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Antenatal smoking and substance-misuse, infant and newborn response to hypoxia

Kamal Ali[1], Thomas Rossor[1], Ravindra Bhat[1], Kim Wolff[2], Simon Hannam[1], Gerrard F Rafferty[1], Anne Greenough[1, 3]

[1]Division of Asthma, Allergy and Lung Biology, MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, King's College London, London, United Kingdom [2]Addiction Sciences Unit, King's College London, London, United Kingdom [3]National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London,

Address for correspondence: Professor Anne Greenough, NICU, 4th Floor Golden Jubilee Wing, King's College Hospital, Denmark Hill, London, SE5 9RS, United Kingdom

Tel: 0203 299 3037; fax: 0203 299 8284; email: anne.greenough@kcl.ac.uk

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ABSTRACT

Objectives: Infants of smoking (S) and substance misusing (SM) mothers have an increased risk of sudden infant death syndrome. We have tested the hypothesis that infants of S or SM mothers compared to infants of non substance misusing, non-smoking mothers (controls), would have a poorer ventilatory response to hypoxia at the peak age of SIDS. In addition, we compared the ventilatory response to hypoxia during the neonatal period and the peak age of SIDS.

Design: Prospective, observational study.

Setting: Tertiary perinatal centre.

Patients: Twelve S; 12 SM and 11 control infants were assessed at 6-12 weeks of age; they had previously been assessed in the perinatal period.

Interventions: Maternal and infant urine samples were tested for cotinine, cannabinoids, opiates, amphetamines, methadone, cocaine and benzodiazepines.

Main outcome measures: Changes in minute volume, oxygen saturation, heart rate and end tidal carbon dioxide on switching from breathing room air to 15% oxygen.

Results: The S and SM infants had a greater decline in minute volume ($p=0.037$, $p=0.016$ respectively) and decline in oxygen saturation ($p=0.031$) compared to controls. In all three groups, the magnitude of decline in minute volume in response to hypoxia was significantly higher in the neonatal period compared to at 6-12 weeks ($p=<0.001$).

Conclusions: Both maternal smoking and substance misuse were associated with an impaired response to a hypoxic challenge at the peak age of SIDS. The hypoxic ventilatory decline was more marked in the neonatal period compared to the peak age for SIDS indicating a maturational effect.

INTRODUCTION

Maternal smoking during pregnancy is the largest, preventable cause of perinatal morbidity [1, 2] and mortality.[3] With the success of the Back-To-Sleep campaign, tobacco exposure is the main risk factor for Sudden Infant Death Syndrome (SIDS). Maternal smoking is associated with at least a three-fold increased risk of SIDS.[4] Illicit drug use in women of reproductive age is increasing.[5] A recent review of nearly 300 centers in the United States, found increases from 2004 through to 2013 in patient admissions, length of stay and resource utilization for infants admitted to NICUs with neonatal abstinence syndrome.[6] Maternal misuse of cocaine [7] and opiates [8, 9] have been shown to increase the risk of SIDS. In the United Kingdom, the CESDI (Confidential Enquiry Stillbirths and Deaths in Infancy) Study demonstrated a significantly higher use of illegal substances in mothers of SIDS than controls 15.9% vs 5.6%.[10]

SIDS has been hypothesized to be due to brainstem abnormalities which could adversely affect ventilatory control.[11] We, therefore, hypothesized that infants of substance misusing mothers or smoking mothers would have a poorer ventilatory response to hypoxia compared to infants of non– substance-misusing, non-smoking mothers at the peak age of SIDS. In addition, we hypothesized that smoking and substance misuse would have an additive effect, and hence any impairment of the ventilatory response to hypoxia would be greater in infants of mothers who both substance misused and smoked. Aims of this study were to test those hypotheses.

In human adults, a rapid increase in ventilation is elicited by hypoxia and only after approximately 15 minutes is there a decline in minute ventilation, but it still remains above the baseline hypoxic values.[12] Both prematurely [13-15] and term born [16] infants have a biphasic response to hypoxia with a transient increase in ventilation that peaks around one minute into the hypoxic challenge followed by a late decline at three to five minutes. The biphasic response to hypoxia may persist beyond the neonatal period.[17, 18] A further aim of this study was to determine if any differences between the S, SM and control groups differed at 6-12 weeks compared to the neonatal period.

