Chapter 4
Tobacco Smoking and Oxidative Stress in Pregnancy

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Abbreviations

CAT	Catalase
GPX	Glutathione peroxidase
LOOH	Lipid hydroperoxide
MDA	Malondialdehyde
OSI	Oxidative stress index
ROS	Reactive oxygen species
SOD	Superoxide dismutase
TAC	Total oxidant capacity
TOS	Total oxidant capacity

Introduction

Cigarette smoking undoubtedly represents one of the greatest current health problems, if not the greatest, facing us. Pregnant women have smoking cessation rates only as high as 15–20 % [1]. Cigarette smoking probably contributes the greatest single share of causality to a variety of lethal and disabling effects on health [2]. It is well known that adverse pregnancy outcomes are related to tobacco smoking during pregnancy [3–6]. Most tobacco toxins have a low molecular weight and high

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water solubility and therefore readily cross the placenta [7]. Maternal smoking also impairs placental development and anatomy and functions [8, 9]. Active smoking (AS) or passive smoking (PS) (or secondhand smoking, environmental tobacco smoke) in pregnant women results in intrauterine growth retardation [3] and an increased risk of spontaneous abortion [10]. In addition, prenatal exposure to tobacco smoking may lead to higher risk of sudden infant death syndrome [4], reduction of pulmonary function in healthy neonates [11], and wheezy bronchitis in children [12]. Furthermore, reduced lung function in infancy resulting from prenatal exposure to smoking may lead to abnormal lung function in childhood and track into adulthood [13]. Several mechanisms have been postulated to explain such effects. Cigarette smoke contains an abundance of compounds emitted in gases and condensed tar particles, many of which are oxidants and pro-oxidants capable of producing reactive oxygen species (ROS) [14]. The enhanced production of ROS by smoke is related to increased free radical production, antioxidant depletion, and oxidative stress [15–19], which can result in the oxidation of lipids, induction of DNA single-strand breakage, inactivation of certain proteins, and the disruption of biological membranes [20, 21]. One possibility given credence by several in vitro studies [22–26] is that cigarette smoke, rich in free radicals and oxidizing species, depletes plasma antioxidants [14–19, 27]. Cigarette smoking causes oxidative stress in pregnant women and may have a similar effect in fetuses [15].

Quantifying Tobacco Smoke Exposure

Most studies of the effects of AS or PS during pregnancy and on neonates have used questionnaire reports of exposure, although some have used biochemical measures to validate smoking habits [28, 29]. Apart from the problem of reporting bias, the definition of what a “smoker” is and what characterizes smoking varies between studies. Many early studies have described women simply as smokers or nonsmokers [28]. Because of the variable quality of smoking data obtained from questionnaires, recent studies that quantified smoking have usually assessed maternal serum, urine, or hair samples, obtained during the first half of pregnancy, and umbilical serum, urine, or hair samples, obtained at delivery, by measuring the concentration of the nicotine metabolite cotinine [29, 30]. The lower limit of detection was 0–10 ng/ml for both nicotine and cotinine, with an assay calibration curve of 10–200 ng/ml, and subjects with cotinine levels >2–14 ng/ml were considered smokers [9]. Self-reported abstinence was defined as no smoking during the previous 7–10 days.

Distinguishing between passive smokers and nonsmokers was more difficult, and the assay did not accurately discriminate between these exposure groups in all patient types, especially in pregnant women. There are a number of possible explanations for this [30]. First, there was a real overlap in the samples’ cotinine from passive and unexposed subjects. This is largely attributable to the fact that even

those reporting no exposure to cigarette smoke can still be exposed to small amounts. Quantifying exposure of nonsmokers has been problematic in most studies. Passive smoking depends on a number of factors, including number of smokers, their proximity to the subject, the number of cigarettes smoked, the size of the space, the ventilation of that space, and the duration of exposure. Moreover, interindividual variability in the conversion of nicotine to cotinine may also make it difficult to discriminate between passive and unexposed nonsmokers. The metabolism of nicotine to cotinine varies with age, ethnicity, and sex [31].

