

# Sudden infant death syndrome (SIDS), substance misuse, and smoking in pregnancy

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**Abstract:** In the developed world, sudden infant death syndrome (SIDS) remains the leading cause of death in the post neonatal period. This review highlights the association between maternal substance misuse and SIDS, and discusses whether the increased risk is explained by abnormalities of respiratory control. Substance misuse during pregnancy is common, and although the incidence of smoking has declined in recent years among pregnant women, an increasing proportion of mothers of infants who have died of SIDS smoke. The risk of SIDS is increased in women who take opiates, but not cocaine or marijuana, although infants exposed to either of these drugs suffer morbidity, including reduced birth weight. Nicotine exposure increases the risk of SIDS, particularly if both parents smoke, and there is a dose-dependent effect. A variety of respiratory abnormalities have been described in the infants of substance abuse mothers, which may increase their risk of SIDS. These abnormalities include a reduced ability to recover from prolonged apnea and a blunted response to hypoxia and hypercarbia. These results are consistent with postmortem brainstem abnormalities reported among SIDS victims.

**Keywords:** sudden infant death syndrome, nicotine, opiates

## Introduction

Sudden infant death syndrome (SIDS) is the sudden death of an infant younger than one year of age, which remains unexplained after a formal investigation into the circumstances of death. This investigation includes performing a complete autopsy, examining the scene of death, and reviewing the infant's clinical history.<sup>1</sup> In the developed world, SIDS remains the leading cause of death in the postneonatal period.<sup>2</sup> Maternal substance abuse is increasing and has been linked to an increased risk of SIDS, but the pattern of drug abuse is changing. The aim of this review is to explore whether the increased risk of SIDS relates to particular types of substance abuse, and whether it is explained by abnormalities in respiratory control.

## Prevalence of substance misuse during pregnancy

A survey carried out by the Office for National Statistics on behalf of the Department of Health showed that approximately one in a thousand women in Great Britain is dependent on opioids; the majority of these women were of child bearing age.<sup>3</sup> Anonymous urine testing in pregnant mothers in the East of London found that 10.6% of urine samples were positive for illicit drugs.<sup>4</sup> A similar study in South London highlighted that 16% of women at pregnancy booking had evidence of substance misuse on the basis of urine toxicology screening,<sup>5</sup> suggesting that one in six women in South London

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were using drugs in early pregnancy. The majority were using cannabis, but this has adverse effects (see later).<sup>5</sup> A survey of English and Welsh maternity units in 1993 estimated the number of babies born to substance-abusing mothers was 0.81 per 1000 deliveries.<sup>6</sup>

A higher prevalence of maternal substance misuse has been reported from some, but not all, population-based studies in the United States. Ostrea and colleagues reported a 31% prevalence of cocaine use during pregnancy based on toxicological screening of meconium at birth; 44% of 3010 babies tested positive for opiates, cocaine, or cannabis.<sup>7</sup> A study in Boston, in which cocaine use was assessed by interviews during pregnancy and urine samples obtained prenatally and immediately postpartum demonstrated that 28% of urine samples tested positive for marijuana and 17% for cocaine or its metabolites.<sup>8</sup> Of the cocaine users, 24% denied use at the time of the interview and were identified solely by urine assay.<sup>8</sup> A study from Florida, however, reported only a 14.5% prevalence of maternal substance misuse during pregnancy.<sup>9</sup>

Maternal substance misuse behavior is changing, with the emergence of synthetic drugs such as mephedrone, also referred to as 'Meow Meow' or 'M-Cat'. A Home Office report on the use of khat, a shrub which is chewed for its stimulatory effects predominately by people from east Africa and the Arabian peninsula, found that in four UK cities (London, Bristol, Birmingham, and Sheffield) 34% of the 602 Somalis interviewed reported using the plant leaves.<sup>10</sup>

Estimates of smoking prevalence during pregnancy are usually based on self-reported information, but simultaneous use of biochemical markers such as cotinine has shown that pregnant women may conceal how much they smoke.<sup>11,12</sup> Nevertheless, globally there appears to have been a significant decline in maternal smoking during pregnancy. Data from the United States Department of Health and Human Services showed that 10.4% of pregnant women smoked during pregnancy in 2004 compared to 12% in 2000 and 20% in 1989. A comparable decline in maternal smoking was also reported in national data from Sweden and Denmark;<sup>13</sup> in 1983, 31% of pregnant women aged between 18 and 24 years smoked compared to 13% in 2000. Recent data on the prevalence of maternal smoking during pregnancy in the United Kingdom were provided by the infant feeding survey in 2005.<sup>14</sup> These results highlighted that 33% of women smoked at some time in the year before or during pregnancy. Approximately half of the women who admitted to smoking, smoked before pregnancy but reported that they gave up usually on confirmation of pregnancy, whereas the other half smoked throughout pregnancy.

