MEREDITH S. TART

Fertility Control in Captive White-Tailed Does via GnRH Agonist or Prostaglandin $F_{2?}$

(Under the Direction of ROBERT J. WARREN)

I conducted 2 fertility control experiments to test the efficacy of a gonadotropin releasing hormone (GnRH) agonist as a contraception method, and prostaglandin $F_{2?}$ ($PGF_{2?}$) as a contragestation method, in captive white-tailed deer (*Odocoileus virginianus*) does. My research with 12 mg GnRH agonist found that maximum efficacy was reached in does treated during October with subcutaneous implants, where efficacy was 100% the first year (n=7) and 25% the second year (n=4). Both May implant and October biobullet treatments were 100% effective the first year, but 0% effective the second year. Finally, applying treatments in May did not hinder the does' current pregnancies from being carried full-term. My research with 25 mg $PGF_{2?}$ found that the biobullet treatment was 33% effective in the first mid-gestation (FMG) group (70-88 days of gestation) and 100% effective in the second mid-gestation (SMG) group (89-105 days of gestation).

INDEX WORDS: White-tailed deer, contraception, contragestation, fertility control, GnRH agonist, prostaglandin-F_{2a}

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by

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CHAPTER 1

INTRODUCTION, LITERATURE REVIEW, AND THESIS FORMAT

INTRODUCTION

White-tailed deer (*Odocoileus virginianus)* populations in North America increased remarkably in the latter half of the twentieth century (Warren 1997). High reproductive efficiency and a superior ability to adapt to different environments have enabled white-tailed deer to become overabundant in many urban and suburban areas. Originally, an adequate number of predators and hunting by humans helped keep deer population numbers in check (Warren 1991). The number of natural predators of deer has declined, and hunting by humans cannot be used in some areas. Consequently, for the last two decades deer have increasingly interacted with humans in urban and suburban areas (Warren 2000). This interaction has led to increased damage to lawns and ornamental plants, along with an increasing number of deer-vehicle collisions (Conover 1997).

LITERATURE REVIEW

As with most wildlife, there are positive and negative values associated with white-tailed deer. Positive values represent recreational value to hunters and sightseers, as well as providing food for people and wild carnivores. In 1991, these positive values had an estimated $14 billion in economical value (Conover 1997). Negative values of abundant deer represent property damage and human injuries resulting from deer-vehicle collisions and deer damage to agricultural crops. In 1991, these negative values caused an estimated $1 billion in vehicle damage, $100 million in crop damage, and $750 million in timber damage (Conover 1997). In 1996, white-tailed deer caused more than $250 million damage to metropolitan homes (Conover 1997). Therefore, white-tailed deer have a net positive value of greater than $12 billion per year (Conover 1997).

There tends to be less support from the public for controlling white-tailed deer populations in urban and suburban areas by lethal means than non-lethal means (Messmer et al. 1997). Therefore, administrators, fish and wildlife agency managers, and biologists have recently considered alternative methods to remedy this problem. One population control method, the reintroduction of predators, has no applicability in suburban and urban areas. A method of herd reduction that is frequently suggested by local residents is the live capture and relocation of deer, but this procedure normally results in a high mortality rate (47.9% mortality) due to stress (DeNicola and Swihart 1997, Cromwell et al. 1999). Live capture and relocation also are not economically efficient, and available space for relocation is quickly declining because it is either reaching or at carrying capacity.

Another possible control method is fertility control. This method is currently being researched further and may have potential for controlling deer populations (Warren 2000). Does are the primary target in this method. Treating bucks with fertility control is inefficient because of their polygamous breeding habits. If the bucks in one territory were all treated successfully, reproductively competent bucks from elsewhere would not be prevented from moving into or through the treatment area to breed with the does (Warren 2000).

There are two modes by which fertility control can work: contraception and contragestation (Warren 2000). Contraception prevents conception, either by preventing ovulation or by preventing the sperm and ovum from joining. It involves the use of immunocontraceptive vaccines or synthetic steroid hormones. Immunocontraceptive vaccines must be injected, and annual boosters are required for prolonged infertility

(Warren et al. 1995). In captive white-tailed deer, synthetic steroid hormones were effective when administered orally or via implants (Warren et al. 1995), but in the wild, a nontarget species might be affected inadvertently by their consumption of treated bait.

Contragestation occurs after conception in order to terminate pregnancy. It has been implemented recently in deer through the use of prostaglandin (DeNicola et al. 1997). Contragestation may be considered a lethal or non-lethal means of fertility control, depending on when an individual believes life begins (i.e., whether it is prepartum or postpartum). However, some favor prenatal over postnatal (i.e., adults) lethal removal. Both contraception and contragestation have been successful only when treating deer individually, and most deer have to be retreated annually. The annual retreatment of deer, in some cases, challenges the cost effectiveness of fertility control (Nielson et al. 1997).

GnRH agonist

A new possible contraception method is the use of gonadotrophin releasing hormone (GnRH) agonists. Endogenous GnRH is released from the hypothalamus and, upon reaching the pituitary, stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). GnRH agonists have substituted amino acids within the GnRH molecules to increase the half-life of the agonists and increase their affinity for the GnRH receptor in the pituitary (Karten and Rivier 1986). By remaining in the hypothalamo-hypophyseal portal vessels longer, the GnRH agonists out-compete the endogenous GnRH for pituitary receptors (Karten and Rivier 1986), resulting in a decrease in the production of endogenous GnRH due to negative feedback. Therefore, the normal fluctuations of endogenous GnRH are no longer present, preventing fluctuations of FSH and LH.

In cattle, the acute response to the GnRH agonist, Deslorelin? , is increased FSH and LH secretion (Chenault et al. 1990). The chronic response is reduced gonadotrophin secretion due to the downregulation of the GnRH receptors (Hazum and Conn 1988), which prevents ovulation (Chenault et al. 1990). This was the case with cows and heifers treated subcutaneously with 12 mg of Deslorelin? ; they did not ovulate for at least 15 months (Jochle, W., pers. commun.). Because a white-tailed deer doe weighs approximately 70 kg, whereas a cow weighs about 300 kg, it is possible that does treated with 12 mg Deslorelin? may not ovulate for 2 years or more, thereby eliminating the need for annual retreatments.

