

# Clinical Efficacy of Whelping Induction Protocol using Mifepristone in Advanced Pregnant Bitches

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**Abstract:** *An efficient and safe protocol for induction of whelping in dogs is an important emerging option in canine reproduction as an alternative to elective/planned caesarean. The aim of the present study was to assess the efficacy and safety of whelping induction in advanced pregnant bitches with oral administration of mifepristone. The study was conducted in 24 bitches in advanced pregnancy usually considered for a planned elective caesarean. These animals were administered mifepristone at the rate of 2.5-3 mg/kg late pregnancy body weight, orally twice daily, at 8 h interval for a single day. The average time taken for induction of whelping was  $23.58 \pm 2.47$  (range 8-67) h in 23 bitches which responded positively to the protocol (95.83% response rate). Within 24 h of initial dose of mifepristone 17 bitches (70.83 %) whelped and within 36 h five more whelped (91.6%). It was also found that the expulsion phase length in 23 bitches which whelped averaged  $3.82 \pm 0.47$  (range 1-10) h and the percentage of still births was 10.8 per cent. The administration of mifepristone in dogs in advanced pregnancy can be considered as a good alternative to surgical management especially when the foetal heart rates are above critical limits and the foetal head diameter does not pose a threat by way of foeto-maternal disproportion so as to prevent a normal whelping after induction.*

**Keywords:** whelping induction; advanced pregnancy; bitches; mifepristone

## 1. Background

An accurate prediction of date of whelping in the bitch can prevent or minimize reproductive losses by appropriate clinical interventions. Due to the variation in the timing of ovulation, multiple breeding dates and the prolonged longevity of canine spermatozoa in the uterus it is often difficult to predict the whelping date. Veterinarians are often under pressure to resort to caesarean sections especially in precious pregnancies due to numerous requests from anxious dog owners. The search for an efficient and safe protocol for induction of whelping in dogs is an important field in canine reproduction.

The average gestation period (interval from first mating to parturition) was 63 or 64 days although it could range from 56-68 days [1]. In contrast, the gestation length defined from pre-ovulatory LH peak was reported to be  $65 \pm 1$  day [2]. Many at times breeders may not have estimated the progesterone profile to detect the day of LH peak and therefore using these values for prediction is not practical. Therefore, any stress to the dam or foetus/es during advanced pregnancy or an abnormally prolonged gestation may demand a planned or elective caesarean.

In bitches, during gestation, the corpora lutea are the sole source of progesterone (P4) which is necessary for maintaining pregnancy [3]. Prolactin and possibly gonadotrophic hormones have definite role in maintaining the corpora lutea during the second half of the luteal phase or gestation [4,5,6]. A sharp decline in the plasma P4 concentration before whelping appears to be essential for whelping even though the factors responsible for pre-partum luteolysis still remains unclear [7,8].

Progesterone receptor blockers like aglepristone and mifepristone are competitive antagonists of P4 receptor [9-15]. On perusal of literature it was observed that even though mifepristone has been suggested as a drug for induction of whelping, reports pertaining to the dose, stage of pregnancy when the drug can be used safely for dam and litter, time required for induction, puppy survival rates and complications, if any, when the drug was used for clinical induction of whelping, were scanty.

The aim of the present study was to assess the efficacy and safety of induction of whelping in advanced pregnancy in bitches with oral administration of mifepristone.

## 2. Method of Research

### Case selection

The study included 24 apparently healthy bitches of different breeds in advanced pregnancy between one to eight years of age. The breed wise break up of animals was as follows; Rottweiler (n = 12), Labrador (n=5), Dachshund (n= 5), German Shepherd (n=1) and Pug (n = 1).

### Criteria for selection

The criteria for selection included mainly those usually considered for a planned elective caesarean *viz.*, a bitch with previous history of dystocia, to maximise puppy survival in a particularly precious breeding, any stress to the dam or foetus/es or an abnormally prolonged gestation. Various stress factors for the dam included inappetence, vague signs of illness without any progress or elevated body temperature (considering the physiological state a temperature above 99-100 °F was suggestive of some kind of foetal or maternal stress). The protocol was also performed in cases of consistently slow foetal heart rates (<150 bpm) [16] or when the rectal temperature of the dam

was below 99 °F where a planned elective surgery could be safely performed[17].

