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Research Article

Effects of Chronic Cocaine Administration during Pregnancy on Pre and Postpartum Maternal Behavior

Maria del Pilar Santacruz*

Department of Psychologies, Universidad Católica de Colombia, Colombia

***Corresponding Author**: Maria del Pilar Santacruz, Department of Psychologies, Universidad Católica de Colombia, Colombia.

Received: October 28, 2019; **Published:** December 17, 2019

Abstract

In order to identify the effects of chronic cocaine administration (CCA) during gestation on prepartum and postpartum maternal behavior (MB) in mice, prior studies conducted at the Faculty of Psychology, Universidad Católica de Colombia [Catholic University of Colombia], evaluating the effects of cocaine administration (10, 20, 25, 30, 40 and 50 mg/kg) on prepartum and postpartum maternal behavior were reviewed. It was found that CCA (10, 20 and 30 mg/kg) during gestation disturbed prepartum and postpartum MB. Alterations found on postpartum MB were dose related. Major alterations were found with CCA at a level of 40 mg/kg, when the administration took place from the first day of gestation. On the other hand, when CCA (25 and 50 mg/kg) initiated on the eighth day of gestation, no effects were found on MB. It is concluded that the treatment regime of chronic cocaine administration is more important than the dosage.

Keywords: *Cocaine during Pregnancy; Prepartum and Postpartum Maternal Behavior*

Introduction

World drug use has increased in a worrying manner. During the period from 2009 to 2017 the increase was 30% [1]. Cocaine is still one of the most popular substances and occupies the fourth place with the highest consumption in the world. In 2017, the annual prevalence ranged from 0.35% to 0.37% [1,2]. In Latin America, consumption of this substance increased among people aged 12 to 34 years, and the highest consumption was in the range of 18 to 34 years. In general, men consume more than women; in Colombia the ratio is 6:1 and it is the Andean country with one of the highest rates of cocaine use among university students, where the past years prevalence increased from 2.4% in 2009 to 2.7% in 2016 [2].

Cocaine, like other stimulants, increases sexual activity and risky sexual behaviors, including early sexual initiation, multiple sexual partners, low use of condoms and/or contraceptives and unprotected sex [3], which increases the risk of unplanned or poorly programmed pregnancies and of contracting various sexually transmitted diseases [4].

Cocaine use during pregnancy is very common. In 2013, The National Survey of Drug Use in the U.S. showed that 5.4% of pregnant women used illicit drugs such as cocaine [5] and in 2015, cocaine was the second most commonly used illicit substance among pregnant women, where 3.4% of them had used this drug during the last month of that year [5,6]. Ventura [7] found that among the Brazilian population consuming crack in the capital Brasilia, 10% of the women were pregnant, more than half of them had been pregnant at least once since they started consumption and 8% of those who used crack, didn't know they were pregnant. The authors point out that these data are consistent with those found in the United States.

Cocaine used during pregnancy disrupts the baby's development from three simultaneous routes: it reaches the brain of the fetus through the placenta and increases the levels of Catecholamines (CA) and serotonin (5HT), which alters growth and neuronal organization, disrupting cortical architecture and physiology [8]. Due to its vasoconstrictor effects, cocaine reduces blood flow, the provision of oxygen and nutrients, and decreases glucose metabolism; added to its anorexic consequences, it also retards intrauterine growth and the fetus anatomical-functional development [8]. It is also an early stressor that alters homeostasis of the placental/fetal neuroendocrine microenvironment, increasing the susceptibility to suffer from physical and mental health problems, such as cardiovascular and metabolic alterations, as well as neurobehavioral disorders including high reactivity to stress, impulsivity and aggressiveness, apathy, psychosis and drug abuse [8-10]. This susceptibility persists until old age and the permanence of these modifications is explained through reprogramming epigenetics [8].

Eiden., *et al.* [9] propose a fourth way in which cocaine disrupts the infant's development: it refers to the problematic mother/child interactions, characteristic of an inadequate or deficient maternal behavior which perpetuates child abuse. The addicted mothers are insensitive to the signs and needs of their babies; their role as mothers generates stress to them and they do not find gratification in the interactions with their children; they are negligent, have erratic behavior, are punitive, aggressive and little tolerant, which makes infants to be at high risk of abuse [11].

In addition, cocaine addiction causes them anxiety and depression which is detrimental to the mother/child relationship and increases the risk of abuse and/or neglect. The maternal behavior of the addicted mother is the result of the biological imbalance produced by drug abuse and the dysfunctional environment in which she has developed (poor family relationships, unstable homes, high levels of domestic violence, poverty and limited nutritional, educational and health resources), which deeply damage the baby's future cognitive-emotional development [9,12,13]. Inappropriate, absent and poor quality maternal behavior is associated with the appearance of behavioral problems, internalizing and externalizing disorders, high-risk behaviors such as substance abuse, truancy, juvenile delinquency and antisocial behaviors [10,14-16].

In this way, from conception, the baby is exposed to the biochemical and behavioral imbalance (caused by drug abuse) of the addicted mother [17], so the effects of Prenatal Cocaine Exposure (PCE) on neurodevelopment could be a product of the drug or the environment independently, or the interaction of these two aspects.

Cocaine use during pregnancy affects the health of the mother and that of her child, damages the cognitive-emotional and behavioral functioning of the infant, due to the various physical, functional and behavioral disorders [17,54]. The most common ones associated with PCE are high emotional reactivity, poor levels of alertness and attention, learning and memory failures, problematic social relationships [18] such as aggression, delinquency and substance abuse [7,13,19]. Also, there is an increased risk of sexual initiation before the age of 15 (only in women), which is associated with the increase in teenage pregnancy and perpetuates this problem [3].

