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RESEARCH ARTICLE

A Survey of Bonobo (*Pan paniscus*) Oral Contraceptive Pill Use in North American Zoos

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Contraception is an essential tool in reproductive management of captive species. The Association of Zoos and Aquariums (AZA) Reproductive Management Center (RMC) gathers data on contraception use and provides recommendations. Although apes have been given oral contraceptive pills (OCPs) for at least 30 years, there have been no published reports with basic information on why the pill is administered, formulations and brands used, and effects on physiology and behavior. Here, we report survey results characterizing OCP use in bonobos (*Pan paniscus*) housed in North American zoos, as well as information accumulated in the RMC's Contraception Database. Of 26 females treated, there have been no failures and nine reversals. The most commonly administered OCP formulation in bonobos contained ethinyl estradiol (EE) 35 μg/norethindrone 1 mg. Few females on combined oral contraceptives (COCs) were given a continuous active pill regimen; a hormone-free interval of at least 5 days was allowed in most. Crushing the pill and mixing with juice or food was common. Females on COCs seldom experienced breakthrough estrus or bleeding, while these conditions were sometimes observed for females on continuous COCs. All females on COCs exhibited some degree of perineal swelling, with a mean score of 3 or 3+ most commonly reported. Behavioral changes included less sexual behavior, dominant females becoming subordinate, and a negative effect on mood. No appreciable change in weight was noted. Taken together, these results indicate that OCPs are an effective and reversible contraceptive option for bonobos that can be used by zoos and sanctuaries to limit reproduction. Zoo Biol. 35:444–453, 2016. © 2016 Wiley Periodicals, Inc.

Keywords: bonobo; contraception; birth control pills

INTRODUCTION

Careful reproductive management is critical for sustainable captive animal populations. In North America, the Association of Zoo and Aquariums (AZA) Species Survival Plans (SSPs) are responsible for selecting breeding pairs that satisfy genetic and demographic goals for each managed population. Because only a subset of individuals is recommended to breed each year, contraception may be used in the remainder until they are needed for breeding. For over 25 years, the AZA Reproductive Management Center's (RMC) Contraception Program has served the AZA community by providing information on the safety, efficacy, and reversibility of contraceptives. The RMC plays an essential role in captive reproductive management by providing up-to-date recommendations for each of the diverse mammalian taxa in AZA institutions, to assist zoo personnel in selecting the most appropriate product.

In great apes, the most commonly used form of contraception is the combined oral contraceptive (COC) pill marketed for humans [Porton and DeMatteo, 2005; RMC Contraception Database]. COCs are comprised of synthetic forms of estrogen and progesterone in varying doses that inhibit pituitary gonadotropins, which subsequently suppresses follicular growth and ovulation. In contrast to COCs, progestin-only pills (POPs) contain no

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estrogen. Some consider these safer, because of concerns about estrogen-related side effects, but they are also somewhat less effective than COCs [Zapata et al., 2013]. However, POPs are the best choice for lactating mothers [McCann and Potter, 1994; Faculty of Sexual and Reproductive Healthcare, 2008].

According to the RMC Contraception Database (RMC DB), the first reported use of a COC in a captive ape, a chimpanzee (*Pan troglodytes*), was in 1984. The RMC has since amassed over 1,000 records for lesser and great apes treated with oral contraceptive pills (OCPs; i.e., COCs and POPs), including gibbons (*Hylobates lar*, *Hylobates moloch*, *Nomascus gabriellae*, *Nomascus leucogenys*) siamangs (*Symphalagus syndactylus*), chimpanzees, gorillas (*Gorilla gorilla*), orangutans (*Pongo pygmaeus*), and bonobos (*Pan paniscus*).

Although, a wealth of data exists on OCP use in women, few studies have reported on OCP use in captive apes. Goodrowe et al. [1992] demonstrated effectiveness of Demulen® 50 (a COC) in suppressing ovarian cycling in female lowland gorillas, as well as resumption of cycling upon termination. The effects of OCPs on sexual behavior have been described in chimpanzees [Nadler et al., 1993] and gorillas [Sarfaty et al., 2012]. Nadler et al. [1992] also explored the relationship between sexual swellings and increasing doses of estrogen in chimpanzees. They found that anogenital swelling levels were steady throughout the cycle rather than exhibiting a cyclical pattern. Furthermore, swelling scores increased as estrogen doses increased from 50 to 100 to 400 μg. These results suggest that swelling was the direct effect of the synthetic estrogen on perineal tissue and highlighted the importance of estrogen to progestin ratio in modulating sexual swellings in chimpanzees [Nadler et al., 1992]. Bettinger [1994] specifically investigated estrogen dose in COCs, as well as administration of placebo pills, on sexual swelling in chimpanzees. Females given placebo pills exhibited more days of swelling and higher-score swellings than females on a continuous regimen. There were differences among females receiving the same formulation, yet pills with 20 μg of estrogen were associated with more swelling days than those with 50 μg. Although, this appears to contradict the outcome reported by Nadler et al. [1992], the results in the Bettinger study may be an indirect effect of the synthetic estrogen dose. That is, lower exogenous estrogen may be less effective at suppressing follicle growth and thus be associated with production of more endogenous estrogen.

