Case Report

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Case Study: Efficacy Trial for Peptide Treatment for Fertility

Augusta Wellington[1]*, Jonathan RT Lakey[2,3], Alana Williams[1], Mike KS Chan[1], Michelle BF Wong[1], Marcelle Gisain[2], Caroline Mosessain[2], Orn Adalsteinsson[2] and Desiree CT Cox[1]

[1]*BioPep Technology, USA*

[2]*European Wellness Group, Germany*

[3]*University of California, Irvine- Department of Surgery and Biomedical Engineering, USA*

ABSTRACT

Background: The ability to improve the reproductive health in mammals is desirable for many reasons, including to protect genetic diversity. Genetic information in calculating the inbreeding coefficient (COI) as well as the coefficient of relations (meaning the relationship of a relative's blood within a pedigree) (COR). This information is quintessential and can improve the understanding of genetic variability and contributions from each ancestor.

Methods: Due to the mechanism by which Organo Peptides/organelles (MO) have been shown to have regenerative effects in pre-clinical models, we theorized that peptides may help improve breeding ability, number of live births and frequency of estrus cycles. In this case report, we hypothesized that peptide therapy may improve fertility in the 4 canine subjects. A case study was done on 4 canines to assess their responses to MO injection protocols.

Results: The course of peptide therapy appeared to help normalize the estrus cycle of Subjects A and B. Both A and B showed an increase in their estrus cycles from once a year to twice compared to their non-peptide (MO) use cycles. Subject C's estrus cycle remained at twice per year. Subject D increased from no estrus to a having a peptide (MO)-induced estrus cycle. Following the use of MO peptides, Subject C produced a litter of 9 pups and Subject D produced a single pup.

Conclusions: Though limited conclusions can be drawn from this case study; it suggests a role for peptide therapy in canine fertility that should be further investigated. Future studies will need to be done to increase the number of subjects and further, to study the effects on male canines.

KEYWORDS: Canine fertility; Peptide therapy: Nano organo peptides; Mito organelles; Signaling peptides

INTRODUCTION

Canine breeding in species with low genetic diversity can present challenges with timing of estrus, based on progestrone readings, and the lutenizing hormones surge, which determines ovulation. There needs to be a consistency of timing between estrus and the low resulting birthrates of healthy pups. Peptide therapy is the use of targeted signaling peptides, which are amino acid chains, to instruct cells on the functions they need to perform [1]. Peptides are linear polymers formed by a series of amino acid residues that are linked together through peptide bonds [2]. Whereas proteins typically contain between 50 and 2000 amino acid residues and have a mean molecular weight between 5.5 and 22kDa, peptides are composed of less than 50 residues and range below the weight for that of proteins. Among cells, a unique set of

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Address for correspondence: Augusta Wellington, BioPep 4621 Technology Dr, Golden, CO, USA

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proteins and peptides are produced that have different functions in regulating biological homeostasis (MF+, 2016). Short peptides have been demonstrated to play an important role in the modulation of transcription, transmission of biological information, and in restoring genetically conditioned alterations occurring with age [3]. These peptides are signaling molecules that act as regulatory factors through their interaction with DNA and histone proteins. Moreover, the physiological process of aging is highly influenced by the peptidergic regulation of homeostasis and is related to the aging of cells, tissues, and organs [3].

We hypothesize that the use of peptides may be beneficial in improving fertility. Since peptides are metabolized into individual amino acids, they are recycled by the body. This contrasts with many drug therapies, which are either eliminated or can accumulate causing toxicity or side effects. Nano Organo Peptides (NOPs) are only 3 nm in size and have a molecular weight of less than 10kDA [4]. NOPs are procured from mammalian stem cells and are processed through a proprietary parallel-extraction process but are unique in that they undergo multiple ultrafiltrate steps through specialized Millipores to receive the cellular material within the cell, known as the molecular-level ultrafiltrates. NOP contents are extracted from organ specific cells with an initially high molecular mass and separated through such ultrafiltration steps through by micro-Millipore filters that only allow substances with a molecular mass of less than 10 kDa to pass, thereby accounting for their small molecular weight. Moreover, the low molecular weight and high solubility of NOPs permit them to be delivered both sublingually and via injection (subcutaneous or intramuscular). NOPs have been investigated for a variety of applications including cosmetics [5] and regenerative organ repair [6]. In this case report, we hypothesize that peptide therapy uses cell signaling in the specific organs and may improve fertility in the 4 canine subjects [7].