$\underline{PGF_{2?}}$

In domestic livestock, prostaglandins are used to synchronize estrus and induce parturition (Lauderdale 1972, Copeland et al. 1978, Kirton and Kimball 1984). Regression of corpora lutea (CL) is caused by prostaglandins that are present in the uterine tissue during late gestation (Kirton and Kimball 1984). Regression of the CL reduces blood progesterone levels in white-tailed deer, aiding parturition or abortion if induced early in pregnancy (Plotka et al. 1977, 1982). Goding (1974) hypothesized that prostaglandin $F_{2?}$ (PG $F_{2?}$) was the major naturally occurring luteolytic factor responsible for CL regression. Studies on red deer (*Cervus elaphus*) (Asher et al. 1995) and livestock (Kirton and Kimball 1984) supported this hypothesis. Three studies on white-tailed deer used prostaglandins as an abortifacient (Becker and Katz 1994, DeNicola et al. 1997, Waddell et al. 2001). Waddell et al. (2001) observed aberrant doe behavior and efficacy of $PGF_{2?}$ when applied during late gestation. Prolonged contractions and partial fetus consumption were among the noted aberrant doe behaviors.

OBJECTIVES

<u>GnRH agonist</u>

The objectives of this study were to determine if a single treatment with a GnRH agonist would be effective in preventing estrus for multiple breeding seasons, and to determine whether subcutaneous or intramuscular administration was more effective in white-tailed deer does. Because 12 mg of Deslorelin? suppressed ovulation in 300 kg cows for at least 15 months (Jochle, W., pers. commun.), I hypothesized that this same dose would suppress ovulation in 70-kg does for at least 15 months. Depending upon the time of application, 15 months may encompass 2 breeding seasons. Because the intramuscular implants would be expected to degrade earlier due to muscle tissue's high transportation rate of blood and other fluids, I hypothesized that the subcutaneous implants would remain effective longer than the intramuscular implants.

<u>$PGF_{2?}$</u>

My objective was to observe behaviors after white-tailed does were treated with $PGF_{2?}$ during mid-gestation (70-105 days). When $PGF_{2?}$ was administered during early gestation (40-59 days) in a previous study, 2 of 8 does aborted but rebred and delivered fawns (Waddell et al. 2001). Administering $PGF_{2?}$ during late gestation (113-154 days) caused 7 of 8 does to abort and none rebred, but consumption of fetuses by does occurred (Waddell et al. 2001). Therefore, I hypothesized that application of $PGF_{2?}$ during mid-gestation would result in a combination of maximum efficiency (i.e., high abortion rates) with minimum rebreeding and no aberrant behavior by does.

FORMAT

This thesis is written according to the manuscript guidelines for the journal *Zoo Biology*. Chapter 1 is a review of population control and fertility control methods utilized in white-tailed deer and other ruminants. Chapter 2, titled "The Effects of a GnRH agonist on Fertility in White-tailed Deer," describes the contraception study. Chapter 3, titled "Efficacy and Behavioral Observations for Does Treated with Prostaglandin $F_{2?}$ During Mid-gestation," describes the contragestation study. Chapter 4 concludes by summarizing these findings and addressing their applications by urban deer managers in suburban/urban environments.

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CHAPTER 2

THE EFFECTS OF A GNRH AGONIST ON FERTILITY IN WHITE-TAILED DEER[1]

[1] Tart, M.S., R.J. Warren, D.A. Osborn, W. Jöchle, and D.J. Kesler. To be submitted to Zoo Biology.

ABSTRACT

White-tailed deer (*Odocoileus virginianus*) have become overabundant in many urban and suburban areas. In some of these areas lethal methods of population control may not be an option. Therefore, recent research has examined the effectiveness of fertility control methods. Previous research with heifers found that the contraception agent, GnRH agonist, suppressed ovulation for at least 15 months. The purpose of this study on white-tailed deer does was to determine if one treatment with a GnRH agonist would be effective in preventing estrus for multiple breeding seasons, and to determine if administration by subcutaneous implant or intramuscular biobullet was more effective. The GnRH agonist, Deslorelin? (12 mg), was administered subcutaneously or intramuscularly in May or October of 1999 to 24 captive adult does, thus forming 4 treatment groups, to determine its effectiveness and length of effectiveness in estrus suppression. October implant treatments were 100% effective the first year and 25% effective the second year. October biobullet and May implant treatments were 100% effective the first year, but 0% effective the second year. May biobullet treatments were not effective in either year. Remote delivery via biobullet in the late summer or early fall may be an effective contraceptive if administered annually.

INTRODUCTION

High reproductive efficiency and a superior ability to adapt to different environments have enabled white-tailed deer (*Odocoileus virginianus)* to become overabundant in many urban and suburban areas. Originally, an adequate number of deer predators and hunting by humans kept deer population numbers in check (Warren 1991).

The number of natural predators of deer has declined and hunting by humans cannot be used in some areas (Warren 1991).

Another possible population control method is fertility control. A new contraception method is the use of gonadotrophin releasing hormone (GnRH) agonists. Endogenous GnRH is released from the hypothalamus and, upon reaching the pituitary, stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). GnRH agonists have substituted amino acids within the GnRH molecules, which increase the half-life of the agonists and increase their affinity for the GnRH receptor in the pituitary (Karten and Rivier 1986). By remaining in the hypothalamo-hypophyseal portal vessels longer, the GnRH agonists out-compete the endogenous GnRH for pituitary receptors (Karten and Rivier 1986). As a result there is a decrease in the production of endogenous GnRH due to negative feedback. Therefore, the normal fluctuations of endogenous GnRH are no longer present, which ultimately prevent the fluctuations of FSH and LH.

In cattle, the acute response to the GnRH agonist, Deslorelin? , is increased FSH and LH secretion (Chenault et al. 1990), but the chronic response is reduced gonadotrophin secretion due to the downregulation of the GnRH receptors (Hazum and Conn 1988). Thus, ovulation is prevented (Chenault et al. 1990). This was the case with cows and heifers treated subcutaneously with 12 mg of Deslorelin? ; they did not ovulate for at least 15 months. The reproductive endocrinology of cattle is similar to that of white-tailed deer (Lincoln 1985). A white-tailed deer doe weighs approximately 70 kg, whereas a cow weighs about 300 kg. It is possible, therefore, that does treated with 12 mg Deslorelin? may not ovulate for 2 years or more, thereby eliminating the need for annual retreatments.