Smoking During Pregnancy

Tobacco use started several centuries ago and increased markedly after the invention of the cigarette-making machine. Behaviors pertaining to tobacco use have changed significantly over the past century. Compared with 1964, smoking prevalence rates have halved from 40 to 20 % in the United States, and as a result there has been a slow but steady decline in the rates of tobacco-induced diseases [32]. While the smoking habit is decreasing in developed countries, tobacco use is increasing in developing countries [33]. Once people start smoking, they find it difficult to quit. This is due to the addictive effect of nicotine in tobacco smoke. Pregnant women have smoking cessation rates only as high as 15–20 % [1]. Various studies showed that maternal nicotine exposure during pregnancy and lactation via tobacco smoke of nicotine replacement therapy program the offspring to develop compromised lung structure later in life with consequent compromised lung function. This implies that nicotine replacement therapy is not an option to assist pregnant or lactating smokers to quit [33]. It is best to quit smoking before getting pregnant.

Thirdhand Smoke

New research shows that thirdhand smoke (THS) is a complex phenomenon resulting from residual tobacco smoke pollutants that cling to the clothing and skin of smokers and to surfaces, couches, and carpets in indoor environments [34]. These pollutants, reemitted into the gas phase or reacting with oxidants or other compounds, persist long after the smoke from a cigarette or cigar has cleared. Thus, THS exposure consists of unintentional intake (mainly through inhalation but also via ingestion and dermal routes) of tobacco smoke and other related chemicals that occurs in the absence of concurrent smoking.

To achieve a better understanding of the health effects attributable to THS, future research should evaluate the risk in pregnant women, fetuses, neonates, and other populations.

Oxidant and Antioxidant Molecules

Pro-oxidant molecules can have free radicals or they can catalyze or initiate reduction/oxidation (redox) reactions that result in the production of free radicals or ROS such as the superoxide anion (O_2^-), hydroxyl radicals (HO.), and hydrogen peroxide (H_2O_2), which initiate oxidative chain reactions resulting in oxidative damage to DNA, proteins, and lipids [14, 20, 24]. These oxidized molecules can be measured in biological fluids, being protein carbonyls, as a marker of protein oxidation and thiobarbituric acid reactive species (TBARS), lipid hydroperoxide (LOOH), malondialdehyde (MDA), and total peroxide as markers of lipid oxidation, the most frequently oxidative stress markers measured in humans [35, 36].

Enzymes that can catalyze free radical-producing redox reactions include certain hydroxylases, oxidases, oxygenases, peroxidases, and synthases. The body, on account of its susceptibility to oxidative insult, is naturally provided with efficient enzymatic and nonenzymatic antioxidant systems. A series of enzymes also act as scavenging systems, including superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT). These enzymes are the first line of defense against ROS and are generally referred to as primary antioxidants [15]. The level of CAT, which is a peroxisomal hydrogen peroxide-consuming enzyme, increases in chronic smokers, whereas the levels of several antioxidant enzymes, such as CuZnSOD, glutathione transferase (GST), and GPX, appear to decline in smokers with long smoking histories [20].

Plasma has various nonenzymatic antioxidant molecules. Albumin; uric acid; bilirubin; vitamins C, E, and A; β-carotene; and ceruloplasmin are the major antioxidant components of plasma. Total antioxidant capacity (TAC) represents practically all of them. Albumin has about half of the total antioxidant capacity of plasma [37, 38]. Plasma thiol contents originate from albumin and act as the antioxidant component of plasma.

Analytical methods of oxidant [39–43]/antioxidant [37, 38, 44, 45] parameters were described, from highly complex, time-consuming, and expensive procedures such as chemiluminescence-HPLC assay to more rapid, inexpensive, and sensitive techniques such as automated-colorimetric methods.

