Available online at www.sciencedirect.com
SCIENCE DIRECT®
Theriogenology
ELSEVIER
Theriogenology 64 (2005) 766–775
www.journals.elsevierhealth.com/periodicals/the

Induction and synchronization of estrus in dogs

Michelle Anne Kutzler *

158 Magruder Hall, College of Veterinary Medicine, Oregon State University, Corvallis, OR 97331, USA

Abstract

Indications for estrus induction in the bitch include missed breeding opportunities or conception failure, the treatment of primary or secondary anestrus and synchronization of ovulation for embryo transfer programs. Reported methods for canine estrus induction include the use of synthetic estrogens (diethylstilbesterol), dopamine agonists (bromocryptine and cabergoline), GnRH agonists (lutrelin, buserelin, fertirelin, deslorelin, and leuprolide) and exogenous gonadotropins (luteinizing hormone, follicle stimulating hormone, human chorionic gonadotropin, pregnant mare serum gonadotropin, and human menopausal gonadotropin). These methods vary widely in efficacy of inducing estrus, as well as in the fertility of the induced estrus. The applicability of some of these methods for clinical practice is questionable. This review will summarize published reports on estrus induction and synchronization in bitches and summarize preliminary results using a long-acting injectable preparation of deslorelin.

Keywords: Dog; Estrus induction; GnRH agonist; Dopamine agonist; Gonadotropin

1. Introduction

There are many indications for estrus induction in the bitch. Estrus induction is clinically useful in conjunction with routine breeding management when breeding opportunities are missed or following conception failure and may also be used as a treatment for primary anestrus. The onset of puberty typically occurs between 6 and 12 mo of age in dogs. Absence of estrous cycling by 24 mo of age may be indicative of hypothalamic-pituitary-ovarian axis malfunction and warrants detailed reproductive evaluation, which may include estrus induction. The average interestrous interval in the

* Tel.: +1 541 737 6952; fax: +1 541 737 8651.
E-mail address: michelle.kutzler@oregonstate.edu.

0093-691X/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.theriogenology.2005.05.025

dog is 7 mo but varies in fertile bitches from 16 to 56 wk [1] with the exception of the Basenji breed in which the interestrous interval is 12 mo [2]. Estrus induction may also be used as a treatment for secondary anestrus (interestrous interval >12 mo). In addition, reliable synchronous estrus induction is a necessity for canine embryo transfer programs.

There is convincing anecdotal evidence that a ''dormitory effect'' occurs in canids, such that co-housing bitches in mid to late anestrus with proestrous or estrous bitches will shorten the duration of anestrus by 30 d or more in anestrous bitches [3]. It is assumed that this phenomenon of ''natural'' estrus induction is mediated by pheromones but the mechanism by which an increase in gonadotropin secretion is mediated is not known. However, since 1939, there have been more than forty protocols investigating pharmacological estrus induction in bitches. The protocols and results from these studies are summarized in Tables 1–4. The following definitions should be used when interpreting information from these tables:

(a) *Proestrus*: Onset of vulvar edema and/or serosanguinous discharge.
(b) *Estrus*: Onset of either behavioral signs (willingness to allow mating) or vaginal epithelial exfoliative cytology (>90% cornification).
(c) *Ovulation*: Determination of a progesterone concentration >5 ng/mL or presence of corpora lutea visualized on the ovaries.
(d) *Pregnancy*: Existence of embryos within the uterine tubes or uterus.

