Journal of Advances in Medicine and Medical Research

33(14): 1-9, 2021; Article no.JAMMR.69710
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Maternal Smoking Status Assessed by Breath Carbon Monoxide Measurements. Association with Fetal Growth and Nicotine Withdrawal Syndrome in Newborns

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Authors' contributions

This work was carried out in collaboration among all authors. Author SK-K designed the study, performed the statistical analysis, wrote the protocol, wrote the first draft of the manuscript.and managed the literature searches. Author LL participated to the study design, data collection and analysis and author PH managed the analyses of the study and manuscript critical review. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2021/v33i1430965
Editor(s):
(1) Dr.Chan-Min Liu, Xuzhou Normal University, China.
Reviewers:
(1) Mulugeta Hailu, Wachemo University, Ethiopia.
(2) Aye Aye Myint, University of Medicine Mandalay, Myanmar.
Complete Peer review History: http://www.sdiarticle4.com/review-history/69710

Original Research Article

Received 06 April 2021
Accepted 11 June 2021
Published 15 June 2021

ABSTRACT

Background: Maternal smoking during pregnancy is a recognized public health hazard with ill effects on fetal development. Whether infants exposed to tobacco smoke in-utero present with nicotine withdrawal syndrome (NWS) is debated
Aim: To evaluate maternal smoking status by measures of breath CO and analyze its association with fetal growth and Nicotine withdrawal syndrome in newborns.
Methods: Full-term infants were divided into smokers and control groups. Infants' birth parameters correlated with maternal smoking status, neonates' neuro-behavior assessed during the first 72 hours of life by the Finnegan score.
Results: 29 mother-infant pairs were recruited [11 (4M) smokers' group; 18 (8M) control group].

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Smokers were younger (27.2 years versus 29.4 years in the control group, NS), unmarried (P < 0.001), from low socio-economic classes (P < 0.001), and less educated (P < 0.001). Infants born to smokers were lighter in comparison to controls (P < 0.05), the difference in mean BW was more marked in boys (P<0.001). Mean infant BW was also inversely correlated with maternal breath CO: 3213 g (< 5 PPM group), 3185 g (6 - 10 PPM group), and 3176 g (11 - 20 PPM group) (r = 0.952). Assertion of reduction in the smoking habit during gestation was discordant with measured breath CO in smokers, meaning most smokers did not reduce their tobacco consumption substantially. NWS was difficult to ascertain with the Finnegan score, but infants born to smokers presented with symptoms such as irritability, tremors, increased spontaneous Moro's reflex, and poor sleep. They also presented often signs that have the highest scoring items.

Conclusion: Measures of breath CO are reliable in evaluating fetal effects of maternal smoking during gestation. Infants born to smokers present signs in favor of NWS lasting up to 72 hours. Babies require only nursing, no medication is necessary.

Keywords: Maternal smoking/pregnancy/expired; CO/fetal growth/nicotine; withdrawal syndrome.

1. INTRODUCTION

Maternal smoking during pregnancy is a public health hazard with known ill-effects on fetal development since the first report by Simpson in 1957 [1].

Smoking during pregnancy increases preterm births and miscarriage [2,3], congenital malformations [4], sudden infant death syndrome (SIDS) [5], and the susceptibility to asthma and ear infections in offspring [6,7].

Smoking throughout pregnancy also impairs the cerebral mass in infants [8] and interferes with organ development [9]. Fetal growth restriction induced by maternal smoking is associated with important morbidity and mortality; affected infants are at high risk of developing metabolic syndrome in adulthood [10–12].

In France, nearly one-third of teenagers aged 13 - 18 years are smokers [13,14]. Although several studies report a global trend towards a reduction in female smoking, from 32 % in 2002-2003 to a little less than 16 – 17% today, there seems to exist a large variation in incidence between age groups, and between countries [14,15].

A reduction in smoking prevalence in French adolescents, with only 23% of them reporting being regular smokers, was recently reported [16].

Cigarette smoke is a concentrate of several components, containing more than 4000 toxic compounds of which carbon dioxide, carbon monoxide, cyanhydric acid, volatile organic compounds, nickel, cadmium, free radicals, and nicotine are the most known. All have been shown to cross the fetoplacental barrier and can, therefore, interfere with the fetal environment and development. Nicotine, the most studied component both in experimental animal models as well as in humans, crosses the fetoplacental barrier in concentrations that increase with the duration of gestation [17].