## SIDS and substance abuse during pregnancy

### Cocaine

Some reports suggested that the SIDS rate was higher in infants who were exposed to cocaine prenatally. In one report, the SIDS rate was 15% amongst 66 infants who were prenatally exposed to cocaine compared to 4% amongst infants exposed to opiates.<sup>15</sup> A study in California found that of the 1137 infants born of substance-abusing women (16% of total births), 85% were exposed to cocaine. Ten died of SIDS at an incidence rate of 8.8/1000,<sup>16</sup> which was significantly higher than the incidence of SIDS among the 5946 infants who had no drug exposure (1.3/1000).<sup>16</sup> In contrast, in a study of 175 cocaine-abusing mothers and 821 controls, only one infant of the cocaine abusing mothers died, yielding a SIDS incidence of 5.6/1000, which was similar to the incidence of 4.9/1000 amongst nonexposed offspring.<sup>17</sup>

In addition, in a study of 1780 SIDS cases from a population of more than a million infants in New York City between 1979 and 1989, SIDS rates were 5.89 per 1000 births for drug-exposed infants compared to 1.39 per 1000 control infants.<sup>18</sup> When adjustment was made for confounders, the association between increased SIDS rates and drug use remained significant for opioid use (methadone, heroin, or methadone and heroin), but not for cocaine alone or cocaine with opioids. A subsequent meta-analysis of 10 studies reported that the incidence of SIDS in infants born to mothers who used cocaine during pregnancy, highlighting that the pooled odds ratio (OR) for SIDS was 4.10 (95% confidence interval [CI]: 3.17–5.30),<sup>19</sup> but there was no increased risk of SIDS related to prenatal cocaine exposure compared to exposure to other drugs (Figure 1). In addition, it has been emphasized that as cocaine use is correlated with many potential risk factors, large sample sizes and multivariate statistical techniques are needed to determine whether cocaine use is an independent

- Cocaine – no increased risk (meta-analysis of ten studies)<sup>19</sup>
- Heroin and methadone – increased risk (two large case series)<sup>21,22</sup>
- Methadone – increased risk (population-based study)<sup>23</sup>
- Marijuana – increased risk for paternal but not maternal use (telephone interviews after death)<sup>25</sup>
- Smoking increased risk (large epidemiological studies)<sup>35,36</sup> (dose-dependent effect)<sup>39,40</sup>

**Figure 1** SIDS and substance abuse during pregnancy.

risk factor for adverse neonatal outcomes.<sup>8</sup> In one series,<sup>8</sup> cocaine users were significantly less likely than nonusers to be married, but were more likely to have sexually transmitted diseases, prior low birth weight infants, spontaneous and elective abortions, and greater use of alcohol, cigarettes, and other illicit drugs during pregnancy.

## Opiates

Infants born to opiate-abusing mothers have been shown to be five to ten times more likely to be at risk of SIDS than the general population.<sup>20</sup> A study from New York examining a cohort of 383 infants born of substance-abusing mothers recorded a SIDS incidence of 20.9 per 1000 infants.<sup>21</sup> The study found that no SIDS deaths were attributable to heroin use alone, but 4 of 106 infants who were born to mothers who abused heroin and methadone died of SIDS.<sup>21</sup> The other four cases of SIDS were born to 182 mothers who were on a methadone treatment program.<sup>21</sup> Chavez et al reported 17 cases of SIDS in infants born to 688 drug-using mothers (24.7 per 1000 births).<sup>22</sup> Although 14 of the 17 mothers of SIDS victims were enrolled in methadone treatment programs, the majority of the mothers continued to use other drugs such as heroin, cocaine, diazepam, and amphetamines. A recent retrospective, Australian study of all live births to women in New South Wales during the period encompassing 1995–2002 found that the infant mortality rate was high amongst infants whose mothers were on methadone during pregnancy (24.3 per 1000 live born infants).<sup>23</sup>

## Marijuana (cannabis)

Marijuana is the most frequently used illicit substance in the Western world; 32% of those living in urban areas in the United States (US) were reported to use marijuana.<sup>24</sup> Maternal use of marijuana, however, does not appear to increase the risk of SIDS. In a case-control study in southern California examining 239 infants who died of SIDS and 239 matched healthy infants, no association between maternal recreational drug use and SIDS was found.<sup>25</sup> Similarly, in a study carried out in the UK (the Avon Longitudinal Study of Pregnancy and Childhood), the use of cannabis during pregnancy was not associated with an increased risk of perinatal mortality or morbidity; however, frequent and regular use of cannabis during pregnancy was associated with a small but statistically significant reduction in birthweight.<sup>26</sup>