2. Gonadotropins

Factors regulating the duration of anestrus within individual female dogs are not known but the termination of anestrus in bitches is associated with increased serum concentration or pulse frequency of luteinizing hormone (LH) [3]. Serum follicle stimulating hormone (FSH) concentrations are increased throughout much of canine anestrus while LH concentrations are low except near the end of anestrus [3]. However, both LH and FSH appear to be follicotropic in the dog as administration of pharmacologic doses of either LH or FSH alone induces estrus (Table 1) [3,4]. An estrus induction protocol was established with combined dosages of FSH and LH designed to resemble the gradual increase of endogenous FSH coincidentally with the LH increase during proestrus [4]. However, this protocol was not successful (Table 1). It is important to note that a slight but significant increase in serum estradiol concentration occurs before the onset of proestrus, roughly 30 d before the onset of estrus [5]. The functional significance of this increase in estradiol is not known but it may prime the hypothalamic-pituitary-ovarian axis thereby initiating an increased rate of pulsatile LH release. This mechanism is supported by the successful induction of fertile estrus in bitches following administration of diethylstilbesterol (DES) (Table 1) [6,7]. In addition to exogenous pituitary gonadotropins, pregnant mare serum gonadotropin (PMSG), human chorionic gonadotropin (HCG), and human menopausal gonadotropin (HMG) have been used for estrus induction in bitches [8–11]. The most widely studied gonadotropin for estrus induction in the dog is PMSG, with protocols ranging from daily to weekly injections using either subcutaneous or intramuscular routes

Table 1
Gonadotropins and estrogens used for estrus induction in the bitch

Reference	No. of bitches	Protocols		Results		
		Estrus induction	Ovulation induction	Proestrus%/estrus%	Ovulation%	Pregnant%/whelped%
[4]	5	FSH 0.77–1.1 mg/kg IM once	None	60 (in 5–12 d)/20	40	20 (pregnant)
[4]	4	FSH 0.077–0.11 to 1.23–1.78 mg/kg IM SID for 10 d (double the dose of FSH every 2 d)	None	50 (in 7 d)/25	50	0 (pregnant)
[4]	5	FSH 0.077–0.11 to 1.23–1.78 mg/kg IM every 48 h (repeat low dose once then double the dose of FSH every 2 d); LH 0.077–0.11 to 0.38–0.55 mg/kg IM every 48 h (repeat low dose four times then double the dose of LH on the last 2 treatments); FSH and LH injections are given on days 1, 3, 5, 7, 9 and 11	None	0/0	0	0/0
[35]	5	DES 0.19–0.21 mg/kg SID PO for 14 d; FSH 0.38–0.42 mg/kg IM on 9th and 11th d	hCG 37.9–42.4 IU/kg IM on 5th d of proestrus	80 (proestrus)	20	Not given
[6]	5	DES 5 mg/dog[a] PO SID for 6–9 d until proestrus occurs	None	100/100	100	100/100
[36]	13	DES 0.1–0.2 mg/kg SID PO for 14 d; FSH 0.2–0.4 mg/kg IM on 5th, 9th, and 11th d	None	69 (estrus)	46	31(pregnant)
[10]	16	LH 0.1 IU/kg TID for 7 d	None	100/44	44	37.5/37.5
[11]	10	HMG 1–7 IU/kg SID IM for 9 d	None	90/60	60	40/40

[a] Mongrel dogs were used but weight was not given.