Yet despite the prevalence of OCP use in captive great apes, basic information about why institutions are using contraception, formulations or brands chosen, and how the pills are administered is lacking in the published literature, as are data pertaining to effects on behavior and physiology in orangutans and bonobos. Zoos must contend with a myriad of challenges that do not exist in the human world, such as whether using hormonal contraception will disrupt troop stability, whether it will affect introductions to new individuals, whether females will come into estrus, and whether perineal swellings will be suppressed. Furthermore, efficacy is predicated on compliance, so those administering pills must ensure the animal does not regurgitate or hide its medication.

To begin addressing the knowledge gap of OCP use in great apes, the RMC approached the Bonobo SSP to request their participation in development of an OCP survey to gather data on these basic types of information. The SSP bonobo population was founded in 1966 and consists of 86 individuals (35 males and 51 females) housed at seven AZA institutions and one institution in Japan [Reinartz, 2014]. The primary aim of this study was to characterize OCP use in captive bonobos housed in AZA institutions using a survey asking why OCPs were used, length of placebo interval if any, and effects on physiology (e.g., sexual swellings) and behavior (e.g., sexual behavior and aggression). Results will be used by the RMC and Bonobo SSP to generate guidelines for the population and by sanctuaries that are in need of effective reproductive management tools.

MATERIALS AND METHODS

In May 2013, the institutional representative (IR) from each of the seven AZA institutions housing bonobos was asked to complete a survey about OCP use. The survey, administered online using Survey Monkey® (http://www.surveymonkey.com), was developed by the RMC with input from the SSP Coordinator and key advisors, including the Veterinary and Reproduction Advisors. Responses, collected between May 2013 and February 2014, were exported from Survey Monkey into MS Excel (2014).

Survey questions were divided among four sections: Administration, Physiological Response, Behavior, and Other. The pill Administration section inquired about brand and formulation used, whether and how frequently placebo pills were administered, and whether institutions experienced problems with regurgitation or refusal to ingest pills and how they handled those challenges. The second set of questions addressing physiological responses to the pill asked whether females experienced breakthrough signs of estrus or bleeding, as well as sexual swelling, and which week of the pill pack those events were most commonly observed. We also asked whether there were changes in sexual interest from the male. The Behavior section included questions about aggression and hierarchy shifts. The behavior questions relied on the respondents' intimate knowledge of the animals and did not include a formal data collection protocol. The set of questions for other gathered basic information on weight changes and contraceptive failures.

During survey development, it became clear that OCPs were not always administered to bonobos in the traditional cyclic pattern used by women (i.e., 21 days of active pills followed by 7 days of placebo pills). Instead, some institutions administered 28–35 active days of pills before

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the hormone-free interval to more closely mimic the natural average cycle length of bonobos, with inter-menstrual intervals reported to be, on average, 34 [Vervaecke et al., 1999] or 35 days [Paoli et al., 2006]. We also wanted to consider institutions that gave COCs continuously without a hormone-free interval. Thus, sections two and three (Physiological Responses and Behavior) were further subdivided to ask about females given <28 days of active pills (<28 DAP), those given 28–35 days of active pills (25–35 DAP), and those given >35 days of active pills (>35 DAP). Historic data regarding contraceptive use were drawn from the RMC's DB.

RESULTS

All seven of the AZA accredited bonobo holding facilities completed at least part of the survey, reporting on 23 females. The survey was completed three times for two females at the same institution, each survey representing a different pill formulation. Thus, survey data were at least partially submitted for 27 contraceptive bouts.

Pill Administration

A summary of pill formulations used by proportion of females treated is presented in Table 1. Oral contraceptives have been administered at some time at all seven bonobo holding institutions. The most commonly reported reason for using contraception included pregnancy prevention (51.7%), followed by space constraints (24.1%), medical reason (10.3%), other (10.3%), and because the female lacks maternal skills (3.4%). Oral contraceptive pills were the most commonly used product; 78.6% of females were being administered the pill at the time of the survey with 21.4% of females using a different type of contraceptive that was not specified.