CASE REPORT

Subject A is a 5-year-old rare breed Shiloh Shepherd and sibling to subject B. This female has been bred once, which resulted in a single live birth. Her heat cycles were erratic with an unpredictable amount of time between each estrus. Injections were started to attempt to bring the subject into estrus (Table 1). Subject B is a 5-year-old rare breed Shiloh Shepherd and sibling to Subject A. This female has been bred once, which have resulted in 7 live births. Her heat cycles were erratic with an unpredictable amount of time between each estrus.

Table 1: Subject an injection chart time frame, dose and adverse reactions noted.

Days Since Start	Injection	MO	Reaction
0	2.5ml each	Adrenal cortex, Liver, Placenta and Ovary	No adverse reaction, behavioral changes and seemingly more interested in my other dogs pups
5	2.5ml each	Adrenal cortex, Liver, Placenta and Ovary	No adverse reaction
10	2.5ml each	Adrenal cortex, Liver, Placenta and Ovary	No adverse reaction
15	2.5ml each	Adrenal cortex, Liver, Placenta and Ovary	No adverse reaction
20	2.5ml each	Adrenal cortex, Liver, Placenta and Ovary	No adverse reaction
25	2.5ml each	Adrenal cortex, Liver, Placenta and Ovary	No adverse reaction
30	2.5ml each	Adrenal cortex, Liver, Placenta and Ovary	No adverse reaction
35	2.5ml each	Adrenal cortex, Liver, Placenta and Ovary	No adverse reaction
40	N/A		Heat cycle started
45	2.5ml each	Adrenal cortex, Liver, Placenta and Ovary	No adverse reaction
50	2.5ml each	Adrenal cortex, Liver, Placenta and Ovary	No adverse reaction

Table 2: Subject B peptide injection protocol and any adverse reactions.

Days	Injection	MO	Adverse Reaction
0	2.5ml each	Adrenal cortex, Liver, Placenta and Ovary	First day of heat, no adverse reaction
5	2.5ml each	Adrenal cortex, Liver, Placenta and Ovary	No adverse reaction
6	2.5ml each	Adrenal cortex, Liver, Placenta and Ovary	No adverse reaction

NOP injections were started to attempt to bring the subject into estrus (Table 2) with Certificates of Analysis outlining concentration, pH, and sterility in Appendix 1. The first peptide-assisted breeding attempt with Subjects A and B was run at the time time. Both Subjects A and B began estrus and progesterone levels were monitored to identify and facilitate the optimum time to breed (Figure 1).

At Day 30 day after breeding/insemination, an ultrasound was preformed, and no puppies were detected in utero. At the time of ultrasound on May 8th, no puppies were observed in utero. It was discovered that Subject B had pyometra and was put on a course antibiotic for 14 days. Pyometra occurs because of hormonal changes in the female's reproductive tract following estrus (heat) when the lining thickens in preparation for pregnancy. If pregnancy does not occur, a secondary infection can occur because the cervix is open and white blood cells are inhibited from entering the uterus during estrus to allow sperm to safely enter the reproductive tract.

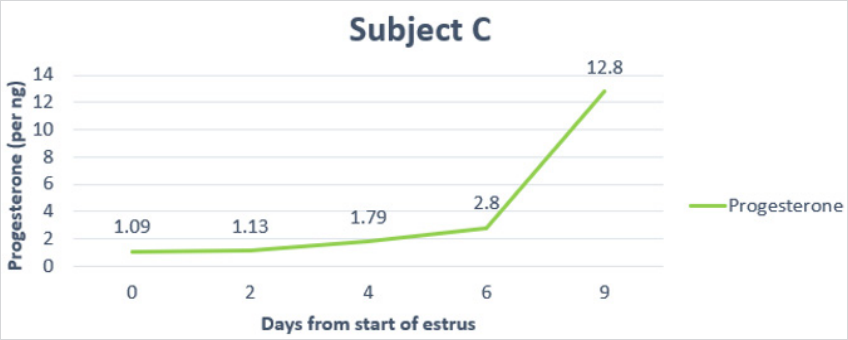

Figure 1: Hormone monitoring of progesterone for Subjects C prior to breeding.

