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Medical management of canine high-risk pregnancies with single pup syndrome#

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Abstract

Bitches carrying a single pup can be considered as high-risk pregnancy with a greater risk of uterine inertia and obstructive dystocia. Successful management of singleton pregnancies in dogs requires early identification of the condition and the implementation of a safe and effective management plan that minimises negative effects on both the mother and the newborn. The present study investigated the efficacy and safety of a combination of progesterone receptor antagonist, mifepristone and prostaglandin E1 analogue, misoprostol in induction of whelping in six bitches with singleton litter. All the bitches in the treatment group successfully whelped viable puppies (100 per cent) with no clinical intervention, whereas the spontaneously whelped bitches with single pup was associated with a greater number of still births (50 per cent) and clinical interventions (100 per cent).

Keywords: Single pup syndrome, mifepristone, misoprostol

Higher risk of maternal, foetal and/or perinatal morbidity or mortality can be expected in high-risk pregnancies than the normal whelping. In singleton pregnancy, the inadequate stimuli to initiate parturition cascade can lead to extended duration of gestation and chances of dystocia will be high due to foetal oversize and inadequate uterine stimuli (Smith, 2007). Medical induction of whelping is a critical life-saving intervention in such high-risk pregnant dogs carrying single pup, that reduces adverse outcomes and can avoid complications associated with a caesarean section (CS). Progesterone receptor antagonists such as aglepristone and mifepristone were proved

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successful for induction of whelping (Niharika, 2014; Jayakumar *et al*., 2017; Simon *et al*., 2017). In this context, an accurate prediction of the whelping day is imperative for the veterinarian to allow better planning for labour induction so as to improve neonatal survival and minimise neonatal death.

Induction of whelping using mifepristone alone, without any uterotonic agents may lead to incomplete parturition due to inadequate prepartal elevation of $PGF_{2\alpha}$ (Baan *et al*., 2005). There are reports of successful induction of whelping with combinations of progesterone receptor antagonists and uterotonic agents such as $PGF_{2\alpha}$ or oxytocin (Niharika, 2014; Raheema, 2018). Augmentation of labour with traditionally used uterotonic agents like oxytocin is difficult in a home setting and at that time there is a demand for an alternate and safe uterotonic agent. Misoprostol, a prostaglandin E1 (PGE1) analogue is characterised by strong uterine contracting effects and is used extensively in human obstetrics for labour augmentation and cervical relaxation at low to high doses with different time intervals and different routes (Tang *et al*., 2007). Intravaginal administration of misoprostol along with mifepristone have resulted in successful induction of whelping in canine high-risk pregnancies with small litter size in terms of neonatal survivability as well as less requirement of medical and surgical assistance for completing the whelping process (Raheema, 2018; Peetala *et al.*, 2019). However, studies on the reliability of oral misoprostol as uterotonic agent in augmentation of labour in bitches with single pup are lacking in veterinary literatures. Hence, this study focused on the efficacy and safety of mifepristone in combination with oral misoprostol for the management of high-risk pregnancies in dogs with singleton litter.

Materials and methods

Bitches presented to Teaching Veterinary Clinical Complex, Mannuthy for confirmation of pregnancy was utilised for the study. The study population included breeds such as Beagle (n=3), Labrador Retriever (n=3), Siberian Husky (n=2), German Shepherd (n=1), Pug (n=1), Rottweiler (n=1) and Shiba Inu (n=1) aged between 1.5 to 4 yr. These bitches were confirmed pregnant by transabdominal ultrasonography between 30 to 62 days of last breeding date and the expected day of delivery was determined using the formula DBP (d) = (BPD-25.11)/0.61 for small sized breeds and (BPD-29.18)/0.7 for medium and large sized breeds, where DBP is days before parturition and BPD is biparietal diameter (Luvoni and Grioni, 2000). Radiography performed after 55 days of gestation confirmed the presence of single foetus. Considering the risk associated with singleton pregnancy, all the six animals with average foetal heart rate (FHR) of 221.33 ± 4.53 bpm were subjected to medical induction of whelping at 62 d of gestation based on sonographic foetal biparietal diameter. Mifepristone was administered orally @ 5 mg/kg b.wt. followed by misoprostol @ 5 µg/kg b.wt. orally at four-hour interval after the onset of cervical relaxation until completion of whelping or upto a maximum of four doses. The serum progesterone levels were estimated on the day of commencement of induction treatment and on the day of initiation of whelping.

