups. Despite the onset of FGR, early or late, chronic exposure to unfavorable intrauterine environment dictates adverse fetal programming and perinatal outcomes.

#### *Pathophysiology of FGR*

The most common pathophysiological explanation for FGR is impaired fetal oxygen delivery mainly due to decreased oxygen-carrying capacity. This can occur due to maternal diseases causing decreased oxygen-carrying ca-



**Fig. 1.** Acetylcholine receptor activation and hormonal release due to PMSE.

capacity (e.g., chronic hypertension, pregnancy-associated hypertension, heart disease, smoking), dysfunctional oxygen ( $O_2$ ) delivery system secondary to maternal vascular disease (e.g., persistent maternal exposure to hypoxic/toxic environment, vascular disease), or placental damage resulting from maternal smoking, illicit drug use or autoimmune diseases.

Furthermore, both nicotine and cotinine levels in serum concentration have been inversely related to the mean neonatal birth weights. Besides nicotine and cotinine, which are the major nicotine metabolites, CO has the highest concentration in cigarette smoke, and a higher affinity to hemoglobin than oxygen. Fetal exposure to CO prevents  $O_2$  unbinding; thus, it is converted to carboxyhemoglobin. The latter reduces the tissue oxygenation via competitive inhibition with oxyhemoglobin and left-shift dissociation curve, known as the Haldane effect [36]. Therefore, maternal CO-prolonged exposure can confer significant permanent damage to fetal brain that is sensitive to hypoxia [37]. Cd, another cigarette component has been proven to be both embryotoxic and teratogenic in animal species [38]. In the maternal blood and placentas, elevated Cd concentrations were inversely related to zinc (Zn) level in cord blood, suggesting that Cd may hinder Zn transfer to the fetus that may cause FGR [39, 40].

### Impact of PMSE

The exact mechanism behind FGR after PMSE is unclear. However, many studies have documented a strong impact of PMSE on the fetal growth through its effect on placentation, birth weight, and perinatal outcomes.

#### Placentation

Placentation is a complex process. As the placenta develops, the villous system undergoes remodeling. Any interruption in the placental vasculature development and remodeling may lead to adverse pregnancy outcomes. Numerous studies have shown that placentas of smoking mothers had a reduction in the number of cytotrophoblasts, increased thickness of the villous membrane as well as accumulation of Cd with a reduction in fetal capillary volume [41, 42]. These studies concluded that oxygenation and the passage of nutrients may be limited by these changes. All these placental changes have been inversely related to fetal growth.

As mentioned, maternal nicotine exposure is known to induce vasoconstriction in placental vasculature, decrease placental blood flow, and reduce trophoblast invasion leading to a delay in the establishment of the fetal-maternal circulation [43]. The subsequent reduction

in oxygen supply may cause placental hypoxia, which is also a trigger for further placental modifications including alternations in both the vasculature and uterine wall invasion in order to maintain blood supply to the fetus [44]. Placenta previa is one of the most common examples of impairment in placental vasculature development. Several studies have shown an association between increased incidence of placenta previa and the dose of tobacco consumed [45]. However, the exact mechanism whereby PMSE induces placenta previa remains speculative.

### *Birth Weight*

Numerous studies concluded that neonates born to smoking mothers had significantly decreased birth weights compared to nonsmokers [46]. A Brazilian study presented a decrease in the average birth weight of 223.4 g and a reduction in both birth length and head circumference of 0.94 and 0.69 cm, respectively, of neonates born to smoking mothers [47].

Indeed, it is known that the fetus gains 95% of its weight in the last 20 weeks of gestation; however, researchers have proven that early pregnancy smoking cessation has the greatest impact on birth weight. The infants of patients who are able to stop smoking early in gestation will have a birth weight comparable to that of infants born to nonsmokers [48].

A significant decrease in fetal size, brain, lung, kidney, and placental volumes was noted in the smoking versus the nonsmoking pregnant group using magnetic resonance imaging to determine the influence of PMSE [49]. The reduction in the fetal organ sizes was noted as early as 22 weeks of gestation; however, no further information was provided about the duration of PMSE and the actual timing of fetal insult.