According to the surveys and the RMC DB, 12 brands of OCPs have been used in captive bonobos in the U.S. When combining survey results and historic RMC DB, the most commonly administered pill formulation has been ethinyl estradiol (EE) 35 μg/norethindrone 1 mg. Other formulations reported in the survey included mestranol 50 μg/norethindrone 1 mg (22.2%), EE 35 μg/norethindrone 0.50/0.75/1 mg (7.4%), EE 30 μg/drospirenone 3 mg (7.4%), EE 20 μg/norethindrone 1 mg (3.7%), and 20/10 μg EE/desogestrel 0.15 mg (3.7%) (Table 1). The RMC DB contains information about two females treated with POPs (norethindrone 0.35 mg), whereas no females in the survey were reported to be given POPs.

All females (100%) reported in the survey were administered COCs as opposed to POPs. Three were given a continuous regimen of COCs; additionally, some institutions did not administer placebo pills, but still allowed for a hormone-free interval in which no pills were given. Regarding number of consecutive active pills, nearly equal proportions of females were given <28 DAP and 28–35 DAP and the three females were given >35 DAP (Table 2).

Each institution was asked if females refused to ingest and/or regurgitated the pill. The majority of females never or infrequently refused their pills. The most common method to ensure compliance was offering pills in a food or drink that is rarely refused, with juice being the most popular delivery

TABLE 1. Summary of oral contraceptive formulations used in captive bonobos in North American zoos

Pill name	Progestin	Dose (mg)	Estrogen	Dose (μg)	Number of individuals (survey)	Percentage of females (survey)	Number of individuals (RMC DB)	Percentage of females (RMC DB)
Apri	Desogestrel	0.15	Ethinyl estradiol	30	1	3.7	3	10.7
Camila	Norethindrone	0.35	None	0	0	0	1	3.6
Junel 1/20	Norethindrone	1	Ethinyl estradiol	20	2	7.4	0	0.0
Loestrin 21	Norethindrone	1.5	Ethinyl estradiol	30	0	0	2	7.1
Microgestin 1/20	Norethindrone	1.0	Ethinyl estradiol	20	1	3.7	0	0
Mircette	Desogestrel	0.15	Ethinyl estradiol	20/10	0	0	1	3.6
Necon 1/35	Norethindrone	1.0	Ethinyl estradiol	35	7	25.9	7	25.0
Necon 1/50	Norethindrone	1.0	Mestranol	50	6	22.2	5	17.9
Norethindrone	Norethindrone	0.35	None	0	0	0	1	3.6
Nortrel 1/35	Norethindrone	1.0	Ethinyl estradiol	35	6	22.2	3	10.7
Ortho-Novum 7/7/7	Norethindrone	0.5/0.75/1.0	Ethinyl estradiol	35	2	7.4	3	10.7
Yasmin	Drospirenone	3.0	Ethinyl estradiol	30	2	7.4	2	7.1

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TABLE 2. Survey outcomes pertaining to pill administration

Question	Responses given	Number of individuals	Proportion of individuals (%)
Regarding Placebo Pills			
If using COCs, how do you give the oral contraceptive pills?	Full pack, with placebos	9	40.1
	Always skip placebos	9	40.1
	Occasionally give placebos	0	0
	Use brand with 3-month regimen	4	18.2
How many consecutive days of placebo pills do you administer?	N/A	3	11.1
	7 days with no active or placebo pills given	1	3.7
	Seven	16	59.3
	5 days with no active or placebo pills given	7	25.9
How many days of active pills do you administer?	<28	12	44.4
	28–35	11	40.7
	>35	3	11.1
Regarding Ingestion			
Do you hide the pill in a food item?	Yes	13	68.4
	No	6	31.6
Do you hide the pill in juice?	Yes	19	100
	No	0	0
If you hide the pill in food, do you crush it first?	Yes	13	100
	No	0	0
If you hide the pill in juice, do you crush it first?	Yes	10	55.6
	No	8	44.4
Does your female refuse to ingest and/or spit out the pill?	Yes, but infrequently	8	38.1
	Yes, frequently	1	4.8
	No, never observed	12	57.1

medium. However, pills were more likely to be crushed before being hidden in food than in juice (Table 2).

Physiological Response

Survey respondents were asked whether they ever observed breakthrough bleeding or estrus while a female was on OCPs. The majority of females administered <28 and 28–35 DAP never experienced breakthrough bleeding or estrus, but these conditions were sometimes observed in all females given >35 DAP (Fig. 1). Sexual swelling was commonly observed across the three categories of DAP. Furthermore, no females were reported to have a complete absence of sexual swellings for any of the three categories of active pill administration (Fig. 2a). In addition to frequency of sexual swelling, respondents were asked about the maximum swelling grade typically observed, with options of 0, 1, 2, 3, 3+, and N/A. At least a Grade 1 swelling was reported for all females, with a grade of 3+ being the most commonly observed (Fig. 2b).

