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**SPECIAL ARTICLE**

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## *The influence of smoking on fertility, pregnancy and lactation*

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### **Abstract**

**Objective:** to describe the influence of smoking on different phases of the reproductive process, fecundation, pregnancy and lactation, drawing special attention to the mechanisms of action of the main toxic components found in cigarettes. To suggest prophylactic measures for environmental control and how to reduce children's exposure to tobacco smoke.

**Sources:** nonsystematic literature review using MEDLINE database.

**Summary of the findings:** smoking has a negative effect on different phases of the reproduction process, by direct action of main toxic components, nicotine and carbon monoxide. Smoking reduces fertility, compromises the length of gestation and infant birthweight. Smoking mothers also have reduced breast milk production and shorter lactation, which affects infant weight gain through unclear mechanisms in which prolactin may probably be involved.

**Conclusions:** smoking compromises reproductive function quality in different phases, acting mainly on intrauterine and extrauterine development of infants. Since during pregnancy and lactation women are in closer contact with health professionals, antismoking campaigns should be especially addressed to this period.

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### **Smoking**

Environmental tobacco smoke can derive from two sources: central smoke (CS) and peripheral smoke (PS). CS comes from inhaling cigarette smoke, is produced at high temperatures (above 950 degrees C), and pollutes the environment after being drawn in, filtered by the lungs, and exhaled.<sup>1-3</sup> This is the main source of exposure in active smokers.

PS is produced at lower temperatures (approximately 350 degrees C) during slow burning of the cigarette, between inhalations. Approximately 85% of environmental tobacco smoke is a result of PS, which is released directly to the environment as a result of spontaneous burning of the extremity of the cigarette. This element of cigarette burning differs from CS inhaled by active smoking in the sense that it is not filtered by the cigarette filter nor by the column of tobacco, and the resulting nicotine is in the gaseous stage.<sup>1,4</sup>

Approximately 4,720 different elements have been identified in cigarette smoke,<sup>5,6</sup> including pharmacologically active, mutagenic, and carcinogenic elements. The composition of each cigarette can vary according to type of tobacco leaf used, to region in which tobacco was planted, to techniques used in processing, and to fermentation.

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Roughly 10% of these components make up the particulate phase of cigarette smoke, which contains nicotine and tar (polycyclic aromatic hydrocarbon compounds: phenols, benzopyrenes, benzenes). The remaining 90% contains carbon monoxide, carbon dioxide, cyanides, aldehydes, and several other organic compounds.<sup>7,8</sup>

Tobacco smoking produces deleterious effects on the organism, thus affecting health in several ways. In this sense, alterations of the respiratory tract represent the most important effects. It is important to underscore chronic obstructive pulmonary disease (COPD) and greater incidence of lung cancer among smokers, also considering the relation with increasing rates of cigarette consumption. In other human organs, there are various diseases associated to tobacco in both active and passive smoking. These diseases include neoplasias of several organs and tissues, peripheral vasculopathies, coronary insufficiency, sexual impotence, and also increased incidence of acute respiratory infections in children, and so on.<sup>9</sup>

The acute effects of passive smoking on human health are clear, eye and respiratory tract irritation and the effects related to risk for fire.<sup>4</sup> Chronically, however, the effects of passive smoking are important and more severe; also, the chronic effects of passive smoking are difficult to prove.

The assessment of health risks attributed to passive smoking presents reasonable grounds for epidemiological studies on situations in which relative risk of passive smoking, in relation to nonsmokers, is high. For example, in nonsmokers married to smokers, exposure to tobacco based on measurements of cotinine is approximately 1% of active smoking, considering a consumption of 20 cigarettes per day. In diseases to which the risk of smoking 20 cigarettes per day represents a 20-fold higher risk, the expected additional risk for passive smoking would be 20% and the relative risk 1.2.<sup>4</sup>

However, for several diseases related to smoking in general, the expected increase in risk for diseases cannot be detected by epidemiological studies on passive smoking. In these diseases, the risk for smokers of 20 cigarettes per day is approximately twofold higher (or 100%) in comparison to nonsmokers; whereas the excess risk associated to passive smoking is 1% (1% of the excess risk 100% associated to passive smoking), which would be difficult to demonstrate.<sup>4</sup>

### Smoking and fertility

In the case of women, smoking reduces overall fertility with an evident delay on the first gestation.<sup>10</sup> In a study with 678 volunteer female patients, Baird and Wilcox<sup>11</sup> observed that the group of smokers presented 3.4-fold higher probability of taking more than one year to conceive (after trying to impregnate) than nonsmokers. The authors estimated that fertility of smokers was 72% that of nonsmokers; this difference increased in major smokers. However, they also observed that fertility was not affected by husbands who smoked.