The maternal smoking dose-dependent effect on fetal weight has been established. For each additional cigarette smoked per day in the third trimester, there was an estimated 27-g reduction in birth weight [50]. Furthermore, changes in the number of daily smoked cigarettes induced changes in the fetal growth curve [51].

Due to the complexity of cigarette composition, it is not clear which of the tobacco components contributes to the reduction in birth weight. However, it is established that cigarette components influence the uterine blood flow and consequently fetal weight.

Doppler studies have been used to demonstrate velocity and wave flow variation between smoking and nonsmoking mothers. A change in the uterine Doppler flow velocity waveform was detected among smoking mothers

[52]. Another study found an acute 76% increase in the pulsatile index (PI) of the umbilical artery after maternal smoking [53]. However, other studies found no effect on blood flow, velocity, diameter, and the systolic/diastolic ratio, PI, and refractive index in the uteroplacental or fetal blood vessels [54]. This may indicate that the PMSE effects on placental vasculature are not consistent among smoking mothers.

In addition to the PMSE, both the fetus and neonate can have environmental tobacco exposure, known as secondhand smoking. Studies have shown that secondhand smoking exposure is about 22–30% [55]. Also, PMSE effects, whether active or involuntary exposure, appear to be stronger among older mothers [56, 57]. In comparison to other risk factors in the prenatal period, smoking is considered one of the most harmful with neurobehavioral complications [58].

FGR risk may vary by racial and ethnic groups. Studies noted stronger effects among African-American mothers. These variations may be due to differences in nicotine metabolism among racial groups and/or differences in smoking and exposure patterns [59]. Furthermore, certain populations with genetic polymorphisms may be more vulnerable to damage due to alterations in the metabolic pathways [60].

Neonatal birth weight depends on 2 factors: (1) the gestational age of the fetus at the time of delivery, and (2) the proportion of fetal growth during pregnancy until birth. All the data strongly indicate that PMSE causes preterm labor and reduction in both fetal growth and size. Moreover, the data suggest that fetal programming may vary according to the in utero fetal tobacco exposure timing, maternal/fetal nicotine concentration and maternal susceptibility.

### **Perinatal Outcomes**

Table 1 shows the relative risk of the adverse pregnancy outcomes associated with PMSE from different studies [61–63].

#### *Reduced Fertility, Spontaneous Abortions, and Preterm Delivery*

Strong association between reduced fertility, spontaneous abortions, preterm labor and female smoking habits has been established by using the level of cotinine to verify tobacco exposure [64, 65].

**Table 1.** Maternal and perinatal smoking-related adverse outcomes

Adverse pregnancy outcome	Relative risk
Infertility	1.2–3.6
Ectopic pregnancy	1.5–2.5
Spontaneous abortion	1.0–1.8
Placental abruption	1.4–2.4
Placenta previa	1.5–3.0
Preeclampsia	0.5–0.7
PPROM	2.8
Preterm birth	1.2–1.6
Stillbirth	1.3–1.8
LBW	1.75
Neonatal mortality	1.2–1.4
Hospitalization of infant or child	1.5–2.0
SIDS	1.33
Oral clefts	1.2–1.6

PPROM, preterm premature rupture of membranes; LBW, low birth weight; SIDS, sudden infant death syndrome.

### *Congenital Anomalies*

The effect of PMSE on the risk of fetal congenital abnormalities has been thoroughly investigated. Pijpers et al. [66] detected a significant increase in fetal heart rate following maternal smoking. The Atlanta and British meta-analysis studies have noticed a significant positive correlation between PMSE and fetal heart defects including conotruncal defects, atrial septal defects, atrioventricular septal defects, and transposition of the great arteries [67, 68]. They have also noticed increased risk for cleft lip with or without cleft palate, clubfoot, craniosynostosis, and gastroschisis [69].