However, these studies have difficulty in isolating the enormous risk factors that simultaneously affect the development of children of addicted mothers, so these effects cannot be attributed to cocaine with certainty. The various confounding variables promote studies of Maternal Behavior (MB) with rodents, since the offspring, as with the human being, need MB to survive and mature. MB of rodents is well characterized and allows to easily determine any variation in it as a result of some external or internal agent. It is an optimal model that facilitates control of the various confounding variables.

MB draws together a series of interactions aimed at caring for the babies, so that they can survive and mature [20], in such a way that an adequate MB must guarantee the survival of the offspring, provide food, thermoregulation, hygiene and protection to them; part of this protection consists of the maternal aggression towards an unfamiliar individual [21,22].

Delivery of infants divides MB into two phases: The antepartum phase, which begins from conception and becomes more evident in times close to the offspring's birth. During this phase most of the behavioral patterns are aimed at preparing for the arrival of the young: nest building, digging, excavating, and some motor and exploratory activities, in addition to hyperphagia and hyperdipsia [22,23]. With delivery, the mother and the offspring constitute a critical dyad that promotes the survival of the newborn. MB begins with behaviors that involve contact with her infant, where the mother exhibits different behavioral patterns responding to the signals of the young, product of hormones and neuropeptides triggered by childbirth and which continue thereafter. The infant stimulates MB with crying, smell, temperature and movement. In the early postpartum, a higher MB is observed, which decreases as the mother promotes the independence of the offspring (s). In the final stages the mother shows rejection towards her infants, which helps to achieve weaning [9,14,24].

After delivery, breastfeeding, grooming, anogenital licking and hauling or nest moving are found [9,20]. In the second phase, the maintenance of MB is elicited largely by the behavioral signals or patterns shown by the infant. And in the third, both the mother and the offspring are actively involved in the termination of maternal behavior, or weaning [20,25]. Throughout this period, maternal responsiveness is critical for the survival and subsequent development of the newborn. Hormonal changes in pregnancy and childbirth promote parenting behaviors in interaction with newborn behaviors, so that the interaction between hormones and the behavior of the offspring is basic to understand parental behavior [9,14,24,26].

It has been found that cocaine in different forms of administration -acute, chronic and intermittent- applied during pregnancy, causes detriment of MB. The degree of deterioration is proportional to the dose: those under 30 mg/kg, do not affect the onset of MB, or slightly affect it [12]. The observation time of MB is also fundamental, since, with delivery, the intensity and incidence of this behavior is the highest, and it is reduced over time until weaning [12,24,25].

Weaver., *et al.* [26] found that acute cocaine treatment (20 or 40 mg/kg) disturbed MB until 4 hours after its application. At 16 hours, these effects had disappeared and females treated with cocaine behaved the same way as the control ones, which shows that MB is affected only when cocaine is in the plasma. When blood levels of cocaine return to zero, the effects disappear and no residual repercussions are found.

There are few studies about the effects of chronic administration of cocaine on MB during the prepartum stage, perhaps because there are few indexes to evaluate. Among these, the most important is nest building, which has been affected by cocaine [28], found that the administration of cocaine (15 mg/kg), three times a day (45 mg/kg) from day 8 to 18 of gestation, results in a reduced ability of the rats for nest building: they used less material and did not finish the outside thereof. The quality of the nests was significantly lower compared to the mothers treated with saline solution.

The vast majority of studies focus on postpartum MB rates, where the effects of chronic or intermittent administration of cocaine are evaluated [29], found that chronic cocaine administration (CC) of 15 mg/kg twice daily from day 1 to 20 of gestation, or intermittent (IC), on days 2, 3, 8, 9, 14, 15 and 20 of postpartum, altered the onset of MB, reduced bending towards the young, increased the duration of nest building, as well as the frequency and duration of motor behaviors such as self-grooming, rearing and others. CC had more negative effects than IC, although these effects were reduced throughout the postpartum period because they are related to the presence of cocaine in the rat's system. They also found inter-generational effects: mothers who were Prenatally Exposed to Cocaine (PCE) showed greater latency of MB onset, delay or deterioration of nest building, reduction of bending down to the young, licking and touching the pups and spending more time resting or lying on puppies, without stimulating breastfeeding. Similarly, Mc Burray., *et al.* [30] found that CC administration (15 mg/kg) twice daily during the first 20 days of pregnancy did not alter maternal aggression (MA). Instead, on the 8th day after delivery, the IC applied during pregnancy (days 2, 3, 8, 9, 14, 15, 20) and postpartum (days 2, 3, 8, 9, 14, 15, 20) reduced aggression, assessed on the 8th postpartum day. On the 12th day no differences were found between the groups. Mothers who received PCE on the 8th day, showed high MA towards the intruder which can be attributed to prenatal treatment with cocaine or to parenting conditions. The intergenerational effects of the increase in MA are related to the alteration of the oxytocin system produced by prenatal treatment.

PCE at 20 mg/kg (s.c) from day 7 to 17 of gestation, increased the latency of the offspring retrieval only on the 4th postpartum day, so there are slight effects of the PCE on the latency of pup-retrieval and slight intergenerational consequences [31]. The administration of either chronic or intermittent cocaine can alter MB and that of their daughters; it can have intergenerational effects due to the PCE, in addition to parenting conditions, which help to maintain and perpetuate this problem.

