



Changes in the Behavior Pattern of Female Capuchin Monkeys After Chronic Administration of Hormonal Contraceptives

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Abstract

The benefits of hormonal contraceptives are undeniable; however, these drugs are also related to numerous adverse and side effects, especially physiological parameters. Although there are several reports of changes in behavioral patterns, there are controversies about the impact of hormonal contraceptives on these aspects. Therefore, this issue needs to be investigated how changes in users' behavior affect their self-esteem and quality of life. Furthermore, there is a need for studies that relate the effect of contraceptives on the expression of behaviors, as few animal models seek to elucidate these effects. In this sense, this study aimed to evaluate the behavioral aspects of female monkeys after the administration of hormonal contraceptives. For this, six adult female monkeys were used. This study received five administrations of kelp acetophenide and estradiol enanthate, a combined hormonal contraceptive substance. The females received a dose of 0.10ml every 21 days, i.e., once every menstrual cycle. Behavioral aspects were monitored daily before, during, and after the administration of the hormonal contraceptive. In addition, the frequency of sexual behavior and the duration of non-sexual behavior were observed. For this purpose, each female was observed for 20 minutes continuously for five cycles, all experiment phases. Thus, it was observed that administrations of the algal acetophenone and estradiol enanthate composition promoted a decline in the frequency of sexual behavior in female capuchin monkeys. Finally, it is necessary to report that in addition to the adverse effects on the behavior of users, contraceptives bring collection effects to physiological aspects, which can be severe. Thus, it is necessary to have wide dissemination of these adverse and side effects because women need to know about such physiological and behavioral impairments, which can be severe for their health.

Keywords: Behaviour; Monkeys; Contraceptive Hormone; Sexual

Introduction

Since its discovery, it has been estimated that more than 100 million women worldwide [1,2]. Hormonal contraception includes

a set of methods that allow planning, space, and avoiding pregnancy, modulating fertility to the reproductive expectations of the family [3]. Such techniques consist of synthetic female hormones,

which can be combined. There is the presence of estrogen and progesterone; or not combined, just progesterone [4]. Both compositions are secure, such as contraceptive effects, but the combined ones are more related to side effects and undesirable [5,6].

Estrogen-containing compositions have been known to increase the risk of thrombosis due to changes in blood coagulation factors [5-7], weight changes, and, consequently, the development of cardiovascular diseases [7,8]. Additionally, they promote increased anxiety and behavioral changes [9]. Many women report irritation and mood swings when they use hormonal contraceptives [10]. Furthermore, about libido or sexual behavior, users report a reduction in sexual desire during the use of these drugs [11,12].

The effects of hormonal contraception on users' sexual behavior are controversial because female sexuality can be influenced by biological, psychological, social, and culture [13]. However, a significant proportion of users report lower satisfaction and sexual desire after using contraceptives [10-12]. Furthermore, it is known that contraceptives have anovulatory action, and one of the main physiological effects is precisely on the hormonal profile. In this sense, there will likely be a commitment to female sexuality that needs to be investigated. Thus, the present study proposal sought to analyze the effects of chronic combined hormonal contraceptive use on behavioral patterns of adult capuchin females.

Capuchin monkey females stand out as animal models in several areas, including studies on physiology [14,15], reproductive strategies [16,17], reproductive systems [18], and morphology of the ovarian cycle [19,20]. The main characteristics for the successful use of the capuchin monkey as an experimental subject are related to the fact that these animals have an inclusive repertoire of sexual behavior, and the menstrual cycle is similar to that of females. In addition, they present other physiological, morphological, and anatomical similarities with the human species [21]. Together, these characteristics justify the choice of this animal model for this study.

Materials and Methods

Subjects and study site

First, even before the beginning of the exception, the present study was submitted to the Ethics Committee on Animal Research (CEUA) of the Medical School of the University of Brasilia (UnB). It was approved according to document 101375/2011 from UnBdoc. All ethical precepts stipulated by CONCEA (National Council for

the Control of Animal Experimentation) were observed. The use of experimental animals is by the Auroca Law (no. 11,794), which regulates animal experimentation in Brazil.

This study used 12 females of capuchin monkeys (*Sapajus libidinosus*), with a mean age of 10 years. At this age, the females are considered reproductive and adult [21]. In addition, six vasectomized adult males with a mean age of ± 16 years participated in the study. However, these males participated only as their companions for the females studied. For experimental purposes, the animals were kept in groups composed of the triad (2 ♀ female and 1 ♂ male).