#### **Treatment protocol of mifepristone**

After clinico-gynaecological examination, these animals were administered mifepristone at the rate of 2.5 mg/kg late pregnancy body weight for bitches above 20 kg and 3.0 mg/kg for those below 20 kg, orally twice daily at 8 h interval for a single day. Those animals that did not whelp after 24 h of initial mifepristone administration were given oxytocin at the rate of 0.15 IU /kg body weight subcutaneously.

#### **Clinical interventions to accelerate parturition**

The usual clinical interventions to accelerate parturition such as administration of 10 per cent calcium gluconate solution at the rate of 0.5-1.5 ml/kg intravenously [18], 25 per cent dextrose at the rate of 5-25 ml per bitch intravenously [19] and oxytocin 2-5 IU total dose and repeated at 60-90 min interval were resorted to, wherever necessary. Digital manipulation or forceps delivery using whelping forceps was done in cases where it was needed.

#### **Observations and Follow up**

The gestational age on the day of initial treatment based on last breeding date given by the owner and the lowest foetal heart beat (beats per minute- bpm) in each litter based on B mode ultrasonography were recorded. The rectal temperature of the bitches on the day of treatment and 24 h after treatment wherever possible (only 9 animals were presented after 24 h for review) were measured.

The time taken for induction of whelping (duration in hours from initial dose of mifepristone to whelping), expulsion phase length (time duration between first to last pup delivery), puppies born live and stillborn were also recorded.

#### **Statistical analysis**

Statistical analysis was performed using SPSS for windows version 21 (SPSS Inc., Chicago, USA).

### **3. Results**

The mean gestational age of the 24 bitches in the study from last breeding date was  $64.13 \pm 0.414$  (range 61-68) days at the time of first dose of mifepristone (Table 1). The average rectal temperature of these animals were  $101.16 \pm 0.22$  (range 99.6 to 104.0) °F. The foetal heart rates ranged from 0 - 200 (mean  $135.17 \pm 13.19$ ).

#### **Time taken for induction of whelping**

The average time taken for induction of whelping (delivery of first pup) was  $23.58 \pm 2.47$  (range 8-67) h in 23 bitches which responded positively to the protocol (95.83% response rate). Within 24 h of initial dose of mifepristone 17 bitches (70.83 %) whelped and within 36 h five more whelped (91.6%). A Rottweiler which had a singleton pregnancy took 67 h to deliver the stillborn puppy which had feeble heart beats at the time of initial ultrasonography. One of the bitches in which none of the foetuses exhibited any heart beat at the time of initial ultrasonography did not

respond to treatment within 24 h and a Caesarean section had to be resorted to in that case (Figure 1).

#### **Expulsion phase length**

It was also found that the expulsion phase length in 23 bitches which whelped averaged  $3.82 \pm 0.47$  (range 1-10) h.

#### **Puppy viability at birth**

A total of 111 puppies were produced by the 24 bitches in the study out of which 19 were still born (17.12 % of still birth, 82.88% live birth). Among the still births 7 puppies were produced by two bitches in which the foetal heart rates were nil at the time of initial ultrasonography. Thus, if these two bitches were excluded, the percentage of actual still births (n=12) would be 10.8 per cent.

#### **Complications or side effects**

None of the bitches exhibited any complications or side effects after administration of mifepristone.

#### **Follow up**

The average fall in rectal temperature 24 h after initial dose of mifepristone was  $1.2 \pm 0.24$  (range 0.66 - 1.74) °F in nine bitches which were presented for review on the following day. Since the cases included in the study were client owned clinical cases from distant places, most of the bitches that responded positively to treatment were not presented for check up on the next day.

### **4. Discussion**

The mean gestational age of the 24 bitches in the study at the beginning of induction trials was  $64.13 \pm 0.414$  days which was well within the normal gestation period reported[1]. The significant fact to be considered in this discussion is that gestational period was calculated from the last breeding date in view of the fact that this was the most reliable history that could be considered. And this breeding would have taken place three days after the first breeding.