The objectives of this study were to determine if a single treatment with a GnRH agonist would be effective in preventing estrus for multiple breeding seasons, and if subcutaneous or intramuscular administration was more effective in white-tailed deer does. Because 12 mg of Deslorelin? suppressed ovulation in 300 kg cows for at least 15 months, we hypothesized that this same dose would suppress ovulation in 70-kg does for at least 15 months. Depending upon the time of application, 15 months could cover 2 breeding seasons. Furthermore, the intramuscular implants would be anticipated to break down more quickly than subcutaneous implants due to muscle tissue's high transportation rate of blood and other fluids. Therefore, we hypothesized the subcutaneous implants should remain effective longer than the intramuscular implants. Despite potential physiological advantages of subcutaneous implants, intramuscular administration via the biobullets may have more potential for field use. During late summer or early fall because, in the southeastern U.S., deer experience a second nutritional stress period at this time and may be more easily baited to biobullet administration sites (Harlow 1977). Also, biobullets do not require as much time, personnel, and economic investment as do subcutaneous implants and do not produce nearly the stress of capturing and implanting.

MATERIALS AND METHODS

This experiment was conducted at the University of Georgia's Captive Deer Research Facility. This facility provided a controlled environment for application of treatments and monitoring does for estrus. Deslorelin? (12 mg) was administered subcutaneously and intramuscularly to determine its effectiveness and length of effectiveness in suppressing estrus. Unlike in the wild, captive deer offer the opportunity to assess the effectiveness of treatments on individual does for multiple breeding seasons. We handled and treated all deer in compliance with requirements of the University of Georgia's Institutional Animal Care and Use Committee (IACUC# A970193).

Our 2 seasonal groups were the May treatment group and the October treatment group. Does were assigned randomly to either the May or October treatment group. The does in the May 1999 treatment group were pregnant (mid- to late-gestation) from the 1998 breeding season and were administered Deslorelin® during May 1999. The October 1999 treatment group received treatments in early October before breeding so these does were in a state of anestrus and not pregnant. Within each treatment group, does were assigned randomly to either the subcutaneous administration method or the intramuscular administration method. A total of 24 does each individually marked with numbered ear tags, all greater than 1.5 years old, was used. Five does were assigned randomly to each administration method in the May treatment groups, and 7 does were assigned randomly to each administration method in the October treatment groups.

The experiment did not include a control group. Long-term observations at the University of Georgia's Captive Deer Research Facility have documented conception rates greater than 98%. Therefore, we assumed that untreated does would have conceived. Our objective was to determine the difference between the 2 administration methods, not whether an untreated doe would become pregnant or not.

Does designated to receive the subcutaneous administration method were captured and handled in a squeeze chute for placement of implants. This was the only time during the experiment that the does were captured and handled. Does receiving the intramuscular administration method did not require capture and handling because administration occurred via biobullet as described by Jacobsen et al. (1995).

Does in the May treatment group were observed multiple times a day throughout the remainder of pregnancy. Observations were made to document any abnormal behavioral patterns that might have resulted from the treatments. After the October treatment group was treated, the May and October treatment groups were combined in a single outdoor enclosure, and bucks were introduced into the herd (mid-October 1999). This served as the first observed breeding season post treatment. In spring 2000, before fawning began (early May), the does were penned individually to determine individual pregnancy status and fawn production. In fall 2000, the October and May treatment groups were again combined in an enclosure with bucks (mid-October). This was considered the second observed breeding season. In spring 2001, before fawning began (early May), the does were penned individually to determine individual pregnancy status and fawn production. Data were recorded during each fawning period, after each of the 2 breeding seasons. Data recorded for each treatment group included reproductive performance (if they became pregnant or not) of each doe. The data were analyzed utilizing chi-square tests for homogeneity of proportions (Zar 1984).

RESULTS

During the course of our 2-year experiment, 10 does died due to injuries that were unrelated to GnRH treatments, thus our final sample size was 14 does (Table 1). All does (n=10) treated in May 1999 were pregnant when treated, and they all successfully delivered their fawns (Table 1). All does treated in May with biobullets produced fawns

Table 1. Reproductive data for white-tailed does treated with GnRH agonist at University of Georgia Captive Deer Research Facility, May 1999 to August 2001.

		Spring1999		Spring2000		Spring2001	
Treatment Date	Administration Method	No. Deer	No. Pregnant (%)	No. Deer	No. Pregnant (%)	No. Deer	No. Pregnant (%)
May 1999							
	Biobullet[a]	5	5 (100)	5	5 (100)[c]	2	2 (100)
	Implant	5	5 (100)	5	0 (0)[c]	4	4 (100)
October 1999							
	Biobullet	-[b]	-	7	0 (0)	4	4 (100)
	Implant	-	-	7	0 (0)	4	3 (75)

[a] Biobullet is an intramuscular treatment; implant is a subcutaneous treatment.

[b] Does in the October 1999 treatment group were not utilized in Spring 1999.

[c] May biobullet 2000 vs. May implant 2000; $P<0.05$; Chi-square test.

in 2000 (n=5) and 2001 (n=2) (Table 1). In contrast, no does treated in May with implants produced fawns in 2000 (n=5), so 100% efficacy was observed (Table 1). However, all of these does (n=4) subsequently became pregnant and produced fawns in 2001 (Table 1).

Does treated in October did not become pregnant in 2000 regardless of whether they were treated via biobullet (n=7) or implant (n=7) (Table 1). Therefore, 100% efficacy was observed in both groups for the 2000 fawning season. In 2001, all of the October biobullet does (n=4) produced fawns for 0% efficiency compared to 25% efficiency (1 of 4) in the October implant does (Table 1).

DISCUSSION

The May implant, October biobullet, and October implant treatments were 100% effective during the first breeding season after administration. The following breeding season, the May implant and October biobullet treatments were 0% effective. Biobullets may have dispersed Deslorelin® more quickly than subcutaneous implants due to muscle tissue's high transportation rate of blood and other fluids. The May implant had been in the does 4.5 months before the October implants were ever placed, thus probably depleting the hormone sooner. As a result, a 0% efficacy rate was observed in May implant treated does, compared to the 25% efficacy rate displayed by the October implant group during the second breeding season.

Confounding factors were probably minimal because the experiment was conducted in a controlled environment. However, our sample sizes did decrease during the 3-year study due to the loss of does from death unrelated to the treatment. Originally, the sample sizes of 5 (May) and 7 (October) in each combination of treatment groups and administration methods were adequate.