There were 14 responses to the open-ended question of mean number of days the female typically remained at

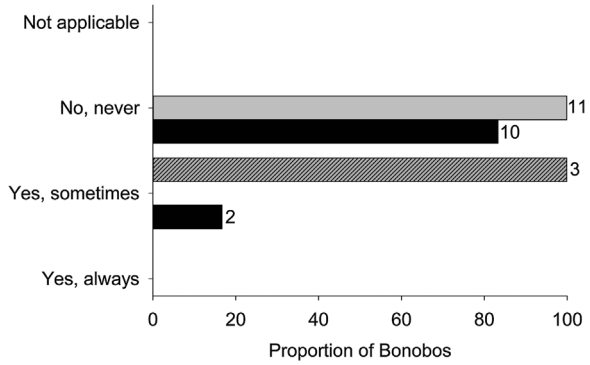

Fig. 1. Proportion of female bonobos that experienced breakthrough bleeding or estrus while on contraception for females administered <28, 28–35, and >35 days of active pills. Numbers to the right of the bars indicate the number of females represented in each response category. Solid bars represent females given <28 days of active pills, gray bars females given 28–35 days of active pills, and hatched bars females given >35 days of active pills.

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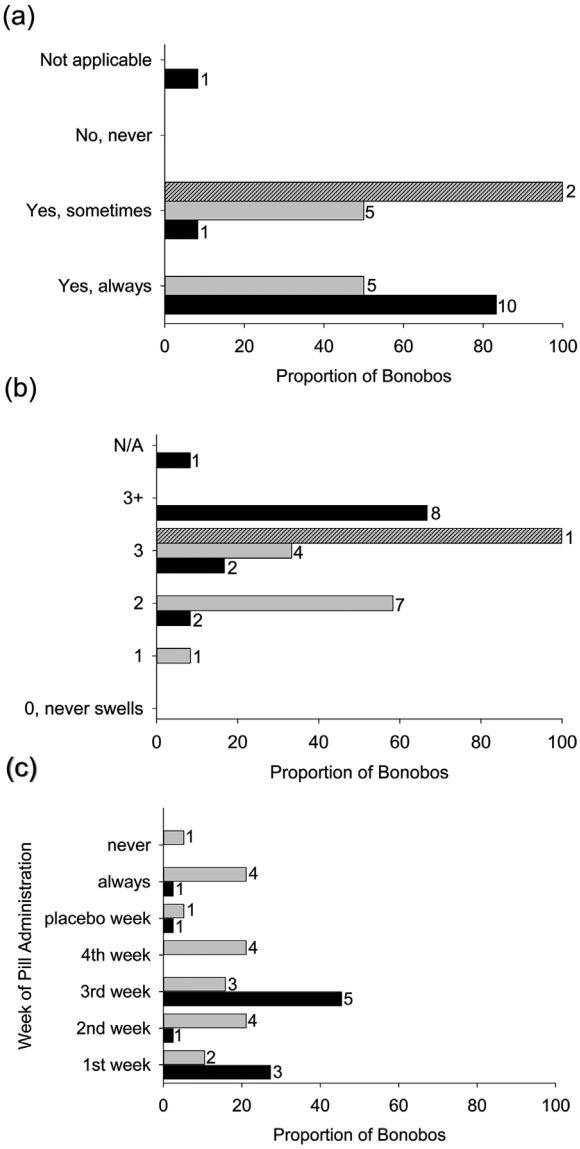

Fig. 2. Proportion of female bonobos administered <28, 28–35, and >35 days of active pills that **(a)** experienced sexual swellings while on contraception, and **(b)** typically experienced each of the grades of sexual swellings. **(c)** Week during pill pack that female bonobos typically exhibit maximum swelling for females administered <28 and 28–35 days of active pills. Numbers to the right of the bars indicate the number of females represented in each response category. For **a**–**c**, solid bars represent females given <28 days of active pills, gray bars females given 28–35 days of active pills, and hatched bars females given >35 days of active pills.

maximum swelling. Seven females remained at maximum for 2 days (50%), and one female each (7.1%) at 7, 5, and 4 days, respectively. For one female (7.1%), the mean number of days varied, associated with dominance changes. Finally, three females (21.4%) exhibited constant sexual swellings at a Grade 2.