The adjusted mean birth weights of babies who are born to women who used cannabis at least once per week before and throughout pregnancy were 90 g lighter than offspring of other women.<sup>26</sup> In a study in South London,<sup>15</sup> cannabis use in

early pregnancy was also associated with a reduction in birth weight, a lower gestational age at delivery, and an increased risk of prematurity. A case-control study of 239 infants who died of SIDS also demonstrated that maternal recreational drug use in pregnancy was not associated with an increased risk of SIDS. It was noted that paternal marijuana use during conception (OR = 2.2, 95% CI: 1.2–4.2), pregnancy (OR = 2.0, 95% CI: 1.0–4.1), and postnatally (OR = 2.8, 95% CI: 1.1–7.3) was significantly associated with an increased risk of SIDS after adjusting for paternal smoking and alcohol abuse. The results of that study, however, were from telephone interviews of parents 6 to 12 months after the infant's death,<sup>25</sup> and it would be important to undertake further investigation to confirm or refute this association.

## Stimulants

Twenty million people consume khat on a daily basis in Africa, and a further 10 million people worldwide may use it regularly.<sup>27</sup> The effect of chewing khat leaves produces a stimulatory and euphoric sensation similar to that produced by a mild amphetamine. Although, there are no studies reported which have explored the association between maternal use of khat during pregnancy and subsequent SIDS, use of khat is associated with low birth weight,<sup>28</sup> a risk factor for SIDS.

Mephedrone (4-methylmethcathinone) is a novel synthetic stimulant drug that has recently become popular in the UK and Europe. A recent survey found that mephedrone was the sixth most frequently used drug after tobacco, alcohol, cannabis, cocaine, and 3,4-methylenedioxymethamphetamine.<sup>29</sup> The survey highlighted that the majority of ephedrine abusers were of young age; the drug has comparable abuse potential to cocaine.<sup>29</sup> There are no reports investigating ephedrine use and SIDS.

## Smoking

Steele and Langworth<sup>30</sup> conducted the first epidemiological study examining the association between maternal smoking and SIDS, and reported an odds ratio of 2.4, which was not significantly reduced when low birth weight was taken into consideration. Heavy smoking is associated with a dose-dependent adverse effect on birth weight.<sup>31</sup> Since the “Back to Sleep” campaign, it has become known that cigarette smoke exposure is the leading independent risk factor for the occurrence of SIDS.<sup>32,33</sup> Although in some areas in the UK the overall SIDS rate is reduced, the proportion of SIDS victims whose mothers smoked during pregnancy has increased from 57% in the 1980s to 86% in 2003.<sup>34</sup>

Maternal smoking has been shown to be a significant risk factor for SIDS in a large number of epidemiological studies. According to both a National Institute of Child and Human Development study<sup>35</sup> and a prospective Australian study in Tasmania,<sup>36</sup> maternal smoking was more common amongst mothers of SIDS victims (OR = 3.8, and OR = 3.0, respectively). Smokers differ from nonsmokers with regard to other risk factors for SIDS; smokers tend to be unmarried mothers, come from a lower socioeconomic class, have greater numbers of pregnancies, and give birth to babies with low birth weight; however, after adjusting for factors including socioeconomic pregnancy, infants of mothers who smoke remain at an increased risk of SIDS.<sup>13</sup>

Both in-utero and ex-utero passive exposure to smoking increases the risk of SIDS. In one study, after adjusting for demographic risk factors, the odds ratio for SIDS among normal birth weight infants was approximately two for maternal smoking only during infancy and three for maternal smoking both during pregnancy and infancy.<sup>37</sup> A combination of paternal smoking, postnatal exposure, and in-utero maternal smoking increased the risk of SIDS when compared to in-utero maternal smoking alone (OR = 2.5 and 2.9 compared to OR = 2.1).<sup>34</sup> Maternal smoking is associated with a higher risk of SIDS when compared to paternal smoking. A case control study undertaken in Scotland showed that exposure to cigarette smoke increased the SIDS risk much more if the mother or both parents smoked as compared to paternal smoking alone.<sup>38</sup>

A dose-dependent effect of exposure to tobacco smoking and the risk of SIDS has been demonstrated. In the New Zealand cot death study (which included 162 SIDS deaths),<sup>39</sup> the OR was 1.87 when exposure was less than 10 cigarettes per day, 2.64 when infants were exposed to 10–19 cigarettes, and 5.06 when infants were exposed to more than 20 cigarettes per day.<sup>39</sup> Similarly, MacDorman et al reported an OR of 1.6–2.5 if the mothers smoked between 1 and 9 cigarettes per day during pregnancy, and 2.3–3.8 if the mothers smoked more than 10 cigarettes per day.<sup>40</sup> Although low birth weight was identified as a strong risk factor for SIDS, the addition of low birth weight to the models lowered the odds ratio for maternal smoking only slightly, suggesting that the effect of smoking on SIDS is not mediated through birth weight.