METHODS

Infants were eligible for entry into the study if they were born at 36 weeks of gestational age or greater at King's College Hospital NHS Foundation Trust and had been assessed in the neonatal period prior to maternity unit discharge, that is at less than 10 days of age. The results from the neonatal period have been published.[19] Informed written parental consent was obtained and the study was approved by the Guy's and St Thomas's Hospitals NHS Foundation Trust Research Ethics Committee.

Three groups were recruited:

1. Infants of mothers who gave on antenatal screening a history of substance misuse during pregnancy (SM infants).
2. Infants of mothers who gave a history of smoking during pregnancy and the postpartum period (S infants).

3. Infants of mothers who neither smoked nor misused substances during pregnancy and the postpartum period (controls).

Maternal and antenatal smoking was defined as any history of daily smoking regardless of the number of cigarettes smoked per day and was confirmed by maternal and infant urinary cotinine analysis performed in the immediate perinatal period. Substance misuse was defined as use of any illicit drugs during pregnancy and confirmed by urine analysis during pregnancy and in the immediate perinatal period.

Hypoxic challenge

Physiological measurements were carried out when the infants were in quiet sleep. Sleep state was determined by observation of the behavioural state.[20] An infant was defined as being in quiet sleep when their eyes were closed, with no body or eye movement, no vocalization and their respiratory rate was regular. The hypoxic challenge was delivered via a facemask and custom-made open circuit system using 15% oxygen in balanced nitrogen from a cylinder (BOC Gases, UK). The facemask was placed over the infant's mouth and nose, therapeutic putty was put around the rim of the facemask to ensure an airtight seal around the face. Respiratory flow was measured using an appropriately sized pneumotachograph connected to the face mask (Mercury F10L, G M Instruments, Kilwinning, Scotland) with a dead space 0.8 ml and a resistance of 1.4 $cmH_2O/L/second$. The distal end of the pneumotachograph was connected to a two-way non-rebreathing valve contained within the open circuit system. A constant flow of medical air

from a cylinder (BOC Gases, UK) was delivered to the inspiratory port of the two-way non-rebreathing valve via length of wide bore (20mm), low resistance tubing. The pneumotachograph was attached to a differential pressure transducer/amplifier (13-4615-70, Gould, Cleveland OH, USA). Data were acquired and displayed in real time on a PC computer running Spectra software (Grove Medical, London, UK) with 100 Hz analog to digital sampling (PCI-MIO-16XE-50, National Instruments, Austin TX, USA). Tidal volume was determined by digital integration of the flow signal by the acquisition software. Inspired and expired gases were sampled continuously using a small cannula inserted through the facemask and positioned close to the infant's mouth. Oxygen saturation and heart rate were measured using a pulse oximeter (Masimo rainbow SET Pulse Oximetry).

During quiet breathing, the infants were switched from breathing room air to 15% oxygen in nitrogen (BOC Gases, UK). The final minute of tidal breathing in air was used as the baseline value. The hypoxic challenge was maintained for five minutes, but terminated if the oxygen saturation level fell below 85%. Infants respond to hypoxia with a biphasic response. The responses to the hypoxic challenge were determined by:

1) The magnitude of increase in minute ventilation from baseline to the peak ventilation
2) The magnitude of decline in minute volume from the peak to the lowest minute volume

3) The change in the oxygen saturation level from baseline to the lowest oxygen saturation level.
4) Magnitude of increase in heart rate from baseline to peak in response to hypoxic challenge
5) Changes in end tidal CO_2 ($ETCO_2$) with hypoxia

The time to peak minute ventilation was noted, as was the time to the lowest SaO_2.

STATISTICAL ANALYSIS

The data were tested using the Kolgorove Smirnov test and found to be not normally distributed. Differences between in the three groups were assessed for statistical significance using the Kruskal-Wallis one-way analysis of variance for continuous variables and Chi-square for categorical variables. Differences between results in the neonatal period and at 6-12 weeks post term were assessed for statistical significance using the paired Wilcoxon rank sum test. Analysis was performed using SPSS version 22.0 (SPSS, Inc., Chicago, IL).