The mother/infant bond is very strong and the gratifying properties of their offspring are dominant for the mother, in direct relation to the postpartum time. Based on the paradigm of conditioned place preference [32], compared the reinforcing value of cocaine (10 mg/kg) vs the offspring of nursing mothers, for which they were tested on postpartum days 8, 10 and 16. The mother rats preferred the signals associated with the offspring on day 8, although on days 10 and 16 they chose the place associated with cocaine. Mattson., *et al.* [33] based on the previous study, examined breastfeeding mothers on the 10th postpartum day, for being the midpoint of MB transition. There were mothers who preferred the signals associated with cocaine and mothers who preferred the signals associated with the offspring. Although no differences in MB were found between the groups, the authors explain that mothers distinguish the reinforcing properties of their offspring and those of cocaine, so MB is not affected.

One of the reasons that explains maternal negligence caused by cocaine is that this is basically due to the inability of the offspring to elicit MB, which is generated by PCE, rather than by the reduction in maternal responsiveness. Cox [14] found that treatment with cocaine 15 mg/kg given to rats twice daily, from the first to the 20th day of gestation (G1-G20), decreased MB directed to their young. The reduction of the mother's preference was related to the alterations in the infants' calls to elicit MB. PCE damaged the ability of the offspring to request MB. This was more evident in the early postpartum period and the males were more vulnerable [14,34,55], PCE alters the ability to stimulate MB, or maternal negligence could be caused by the effects of CC administration, or also by the interaction of reduced maternal responsiveness with decreased ability of the offspring to stimulate MB. In addition, PCE can subsequently damage MB by its intergenerational effects.

Another way by which CC could alter MB is by increased anxiety. Williams., *et al.* [35] found that the daily administration of cocaine (30 mg/kg) during days 1 - 20 of pregnancy produced an increase in anxiety in rats whose performance in the open field and forced swimming tests was observed on the 5th postpartum day. They also exhibited higher levels of corticosterone (as an indicator of stress). The high sensitivity to stress manifested in an exacerbated hormonal and behavioral response could explain some deficiencies in MB, since these correlate with low levels of oxytocin, as a consequence of chronic cocaine treatment during pregnancy. In addition, these effects on the regulation of peripheral oxytocin in rats are long lasting.

Cocaine administered during pregnancy alters MB, either by delaying its onset, or some specific parameters, such as behaviors directed to the offspring. The permanence of these effects depends on the dose, the time of administration and the treatment conditions. Nevertheless, the intergenerational effects highlight the permanence of the consequences of the chronic administration of cocaine, which in humans would be seen as the perpetuation of the drug abuse problem.

Taking into CCAount the importance of maternal behavior (MB) in the subsequent functioning of the offspring, the effects of different doses of cocaine on diverse prepartum and postpartum MB parameters were assessed. This was carried out through animal models, in order to isolate many variables that are related to women addicted to cocaine.

Different doses were evaluated, starting with 10 mg/kg to end with the 50 mg/kg dose, and thus establish whether the effects are related to the doses, or the time of cocaine administration during pregnancy, or the interaction of these two variables. The aim was also to determine the permanence of these effects, so observations were made in the prepartum and postpartum phases to carefully monitor different patterns of maternal behavior.

Objective of the Study

The objective of this paper was to review the studies carried out at the Faculty of Psychology of the Catholic University of Colombia, about the effects of chronic cocaine administration in different doses (10, 20, 25, 30, 40 and 50 mg/kg) on various patterns of maternal behavior of mice, both prepartum and postpartum. This analysis was carried out starting with the use of a small dose of cocaine and the subsequent progressive increase of it until reaching 50 mg/kg.

Method

Designs: For the evaluation of the effects of chronic administration of cocaine in the different doses tested, repeated measures experimental designs with control group were used. Repeated measures refer to daily observations of different parameters of maternal behavior, both for control and experimental groups. A control group was always included in all the research carried out in order to make comparisons with the cocaine administration group.

Subjects: In all investigations female mice strain CD1 were used, except for the 30mg/kg cocaine group in which mice strain C57 were used.

Substances: The different doses of cocaine were dissolved in 0.9% saline solution. These were administered daily during pregnancy in the period that varies from 18 to 20 days, as specified below (Table 1 and 2), subcutaneously (s.c.), in a volume of 0.5 ml. These administrations were performed using a double-blind method.

Site: The present investigations were carried out in the research module with animal models of the Psychology Laboratory of the Catholic University of Colombia (LAPSUCC, for its Spanish acronym).

Instrument: Ethogram of prepartum and postpartum maternal behavior, adapted from Silverman [36,37].

This ethogram includes:

Prepartum Maternal behavior

- Nest building: The female presents a temporary and spatial organization of her territory, where she accumulates sawdust in a quadrant of the box forming the nest
- Rearing: The female assumes a vertical position raising her front legs and holding herself on her back legs.
- Climbing: The female walks clinging to the mesh tops of the cages with her legs.
- Digging: Is a form of nesting behavior that involves the removal of substrate material from a certain spot.
- Scrape-dig: A series of forepaw movements alternated by backwards kicking of both hind legs simultaneously. This results in the heap under the abdomen of the animal being moved further back.
- Carry: Carry material for the nest.