Table 2
Pregnant mare serum gonadotropin used for estrus induction in the bitch

Reference	No. of bitches	Protocols		Results		
		Estrus induction	Ovulation induction	Proestrus%/estrus%	Ovulation%	Pregnant%/whelped%
[37]	18	PMSG 187 MU[a]/dog[b] IM once	hCG 50 MU[a]/dog[b] at time of PMSG injection	78 (estrus in 2–6 d)	Not given	50 (whelped)
[12]	6	PMSG 500 IU/dog[b] SID SQ for 8–9 d	hCG 500 IU/dog[b] SC on 10th d of treatment	100 (estrus in 10–14 d)	100	Bitches were not bred[c]
[38]	6	PMSG 31.2–71.4 IU/kg SID SC for 10 d	hCG 31.2–71.4 IU/kg SQ on 10th d of treatment	50 (estrus)	50	50/50
[38]	7	PMSG 15.6–35.7 IU/kg SID SC for 10 d	hCG 31.2–71.4 IU/kg SQ on 10th d of treatment	57 (estrus)	57	57/57
[38]	12	PMSG 20 IU/kg SID SC for 10 d	hCG 31.2–71.4 IU/kg SQ on 10th d of treatment	58 (estrus)	58	58/58
[39]	8	PMSG 44 IU/kg SID IM for 9 d	hCG 25–50 IU/kg IM on 10th d of treatment	100 (estrus in 5–19 d)	80	60 (pregnant)
[39]	5	PMSG 44 IU/kg SID SQ for 9 d	hCG 25–50 IU/kg IM on 2nd d of estrus	80 (estrus in 9–11 d)	80	60 (pregnant)
[40]	8	PMSG 110 IU/kg IM up to three times at 7 d intervals	None	100 (estrus)	87.5	Not given
[40]	3	PMSG 110 IU/kg IM up to three times at 7 d intervals	hCG 37–62.5 IU/kg IM on 1st d of estrus	100 (estrus)	100	Not given
[41]	8	PMSG 18.9–31.2 IU/kg SID SQ for 14–20 d	hCG 37–62.5 IU/kg SC on 1st d of estrus or 21st d of treatment	87.5/62.5	75	Not given
[42]	Not given	PMSG 20–50 IU/kg IM twice at 6 d intervals	hCG 500–1000 IU/dog[d] IM on 1st and 2nd d of estrus	100/60	Not given	Not given
[43]	15	PMSG 27.8–41.7 IU/kg SID IM for 10 d	hCG 27.8–41.7 IU/kg IM on 10th d of treatment	100/87	100	20/20
[43]	5	PMSG 27.8–41.7 IU/kg SID IM for 10 d	Gonadoliberin 0.003–0.004 mg/kg IM on 10th d of treatment	100/60	100	0/0
[13]	11	PMSG 44 IU/kg SID IM for 9 d	hCG 25–100 IU/kg IM on 10th d of treatment	100/64	64	13/13[c]
[8]	17	PMSG 20 IU/kg SID IM for 10 d	hCG 500 IU/dog[e] IM on 10th d of treatment	100 (proestrus in 4–6 d)	Not given	35/0
[8]	6	PMSG 20 IU/kg SID IM for 5 d	hCG 500 IU/dog[b] IM on 5th d of treatment	100 (proestrus in 4–6 d)	Not given	50 (pregnant)
[14]	14	PMSG 20 IU/kg SID IM for 5 d	hCG 500 IU/dog[b] IM on 5th d of treatment	100 (estrus)	Not given	43 (pregnant)[c]

[a] Mouse units.
[b] Beagle dogs used but weight not given.
[c] Premature luteal failure.
[d] Breed and body weight of dogs not given.
[e] Niederlauf dogs used but weight not given.

Table 3
Dopamine agonists used for estrus induction in the bitch

Reference	No. of bitches	Protocol	Results	
		Estrus induction	Proestrus%/estrus%	Pregnant%/whelped%
[9]	6	Bromocryptine 0.02 mg/kg PO BID until proestrus	100 (proestrus in 47 ± 2 d)	
[3]	5	Bromocryptine 0.05 mg/kg PO BID until proestrus	80 (proestrus in 28 d)	Not given
[22]	48	Bromocryptine 0.3 mg/bitch for 3 d, then 0.6–2.5 mg/bitch PO SID continued 3–6 d after onset of estrus	100 (estrus)	83 (pregnant)
[44]	Not given	Bromocryptine 0.10 mg/kg PO until proestrus	80 (proestrus in 17–28 days)	Not given
[45]	5	Cabergoline 0.005 mg/kg PO SID from 30 d past the LH peak until onset of proestrus	80 (proestrus in 29.75 ± 5 d)	0 (pregnant)
[21]	5	Cabergoline 0.005 mg/kg PO SID until 3–8 d after onset of proestrus or 40 d	80 (proestrus in 20 ± 3 d)	60 (pregnant)
[21]	5	Cabergoline 0.005 mg/kg PO SID until 3–8 d after onset of proestrus or 40 d	100 (proestrus in 14 ± 3 d)	100 (pregnant)
[21]	5	Cabergoline 0.005 mg/kg PO SID until 3–8 d after onset of proestrus or 40 d	100 (proestrus in 6 ± 1 d)	80 (pregnant)
[33]	12	Cabergoline 0.005 mg/kg PO SID until progression of proestrus to estrus	83 (proestrus in 23.5 ± 3.2 d)	83 (pregnant)