In conclusion, maximum efficacy was achieved in the does treated in October with subcutaneous implants, where efficacy was 100% the first year and 25% the second year. May biobullet treatments were not effective during any years. The May implant and October biobullet treatments were 100% effective the first year, but 0% effective the second year. Finally, applying treatments in May to does in mid- to late-gestation did not hinder the does' pregnancies from being carried full-term.

Although heifers did not ovulate for at least 15 months when given the same treatment that we applied to does, some biological differences must be taken into account. There is a body size difference between heifers (300 kg) and does (70 kg), and a doe's metabolic rate is probably significantly higher than a heifer's metabolic rate (Moen 1973:116-117) due to the behavioral requirements their different habitats place on them in order to survive.

The October biobullet, October implant, and May implant treatments were effective annual contraception fertility control methods. However, applying implants requires more time, personnel, and economic investment and are more stressful to the deer. With respect to implanting deer, it would probably be easier to bait deer in late winter than early fall due to limited food resources. Remotely deliverable biobullets may have potential for being used in the field during late summer (October) because, in the southeastern U.S., deer experience a second nutritional stress period at this time and may be easily baited to administration sites (Harlow 1977). Few other remotely deliverable contraceptives are effective in the fall. Norgestamet administered remotely via biobullets has been shown to be an effective annual contraceptive in deer (Jacobsen et al. 1995). However, Deslorelin? is an amino acid, which is more likely to be approved for use by the FDA than a steroid compound, such as norgestamet.

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CHAPTER 3

EFFICACY AND BEHAVIORAL OBSERVATIONS FOR DOES TREATED WITH PROSTAGLANDIN $F_{2?}$ DURING MID-GESTATION[1]

[1] Tart, M.S., R.J. Warren, D.A. Osborn, and D.J. Kesler. To be submitted to Zoo Biology.

ABSTRACT

White-tailed deer (*Odocoileus virginianus*) have become overabundant in many urban and suburban areas. In some of these areas lethal methods of population control may not be an option. Therefore, recent research has examined the effectiveness of fertility control methods, such as the contragestation agent, prostaglandin-$F_{2?}$ ($PGF_{2?}$). Previous research with deer has shown that $PGF_{2?}$ treatments during early gestation (35 – 65 days) were ineffective. Treatments administered during late gestation (112 – 154 days) were more effective, but many does demonstrated prolonged labor contractions and cannibalized their aborted fetuses. The objectives of our study were to determine the effectiveness of $PGF_{2?}$ in terminating pregnancies during mid-gestation (70 – 105 days) and to observe behavior displayed by does after abortion. We treated 3 pregnant does with placebo biobullets (i.e., controls), and all 3 subsequently fawned. Two of 6 pregnant does treated with biobullets containing 25 mg $PGF_{2?}$ during 70 – 88 days gestation aborted (33% efficacy), but we did not observe prolonged contractions or cannibalism. Three of 3 pregnant does similarly treated during 89 – 105 days gestation aborted (100% efficacy), but 2 of these does cannibalized their fetus. Video monitoring of doe behavior revealed that mid-gestation (70-105 days) treated does displayed visible contractions that were not observed in control does, but these were less pronounced than those observed in does treated during late gestation (112 – 154 days). Thus, mid-gestation treatments with 25 mg $PGF_{2?}$ may provide optimum efficacy while avoiding behavioral complications (i.e., prolonged contractions and cannibalism).

INTRODUCTION

The lack of support by the public for controlling overabundant white-tailed deer (*Odocoileus virginianus)* populations in urban and suburban areas by lethal means (Messmer et al. 1997) has prompted administrators, fish and wildlife agency managers and biologists to turn their efforts towards alternative methods to remedy this problem (Warren 1995, Muller et al. 1997). One possible alternative method is fertility control. There are two modes by which fertility control can work: contraception and contragestation (Warren 2000). Contragestation occurs after conception to terminate pregnancy and has been implemented recently in deer through the use of prostaglandin (DeNicola et al. 1997).

In domestic livestock, prostaglandins are used to synchronize estrus and induce parturition (Lauderdale 1972, Copeland et al. 1978, Kirton and Kimball 1984). Regression of corpora lutea (CL) is caused by prostaglandins that are present in the uterine tissue during late gestation (Kirton and Kimball 1984). Regression of the CL reduces serum progesterone levels, which aids in parturition or abortion if induced early in pregnancy (Plotka et al. 1977, 1982). Prostaglandin $F_{2?}$ ($PGF_{2?}$) was hypothesized (Goding 1974) as the major, naturally occurring luteolytic factor responsible for CL regression in ewes. This hypothesis has been supported by studies of red deer (*Cervus elaphus)* (Asher et al. 1995) and livestock (Kirton and Kimball 1984). Three studies have used prostaglandins as an abortifacient in white-tailed deer (Becker and Katz 1994, DeNicola et al. 1997, Waddell et al. 2001). One of these studies observed fetus expulsion and consumption (Waddell et al. 2001).

The objective of this experiment was to determine the effectiveness of $PGF_{2?}$ in terminating pregnancies during mid-gestation in white-tailed deer. Previous research showed that when $PGF_{2?}$ was administered during early gestation, 2 of 8 does aborted but rebred and delivered fawns (Waddell et al. 2001). Administering $PGF_{2?}$ during late gestation resulted in 7 of 8 does aborting and none rebred, but consumption of fetuses by does did occur (Waddell et al. 2001). We hypothesized that application of $PGF_{2?}$ during mid-gestation would result in a combination of maximum abortion rates with minimum rebreeding and no abnormal behavior by does.

MATERIALS AND METHODS

Study design and treatments

This study was conducted at the University of Georgia's Captive Deer Research Facility. The facility includes a 19-stall barn with several outside enclosures. Deer were watered and fed (16% protein deer food) ad libitum. Starting 1 November 2000, does were checked daily for estrus by a capable breeding buck. The buck was allowed to breed the does, and dates of estrus were recorded. We handled and treated all deer in compliance with requirements of the University of Georgia's Institutional Animal Care and Use Committee (IACUC# A970193).

Does at this research facility average about 200 days gestation (unpublished data). Therefore, mid-gestation was defined as 70-105 days. According to the doe's date of estrus, each doe was placed in either the first, mid-gestation (FMG) treatment group (treated at 70-88 days of gestation) or the second, mid-gestation (SMG) treatment group (treated at 89-105 days of gestation). Each treatment group contained 6 does treated with 25 mg of $PGF_{2?}$. Five control does also were present in the study and treated with a placebo biobullet. Treatments were administered via biobullet (DeNicola et al.1996) at a range of 5-6 m.