The risk of SIDS has been reported to be increased amongst infants born to mothers who were smokers and shared a bed with their infant,<sup>32</sup> but other studies have not shown such an association.<sup>41,42</sup> In a prospective cohort study of almost 10,000 infants in a high risk population

(of whom 53 infants subsequently died of SIDS),<sup>42</sup> the cotinine level in the infant's urine of nonbed-sharing mothers was half that of infants of bed-sharing mothers. These results indicate that smoking in an infant's bedroom increases the infant's exposure to passive smoke. Nevertheless, there was no increased risk of SIDS noted in bed-sharing infants of mothers who smoked.

## Pathological abnormalities in SIDS victims

Delayed myelination of the central nervous system – particularly in the somatomotor, limbic, and paralimbic regions – is seen in SIDS cases, suggesting a central nervous system insult may contribute to SIDS.<sup>43</sup> Structural abnormalities in the respiratory control regions of the brainstem have been reported in infants who died of SIDS.<sup>44,45</sup> In addition, when compared with age matched controls who died from accidents or acute diseases, SIDS victims exhibited increased astrogliosis in the reticular nuclei, the solitary tract nucleus, the dorsal nucleus of the vagus nerve, and the nucleus olivaris inferior.<sup>46</sup> In one study,<sup>46</sup> the degree of gliosis in the nucleus olivaris inferior related to the magnitude of smoking during pregnancy in SIDS victims. Lesions in the nucleus olivaris inferior have been suggested to contribute to autonomic dysfunction.<sup>47</sup>

Prenatal nicotine exposure results in cell death in the brainstem of animal models.<sup>48</sup> The effects of prenatal smoking may be mediated by nicotine and carbon monoxide effects on the placental circulation leading to fetal ischemia or hypoxia.<sup>49,50</sup> There is, however, evidence from animal studies that many pathological findings in the central nervous system can also be induced by levels of nicotine that do not compromise utero-placental function.<sup>51</sup> In human fetuses, high concentrations of nicotine binding sites in brainstem tegmental nuclei related to cardiopulmonary integration during mid-gestation may make those areas more susceptible to nicotine toxicity during critical periods of brain development.<sup>52</sup> Measurements of nicotine and its metabolites in babies dying from SIDS indicate that significant exposure had occurred around the time of death.<sup>53,54</sup> High levels of cotinine in the pericardial fluid of SIDS victims who were cosleeping and had focal organ lesions in the liver and the heart have also been reported.<sup>55</sup>

Apoptosis in the brainstem nuclei involved in facial sensations and the position of the head has been reported in infants of smoking mothers.<sup>56</sup> Reduced sensory loss in the face could result in an inability of the infant to correctly determine the orientation of his or her face whilst asleep,



and hence the infant may possibly suffocate if placed in the prone position.<sup>57,58</sup>

## Respiratory control abnormalities in infants of substance-abusing mothers

A variety of respiratory abnormalities has been reported in infants of substance-abusing mothers. A significantly smaller fall in end-tidal carbon dioxide levels in response to a hypoxic challenge, and a significant impairment in arousal responses to hypoxia in infants of substance-abusing mothers have been reported.<sup>59</sup> Reduced carbon dioxide sensitivity in newborns of substance-abusing mothers has also been highlighted.<sup>60</sup> It has been postulated that ventilatory control abnormalities could lead to abnormal sleeping ventilatory patterns,<sup>61</sup> which might contribute to the increased risk of SIDS among infants of substance-abusing mothers. Indeed, in one study,<sup>61</sup> 32% of pneumograms from substance-abusing mothers were abnormal compared to 9.3% of pneumograms among controls. The infants of substance-abusing mothers had longer sleep times, a higher total duration of apneas greater than or equal to 6 seconds, and more periodic breathing.<sup>61</sup>

Abnormalities specific to certain types of prenatal drug exposure (including cocaine and methadone) have been reported. Infants prenatally exposed to cocaine had a higher incidence of cardiorespiratory pattern abnormalities; that is, more frequent apneas and greater intervals of periodic breathing than infants exposed antenatally to methadone.<sup>15</sup> Apnea density and episodes of periodic breathing exceeded the 95th percentile for normal infants among 38% of cocaine-exposed infants, but only 6% (one in 18) of methadone-exposed infants.<sup>15</sup> In addition, five infants exposed to cocaine (but no infants exposed to methadone) had apnea.<sup>15</sup>

A higher frequency of respiratory pauses and a greater decrease in minute ventilation in response to facial air stream stimulation has been reported in infants exposed prenatally to cocaine compared to controls.<sup>62</sup> Nevertheless, an increase in SIDS risk was not found in infants of mothers who used cocaine in pregnancy,<sup>19</sup> highlighting that further studies are required to determine the contribution of respiratory control abnormalities involved in SIDS.