Six bitches with singleton pregnancies presented to the hospital with signs such as restlessness, greenish vaginal discharge or abdominal straining were taken as control animals. Parturition was initiated in all the bitches of control group which was confirmed by the presence of foetal bag or foetus on vaginoscopic examination. When no progression of labour was noticed like absence of straining efforts, the bitches were treated with intravenous administration of 25 per cent dextrose @ 5-25 mL per bitch, along with 10 per cent calcium gluconate @ 0.2-0.5 mL/kg b.wt., but not exceeding a total dose of 10 mL and oxytocin (PITOCIN) @ 2 IU per bitch IM 15 min after calcium administration. Obstetrical interventions such as lubrication with carboxy methyl cellulose, feathering, traction by hand/whelping forceps were performed. Unsuccessful cases were immediately subjected to caesarean section (CS).

The efficacy of the treatment protocol was evaluated compared to the bitches that initiated parturition spontaneously, based on the still birth rate, duration of whelping and

number of vaginal deliveries without any clinical interventions.

Results and discussion

In the treatment group, the animals confirmed of single pup syndrome and foetal heart rate (FHR) of more than 200 bpm were subjected to medical induction of whelping with progesterone receptor antagonist, mifepristone at 62 d of gestation determined based on the sonographic foetal head diameter. The six bitches in the control group were presented with signs of parturition and transabdominal ultrasonography revealed 65 to 70 d of gestational age. In three of the six bitches in control group, foetal heart beat was absent indicating dead foetus. In single pup pregnancies, inadequate stimuli for initiation of parturition *ie.* insufficient cortisol release from the foetus to stimulate $PGF_{2\alpha}$ production by fetoplacental unit which causes luteolysis, result in prolonged gestation (Smith, 2007). Three dogs in the control group experienced foetal death due to their extended gestation period compared to the induced dogs. This can be attributed to the inability of zonary placenta to meet the increased demands of the growing foetus, as well as the lack of early prediction of the whelping day through ultrasonographic examination.

In all the bitches under study, expected date of parturition and thus the gestational age was determined based on sonographic foetal biparietal diameter. As the dogs were presented with only breeding records and no peri-oestrous parameters available, ultrasonography was useful for successful estimation of the gestational age (Sridevi, 2013). It is essential to make sure that the foetus has accomplished but not exceeded its required gestational age before delivery. High accuracy of whelping prediction based on the foetal biparietal diameter was reported by Luvoni and Grioni (2000). Hence, the sonographic foetal determinants of head diameter were used in this study to determine the gestational age. When the gestational age was determined not less than 62 d, the dogs were subjected to whelping induction.

Physiological examination revealed elevated respiratory (34.01±1.18 and 33.83 ± 0.86 per minute) and pulse rate (118.25±2.78 vs 120 ± 2.77 per minute) in treatment and control dogs, respectively. This could be attributed to the increased metabolic demand, oxygen consumption and cardiovascular function in pregnancy (Lamm and Makloski, 2012). Haematology revealed that all pregnant bitches were under a physiological stage of anaemia characterised by lower values of TEC (4.61 ± 0.16 Vs 4.32 ± 0.12×10^{6}/µL), VPRC (32.95 ± 1.37 Vs 31.02 ± 1.79 per cent) and haemoglobin concentration (11.32 ± 0.17 Vs 10.89 ± 0.67 g/dL) which could be attributed to the increased plasma volume in order to meet the increased metabolic demands of the foetuses and subsequent haemodilution (Ryan and Wagner, 2006 and Magnus *et al*., 2023).