The average temperature of these animals at the commencement of treatment was  $101.16 \pm 0.22$  °F which can be considered to be an elevated temperature in view of the physiological state of the animal. Small falls in temperature is usually observed during the last week of pregnancy as serum P4 declines and rectal temperature decreases below baseline abruptly by 2-3 °F around 6 to 24 hours prior to whelping [20-23]. The foetal heart rates of most of the bitches averaged  $135.17 \pm 65.63$  bpm and therefore most of these litter were having foetal heart beats below the critical levels suggested [16] and an immediate surgical management was otherwise warranted.

The average time taken for delivery of first puppy after the administration of mifepristone in 23 out of the 24 bitches was 23.58 h. The percentage of bitches that whelped within 24 h of the first dose of mifepristone was 70.83 whereas within 36 h, it became 91.6. The average fall in rectal temperature 24 h after the initial dose of mifepristone was

1.2 ± 0.24 °F which indicated the possibility of a lowering of P<sub>4</sub> in response to its antiprogestosterone effect [13,24]. Detailed studies with regard to the hormonal profile are further warranted.

The actual stillbirth percentage of 10.8 % observed in the study was within the normal stillbirth percentage of 10.9 % reported [25]. It could also be inferred that if the induction is done before the foetal heart rates reach the critical levels puppy survival could be improved greatly.

The results of the study broadened our understanding of both the efficacy of mifepristone in whelping induction protocols as well as its safety from the point of view of both dam as well as off spring wellbeing.

The present study concluded with the observation that the administration of mifepristone in dogs in advanced pregnancy can be considered as a good alternative to surgical management especially when the foetal heart rates are above critical limits and the foetal head diameter does not pose a threat by way of foeto-maternal disproportion so as to prevent a normal whelping after induction. However, the role of oxytocin 24 h after the first dose of mifepristone as well as the necessity of having a twice daily administration of mifepristone remains to be assessed after further research.

## 5. Competing interests

The authors declare that they have no competing interests.

## 6. Author Contributions

SS participated in the designs of the study, carried out the initial trials, recruitment of cases, clinical management, follow up of cases and the manuscript writing. LBK, RSN and SAPS participated in the collection of references for the study, assisted in the recruitment, clinical management and follow up of cases. All authors read and approved the final manuscript.

