



Submitted on: 01/04/2023

Approved on: 05/21/2024

ORIGINAL ARTICLE

Amplitude Integrated Electroencephalography assessment in newborns greater than 35 weeks of gestational age exposed to crack and/or cocaine prenatally

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Keywords:

Infant,
newborn,
diseases,
Drug users,
Intensive Care Units,
neonatal.

Abstract

Objective: To evaluate the findings of video aEEG/EEG brain monitoring in newborns of mothers who used cocaine and/or crack during pregnancy and to describe the epidemiological profile of these mothers and infants. **Methods:** Descriptive prospective study carried out from August 2019 to February 2020. We included newborns with a gestational age = 35 weeks and a history of maternal use of crack or cocaine during pregnancy. Newborns underwent video aEEG/EEG monitoring for 24 hours in the first 48 hours of life. The assessment of neonatal abstinence syndrome was performed using the Finnegan Score. Demographic and clinical data were analyzed. The Intergrowth-21 curve was used to classify the anthropometric measurements described. Capurro and New-Ballard methods were standardized for determining gestational age in newborns. **Results:** 12 newborns met the criteria; all scored from 0 to 7 according to the Finnegan score in the first 6 hours of life. In the 30th hour of life, 10 (91%) scored between 0 and 7 and 1 neonate between 8 and 11, considered altered with the need for treatment. At 72 hours of life, the 12 newborns evaluated had scores between 0 and 7. The background electroencephalographic activity pattern in the first 48 hours of life was continuous, with the presence of a sleep-wake cycle in all cases. **Conclusions:** Newborns of drug-using mothers may have an early maturation pattern on electroencephalographic assessment. More studies are needed to assess this relationship better.

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INTRODUCTION

According to the World Health Organization (WHO), the use of drugs licit and illicit, is currently among the 20 greatest risk factors for health problems, with devastating physical, social and psychological effects¹. Brazil is the second largest market for cocaine and/or crack consumption worldwide in an absolute number of users².

The cocaine and the crack cross the blood-brain barrier reaching brain concentrations up to four times higher than plasma concentrations; it affects the central nervous system (CNS), which can significantly affect cortical neuronal development and cause morphological abnormalities in various structures³. Impairments in the development of cognitive and executive function are particularly related to cocaine, such as changes in posture, reflexes and movement, and a decrease in the interactive capacity, response to environmental stimuli and changes in emotional reactivity to socialize⁴.

The activities of the enzymes that metabolize cocaine are reduced in pregnant women and newborns⁵. Also, cocaine is rapidly transported across the placenta; the amniotic fluid functions as a reservoir, continuously exposing the fetus to the drug even if the pregnant woman discontinues use⁶. The indirect effects of cocaine in the pregnant woman are related to vasoconstriction, tachycardia, uterine irritability and maternal malnutrition, which increases the occurrence of preterm labor, placental abruption, intrauterine growth restriction, and decreased head circumference (HC) in the newborn⁷. Other alterations such as intestinal atresia and genital/urinary anomalies such as cryptorchidism, hydronephrosis and Prune Belly syndrome are described in fetal exposure to cocaine⁸.

The action of cocaine metabolites, which are calcium chelators, increases cellular excitability in the brain, which is one of the factors contributing to seizures and changes in cerebral activity evidenced on electroencephalogram (EEG) as greater irritability of the central nervous system, with sharp traces with spikes^{9,10}.

Despite the knowledge about the actions of these drugs in newborns, little is known about the effect of these substances on the brain electrical activity of these patients.

Amplitude integrated electroencephalography (aEEG) is a validated clinical tool that provides non-invasive, simplified, bedside monitoring on an ongoing basis and is increasingly used in the NICU for assessment of brain function by assessing cerebral background electrical activity, sleep-wake cycle, and detection of epileptic seizures¹¹. The interest in this methodology has been increasing due to the tendency to seek interventions for newborns at high risk for brain injury, reducing the neurological sequelae resulting from the neonatal period¹².

A new tool can associated aEEG to the raw EEG and video imaging (video aEEG/EEG) and it is an alternative method for bedside monitoring and improve the accuracy in seizure detection with a greater sensitivity¹³. Video aEEG/EEG is useful

to guide diagnosis and treatment and shows good predictive value of neurological outcomes¹³. However, it is important to mention that the accuracy rates are highly dependent on user's experience, and telehealth may play a role in providing the necessary expertise in video aEEG/EEG monitoring.