Oxidant Status

The values of lipid peroxidation products can be used as an index of oxygen free radical generation. The measurement of LOOH, MDA, and total oxidant status (TOS) provides a sensitive index of lipid peroxidation and oxidative stress [43, 46, 47]. It has been argued that the increased production of ROS associated with smoking may exceed the capacity of the oxidant defense system, resulting in oxidative damage to selected proteins, lipids, and DNA [48–50]. Chelchowska et al. reported that the level of MDA was significantly higher in the cord blood of newborns of

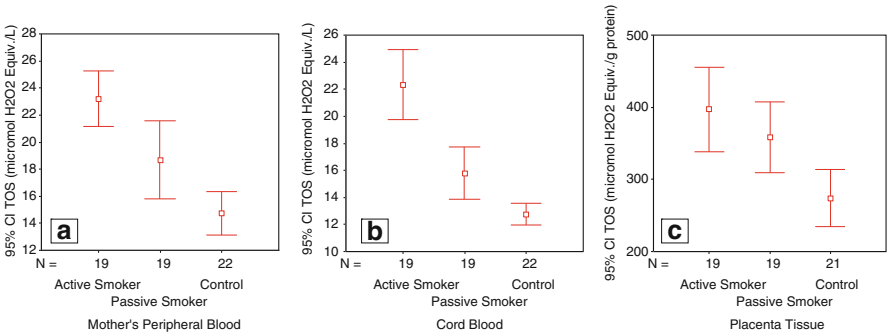

Fig. 4.1 Box plot graphic of mother's peripheral blood (**a**), cord blood (**b**), and placenta tissue (**c**) TOS levels in active smokers, passive smokers, and controls. Differences are significant between the groups ($P<0.05$)

smoking mothers [36]. Aycicek et al. found that LOOH and TOS levels were significantly higher in active and passive smokers than in the controls. They also reported [15, 27] that the TOS levels of the mother's peripheral blood, cord blood, and placenta tissue were significantly higher in active smokers than in passive smokers and controls. These levels were also significantly higher in the passive smokers than in the controls (Fig. 4.1). Arguelles et al. [51] measured levels of serum lipid peroxides in newborns and their mothers and observed significantly higher peroxidation in the newborns, as well as a positive correlation between the levels measured in the newborns and mothers exposed to tobacco smoke.

Protein carbonyl content levels, a parameter of protein oxidation during pregnancy and in newborns, were increased in pregnant women when compared with nonpregnant subjects [51]. Arguelles et al. reported a significant effect of tobacco smoke exposure on protein carbonyl levels in newborns and mothers [52]. In contrast, Rossner et al. performed a similar study and did not find any relation between tobacco smoke exposure and protein carbonyl levels [51].

Rossner et al. [52] and Daube et al. [53] analyzed oxidative damage to DNA by measuring the levels of 8-hydroxydeoxyguanisine (8-OHdG) in the placenta. They did not find a difference in 8-OHdG levels between the placentas from women exposed and not exposed to tobacco smoke, even though the mean values of plasma cotinine were twofold higher than in subjects from another study [51]. Moreover, in Yin et al. [54], the comparison of 8-OHdG levels in placental DNA from women exposed and not exposed to tobacco smoke based on plasma cotinine levels also did not show a significant difference, although the levels of 8-OHdG in women exposed to tobacco smoke were higher than those in women not exposed. Sbrana et al. [55] demonstrated that the tobacco-mediated metabolic gene pathway perturbations manifest with significant placental accumulation of both 4-hydroxy-2-nonenal (4-HNE, a marker for oxidative lipid damage) and 8-hydroxydeoxyguanisine (8-OHdG, a marker of DNA damage) showed increased levels in the placenta of smokers compared with controls.