The animals used in this study were kept at the Primatology Center of the University of Brasilia (CP-UnB), according to the Brazilian Institute of the Environment and Renewable Natural Resources (IBAMA) rules of maintaining animals in captivity. THE CP-UnB is a scientific breeding site (No Registro IBAMA 1/53/1999/000006-2) linked to the Institute of Biological Sciences of UnB, physically located in The Clean Water Farm (16°30' S, 46°30' O) in the administrative region of Vargem Bonita-Distrito Federal (DF) about 30 km from downtown Brasilia. The UnB Farm has 4,340 ha, half of which corresponds to the environmental protection area and integrates an essential ecological corridor in the Federal District. In CP-UnB, the animals are kept in nurseries located in the gallery forest in natural luminosity, temperature, and humidity conditions. Each enclosure has 4m x 2m x 3m (depth, width, and height, respectively). It has an internal division system with a guillotine door that separates the experimental subject from its companions(s) during the practical sessions. Inside the enclosures, there was a nest box, which functions as shelter and protection for animals and ropes and perches for environmental enrichment purposes.

Procedure

Administration of acetofenide algestona and estradiol enanthate

The hormonal contraceptive administered in female capuchin monkeys was combined with algestone acetophenide and estradiol enanthate, which is called a combined hormonal contraceptive. Each ampoule (1ml) contains 150 mg of algestone acetophenide (dihydro-progesterone) and 10 mg of estradiol enanthate in its composition. However, allometric calculations were made for the administration of this hormonal contraceptive based on each female's body weight and mass. These calculations were based on

the study by Pachaly and Brito (2000) [22], which allows the adaptation of this composition in a single dose of 0.10 ml.

Treatment using kelp acetophenone and estradiol enanthate was administered in monkeys after baseline. The contraceptive was issued as a single dose, intramuscularly, and with the aid of a syringe (1ml) with a 30x7 needle. As the study investigates the acute use of the contraceptive combination, each female received only one 01 administration of contraceptive. The veterinarian made all administrations of the CP-UnB.

Behavior observations

Behavioral observations were made throughout all phases of the study. Each female was monitored daily, Monday to Friday, for 20 minutes a day, being one observation in the morning period (9:00 to 12:00) and another in the afternoon (14:00 to 17:00). Thus, the behavioral sampling sessions lasted 10 minutes in the morning and 10 minutes in the afternoon for each of the 12 capuchin monkey females studied.

For behavior analysis, the animal-focal sampling method [23] was used, with two types of continuous (duration) and instantaneous (frequency) records [24]. Thus, endless forms allowed the observation of the period of non-sexual behaviors (scavenging, stereotyping, and agonism) (Table 1). On the other hand, instantaneous recording allowed the monitoring of the frequencies of sexual behaviors (raising eyebrows, looking at each other, tilting head, smiling, massaging breasts, genitals, and armpits, and attempting copulation, copulation, arm and touch, and running) - Table 2, which were noted at a fixed interval of 15 seconds during each 10-minute observation session. It is also worth mentioning that each female was monitored for 37 hours throughout the study. Thus, the study had a total duration of 444 hours of observations.

| Behavior | Descriptions |
|------------|---|
| Grooming | Pick up hair or parasites in another animal |
| Stereotype | Meaningless behaviors, of course |
| Agonistic | Fights or threats between individuals |

Table 1: Descriptions of the categories of non-sexual behaviors observed in nail monkey females of the Primatology-UnB Center.

| Sexual Behaviors | Descriptions |
|-------------------|---|
| Raise eyebrows | Move your eyebrows up and down |
| Mutual look | Female faces male or both look at each other |
| Tilt the head | The head is laterally tilted relative to the vertical plane |
| Smile | Move your lips in a smile shape for the fellow |
| Manipulate breast | One arm is extended until the breast becomes apparent, and with the hand of the other arm, it is massaged or manipulated. |
| Masturbation | The intimate region of the female is manipulated with her hand in the form of masturbation |
| Copulation | Accept the male mount and allows copulation |

Table 2: Descriptions of the categories of sexual behaviors observed in females of capuchin monkeys of the Center for Primatology-UnB.