Suonio *et al.*<sup>12</sup> carried out a study in Finland with 2,198 women who suspended use of birth control. The results indicated that the longer women took to get pregnant, the more significant the effect of smoking, even in minor smokers. The effect of smoking on fertility seemingly depended, in most cases, on the dose involved. The authors concluded that maternal smoking affected fertility more significantly than smoking by the father, which indicates that the female reproductive system is more vulnerable to smoking than the male's. Bolumar, Olsen and Boldsen presented similar findings in a multicenter study.<sup>13</sup>

More recently, Jensen *et al.*,<sup>14</sup> while studying 430 Danish couples, found an association between current smoking and reduction in female fertility (Odds Ratio = 0.67; 95% CI 0.42-0.93), especially in women who were also exposed in utero (OR = 0.57; 95% CI 0.36-0.91). Moreover, the authors suggest that intrauterine exposure to tobacco compounds can later affect the fertility of males, whereas present smoking did not reduce fecundability significantly.

Delay in conception can be the result of a wide variety of adverse effects such as interference in gametogenesis or fertilization, difficulties in egg implantation, or subclinical loss of pregnancy. Studies with animals have suggested that tobacco compounds can affect fertility from gametogenesis to implantation.<sup>15</sup>

The explanatory mechanisms for the effect of smoking on future reproductive potential are uncertain and controversial. Women who were exposed to smoking in intrauterine but not in adult life presented a reduction in fertility in comparison to those who had no direct exposure to tobacco.<sup>14</sup> On the other hand, other studies have indicated

Effects on fertility	Mechanisms	Reference
Reduction in fertility of women	Interference on gametogenesis; implantation failure	Baird & Wilcox, 1985 <sup>11</sup>
Early menopause	Reduction of estrogen levels	Bolumar <i>et al.</i> , 1996 <sup>13</sup>

that smoking reduces fertility only during exposure; when women quit smoking, their fertility is restored to normal.<sup>13</sup>

Consequences of smoking by parents on the fertility of their female offspring have been suggested by animal studies. Exposure of mice in utero to benzopyrene, a component of cigarettes, resulted in later negative effects on fertility; this finding may have been related to destruction of primary oocytes.<sup>16</sup> Weimberg *et al.*<sup>17</sup> studied intrauterine life exposure to cigarettes in a retrospective investigation of women in North Carolina, USA. The authors observed a reduction of up to 50% in fertility in adult life (fecundability rate = 0.5; 95% CI 0.4-0.8).

Smoking by men is associated with modest reductions in semen quality including sperm concentration, motility and morphology and potential effects on sperm function (in addition to alterations in hormone levels). Despite the fact that studies have not shown an association between reduction in male fertility and paternal smoking, it is recommended that men with marginal semen quality who wish to have children may benefit from quitting smoking, since several small studies indicate the potential for improved semen quality after quitting smoking.<sup>18</sup>

### Smoking and gestation

Smoking during gestation causes serious, well-known effects on intrauterine growth of babies. The greater risk for prematurity and low birthweight in pregnant women who smoke occurs during the third trimester; this risk increases proportionally to the number of cigarettes smoked.<sup>24</sup> Women who smoked during the second and/or third trimester presented the same risk than those who smoked from beginning to end of pregnancy. Thus, it is possible that smoking has a greater effect on decreasing fetal growth during the third trimester.<sup>25</sup>

In general, the number of cigarettes smoked by women decrease during gestation.<sup>25</sup> A small decrease in the

percentage of pregnant women who smoke has been reported for the past few decades (35.7% in 1982 to 33.5% in 1993; *P* less than 0.05); moreover, the number of cigarettes smoked during pregnancy has also decreased.<sup>26</sup> A retrospective study has reported that 21% of women smoking during pregnancy were able to quit this habit by the time of delivery.<sup>25</sup> Abandoning the habit of smoking during pregnancy was more common in women with higher levels of schooling and income.<sup>26,27</sup>

However, nonsmoking does not seem to be final. In a study assessing maintenance of nonsmoking postpartum by women who stopped smoking during pregnancy, the authors observed that six weeks after delivery, 26% of women who had quit started smoking again; and after the third month postpartum, 43% started again.<sup>28</sup>

The effects of smoking during pregnancy on the fetus have opened a new chapter on the health consequences of smoking. The fetus is not like a passive smoker who inhales cigarette smoke involuntarily from the environment; rather, the fetus is a highly vulnerable being in a stage of high risk for involvement of growth. Smoking during pregnancy exposes the fetus not only to cigarette smoke compounds that traverse the placenta, but also to alterations in placental oxygenation and metabolism, and to changes in the mother's own metabolism secondary to smoking.<sup>29</sup>