Video and real-time monitoring

Does were stalled individually for 10 days after treatment. Each stall contained a Panasonic? (Panasonic? Broadcast and Digital Systems Company, One Panasonic? Way, Secaucus, New Jersey) surveillance video camera (WV-BP310), linked to a Panasonic? sequential switcher (WJ-SQ208), time-lapse recorder (AG-RT600P) and color video monitor (CT-1386YWD). Does were video-monitored using a cycle of 100 total seconds for the control group and 120 total seconds for the FMG and SMG, allowing 20 seconds per doe in a continuous loop. During each of the 10 days of video-monitoring, does were individually transferred to a narrow runway for inspection of any signs of abortion. Each stall also was checked daily for any sign of an abortion.

Pregnancy verification

We physically restrained each doe and collected blood by jugular venipuncture at 50-68 days post-breeding for the FMG and 47-63 days post-breeding for the SMG. Blood samples were centrifuged for 5 minutes at 900?g. Duplicate sera samples were collected and frozen at -20?C until shipped for analysis by ovine-pregnancy-associated glycoprotein (oPAG) and progesterone radioimmunoassays. We considered does with oPAG and progesterone blood concentrations of >1.0 ng/ml to be pregnant (Plotka et al. 1977, Osborn et al. 1996).

Treatment efficacy

Once the 10-day observational time of each treatment group was completed, the does were released into a pen with competent breeding bucks for possible rebreeding.

From May until June, does were placed individually in stalls to observe fawning activity for determining treatment efficacy. Does were placed back into stalls, individually, from September through November to determine if they fawned, which would indicate rebreeding after treatment.

Behavior

In each video-monitoring cycle of 100 total seconds for the control group and 120 total seconds for the FMG and SMG, each doe was recorded continuously for 20 seconds. During the 10 days of video-monitoring, does were individually monitored for specific pre-parturition and parturition-like behaviors (Townsend and Bailey 1975). These behaviors were pacing (P), frequent licking of lips (L), ears lowered parallel to facial plane (E), tail elevation (T), licking genital and mammary surfaces (G), increase in urination and defecation frequencies (U), visible contraction (C), restless bedding (B), smelling aborted tissue (S), and licking/consuming aborted tissue (A). When these behaviors were observed, the different behaviors and number of times the behavior occurred were recorded and expressed as number of occurrences per 24-hour day. We only analyzed behavioral data observed on days 1, 3, 4, 5, 6, and 7 of the video-monitoring period. Day 1 was observed to note any immediate behavioral changes as a result of treatment with the biobullet (placebo and treated). We anticipated seeing abnormal behavior on day 4 and 5 based on observations by Waddell et. al. (2001). From that starting point, we observed previous or subsequent days if doe behaviors were observed.

Aborted fetuses were left in the stalls for several hours to record the does' behaviors toward them. Aborted fetuses were measured and unusual characteristics were noted. Fetuses were then placed in bags, labeled, and frozen. Ages of fetuses were determined based on length and weight (Hamilton et al. 1985).

Statistical analyses

Data on treatment efficiency were analyzed statistically using a Chi-square test and two-by-two contingency table (Dowdy and Wearden 1991). We compared FMG to SMG and the control group, and we compared SMG to the control group. If FMG and SMG were not significantly different, they were pooled and compared to the control group.

We used ANOVA (SAS 1990) to test for differences in frequency of expression of each behavior among the control, FMG, and SMG groups by each day. We tested data for homogeneity of variances. If necessary, data were transformed using square-root transformation prior to conducting statistical analyses. If a difference was detected, then the ANOVA was followed by a Tukey's test. When there were no significant differences ($P > 0.05$) between groups, we pooled that day's data and conducted a t-test in SAS to compare all treated does to the control does. Significance was accepted at P ? 0.05. Transformed data were untransformed prior to calculating means and standard errors for the results.

RESULTS

Pregnancy verification

Blood-based pregnancy tests or dates of fawning confirmed that 3 SMG does were pregnant when treated with $PGF_{2?}$ and 3 were not pregnant (Table 1). Only pregnant does were included in our analyses (i.e., adjusted n=3). Blood-based pregnancy tests or dates of fawning confirmed that 3 control does were pregnant when treated with

Table 1. Reproductive data for captive white-tailed deer does treated with $PGF_{2?}$ at University of Georgia Captive Deer Research Facility, fall 2000 to summer 2001.

Group[a]	No. deer	No. pregnant	No. fawned (%)
FMG	6	6	4 (67)
SMG[b]	6	3	0 (0)
Control[b]	5	3	3 (100)

[a] FMG = First mid-gestation; SMG = Second mid-gestation

[b] SMG vs. Control; $P<0.05$; Chi-square test.

$PGF_{2?}$ and 2 were not pregnant; therefore, the adjusted n=3. Pregnancy at the time of treatment was verified for all 6 FMG does.

Treatment efficacy

All pregnant control does (n=3) fawned (Table 1). In the FMG, 4 of 6 pregnant does fawned (Table 1). No does fawned in the SMG group (Table 1). FMG did not differ ($P > 0.05$) from SMG, but SMG did differ ($P < 0.05$) from control (Table 1). Pooling FMG and SMG produced a mean of 56% efficacy, and did not differ statistically from the control group.

Behavior

Responses observed from application of treatments via biobullets varied. Most does flinched or jumped slightly. Two does stumbled and fell after being shot with the biobullet. However, 1 doe did not flinch or hold her hind leg up after application.

Behaviors involving restless bedding, smelling aborted tissue, and licking/consuming aborted tissue were observed infrequently. On Day 3, the SMG does displayed a mean of 8 instances/day ($\pm$ 8.0 SE) of smelling aborted tissue and 8 instances/day ($\pm$ 8.0) of licking/consuming aborted tissue. On Day 5, treated groups displayed a mean of 0.1 instances/day ($\pm$ 0.1) of restless bedding, 2.7 instances/day ($\pm$ 2.7) of smelling aborted tissue, and 2.3 instances/day ($\pm$ 2.3) of licking/consuming aborted tissue. Two partially consumed aborted fetuses were found during daily stall inspections of 2 SMG does.