of administration (Table 2). However, premature luteal failure with subsequent shortening of diestrus and pregnancy loss has been reported following the use of PMSG [12–14].

3. Prolactin

Prolactin appears to play a part in canine interestrous intervals, possibly by affecting gonadotropin secretion and/or ovarian responsiveness to gonadotropins. Suppression of prolactin secretion by administration of dopamine agonists shortens the duration of anestrus [9,15] or induces estrus in cases of prolonged anestrus [16,17]. However, prolactin inhibition alone is not sufficient to terminate anestrus in bitches as the administration of a seratonin antagonist (metergoline) suppresses prolactin concentrations similar to concentrations observed with dopamine agonists (bromocryptine and cabergoline), but does not induce estrus [18]. It does appear that prolactin inhibition is necessary for estrus induction to occur. Bitches that did not respond to dopamine agonist therapy (e.g. proestrus was not initiated) did not have a decrease in prolactin concentrations [3]. These observations suggest that an inhibition of prolactin secretion may regulate the initiation of

Table 4
Gonadotropin releasing hormone and agonists used for estrus induction in the bitch

Reference	No. of bitches	Protocols		Results	
		Estrus induction	Proestrus%/estrus%	Ovulation%	Pregnant%/whelped%
[36]	36	GNRH 0.000015–0.000500 mg/kg IV every 90 min for 7–9 d	72 (proestrus in 5.1 ± 0.4 d)/56	44	33 (pregnant)
[46]	8	GNRH 0.000096–0.000139 mg/kg IV every 90 min for 11–13 d	100 (estrus within 23 d)	87.5	87.5 (pregnant)
[47]	8	GNRH 0.000040–0.000430 mg/kg IV every 87 min for 9 d	75 (within 2–4 d)/62.5	50	37.5 (pregnant)
[48]	10	Buserelin 0.0015 mg/kg SQ TID for 11 d and 0.00075 mg/kg SQ TID for 3 d	30 (proestrus in 18.6 ± 4.7 d)	20	20 (pregnant)
[24]	24	Lutrelin 0.0017–0.0025 mg/kg/d for 14–28 d, via SQ osmotic mini pump	87.5 (proestrus in 5.1 ± 0.4 d)	75	37.5[a]
[49]	18	Leuprolide 0.10 mg/kg SQ once[b]	100 (estrus within 7–15 d)	83	78
[25,26]	7	Deslorelin 2.1 mg implant/dog[c] SQ once	100 (proestrus within 6–10 d)	100	43 (pregnant)[a]
[33]	6	Deslorelin 2.1 mg implant/dog[c] subvulvar once	100 (proestrus within 5–6 d)	100	67 (pregnant)
[33]	5	Deslorelin 2.1 mg implant/dog[c] subvulvar once	100 (proestrus within 5–6 d)	80	40 (pregnant)
Kutzler MA (unpublished)	3	Deslorelin 1.5 mg/dog[d] IM once	100 (proestrus within 5–6 d)	100	100/100

[a] Premature luteal failure.
[b] Ovulation induction agent used; fertirelin 0.003 mg/kg IM given on 1st d of estrus.
[c] Beagle dogs were used (5.4–13.6 kg).
[d] Lakeland Terrier dogs were used (6.8–9.1 kg).

proestrus. Kooistra et al. reported that follicle development and resulting estrus induction with bromocryptine was associated with an increase in plasma FSH concentration without a concomitant increase in plasma LH concentration [19]. It is important to note that in normal cycling bitches, prolactin concentrations during late anestrus do not change prior to the onset of proestrus [20].