Among the several tobacco compounds that affect the process of gestation, the more important are nicotine and carbon monoxide (CO). Nicotine affects the cardiovascular system causing the release of catecholamines into blood of the mother and, consequently, results in tachycardia, peripheral vasoconstriction, and reduction of placental blood flow.<sup>30-32</sup>

The vascular effects of nicotine are well-understood and proven. The acute effect of nicotine causes reduction of intervillous blood flow; this is correlated with the increase in production of catecholamines in maternal blood circulation. As a result, there is a reduction in uterine and placental perfusion and a consequent poor fetal oxygenation and nutrition.<sup>20,30</sup>

Effects on gestation	Mechanisms	Reference
Poor nutrition and chronic fetal hypoxia	Reduction of hemoglobin capacity to transport and release oxygen;	Longo <sup>21</sup>
	Decline in prostacyclin production (vasodilator) in umbilical arteries.	Stoel <i>et al.</i> <sup>22</sup>
Induction of spontaneous abortions and preterm births.	Accumulation of cotinine favoring the action of prostaglandin E2.	Rama <i>et al.</i> <sup>23</sup>

In the fetus, nicotine reduces placental perfusion due to its vasoconstricting effect. It also traverses the placental and hematoencephalic barriers very easily, thus rapidly affecting the fetus and possibly causing direct damage.<sup>33</sup> Quingley et al.<sup>34</sup> attributed to nicotine the increase in fetal cardiac frequency that occurs after use of cigarettes by the mother. The effects of nicotine occur through the increase in production of catecholamines, which are responsible for vasoconstriction and decrease in uterine perfusion. Others have reported that it is unlikely that increase in cardiac frequency occurs due to the traversing of maternal catecholamines to the fetus. The hypothesis that nicotine rapidly crosses the placental barrier and acts on the neuroendocrine system of the fetus, thus releasing catecholamines in circulating blood, is more widely accepted.<sup>35</sup>

More recently, Rama et al. verified that cotinine, the nicotine metabolite, favors the vasoconstricting action of prostaglandin E2, and that the accumulation of cotinine in fetal circulation can contribute to induction of premature labor and spontaneous abortion in smokers.<sup>23</sup>

Combination of CO with maternal and fetal hemoglobin, causing hypoxia in the mother and the fetus, can be one of the factors for chronic fetal distress in women who smoke during pregnancy. Studies have shown that high levels of CO have deleterious effects on gestation and lead to a clinical status of chronic hypoxemia of the fetus.<sup>21,36,37</sup>

CO is an important compound in cigarette smoke; it traverses the placenta very rapidly possibly due to simple or facilitated diffusion. Consequently, CO levels in fetal blood can be 10 to 15% higher than that of maternal blood. Hemoglobins have CO affinity approximately 220 times greater than that of oxygen. When connected to a hemoglobin, CO increases the oxygen affinity of the remaining hemoglobins, thus left-shifting the oxyhemoglobin saturation curve. This means that oxygen tension in blood will drop to values lower than normal before oxygen is released from the hemoglobin. This effect can be especially important for the

fetus, considering that its partial oxygen pressure in arterial blood is normally low, approximately 20 to 30 mmHg, in comparison to adult values, approximately 100 mmHg. Since CO dislocates the oxygen from the hemoglobin in arterial blood, it also reduces the capacity of arterial blood to transport oxygen. Hence, the CO effects on tissue oxygenation are twofold: reduction in oxygen transportation capacity and left-shifting the oxyhemoglobin saturation curve.<sup>21</sup>

Other studies have indicated that fetuses from mothers who smoke during pregnancy present an increase in circulation of lactates, with subsequent considerable increase in CO and hyperglobulia in blood. Viggiano et al.<sup>36</sup> proved this situation by obtaining significantly higher levels of hematocrits and hemoglobins in umbilical cord blood of concepti of active smokers in comparison to those of nonsmokers and passive smokers.

In sum, chronic smoking during pregnancy possibly induces fetal hypoxia by two separate, though associated, means. On the one hand, there is the acute effect of release of catecholamines, which is induced by nicotine and leads to episodes of fetal hypoxia following maternal vasoconstriction and reduced uterine perfusion. On the other, there is the prolonged increase in fetal carboxihemoglobin, which results in sustained fetal hypoxia.

### Smoking and lactation

Lactation represents an important period for the physical and psychological development of babies; breastfeeding is responsible for reduction of infant morbidity and mortality rates in the first year of life, especially in developing countries.