Thus, this study aims to evaluate the findings of brain monitoring with video aEEG/EEG in newborns born to mothers who used cocaine and/or crack during pregnancy and to describe the epidemiological profile of these mothers and their infants during the period of hospital stay.

METHODOLOGY

This is a prospective descriptive study carried out from August 2019 to February 2020 at the Department of Obstetrics and Gynecology and Neonatology Service of Irmandade da Santa Casa de Misericórdia de São Paulo. This study was approved by the hospital's Research Ethics Committee under the number 3.853.199.

This study was carried out with a convenience sample and the newborns were recruited only during the pre-determined study period.

The inclusion criteria were newborns with gestational age (GA) equal to or greater than 35 weeks, with a history of maternal use of crack or cocaine during pregnancy, reported by the mother herself in a questionnaire applied after delivery (appendix 1). The cutoff on GA was in accordance with the institutional protocol to monitor late preterm e term infants with history of crack or cocaine use during pregnancy.

In these cases, as a routine in mothers with a rapport of drug use, for confirmation, it was searched cocaine metabolites in the urine of the newborns. For that, we used The Cocaine Test from Inlab Confiança, which is a rapid, strip chromatographic immunoassay test for use in the qualitative detection of cocaine metabolite in human urine, with a cut-off of 300 ng/ml and is based on competitive binding by antibodies between the conjugated drug immobilized on the membrane and the drug or its metabolite. The urine sample collected can be used at any time of the day.

The newborns underwent video aEEG/EEG monitoring for 24 hours within the first 48 hours of life. The assessment for neonatal abstinence syndrome was performed using the Finnegan Score at the 6th, 30th and 72nd hours of life in all eligible infants.

The demographic data analyzed in the children of mothers who used crack and/or cocaine were sex, birth weight (BW), length and head circumference (HC) at birth, and Apgar score. Infants were classified into fetal growth patterns as small for GA (SGA), symmetrical or asymmetrical, and adequate for GA (AGA). The Intergrowth-21st curve was used to classify the anthropometric measurements described; AGA if the weight for gestational age percentile between 10 and 90, SGA if below the 10th percentile, symmetrical if PC <p10 and asymmetric if PC ≥p10. According to the Intergrowth table, microcephaly

was defined as head circumference less than two standard deviations, considering GA at birth and sex¹⁴. The Capurro or New-Ballard methods were standardized for determining GA in term and preterm newborns, respectively.

The presence of infection during hospitalization, including treatment of congenital syphilis, and the presence of congenital malformations were also analyzed.

The evaluation of prenatal care was performed by analyzing the questionnaire and the pregnant woman's card, and prenatal care was considered adequate when six consultations or more were carried out and started in the first trimester of pregnancy.

All newborns were monitored with three-channel video aEEG/EEG (C3-P3, C4-P4 and P3-P4)¹⁵. The recorded video aEEG/EEG traces were analyzed in real-time by three experienced readers at a remote monitoring center. Background activity patterns and the sleep-wake cycle were classified according to the Hellström-Westas classification¹⁶.

Seizure activity was defined as an abrupt increase in the minimum and maximum amplitudes associated with an evolutionary, stereotyped and rhythmic trace pattern, with repeated forms such as peaks or sharp traces observed in the raw EEG, with a minimum duration of 10 seconds¹⁷. Single seizures (SS) were defined as one electrographic seizure per season; repetitive seizures (RS) were defined as more than one electrographic seizure per season, but less than one electrographic seizure in a 10-minute period; status epilepticus (SE) was defined as (a) continuous seizure activity for at least 30 minutes or (b) recurrent seizures for more than 50% of the recording time, ranging from one to three hours¹³.

RESULTS

During the period evaluated, 744 newborns were born at the Irmandade da Santa Casa de Misericórdia de São Paulo. Regarding the live births in this period, 14 (1.9%) met the study entry criteria, but due to the unavailability of the video aEEG/EEG device, only 12 newborns were monitored.

Table 1 shows the sociodemographic and obstetric data of women who used crack and/or cocaine during pregnancy.

Table 2 shows the frequency of illicit drug use of women using crack and/or cocaine during pregnancy.

Table 3 shows the data related to the epidemiological profile of the newborns.

Regarding the Finnegan score, in the first 6 hours of life, all newborns had a score from 0 to 7. At the 30th hour of life, 10 (91%) newborns scored between 0 and 7 and 1 newborn (9%) scored between 8 and 11, considered altered in need of treatment. At 72 hours of life, the 11 newborns evaluated scored between 0 and 7.