Dopamine agonists successfully induce fertile estrus in most bitches (Table 3) but can be cost prohibitive in the United States, where these drugs are not readily available for veterinary use. In addition, this method of estrus induction may require >30 d of treatment before the onset of proestrus occurs, which is dependent upon the stage of anestrus (early versus late anestrus) [21]. Lastly, centrally acting dopamine agonists (e.g. bromocryptine) commonly induce vomiting. Habituation to bromocryptine, beginning with lower doses initially, is reported to almost completely eliminate emesis as a side effect of treatment [22].

4. GnRH

Pulsatile secretions of gonadotropin releasing hormone (GNRH), a hypothalamic decapeptide, are released every 70–90 min to mediate the synthesis and release of pituitary LH and FSH [23]. Pulsatile administration of GNRH at doses of 0.2–0.4 μg/kg at 90 min intervals is sufficient to obtain increases in LH similar to the endogenous pulses that normally occur at the end of proestrus [3]. However, estrus induction protocols using short-acting native GnRH or GnRH agonists are not clinically applicable due to the expense of pulsatile infusion pumps or need for hospitalization during continuous intravenous infusion (Table 4).

It is important to note that increases in LH do not need to be pulsatile to induce estrus [3]. Constant infusion or release of a GnRH analog (lutrelin, deslorelin, and leuprolide) via a subcutaneous osmotic mini pump or implant resulted in similar estrus induction and pregnancy rates as GnRH pulsatile infusion, provided that the GnRH agonist therapy is discontinued after ovulation [3,24]. Premature luteal failure resulting in a shortened diestrus with subsequent pregnancy loss has been reported with GnRH agonist therapy for estrus induction [24–26]. Prolonged administration of GnRH agonists resulted in pituitary overstimulation, suppression of LH secretion, decreased luteal responsiveness to LH, and decreased progesterone secretion [27–29].

By making molecular changes to native GnRH, more than 700 GnRH agonists have been synthesized that have an increased receptor affinity and enhanced stability [29]. Deslorelin is a D–Trp^{6}–Pro^{9}–des–Gly^{10}GnRH analogue with two amino acid substitutions. Veterinary clinical applications of deslorelin in canids were first introduced by Trigg et al. during an investigation for a novel contraceptive (Suprelorin®), which is now commercially available in Australia (Peptech Animal Health, North Ryde, New South Wales) [30]. Preliminary investigations with this product demonstrated that it induced estrus in all anestrous bitches treated initially, which was followed by prolonged estrus suppression [31,32]. Ovuplant® (Fort Dodge Animal Health, Overland Park, KS, USA) is a biodegradable, sustained release, subdermal implant containing 2.1 mg of deslorelin, licensed for use in horses. According to label claims, Ovuplant® induces ovulation in

mares within 48 h. Previous studies in dogs with this product demonstrate its reliability for inducing a rapid and synchronous estrus [25,26,33]. However, the availability of this form of deslorelin (Ovuplant®) in the United States has been limited in the past 2 yr due to manufacturing problems, leading to a need for investigations into alternative deslorelin preparations.

BioRelease™ deslorelin (BET Pharmacy; Lexington, KY, USA) contains 1.5 mg/mL of deslorelin in a proprietary biocompatible liquid vehicle for intramuscular injection in mares. This is a compounded product and has not been approved for use in any species by the Food and Drug Administration. However, research in mares suggests that this product is effective at inducing ovulation [34]. Preliminary clinical investigations using BioRelease™ deslorelin are underway at the Oregon State University Veterinary Teaching Hospital. Three client-owned Lakeland terrier bitches have received one 1 mL (1.5 mg) injection of BioRelease™ deslorelin in the epaxial or semimembranosus muscle. Two of the three bitches previously had estrus induced within the past 12 mo with either cabergoline (5 μg/kg SID PO until onset of proestrus) or Ovuplant® (vulvar implant removed initial rise in serum progesterone concentrations), which resulted in normal pregnancies. All three bitches treated with BioRelease™ deslorelin came into proestrus within 3–5 d, ovulated and had successful pregnancies.