### *Neurodevelopmental Effect*

An association between maternal smoking and children's lower neurodevelopmental progress including verbal skills, language, reading abilities, and general intelligence skills has been proven. Data from studying the evoked brain responses of infants born to smoking mothers showed atypical patterns of brain organization. Hence, it is suggested that nicotine has a direct effect on the developing fetal brain, causing permanent abnormalities in neurotransmitter regulation [70]. These results indicate that healthy infants who were prenatally exposed to smoking are linked to significant changes in brain physiology that may influence their school performance later on [71]. Furthermore, studies have agreed that offspring of smoking mothers are more vulnerable to mental disorders such as conduct disorder, attention deficit hyperactivity disorder, and cognitive dysfunction [72].

### *Cardiovascular Effect*

It is well established that cigarettes contain a number of metals, including Cd, lead, and mercury, which catalyze the oxidation of cellular proteins and hence lead to the damage of the vascular wall and the endothelial dysfunction [73]. Also, smoking can enhance platelet-vessel wall interactions through impairing prostacyclin production. Ultimately, this may reduce the elastic properties of the aorta and other arteries, resulting in stiffness of the vessel wall [74]. Apart from these, secondhand exposure to smoking poses a significant cardiovascular health hazard as it impairs endothelium-dependent vasodilation of the coronary arteries and reduces coronary flow reserve [75]. Thus, it is estimated that secondhand smoking increases the risk of developing cardiovascular diseases by 25–30% [76].

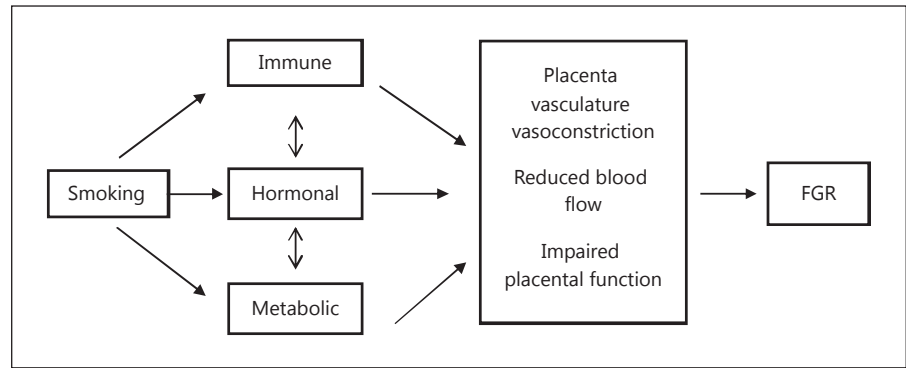
Studies have detected an increase in arterial blood pressure in children who were exposed to maternal smoking [77, 78]. Studies demonstrated that PMSE was associated with higher blood pressure and a rise in total cholesterol profile in their adult life [79]. Furthermore, persistence of the increased arterial resistance during early life may predispose these fetuses to develop hypertension, left ventricular hypertrophy and cardiovascular disease in adulthood [80, 81]. These findings may suggest that increased arterial resistance in response to PMSE affects the left atrium and aortic root development in postnatal life [82].

### *Sudden Infant Death Syndrome*

Sudden infant death syndrome (SIDS) is the unexplained death of a seemingly healthy infant [83]. Its etiology is still unidentified; however, there is a 2-fold increase in the incidence of SIDS among smoking mothers. Also, SIDS has been associated with secondhand smoke exposure [84].

### **Assessment of Cigarette Smoking**

Exposure to cigarette smoking can be assessed by 3 means: (1) environmental measurements of the smoke component in the air, (2) self-reporting through questionnaires, and (3) measuring concentrations of smoke components in the body. Environmental measurements obtained by air sampling are suboptimal and do not reflect exposure. Questionnaires are most commonly used for assessing tobacco exposure. However, the reliability of self-reporting has been found to be inaccurate due to awareness of the stigma of smoking during pregnancy [85].