For females given <28 DAP and 28–35 DAP, respondents were asked at which week of pill administration maximum swelling was typically observed. In both categories, maximum swelling was rarely noted during the placebo week and more commonly seen in other weeks, especially during week 3 for females given <28 DAP and during weeks 2, 4, and always for females given 28–35 DAP (Fig. 2c). Because >35 DAP administration is essentially continuous, the week of maximum swelling could not be assessed.

Behavior

Changes in sexual interest, aggression, and hierarchy were surveyed, based on the observations of the respondent. There were no instances in which males solicited females on OCPs more often for any of the three categories of DAP, with less sexual interest and no change in interest more commonly observed (Fig. 3). Institutions were asked if sexual interest or copulation was observed during a particular week of pill administration and were allowed to check all that applied to each female. For females receiving <28 DAP, sexual interest

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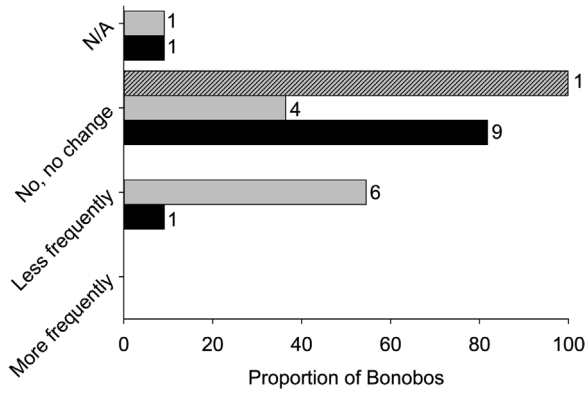

Fig. 3. Summary of changes in male interest and solicitation for female bonobos administered <28, 28–35, and >35 days of active pills. Numbers to the right of the bars indicate the number of females represented in each response category. Solid bars represent females given <28 days of active pills, gray bars females given 28–35 days of active pills, and hatched bars females given >35 days of active pills.

or copulation was always observed in 61.5% of females, and never observed in 7.7%. The responses of week 1, week 2, week 3, placebo week, and never were each marked once (7.7%, respectively). For females given 28–35 DAP, no sexual interest or copulation was noted for 22.2% of females, but those behaviors were always observed in an equal proportion of females (22.2%). Sexual behaviors or copulation were observed during every week of pill administration, including week 1 (11.1%), week 2 (16.7%), week 3 (16.7%), week 4 (5.6%), and the placebo week (95.6%). Because pill administration was ongoing for females receiving >35 DAP, data about timing of sexual interest were not collected.

The overwhelming majority of females did not demonstrate any change in aggression (95.5%) while on OCPs, and an increase in aggression was observed in only one (4.5%). In 50% of females, no behavioral change was observed, and no change except less mating was noted for 42.9% of females. One female was described as appearing more "grouchy" while on Yasmin (7.1%).

The final behavioral question concerned whether changes in hierarchy occurred for females on OCPs. Most females (86.4%) did not shift positions, no females that were submissive became more dominant, no middle-rank females became more dominant, and no middle-rank females became more submissive. The remaining females (13.7%) had been dominant and dropped in rank.

Other

Weight changes (average 1.8%, SE = 0.02%) were reported for seven females treated with COCs, five of which experienced slight increases and the other two slight decreases.

Historic RMC Data

No failures and nine reversals have been reported to the RMC DB for 28 contraceptive bouts for 18 bonobos treated with 12 different types of OCPs (Table 1) at 6 U.S. institutions. Reversals have occurred after treatment with Necon 1/50 ($n = 1$), Loestrin 1/20 ($n = 1$), Ortho–Novum 1/35 ($n = 1$), Nortrel 1/35 ($n = 3$), and Necon 1/35 ($n = 3$). One 16-year-old female given Nortrel 1/35 had a stillbirth prior to a live birth the following year. Another female had two stillbirths around age 28 and a thyroid abnormality in the 9 years between discontinuation of COCs and having a live birth. The average time from discontinuation to parturition date was 2.84 years ($n = 9$, SE = 0.82). However, records of number of females given a breeding recommendation or allowed to reverse are incomplete, so a reversal rate cannot be calculated. One adverse event, a large uterine fibroid, was found at necropsy in a 62-year-old treated with COCs for 12 years up until her death, although its association with contraceptive treatment was not established.

DISCUSSION

Pill Administration

Survey results, along with historic RMC DB records, indicate that OCPs are an effective method of contraception for bonobos, with no failures reported to date. Although preventing pregnancy was the most common reason for treating females with OCPs, results suggest that OCPs can be used for secondary reasons that also fall under the pregnancy prevention umbrella, such as allowing a young female to mature and space constraints, but also for medical reasons. In two cases, OCPs were used to reduce the number of seizures in females with suspected catamenial epilepsy [Gerlach et al., 2011]; the medical reason was unspecified in the third female.