5. Conclusion

Many protocols exist for reliable estrus induction in bitches. However, fertility with induced estrous cycles is variable. In addition, some methods are too expensive or labor intensive to be suitable for clinical veterinary practice. None of the drugs listed herein are approved for the treatment of estrus induction in bitches in the United States. However, cabergoline (Galastop®; Boehringer) is licensed for estrus induction in bitches in Europe. Owners should be cautioned that many of these treatments are still experimental.

References

[1] Christie DW, Bell ET. Some observations on the seasonal incidence and frequency of oestrus in breeding bitches in Britain. J Sm Anim Pract 1971;12:159–67.
[2] Fuller JL. Photoperioidic control of estrus in the Basenji. J Hered 1956;47:179–80.
[3] Concannon PW. Biology of gonadotropin secretion in adult and prepubertal female dogs. J Reprod Fertil 1993;47(Suppl.):3–27.
[4] Shille VM, Thatcher MJ, Simmons KJ. Efforts to induce estrus in the bitch, using pituitary gonadotropins. J Am Vet Med Assoc 1984;184:1469–73.
[5] Jeffcoate IA. Endocrinology of anestrous bitches. J Reprod Fertil 1993;47(Suppl.):69–76.
[6] Bouchard GF, Gross S, Ganjam VK, Youngquist RS, Concannon PW, Krause GF, et al. Oestrus induction in the bitch with the synthetic oestrogen diethylstilboestrol. J Reprod Fertil 1993;47(Suppl.):515–6.
[7] Moses DL, Shille VM. Induction of estrus in greyhound bitches with prolonged idiopathic anestrus or will suppression of estrus after testosterone administration. J Am Vet Med Assoc 1988;192:1541–5.
[8] Arnold S, Arnold P, Concannon PW, Weilenmann R, Hubler M, Casal M, et al. Effects of duration of PMSG treatment on induction of estrus, pregnancy rates and the complications of hyperestrogenism in dogs. J Reprod Fertil 1989;39(Suppl.):115–22.

