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HEALTH SCIENCES

Neonatal outcomes associated with tobacco, alcohol, and crack use during pregnancy in three Neonatal Intensive Care Units

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Abstract: Despite the prevalence of substance use during pregnancy, studies focusing exclusively on Neonatal Intensive Care Units (NICU) admissions remain limited. This study investigates the impact of maternal use of tobacco, alcohol, and/or crack, on neonatal outcomes among infants admitted to three Brazilian NICUs. Additionally, the investigation explores the impact of substance use on DNA damage in newborns. Over a one-year period, data from 254 newborns were collected through medical records, accompanied by blood samples. Findings revealed that 16.1% of newborns had mothers reporting substance use during pregnancy. Significant associations were found between maternal substance use and adverse neonatal outcomes, including low birth weight, preterm birth, and sexually transmitted infections. Maternal variables linked to substance use encompassed non-white skin color, low education, non-masonry housing, lower income, diseases in other children, and fewer prenatal consultations. Notably, neonatal DNA damage showed no significant association with substance use. Our results underscore the substantial impact of maternal substance use on NICU-admitted infants, emphasizing the necessity for targeted interventions that address both neonatal health and maternal well-being, thereby underscoring the crucial role of comprehensive care in NICU settings.

Key words: DNA damage, Gestation, Maternal prevalence, Newborn, NICU, Substance use.

INTRODUCTION

In 2021, as reported by the United Nations Inter-agency Group for Child Mortality Estimation (UN IGME), nearly two million stillbirths and 2.3 million liveborn infants succumbed within their initial 28 days of life (i.e., neonatal deaths) (UN IGME 2023a, b). Since the turn of the millennium, there has been a noteworthy 42 percent decline in the global neonatal mortality rate, reaching 18 deaths per 1,000 live births in 2021, down from 31 deaths per 1,000 in 2000 (UN IGME 2023a). Similarly, the worldwide stillbirth rate experienced a 33 percent decrease, dropping to 14 deaths per 1,000 live births in 2021, compared to 21 deaths per 1,000 in 2000 (UN IGME 2023a). Despite substantial multifaceted improvements contributing to the reduction of these indices in recent years, persistent issues continue to cast shadows over these figures (Horbar et al. 2017, Lawn et al. 2023). Maternal substance abuse, encompassing substances such as tobacco, alcohol, and illicit drugs like crack, stands out as a major contributing factor to stillbirths and neonatal deaths. Even in instances where substance abuse does not result in fatality, it can inflict adverse effects on the fetus, necessitating extensive care upon birth and admission to

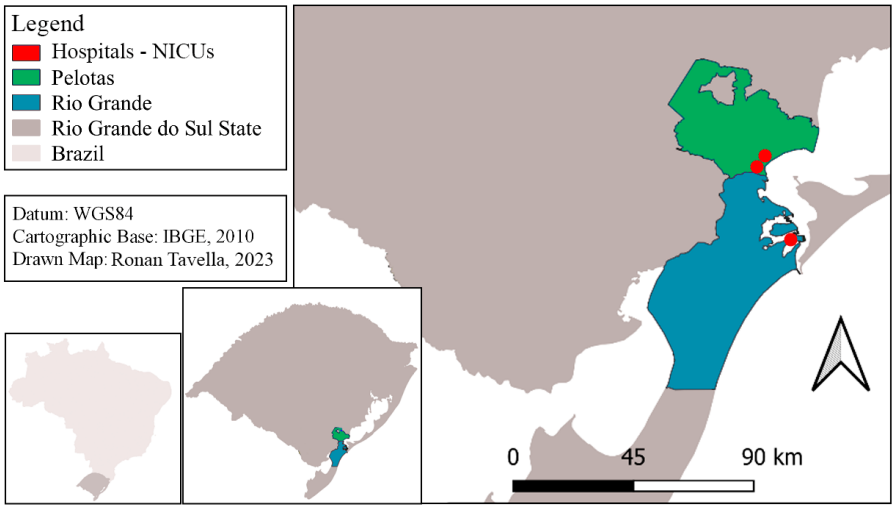

Figure 1. Map of the location of the NICUs that participated in the study.

Neonatal Intensive Care Units (NICUs) (Salihu & Wilson 2007, Mcqueen et al. 2015).