The second injection study was done on Subject A and B following a failed first attempt. Both Subjects entered estrus 6 months later. Subject B receieved Ovary, Pituitary, Liver and Thymus peptides as set out in Table 2. Subject A was a treated as a control for the second study and receieved no peptides (Table 3).

Table 3: Subject B peptide injection protocol, injection days, dose, sources of peptide and any adverse reactions.

Days	Injection	MO	Reaction
0	1.5ml each	Ovary and Thymus	No adverse reaction
1	1.5ml each	Pituitary and Liver	No adverse reaction
5	1.5ml each	Ovary and Thymus	No adverse reaction
6	1.5ml each	Pituitary and Liver	No adverse reaction
10	1.5ml each	Ovary and Thymus	No adverse reaction
11	1.5ml each	Pituitary and Liver	No adverse reaction
16	1.5ml each	Ovary and Thymus	No adverse reaction
17	1.5ml each	Pituitary, Liver and Adrenal Cortex	No adverse reaction
22	1.5ml each	Ovary and Pituitary	No adverse reaction

Table 4: Subject C peptide injection protocol and adverse reactions.

Days From Start	Injection	MO
0	1.25ml each	Adrenal Cortex and Liver
5	1.25ml each	Adrenal Cortex and Liver
10	1.25ml each	Adrenal Cortex and Liver
13	1.25ml each	Liver, Thymus, Ovary and Pituitary
16	1.25ml each	Liver, Thymus and Ovary
19	1.25ml each	Liver and Thymus
24	1.25ml each	Liver and Thymus

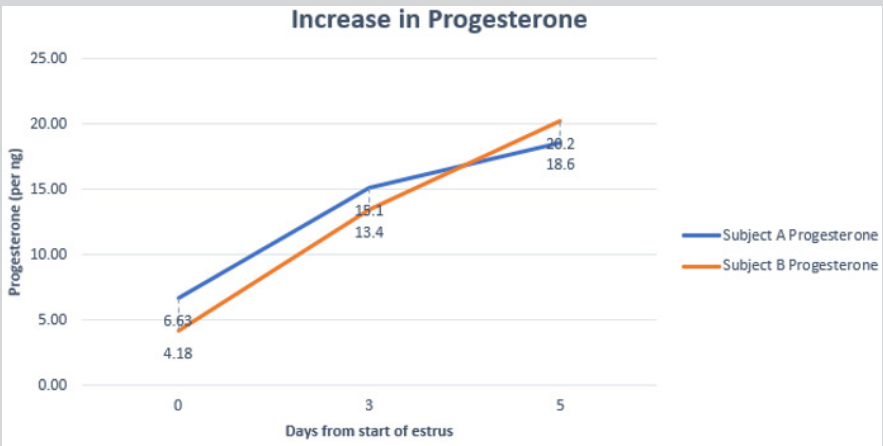

Figure 2: Hormone monitoring of progestrone for Subjects A and B prior to breeding.

Progesterone was monitored (Table 4) from start of estrus to identify and facilitate the optimum time for breeding (Figure 2). Subject C is a 4-year-old rare breed Shiloh Shepherd. This female was bred twice naturally, and the third time with peptide treatments. The first litter resulted in 2 viable pups (without peptide treatment), the second litter (without peptide treatment) resulted in 5 live births. The third litter following peptide treatment resulted in 9 live pups.

Adrenal cortex injections were started at the start of the heat cycle as determined by blood testing for the increase in hormone tracking and given every 5 days. Progesterone levels were monitored until the Subject was bred. The injections were halted once the dog was bred, as previous trials have shown that the adrenal cortex peptide can act akin to cortical steroids and can cause spontaneous abortion (Figure 3).

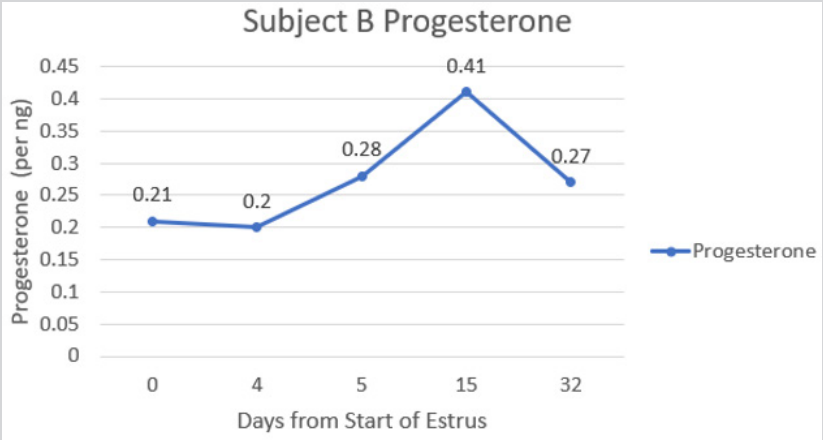

Figure 3: Hormone monitoring of progestrone for Subjects A and B prior to breeding.