Postpartum maternal behavior

- Breastfeeding: The mother lays on her side or on top of her offspring to breastfeed them.
- Nest repair: includes:
- Nest building: In which the female presents a temporary and spatial organization of her territory, where she accumulates sawdust in a quadrant of the box forming the nest;
- Nest moving: Which consists of moving the location;

- Cleaning nest: The mother eats the feces or throws them out of the nest with her back or front legs.
- Depth of nest: Provides a quantitative measure of nest building about deep nest length
- Pup retrieval: The mother returns her pups to the nest holding them with her teeth by the neck, each time any pup gets away from it.
- Maternal grooming: The mother cleans the pups' bodies with her tongue or legs.
- Warmth for offspring: The mother provides warmth to her pups by covering them with her body.
- Anogenital licking: The mother licks the abdominal, anal, genital, and urinary areas to stimulate the pup defecation and urination.
- Pups' body sniffing: The female tracks with her nose her pups' bodies.
- Self-grooming: The female cleans her body with her tongue or her back or front legs.
- Environmental sniffing: The female sniffs the environment making head movements.
- Rearing: The female assumes a vertical position raising her front legs and holding herself on her back legs.
- Locomotion: The female moves across the cage floor.
- Climbing: The female walks clinging to the mesh tops of the cages with her legs.
- Digging: Is a form of nesting behavior that involves the removal of substrate material from a certain spot.
- Scrape-dig: Is a form of digging behavior, that usually occurs at the beginning of the nesting behavior sequence.
- Carry: Carry material for the nest.
- Drink: The female laps from the spout.
- Eat: The female consumes food from the feeder.
- Rest: The female reposes with her eyes closed and remains still.
- Sleep: The female lies coiled up with her eyes closed.

Procedure

In all the investigations, after delivery, the mothers remained with their young until weaning at 21 days. During the time specified in each investigation the interactions of each mother with their young were analyzed for 15 minutes a day, always starting at the same time. To do this, the frequency of presentation of the behavioral indices previously identified in the modified Silverman ethogram (1978) was recorded every 5 seconds, in blocks of 5 minutes in a row. After half an hour, recording was performed again in the same way for 5 minutes, until completing 15 minutes daily [37].

Results

Data were analyzed with ANOVAS or MANOVAS, with an Alpha less than or equal to 0.05. Table 1 and 2 summarize the different studies, the dose and the chronic administration time of cocaine (CCA), along with the behavioral guidelines of maternal behavior (MB) in the prepartum (Table 1) and postpartum (Table 2). Significant differences are presented with an asterisk ** and the observation in which they were found. When no differences were found between the groups, it is indicated with "no differ".

As can be seen in table 1, only a significant behavioral pattern was found ($F = 4.94$, $p \leq 0.05$.) Tukey ($dfs = 9.58$, $p \leq 0.05$) consisting of a greater nest area noted in the third observation of the groups treated with cocaine (10 mg/kg and 20 mg/kg) vs. the control. Regarding nest building, a total of 12 observations were made, the first three from the prepartum and the following from the postpartum.

In the group treated with cocaine (30 mg/kg), a significant decrease in rearing was found ($F = 7.819$, $p < 0.01$), only in the third observation.

	Experiment I		Experiment II	Experiment III
Doses	Cocaine (10 mg/kg)	Cocaine (20 mg/kg)	Cocaine (30 mg/kg)	Cocaine (40 mg/kg)
Cocaine administration	20 days G1 -G20	20 days G1 -G20	20 days G1 -G20	18 days G1-G18
Observation	3 days	3 days	5 days	11 days
	21 days Total	21 days Total	25 days Total	22 days Total
Digging	No differ.	No differ.	No differ.	No differ.
Scrape-dig	No differ.	No differ.	No differ.	No differ.
carry	No differ.	No differ.	No differ.	No differ.
Nets building: Nest area	3ª Obs**	3ª Obs**	No differ.	No differ.
Rearing			3ª Obs**	

Table 1: *Synthesis of the findings in the four studies carried out on prepartum Maternal Behavior: study, dose of cocaine used, time of administration and observation of the different behavioral patterns.*

Note: *Experiment I [38], Experiment II [39], Experiment III [40].*

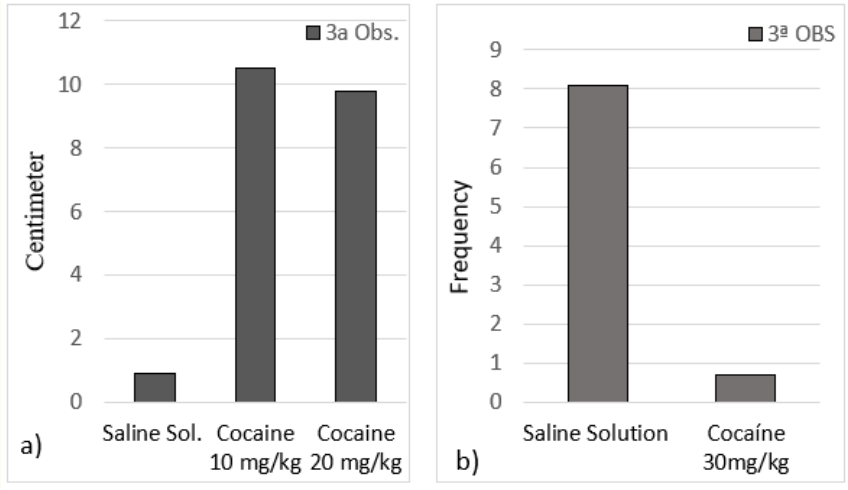

Figure 1: *Prepartum Maternal Behavior: a) Nest area in the groups treated with cocaine (10 and 20 mg/kg) and the control group in the third observation b). Frequency of the rearing in the groups treated with saline and in the treated with cocaine (30 mg/kg) on the third observation.*

Table 2 summarizes the results of comparisons of the frequencies of the different behavioral patterns of postpartum maternal behavior (MB), with the different doses of cocaine used (10 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 40 mg/kg, and 50 mg/kg).

As in the previous table (Table 1), the dose of cocaine used, the days of administration during pregnancy, the observation time of the behavioral patterns of MB and the differences found are described. If no differences are found, it is indicated with "no differ".

