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No heat ... induce heat.

All of the methods reported, when assessed in repeated or large studies **have a significant failure rate** and involve one or more of the following drawbacks: >>>>>>>>>>
Smaller than normal litters in a significant percentage of successful attempts;
Disruption and possible prolongation of the normal cycle;

Theoretically a possibly increased risk of reproductive tract disease due to premature and possibly excessive stimulation of the reproductive tract by the administered hormones or changes in endogenous hormones provoked by the treatment.

Nevertheless, interest remains high in the development of methods that may be safe enough for the female dog with fewer drawbacks, and/or have a sufficiently high success rate as to merit clinical application in the course of breeding management.

Furthermore, some of the current methods would appear to have significant merit for application in cases of prolonged anestrus and for enhancing fertility of research bitches in colonies of dogs maintained as animal-models of heritable or genetically-based diseases of interest in human or veterinary medicine.

Overview:
Some of the methods currently or recently in use as research and/or clinical approaches to the induction of fertile estrus in dogs include:

1, the use of exogenous estrogen to prime the hypothalamic-pituitary-ovarian axis so as to either induce a false pro-estrus that is expected to be followed by a normal proestrus or induce a proestrus that will progress in a fertile estrus when supplemented with a subsequent gonadotrophin administration;

2, the administration of one or more exogenous gonadotropic hormone preparation to stimulate an ovarian response that results in proestrus followed by a fertile estrus with either spontaneous ovulation or ovulation induced by additional hormone (hCG or GnRH) administration;

3, the administration of gonadotropin releasing hormone (GnRH) or a GnRH-agonist in a manner that elicits pituitary release of endogenous gonadotrophins LH and FSH sufficient to provoke an ovarian response that produces normal proestrus and subsequent fertile estrus and spontaneous ovulations;

4, the administration of a dopamine agonist that provokes hypothalamic or pituitary hormone responses that lead in time to a premature but otherwise apparently natural proestrus and fertile estrus.

Variable responses.
It is important to emphasize the term "fertile estrus" and to consider using the term "fertile proestrus" because the stimulation of ovarian activity in a bitch can lead any of the following responses:

1. a "false proestrus" that fails to progress into an estrus or estrus-like changes in behavior and/or reproductive tract morphology;
2. a "false estrus" that follows an induced proestrus and involves many, most or all of the behavioral and orphological changes associated with a normal fertile estrus but is non-ovulatory;
3. a "fertile estrus" that follows an induced proestrus & that has most or all of the characteristics of a normal, spontaneous estrus;

4, in some cases, a "fertile quasi-estrus" or "fertile proestrus" that involves most or all of the endocrinological changes seen in normal proestrus and estrus as well as a fertile ovulation, but also involves a less than normal change in vaginal cytology, vulval swelling and/or receptive behavior, or even an absence of receptive behavior, with fertility only demonstrable by appropriately timed artificial insemination.
It is because of such variation in "responses" to many protocols that the bitch should be carefully monitored for clinical signs including vaginal cytology and changes in vulval and vaginal morphology, as performed for any critical managed breeding, and also monitored for changes in circulating progesterone concentrators that can differentiate between a false and ovulatory estrus.

Normal cycles.
The basic endocrinology of the normal ovarian cycle in dogs involves the following observed changes in peripheral concentrations of hormones and accompanying clinical changes.

Anetrus.
During anestrus, progesterone concentrations decline to their lowest values, typically well below 0.5 ng/ml;
estradiol concentrations are typically observed to be low, but in some are cases variable;
follicle stimulating hormone (FSH) concentrations while variable are typically much higher than seen at other stages of the cycle (except for during the preovulatory gonadotrophin surge);

Luteinizing hormone concentrations are variable, but are on average typically low in comparison to those seen in most other stages of the cycle, with pulsatile elevations in LH occurring at very reduced intervals, often less than every 8-12 h.

Proestrus.
Onset.
The normal stimuli for the initiation of proestrus and the associated sequence of changes in hypothalamic, pituitary and ovarian activity are not fully understood.
However, shortly before the onset of proestrus there is an increase in the frequency of pulsatile elevations in LH and often in those of FSH, with pulse intervals of 1-2 h or less, and a resulting large increase in the mean LH concentration that in terms of percentage increase is far greater than any corresponding increases in mean FSH.
The presumptive basis of this change in pituitary hormone secretion is an increase in the pulse frequency and possibly pulse magnitude of the GnRH released by the hypothalamic GnRH-secreting neurons and possible changes in the sensitivity of the pituitary to GnRH.