Table 5: Subject D peptide injection protocol and adverse reactions.

Days from start	Injection	MO	Reaction
0	1ml each	Pituitary and Ovary	No Adverse Reaction
3	1ml each	Ovary	No Adverse Reaction

Subject D is a 7-year-old champion pure breed Collie and has been bred 3 times. The first breeding resulted in a single stillborn pup on January 2, 2018. The second breeding resulted with live 3 male puppies on September 2018. She has had no heat cycle since the second breeding in 2018 until May 2021 (Table 5). With organ specific peptide treatment, she produced a single, live birth (Figure 4).

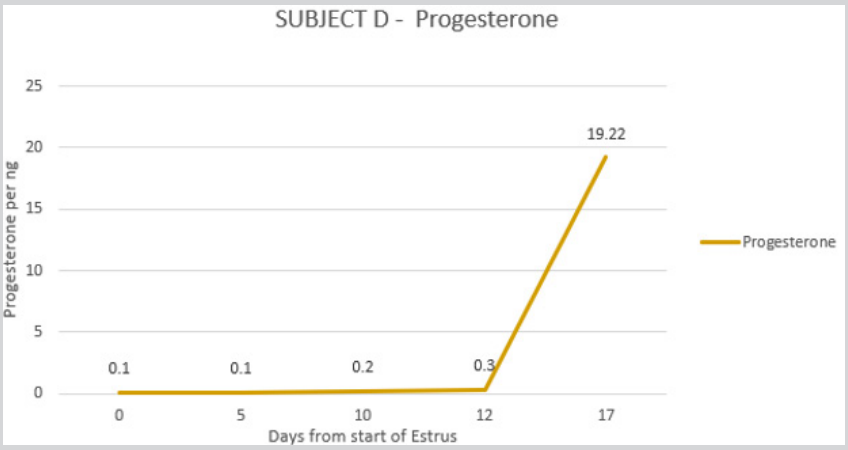

Figure 4: : Subject D peptide injection protocol and reactions.

Results

For Subject A, B, and D, the course of peptide therapy appeared to help normalize the estrus cycle, making it occur at a more regular interval than previously observed. Subject B developed an infection after artificial insemination was performed, although this may have been coincidental. Following MO peptide therapy, Subject C produced a litter of 9 pups and Subject D produced a single pup.

Conclusion

Notwithstanding the encouraging results shown in this case study, it should be noted that we cannot conclusively correlate and

for conclusions due to the limited subjects in this study, and the difference in injection protocols used. This case study has shown that using peptide therapy can induce an estrus cycle and possibly increase the litter number of puppies. Subject C's previous litters had consisted of two litters of 3 pups and a second of 5 pups without the use of peptides.Following the MO peptide treatment produced a third litter of 9 pups, a significant increase. Subject D had no estrus in 3 years and following the peptide injections had a rapid increase in progesterone levels, with no adverse effects observed. However, it suggests a role for peptide therapy in canine fertility that should be further investigated. Future studies will need to be done to increase the number of subjects and further, to study the effects on male canines.

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Appendix : Certificates of Analysis for NOP treatment concentration, pH and sterility.

BADEN RESEARCH & TESTING LAB

Issue Date : 19/11/2019
Report No : BRL-NOP-1905
Batch No : 311019

CERTIFICATE OF ANALYSIS

Sample ID : BRL/LAB/NOP/Lung
Sample Description : NOP Lung
Tested Date : 31/10/2019
Result Date : 01/11/2019

ANALYSIS RESULTS

Test	Method	Acceptance Criteria	Result
Concentration	BCA Analysis	>300 mcg per 2.5 ml vial	Pass
pH	Potentiometric pH meters	pH 6.5-8.0	Pass
Sterility	Automated bacterial detection	Absence of microbial contamination	Pass

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