Within each day of observation, no significant differences were observed among groups in the occurrence of behaviors of pacing or frequent licking of lips during all days of observation (Table 2). During Day 1, does in the SMG group displayed the behavior of ears lowered parallel to the facial plane significantly less frequently (*P* = 0.0317) than does in the control or FMG (Table 2). Also, during Day 1, behaviors of tail elevation (*P* = 0.0368) and licking genital and mammary surfaces (*P* = 0.0238) were observed significantly more frequently in the control group than the SMG group (Table 3). During Day 3, does in the SMG group displayed the behaviors of ears lowered parallel to the facial plane (*P* = 0.0041; Table 2) and visible contractions (*P* = 0.0258; Table 3) significantly more often than does in the control or FMG groups. Also, does in the SMG group displayed the behaviors of tail elevation (*P* = 0.0454) and licking genital and mammary surfaces (*P* = 0.0171) significantly more than does in the control group (Table 3). In Day 4, does in the SMG group displayed the behavior of ears lowered parallel to the facial plane significantly less often (*P* = 0.0482) than does in the control group (Table 2). In Day 6, does in the control group displayed the behavior of ears lowered parallel to the facial plane significantly more frequently (*P* = 0.0120) than does in the treatment groups (Table 2).

DISCUSSION

Treatment efficacy

The $PGF_{2?}$ treatment was 33% effective in FMG does and 100% effective in SMG does. The FMG does were treated at 10 to 12 weeks of gestation, whereas the SMG does were treated at 13 to 15 weeks of gestation. However, it is unlikely that a few weeks' difference would cause such a range in treatment efficacy. The efficacy of FMG was determined from a sample size of 6 pregnant does, whereas the efficacy of SMG was determined from a sample size of 3. Efficacy was determined by considering only does that were pregnant. Therefore, 100% efficacy from a sample size of 3 may not be as

Table 2. Pacing (P), lip licking (L), and paralled ear orientation (E) behaviors (number of occurrences per 24 hours) for pregnant white-tailed does treated with PGF_{2a} or placebo biobullets at University of Georgia Captive Deer Research Facility, February to April 2001.

			Behavior[a]					
			P		L		E	
Day	Group[b]	n	$\bar{X}$	SE	$\bar{X}$	SE	$\bar{X}$	SE
1	Control	3	0	0	0	0	53.0 A[c]	31.8
	FMG	6	6.8	3.1	0.3	0.2	25.7 AB	6.6
	SMG	3	0	0	0	0	0.3 B	0.3
3	Control	3	0	0	0	0	0 B	0
	FMG	6	0.8	0.4	0	0	0.3 B	0.2
	SMG	3	0	0	0	0	29.7A	14.8
4	Control	3	79.7	66.5	0	0	111.3A	42.6
	FMG	6	7.7	2.4	0	0	64.8AB	17.0
	SMG	3	1.0	1.0	0	0	9.7 B	6.9
5	Control	3	69.0	53.2	0	0	72.3	18.2
	Treated	9	8.7	5.2	0.6	0.6	53.8	12.1
6	Control	3	16.3	11.7	0	0	79.7A	44.8
	Treated	9	9.9	3.7	0.1	0.1	6.4B	3.4
7	Control	3	4.3	4.3	0	0	0	0
	Treated	9	5.9	1.7	0	0	5.7	5.4

[a] P = pacing; L = frequent licking of lips; E = ears lowered parallel to facial plane.

[b] FMG = first mid-gestation; SMG = second mid-gestation; Control videotaped from 23 February 2001 to 4 March 2001; FMG videotaped from 8 February 2001 to 17 February 2001; SMG videotaped from 26 March 2001 to 4 April 2001.

Table 2, continued.

[c] For each behavior, group means followed by dissimilar letters are significantly different ($P < 0.05$; Tukey's Test for comparisons of control, FMG, and SMG, or t-test for control vs. treated).

Table 3. Elevated tail (T), genital licking (G), urinating frequency (U), and visible contraction (C) behaviors (number of occurrences per 24 hours) for pregnant white-tailed does treated with PGF_{2a} or placebo biobullets at University of Georgia Captive Deer Research Facility, February to April 2001.

			Behavior[a]							
			T		G		U		C	
Day	Group[b]	n	$\overline{X}$	SE	$\overline{X}$	SE	$\overline{X}$	SE	$\overline{X}$	SE
1	Control	3	5.0 A[c]	1.7	4.0 A	0.6	0.3	0.3	0	0
	FMG	6	1.5AB	0.6	1.7AB	0.7	1.0	0.6	0	0
	SMG	3	0.5 B	0.3	0.2 B	0.2	0.3	0.2	0	0
3	Control	3	1.7 B	0.7	0 B	0	1.3	0.3	0 B	0
	FMG	6	4.8AB	2.5	1.2 AB	0.4	3.0	1.9	0 B	0
	SMG	3	16.7A	7.2	5.0 A	2.5	1.3	0.3	1.0 A	0.6
4	Control	3	13.0	1.5	6.0	1.5	4.0	0.6	0	0
	FMG	6	13.7	3.1	6.7	2.0	13.3	10.8	0	0
	SMG	3	13.0	5.1	5.7	2.6	2.3	0.3	0	0
5	Control	3	10.3	4.4	6.7	3.8	1.7	0.3	0	0
	Treated	9	28.0	12.5	13.7	3.6	5.4	3.6	4.2	3.7
6	Control	3	12.3	4.2	10.0	5.1	2.0	0.6	0	0
	Treated	9	19.4	6.9	8.4	2.7	7.3	4.7	1.6	1.6
7	Control	3	2.7	1.8	1.7	0.9	0.7	0.7	0	0
	Treated	9	14.2	4.7	5.6	1.6	4.2	2.6	1.1	1.1

[a] T = tail elevation; G = licking genital and mammary surfaces; U = urinating and defecation frequencies increase; C = visible contractions.

Table 3, continued.

[b] FMG = first mid-gestation; SMG = second mid-gestation; Control videotaped from 23 February 2001 to 4 March 2001; FMG videotaped from 8 February 2001 to 17 February 2001; SMG videotaped from 26 March 2001 to 4 April 2001.

[c] For each behavior, group means followed by dissimilar letters are significantly different ($P < 0.05$; Tukey's Test for comparisons of control, FMG, and SMG, or t-test for control vs. treated).

definitive as a 33% efficacy rate from a sample size of 6. Another possible source of variation may be random error through the randomization process. Normal biological variability may affect pregnancies or the response of individual does to $PGF_{2?}$ treatment. We shot does with the biobullets while they were at close range (less than 6 m) and individually stalled. Shot placement on each doe was verified, so we do not expect variation due to lost doses or varying locations of administered shots because all were shot in the hindquarter.