Current research suggests that these events can be triggered by pheromones and/or by natural rhythms in hypothalamic activity but only after sufficient diminution of the endocrine actions of the progesterone produced during the luteal phase of the previous ovarian cycle.
Part of the mechanism involved appears to involve increased activity hypothalamic dopaminergic neurons or increased responsiveness of dopamine-sensitive cells, and possible inhibitory effects of prolactin, because the administration of prolactin-lowering doses of a dopamine agonist can often result in the premature initiation of the next ovarian cycle.
The increased LH along with FSH acts to stimulate a cohort of follicles to develop into estrogen-secreting proestrus follicles.

Proestrus and Estrus.
(Here proestrus and estrus refer, respectively, to the phases of the "heat" period just before and just after the onset of the preovulatory LH surge.

This may be the time of the often abrupt transition from proestrus to estrus behavior in many bitches, although the behavioral shift can occur 1-3 days earlier, or 1-4 days later and may not be abrupt.

Mean onset of estrus behavior is 1 day after the LH surge.

Throughout most of the 5 to 20 or more days of proestrus there is a progressive increase in circulating estradiol froma cohort of rapidly developing ovarian follicles, and a progressive decline in LH and FSH concentrations as a result of the inhibitory effects of estradiol and inhibin form the ovaries on pituitary gondadotropin secretion.
Peak concentrations of estradiol in late proestrus prepare the pituitary and hypothalamus for an ensuing surge-release of LH and FSH.

This surge, i.e. the “LH surge”, and the presumed concurrent hypothalamic GnRH surge, apparently occur in response to the failure of fully-developed proestrus follicles to further increase circulating estradiol, to an absolute decline in estradiol at the completion of proestrus-follicle development that reflects limited estradiol secretion combined with increased estradiol metabolism and clearance, and a stimulatory effect of a concomitant rapid rise in concentrations of progesterone that cannot be separated temporally from the initial increase in LH during the preovulatory surge in LH concentrations..

The “preovulatory” LH surge may last 1-3 days, and the FSH surge although typically less dramatic lasts about 1 day longer due to its slower metabolic clearance.

Estradiol continues to decline throughout the 6-11 days of endocrinological estrus, here defined as beginning with the onset of the LH surge and ending with the change typically referred to as the ‘metestrus’ or ‘diestrus’ “shift” in vaginal cytology.
LH and FSH are also low during estrus.

Progesterone increases almost imperceptibly during mid proestrus from less than 0.2 ng/ml top between 0.3 and 0.6 ng/ml, and then in late proestrus at the onset of the LH surge increases rapidly from value of 0.3-0.6 to values of 0.9 to 3.0 ng/ml during the first 12-24 h of the LH surge;
Between the LH surge (Day 0) and ovulation on Day 2 after the LH surge, progesterone is variable but typically increasing at values between 2 and 5 ng/ml;
By Day 4, and two days after ovulation, progesterone is typically 3-8 ng/ml, and by Day 6 after the LH surge is typically between 6 and 12 ng/ml.

Gondaotrophin administration.

The earliest studies utilized serial administrations of proestrus- inducing FSH or FSH-like gonadotropin preparations including PMSG for 10 or more days (with or without later administration of an ovulation inducing dose of an LH-like hormone such as hCG.

Gonadotropin administrations have varied in source, dosage, and bio-potency, as well as in pattern and frequency of administration, and efficacy has ranged from 0 to 30%, and repeatability has been a problem.

PMSG administration at doses of 20 i.u./kg/day for 10 days often causes hyper-secretion of estrogen and has the potential to cause uterine dysfunction and/or uterine disease.

Improved pregnancy rates (50%) occurred when PMSG (20 i.u./kg/d) was administered for only 5 days and immediately followed by hCG (500 i.u./dog once on day 50, the latter as a proestrus-enhancing treatment that apparently further stimulates ovarian follicle development such that the induced proestrus progresses and spontaneously culminates in an estrus in which ovulation occurs during spontaneously (Arnold et al, 1989).

The hCG may have provided a stimulus similar to that provided by increased endogenous LH pulses during natural cycles.

Another approach has been to use an LH-like hormone preparation to induce a proestrus, i.e., HMG with a 1:1 ratio of LH to FSH biopotencies, and to then allow the induced proestrus to proceed spontaneously to an estrus in which the ovulation rate appears to be about 90 % and the fertility rate about 50%.

This use of HMG (2-4 IU/kg/d x 9 d) with its relatively high “LH-content” has been suggested to better substitute for the natural pre-proestrus increase in LH seen in the normal ovarian cycle (Wanke et al, 1997).

During the week prior to natural proestrus, the increase in plasma LH pulse frequency is more obvious, is of greater relative magnitude, and involves a greater percent increase in mean concentrations than any corresponding increase in FSH secretion.

Fertile estrus has also been induced by frequent injections of purified LH.

Estrogen pre-treatments.

Estrogen preparations have been administered as a means to "prime" the bitch for subsequent serial administrations of proestrus-inducing gonadotropin preparations including PMSG or FSH with or without later administration of an ovulation inducing hormone such as hCG.