The electroencephalographic background activity pattern evidenced by video aEEG/EEG through monitoring for 24 hours within the first 48 hours of life was continuous

Table 1. Sociodemographic and obstetric characteristics of women using crack and/or cocaine during pregnancy.

Variables	N	%
<i>Age</i>		
20-34	11	91.7
>=35	1	8.3
<i>Ethnic Group</i>		
White	4	33.3
Black	3	25.0
Mixed	5	41.7
<i>Marital Status</i>		
Married or stable union	3	25.0
Single	9	75.0
<i>Home</i>		
Fixed housing	9	75.0
Homeless	3	25.0
<i>Professional Activity</i>		
Unemployed	9	75.0
Informal work	3	25.0
<i>Education</i>		
Illiterate	3	25.0
<8 years	5	41.7
8-11 years	3	25.0
≥11 years	1	8.3
<i>Number of Pregnancies</i>		
2	2	16.7
≥3	10	83.3
<i>Prenatal follow-up</i>		
Adequate	1	8.3
Inappropriate	2	16.7
Absent	9	75.0
<i>Delivery</i>		
Natural	7	58.3
Cesarean	5	41.7
<i>Premature Rupture of Membranes</i>		
>18h	3	25.0
<18h	9	75.0
<i>VDRL Reagent at Hospitalization</i>		
Yes	8	66.7
No	4	33.3

Table 2. Illicit drugs frequency use of women using crack and/or cocaine during pregnancy.

Variables	N	%
<i>Smoking</i>		
1-10 units/day	2	16.7
10-20 units/day	7	58.3
> 20 units/day	1	8.3
No information	2	16.7
<i>Alcohol Consumption</i>		
Daily	5	41.7
1-3 times/week	2	16.6
No	5	41.7
<i>Use of Another Illicit Drug</i>		
Yes	5	41.7
No	7	58.3
<i>Frequency of Crack/Cocaine Use</i>		
Daily	9	75
3-6 times/week	3	25
<i>Crack/Cocaine use time before childbirth</i>		
Up to 24 hours	9	75
1-3 days	1	8.3
>3 days	2	16.7
<i>Believes that the use can be harmful to the newborn</i>		
Yes	6	50
No	4	16.7
Unaware	2	33.3

with a SWC in the 12 cases evaluated (100% of the newborns). Seizures are not identified in any newborn.

DISCUSSION

This study presents the results of monitoring babies born to mothers who use crack and/or cocaine in a hospital in the city of São Paulo in Brazil. A continuous pattern in the background activity with SWC was verified in all the cases, and 33.3% of the newborns had incomplete GA between 35 and 37 weeks, therefore considered late preterm. Such manifestation can indicate the integrity and coordination capacity in the brain, and its increasing occurrence in preterm infants indicates brain maturity. According to literature data, cyclic variations of aEEG suggestive of immature SWC can be observed in newborns between 26 and 27 weeks of gestation. SWC also develops with increasing maturation, and from 31 to 32 weeks of gestation, periods of peaceful sleep are discernible on aEEG as periods that increase the width between the amplitude bands¹⁸.

Table 3. Characteristics of newborns born to mothers who use crack and/or cocaine.

Variables	N	%
<i>Sex</i>		
Female	5	41.7
Male	7	58.3
<i>Gestational Age Birth</i>		
35-36 6/7 weeks	4	33.3
≥37 weeks	8	66.7
<i>Apgar Score in the 5 Minute</i>		
≥7	12	100
<i>Birth weight</i>		
>2500 g	7	58.3
<2500 g	5	41.7
<i>Growth Pattern According to GA</i>		
Symmetrical SGA	2	16.7
Asymmetric SGA	5	41.7
AGA	5	41.7
<i>Head Circumference at Birth</i>		
>p10	8	66.7
<p10	4	33.3
<i>Length at Birth</i>		
<p10	7	58.3
Between p10 and p50	5	41.7
<i>Treatment of Presumed Congenital Syphilis</i>		
Yes	8	66.7
No	4	33.3
<i>Infection Treatment</i>		
Sepsis	1	8.3
No sepsis	11	91.7
<i>aEEG Standard</i>		
Continuous with CSV	12	100
<i>Reagent Strip Test in Urine</i>		
Positive	11	91.7
Unrealized	1	8.3
<i>Associated Congenital Malformations</i>		
Yes	1	8.3
No	11	91.7