[9] van Haaften B, Dieleman SJ, Okkens AC, Bevers MM, Willemse AH. Induction of estrus and ovulation in dogs by treatment with PMSG and/or bromocriptine. J Reprod Fertil 1989;39(Suppl.):330–1 [abstract].
[10] Verstegen J, Onclin K, Silva L, Concannon P. Termination of obligate anestrus and induction of fertile ovarian cycles by administration of purified pig LH. J Reprod Fertil 1997;111:35–40.
[11] Wanke M, Farina J, Loza M, Rebuelto M, Concannon P. Induction of oestrus in bitches with normal and persistent anestrus using human menopausal gonadotropin (hMG). Theriogenology 1997;47: 935–42.
[12] Jones GE, Boyns AR, Bell ET, Christie DW, Parkes MF. Immunoreactive luteinizing hormone and progesterone during pregnancy and following gonadotropin administration in beagle bitches. Acta Endocrinol 1973;72:573–81.
[13] Nakao T, Yukiyo A, Fukushima S, Moriyoshi M, Kawata K. Induction of estrus in bitches with exogenous gonadotropins, and pregnancy rate and blood progesterone profiles. Jpn J Vet Sci 1985;47:17–24.
[14] Weilenmann R, Arnold S, Dobeli M, Rusch P, Zerobin K. Estrus induction in bitches by the administration of PMSG and HCG. Schweiz Arch Tierheilkd 1993;135:236–41.
[15] Okkens AC, Bevers MM, Dieleman SJ, Willemse AH. Shortening of the interestrous interval and the lifespan of the corpus luteum of the cyclic dog by bromocriptine treatment. Vet Q 1985;7:173–6.
[16] Arbeiter K, Brass W, Ballabio R, Jochle W. Estrus induction and fertility with cabergoline, a prolactin inhibitor, in the bitch. J Small Anim Pract 1988;29:781–8.
[17] Jochle W, Arbeiter K, Post K, Ballabio R, D'Ver AS. Effects on pseudopregnancy, pregnancy and interoestrous intervals of pharmacological suppression of prolactin secretion in female dogs and cats. J Reprod Fertil 1989;39(Suppl.):199–207.
[18] Okkens AC, Kooistra HS, Dieleman SJ, Bevers MM. Dopamine agonistic effects as opposed to prolactin concentrations in plasma as the influencing factor on the duration of anestrus in bitches. J Reprod Fertil 1997;51(Suppl.):55–8.
[19] Kooistra HS, Okkens AC, Bevers MM, Popp-Snijders C, van Haaften B, Dieleman SJ, et al. Bromocryptine-induced premature oestrus is associated with changes in the pulsatile secretion pattern of follicle-stimulating hormone in beagle bitches. J Reprod Fertil 1999;117:387–93.
[20] Olson PN, Bowen RA, Behrendt M, Olson JD, Nett TM. Concentrations of reproductive hormones in canine serum throughout late anestrus, proestrus and estrus. Biol Reprod 1982;27:1196–206.
[21] Verstegen J, Onclin K, Silva L, Concannon P. Effect of stage of anestrus on the induction of estrus by the dopamine agonist cabergoline in dogs. Theriogenology 1999;51:597–611.
[22] Zoldag L, Fekete S, Csaky I, Bersenyi A. Fertile estrus induced in bitches by bromocrytpine, a dopamine agonist: a clinical trial. Theriogenology 2001;55:1657–66.
[23] Hull ME, Kenigsberg DJ. Gonadotropin releasing hormone: function and clinical use. Lab Manag 1987;25:51–8.
[24] Concannon PW. Induction of fertile oestrus in aneostrus dogs by constant infusion of GnRH agonist. J Reprod Fertil 1989;39(Suppl.):149–60.
[25] Kutzler MA, Wheeler R, Volkmann DH. Serum deslorelin concentrations in bitches after Ovuplant® administration. Proc Ann Meet Soc Theriogenology Vancouver 2001;13 [abstract].
[26] Kutzler MA, Wheeler R, Volkmann DH. Canine estrus induction using the GnRH agonist, deslorelin. Proc Ann Meet Eur Vet Soc Small Anim Reprod Milan 2001;147–8 [abstract].
[27] McRae GI, Roberts BB, Worden AC, Bajka A, Vickery BH. Long-term reversible suppression of oestrus in bitches with nafarelin acetate, a potent LHRH agonist. J Reprod Fertil 1985;74:389–97.
[28] D'Occhio MJ, Aspden WJ. Endocrine and reproductive responses of male and female cattle to agonists of gonadotrophin-releasing hormone. J Reprod Fertil 1999;54(Suppl.):101–14.
[29] Jacobi GH, Wenderoth UK. Gonadotropin-releasing hormone analogues for prostate cancer: untoward side effects of high-dose regimens acquire a therapeutical dimension. Eur Urol 1982;8:129–34.
[30] Trigg TE, Wright PJ, Armour AF, Williamson PR, Junaidi A, Martin GB, et al. Long-term reversible desexing of male dogs and oestrus postponement of bitches, using a GnRH analogue implant. Proc Adv Dog Cat Exotic Carniv Reprod Oslo 2000;21 [abstract].
[31] Trigg TE, Wright PJ, Armour AF, Williamson PE, Junaidi A, Martin GB, et al. Use of a GnRH analogue implant to produce reversible long-term suppression of reproductive function in male and female domestic dogs. J Reprod Fertil 2001;57(Suppl.):255–61.

