BIRTH CONTROL OPTIONS

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INTRODUCTION

One goal of the Orangutan Species Survival Plan (SSP©) is to maintain 90% of the original genetic diversity of the wild born populations. These genetic goals need to be met within the constraints of limited housing. Yearly breeding recommendations take both factors into account typically resulting in more individuals recommended not to breed than to breed.

For the animal manager that needs to prevent reproduction three basic options are available: 1. separation of the sexes, 2. reversible contraception, 3. permanent sterilization. Selection of the most appropriate method of birth control should be based on the following factors: the efficacy and safety of the birth control method in orangutans and/or related species, the medical history of the individual animal, behavioral considerations, management/logistic factors, and the reproductive future of the individual.

If the manager selects a reversible contraceptive, it should be understood that use of these methods in exotic species is in most part still experimental. Consider that years of research are devoted to the development of a contraceptive method for humans yet even after distribution, research is continued via retrospective studies. Development of contraceptive methods for the exotic mammals we manage in zoos is based on previous research with the product, the reproductive physiology of the species, the results of its use in related species (where applicable), and retrospective analysis of its use in that species.

In regards to selecting an effective and safe birth control method for orangutans, humans represent an excellent model. Four of the reversible contraceptive methods used in orangutans are used in humans (birth control pills, Norplant, Depo-Provera, and vas plug). Retrospective analysis of the use of all reversible methods of contraception in zoo mammals is ongoing through the American Zoo and Aquarium Association (AZA) Contraception Database. Much of the information in this report is based on data from the Contraception Database.

METHODS OF CONTRACEPTION

Contraceptive methods can be permanent or reversible and male or female directed.

PERMANENT CONTRACEPTION

Vasectomy

A chemical or surgical vasectomy offers permanent sterilization of a male without the loss of steroidogenesis. Normal male behavior, including breeding behavior, is not affected by a vasectomy. A vasectomized male should be prevented access to a reproductive female for at least 30 days after the procedure. When carried out by an experienced and skilled surgeon, the procedure can be reversed in humans. To date, this has not been tried in orangutans.

Castration

Castration is a surgical procedure which removes the testicles and consequently the production of testosterone. The resulting effect on the behavior of the male will be partially dependent on the age at which the male is castrated. Further research on the relationship between the age of castration and the subsequent behavior of the male is needed.

Tubal Ligation

This surgical procedure ties the female's fallopian tubes, thereby preventing pregnancy but not the production of the sex steroids. The female orangutan will continue to exhibit normal menstrual cycles and concomitant sexual behavior.

Hysterectomy

A hysterectomy is the surgical removal of the uterus without the removal of the ovaries. Thus the female orangutan will not menstruate but should continue to exhibit normal sexual behavior.

Ovariohysterectomy

This surgical procedure removes the uterus and the source of female sex steroids, the ovaries. The female will not menstruate, and may discontinue exhibiting some or all components of sexual behavior. Again, further research on the relationship between the age of ovariohysterectomy and subsequent manifestation of sexual behavior is needed.

Information on Surgical Procedures

The Veterinary Advisor to the Orangutan SSP©, should be contacted for appropriate protocols for all the above surgical procedures. The ease with which any of the surgeries can be carried out will, in part, be based on the physical condition of the individual animal. Any institution considering permanent sterilization is requested to contact the Orangutan SSP©

Veterinary Advisor for updated information regarding the procedure in this species.

REVERSIBLE CONTRACEPTION - MALE DIRECTED

To date, there are no reversible contraceptive methods available to male non-human primates. Several male directed methods are involved in research trials and are not currently available for general use. Some of the methods are described below for informational purposes.

Vas Plug
A small silicone plug injected directly into both vas deferens. This method is used in human males and has been tested in a number of non-human primates. Successful insertion of the plug has been greater in large versus small primates. Several chimpanzees and one orangutan have received vas plugs. To date the method has not been reversible in non-human primates.

Bisdiamine
A chemosterilant that inhibits spermatogenesis but not hormone synthesis. This method was shown to be effective in human males, but because of medical complications associated with the interplay of alcohol and bisdiamine, potential commercialization of the product was discontinued. Current research is centered on the use of bisdiamine in male carnivores and may extend to primates in the future. This method requires daily oral treatment.