Few studies report EEG findings in the evaluated population, and there are no data in the literature on studies with aEEG. Doberczak et al. (1988)¹⁹ performed electroencephalographic evaluation in infants exposed to cocaine alone in utero, and they found abnormalities in 17 (45%) of 38 during the first week of life, but EEG abnormalities persisted after three months in only one case. In another study conducted by Doberczak et al. (1988)²⁰, focusing on EEG patterns, 90% of children with prenatal cocaine exposure had deficits in neurophysiological behavior, and more than 50% had abnormal EEGs. At week 2, only 20% of infants had abnormal EEGs, and between 3 and 12 months of age, only one child in 10 had abnormal EEG patterns. These results suggest that abnormal brain function appears soon after prenatal exposure to cocaine.

On the other hand, a study points to the possibility that infants exposed to the metabolite of cocaine and/or crack in utero obtained early acquisition of the mature pattern of peaceful sleep, translated by the presence of SWC more frequently when compared to those who did not suffer exposure to the drugs. Early maturation of silent sleep could indicate accelerated biological development. One of the possible mechanisms would be through the alteration of the noradrenaline metabolism in the locus coeruleus, a place of fundamental importance for sleep modulation and in the beginning and maintenance of REM sleep⁸.

About the epidemiological profile, mothers had a low level of education, and school dropout may be related to low performance due to learning difficulties as an effect of cognitive impairment caused by the chronic use of psychoactive substances²¹. In addition, none of the mothers described formal work. In a study carried out by Ribeiro et al. (2010)¹⁸, it was observed that cocaine and/or crack users are often unemployed after a few months of starting to use these drugs, this happens due to loss of interest in work or difficulty in obeying the rules.

The high percentage of pregnant women (66.7%) with a presumed diagnosis of syphilis stands out. In the evaluated population, poor self-care due to the drug user condition and no access to general health information can culminate in prenatal negligence. Then, the absence of prenatal care or irregular follow-up, as seen in 91.7% of the population studied, and was also demonstrated in studies carried out by Klein et al. (1993)²². The increased frequency of syphilis related to vertical transmission in these pregnant women was also described in a study by Bauer and Shankaran et al. (2002)²³. This reality presents itself as a major public health problem because, in addition to the negative effects caused by drugs on the maternal organism, the consumption of these substances facilitates the spread of communicable diseases to fetal health¹⁸. Furthermore, as demonstrated in a study by Soares et al. (2016)²⁴ in 2016, multiparity is a predominant factor.

As described by Botelho et al. (2013)²⁵, the association of consumption of other drugs, such as alcohol, tobacco and

cocaine, is common in this population. This data is observed in the present study, with an association between cocaine and/or crack and smoking in 83.3% of pregnant women.

In the current study, 33.3% of the newborns were premature, and more than half had impaired intrauterine growth, in agreement with the literature²². And 66.7% of the newborns had a reduction in HC, below the 10th percentile, and 33.3% had microcephaly. As a predisposing factor, uteroplacental vascular insufficiency stands out, which, associated with maternal anorexia, impairs the transfer of nutrients and oxygen to the fetus. Concomitantly, the increase in catecholamines induced by cocaine can increase fetal metabolism, leading to greater consumption of nutrients²⁶.

A longitudinal study by Covington et al. (2022)²⁷ revealed that, in addition to weight, birth length is significantly affected by cocaine use during pregnancy, even after controlling for confounding factors such as GA, pre-pregnancy weight, and alcohol or cigarette consumption. Such findings correspond to those found in this study, where 58.3% had a length shorter than the 10th percentile, and of these, 33.3% had a length shorter than the 3rd percentile. One case of fetal malformation (myelomeningocele) can be explained by the possible teratogenic effect of psychoactive substances on the central nervous system, causing neural tube defects²⁸. Evidence of myelomeningocele was also described by Alencar et al. (2011)²⁹.

Regarding the analysis of cocaine metabolites in urine, the method's advantages are the easy collection and the presence of metabolites, usually in high concentrations in the test. A limitation is that are reports of cases of false negatives, which were not verified in this study, in addition to positivity being normally related to recent drug use⁶. However, White et al. (2003)⁵ found evidence of reduced activity of the enzymes that metabolize the drug (hepatic and plasma cholinesterases) in infants and pregnant women, which may justify the presence of the metabolite in the newborn's urine for a longer time. Some studies mention that they can remain detectable for up to 7 to 10 days³⁰.