SAMPLE SIZE

We recruited 61 infants (21 SM, 21 S and 19 controls) in the neonatal period. That sample size allowed detection of a difference equivalent to one standard deviation in each outcome between the three groups with 80% power at the 5% level. A similar magnitude of difference had been

detected in the ventilatory response to added dead space between newborns of smoking and non-smoking mothers.[21]

RESULTS

Thirty-five of the 61 infants were recruited in the neonatal period completed the follow up studies at 6-12 weeks of age. There were no significant differences in gestational age, birth weight, gender, mode of delivery or maternal age between those who did and did not complete the follow up studies (Table 1). Twelve substance-misuse (SM), 12 smoking (S) and 11 control infants were assessed at 6-12 weeks of age (Table 2). There were no significant differences between the groups with regard to the weight, gender, age at the study or maternal age.

The urine analysis in the immediate postpartum period demonstrated that all the mothers of SM infants were also smoking, but that none of the mothers of the controls were smoking. The urine analysis also demonstrated that none of the mothers of S infants or the controls had been substance misusing. In the SM group, urine analysis in the immediate post partum period demonstrated seven women were on methadone, two had misused cocaine and three had misused multiple drugs.

There was no significant difference between the groups in baseline minute volume ($p=0.17$) (Table 3). The initial increase in minute volume during the hypoxic challenge did not differ significantly between the groups ($p=0.309$) (Table 3). There were no significant differences in the time to

peak minute ventilation between the groups (p=0.056). The magnitude of the subsequent decline in minute volume varied significantly between the groups (p=0.02) with a greater magnitude of decline occurring in the S (p=0.037) and the SM infants (p=0.016) compared to controls (Table 3) (Figure 1). The baseline $ETCO_2$, the $ETCO_2$ decline and the $ETCO_2$ increase with hypoxic ventilatory decline did not differ significantly between the groups (Table 3).

There were no significant differences in the baseline oxygen saturation or baseline heart rate between the groups (Table 4). The percentage decline in oxygen saturation was significantly different between the groups (p= 0.031). The time to the lowest oxygen saturation was greater in the controls than the infants of S (p= 0.036) or SM (p= 0.014) mothers (Table 4). There was a significantly higher increase in heart rate with the hypoxic challenge in the controls compared to S (p= 0.05) and SM (p= 0.01) infants.

Comparison of the results in the neonatal period and at 6-12 weeks of age showed that the baseline minute volume was significantly higher in the neonatal period (p=0.009). There were no significant differences in the magnitude of the increase in ventilation between the two study periods, but the magnitude of decline was significantly higher in the neonatal period compared to 6-12 weeks of age (p< 0.001) (Table 5) (Figure 2).

DISCUSSION

We have demonstrated that at the peak age of SIDS infants of SM and S mothers had a greater magnitude of decline in ventilation in response to a hypoxic challenge compared with controls. Importantly, we have demonstrated that maternal substance misuse and smoking have an additive adverse effect on the response. We also demonstrate a greater percent decline in oxygen saturation in response to hypoxia in the SM and S infants compared to controls. In addition, the SM and S infants reached the lowest saturation level earlier in the course of the hypoxic challenge. These effects were greater in the SM infants. Previous studies have higlighted that maternal smoking or substance-misuse impairs the infant ventilatory and arousal responses to a hypoxic challenge out with the neonatal period.[11, 22, 23] Infants of smoking mothers had a blunted response to a hypoxic stimulus [22] at 24 months of age. Similarly, at two to three months of age, infants of smoking mothers compared to controls had impaired arousal responses in response to a hypoxic challenge.[11] Furthermore, a smaller fall in end-tidal carbon dioxide and impaired arousal responses in response to a hypoxic challenge in infants of substance-abusing mothers at nine weeks of age has been demonstrated.[23]

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The increase in heart rate in response to hypoxia was greater in the controls than the SM or S infants. The ventilatory response to hypoxia increases lung stretch receptor activity via cardiac vagal motoneurons resulting in tachycardia.[24-27] In term born infants aged 2-82 days, maternal smoking affected the magnitude and the time course of heart

rate increase in response to hypoxia compared to controls.[28] The effect of maternal substance misuse on the cardiac response to a hypoxic challenge has not previously been reported.