The behavioral expressions observed and presented by the females (Table 1 and Table 2) were described according to the studies by Fragaszy, *et al.* (2004). Note that the behavior analysis was performed by two experimenters per period, who were responsible for conducting the observations. First, a reliability test was carried out among observers to obtain at least 90% reliability. Initially, a baseline of the animals' behavior was obtained to verify the reliability of the data, which was calculated according to the specific methodology documented in the literature [24]. Then, the animal behavior was recorded using the Etholog computer program (2.25) made available free of charge by the University of São Paulo- USP.

Data analysis

Data on non-sexual behaviors were analyzed on average (\pm EPM) of the time at hours presented for each female monitored. The means are presented according to the percentage of time spent for each behavioral category. Sexual behavior was analyzed according to the sum of the frequency of all expressions presented by each female of these behaviors.

Statistically, the behavioral data of the baseline and contraceptive hormone phases were analyzed and behavioral. The data were

statistically analyzed using the IBM software® Statistical Package for Social Sciences (SPSS) version 23 by applying the procedures. The means were considered significantly different when we obtained $p \leq 0.05$ values. It is worth mentioning that the results are presented at the time of hormonal contraceptive administrations, which represent 05 administrations.

Results and Discussion

In the graphs of Figure 01, the expressions of sexual and non-sexual behavior of capuchin monkey females in the two experimental phases in phase 0 (represents the baseline phase) and phases 1st, 2nd, 3rd, 4th, and 5th (hormonal contraceptive administrations) are illustrated. As shown in Figure 01-A, a change in the frequency of sexual behavior of capuchin monkey females during baseline phases and hormonal contraceptive administrations was observed ($F_{5, 64} = 1,67; p = 0,05$). It can be observed that there were no changes in the non-sexual behavior of grooming ($F_{1,67} = 1,08 p = 0,30$) figure 01-B; stereotyping ($F_{1,67} = 2,85 p = 0,09$) figure 01-C. However, for the agonistic behavior, an increase in the duration of this behavior was observed when the monkeys were being treated by the hormonal contraceptive ($F_{4,67} = 4,27 p = 0,05$) during contraceptive administrations, figure 1A-D.

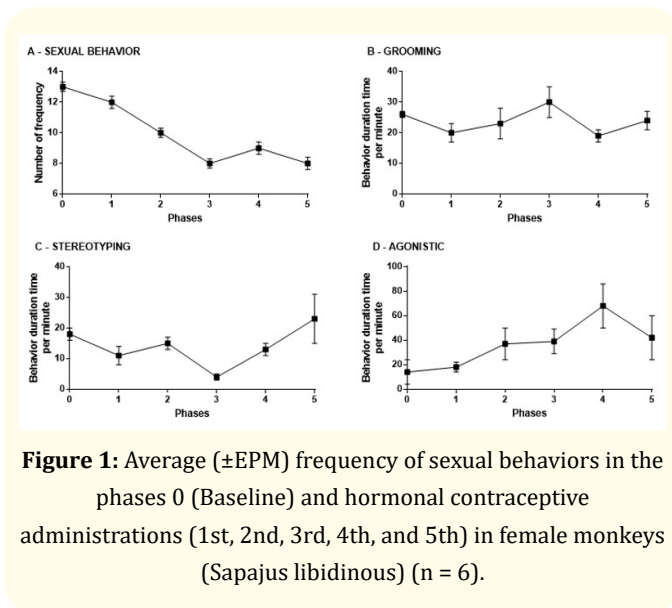
Administrations of algestone acetophenide and estradiol enan-

thate composition promoted a decline in the frequency of sexual behaviors in capuchin monkey females. No alterations were observed in the non-sexual behavior of grooming and stereotypes of the macacas. However, it is possible to keep that the agonistic behavior increased the phases in which they received hormonal contraceptives.

Studies have pointed out that the use of hormonal contraceptives affects women’s behavior [10-12]. About sexual conduct, a significant portion of users reports lower satisfaction and sexual desire after using hormonal contraceptives [11,12]. Anovulatory action depends precisely on the hormonal profile, so hormonal contraceptive users usually have androgen deficiency, especially testosterone [12]. Libido in women is associated with androgens, especially testosterone. In this sense, there is an impact on sexuality due to decreased testosterone concentration [12,13]. There is evidence that low circulating concentrations of testosterone determine significant changes in female sexual function and, currently, sexual desire, with orgasm and even with the amount of sexual intercourse the individual maintains [25].