REVERSIBLE CONTRACEPTION - FEMALE DIRECTED
Essentially all reversible birth control methods now in use are female directed. This section will provide cursory information on several methods involved in research trials and detailed information on methods used in orangutans.

Immunocontraception: Porcine Zona Pellucida Vaccine
Research with the porcine zona pellucida (ZP) vaccine has included non-human primates but data on efficacy, reversibility, and long-term effects are not yet available. To date, the Contraception Advisory Group (CAG) does not recommend this form of contraception in any individual that is needed for future reproduction. This because further research is needed to determine if individuals administered long-term ZP treatment can be reversed.

Melengestrol Acetate (MGA) Implant
Not commercially available, this implant was first developed and distributed by Dr. U.S. Seal. The MGA implant is now produced by the Contraception Advisory Group of AZA. The MGA implant is made of a silicon rod that contains the synthetic progestin melengestrol acetate. The implants are distributed by weight, with MGA comprising 20% of the implant weight, i.e., a 5 gram implant contains 1 gram MGA (Plotka, personal communication).

Institutions ordering the implant are requested to provide information on the female's body weight to allow for more individualized dosing. It is the most commonly used contraceptive in zoo mammals, including orangutans.

Database Sample Size and Duration of MGA Implant Use
Information from the contraception database shows that 116 MGA implants have been distributed to North American zoos for use in orangutans (March 1994 data). The Contrapceptive Advisory Group received follow up data for 71 of the implant bouts. Eight of the 71 implants were reported lost; two of the undetected losses resulted in unplanned pregnancies. Loss of an implant can be due to several causes including the implant being groomed out by a social partner, the development of a localized infection causing implant expulsion, or dehiscing of the incision site.

Several steps can be taken to prevent implant loss. First, the implant should be gas sterilized and allowed to air dry for 7 days prior to insertion. Secondly, a newly implanted female should be separated from social companions for 5 to 7 days to allow the incision site to fully heal. Another suggestion is to insert an ID microchip in the MGA implant. With the current technology, reading distance for microchips is only 8 inches but because many orangutans will come close to their caretakers, scanning the female should be feasible in many cases. This will allow the caretaker to monitor implant presence long after hair has grown over the shaved area. In addition, because implants have been shown to migrate, the value of a microchip is also realized at the time of implant removal.

The duration of MGA implant effectiveness is not known for each species in which it is used, consequently the basic recommendation has been to replace the implants after two years. In an attempt to assess duration of effectiveness, data on implant use in orangutans was analyzed. Duration of use is presented in Table 1, with data divided into two implant status categories. The first category comprises data on MGA implants that have been removed and thus comprise a "completed bout" of implant use. Six implants were left in for longer than the recommended two years and remained effective. Excellent data was provided by the Sacramento Zoo where the staff monitored one female's urine for menses throughout the entire time she was implanted. Daily testing with Hemastix® (See Development, Reproduction and Birth Management Chapter, this volume) documented that the female ceased menstruating for 30 months. Menses resumed at 30.5 months at which time the staff replaced the female's implant.

The second category includes data from 35 implants that were reported still in place or not yet (never) removed. Thirteen of the 35 implants were reported in place for 31 months or longer. This information is potentially misleading because it is based on sketchy historical records which can never be confirmed.

Failures
A failure is strictly defined as a pregnancy that occurs while the birth control method is **known** to be in place at the time of conception. In regards to the MGA implant, if a pregnancy occurs because the implant was lost, or if the female is mistakenly and unknowingly implanted after conception has occurred, it is not defined as a failure of the hormonal treatment. To date, **no** failures have been reported in orangutan females with MGA implants known to be in place.

MGA Implant Use During Pregnancy
One female was unknowingly implanted approximately 40-45 days into her pregnancy. This female did give birth to a live, healthy offspring. Another female, who was nursing an adopted infant, continued to lactate after being contracepted with an MGA implant.