	Experiment I.		Experiment IV.	Experiment II	Experiment III.	Experiment IV.
Cocaine	(10 mg/kg)	(20 mg/kg)	(25 mg/kg)	(30 mg/kg)	(40 mg/kg)	(50 mg/kg)
Administration time	20 days G1 -G20	20 days G1 -G20	14 days G8-G21	20 days G1 -G20	18 days G1-G18	14 days G8-G21
Maternal Behavior observation	18 days	18 days	20 days	20 days	11days	20 days
	21 daysTot	21 daysTot	20 daysTot	25 daysTot	22daysTot	20 daysTot
Nest building			No differ.		No differ.	No differ.
Nest depth			No differ.	15ª Obs: **	No differ.	
Cleaning nest	No differ.	No differ.	No differ.	No differ.	No differ.	No differ.
Breastfeedeng	No differ.	No differ.	No differ.	No differ.	No differ.	No differ.
Maternal grooming	No differ.	No differ.	No differ.	No differ.	No differ.	No differ.
Warmth for offspring			No differ.		No differ.	No differ.
Pup retrieval	No differ.	No differ.	No differ.	No differ.	No differ.	No differ.
Warmth for offspring	17 obs **	17 obs **		No differ.		
Anogenital licking	No differ	No differ	No differ	No differ	No differ	No differ
Pups' body sniffing	No differ	No differ	No differ	No differ.	5ª y 9ª Obs**	No differ
Self-grooming	No differ.	No differ.	No differ.	6ª Obs: **	1ª Obs **	No differ.
Dig up	No differ.	No differ.	No differ.	No differ.	No differ.	No differ.
excavate	No differ.	No differ.		No differ.	No differ.	
carry	No differ.	No differ.		No differ.	No differ.	
Environmental sniffing		Obs 18 **	No differ.	No differ.	No differ.	No differ.
Locomotion			No differ.		No differ.	No differ.
Rearing			No differ.	No differ	3ª Obs: **	No differ.
Climbing			No differ.		No differ.	No differ.
Drink:	No differ.	13 y 18 **	No differ.		No differ.	No differ.
Eat	No differ.	No differ.	No differ.		8ª Obs **	No differ.
rest			No differ.		No differ.	No differ.
Sleep			No differ.			No differ.

Table 2: *Summary of the results of the six studies conducted on postpartum maternal behavior: dose, time of administration of cocaine during gestation (G) and of observation of the different behavioral patterns of maternal behavior. Note. Experiment I [38], Experiment II [39], Experiment III [40], Experiment IV [37].*

With the chronic treatment of cocaine (10 and 20 mg/kg) only a significant decrease was found ($F = 6.0$ $p < 0.05$) and (Tukey dfs 6: 0 $p < 0.05$) in the warmth for offspring in the 17th observation. With a cocaine dose of 20 mg/kg, in the 18th observation, environmental sniffing significantly decreased ($F = 3.93$ $p < 0.05$) and (Tukey dfs11.40 $p < 0.05$). Drinking increased significantly in the 13th observation ($f = 4.56$ $p < 0.05$, Tukey dfs1.80 $p < 0.05$) in the two groups of cocaine (10 and 20 mg/kg); with the dose of 20 mg/kg the increase was greater. In the 18th observation of the group treated with the dose of 10 mg/kg this behavior significantly increased ($F = 16.2$ $p < 0.05$). No differences were found in the other behavioral patterns.

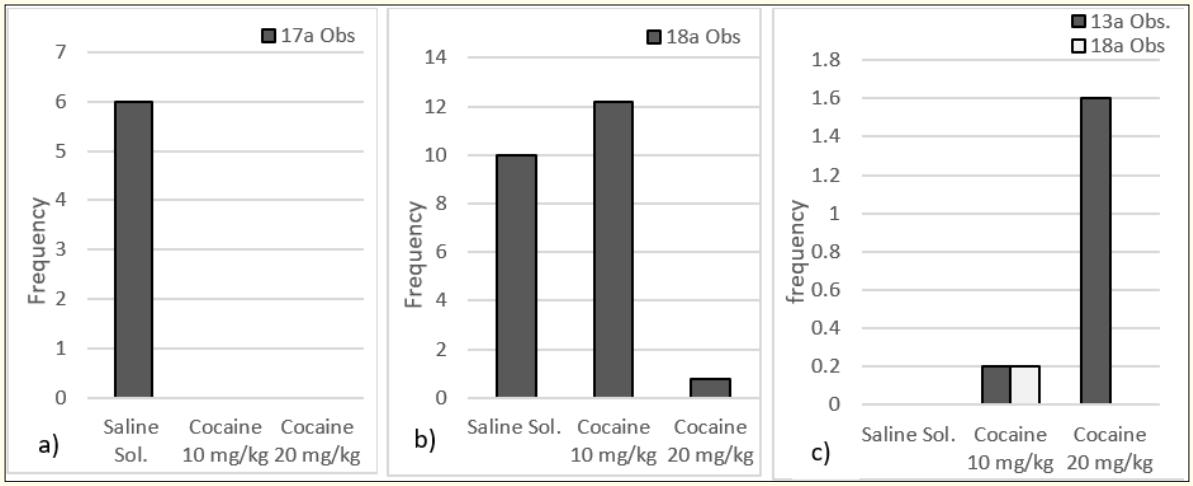

Figure 2: *a) Warmth for offspring in the three groups: treated with Sol. Saline and cocaine (10 and 20 mg/kg) on the 17th observation. b) environmental sniffing, in the group of Sol. Saline and cocaine (10 and 20 mg/kg) on the 18th observation. c) drink in treated groups with Solution Saline and cocaine (10 and 20 mg/kg) on the 13th and 18th.*

In none of the MB patterns of the groups treated with cocaine (25 mg/kg and 50 mg/kg) significant differences were found in the frequency of emergence of these behaviors [37].