Antioxidant Status

The potential damage that can be caused by free radicals is normally minimized by the antioxidant systems. In passive smoking infants, several components of the antioxidant defense system have been reported to be impaired as compared with those of infants not exposed to smoking [40]. Chelchowska et al. [36] reported that the level of TAC was significantly decreased in the cord blood of newborns of smoking mothers. Fayol et al. [18] demonstrated that the TAC level was low in the infant cord blood of passive smoking mothers but that this was not the case in the infants of active smokers. Aycicek and Ipek [15, 27] found that maternal peripheral blood, cord blood, and placental tissue TAC levels were lower in active and passive smokers than in controls (Fig. 4.2), and positive significant correlations were found between placenta tissue TAC and cord blood TAC levels (Fig. 4.3). It is also reported that mothers who smoke, even if they did not smoke during pregnancy, have a higher oxidative stress parameter [51]. Thus, these mothers have a high concentration of serum lipid peroxidation and protein carbonyl content and decreased TAC.

Positive significant correlations were found between maternal cigarette exposure and placenta, cord blood, and maternal peripheral blood TOS and OSI levels, while a negative significant correlation was found between number of cigarettes exposed to and birth weight and head circumference and between placenta and cord blood TAC levels [15, 27].

Uric acid is a well-known low-molecular-weight water-soluble plasma antioxidant [38, 56]. Several clinical studies in humans have demonstrated increased uric acid production as a result of oxidative stress, such as that related to smoking [57]. Fayol et al. reported that the uric acid levels in the cord blood of passive smoking infants were significantly higher than those in the cord blood of controls [18].

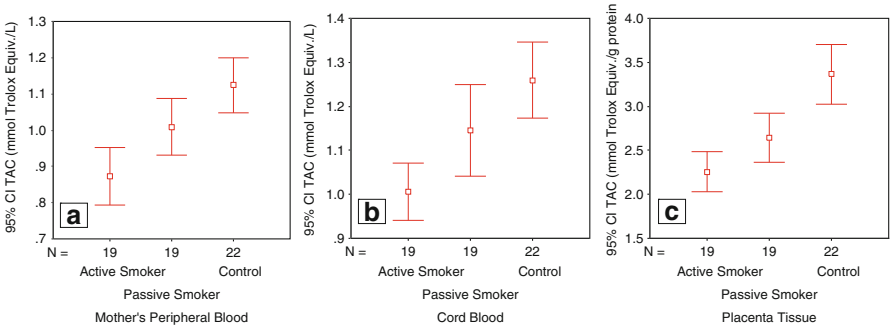

Fig. 4.2 Box plot graphic of maternal peripheral blood (**a**), cord blood (**b**), and placenta tissue (**c**) TAC levels in active smokers, passive smokers, and controls. Differences are more significant between active and passive smokers than controls ($P < 0.05$)

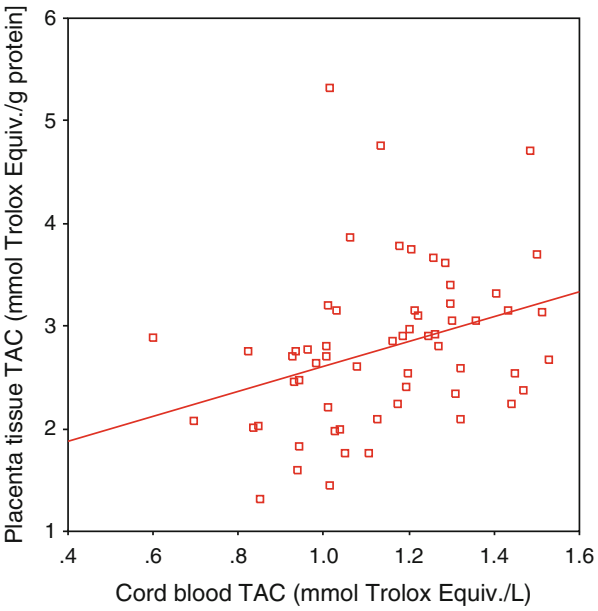

Fig. 4.3 Correlation graphic of TAC levels in placental tissue and cord blood ($r=0.303$, $P=0.010$) in smoker mothers

However, Aycicek and Ipek [15] found that plasma uric acid levels were slightly higher in active smokers than in passive smokers and controls, but the difference was not statistically significant.