[32] Wright PJ, Verstegen JP, Onclin K, Jochle W, Armour AF, Martin GB, et al. Suppression of the oestrous responses of bitches to the GnRH analogue deslorelin by progestin. J Reprod Fertil 2001;57(Suppl.):263–8.
[33] Kutzler MA, Wheeler R, Lamb S, Volkmann DH. Deslorelin implant administration beneath the vulvar mucosa for the induction of synchronous estrus in bitches. Proc Ann Meet Eur Vet Soc Small Anim Reprod Liege 2002 [abstract].
[34] Stich KL, Wendt KM, Blanchard TL, Brinsko SP. Effects of a new injectable short-term release deslorelin in foal-heat mares. Theriogenology 2004;62:831–6.
[35] Shille VM, Thatcher M-J, Lloyd ML, Miller DD, Seyfert DF, Sherrod JD. Gonadotrophic control of follicular development and the use of exogenous gonadotrophins for induction of oestrus and ovulation in the bitch. J Reprod Fertil 1989;39(Suppl.):103–13.
[36] Concannon P, Lasley B, Vanderlip S. LH release, induction of oestrus and fertile ovulations in response to pulsatile administration of GnRH to anoestrous dogs. J Reprod Fertil 1997;51(Suppl.):1–54.
[37] Scrogie NJ. The treatment of sterility in the bitch by use of gonadotrophic hormones. Vet Rec 1939;51: 265–8.
[38] Thun R, Watson P, Jackson GL. Induction of estrus and ovulation in the bitch, using exogenous gonadotropins. Am J Vet Res 1977;38:483–6.
[39] Archbald LF, Baker BA, Clooney LL, Godke RA. A surgical method for collecting canine embryos after induction of estrus and ovulation with exogenous gonadotropins. Vet Med Small Anim Clin 1980;75:230–8.
[40] Wright PJ. The induction of oestrus and ovulation in the bitch using pregnant mare serum gonadotropin and human chorionic gonadotrophin. Aust Vet J 1980;56:137–40.
[41] Wright PJ. The induction of oestrus in the bitch using daily injections of pregnant mare serum gonadotrophin. Aust Vet J 1982;59:123–4.
[42] Chakraborty PK, Wildt DE, Seager SWJ. Induction of estrus and ovulation in the cat and dog. Vet Clin N Am Small Anim Pract 1982;12:85–91.
[43] Chaffaux S, Locci D, Pontois M, Deletang F, Thibier M. Induction of ovarian activity in anoestrous beagle bitches. Br Vet J 1984;140:191–5.
[44] Concannon PW, Verstegen J. Estrus induction in dogs: use of gonadotropins, therapies and dopamine agonists. Proc Ann Meet Soc Theriogenology Montreal 1997;245–7.
[45] Jeukenne P, Verstegen J. Termination of diestrus and induction of oestrus in diestrous non pregnant bitches by the prolactin antagonist cabergoline. J Reprod Fertil 1997;51(Suppl.):59–66.
[46] Cain JL, Cain GR, Feldman EC, Lasley BL, Stabenfeldt GH. Use of pulsatile intravenous administration of gonadotropin-releasing hormone to induce fertile estrus in bitches. Am J Vet Res 1988;49:1993–6.
[47] Vanderlip SL, Wing AE, Felt P, Linkie D, Rivier J, Concannon PW, et al. Ovulation induction in anestrous bitches by pulsatile administration of GnRH. Lab Anim Sci 1987;27:459–68.
[48] Rota A, Mollo A, Marinelli L, Gabai G, Vincenti L. Evaluation of cabergoline and buserelin efficacy for oestrous induction in the bitch. Reprod Dom Anim 2003;38:440–3.
[49] Inaba T, Tani H, Gonda M, Nakagawa A, Phmura M, Mori J, et al. Induction of fertile estrus in bitches using a sustained-release formulation of a GnRH agonist (leuprolide acetate). Theriogenology 1998;49:975–82.