Females treated with cocaine (30 mg/kg) showed a significant lower number of rearings in the 6th observation ($F = 5,293$, $p = 0.01$) and a significant smaller nest depth in the 15th observation ($F = 13,28$, $p = 0.01$). No differences were found in the other indices evaluated, nor in the total frequency of the nest depth (Figure 3).

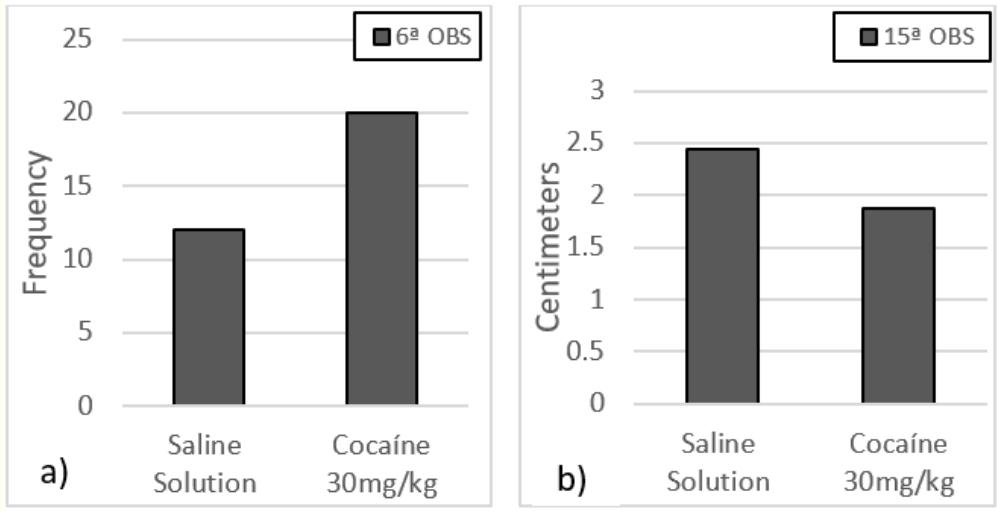

Figure 3: *a) Frequency of Self-grooming in the sixth observation (first postpartum) and b) of the depth of the nest in the 15th observation (10th of the postpartum).*

The group treated with cocaine (40 mg/kg), presented a significant better self-grooming behavior (Mann-Whitman U p = 0.02), only in the first observation. Similarly, in the 8th observation it was found that the females of this group ate with a significant higher frequency than the control females (Mann-Whitman U p = 0.025). The rearings, however, were significantly less frequent in the group treated with cocaine (Mann Whitman's U p = 0.01), only in the third observation. In the same way, regarding pup's body sniffing, the group treated with cocaine presented a significant reduction of this behavior in the 5th and 9th observation. In the other observations no differences were found between the groups, nor in the total of these behaviors (Figure 4).

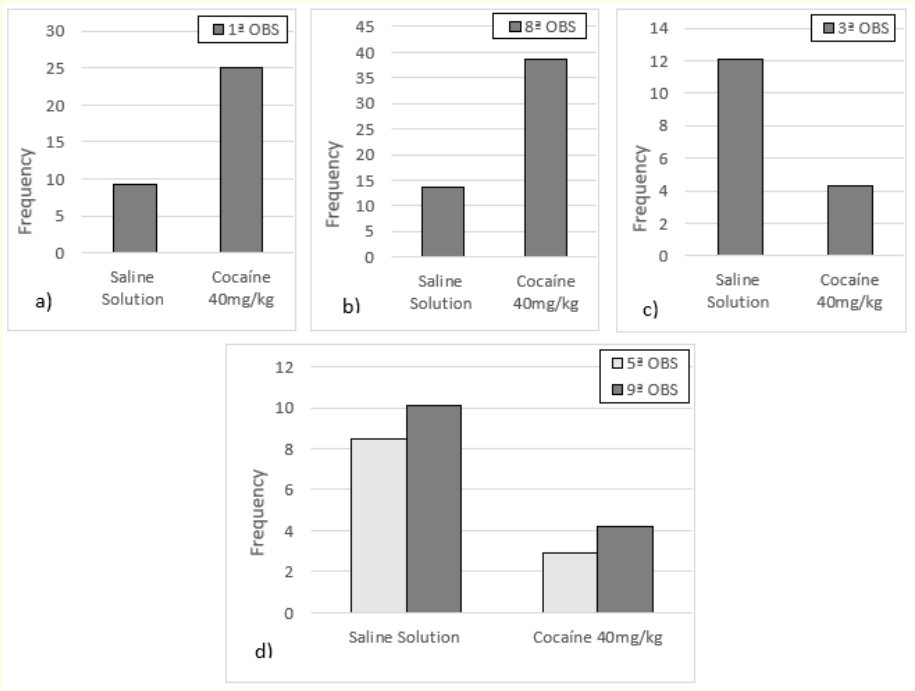

Figure 4: *a) frequency of Self-grooming in the groups treated with saline solution and cocaine 40 mg/kg at the first observation. b) frequency of eating in the 8th observation c) of the rearing in the third observation and d) of the Pups' body sniffing in the 5th and 9th observation*

In all the doses tested, the significant variations of these parameters were found over time; proximal behaviors were reduced, motor behaviors increased and self-maintenance ones remained stable.