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One study reported that the biphasic response had disappeared by ten days of age [29], while others have reported that the immature biphasic response to hypoxia persisted into the second month of postnatal life in both prematurely born [30] and term born infants.[31] Another study showed that the biphasic response to hypoxia persisted in both quite and active sleep at five to six months of age [18, 29] Our results confirm the persistence of the biphasic response to hypoxia at 6-12 weeks.[30, 31] The magnitude of decline in minute volume in response to hypoxia was less marked at 6-12 weeks of age compared to the neonatal period, reflecting a maturational effect.

Our study has strengths and some limitations. We have been able to study the ventilatory response to hypoxia in three groups whose status was confirmed by urinary analysis in the immediate post partum period. Although, we were only able to follow approximately half those recruited in the neonatal period, there were no significant differences in the demographics of those who were and were not followed-up. We were unable to separate the effects of smoking and substance misuse as all of the mothers in the SM group also smoked. To our knowledge this is the first study which has compared the responses to hypoxia in infants of

SM/S mothers and S mothers both at the peak age for SIDS and in the early neonatal period.

In conclusion, we have demonstrated a change in the ventilatoy response to a hypoxic challenge over the first months after birth. Nevertheless, at the peak age for SIDS, there was a greater decline in minute ventilation in response to hypoxia in the infants of smoking mothers and substance misusing mothers and, in particular the infants of substance misusing smoking mothers. This may make them more vulnerable to SIDS.

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Contributors: AG and RB designed the study, KA collected the data and with KW was responsible for the drug screening. KA and TR undertook the analysis. All authors were responsible for the production of the manuscript.

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Competing interests: None to declare.

What is already known on this topic:

- Maternal smoking is associated with at least a three fold risk of SIDS.
- There is a higher use of illegal substances in mothers of SIDS than controls.
- SIDS has been hypothesized to be due to brainstem abnormalities which could affect ventilatory control.

What this study adds:

- The hypoxic ventilatory decline was more marked in the neonatal period than at 6-12 weeks.
- Infants of substance misuse or smoking mothers, however, had a greater decline in minute volume in response to hypoxia at 6-12 weeks.
- The effect was greater in infants whose mothers both smoked and substance misused.

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Table (1) Comparison of the infant demographics and maternal age between those who did and did not complete the follow up study

	Follow up completed (n=35)	No follow up (n=26)	P value
Gestational age (wks)	38 (36-40)	39 (36-42)	0.355
Birth weight (gm)	2850 (1730-4970)	3092 (1860-4460)	0.08
Gender (male)	21 (60%)	16 (61.5%)	0.126
Mode of delivery (SVD)	25(71.4%)	18 (69.2%)	0.640
Maternal age (yrs)	28 (18-40)	31 (18-43)	0.233

Table (2) Demographics of the infants who completed the follow up studies by smoking and substance misuse status

	Control	S	SM	P value
Weight (kg)	4.5 (3.66-6.68)	4.5 (4-6.5)	4.36 (3.5-5.6)	0.474
Gender (male)	7 (63.6%)	8 (66.7%)	5 (41.6%)	0.405
Age at study (wks)	8 (6-12)	8 (7-10)	8 (6-11)	0.954
Maternal age (yrs)	30 (20-37)	29 (22-40)	30 (20-40)	0.845

Table (3) Changes in minute ventilation and $ETCO_2$ in response to hypoxia by maternal smoking (S) and substance-misuse status

	Control	S	SM	P value
Baseline minute volume (ml/kg/min)	270 (200-400)	315 (260-475)	325 (220-430)	0.17
Increase in minute volume (ml/kg/min)	60 (20-200)	50 (0-90)	55 (0-120)	0.309
Time to peak minute ventilation (s)	150 (55-310)	80 (50-130)	75 (25-155)	0.056
Decline in minute volume (ml/kg/min)	40 (0-140)	80 (50-140)	100 (40-130)	0.02
Baseline $ETCO_2$ (mmHg)	38 (33-46.5)	35 (30-42)	34.5 (32-43.5)	0.23
Decline in $ETCO_2$ (mmHg)	3.5 (1-5)	3 (0-8)	3 (2-7)	0.837
Increase in $ETCO_2$ (mmHg)	2.5 (1-6.5)	5 (2-6.5)	5 (3-10)	0.052

Table (4) Changes in oxygen saturation (SaO_2) and heart rate with hypoxic challenge by maternal smoking and substance misuse status