Reversals
Data on reversals is limited because only two females have had their MGA implants removed for the purpose of reproduction. One female, Studbook # 909, had been continually contracepted for 22 months (two different implants). The female was placed with a new male 3 months post implant removal and conceived 4.5 months thereafter. The second female, Studbook # 275, had been implanted for 24.5 months when the implant was removed for reproduction. This female had immediate access to a male and conceived 2.5 months later.

Birth Control Pills
Human birth control pills are available in different formulations, from the progestin only pill to a variety of combined estrogen/progesterone pills. The human regime is 21 days of hormone treatment and 7 days of a placebo, a regimen that allows women to menstruate. The majority of great apes that have been contracepted with birth control pills have followed the same regimen. Birth control pills are the second most frequently used reversible contraceptive method in orangutans.

Database Sample Size and Duration of Use
The database contains information for 15 orangutans contracepted with birth control pills. Seven formulations have been used in orangutans, Table 2 provides data on the brands and duration of use.

Failures
Four pregnancies occurred while females were being contracepted with birth control pills. One pregnancy was traced back to a period of five days when the female refused to shift off display thereby preventing caregivers from treating her. This particular female had been successfully contracepted with Ortho-Novum 1/50 for 16.5 months.

At a different institution, a female conceived after 34.5 months of successful contraception with Ortho-Novum 1/50. At a third institution, two females on Norinyl 1 + 35 conceived after 19 and 26 months treatment. In all three of the latter cases the caretakers reported the females were reliably consuming their pills.

Use of Birth Control Pills During Pregnancy
Because all of the above four females unexpectedly became pregnant, they continued to be treated with birth control pills for a period of time. One female was treated for at least a month, two females throughout half their pregnancy, and the fourth was taken off the pill when the infant was discovered. All infants were liveborn and no complications were reported.

Reversals
No females have been deliberately taken off the pill for the purpose of reproduction.

Norplant
Norplant, developed for use in women, is a contraceptive implant that contains the synthetic progestin, levonorgestrel. The Norplant kit, available through Wyeth, constitutes six slender capsules each containing 36 mg levonorgestrel for a total dose of 216 mg. In humans, Norplant is said to be effective for 5 years. However, informational inserts distributed with Norplant kits indicate that the probability of failure increases in women over 110 lbs (failure rates: < 100 lbs = .2; 110-130 lbs = 3.4; 131-153 lbs = 5.0; > 153 lbs = 8.5).

Database Sample Size and Duration of Use
Information is available for nine female orangutans that were contracepted with Norplant in the 1980's. These implants were obtained through the Population Council and were formulated at 70 mg levonorgestrel per capsule. Each female was implanted with two capsules, totaling 140 mg levonorgestrel. Norplants were electively removed in seven of the nine females. Five of the seven were contracepted for between one to two years, two were successfully contracepted for four years. Of the remaining two females, one conceived after 14 months, however the presence of the Norplant was never confirmed and was most likely lost. The second female conceived after 51 months, indicating that the 140 mg dose, which is 76 mg less that the dose currently recommended for humans, was effective for over four years.

No orangutans have been contracepted with the current commercially available Norplant.

Failures
No confirmed failures have been reported in orangutan females known to be

contracepted with 140 mg Norplant. One female most likely conceived due to implant loss. Unlike the MGA implant, the Norplant is too narrow (and there are too many capsules) to allow microchip insertion. The fact that one female conceived after 51 months is more accurately viewed as providing data on duration of efficacy.

Reversals
Because we do not know the actual duration of efficacy of the 140 mg Norplant, we cannot calculate the time to reversal for the above mentioned female that conceived.

Depo-Provera
Depo-Provera contains the synthetic progestin, medroxyprogesterone acetate in an injectable form. This contraceptive method was recently approved by the Food and Drug Administration (FDA) for use in women. The human dose is 150 mg every 90 days.

Database Sample Size and Duration of Use
Only one orangutan has been contracepted with Depo-Provera. This female was administered the human dose of 150 mg for a total of three treatments (total of 9 months). The female was successfully contracepted.