Discussion

After reviewing the effects of Chronic Cocaine Administration (CCA) in doses of 10 mg/kg; 20 mg/kg; 25 mg/kg; 30 mg/kg; 40 mg/kg and 50 mg/kg applied during gestation in different parameters of prepartum and postpartum maternal behavior, it is observed that: From the first day of gestation, CCA (10, 20 mg/kg) temporarily decreased the nest area and CCA (30 mg/kg) reduced rearings, in both cases only in the third observation (the last one of the prepartum phase).

Assessment of prepartum MB was done half an hour after cocaine administration, when the drug was still in the blood, which may be the explanation for the disappearance of these effects in subsequent observations, because cocaine was administered only during prepartum. The transitory alterations of cocaine in these behavioral patterns, as reported in the study by Vernotica., *et al.* [27], are

possibly due to the fact that cocaine was in the blood, since later, when cocaine was no longer applied, the MB of the group treated with cocaine was similar to the control group.

The alteration of nest building, both in area or depth, prevents the provision of shelter and the protection of offspring from predators [41]. Prepartum MB revolves around behaviors aimed at nest building and its location within a safe environment, which is analyzed through rearings and other motor behaviors, such as climbing [36]. So that strong but transient effects of CCA (10, 20 mg/kg and 30 mg/kg) can be inferred in the prepartum MB.

Regarding postpartum MB, it was found that CCA (10, 20, 30 and 40 mg/kg) administered from the first day of gestation, disturbed that behavior in a dose-related way. With lower doses the impact was less compared to the high doses. The severity of these alterations is related to the affected behavioral pattern and the postpartum time when the changes were manifested since this has to do with the development of the offspring, which is completed on day 21st, when weaning occurs [42,43].

Among proximal behaviors, which imply closeness between the mothers and the young, it was found that CCA (10 and 20 mg/kg) reduced the frequency of providing warmth for offspring observed on the 17th postpartum day. These changes in MB were found in a period close to weaning, when the offspring have greater independence and maturity, have developed their thermoregulatory abilities and rely on the other members of their litter to provide heat. They have greater locomotion, which enables them to move away from the nest and numerous motor behaviors. Therefore, the reduction of this behavior only at this time, indicates its transitory effects and reveals a slight impact of CCA on MB, due to the offspring's level of development [44].

CCA (20 mg/kg) decreased environmental sniffing on the 18th observation, a behavior whereby the mother explores the environment to determine the safety that surrounds her young. Therefore, it is one of the protective motor behaviors. Additionally, the less exploration indicates greater anxiety [35]. However, the transient effects on the 18th postpartum day, when MB is already disappearing due to its closeness to weaning, determine that this alteration is not transcendental for the offspring [24].

This same dose increased drinking on the 13th and 18th observation, which cannot be adequately explained. Church and Rauch [45] attribute drinking increase to the diuretic effects of cocaine; however, when this increase was found, cocaine was not detected in the blood, because it was applied only during gestation. It could also be attributed to breastfeeding and the need to drink more water, although this increase did not affect total water consumption, which was similar to that of the control group.

CCA (30 mg/kg), decreased the depth of nest during the 10th observation. These failures in nest building, although temporary, reduce the quality of the nest, because they prevent both the preservation of heat and protection, which are two of its more important functions. Heat preservation is of vital importance for the offspring, due to their poor thermoregulatory abilities, which are still evident during the 10th observation. In addition, the nest must be built to facilitate breastfeeding and it also serves as a shelter and protection from predators [41,46].

Although no alterations were found in subsequent observations, the damage of cocaine on MB could be noticed, because it affected an index of vital importance and in a critical period for the survival of the offspring. The decrease in the depth of the nest places offspring at an imminent risk of being predated, because it does not hide them properly. Quiñones-Jenab [28] also found alterations in the quality of the nest produced by cocaine in terms of the material used and the lack of enclosure in the external area of this.

With this same dose, self-grooming was increased in the first observation, which could be related to greater anxiety in the early postpartum period, because the emission of this behavior reduces stress [35,47,48] and always occurs before an anxiety-producing stimulus, which in this case could be their litter. The increase in self-grooming, compared to early postpartum control could be attributed

to the anxiety effects produced by the litter on the mother [47,48]. Another possibility is that this increase is due to cocaine withdrawal, as suggested by Vernotica., *et al.* [27] since the last administration had taken place a day earlier. However, it would be important to corroborate this assumption in later studies.

CCA (40 mg/kg) reduced pup´s body sniffing in the fifth and ninth observations, that is, in the early postpartum period. This sniffing is a maternal pattern that precedes numerous behaviors such as licking, grooming and giving warmth to the offspring and of course, to breastfeeding. These differences occurred in the early postpartum period, when the development of the offspring is still very precarious [42,43]. When the mother sniffs the pup's body, she perceives their olfactory and thermal signals, so she then provides them with licking, grooming and breastfeeding, behaviors that facilitate optimal development for the offspring [43]. However, in the present case, no significant differences were found with the control group in the other proximal behaviors, which shows that the effects of this drug were selective on this particular behavior, without altering the others. Therefore, there is a reduced impact of CCA on postpartum MB [44].

The increase in self-grooming on the first observation, due to chronic cocaine treatment (40 mg/kg) could indicate, as with the 30 mg/kg dose, the appearance of early postpartum anxiety due to the presence of the litter. Self-grooming begins in the presence of an anxiety producing stimulus, which is similar to the findings reported by Williams., *et al.* [35], who explain that CCA causes anxiety, because it increases levels of adrenocorticotrophic hormone- ACTH [11]. Self-grooming is involved in the maintenance of hygiene and other physiologically important processes, including skin stimulation, thermoregulation, social communication and stress reduction [47,48]. This increase was noticed only in this observation, so it could also be due to the anxiety resulting from the withdrawal of cocaine but these effects did not last.