It is well known that the conventional EEG is the gold standard of care as an punctual exam or monitoring tool for newborns at high risk for brain injury, allowing the assessment of brain function and activity, as well as the seizures detection. One limitation of this study is that the conventional EEG was not realized in those newborns recruited on this study because it was not available on the service during the period of assessment.

In conclusion, newborns of mothers who use cocaine/crack may have a pattern of early maturation in electroencephalographic evaluation and repercussions on growth and neurodevelopment. Further studies are needed, preferably in very premature newborns, to better assess the relationship between the presence of the cocaine and/or crack metabolite and the early acquisition of the mature pattern in the aEEG, which would imply a higher presence of SWC in this

population. The long-term assessment of these implications for the neurodevelopment of these patients and the approach to the topic from a multidisciplinary perspective is essential to improve the follow-up of pregnant women from prenatal care to their need for rehabilitation.

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APPENDIX 1

Epidemiological Profile Questionnaire

File/ Mainframe: _____ Date: _____

Maternal Data:
Age _____ Marital Status ☐ Married ☐ Divorced ☐ Single ☐ Widow
Ethnicity _____

Housing Conditions: District _____ Rooms _____

Activity and Income: Do you work? ☐ Yes ☐ No Hours per week _____
Registration? ☐ Yes ☐ No
Monthly income _____ Family income _____

School: Primary ☐ Complete ☐ Incomplete
Secondary ☐ Complete ☐ Incomplete
University ☐ Complete ☐ Incomplete
Literacy ☐ Yes ☐ No

Obstetric History: N° of Pregnancies _____ N° of Births _____ N° of Abortions _____
Age at first pregnancy _____ If had an abortion, cause? _____
Previous children ☐ Healthy ☐ Have any pathology If have any pathology, witch? _____

Prenatal Follow-up: ☐ Yes ☐ No N° of consultations _____
Complications? ☐ Yes. ☐ No If yes, witch? _____

Current Delivery Characteristics: Type ☐ Normal ☐ Forceps ☐ Caesarea
Complications ☐ No ☐ Meconium ☐ DPP ☐ PP ☐ Prematurity ☐ Membrane Rupture
☐ Infection ☐ Others _____

Medical Treatments: Do you use any routine medication? If yes, which one or which ones? -
Do you self-medicate? If yes, with which drug(s)? _____

Smoking: ☐ Yes ☐ No How many cigarettes a day? ☐ 1-10/day ☐ 10-20/day ☐ More

Alcohol Consumption: ☐ Daily ☐ 1-3/ week ☐ <1x/week ☐ 1-3x/month ☐ 1x/month
Favorite drink _____ When you drink? _____ How much do you drink? _____
Did you drink during pregnancy? ☐ Yes ☐ No

Drug Use: What drugs have you already heard of? _____
Where did you obtain the information? ☐ TV ☐ Magazine ☐ School ☐ Friends ☐ Others
Do you know someone who uses drugs? ☐ Yes ☐ No
Does your partner use drugs? ☐ Yes ☐ Not If not, have him tried it or used it in the past? ☐ Yes ☐ No
If yes, type of drug used by the partner _____ Form of administration _____
What is the frequency of use? ☐ Daily ☐ 3-6x/week ☐ 1-3x/month ☐ 1-2x/ 3 months
Do you use any kind of drug? ☐ Yes ☐ No If not, have you tried or used it in the past? ☐ Yes ☐ No
If yes, what is the form of administration? _____
What is the frequency? ☐ Daily ☐ 3-6x/week ☐ 1-3x/month ☐ 1-2x/ 3 months
Time between last use of crack and/or cocaine before delivery _____
Do you think the drug could harm the baby? ☐ Yes ☐ No
What do you believe that the drug can cause in your baby? _____

Newborn Data: Gestational age _____ weeks Birth weight _____ g
Cephalic perimeter _____ cm Length _____ cm
☐ Small for gestational age ☐ Adequate for gestational age ☐ Big for gestational age
Apgar 1' _____ 5' _____ 10' _____
Pathologies in Hospitalization: Infection ☐ Yes ☐ No ☐ Mild ☐ Severe
Jaundice ☐ Mild ☐ Moderate ☐ Severe
Metabolic disorders? ☐ Yes ☐ No If yes, which? _____
Congenital malformations? ☐ Yes ☐ No If yes, which? _____
Eutrophic? ☐ Yes ☐ No
Presence of withdrawal-related symptoms? ☐ Yes ☐ No If yes, which? _____