	Control	S	SM	
Baseline SaO_2 (%)	100 (97-100)	100 (94-100)	99 (97-100)	0.719
Change in SaO_2 with hypoxia (%)	7 (4-10)	11 (2-16)	10 (5-18)	0.031
Time to lowest SaO_2 (s)	120 (60-200)	100 (40-180)	90 (40-120)	0.032
SaO_2 below 85% (n)	0 (0%)	6 (50%)	2 (16.7%)	0.014
Baseline heart rate (beat/min)	125 (90-150)	135 (115-145)	140 (128-150)	0.062
Increase in heart rate with hypoxia (beat/min)	10 (5-30)	6 (0-15)	5 (0-10)	0.033

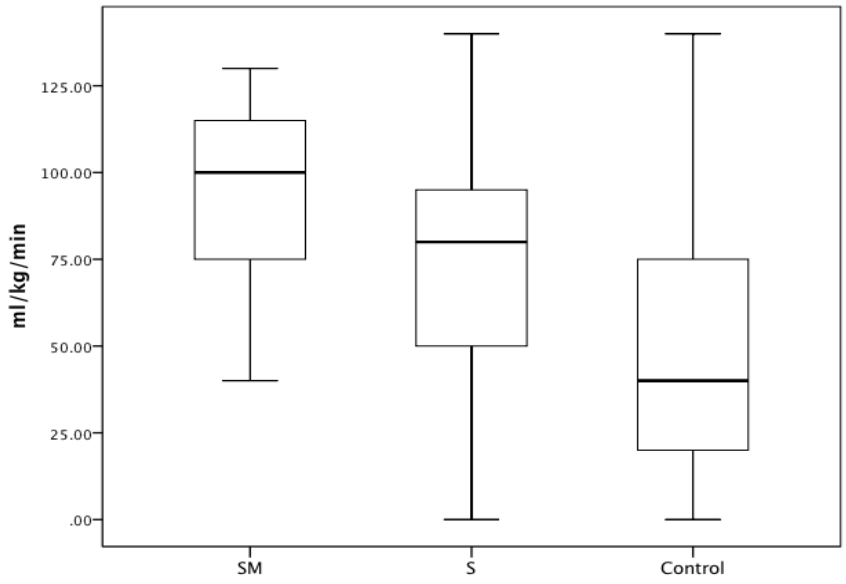
Table (5) The ventilator response to hypoxia in the neonatal period and 6-12 weeks

	Neonatal	6-12 weeks	P value
Baseline minute volume (ml/kg/min)	344 (203-614)	300 (200-475)	0.009
Increase in minute volume (ml/kg/min)	47 (0-374)	55 (0-200)	0.221
Decline in minute volume (ml/kg/min)	136 (15-444)	80 (0-140)	<0.001

FIGURE LEGENDS

Figure 1: Box and whisker plot of the magnitude of decline in minute volume by maternal smoking (S) and substance-misuse (SM) status

Figure 2: Box and whisker plots of the magnitude of decline in minute ventilation with hypoxia by maternal smoking (S) and substance-misuse (SM) status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100.00
75.00
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SM
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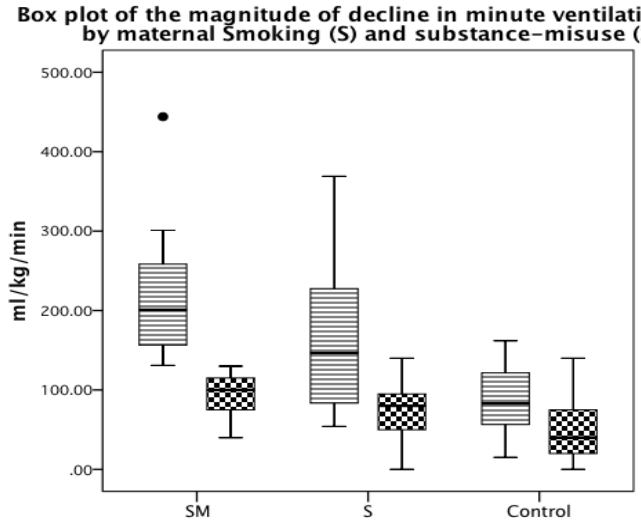

Box plots with horizantal lines represents neonatal studies. Dotted box plots represents studies at 2-3 months of age