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## References

- [1] Concannon, P.W. Physiology of reproduction, In: Small Animal Reproduction and Infertility. Burke, T.J. (eds.) Lea and Febiger. *Small Animal Reproduction and Infertility*. Philadelphia. 1986, 23-77.
- [2] Concannon, P. and Rendano, V. Radiographic diagnosis of canine pregnancy: onset of foetal skeletal radiopacity in relation to times of breeding, preovulatory luteinizing hormone release, and parturition. *Am. J. Vet. Res.* 1983, **44**: 1506-11.
- [3] Tsutsui, T. Effects of ovariectomy and treatment on the maintenance of pregnancy in the bitch. *Nippon JuigatuZasshi*. 1983, **45**: 47-51.
- [4] Post, K., Evans, L.E., Jochle, W. Effects of prolactin suppression with cabergoline on the pregnancy of the bitch. *Theriogenology*. 1988, **29**: 1233-43.
- [5] Okkens, A.C., Bevers, M.M., Dieleman, S.J., Willimse, A.H. Evidence of prolactin as the main luteotrophic factor in the cyclic dog. *Vet. Quart.* 1990, **12**: 193-201.
- [6] Onclin, K., Verstegen, J.P., Concannon, P.W. Time-related changes in canine luteal regulation: *in vivo* effects LH on progesterone and prolactin during pregnancy. *J. Reprod. Fertil.* 2000, **118**: 417-24.
- [7] van der Weyden, G.C., Taverne, M. A.M., Dieleman, S.J., Wurth, Y., Bevers, M.M. and Van Oord, H.A. Physiological aspects of pregnancy and parturition in dogs. *J. Reprod. Fert.* 1989, **39**: 211-24.
- [8] Concannon, P. W., Isaman, L., Frank, D.A., Michael, F.J. and Currie, W.B. Elevated concentrations of 13,14-dihydro-15-keto-prostaglandin F-2 $\alpha$  in maternal plasma during prepartum luteolysis and parturition in dogs (*Canis familiaris*). *J. Reprod. Fert.* 1988, **84**: 71-77.
- [9] Van look P.F.A., Bygdeman, M. In: Milligan S.R. Editor. *Anti-progestational steroids: a new dimension in human fertility regulation*. Oxford Reviews of Reproductive Biology. OUP; 1989. 1-16.
- [10] Cadepond, F., Ulmann, A. and Baulieu, E.E. RU486 (mifepristone): Mechanisms of action and clinical uses. *Annu. Rev. Med.* 1997, **48**: 129-56.
- [11] Galac, S., Kooistra, H.S., Butinar, J., Bevers, M.M., Dieleman, S.J. and Voorhout, G. Termination of mid gestation pregnancy in bitches with aglepristone, a P4 receptor antagonists. *Theriogenology*. 2000, **53**: 941-50.
- [12] Fieni, F., Marnet, P. G., Martal, J., Siliart, B., Touzeau, N., Bruyas, J.S. and Tainturier, D. Comparison of two protocols with a progesterone antagonist aglepristone (RU534) to induce parturition in bitches. *J. Reprod. and Fert. Suppl.* 2001, **57**: 237-242.
- [13] Baan, M., Taverne, M.A.M., Kooistra, H.S., de Gier, J., Dieleman, S.J. and Okkens, A.C. Induction of parturition in the bitch with the progesterone-receptor blocker aglepristone. *Theriogenology*. 2005, **63**: 1958-1972.
- [14] Baan, M., Taverne, M. A. M., de Gier, J., Kooistra, H.S., Kindahl, H., Dieleman, S. J. and Okkens, A. C. Hormonal changes in spontaneous and aglepristone-induced parturition in dogs. *Theriogenology*. 2008, **69**: 399-407.
- [15] Fieni, F. and Gogny, A. Clinical protocol for the induction of parturition in the bitch [abstract]. In: England, G., Concannon, P. and Schäfer-Somi, S. (Eds.), *Proceedings of the 6th International Symposium on Canine and Feline Reproduction & 6th Biannual European Veterinary Society for Small Animal Reproduction Congress*; 9<sup>th</sup> - 11<sup>th</sup> July, 2008, Vienna, Austria. European Veterinary Society for Small Animal Reproduction, University of Veterinary Science.
- [16] Kim, Y. H., Travis, A. J. and Meyers-Wallen, V.N. Parturition prediction and timing of canine pregnancy. *Theriogenology*. 2007, **68**: 1177-1182.

- [17] Smith, F.O. Challenges in small animal parturition— Timing elective and emergency cesarian sections. *Theriogenology*.2007, **68**: 348–353.
- [18] Noakes, D.E., Parkinson, T.J. and England G.C.W. *Veterinary reproduction and obstetrics*. (9<sup>th</sup>Ed.). 2009, 245
- [19] Ramsey. I. In: Ramsey (ed).*BSAVA small animal formulary*. (7<sup>th</sup> Ed). British small animal veterinary association, Gloucester.2011.
- [20] Concannon, P. W., Powers, M. E., Holder, W and Hansel, W. Pregnancy and parturition in the bitch. *Biol. Reprod*. 1977.**16**: 517–526.
- [21] Johnston, S. D., Root Kustritz, M. V. and Olson, P. N. S. In: Canine and Feline Theriogenology(2<sup>nd</sup>Ed.). Philadelphia, WB Saunders. 2001,122-128.
- [22] Linde-Forsberg C. Abnormalities in pregnancy, parturition andthe periparturientperiod. In: Ettinger S.J., Feldman E.C.(eds).Textbook of veterinary internal medicine. 6th Ed., Elsevier Saunders; 2005, 1655–67.
- [23] Johnson C.A. Pregnancy management in the bitch. *Theriogenology*. 2008, **70**: 1412–1417
- [24] Concannon, P .W., Yeager A., Frank, D and Iyampillai, A. Termination of Pregnancy and induction of premature luteolysis by the anti progestagen, mifepristone in dogs. *J. Reprod Fertil* .1990, **88**: 99 – 104.
- [25] Indrebø,A., Trangerud,C. and Moe,L. Canine neonatal mortality in four large breeds.*Acta.Vet.Scand*.2007, 49(Suppl.1):S2website:<http://www.actavetscand.com/content/49/S1/S2>