Consequent to its chemical similarities with acetylcholine, nicotine settles on the cholinergic receptors, and generates its receptors, becoming an acetylcholine agonist. It stimulates the dopaminergic neurons which have psychoactive properties. Nicotine is involved in two ways in the urge to smoke:

- firstly, through positive reinforcement via the sensation of pleasure, stress management, appetite suppression, and effects on concentration,
- secondly, its negative reinforcement is defined by craving characterized by anxiety, irritability, nervous tension, difficulty concentrating.

In smokers, plasma nicotine level reaches a plateau with concomitant receptor desensitization during the day. The lack of additional nicotine intake for several hours entails a rapid re-sensitization, with the unsaturated receptors provoking a craving sensation comparable to a withdrawal syndrome.

Most studies on the ill effects of maternal smoking during gestation have mainly focused on its consequences on fetal growth. Only a few have addressed the issue of the existence or not, of an NWS in infants exposed in-utero [18–23].

Moreover, the existing evidence is not clear-cut as studies have reported conflicting results, with

some advocating for its existence [18–22] and others denying it [24]. Nearly all these studies have assessed maternal smoking status both by self-reporting and cotinine bioassay (plasma or saliva). The measure of exhaled carbon monoxide (CO) is being, nowadays, increasingly used to assess smoking status during pregnancy, with results that are comparable to cotinine assay [25]. Besides, a correlation has been shown between levels of maternal expired CO and that of their newborns [26].

Our objectives were, therefore, to address the questions as to whether:

- Maternal smoking status assessed by self-reporting and measure of breath CO was reliable in evaluating effects on fetal growth, and whether nicotine withdrawal syndrome (NWS) exists in infants who were exposed in-utero, by closely observing and evaluating them during their first seventy-two hours of life.

2. POPULATION AND METHODS

Study type: a prospective case-control study carried out in a level 3 maternity unit of Poitiers University Teaching Hospital, France, over a period of four months, within the framework of a Midwifery Master Degree dissertation.

Before inclusion, we sought and obtained the local Ethics committee approval, after which we approached and obtained signed informed consent from each participating pregnant mother. We then recruited, exclusively, term-born infants (Gestational age ≥ 37 weeks, defined according to the date of last menses and/or the first obstetric ultrasound). Infants were classified into two categories: Group I (born to mothers who smoked during pregnancy), and Group II those born to non-smokers, the control group).

We excluded infants born to mothers with co-addiction (alcohol and/or drug abuse), those born to mothers with chronic illnesses, or on psychotic drug therapy, those with intrauterine growth retardation (IUGR) secondary to pregnancy-induced hypertension or idiopathic, and those with fetal malformations. Infants diagnosed with hypocalcemia, hypoglycemia, and seizures were also excluded.

Upon admission to the Labor ward, a questionnaire was filled with the patient by the on-call midwife or the midwife trainee. The questionnaire contained items on smoking status (number of cigarettes smoked, since when smoker, time of the last cigarette consumed, changes in smoking habits during pregnancy (increase or decrease expressed in the number of cigarettes smoked per day during the first, second, and third trimester of gestation), whether the person had received any information on the ill-effects of smoking during pregnancy (on the fetal outcome), whether any assistance to quit smoking was offered and by who, life habits, marital status, past obstetric history, level of education (categorized as primary school, secondary or higher), partner's smoking status, personal birth weight and actual BMI (calculated as weight divided by the square of height in meter) and professional status categorized as employed, unemployed, intermediate and higher intellectual professions [27].

The smoking status was, then measured, for all participants, by testing the amount of CO in the expired air using a CO analyzer that utilizes single-use disposable mouth tips (Eolys®, manufactured by Eolys, France). According to the results obtained with the analyzer, four levels of smoking were defined as following [28]:

(a) Expired CO < 6 PPM (no intoxication)
(b) 6 to 10 PPM (mild smoking)
(c) 11 to 20 PPM (important active smoking or prolonged passive smoking)
(d) > 20 PPM (intense active smoking).

No measure of urinary cotinine was performed owing to financial constraints.

We also recorded, for each child, the Apgar score, cord venous blood pH results, and the usual anthropometric measures of birth weight (BW), length (BL), and cranial circumference (HC).

Owing to Nicotine plasma half-life in human newborns [29], the behavioral assessment was performed for each infant using the Finnegan score [30], assessed on days 0, 1, 2, and 3 of life (three recordings were performed daily, one per nursing team working on 8 hourly shifts blinded to the study hypothesis). Infants scoring ≥ 8 on two consecutive assessments were considered as having symptoms compatible with the nicotine withdrawal syndrome.