Before treatment, none of the dogs had labour initiation as evinced by the absence of cervical dilatation. These dogs were given progesterone receptor antagonist, mifepristone for induction of whelping followed by PGE1 analogue, misoprostol as uterotonic agent. In spontaneous whelping group, three bitches showed signs of whelping like greenish discharge and straining 24 h prior to presentation with non-viable foetuses and rest of three animals exhibited foetal bag on vaginoscopic examination. The dogs in the whelping induced group exhibited a notably reduced gestation period (63.63 ± 0.19 d) in comparison to the canines that gave birth spontaneously (66.83 ± 0.87 d) ($p<0.05$).

Serum progesterone levels on the day of treatment in those bitches where whelping was induced were 3.62 ± 0.31 ng/mL, signifying that the process of whelping has not initiated in these dogs. The levels decreased to 2.27 ± 0.07 ng/mL at the initiation of whelping. This decrease in progesterone concentration after mifepristone administration can be attributed to the binding of antiprogestins to the progesterone receptors of corpus luteum thereby downregulating the expression of StAR (steroidogenic acute regulatory protein) as well as 3β-HSD (3β-hydroxysteroid-dehydrogenase) which are essential for production of progesterone by the CL (Kowalewski *et al*., 2009). In dogs with spontaneous whelping, the serum progesterone levels dropped below 2 ng/mL due to complete

luteolysis (Johnson, 2008). However, in the dogs where whelping was induced, the progesterone concentration was more than 2 ng/ml at the day of whelping. This high concentration of progesterone in circulation might be due to incomplete luteolysis and progesterone receptor blockade caused by the mifepristone. The observed rise can also be attributed to the fact that mifepristone exhibits a higher affinity for progesterone receptors compared to the natural steroid hormone. Furthermore, as mifepristone emulates a reduction in progesterone levels, thereby eliminating negative feedback at the hypothalamus level, it is likely to stimulate the secretion of LH and FSH at the pituitary gland. Consequently, this stimulation results in an augmented secretion of progesterone (Baan *et al.*, 2008).

The bitches of treatment group expressed foetal bag on vaginoscopic examination within a short and predictable time frame 39.80 ± 4.56 h (25.50 -57.83 h) and expulsion of pups were observed between 31.00-65.00 h (47.94 ± 5.04 h) following administration of the first dose of mifepristone. None of the six female dogs exhibiting single pup syndrome required any clinical interventions, and all delivered viable foetuses successfully. In the control group, three dogs delivered vaginally after medical management and three failed to respond to treatment and were subjected to CS. Live birth rate observed in the spontaneous whelping group was 50 per cent. Viable foetuses were delivered by two dogs that underwent CS and one dog that received medical treatment.

In the present study, mifepristone was used in combination with misoprostol. It was observed that all bitches (6/6) delivered live pups without the need of any clinical intervention. On the contrary, in the case of spontaneous whelping, all the female dogs required clinical intervention and only achieved a live birth rate of 50 per cent. Furthermore, the duration required for the expulsion of the pup subsequent to medical intervention exhibited a significant decrease in the treatment group, measuring at 8.32 ±1.18 h, in contrast to the spontaneous whelping, which recorded a considerably longer time of 26.75 ±5.12 h ($p<0.05$). Peetala *et al*. (2019) assessed the efficacy of a whelping induction protocol in six bitches with singleton pregnancy using mifepristone @ 5 mg/kg b.wt. per orally at 12 h interval followed by intra vaginal administration of misoprostol. The misoprostol was administered @ 200 µg for bitches with ≤ 20 kg b.wt. and 400 µg for bitches with > 20 kg b.wt., 12 h after second dose of mifepristone. However, 16.67 per cent of animals (1/6) delivered within 16 h after the first dose of mifepristone without the need for misoprostol to be administered. There was successful whelping induction in all the bitches with 100 per cent live birth rate and no need of additional clinical assistance. All the animals with single pup that initiated whelping spontaneously, suffered dystocia and required medical or surgical assistance during whelping.