The decrease of rearings in the third observation, with CCA (40 mg/kg) implies less environmental exploration that the mother must do to defend her litter from some predator or intruder that can put them in danger (mother/young). This reduction implies less protection for the offspring. In addition, the lower exploration means high anxiety as well as the increase in self-grooming, although these two indices denote anxiety. In the present study these two behaviors were not found simultaneously (3rd and 1st observation respectively); however, they could indicate effects resulting from anxiety [47]. Also with this same dose, an increase in the frequency of eating was found in the eight observation, contrary to the anorexic effects of cocaine. There is no explanation for this because CCA was performed during prepartum, and the moment this behavior was found (eight observation) cannot be the product of cocaine withdrawal, nor of breastfeeding, because this increase was only found in one observation.

From the above it is concluded that the chronic treatment of cocaine (10, 20 and 30 mg/kg) during pregnancy, with the different doses studied, altered prepartum and postpartum MB in a dose-related way (the higher the dose, the higher the disruption indices) and only in the groups in which CCA was performed from the first day of gestation.

Cocaine administration (50 mg/kg and 25 mg/kg) did not affect any index of postpartum MB [37], although observations were made daily from early postpartum to weaning, whereas cocaine doses at 10, 20, 30 and 40 mg/kg affected MB when the administration was carried out from the first day of gestation. When CCA started from the eighth day (50 mg/kg and 25 mg/kg), no MB index was affected. The lack of effects found in these last doses, allows to infer that the treatment regime has a greater impact on MB than the administered dose, since the greatest MB disturbance is found when cocaine is administered from the first day of pregnancy.

The greatest vulnerability found in MB regarding CCA effects is observed when the substance is applied from the beginning of pregnancy, possibly because at this time the neuroendocrine programming occurs and cocaine disrupts this programming along with MB manifestation. On the other hand, when the administration begins eight days after pregnancy, the neuroendocrine changes that regulate MB are probably already established and there are no alterations in it [57].

Although CCA during pregnancy in some cases it did not affect MB, all the doses evaluated in these studies disturbed the pups emotion and cognition, that is, Prenatal Cocaine Exposure (PCE) in all doses and with all treatment regimes disturbed the emotional and cognitive development of female and male mice. Even a higher cocaine consumption was found among them [38-40,49].

MB alterations found in these studies are explained because CCA during pregnancy produces numerous neurobiological and behavioral alterations [25,50,56], both in the mother and pups undergoing PCE. MB is regulated by neurohormonal change and by signals emitted by the offspring from the peri and postnatal periods [51].

Cocaine interacts primarily with numerous neurotransmitters and hormones in areas that regulate MB [52] such as the tonsil, the hippocampus, the paraventricular, supraoptic and medial pre-optic nucleus of the hypothalamus; the basal ganglia, mainly the nucleus accumbens; the olfactory tubercle, the lateral septum, the ventral tegmental area [25]. CCA during pregnancy reduces levels of Oxytocin, prolactin, progesterone, estrogen and mainly vasopressin, as well as those of AD and 5HT, which is reflected in maternal negligence and MB disturbances [11,12,51,52,53,57] CCA during pregnancy disturbs the reinforcement, stress, attention and decision making circuits [34] although there is no clarity regarding the time of pregnancy in which a greater impact of cocaine is found on MB.

Additionally, Prenatal Cocaine Exposure (PCE) from conception disturbs the development of the offspring with greater intensity, and therefore affect the signals (vocalizations, smell and temperature) that they emit to promote MB [34]. Ultrasonic vocalizations, similar to crying in the human infant, are disrupted by PCE in both their frequency, amplitude and complexity, by the decrease in size and laryngeal diameter (due to their low body weight), which modifies the volume of air emitted for each vocalization, and therefore fail to elicit MB [34]. In the present case, a greater impact is observed when PCE was carried out from the first day of gestation, so that the offspring could have presented greater failures to elicit MB compared to those that were exposed from the eighth day of gestation.

In this way, it is confirmed what Mc Burray and Johns [34] point out that all treatment regimes of chronic cocaine administration during pregnancy alter the same systems, although these effects and the intensity of the impact are directly related to the treatment regime.

Knowing what has the greatest impact, either the cocaine treatment regime during pregnancy or the dosage used, requires future experiments aimed at evaluating the impact of cocaine in a dose of 40 mg/kg on MB applied during the last 14 days of gestation and also cocaine administered in a dose of 50 mg/kg from the first day of pregnancy.

Variations in the chronic administration of cocaine carried out only in the prepartum stage and recreated in these studies (time and intensity) could adequately reproduce the conditions of human consumption, since many women stop using cocaine in the postpartum phase, either because they are more monitored at home or in an institution, or because their child may give them the motivation to quit consumption. Therefore, it is important to review what dose of cocaine is used and the intensity of that consumption, as well as the treatment regime that could affect MB. Preclinical studies are critical for the analysis of MB because they guide therapeutic interventions aimed at preventing maternal neglect due to drug addiction.

Conclusion

It is concluded that CCA (10, 20 and 30 mg/kg), during pregnancy disturbed both prepartum and postpartum MB, only that the effect was dose-related. The worst alterations were found with doses of 40 mg/kg, when the administration took place from the first day of gestation. On the other hand, when cocaine was administered at a dose of 25 and 50 mg/kg) and started on the eight day of pregnancy, no effects were found in MB. Thus, it can be affirmed that the chronic cocaine administration treatment regime is more important than the dosage.

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