Similarly to the case of gestation, smoking during lactation has decreased.<sup>43</sup> Huag<sup>44</sup> assessed prevalence of smoking during lactation and observed a decrease from 38% to 26% from 1970 to 1991. Abandoning the habit of

Effects on lactation	Mechanisms	Reference
34% increase in for breastfeeding for less than 6 months; Reduction in maternal milk production, measured by deuterium dilution;	Reduction of serum prolactin due to dopaminergic stimulation.	Horta et al. <sup>38</sup>
Decrease in weight gain of exclusively breastfed babies;	AInhibition of increase in prolactin production induced by suckling;	Vio et al. <sup>39</sup>
Nicotine concentration in milk 2.9-fold higher than serum concentration.	Human milk pH lower than pKa1 of nicotine	Steldinger et al. <sup>42</sup>

smoking during lactation, as in during pregnancy, was more common in women with higher levels of schooling and income.<sup>43</sup>

A study carried out by Horta *et al.*<sup>38</sup> showed that babies whose mothers were smokers presented 1.34-fold (95% CI 1.00-1.80) higher chance of being weaned before six months of age. The authors also observed that the response pattern according to dose was significant and proportional to number of cigarettes smoked per day by the mother. Mothers smoking during the first six months of life the baby presented greater tendency to earlier weaning (OR = 1.44; 95% CI 1.04-1.9).

The consequences of maternal and family smoking on lactation and breastfed children include effects that render its characteristics very particular. In addition to consequences of passive smoking that affect the baby (who is in almost permanent contact with the mother at home) there are the consequences of smoking that affect lactation itself.

In the state of Rio Grande do Sul, Brazil, Oliveira Netto<sup>45</sup> observed that babies of mothers who smoked presented higher levels of cotinine in urine; the author also observed that these levels were even higher when mothers smoked during breastfeeding of the baby. These findings underscore the importance of airways and milk pathways for the exposure of infants to maternal smoking, and, also that this exposure is significantly more intense when the mother smokes during breastfeeding of the baby.

More recently, Mascola *et al.*<sup>46</sup> aimed at separately assessing the importance of breastfeeding and passive smoking on the exposure of infants to tobacco products. The authors observed that breast-fed babies of mothers who smoke presented cotinine levels 10-fold higher than those of formula-fed babies of mothers who smoked. This finding suggests that breastfeeding, even more so than passive smoking, is a determinant factor for the levels of cotinine in babies whose mothers smoke. The results also indicated that cotinine levels detected in breast-fed babies whose mothers smoke are equivalent to those of active smokers.<sup>47</sup>

It is important to keep in mind that cotinine is only a biological marker of smoking. There are no other reports of identification and quantitation of other harmful tobacco components in human milk of mothers who smoke, nor of the adverse effects of other components to the health of infants and children. The exposure via human milk can also be altered due to reduction in production of milk and of fat in maternal milk as a result of smoking.<sup>48</sup>

Nicotine is the second most abundant toxic component in tobacco. Because it is a base alkaloid (pKa1 = 7.8), it can reach concentrations considerably higher in milk than in serum (milk:serum = 2.9 + 1.1) due to the acid pH of milk. There is a correlation between nicotine concentration in milk and serum; higher concentrations are detected 10 minutes after smoking. Due to its short half-life in both serum (80 minutes) and milk (90 minutes), the actual

concentration of nicotine in milk does not depend solely on the number of cigarettes smoked per day. It also depends on the time from last cigarette smoked to beginning of breastfeeding of the baby.<sup>42</sup>

Studies with animals have shown that exposure to smoking decreases concentrations of prolactin and inhibits production of milk.<sup>40,41</sup> Studies with breastfeeding women have also indicated that smoking decreases prolactin concentrations<sup>49</sup> and duration of breastfeeding.<sup>50</sup>

Moreover, breast-fed babies of mothers who smoke gain weight at a slower pace than those of mothers who do not smoke; this suggests that smoking can affect production of milk. In Chile, Vio *et al.*<sup>39</sup> studied daily production of milk in smoking mothers according to deuterium dilution, from one to three months of lactation. The authors observed that these mothers presented a daily production of milk significantly lower than that of nonsmoking mothers ( $693 \pm 110$  vs.  $961 \pm 120$  g/dl; P less than 0.0001). In a later study, Salazar *et al.*<sup>51</sup> observed a 15% decrease in daily weight gain between one and three months of age; this decrease did not affect height gain. Another study indicated that smoking during gestation was related to significantly shorter periods of exclusive breastfeeding (2.6) in comparison to nonsmoking (3.5 months); and also that there was a significant decrease in total duration of lactation (4.2 vs. 5.3 months, respectively).<sup>52</sup>