Maternal use of tobacco, alcohol, and crack has been demonstrated to induce various similar deleterious effects, including an elevated incidence of preterm birth, fetal growth restriction, and low birth weight (US DHHS 2014, Dos Santos et al. 2018, Popova et al. 2021). Tobacco use is also frequently associated with adverse effects on neurodevelopment (Popova et al. 2021, Havard et al. 2022), alcohol consumption with congenital defects (US DHHS 2014, Gauthier et al. 2016), and crack cocaine with placental displacement and preeclampsia (Aghamohammadi & Zafari 2016, Dos Santos et al. 2018). Additionally, individual studies have shed light on numerous other adverse health effects on newborns. Consequently, due to these shared characteristics, the increased rate of admission to NICUs emerges as a virtually unanimous outcome in studies conducted on this topic (Bailey & Diaz-Barbosa 2018, Sturrock et al. 2020).

Despite various studies highlighting this reality, research on populations originating from NICUs that investigate the relationship between adverse outcomes and the use of these substances during pregnancy is scarce. The primary reason for this scarcity lies in the stringent ethical considerations surrounding the examination of a maternal population already profoundly affected by the condition of their newborns, with the aim of safeguarding these vulnerable participants (Janvier & Farlow 2015, Pineda et al. 2023). Consequently, investigations conducted in these treatment units are invaluable and warrant high attention. They offer a unique opportunity to better comprehend neonatal vulnerability and provide crucial clinical insights into maternal and neonatal health integration. This, in turn, facilitates the development of appropriate intervention strategies, as well as the implementation of preventive and supportive measures.

In Brazil, accurate estimates of alcohol, tobacco, and illicit drug use during pregnancy remain elusive, with wide variations depending on the region and the target population studied. Recent studies, utilizing data from the Birth in Brazil Survey—a nationwide hospital-based study conducted from February 2011 to October 2012—have provided some insights. Approximately 14% of pregnant women reported alcohol consumption during gestation (Cabral et al. 2023), while 9.6% admitted to smoking at least once during pregnancy (Domingues et al. 2019).

However, information regarding illicit drug use remains sparse. Nonetheless, a global review conducted by Tavella et al. (2022) on this topic noted that studies in Brazil have documented prevalence rates ranging from 0.5% to as high as 35% of pregnant women using illicit substances during gestation.

In this context, the analysis of neonatal birth conditions and deaths, along with biological information from pregnancy and delivery, enables the construction of data illustrating the actual quality of maternal and child healthcare and potential impacts of maternal habits. In this sense, this study sought to investigate the maternal prevalence and neonatal outcomes associated with tobacco, alcohol, and crack use during pregnancy in three Brazilian NICUs. Additionally, we aimed to explore DNA damage in this neonatal population and its possible associations with the use of these substances.

MATERIALS AND METHODS

Data source

A prospective study was conducted using data from three NICUs situated in the southern region of Brazil, specifically within the state of Rio Grande do Sul. This investigation spanned a one-year period, from July 2017 to June 2018. The included NICUs are affiliated with two hospitals located in the municipalities of Pelotas - Hospital Universitário da Universidade Católica de Pelotas (HU/UCPEL) and Hospital Escola da Universidade Federal de Pelotas (HE/UFPEL), and one in the municipality of Rio Grande - Hospital Universitário da Universidade Federal do Rio Grande (HU/FURG). Data from the Brazilian Live Birth Monitoring Panel (Brasil, 2024) indicate approximately 4,300 and 2,700 live births in the cities of Pelotas and Rio Grande, respectively, during the study year. Additionally, a cohort study conducted in Pelotas demonstrated that NICU admissions in the region accounted for 6.7% of all births in 2015 (Wehrmeister et al. 2019).

Data collection was performed through an instrument developed by the researchers, containing maternal and neonatal data, as well as blood collection from the newborns, after obtaining informed consent from the newborn's responsible family member. The study was conducted following the approval of the Research Ethics Committee in the Health Area (CEPAS-FURG), under approval number 50/2017. The epidemiological profile of the newborns admitted to these NICUs is detailed in a previously published study (da Silveira et al. 2020).

Maternal and neonatal data were collected from medical records available in the NICU, and DNA damage was measured in blood samples collected by the clinical analysis laboratory for routine analyses. The inclusion criteria for the research sample were newborns admitted alive to the NICU in the three evaluated hospitals during the study period, whose parents agreed to participate and signed the informed consent form. Exclusion criteria included cases where it was impossible to confirm the use/non-use of tobacco, alcohol, and/or crack during gestation.