Oxidative Stress Index

In addition to these markers, OSI, which is a cumulative marker of both oxidative and antioxidative power [15, 17, 40], was significantly increased in the cord blood of active and passive smokers (Fig. 4.4). These results are the first on placental tissue. According to the data obtained in the present study, increased TOS levels, decreased TAC, cumulatively increased OSI, and the other antioxidants together with the routine clinical parameters may implicate the presence of oxidative stress in the placenta subsequently in fetuses. In addition, decreased lipophilic antioxidants may play a role in the pathogenesis of atherosclerosis in the fetuses of mothers who are active or passive smokers through increased susceptibility to lipid peroxidation in utero.

It is reported that highly significant positive significant correlations were found between maternal cigarette exposure and placenta, cord blood, and maternal peripheral blood TOS (Fig. 4.4) and OSI levels, while a negative

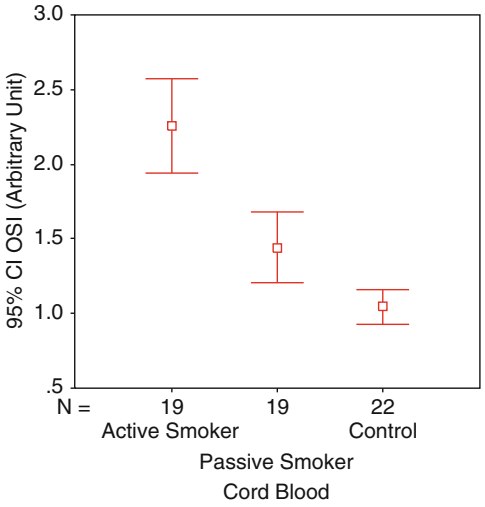

Fig. 4.4 Box plot graphic of placenta tissue OSI levels in active smokers, passive smokers, and controls. Differences are significant between the groups ($P<0.05$)

significant correlation was found between number of cigarettes exposed to and birth weight and head circumference and between placenta and cord blood TAC levels [27].

Antioxidant Enzymes

Cigarette smoking is associated with systemic oxidative stress, leading to an upregulation of antioxidant systems (superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and heme oxygenase (HO)) in some tissues [58]. Smoking throughout pregnancy resulted in elevated expression of the HO enzymes in the placental basal plate region. Smoking did not alter the expression of CAT, SOD, or GPx in any of the placental regions studied. Interestingly, cord blood CAT levels were lower in active and passive smokers than in controls [15].

Ceruloplasmin is a copper-containing glucoprotein with multiple physiological functions, including ferroxidase and oxidase activity. It is induced by inflammatory processes, air pollution, and cigarette smoking [14, 59, 60]. The level of ceruloplasmin was found to be significantly increased in neonates whose mothers were active or passive smokers [61]. However, Aycicek et al. found that ceruloplasmin levels did not differ significantly between each of the three groups (active and passive smokers and controls) and did not find any correlation in their study [15]. Similarly, Fayol et al. reported that cord blood antioxidant parameters strongly correlated with maternal antioxidant status, with the exception of ceruloplasmin [18]. They also stated that an altered neonatal ceruloplasmin concentration may

reflect the effect of cigarette exposure on the antioxidant system of the neonate rather than transplacental transfer of maternal ceroloplasmin. Further investigations are needed to address this issue.

Aycicek et al. found that basal/salt-stimulated PON1 activities were significantly lower in patients who were active smokers than in passive smokers and controls, while LOOH and TOS levels were significantly higher [15]. According to the data obtained in the present study, increased LOOH and TOS levels, decreased PON1 activities, and the presence of other antioxidants together with the routine clinical parameters may implicate the presence of oxidative stress in fetuses. In addition, decreased lipophilic antioxidants and PON1 activities may play a role in the pathogenesis of atherosclerosis in infants of active smoking mothers through an increased susceptibility to lipid peroxidation in utero.