The literature suggests hormonal and behavioral mechanisms to explain these findings. Studies with animals, experimental smoking, or injection of nicotine have clearly shown the inhibitory effect of this drug on the release of prolactin in female rats. A study has shown that nicotine inhibits the increase in production of prolactin induced by suckling in puerperal rats without, however, affecting the release of milk.<sup>40</sup> In another study, female rats were administered nicotine on the fifth day of lactation and compared to controls. The earlier presented prolactin levels ninefold lower than the latter, stopped producing milk, and also most of their pups died of starvation.<sup>41</sup> There is evidence that the effect of nicotine on prolactin secretion is due to activation of nicotine receptors of dopaminergic, tuberoinfundibular neurons, thus releasing dopamine as an inhibitor of prolactin.<sup>53</sup>

Acute and chronic effects of nicotine injection on the release of prolactin in rats were assessed by Hulihan-Giblin *et al.*<sup>55</sup> These authors observed that a single injection of nicotine induced, initially, an increase in prolactin concentration. A single injection of nicotine resulted in desensitization of the prolactin response to a subsequent injection of nicotine given 1 to 2 hr later. The prolactin response to nicotine was restored within 24 hr after a single injection.

The same authors also assessed effects of chronic injections of nicotine on nicotine-induced prolactin release. They observed that treatment with nicotine for 10 days in

male rats (2 daily injections) inhibited the release of prolactin. In this case, the release of prolactin was restored only 14 days after the last chronic injection. Hulihan-Giblin *et al.* concluded that nicotine acts as a temporal antagonist, inactivating nicotinic cholinergic receptors in brain.<sup>55</sup>

In human beings, others have observed that prolactin levels were 40% lower and the time to weaning was shorter in smoking women. Conversely to the studies with animal models, the increase in serum prolactin during breastfeeding was not significantly different between smoking and nonsmoking mothers; moreover, there was also no correlation between prolactin and milk production levels.<sup>49,56</sup>

In smoking women, it is complicated to justify interference on milk production with a single mechanism of hormonal nature due to behavioral and demographic confounding factors. Smoking mothers have more demographic characteristics in common with nonbreastfeeding mothers; babies of smoking mothers take longer to suckle after birth and exert a lower suction pressure, which can also affect endocrine response and milk production.<sup>57</sup>

Current understanding on the relation between hormone levels and milk production is not clear as to what is the causal relation for decrease in milk of smoking mothers. The prolactin levels of smoking mothers who have weaned their babies and of those who continue to breastfeed are not significantly different.<sup>58</sup> Even in normal breastfeeding conditions, it is known that a certain amount of prolactin is necessary for lactogenesis and continued breastfeeding. However, repeated efforts to correlate milk production and maternal production of prolactin have not produced consistent results.<sup>59</sup>

Both lactation and smoking are associated with changes in metabolism of fat. Hopkinson *et al.*,<sup>57</sup> studied the milk of mothers of premature babies and observed a 19% reduction in milk fat in the smoking group. Based on these findings, the authors discussed whether reduction in activity of lipoprotein lipase related to smoking could explain the low concentration of fat in milk and the low production of milk by smoking mothers.<sup>57,60</sup>

Though babies of smoking mothers present different behaviors in breastfeeding, such as episodes of colic<sup>61</sup> and reduction of frequency and amplitude of suckling, these differences do not explain the lower production of milk in mothers of babies who do not suckle. Further studies on the physiological bases for explaining lower production of milk in smoking mothers need to be carried out.

## Conclusions

With the understanding of all the harmful effects of tobacco on both the health of humans and the environment,

it is imperative to work towards decreasing the number of smokers in all population groups. Considering that prenatal healthcare in urban centers of Brazil is almost universal, pregnancy should be regarded as the ideal time to encourage people to quit smoking. It is during pregnancy that contact with healthcare professionals increases, which allows for an opportunity for this encouragement. In this sense, we would like to call the attention of all healthcare professionals involved with maternal and infant assistance to give orientation to smoking pregnant women, underscoring the harmful effects on their health and, especially, on the health of the baby in intrauterine life and after birth.

However, it is also important to encourage breastfeeding even in smoking mothers, since it is well-known that formula-fed babies of smoking mothers are similarly exposed to cigarette pollutants and, moreover, to additional risks for respiratory, gastrointestinal, and allergic diseases and for death. Because of the short half-life of nicotine (approximately one hour and a half), smoking mothers should be recommended to wait approximately two hours after the last cigarette to breastfeed the baby.

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