PRE-PUBERTAL OR JUVENILE CONTRACEPTION

The AZA Contraception Advisory Group has made the basic recommendation that contraceptive steroid treatment should not be initiated in pre-pubertal females due to the paucity of data about pre-pubertal steroid treatment and potential long-term effects on fertility contraindicate steroid contraception before puberty. Because sexual maturity occurs at an earlier age in captivity, the Orangutan SSP© has made the recommendation that all females who reach **5.5 years** and have access to a reproductive male (including housed next to males when separated by wire) **SHOULD** be monitored for cycling. This can be accomplished through daily urine collection and testing with Hemastix® for menstrual blood (See Female Development, Reproduction and Birth Management Chapter, this volume). Once the female initiates menstrual cycling, she should be moved into a non-breeding situation or contracepted. It is important to know that data from North American SSP Orangutan Studbook shows that several males **sired offspring as early as 5.5 years of age**. For this reason, the Orangutan SSP recommends that females housed with or adjacent to males 5.5 years or more of age should be contracepted.

SEXUAL BEHAVIOR OF CONTRACEPTED ORANGUTANS

Nadler (1988) demonstrated that proceptive behavior in female orangutans was hormonally influenced. Laboratory experiments revealed that when males

had full access to females, copulations occurred throughout the cycle. In contrast, when the housing situation was modified so that females could chose to have access to a male (through a creep door), copulations were clustered around the time of ovulation.

An accurate evaluation regarding the influence of reversible contraceptives on the exhibition of sexual behavior in orangutans requires systematic observations. However, some information is available through the Contraception Survey. Caregivers have reported that copulations have been observed in females contracepted with birth control pills and MGA implants (insufficient data available for Norplant and Depo-Provera). Several survey respondents commented that the frequency of sexual activity in MGA implanted females was less than normal. One respondent remarked that sexual behavior was male initiated and that females were not cooperative partners. In contrast, observations of one female contracepted with birth control pills found the female actively solicited her male partner (St. Louis Zoological Park records).

Because male and/or female initiated breeding behavior occurs in contracepted females, copulations cannot be used to confirm whether or not the contraceptive method is in use and effective.

EVALUATION OF SIDE EFFECTS

Assessment of side effects associated with the use of any reversible contraceptive method requires careful documentation before, during, and after contraceptive use. Proper evaluation requires the maintenance of accurate records and, upon the animal's death, a necropsy that thoroughly evaluates the reproductive and other associated systems.

RECORDS AND THE CONTRACEPTION ADVISORY GROUP DATABASE

It is incumbent upon the animal manager to maintain detailed and accurate records on all contracepted animals. Through the AZA Contraception Advisory Group (CAG) data on all mammals contracepted in North American zoos are being maintained in a single database. Compilation of these records into one database will obviously allow more accurate and thorough retrospective analysis of the efficacy, reversibility, and safety of the various contraceptive methods.

The CAG suggests that each institution develop a contraception record-keeping system to allow maintenance of timely and therefore more accurate records. Such records will also facilitate completion of the yearly CAG update surveys distributed in April and due July 1. Systematic records may also have the advantage of alerting the manager to any potential problems with a particular individual (weight gain, behavioral changes, method in use/place,

etc).

Because the information listed below is requested in the contraception survey, the CAG suggests that the institution's records include the following:

1. Individual's ISIS #, studbook #, name, birthdate.
2. If the individual has ever reproduced and date of last offspring (live or stillborn).
3. Type of contraceptive method (brand name if appropriate, dose, if MGA then implant # and wt, etc. and how/where given).
4. Date of initiation.
5. Animal weight; accurate weights of the individual BEFORE and AFTER contraceptive use is very useful data.
6. Dates the contracepted individual has access to a reproductive mate (e.g.: if a female is implanted and introduced to her mate 7 days later, that information should be recorded). If the birth control is ended, record the date the individual has access to a reproductive partner.
7. Date(s) the contraceptive method is ended and reason (ended to allow reproduction, to change to another method, to replace implant, mate died, medical complications, etc.)
8. Date of a birth: if the birth is UNPLANNED it is **very important** to confirm whether the contraceptive method was **in use** at the time of conception and/or parturition (e.g.: was the implant in place or lost, did the female take all her pills, etc.). Record whether the infant was live or stillborn.
9. Note behavioral changes (if any), male or female initiated sexual behavior, dates of copulation, etc.
10. Note physical/physiological effects when applicable (changes in menstrual cycle, blood chemistry, etc.).