Twelve different brands of OCPs used in captive bonobos in the U.S. have been recorded in the RMC DB and reported in the survey. The most commonly administered progestin was norethindrone, with desogestrel and drospirenone also used. Norethindrone and desogestrel are first- and third-generation synthetic progestins, respectively. Drospirenone, a spirolactone derivative, in the newest class generation [Sitruk-Ware, 2006], has strong antimineralocorticoid

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properties, which is desirable for some women because it prevents water rentention and may even lead to weight loss [Oelkers, 2004; Sitruk-Ware, 2006; Schindler et al., 2008; Burkman et al., 2011]. There is conflicting evidence about whether COCs containing drospirenone (e.g., Yasmin®) are associated with an increased risk of venous thromboembolism (VTE), a potentially life-threatening condition. While several studies and reviews have demonstrated an increased risk for users of COCs containing drospirenone compared to those containing older-generation progestins [Gronich et al., 2011; Jick and Hernandez, 2011; Parkin et al., 2011; Sidney et al., 2013; Wu et al., 2013], others have found no difference or non-significant relative risks [Suissa et al., 2000; Lidegaard et al., 2002; Dinger et al., 2007, 2014]. In 2012, the American College of Obstetricians and Gynecologists (ACOG) concluded that the risk of taking COCs containing drospirenone is low and that age and history of deep vein thrombosis should be evaluated on a case-by-case basis by the clinician. Furthermore, they asserted that COCs containing drospirenone should remain available to patients [American College of Obstetricans and Gynecologists, 2012]. With little information available for great apes, the RMC advises caution when selecting a COC containing drospirenone for bonobos. Unless there are specific medical reasons that call for a COC with antimineralocorticoid properties, the RMC recommends the use of COCs that contain alternative synthetic progestins.

Only two bonobos in the survey and three in the RMC DB were treated with the triphasic pill formulation, introduced in the 1980s as a strategy to decrease possible adverse effects of monophasic formulations. The changing concentrations of estrogen and progestin in triphasic pills are designed to mirror hormone fluctuations during the natural cycle [Van Vliet et al., 2011]. A recent comprehensive review comparing efficacy and menstrual bleeding patterns of monophasic and triphasic pills found insufficient evidence to favor triphasic over monophasic pills [Van Vliet et al., 2011]. The RMC agrees with the conclusions of this review and recommends that the first choice of COC for bonobos should be a monophasic pill, but if a female has been given a triphasic pill in the past with no problems, it may be appropriate for her.

Three females were given a continuous regimen of active pills without a hormone-free interval. Historically, women adhered to a 28-day schedule that included 21 days of active pills followed by 7 days of hormone-free placebo pills to mimic the natural human female cycle. However, in the 2000s, extended- or continuous-use regimens were introduced to minimize side effects related to menstruation, reduce or eliminate withdrawal bleeding, increase compliance, and improve ovarian suppression [Legro et al., 2008; Burkman et al., 2011; Christin-Maitre, 2013]. Extended- or continuous-use has been found comparable to traditional, cyclic regimens in safety and efficacy [Anderson and Hait, 2003; Kwiecien et al., 2003; Legro et al., 2008] and patient satisfaction [Coffee et al., 2007]. An extended COC regimen may be considered for additional captive bonobos, especially in females that experience undesirable behaviors such as increased aggression or physiological problems such as excessive sexual swellings during the hormone-free interval.

For both humans and captive apes, OCP efficacy depends on compliance. For women, the challenge is primarily remembering to take the pill everyday; whereas, apes may refuse their daily medication or regurgitate it later when their keeper is out of sight. To overcome this unique challenge, caretakers frequently crush pills and hide them in a favorite treat or in juice, so the full dose is ingested. In our survey, only one female frequently refused to ingest her pill, with 38.1% of females infrequently refusing, and no problems with ingestion reported for the remainder. Both juice and food are popular delivery methods, with nearly all females given their pill in juice. However, just over half of respondents reported crushing the pill before mixing it with juice, while 100% crushed it before mixing with food, although the pill likely dissolves in juice without crushing. Although there are no known data from the human literature on effects of crushing on efficacy, the method has clearly been effective in bonobos. Therefore, the RMC endorses the continued practice of crushing or dissolving the pill and hiding it in food or juice.