Antioxidative Gene Expression

It is reported that smokers showed upregulation of xenobiotic genes (CYP1B1, GSTM1, and CBR3), whose expression was likely directly induced by tobacco smoke exposure. GSTM1 (glutathione S-transferase Mu 1) is implicated in the detoxification of electrophilic compounds, including carcinogens, environmental toxins, and products of oxidative stress [9]. It is stated that cigarette smoke alters the expression of genes involved in oxidative stress, immune and inflammatory responses, xenobiotic metabolism (particularly cytochromes CYP1A1 and CYP1B1), coagulation and fibrinolysis, oncogenesis, DNA repair, structural units of condensed DNA, and extracellular matrix degradation in smokers and their newborns. The majority of genes implicated in the above-mentioned pathways are nonspecifically deregulated and thus represent rather general biomarkers of toxic exposure. In contrast, aldehyde metabolism (e.g., ALDH3) appears to be uniquely modulated by cigarette smoke [62].

Cigarette smoking is associated with altered antioxidant defense enzyme gene expression and regulation in pregnancy. In this context, Vatovova et al. reported increased expression of GPx3 and NXN in placental and fetal cells [9]. GPx3 (glutathione peroxidase 3) is a peroxidase that catalyzes detoxification of hydrogen peroxide and plays a crucial role in protecting proteins and DNA from oxidation caused by smoking [63, 64]. A thioredoxin-related protein, NXM (nucleoredoxin), governs ROS-stimulated Wnt signaling pathway, which is essential for early development and stem cell maintenance [65]. In contrast to expectations, SOD2 (superoxide dismutase 2) expression showed downregulation in peripheral blood cells of smokers, and this finding was confirmed by qRT-PCR [63]. SOD2 encodes a mitochondrial antioxidant enzyme that transforms superoxide into oxygen and hydrogen peroxide, which are less toxic products. A similar decrease in SOD2 levels was found in human neuroblastoma cells exposed to cigarette smoke condensate [66], suggesting that smoking may cause free radical or ROS overcharge, which in turn may be responsible for inhibition of gene expression in antioxidant genes.

Proinflammatory Effect

Passive smoking is increasingly appreciated to have major adverse health effects and to result in a proinflammatory state [67]. It is reported that prenatal and postnatal maternal exposure to environmental tobacco smoke increases neonatal arterial expression of genes that are proinflammatory and induce or contribute to vascular injury while reducing the arterial expression of a gene for angiogenesis [67]. Perinatal and following 1 year of postnatal environmental tobacco smoke exposure, nonhuman primates were found to have increased vascular oxidative stress (protein carbonyls and SOD) and mitochondrial dysfunction/damage (cytochrome oxidase, mitochondrial DNA) that were coupled to reductions in mitochondrial antioxidant capacity and copy number in vascular tissue compared to filtered air-exposed controls [68]. These changes may be responsible for early arterial vascular remodeling that is predisposing to a subsequent vascular disease. Multiple reports have now documented that early and intermediate stage atheroma occurs in children and teenagers [69]. Thus, it is plausible that the potential for increased atherosclerotic disease susceptibility in adulthood following in utero and early life smoke exposure because inflammation and mitochondrial damage and dysfunction in response to tobacco smoke exposure are features of early atherosclerosis.

Summary and Conclusions

Active or passive maternal smoking is associated with important alterations in the oxidant and antioxidant balance in maternal and cord blood and placental tissue and causes potent oxidative stress in all of them. However, future longitudinal studies estimating oxidative markers and antioxidants serially throughout pregnancy may be able to prove the association of elevated oxidant status and diminished antioxidant levels in pregnant women, and the estimation of oxidative stress markers may be predictive of the development health effects of prenatal tobacco smoke.

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