PATHOLOGY RESEARCH

Dr. Linda Munson, a pathologist and member of the CAG, is engaged in research aimed at assessing the long-term effects of reversible contraception in carnivores and primates. Dr. Munson's study includes determining whether certain contraceptive methods cause irreversible changes in the uteri of carnivores and primates and if pathological responses vary by species and/or duration of contraceptive exposure. Every institution that houses orangutans can contribute to this important research by remembering to provide samples to Dr. Munson upon the death of a female.

Please note that there is a standing request for the reproductive tract of any female primate, REGARDLESS of the individual's contraceptive history. The reproductive tract should be prepared and sent to Dr. Munson at the address given below.

DIRECTIONS: Reproductive tracts from either necropsies or ovariohysterectomies would be appropriate. The tracts can be fixed in buffered formalin by immersion of the entire tract for 72 hours if a small incision is made into the lumen of the uterus in each horn. The ratio of tissue to formalin should be 1:10. Fixed tracts can then be wrapped in formalin soaked paper towels, enclosed in a leak-proof plastic bag and shipped by US mail (Federal Express is NOT necessary). The package should be sent to:

Dr Linda Munson
Department of Pathobiology
College of Veterinary Medicine
University of Tennessee
PO Box 1071
Knoxville, TN 37901

WEIGHT GAIN

Weight gain is one side effect that may occur with the use of contraceptive steroids. Indeed, because obesity can have serious health consequences, weight gain is an aspect of contraceptive use that should be carefully monitored by the animal manager.

A current area of research is to investigate whether progestin implants lead to excessive weight gain in orangutan females and whether obesity may trigger the onset of diabetes in this species. To address this issue the Orangutan SSP© Veterinary Advisor and CAG are requesting that orangutan females be weighed before, during, and after contraceptive use and all orangutans (males and females) in the SSP© undergo an evaluation for diabetes. Baseline data on the prevalence of diabetes in the orangutan population will allow a more accurate evaluation of the possible relationship between progesterone contraception and diabetes. This research is being carried out by Dr. Joseph Kemnitz, Wisconsin Regional Primate Research Center. A protocol for collecting samples is included in this chapter.

RECOMMENDATIONS

Until further information is available, the CAG's first choice for a reversible contraceptive for orangutans is the MGA implant. This because:

1. No failures have occurred in female orangutans contracepted with an MGA implant known to be in place and reversals have been successful.
2. Determination of whether the contraceptive hormone is being delivered (pill swallowed, implant in place) is problematic for all the above discussed methods. Using a microchip transponder to monitor the presence of an MGA implant and thereby increase early detection of implant loss, appears to be the best solution at this time.

REFERENCES

Nadler, R.D. 1988. Sexual and reproductive behavior, In: J.H. Schwartz, ed. *Orang-utan Biology*, pp.105-116. New York: Oxford Press.

ASSESSMENTS OF GLUCOSE TOLERANCE AND ADIPOSITY IN ORANG UTANS

Background

The glucose tolerance test (GTT) has been a valuable tool for the assessment of glucose regulation and the diagnosis of diabetes mellitus for decades. The basic test entails administration of a defined quantity of glucose to subjects who have been fasted overnight followed by collection of blood samples at regular intervals for measurement of plasma glucose concentrations. In healthy individuals plasma glucose is initially elevated after glucose administration and then declines exponentially. In individuals with impaired glucose tolerance plasma glucose levels may be higher than normal after glucose administration and they remain elevated longer. Diabetics have elevated plasma glucose concentration even before glucose is administered, as well as higher concentrations in subsequent samples.

The glucose given for the GTT may be given intravenously (IV) or orally (O). The IV-GTT has advantages in that the rate of absorption form the gut is not a variable factor, it can easily and safely be performed on anesthetized animals, and it can be performed in less time than the O-GTT.