The primary outcome utilized was self-reported tobacco, alcohol, and/or crack use during any period of the last pregnancy. Multiple other analyzed variables included maternal socio-economic and demographic factors (age, skin color, marital status, education, type of housing, and family income), health conditions and care (maternal diseases or in other children, prenatal care), and outcomes related to the newborn (birth weight, gestational age, APGAR score, head circumference, congenital malformations, DNA damage, and other health problems). All data were typed doubly in Epi Info software (Version 6, Center for Disease

Control and Prevetion, EUA) and the mistakes were corrected. Subsequently, consistency and coherence assessments were made. In the end, all resulting data were organized and recorded in databases.

Blood sampling and comet assay

Newborn blood samples (approximately 1 ml) were obtained during the routine first-minutes post-delivery collection by the clinical analysis laboratory personnel. The collection involved blood drawn from the newborn's veins into vacutainers containing heparin and ethylenediamine tetraacetic acid (EDTA). Importantly, no additional invasive procedures were applied to the newborns for the purposes of this study. All collected samples were meticulously coded and shielded from light during transportation to the laboratory, where they were promptly processed upon arrival.

The comet assay was performed as per Singh et al. (1988) and followed the procedure described by Tavella et al. (2022). The entire procedure took place under either no or low indirect incandescent light and in a cold environment (2–8 °C) to minimize cell damage. To ensure impartial analysis, all samples and slides were coded for blind assessment. Post assay execution, slides examinations were carried out at 40x magnification using a fluorescence microscope. For each participant, 100 randomly selected nucleoids underwent analysis. Image analysis utilized ImageJ software (Version 1.50i, National Institute of Health, Bethesda, USA), and the parameters for quantifying DNA damage included mean values for tail length, percentage of total DNA in the tail (% of tail DNA), and tail moment.

Data analysis

The prevalence of tobacco, alcohol, and/or crack use was estimated from the overall data. For the analysis of associated factors, the dyad was categorized concerning the use of these substances during pregnancy into Group 1 (mothers reporting the use of any of these substances during any period of pregnancy) and Group 2 (mothers reporting no use of any substances during any period of pregnancy). The association between variables was assessed using Fisher's exact test or the Chi-square test (for categorical data) and the t-test or Mann-Whitney test (for continuous quantitative data). The data was analyzed using STATA software, version 11.2, and the significance level for analyses was considered $p < 0.05$.

RESULTS

The total number of newborns included in the study period was 254, with 147 from HE/UFPel, 65 from HU/UCPel, and 42 from HU/FURG, and 4 were excluded from the study. Among the newborns, 41 mothers (16.1%) reported using some of the three substances during their last pregnancy, 181 mothers (71.3%) reported no substance use during the last pregnancy, and 32 mothers (12.6%) lacked available information on drug use. Of the mothers who consumed substances during pregnancy, 22 (53.6%) reported tobacco use, 14 (34.1%) alcohol use, and 3 (7.3%) crack cocaine use. Three mothers reported the use of multiple substances, with two stating combined alcohol and tobacco use, and one reporting tobacco and crack cocaine use. No other substance use was reported by the investigated population.

Among the maternal variables, socio-economic and demographic factors associated with substance use during pregnancy included skin color, education, housing type, and income (Table I). Non-white skin color, low education levels, non-masonry housing, and lower income were all linked to substance use during

Table I. Maternal socio-economic and demographic variables.

Variable	Total (n)	Substance-using mothers % (n)	Non-substance-using mothers % (n)	p value
Age				0.670
<20	41	16 (6)	20 (35)	
21 a 30	101	51 (20)	45 (81)	
31 40	60	28 (11)	27 (49)	
>40	17	5 (2)	8 (15)	
Skin color				< 0.001
White	145	58 (18)	87 (120)	
Non-white	38	42 (13)	13 (25)	
Marital status				0.160
Lives with partner	46	16 (5)	25 (41)	
Does not live with partner	148	84 (27)	75 (121)	
Education				0.025
Illiterate/Incomplete primary	57	41 (14)	28 (43)	
Completed primary	43	15 (5)	25 (38)	
Completed secondary	61	38 (13)	32 (48)	
Completed tertiary	24	6 (2)	15 (22)	
Housing				< 0.001
Masonry	106	56 (10)	86 (96)	
Other	23	44 (8)	14 (15)	
Family income*				0.004
< 1 MW	11	10 (3)	7 (8)	
1 to 3 MW	104	74 (22)	68 (82)	
3 to 5 MW	22	3 (1)	18 (21)	
> 5 MW	13	13 (4)	7 (9)	

***MW means minimum wage, which in Brazil was approximately R$954.00.**

pregnancy. Additionally, in terms of health conditions and care, the presence of diseases in other children and fewer than 6 prenatal consultations showed significant associations with substance use during pregnancy (Table II).