Infants exposed to methadone in-utero were demonstrated to have decreased sensitivity to a carbon dioxide challenge when compared to controls, as measured by the slope of the ventilatory response curve during the first weeks after birth.<sup>63</sup> The depressed ventilatory response to carbon dioxide lasted on average for 15 days after birth.<sup>63</sup> The majority of women who engage in substance abuse also smoke, and thus some

of the respiratory control abnormalities seen in infants of substance-abusing women may, at least in part, relate to maternal smoking (see below).

Two possible explanations for the increased risk of SIDS in mothers who smoked during pregnancy are a reduced ability to recover from prolonged apnea, or insensitivity to hypoxia or hypercarbia. It was found that continuous infusion of nicotine to pregnant rats from day six of gestation to days five or six postpartum resulted in an impairment in the ability of the newborn pups to auto-resuscitate from primary apnea during repeated exposure to hypoxia.<sup>64</sup> In addition, rat pups exposed to nicotine during fetal life exhibited deficient adrenomedullary catecholamine release in response to hypoxia. As a result, these rats died at the same hypoxic levels that unexposed rat pups survived without major ill effects.<sup>65</sup> These pups also lacked the normal increase in heart rate that should occur in response to hypoxia.<sup>66</sup> Infusion of nicotine in lambs at mean ages of 7, 17, and 27 days resulted in attenuation of the ventilatory response to hypoxia and augmentation of the response to hyperoxia, suggesting that exposure to nicotine altered peripheral chemoreceptor oxygen sensitivity, and it may have also affected the central processing of the chemoreceptor input.<sup>67</sup> Data from animal studies suggest that nicotine interferes with the postnatal resetting of oxygen sensitivity of the peripheral arterial chemoreceptors by increasing carotid body tyrosine hydroxylase mRNA and dopamine release.<sup>68</sup>

In infants aged between 2 and 24 months, prenatal exposure to cigarette smoke resulted in reduced respiratory drive as assessed by measurement of the mouth pressure 100 milliseconds after an airway occlusion at the onset of inspiration ( $P_{0.1}$ ), and a blunted ventilatory response to hypoxia (14% oxygen).<sup>69</sup> A dose response relationship was reported between the number of cigarettes smoked, the results for  $P_{0.1}$ , and the response to hypoxia.<sup>69</sup> Paternal smoking had no influence on the infant's resting ventilation, inspiratory drive, or ventilatory response to hypoxia.<sup>69</sup> It was also found that more infants of smoking mothers failed to awaken in response to a hypoxic challenge at 2 to 3 months of age.<sup>70</sup> Moreover, infants of mothers who smoked antenatally prior to maternity unit discharge (ie, before passive postnatal smoke exposure) had a dampened ventilatory response when compared to controls. This meant that the time constant of the infant's response in increasing their minute ventilation to compensate for the added dead space was longer.<sup>71</sup> Hypercarbia is the most important stimulus to ventilation with added dead space; therefore, these results are compatible with dampened chemoreceptor function in infants exposed to cigarette smoking in utero.<sup>71</sup>

## Summary

The risk of SIDS is increased among the infants of women who abuse opiates or smoke cigarettes during pregnancy, but the risk is not increased among infants of women who abuse cocaine or marijuana. Structural abnormalities in the respiratory control regions of the brainstem have been reported in SIDS victims, and prenatal nicotine exposure results in cell death in the brainstem of animal models. These abnormalities are consistent with the respiratory control abnormalities reported in substance-abusing and/or smoking mothers. These abnormalities include reduced carbon dioxide sensitivity (methadone, nicotine), reduced respiratory drive (nicotine), and a reduced response to hypoxia (nicotine). In conclusion, practitioners caring for women who use or abuse substances and/or smoke during pregnancy need to make the women aware of the increased risk of SIDS. More importantly, such women should be warned of the risk factors and dangers associated with SIDS before they become pregnant.

## Disclosure

The authors report no conflicts of interest in this work.

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