The improved efficacy of gonadotropin administration following estrogen treatments is not well documented, but could be the result of two or more known effects of estradiol.

Individual administrations of estrogen may cause transient suppressions of LH and FSH secretion via classical negative feedback on the hypothalamus and pituitary and be followed in each case by a rebound release of LH and FSH in turn facilitated by a priming effect of the prior estrogen on GnRH secretion and/or pituitary sensitivity to GnRH.

Any such stimulatory fluctuations in LH and/or FSH although undocumented would likely alter the follicular status of the ovary at the time of subsequent gonadotropin administration.

Alternatively or additionally, estrogen might act directly at the level of the ovarian follicles to stimulate antral follicle development to more advanced stages.

Estrogen administration alone.

Some studies and clinical trials demonstrated that short term estrogen treatment alone in some bitches can produce an induced proestrus that persists and is subsequently followed immediately by a fertile estrus, without any gonadotropin administration.

The success rate is variable and appears to have be greatest in bitches that have been observed, claimed or assumed to have experienced a prolonged or persistent anestrus, or to be in late anestrus, prior to estrogen treatment.

The mechanisms involved may include one or both of those previously mentioned.
The report with the greatest success rate administered the estrogen in late anestrus, i.e. after 3-4 months into an induced-anestrus in bitches with a luteal phase was terminated by prostaglandin-F administration. The protocol used diethylstilbestrol, 5mg tablets, p.o., and daily for 6-9 days, i.e. until 2 days into an induced proestrus (Bouchard et al., 1993); the DES dose in mongrel dogs likely approximated 0.2-0.3 mg/kg/d.

GnRH and GnRH-Analog administration.
The increased LH pulse frequency observed prior to spontaneous proestrus has been mimicked in bitches in early or mid-anestrus using the intravenous administration of relatively large doses of native GnRH (0.2-0.5 ug/kg) every 90 minutes to provoke LH pulses at that rate (Concannon et al, 1997).
The initially large LH and FSH pulses become progressively smaller during the GnRH-induced proestrus as they do in natural proestrus, and usually result in a normal proestrus base on observed changes in estradiol, vaginal cytology and external genitalia, and one which is often followed by a spontaneous LH surge and estrus onset before or immediately after the termination of 10-14 days of GnRH administration.
Less frequent injections of large doses of a GnRH agonist have also been successful.
Neither pulse rate nor pulsatility itself appear to be critical in provoking a positive ovarian response.
In fact, constant GnRH-agonist administration for 10-14 days via subcutaneous osmotic-pumps requiring only a single administration have also been observed to result in a high rates of proestrus induction, spontaneous ovulation, and pregnancy (Concannon et al, 1993).
The most successful doses of three GnRH super-agonists estimated to be 160—180 x that of native GnRH ranged from 0.6-1.8 ug LUT /kg/d for lutrelin and approx.

1.0 -1.5 ug NAF/ kg/d for nafarelin or a nafarelin analog, based on recent studies (Concannon et al, unpublished).
Pregnancy rates using lutrelin have been 70-100% in several trials;
The material is not commercially available.
Others have successfully used single subcutaneous injections of buserelin (mixed with silastic), a GnRH-analog with a potency of about 15-30 x native GnRH (Cinone et al, 1996);
The 50 ug/kg dose likely translates into some 4 to 5 ug BUS/kg/d when applied to beagle-sized dogs;
In contrast buserelin at 1.5 mg/kg every 8 h failed to reliably induce proestrus (Rota et al, 2002).
Researchers at Cornell (Kutzler et al, 2002; Volkmann et al, 2005) have demonstrated the successful use of single subcutaneous or sub-mucosal (vulval) insertions of a whole or a half biodegradable capsule containing the GNRH super-agonist deslorelin,
a commercial formulation marketed for ovulation-induction in estrus horses (Ovuplant). Deslorelin has a biopotency about 150 x GnRH and the implants likely provided doses of 4-8 ug/kg/d in beagle-sized dogs based on manufacturer's claimed release rates.
However, pregnancy maintenance and litter sizes varied among trials.
Implants of the agonist leuprolide have also been successfully used.
Except for the lutrelin studies (Concannon, 2005) there have been no published determinations of the optimal dosage
or duration for the other GnRH agonists.
Dopamine Agonist administration.
Several studies have reported the use of a dopamine agonist (DA) administered orally at doses sufficient to lower plasma prolactin
as a means to terminate anestrus either prematurely in normal bitches or therapeutically in cases of prolonged or persistent anestrus.
The efficacy has been anecdotally estimated to be about 70%, and possibly higher in bitches with prolonged anestrus;
The resulting proestrus, when induced, has occurred after a variable duration of treatment ranging from 8 to 40 days;