Interestingly, neonatal outcomes associated with the use of tobacco, alcohol, and/or crack during pregnancy included low birth weight (< 2500 g), preterm birth (gestational age less than 37 weeks), and the presence of sexually transmitted infections (STIs) (Table III). Conversely, none of

Table II. Maternal health conditions and care.

Variable	Total (n)	Substance-using mothers % (n)	Non-substance-using mothers % (n)	p value
Maternal diseases				0.168
Yes	111	74 (23)	64 (88)	
No	58	26 (8)	36 (50)	
Diseases in other children				0.018
Yes	6	11 (3)	2 (3)	
No	148	89 (24)	98 (124)	
Attended prenatal care				0.081
Yes	211	90 (35)	97 (176)	
No	9	10 (4)	3 (5)	
Number of consultations				0.033
< 6	94	57 (21)	41 (73)	
6 or more	120	43 (16)	59 (104)	

the three DNA damage parameters assessed, tail length, % of tail DNA, and tail moment, demonstrated any association with the use of these substances during gestation.

DISCUSSION

Due to the inherent challenges associated with conducting investigations involving neonates in NICUs, studies like ours are indispensable and warrant significant attention. Focusing exclusively on newborns admitted to NICUs, our primary finding highlighted the significant association between maternal use of tobacco, alcohol, and/or crack, and the adverse neonatal outcomes low birth weight, preterm birth, and the presence of sexually transmitted infections. Additionally, our findings identified several maternal variables associated with substance use during pregnancy, including non-white skin color, low education levels, non-masonry housing, lower income, the presence of diseases in other children, and fewer than six prenatal consultations. It is noteworthy that DNA damage in neonates did not show significant associations with the use of tobacco, alcohol, and crack.

Studies consistently demonstrate how the use of substances such as tobacco, alcohol, and illicit drugs like crack affects the intrauterine development of the fetus, resulting in numerous negative neonatal outcomes (US DHHS 2014, Aghamohammadi & Zafari 2016, Sbrana et al. 2016, Gauthier et al. 2016, Dos Santos et al. 2018, Reynolds et al. 2020, Popova et al. 2021, Havard et al. 2022). These outcomes include preterm birth, fetal growth restriction, and low birth weight (US DHHS 2014, Dos Santos et al. 2018, Popova et al. 2021). However, these findings are frequently observed in studies that assess all newborns in specific hospitals and regions. Our study, exclusively focusing on neonates admitted to NICUs, corroborated these findings and also revealed significance in the presence of sexually transmitted infections. This underscores that even within a population of infants requiring specialized care in NICUs, those born to substance-using mothers consistently experience unfavorable outcomes. It emphasizes

Table III. Neonatal outcomes observed in the three NICUs and its associations.

Outcome	Total (n)	Substance-using mothers % (n)	Non-substance-using mothers % (n)	p value
Birth weight				0.044
2500 g or more	57	37 (15)	23 (42)	
< 2500 g	163	63 (25)	77 (138)	
Apgar score at 1'				1.000
0 a 6	116	53 (21)	53 (95)	
7 a 10	103	47 (19)	47 (84)	
Apgar score at 5'				1.000
0 a 6	37	17 (7)	17 (30)	
7 a 10	181	83 (33)	83 (148)	
Head circumference				0.819
Mean / std. Deviation		30.73 / 4.114	30.55 / 4.283	
Gestational age				0.019
37 weeks or more	53	37 (15)	21 (38)	
< 37 weeks	166	63 (26)	79 (140)	
Congenital malformations				0.422
Yes	36	12 (5)	17 (31)	
No	184	88 (35)	83 (149)	
Prematurity without complications				0.322
Yes	29	12 (3)	18 (26)	
No	140	88 (23)	82 (117)	
Genetic syndrome				1.000
Yes	6	2 (1)	3 (5)	
No	214	98 (39)	97 (175)	
Infectious diseases				0.055
Yes	89	29 (12)	43 (77)	
No	132	71 (29)	57 (103)	
STIs				0.009
Yes	6	10 (4)	1 (2)	
No	215	90 (37)	99 (178)	
Respiratory problems				0.322
Yes	145	66 (27)	66 (118)	
No	76	34 (14)	34 (62)	
Complications				0.175
Prematurity or Low Birth Weight	176	73	82	
Other Complications	43	27	18	
Tail Length				0.320
Mean / std. Deviation		.,380 / 0.3857	2.505 / 0.4667	
% of Tail DNA				0.494
Mean / std. Deviation		1.942 / 0.3452	2.016 / 0.3956	
Tail moment				0.470
Mean / std. Deviation		7.595 / 1.695	8.144 / 2.187	

the direct and decisive impact of substance use during pregnancy on neonatal health, providing crucial clinical insights into the integration of maternal and neonatal health.