Nearly, all bonobos have been given COCs containing EE rather than mestranol. These results are not surprising since most past and current COCs contain EE, with fewer containing mestranol, estradiol valerate, or 17ß-estradiol [Gerstman et al., 1991a; Stanczyk et al., 2013]. The dose of the estrogen component has been more closely scrutinized than the estrogen derivative itself. When COCs were first introduced in the 1960s, the majority contained 50 μg of estrogen, but that trend had reversed by 1988 [Gerstman et al., 1991a]. An ideal estrogen dose is the lowest that balances side effects but consistently maintains cycle control [Gallo et al., 2013]. High doses (>50 μg) of estrogen are associated with increased cardiovascular risks such as VTE [Vessey et al., 1986; Gerstman et al., 1991b]; whereas, very low doses (<20 μg) carry a lower risk of cardiovascular effects, but are associated with a higher frequency of bleeding irregularities [reviewed in Gallo et al., 2013]. Overall, effectiveness is comparable between COCs containing <20 μg or >20 μg [Gallo et al., 2013].

Only two females have been reported to be given POPs. POPs are considered a safe contraceptive option for the majority of women and are recommended over COCs for women who are nursing [McCann and Potter, 1994; Faculty of Sexual and Reproductive Healthcare, 2008]. However, the SSP typically allows previously successful bonobos to reproduce again once their offspring is weaned, which would explain why POPs are seldom used in this population. If the SSP decides to use POPs more frequently in lactating mothers in the future, the RMC follows the guidelines of ACOG who recommends starting POPs as early as 2–3 weeks after parturition. Although the World Health Organization [2008] recommends women wait 6 weeks, starting earlier may be appropriate for bonobos since abstinence cannot be enforced. Bonobos may experience

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lactational amenorrhea but because it is unknown when their fertility typically returns, POPs can be used as a back-up measure to prevent pregnancy during lactation.

Physiological Response

Bonobos have been given pills containing no estrogen (POPs) and up to 50 μg estrogen, with the majority receiving 30–35 μg. Based on the human literature, COCs containing 20–50 μg of estrogen would be suitable for bonobos, but the effects of estrogen dose on sexual swellings should be considered. In chimpanzees, COCs containing 20 μg of estrogen resulted in higher-grade and more frequent swellings than 50 μg [Bettinger, 1994]. Sexual contact outside the context of reproduction, and female–female genito–genital (GG) contact in particular, are believed to serve a number of important functions in bonobo society, including alleviating tension, promoting cohesion among troops, enhancing social integration during immigration, and reconciliation [DeWaal, 1987; Thompson-Handler, 1990; Hohmann and Fruth, 2000; Clay and de Waal, 2014]. Eliminating or reducing swellings could potentially disrupt troop harmony or alter stable hierarchical relationships.

Bonobos experience prolonged periods of maximum tumescence compared to chimpanzees [Savage-Rumbaugh and Wilkerson, 1978; Dahl, 1986; Furuichi, 1987; Paoli et al., 2006] which can account for an average of 31.2% of the menstrual cycle [Reichert et al., 2002]. A protracted period of maximum tumescence suggests swelling may not be a reliable signal of imminent ovulation and fertility and so may serve another purpose. In fact, one study found that ovulation did not even occur during the time of maximum tumescence for 30% of cycles monitored [Reichert et al., 2002]. Putting swellings in the context of social interactions, several studies have found significantly higher frequencies of GG rubbing between females with maximum swellings [Hohmann and Fruth, 2000; Paoli et al., 2006; Ryu et al., 2014]. Thus, in matriarchal bonobo society, an extended period of maximum tumescence may be an adaptation that serves the dual purpose of strengthening female–female affiliative bonds in addition to attracting males. While it may be desirable that COCs reduce or eliminate sexual swellings in some primate species to minimize aggression in captivity, female bonobos may need to be allowed to exhibit some period of maximum tumescence to promote social cohesion.

No studies have yet assessed the relationship between COC estrogen dose and perineal swelling in bonobos, but in this survey, all females had at least some degree of sexual swelling for all of the three categories of days of active pill administration. Unlike a previous report on chimpanzees [Bettinger, 1994], no relationship between estrogen dose and degree of swelling could be identified in this survey. Maximum grade swellings of 3+ were reported for the six females administered COCs containing 50 μg of estrogen and for the one female given pills with 20 μg. Interestingly, these seven females were all housed at the same institution. Maximum swelling grades were primarily two or three for females on intermediate estrogen doses of 30 or 35 μg. Swelling grade was only reported for one female given >35 DAP, so the relationship between continuous pill administration and swelling could not be assessed. No clear pattern emerged for the week of maximum swelling for females that were allowed a hormone-free interval. While some respondents pinpointed a particular week, others reported that maximum swellings were always observed. Surprisingly, only two females were reported to swell during the placebo week, which is when we would predict the most swelling to occur due to the withdrawal of ovarian suppressing hormones. Thus, institutions holding bonobos should be prepared for sexual swellings to occur at any point during the pill pack. Although lack of predictability might be a problem when managing more aggressive species, swellings promote social cohesion in bonobos and so regular and even unpredictable swelling may be desirable in this species. Although our dataset is small and swelling grading can be subjective and so vary by institution, these anecdotal reports suggest that additional factors (e.g., social) may influence degree and timing of tumescence, regardless of estrogen dose or inclusion of a hormone-free interval.