It is essential to highlight that the effects of hormonal contraception on the sexual behavior of users are controversial since female sexuality can be influenced by numerous factors, already mentioned in the introduction of this study [13]. Although, several studies indicate that behavioral patterns are directly affected using hormonal contraceptives [26-28]. Thus, the present study infers that the dose administered of algestone acetophenide and estradiol enanthate promoted actions on the behavior of overalls, like those reported by women, which may be due to the reduced testosterone concentrations observed in users of hormonal contraceptives [12].

It is also important to mention that the composition of algestone acetophenide and estradiol enanthate is widely commercialized in Brazil. Women choose intramuscular use of this drug because it has a low commercial cost, safe from conception, and easy access. Although it is a contraceptive that has a positive effect on contraception, this drug can bring numerous side effects, presented in the package leaflet, for example, headache, upper abdominal pain, breast discomfort, and irregular menstruation considered more standard. There are also fewer common effects: weight fluctuation, dizziness, nausea, vomiting, amenorrhea, dysmenorrhoea, hypomenorrhoea, and behavior change.



Because of the mentioned, it is essential to highlight that the contraceptive composition used in the present study brings alterations in behavioral patterns. The package leaflet of this drug is not indicated which behavior is affected, but it is described that there are changes in social behavior, as there are reports of nervousness. In the present study results, it was possible to observe an increase in the duration of agonistic behaviors in the treatment phase with hormonal contraceptives. Thus, reinforcing the thesis that hormonal contraceptives promote change in the behavioral pattern of females.

The agonistic behaviors presented by the overalls are like the stress patterns offered by the women. Many users of hormonal contraceptives report irritation after the use of hormonal contraceptives. Changes in behavioral patterns related to well-being, such as increased anxiety, stress, and mood swings, are common side effects in hormonal contraceptive users [29]. It is noteworthy that changes in mood, anxiety, and stress are also due to the increase in cortisol in users [30,31].

It is impossible to monitor monkeys' mood, sadness, anxiety, and increased satisfaction or sexual desire behaviors. However, the expressions of sexual and non-sexual behaviors of capuchin monkey females were analyzed to evaluate possible behavioral pattern changes. We hypothesized that contraceptive administrations would cause changes in the behavioral parameters of these females. The results showed that the dose administered in capuchin monkeys affected the pattern of sexual behavior. Thus, it is reasonable to consider those hormonal contraceptives and the report of women affect regions of the emotion of these females.

It is possible to observe that hormonal contraceptives are directly correlated with several side effects, which promote changes in users' behavioral profiles and affect several physiological parameters, which deserve to be highlighted in this text. In this sense, it is possible to mention that combined hormonal contraceptives can aggravate well-known risk factors such as hypertension, diabetes, hyperlipidemias, and obesity. In particular, some progestogens are known to decrease high-density lipoproteins (HDL) and cause glucose intolerance, while estrogens can create a state of hyperinsulinemia. Additionally, some progestogens may raise LDL levels and make hyperlipidemia control more difficult. In addition, hyperlipidemias are a known cardiovascular risk factor [32]. Another

severe factor reported by scientific studies is changes in factors related to blood coagulation have also been observed in contraceptive users [14,15,33-35].

It is well established in the literature that there is an increased risk of thromboembolic and thrombotic diseases associated with the use of combined hormonal contraceptives [33,34]. In addition, these results are corroborated in monkeys submitted to treatment with contraceptives [14,15]. Therefore, it is essential to warn users about the relative risk of venous thrombosis under predisposing conditions, as this risk is even higher than women without such medical conditions [33-39].

Conclusion

From the present study, it was possible to consider that:

- Administration of hormonal contraceptives in monkeys promoted changes in behavioral patterns because the results pointed to a reduction in the frequency of sexual behaviors and an increase in the expression of agonistic behaviors.
- There is a need for further studies to evaluate, in animal models, the effects of hormonal contraceptives on behavioral aspects, as there are controversies on this subject in the literature, although many users report these changes.
- It is also necessary that adverse effects be widely disseminated to women because many of them are not yet well understood about the severe risks of hormonal contraceptives in physiological aspects, which go beyond behavior disorders.

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Conflict of Interest

The authors of this study state that there are no conflicts of financial and interests. The interest is the scientific dissemination of the results of this research.

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