Insulin is the hormone that is primarily responsible for the clearance of glucose from the blood. In normal individuals insulin is secreted very rapidly after intravenous glucose administration and then circulating levels decline in conjunction with the falling glucose concentration. Impaired glucose tolerance can be associated with delayed insulin secretion, or increased insulin secretion with relative ineffectiveness of insulin to lower glucose, or attenuated insulin response to the glucose challenge. Knowledge of the pattern of insulin secretion is helpful for understanding the basis of abnormal glucose tolerance and for devising appropriate therapy, e.g., reducing food intake or altering the composition of the diet, increasing exercise, or initiation of daily insulin injections.

Methods

The IV-GTTs that have been done on orang utans at the Brookfield Zoo and the Toledo Zoo were conducted according to the following protocol.

1. The animals are food deprived overnight before the test. Make a note of the length of the period of fasting and the time of day that the test is done.
2. Anesthetize with Telezol® administered by a dart gun (we have also used

ketamine alone or ketamine plus diazepam for rhesus monkeys). Please provide information on the agent used and the dose, even if only approximately known.

3. Using aseptic technique, a catheter (e.g., 16 gauge x 2 1/4 inch) is placed in a superficial vein and kept patent with heparinized saline (4U/ml). If possible, it is a good idea to thread a longer catheter into a larger, more central vessel. Make a note of which vein is used and how far the catheter is internalized.

4. A baseline blood sample (3-6 ml) is collected. Blood is distributed into tow tubes, one (1.5-2.0 ml of whole blood) containing glycolytic inhibitor and anticoagulant (NaF and K-oxylate, Vacutainer® #6383, "grey top") for separation of plasma and the other (remaining volume 2-4 ml, Vacutainer SST® "marble top") for separation on serum. The tube specifications given are preferred, but not absolutely necessary. Either plasma or serum is fine, as long as I know how the sample was handled. If no glycolytic inhibitor is used, then it is very important to keep the sample on ice until they are spun. (If fact, it is a good idea to keep all the samples cold, just in case.)

5. Twenty-five grams of glucose (a 50% dextrose solution or more dilute) is injected through the catheter over a period of one minute. The goal is to get plasma glucose concentration up to about 250mg/ml and 25 g of glucose will usually do this in a young adult orang utan. A 50% dextrose solution can injure small peripheral veins because of its hypertonicity, so mixing 50% dextrose with an equal volume of saline if often a good idea, if it is practical. Sterility of the injected solution is, of course, very important.

6. Blood samples (approximately 4-6 ml) are collected as above at 2, 4, 10, 20, 30, 45, and 60 minutes after the glucose injection was begun. If a sample is missed or is drawn late, it is not necessarily a major problem. Just be certain to record the time that all samples are drawn.

7. In conjunction with the IV-GTT, each animal should be weighed and following measurements taken: crown-rump length or crown-heel length; circumference of the abdomen (at the level of the umbilicus) and chest (at the level of the nipples), upper and lower leg; and abdominal skinfold thickness. A simple tape measure is fine for measuring the circumferences. Harpenden calipers, if available, should be used for measuring skinfold thickness. This information is used to determine relative adiposity, an important variable because obesity is an established risk factor for abnormal glucose regulation.

8. When the plasma and/or serum has been separated and transferred to a storage tube, freeze it and keep frozen. Ship on dry ice to:

Dr. Joseph Kemnitz
Wisconsin Regional Primate Research Center
University of Wisconsin-Madison
1223 Capitol Court
Madison, WI 53715-1299

Fed Ex has worked very well for us. Let us know in advance, so that we can be expecting arrival. It is generally better to ship early in the week.

Office phone: 608-263-3588
Lab phone: 608-265-2354
FAX: 608-263-4031 or 608-263-3524

9. We will do the assays. Glucose is measured in plasma by the glucose oxidase method (Yellow Springs Instruments Co.). Insulin is measured in serum by double antibody radioimmunoassay (Binax, Inc.). Date and our interpretation of them will be sent to you as soon as they are available.