Behavior

The varied behavioral responses does displayed after their biobullet treatments likely corresponded to their individual differences and their individual perceptions of pain. Does were shot at a range of 5-6 m. Therefore, differences in shooting distances should not have been a significant factor. Some does had previously been treated with blow-darts in earlier studies, and were in a state of heightened awareness and stress when they observed the dart gun near their stall.

The significant increases in the behaviors of the control does on Day 1 and Day 6 are probably due to individual variation in behaviors. Some does tended to pace more than others, some tended to squat and urinate when people entered the barn more than others, and so forth. However, on Day 3, the SMG does displayed a significant increase in holding ears parallel to the facial plane (P = 0.0135) and licking genital and mammary surfaces (P = 0.0242) than FMG or control group. On this same day, the SMG does displayed a mean of 0.5 instances/day of displaying contractions (Table 3), 4 instances/day of smelling the aborted tissue, and 4 instances/day of licking/consuming the aborted tissue. When restless bedding, smelling aborted tissue, or licking/consuming aborted tissue were observed, contractions were also observed on those same days. For example, on Day 5, a mean of 0.1 instances/day of restless bedding, 2.7 instances/day of smelling the aborted tissue, 2.3 instances/day of licking/consuming aborted tissue, and 4.2 instances/day of contractions were observed (Table 3).

The partial cannibalism of fetuses could be a resultant abnormality from captivity. Currently, administration of $PGF_{2?}$ during mid-gestation to a wild population of white-tailed does on Kiawah Island, South Carolina, has shown no fetal cannibalism to aborted fetuses (Jim Jordan, personal communication). Also, the partial consumption of fetuses could be due to neurological and hormonal stimuli of the doe to lick and clean her fetus. The doe might not have been able to distinguish between consuming the placental membranes and the beginnings of consuming the dead fetus. Both fetuses were partially consumed from the rear legs up to the neck. The doe might have been trying to stimulate and clean the fetus, and became too aggressive with the process when the fetus did not respond (Waddell et al. 2001). The amount of consumption decreased as the doe progressed from the hind limbs towards the head. The hind limbs and other appendages were probably less calcified and covered by more soft tissue than the head and neck area, thereby being more easily mistaken for placental tissues by the doe. Aborted fetuses from Waddell et al's. (2001) late-gestation group were about 14 in. long with partial hind limb consumption, whereas our mid-gestation aborted fetuses only consisted of heads that were 4 in. long. The application of this treatment in suburban and urban settings favors the mid-gestation treatment because residents and pets are less likely to find aborted fetuses that are smaller, and thus consumed more completely by the does.

The number of pregnant does in the FMG and SMG groups totaled 9, where only 4 of these fawned. Therefore, from a management perspective, this treatment was 56% effective. Early gestation stage treatments were previously found to be 40% effective, and late gestation stage treatments were found to be 88% effective (Waddell et al. 2001). Late gestation treatments, however, had resulted in 7 out of 8 does having prolonged, intense contractions that lasted from 24 to 144 hours and other aberrant behaviors (Waddell et al. 2001). Mid-gestation treatments resulted in few aberrant doe behaviors and no prolonged, intense contractions. We observed 2 does out of 5 displaying contractions that lasted from 24 to 72 hours in which the does were still capable of standing up and walking around when startled. Control does displayed contractions for 3 to 5 hours (Waddell et al. 2001). Also, application at this stage of gestation minimizes rebreeding potential. Therefore, we think administering $PGF_{2?}$ during mid-gestation should be optimum (i.e., maximum treatment efficacy with minimal behavioral abnormalities).

Wildlife biologists who would like to use this management technique would also benefit from more efficient application. Mid-gestation for does in most of the U.S. occurs during late January through March (Hesselton and Hesselton 1982). This time should be ideal because visual obstruction by foliage is at its lowest and baiting does to treatment sites should be most effective since food sources are scarce. Additionally, the biobullet allows remote deliverability, which is both time and cost efficient. However, future research will be needed in order to receive approval from the U.S. Food and Drug Administration before $PGF_{2?}$ could be used routinely in urban deer management programs.

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CHAPTER 4

SUMMARY AND CONCLUSIONS

FERTILITY CONTROL

A possible white-tailed deer population control method is fertility control. Fertility control is currently an active area of wildlife research and success in this area may have important application to unmanaged urban and suburban deer populations (Warren 1995). There are two modes in which fertility control can work: contraception and contragestation (Warren 2000). Contraception prevents conception, either by preventing ovulation or by preventing the sperm and ovum from joining. Contragestation occurs after conception in order to terminate pregnancy. It has been implemented recently in deer through the use of prostaglandin (DeNicola et al. 1997).

I conducted 2 fertility control experiments to test the efficacy of a GnRH agonist as a contraception method, and $PGF_{2?}$ as a contragestation method, in white-tailed deer does. These results are summarized below.

GNRH AGONIST EXPERIMENT

A new possible contraception method is the use of gonadotrophin releasing hormone (GnRH) agonists. Endogenous GnRH is released from the hypothalamus and stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary. GnRH agonists have substituted amino acids within the GnRH molecules, which increase the half-life of the agonists and increase their affinity for the GnRH receptor in the pituitary (Karten and Rivier 1986). By remaining in the hypothalamo-hypophyseal portal vessels longer, the GnRH agonists out-compete the endogenous GnRH for pituitary receptors and result in a decrease in the production of endogenous GnRH due to negative feedback (Karten and Rivier 1986). Therefore, the normal fluctuations of endogenous GnRH are no longer present, which ultimately prevent the fluctuations of FSH and LH.

In cattle, the acute response to the GnRH agonist, Deslorelin? , is an increase in FSH and LH secretion (Chenault et al. 1990), but the chronic response is reduced gonadotrophin secretion due to the downregulation of the GnRH receptors (Hazum and Conn 1988). Thus, ovulation is prevented (Chenault et al. 1990). This was the response of cows and heifers treated with subcutaneous implants containing 12 mg of Deslorelin? ; they did not ovulate for at least 15 months (Jochle, W., pers. commun. Denville, NJ). The reproductive endocrinology of cattle is similar to white-tailed deer (Lincoln 1985). An adult, white-tailed deer doe weighs approximately 70 kg, whereas a cow weighs about 300 kg. It is possible, therefore, that does treated with 12 mg Deslorelin? may not ovulate for 2 years or more, thereby eliminating the need for annual retreatments.