The average appears to be about 20 days;
Duration appears to be dependent on the stage of anestrus, with longer treatment required in early anestrus.
Whether the simultaneous reduction in prolactin is part of the mechanism of action or if the mechanism involves other or additional dopaminergic effects is not known.
However, efficacy appears to depend on a dopamine responsiveness sufficient to also cause suppression of prolactin;
Bitches that fail to experience suppression of prolactin also fail to show a clinical proestrus response.
Two DA treatments reported to be effective have included bromocriptine (Parlodel) at 0.05.or 0.1 mg/kg, p.o., q.d.
Or bid, and cabergoline (Galostop) at 5 ug/kg, p.o, q.d.; administration is until an induced proestrus is pronounced for 2 days or until the onset of estrus.
Conclusions and caveats.
Estrus induction protocols are sufficiently variable in results that they are probably not appropriate to electively terminate anestrus in normal cycling dogs because a failure is likely to cause a cycle interruption with unknown consequences and a delay in an otherwise normal ovarian cycle.
An exception may be the use of a dopamine against where treatment failure does not appear to alter unduly the underlying cycle.
Several protocols may be of benefit in cases of prolonged or persistent anestrus, in that success rates of 50-70% or greater may represent a valid cost benefit ratio in bitches in which resumption of reproductive cycles is considered important.
Likewise, their application can be of use in research bitches in which the added expense of a long anestrus hinders or even precludes cost-effective reproductive or genetic research.
Anestrus status should be confirmed by vaginal cytology and progesterone assay.

Uterine complications that are potential sequellae of estrogen or gonadotrophin treatments that can cause hyper-estrogenization appear not to be of special concern in GnRH-agonist based protocols that are geared to induce a physiologic proestrus.
GnRH-induced estrus 30-60 days into natural or PGF-induced anestrus can have high fertility.
Estrus induced 10-20 days after PGF-induced luteolysis can result in low ovulation rates, low fertility, and/or uterine complications.
Additional studies are needed to determine optimal doses of readily available GnRH agonists, as well as the optimal timing and dosing and application of potentially useful commercial gonadotropins and GnRH implant formulations.
Induce heat cycle drawbacks.

Hormonal control of estrus.
The estrous cycles of dogs are not as easily manipulated as in other species.

Although onset of a particular cycle may be delayed, return to normal cycling is highly variable.
Induction of estrus is expensive, unreliable, and rarely justified; it can succeed only in normal, anestrus animals.

Ovariohysterectomy is the best method to prevent estrus in the bitch and queen.
Long-term suppression of estrus in the bitch may be accomplished with mibolerone, a synthetic androgen.
The dose is 3 µg/kg/day except for German Shepherd Dogs and their crosses, which require 6 µg/kg/day.
Therapy must begin =1 mo before proestrus.
Common side effects are clitoral hypertrophy, vaginitis (especially in prepubertal bitches), increased activity of skin sebaceous glands, mild epiphora, and alterations in hepatic function studies.

Return to estrus after treatment ends is variable but is ~70-90 days.
Conception rates are reportedly normal by the second cycle after treatment.
If given to pregnant bitches, the urogenital system of female puppies will have severe developmental anomalies.
Mibolerone should not be given to cats.
Estrus can be temporarily controlled with megestrol acetate, asynthetic progestogen.

In bitches, megestrol prevents estrus if given at 2.2 mg/kg/day for 8-10 days beginning during the first 3 days of proestrus.
Efficacy is ~93%.
Return to estrus is variable but often is ~2 mo earlier than expected, presumably a result of preventing the normal luteal phase.
When used to postpone an anticipated estrus, megestrol is given at 0.55 mg/kg/day for 32-40 days beginning =7 days before onset of proestrus.
Efficacy is ~97%.
Return to estrus is variable but, if timed properly, approximates the next regularly anticipated cycle.
Side effects include increased appetite, weight gain, and personality changes (usually more docile).
Cystic endometrial hyperplasia may also develop.
Rarely, lactation occurs.
Megestrol is not approved for use in cats in the USA, but European data indicate efficacy for estrus suppression.
In addition to the side effects described above for bitches, cats may develop diabetes mellitus during treatment.
Ovulation can be induced in estrual queens physically or, more reliably, hormonally to produce a luteal phase (diestrus or metestrus) of ~45 days.
Physical methods include mating with a vasectomized tom (very effective) or inserting a sterile swab or glass rod into the vagina.

The latter should be performed repeatedly for best results. Hormonal methods include administration of HCG at 500 IU/cat or Gn-RH at 25 µg/cat.
Both are given IM, daily for 2 days.

The use of progestogens, especially repositol injectable, is discouraged in both dogs and cats because of development of cystic endometrial hyperplasia and subsequent pyometra, mammary neoplasia, and diabetes mellitus.

The use of injectable testosterone, as is practiced commonly in game dogs and racing Greyhounds, frequently leads to future difficulties with fertility.