2.1 Statistics

The data were collected on the Excel program (Microsoft ®), and statistical analyses were

performed with Intercooled Stata 8.2 Software. We used the X^2 test to compare frequencies of occurrences, and Pearson's correlation coefficient to analyze correlation. Due to the smallness of our study population, we used the Wilcoxon test for the comparison of means between groups, the level of significance being P = .05.

3. RESULTS

32 mothers agreed to participate in the study. We excluded 3 patients (1 for associated addictive buprenorphine consumption, and 2 others for no availability of expired CO measures), leaving a study population of 29 mother-infant pairs. 18 mothers reported being non-smokers versus 11 who were active smokers. Smokers were younger with a mean age of 27.2 years [range 18 to 34 years]) in comparison to the non-smokers (mean age 29.4 years [range 20 to 38 years]) (difference not statistically significant). Epidemiological characteristics and socio-professional status of our study population are summarized in Table 1.

Most non-smokers were married (56%), whereas the majority of smokers were single (87%). 9/11(82%) mothers in the smoker group had smoking partners versus only 56% in the non-smokers' group. The mean maternal body mass indexes were 20.5 kg/m² in non-smokers versus 21 kg/m² in smokers.

The smoking habits debut was as early as adolescence in ten mothers (first cigarette at age 16 years on average). One mother had started smoking at the age of 12 years. During pregnancy smoking mothers generally (9 of 11) reduced cigarette smoking from 16 cigarettes/day on average before their pregnancy to 10 cigarettes/day (first trimester), 9 in the second, and only 8/day in the third. However, despite the reported assertion of a reduction in the number of cigarettes smoked on the day of the interview, our analysis of the recorded number of cigarettes smoked daily revealed unchanged tobacco consumption behavior between the first and third trimesters of pregnancy.

3 (27%) of smokers scored less than 5 PPM on the expired CO measurements, 2 (18%) scored between 6 – 10 PPM, 3 (27%) had scores between 11 – 15 PPM, 2 (18%) between 16 – 20 PPM, and only 1 (9%) scored above 20 PMM. More than 82% of smoking mothers in this study had expired CO values that were less than 15 PPM at the time of inclusion.

Nearly all the smokers (82%) had been informed of smoking risk during pregnancy compared to 44% in the non-smokers' group. The sources of information were diverse and included family physicians (8 cases), the family circle (3 cases), midwives (3 cases), the press and prevention campaigns (3 cases), attending obstetrician (2 cases), and friends in a single case. It is of note that some mothers had several sources of information.

Table 1. Maternal epidemiological characteristics

Maternal data	Smokers (n=11)	Controls Controls	P value*
Age (yrs)	27.2	29.4	NS
Maternal BMI (Kg/m²)	20.5	21.0	NS
Marital status			< 0.001
- Married	1 (9%)	10 (56%)	
- Unmarried	9 (87%)	8 (44%)	
- Legal union	1 (9%)	-	
Parity : Primiparae	7 (64%)	7 (39%)	
Multiparae	4 (36%)	11 (61%)	
Smoking status			
- Prior to gestation	11 (100%)	7 (39%)	
- Partner smoker	9 (82%)	10 (56%)	
Profession :			< 0.001
- Unemployed	4 (36%)	2 (11%)	
- Employee	6 (55%)	6 (33%)	
- intermediate profession	-	3 (17%)	
- Higher professions	1 (9%)	7 (39%)	

** X^2 test*

3.1 Modalities of Delivery and Newborn Infants Characteristics

Newborns were delivered at a mean gestational age of 40 weeks. Eight parturients in the smoker group delivered through the normal vaginal route, extraction was aided in 3 cases (2 vacua and 1forceps). No caesarian section was performed. All non-smoking mothers delivered spontaneously by normal vaginal route.

There were 7 girls and 4 boys in the smoker group versus 10 girls and 8 boys in the non-smoker group. The mean birth weight (BW) inversely correlated with the rate of expired CO: 3213 g (< 5 PPM group), 3185 g (6 - 10 PPM group), and 3176 g (11 - 20 PPM group). We calculated Pearson's coefficient of correlation between maternal expired CO and infant birth weight and found a strong correlation between the two variables (r = 0.952).

Overall, infants born to smokers weighed 206 g less than those born to non-smokers ($p < 0.05$). But boys in the smoker group were 292 g lighter than their counterparts in the non-smoking group ($p < 0.001$), whereas girls were only 108 g lighter than those in the control group (difference not significant). Both BL and HC were similar between the two groups (Table 2).