The other main physiological question asked in the survey was whether females experienced breakthrough estrus and bleeding while on COCs. The majority of females administered <28 and 28–35 DAP never experienced breakthrough estrus or bleeding. Responses for three females on >35 DAP indicated they sometimes experienced breakthrough. Women on a continuous COC regimen were found to have significantly fewer light and moderate bleeding days compared to women on a cyclical regimen, but both groups experienced comparable total number of days of bleeding [Kwiecien et al., 2003; Legro et al., 2008]. These results suggest that women on a continuous regimen may have unpredictable episodic spotting while bleeding in women on cyclical COCs primarily, though not exclusively, occurs during the hormone-free interval. Female bonobos on continuous COCs may thus experience some breakthrough bleeding, but it is expected to be light and to decrease over time.

Behavior

Although, direct behavioral observations were not part of the survey, we asked whether changes in behavior occurred while females were on OCPs. Only one female was reported to behave more aggressively, during 1 month of Yasmin treatment, an overall negative mood change that resolved when switched to Nortrel 1/35. No increase in aggression given or received was reported for any of the other formulations. These results are consistent with a study on cynomolgus macaques (*Macaca fascicularis*) which found no effect of COC treatment on aggression rates by dominant females toward subordinates [Shively et al., 1990]. However, that study also found that females given Ovral®

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(EE 50 μg/norgestrel 0.5 mg) spent less time in passive body contact, a measure of affiliative behavior, than controls or females given Demulen® (EE 50 μg/ethynoidiol diacetate 1.0 mg).

In contrast, a later study on cynomolgus monkeys found females treated with Triphasil® (levonorgestrel and ethinyl estradiol tablets) were more likely to receive contact aggression, but that those females also spent more time in close proximity to conspecifics [Henderson and Shively, 2004]. Because monophasic formulations have been shown to be more effective mood stabilizers compared to triphasic pills [Oinonen and Mazmanian, 2002], it would be interesting to replicate the study using monophasic COCs. Two bonobos in the survey were administered a triphasic pill, but no changes in behavior other than less sexual behavior were reported, although one of the females that was dominant dropped in rank. Considering results for all females, either no change or no change except for less sexual behavior was observed, with the exception of the one female on Yasmin that had a mood change. Finally, no change in troop hierarchy was reported for nearly all females except for three dominant females that became subordinate. Taken together, the results from the behavioral questions indicated that few significant behavioral changes occurred. Although, these anecdotal reports are encouraging for management, future research should focus on systematically evaluating effects of OCPs on behavior of captive bonobos.

Other and Historic RMC Data

Although, the body weight dataset was small and could not be analyzed statistically, there was very little weight change in females given COCs. These results are consistent with studies of women [Moore et al., 1995; Berenson and Rahman, 2009], even with long-term COC use [Lindh et al., 2011].

No contraceptive failures were reported for bonobos given OCPs, reported either through the survey or to the RMC DB. Reversal data are limited due to the nature of captive management; not all treated females are later given the opportunity to breed. Reversibility was documented in nine females that gave birth 2.84 years, on average, after the pill was discontinued. Three of the females that reversed were transferred for breeding (one to Europe), so average reversal time may have been extended due to delayed mate access. Additionally, one female gave birth 9 years after discontinuing COCs, finally conceiving after being weaned off thyroid medication. In women, fertility rates of OCP users lagged behind those not using hormonal contraception by several months after discontinuation, but fertility rates were comparable by 1 year among groups [Barnhart and Schreiber, 2009]. We do not have comparable data on fertility rates for non-contracepted bonobos for a comparison, but these results demonstrate that OCPs can be reversible in bonobos.

CONCLUSIONS

1 OCPs are an effective and reversible form of contraception for captive bonobos.
2 Female bonobos continue to have sexual swellings on COCs regardless of estrogen dose and breakthrough bleeding and estrus are rare.
3 Few behavioral changes were reported for female bonobos on OCPs, but because survey results were anecdotal, further research is warranted.
4 Female bonobos starting on COCs for the first time should be administered a monophasic pill that does not contain drospirenone and that contains an estrogen dose of 20–35 μg.

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