In the context of maternal variables associated with the use of these substances during pregnancy, a recurring pattern is observed not only in Brazil but also in other countries worldwide (Moraes & Reichenheim 2007, Porto et al. 2018, Shmulewitz & Hasin 2019, Gosdin et al. 2022). There is a strong interplay among race, low educational attainment, and consequently, low family income, predisposing individuals to the use of tobacco, alcohol, or illicit drugs throughout their lives, including during pregnancy. This behavior is often linked to inadequate social support and a lack of education for these mothers, who find themselves in socially vulnerable situations, particularly in the Brazilian reality, as demonstrated by Moraes & Reichenheim (2007) and Porto et al. (2018) in their studies conducted in Rio de Janeiro and Salvador, respectively.

Addressing the situation at hand, the use of these substances during pregnancy becomes a reflection of broader societal challenges. As our findings suggest, mothers grappling with these substances often find themselves navigating a complex web of socio-economic factors, where issues of race, education, and income intertwine, exacerbating their vulnerability. In the midst of these challenges, it is crucial to acknowledge that the impact of substance use during pregnancy extends beyond individual choices, reaching into the structural inequalities embedded in society. This deeper understanding underscores the need for targeted interventions that go beyond addressing substance use alone. Recognizing these intricate connections is essential for developing holistic interventions that address both substance use and the underlying social determinants, aiming to break the cycle of vulnerability and improve the overall well-being of mothers and their infants.

Global estimates suggest that about 5 percent of pregnant women use one or more addictive substances, with this percentage highly variable across regions and cultures (Wendell 2013). In our study, we observed that 16.1% of mothers utilized some of these substances. However, it is crucial to acknowledge the potential existence of underreporting cases since the data acquisition method relied on medical records, essentially being self-reported. Tavella et al. (2020), in their global review on the prevalence of illicit drug use during pregnancy, demonstrated that in studies based on interviews or questionnaires, the prevalence of use was 1.65%, whereas in studies based on toxicological analysis, it rose to 12.28%. These findings present concerning insights into the recurrent underreporting of cases involving pregnant women using illicit substances. Therefore, it is plausible that participants in our study may not have truthfully reported their substance use due to apprehension, fear, or shame, representing a limitation of our study.

In addition to the aforementioned, the admission rate to NICUs in the study region has been on the rise over the years. A cohort study conducted in the city of Pelotas, one of the cities included in our study, illustrated that the number of NICU admissions in the region increased from 2.7% of all newborns in 1993 to 6.7% in 2015 (Wehrmeister et al. 2019). This growth trend is also observable in other regions across Brazil (Moura et al. 2020), suggesting a broader pattern where maternal habits may increasingly contribute to adverse outcomes in newborns, necessitating specialized care in the early stages of life. Consequently, investigations in this population become paramount, not only for a better understanding of neonatal vulnerability but also to implement and develop intervention and prevention strategies. These efforts aim to

increasingly safeguard both neonatal health and maternal well-being, ensuring comprehensive care for mothers and their infants in the face of evolving healthcare challenges.

CONCLUSIONS

In conclusion, our investigation observed significant correlation between maternal substance use during pregnancy and adverse neonatal outcomes among NICU-admitted infants, including low birth weight, preterm birth, and sexually transmitted infections. Furthermore, we identified maternal factors associated with substance use, such as non-white skin color, low education, and socioeconomic disparities. Interestingly, neonatal DNA damage did not show a significant association with substance use. These findings underscore the urgent need for targeted interventions addressing substance use and its determinants to enhance neonatal health and maternal well-being.

In this sense, future efforts and perspectives should focus on implementing evidence-based screening and intervention programs within NICU settings to identify at-risk mothers early and provide tailored support and resources. Additionally, efforts to address the socio-economic factors contributing to substance use during pregnancy are essential for mitigating its impact and promoting healthier outcomes for mothers and their infants. Ultimately, continued collaboration between healthcare providers, policymakers, and community will be crucial in implementing comprehensive care approaches that prioritize the holistic health of both mothers and their newborns.

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