3.2 Adaptation to the Extra-uterine Life

Each infant's adaptation was assessed using the Apgar score, and cord blood pH when available. Mean Apgar scores (at 1 and 5 minutes of life) were similar between the two groups, so were mean cord blood pH (Table 2). No infant required resuscitation measures at birth.

The rate of breastfeeding initiation was different between the two groups: with only 5/11 (46%) infants being breastfed in the smoker group versus 15/18 (83%) in the non-smoker group.

Table 2. Birth Parameters and Infants' adaptation to extra-uterine life

	Exposed (n=11)	Controls (n=18)	∆Wt	P value
Gender M	4	8		
F	7	10		
Mean BW (all) (g)	3232	3438	206	<0 .05
M	3367	3659	292	< 0.001
F	3154	3262	108	NS
BL (cm)	49.5	50.2		NS
HC (cm)	33.3	34.4		NS
Apgar Score 1 min	9.5	9.8		
5 min	10	10		
Cord pH	7.28	7.28		

BW: birth weight; BL: birth Length; HC: head circumference; ∆Wt: delta weight smokers versus non-smokers. NS: not significant

Table 3. Mean Finnegan scores during the entire Behavioral Evaluation period

	Exposed newborns		Controls		Wilcoxon Test (P value)
	n	Mean	n	Mean	
Day 0 Minimum	8	1.63	11	1.73	0.3
Maximum	8	2.25	11	2.64	0.7
Mean	8	1.83	11	2.18	0.7
Day 1 Minimum	7	1.49	11	2.73	0.2
Maximum	7	3.14	11	2.73	0.4
Mean	7	2.17	11	3.82	.3
Day 2 Maximum	8	2.13	9	1.56	0.5
Minimum	8	5.38	9	2.44	0.02*
Mean	8	3.67	9	2.0	0.1
Day 3 Minimum	8	1.6	11	3.5	0.2
Maximum	8	2.4	11	3.5	0.5
Mean	8	1.97	11	3.5	0.3

** P = .05*

Table 4. Newborn infants with high finnegan score symptoms smokers versus non-smokers

Symptoms	Smokers (n=8)	Controls (n=11)
Watery stools (3pts)	1	-
Projectile vomiting (3pts	1	-
Myoclonus (3pts)	1	-
Tremors at rest (severe) (3pts)	1	-
Tremors (mild) (3pts)	2	1
Frequent spontaneous Moro reflex (3pts)	1	-
Post-feeding sleep (<1 hour) (3pts)	4	4
Frequent cry (3pts)	-	1

3.3 Behavioral Evaluation

The data on behavioral evaluation assessed with the Finnegan score were available only for 11/18 (61%) infants of non-smokers and 8/11 (73%) of smoking mothers (Table 3).

Due to the smallness of our sample and irregularities in infants' evaluation, the statistical analysis was of limited yield. We, therefore, compared both groups concerning those items of the assessment that have the highest scores, in addition to comparing mean Finnegan scores between groups (Wilcoxon test). Infants born to smokers presented with the highest Finnegan scoring symptoms (Table 4).

4. DISCUSSION

This study shows that carbon monoxide levels measured, upon arrival to the labor-room, in pregnant smokers are strongly correlated with infant birth weight. It also shows that infants in the smoking group had higher Finnegan scores overall. Babies born to smokers weighed on average 200 g less than their counterparts born to non-smokers. The difference in BW was more marked in boys. Our results corroborate those reported by Gomez and al. [31]. The infants' BW was more affected than were BL and HC in our study, this being in agreement with the report by Bernstein et al. [32].

Cotinine bioassay (urine or saliva) is regarded as the most reliable method to evaluate exposure to cigarette smoke, it is also the most utilized assessment tool [18-22,24]. Despite its many advantages (accuracy, validity, and sensitivity), its assay is, however, invasive, costly, and time-consuming. Besides, results may be affected by the nicotine replacement therapy [33]. Although the measure of expired CO utilized in this study only reflects recent exposure to tobacco smoke (up to 5 – 6 hours versus 20 hours for cotinine), our results support earlier reports by others and suggest that measurements of expired CO can be used in replacement of cotinine bioassays [26,31]. The strong correlation between infants' mean BW and the maternal levels of breath CO reported here consolidates the idea that the higher the maternal smoking intoxication, the more consequent its effect on the fetal growth parameters at birth.