Successful delivery of healthy viable single puppies following medical induction with mifepristone could be attributed to the timely

Table 1. Efficiency of medical induction of whelping in canine high-risk pregnancy with single pup syndrome

Parameters (Mean ± SE)	Treatment group	Control group	p value
Gestation length (d)	$63.63^{a} \pm 0.19$	$66.83^{b} \pm 0.87$	0.017
Time of expulsion of pup from start of misoprostol administration/ medical management (h)	$8.32^{a} \pm 1.18$	$26.75^{b} \pm 5.12$	0.039
Time interval from initiation of treatment to beginning of whelping (h)	39.80 ± 4.56	-	-
Time of expulsion of pup from start of treatment (h)	47.94 ± 5.04	-	-
Live birth rate (%)	100	50	-
Animals required clinical intervention (%)	0	100	-

Means having different superscripts within a row differ significantly at 5% level

Fig. 1. Determination of gestational age based on sonographic foetal head diameter

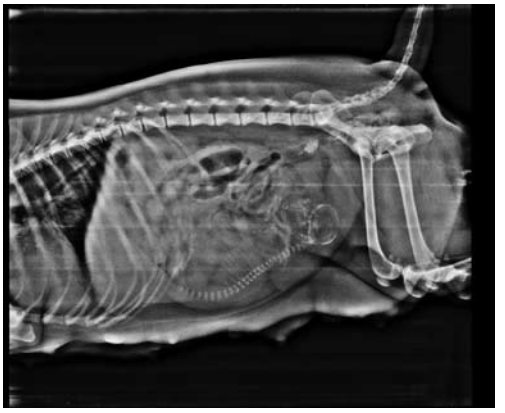

Fig. 2. Radiographic image of singleton pregnancy

intervention and also enhanced foetal lung maturation due to increased cortisol secretion from partial blocking of pituitary glucocorticoid receptors (Bonte *et al.*, 2017). The use of antiprogestin, mifepristone administered at a dosage that allows for effective competition at the progesterone receptor, will lead to the cessation of progesterone-mediated effects. However, due to inadequate prepartal elevation of $PGF_{2\alpha}$, the process of giving birth may be delayed compared to the usual whelping procedure. The nature of singleton pregnancy can also contribute to low $PGF_{2\alpha}$ level. Hence, the incorporation of uterotonic agents such as misoprostol in the mifepristone-based whelping protocol would enhance the puppy outcome in such high-risk dogs with singleton pregnancies. This advantage might be ascribed to the uterotonic impact of misoprostol, coupled with its no adverse effects on the foetus (Raheema, 2018). This finding was confirmed in the current study, as it demonstrated an increased live birth rate in dogs undergoing whelping without any clinical interventions.

In the group of dogs that did not receive treatment, the stimulus that initiates the process of giving birth was insufficient, and the ability of the uterus to contract was compromised due to inadequate stretching caused by a single puppy. As a result, the length of gestation was prolonged, leading to the death of the foetus *in-utero* and ineffective uterine contractions, ultimately resulting in the expulsion of a deceased foetus or dystocia, either due to maternal or foetal factors. Only 50 percent of the puppies were able to survive this condition, and that too solely due to the intervention of medical and surgical procedures. However, in the treated group, combination of misoprostol with the mifepristone-based induction was advantageous in achieving a quicker induction and more regular contractions for a normal whelping process.

Conclusion

It could be concluded that the utilisation of mifepristone in conjunction with misoprostol as an uterotonic agent is both secure and efficacious for the induction of parturition in bitches experiencing single pup syndrome. The reduced necessity for clinical interventions and high live birth rate with the combined use of mifepristone and misoprostol for whelping induction would prove advantageous in a scenario where access to clinical facilities is limited or when the birthing process occurs outside of regular operating hours, when clinical services are rare.

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