**Fig. 2.** PMSE-induced changes and their influence on placental function and FGR.

A valid estimation of the risks associated with PMSE depends on accurate measurements of its concentration in the maternal body. Currently, there is no ideal method of measurement. Cotinine is the biomarker of choice; it is detectable in different body fluids, i.e. blood and urine. In addition, cotinine is eliminated over a longer period, resulting in predicting long-term exposure [86]. Cotinine accumulates in the hair during its growth. Therefore, it can be used as a measure of long-term fetal exposure to smoking.

## Discussion

It is well established that PMSE is toxic to both the mother and the fetus. Women who smoke during pregnancy have been observed to have a higher risk of reduced fertility, spontaneous abortion, and preterm labor. In addition, PMSE induces significant changes to the physiological modifications between the immune-hormonal-metabolic maternal systems during pregnancy. These induced alterations may lead to several unfavorable pregnancy outcomes including impaired placental decidualization and function, FGR, as well as various congenital anomalies (Fig. 2). Although a strong negative correlation between PMSE and FGR has been established, many questions remain unanswered.

Nevertheless, various studies have demonstrated that PMSE reduction/stoppage throughout gestation has a significant impact on minimizing the adverse pregnancy outcomes including miscarriage, preterm delivery, perinatal mortality, and FGR [87, 88]. However, the findings regarding the impact of timing of PMSE cessation/reduction on birth weight have been inconsistent. Some studies have suggested that early pregnancy cessation has the greatest influence on birth weight. Whereas others have

shown that only third-trimester maternal cigarette consumption has the strongest association with low birth weight.

Initial studies of PMSE and its impact on fetal growth have shown various degrees of severity of FGR. Nevertheless, these studies failed to show the exact relation between different nicotine and cotinine levels in both maternal and neonatal cord blood, and its negative influence on the neonatal birth weight. It is essential, however, to determine the toxic levels of PMSE, especially due to the different types of cigarettes, their variable contents and nicotine concentrations.

Another area of uncertainty is the critical timing of fetal insult during pregnancy. For example, with the routine third trimester scan, it is possible to detect FGR due to PMSE; nonetheless, the decline in fetal weight may have started at an earlier trimester. Therefore, scheduled early ultrasound screening in an earlier trimester may assist in timely diagnosis of FGR. Moreover, scheduling screening for PMSE itself in line with earlier ultrasound may help early detection of fetal insult during pregnancy.

Recently, Doppler has been utilized to evaluate fetomaternal adaptation to vascular changes induced by PMSE. However, data from Doppler vascular velocity and waveform changes among smoking mothers have been inconsistent. That may reflect variable levels of maternal and fetal adaptation to hypoxia and vascular resistance induced by PMSE. Moreover, the effects of smoking on placental vascular resistance may have been periodic rather than continuous.

Although different women may be exposed to the same amount of tobacco, they may experience different levels of adverse perinatal outcomes including FGR. Therefore, we can postulate that the variable degrees of maternal susceptibility to PMSE result in different pregnancy outcomes, including new FGR classification. Con-

sequently, such discrepancies raise the question regarding the exact mechanism behind the influence of PMSE on fetal birth weight. While the literature provides ample information on the impact of perinatal smoking on FGR, very little has been reported on the exact mechanisms, which may be related to variable genetic and metabolic maternal susceptibility.

To our knowledge, this is the first article reviewing PMSE and its interrelated influence on the maternal immune-endocrine-metabolic system changes as well as fetal growth. At present, our understanding of the adverse effects of PMSE is limited. While the fetomaternal degrees of modification/adaptation to PMSE-induced changes seem conclusive, the effects of timing of fetal insult, dosage of tobacco exposure, and women's genetic susceptibility on pregnancy outcomes are still unknown. Therefore, more research is required to understand the

exact mechanisms of PMSE-induced changes on the maternal and fetal outcomes. Furthermore, future studies need to consider the triad of mother, fetus, and placenta as one unit in understanding fetal pathology.

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The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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