If the GnRH agonist were effective in deer for at least 2 breeding seasons, then it would become a more economical method of fertility control by being less labor intensive and requiring fewer materials annually. However, the effectiveness of this treatment in the wild depends on the control of fawn production in a significant percentage of does in that population. In the wild, if fawn production were decreased significantly, then would this treatment eventually lead to a decrease in the white-tailed deer population and become a new mode of population control? This captive experiment was necessary to determine the effectiveness of Deslorelin? as a fertility control method in white-tailed deer. If its effectiveness after 1 dose spanned multiple breeding seasons, then it would justify a field study to determine Deslorelin's? long-term effects on population numbers. However, economical feasibility is ultimately the deciding factor.

My research on GnRH agonists found that maximum efficacy was reached in does treated with a GnRH agonist in October with subcutaneous implants, where efficacy was 100% the first year (n=7) and 25% the second year (n=4). May biobullet treatments were not effective in either of the 2 years. Both May implant and October biobullet treatments were 100% effective the first year, but 0% effective the second year. Finally, applying treatments in May did not hinder the does' current pregnancies from being carried full-term.

$PGF_{2\alpha}$ EXPERIMENT

In domestic livestock, prostaglandins are used to synchronize estrus and induce parturition (Lauderdale 1972, Copeland et al. 1978, Kirton and Kimball 1984). Regression of corpora lutea (CL) is caused by prostaglandins that are present in the uterine tissue during late gestation (Kirton and Kimball 1984). Regression of the CL reduces blood progesterone levels, which aids in parturition or abortion if induced early in pregnancy (Plotka et al. 1977, 1982). Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) is hypothesized (Goding 1974) as being the major naturally occurring luteolytic factor responsible for CL regression, and has been supported by evidence in red deer (*Cervus elaphus)* (Asher et al. 1995) and livestock (Kirton and Kimball 1984) studies. Three studies have observed and utilized prostaglandins as an abortifacient in white-tailed deer (Becker and Katz 1994, DeNicola et al. 1997, Waddell et al. 2001). One of these studies observed fetus consumption, reabsorption, and expulsion (Waddell et al. 2001). Aberrant doe behavior, and efficacy of $PGF_{2\alpha}$ when applied during early and late gestation have also been observed (Waddell et al. 2001).

Since $PGF_{2?}$ is effective as a means of fertility control during mid-gestation application, then it could be more efficient than other annual treatments. In the wild, it would be easier to bait a larger number of does for treatment during mid-gestation (approximately February) and the rebreeding potential should be at a minimum. During the winter season, does should be more motivated to feed at bait sites. Also, the seasonal defoliation of vegetation during winter should increase visibility and accuracy of biobullet shots when treating does remotely.

My research on $PGF_{2?}$ found that the treatment was 33% effective in the first mid-gestation (FMG) group (70-88 days of gestation) and 100% effective in the second mid-gestation (SMG) group (89-105 days of gestation). The FMG was treated at 10 to 12 weeks of gestation, whereas the SMG was treated at 13 to 15 weeks of gestation. The efficacy of FMG was determined from a sample size of 6 pregnant does, whereas the efficacy of SMG was determined from a sample size of 3 pregnant does. Efficacy was determined by considering only does that were pregnant. Therefore, 100% efficacy from a sample size of 3 may not be as definitive as a 33% efficacy rate from a sample size of 6.

During Day 1, behaviors of tail elevation ($P = 0.0368$) and licking genital and mammary surfaces ($P = 0.0238$) were observed significantly more frequently in the control group than the SMG group. In Day 6, does in the control group displayed the behavior of ears lowered parallel to the facial plane significantly more frequently ($P = 0.0120$) than does in the treatment groups. The significant increases in the behaviors of the control does on Day 1 and Day 6 were probably due to individual variation in behaviors. Some does tended to pace more than others, some tended to squat and urinate when people entered the barn more than others, and so forth. However, on Day 3, the

SMG displayed a significant increase in holding ears parallel to the facial plane (*P* = 0.0135) and licking genital and mammary surfaces (*P* = 0.0242). On this same day, the SMG displayed a mean of 0.5 instances/day of displaying contractions, 4 instances/day of smelling the aborted tissue and 4 instances/day of licking/consuming the aborted tissue. When restless bedding, smelling aborted tissue, or licking/consuming aborted tissue were observed, contractions were also observed those same days. For example, on Day 5, a mean of 0.1 instances/day of restless bedding, 2 instances/day of smelling the aborted tissue, 1.8 instances/day of licking/consuming aborted tissue, and 3.2 instances/day of contractions were observed. Two fetuses were found and both were partially consumed from the rear legs up to the neck.

FUTURE RESEARCH

Further research needs to address the effectiveness of these fertility control methods in wild populations. A mid-gestation $PGF_{2?}$ study in a suburban or urban wild population appears more economically feasible than a fall GnRH agonist subcutaneous implant study in a wild population. These wild population studies will give wildlife biologists a better idea of the impact these 2 fertility control methods could have when applied in the field.

MANAGEMENT IMPLICATIONS

Cost plays an important role in determining if a fertility control method is realistic in a wildlife management setting. Remote deliverability automatically decreases the cost of application when compared to implants. Baiting in late summer or early fall to administer GnRH agonist biobullets is probably more difficult than administering $PGF_{2?}$ biobullets in late January through March. However, both are effective annual fertility control methods in captive white-tailed deer does. $PGF_{2?}$ may be less acceptable socially because it is an abortion-inducing agent. Both control methods only require 1 dose and are remotely deliverable.

Applications are constructed to test efficacy and safety of chemical compounds in controlled experiments, and the Food and Drug Administration-Center for Veterinary Medicine (FDA-CVM) currently approves, on an individual basis, the use of some types of fertility control compounds in deer for investigational studies. These individual approvals of specific drug use in wildlife studies are not accepted by the FDA as an approved, "labeled" commercial use. However, Deslorelin® is approved in some countries for use in mares and Lutalyse® is approved in several species of human food animals (UpJohn, city, state). The drug manufacturer must identify a substantial market for the use of a specific drug in a wildlife species to be willing to incur the costs that accumulate by attempting to obtain regulatory approval. Obtaining regulatory approval requires the manufacturer to conduct additional efficacy, health, and safety studies. Normally, the market is not substantial enough for manufacturers to attempt to obtain regulatory approval for use in wildlife.

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