It is noteworthy that measures of breath CO are not appropriate in evaluating long-term tobacco exposure in comparison to cotinine bioassay; this probably explains why three of the smoking mothers, in our study, had expired CO levels below 5 PPM at inclusion. Besides, the appropriate cut-off level of expired CO varies considerably in the literature, from as low as 3 PPM to 8 PPM [34]. Our results respond to our research questions which aimed at showing whether maternal smoking during pregnancy assessed by self-reporting with breath CO measure was reliable in differentiating smokers from non-smokers and if evaluating NWS was feasible. As previously shown by others, our results confirm that most female smokers indulge in tobacco consumption early in their adolescence [16,35]. Although a decline in smoking prevalence has occurred in women of child-bearing age in several countries, an unacceptable number of mothers still smoke during their pregnancy [36]. Our findings also reveal that most smokers only rarely modify their smoking practice during pregnancy. Smokers are younger, more often unemployed, of low educational level, and belonging to a lower socio-economic background in comparison to non-smokers. They additionally confirm that the breastfeeding rate remains very low in smokers, as reported by several other researchers and by the French health insurance survey [37,38].

The correlation between the mean infants' BW and the amount of expired CO as shown in this study constitute a working track for targeted public health programs in addition to the already existing quit smoking campaigns.

We observed that newborns exposed in-utero to tobacco smoke had Finnegan scores in the upper limit of the normal ranges, they also showed an increment in their scores from day1 to day 2. Despite the lack of statistically significant difference between infants of smokers and the control group, items with higher Finnegan scores (3 and 4 points) were more frequently observed in infants whose mothers had smoked during pregnancy. These infants also presented, more often, with symptoms such as tremors, sleeping disorders, exaggerated spontaneous Moro's reflex (in reaction to the slightest noise), hyper-excitability, and benign myoclonus. Our observational findings suggest that nicotine withdrawal syndrome exists [19–22]. Moreover, the literature is overall in favor of the existence of NWS. In a study of 33 newborns, Garcia et al. recorded the Finnegan score between 0 and 8 in 11 babies, 4/11 scored between 5 and 7. These infants presented, in addition to high cotinine levels associated with heavy maternal smoking (>20 cigarettes/day), symptoms such as increased irritability and tremors [19]. In contrast, Hugues et al., comparing neonatal withdrawal to nicotine with withdrawal to other substances, concluded that NAS to nicotine does not exist [24]. Several other studies using different assessment tools concluded that NWS was present. Law et al. assessed neonatal behavior in infants born to smokers using the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) and showed that infants exposed in-utero to tobacco smoke were more hyperexcitable, hypertonic, and required more nursing [22]. Two other groups also assessed NWS in newborns using different approaches: the Finnegan score [18] and the Brazelton Neonatal Behaviour Assessment Scale (BNBAS) [38]. Both groups' conclusions were in favor of the existence of NWS.

Our data add to the existing body of evidence on the existence of NWS without confirming it formally. Larger studies using a specific scoring system for NWS are needed. The postnatal care of these newborns requires the implementation of specifically adapted nursing care measures, with the reinforcement of Kangourou and/or NIDCAP type of care, along with efforts to promote breastfeeding in mothers who continue smoking during their hospitalization in maternity units.

This study has some limitations: firstly, the small sample size does not allow clear-cut conclusions. Secondly, the absence of cotinine bioassays may be regarded as a weakness as we cannot compare our results with those that have used cotinine as a marker. Nevertheless, our results suggest that readily available measures of expired CO can be a good alternative to cotinine bioassays in assessing smoking status in pregnant women.

5. CONCLUSION

Based on the existing evidence, nicotine present in tobacco smoke crosses the placental barrier and alters fetal neurodevelopment. The measure of maternal expired CO is reliable in predicting the effects of maternal smoking on fetal growth. Smoking during pregnancy likely induces NWS in neonates early in their postnatal life. Presenting symptoms are often subtle and may go unnoticed. When a behavioral assessment is performed, affected infants present with irritability, tremors, increased spontaneous Moro's reflex and poor sleep, etc. These signs appear after H12 of life and last 48 to 72 hours; they require no specific treatment, but increased nursing care. NWS can be delayed in breastfed infants and, therefore, be confused later with infant colic. Research directed towards the development of appropriate assessment tools for NWS is awaited.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

we sought and obtained the local Ethics committee approval, after which we approached and obtained signed informed consent from each participating pregnant mother.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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