INDUCTION OF WHELPING IN CANINE HIGH RISK PREGNANCIES WITH SMALL LITTER SIZE USING PROGESTERONE RECEPTOR BLOCKER AND PGE_1

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The goals of managing high-risk pregnancies (High-risk pregnancies are those in which high incidence of maternal, fetal and/or perinatal morbidity or mortality is expected to be higher) are to optimize maternal, foetal and perinatal health, maintain lactation and maximize the survival of the pup. Management includes an elective caesarean or medical induction of parturition. The complications with caesarean section can be overcome by medical induction of whelping. The clinical efficiency and safety of medical induction of whelping in full term canine high risk pregnancies with small litter size using mifepristone along with intravaginal application of misoprostol in comparison to spontaneous whelping was studied.Better induction efficiency in the dam and a satisfactory neonatal survival was the outcome of the study.

Keywords: Canine, High risk pregnancies, Mifepristone, Misoprostol, Small litter size.

Factors such as infectious causes, advanced age of the female, previous pregnancy loss, brachycephalic breed and litter size influence pregnancy in dogs and contributes to its categorization as high risk (Johnson, 2008). Litter size less than three was usually considered to be a high-risk pregnancy in dogs from a probable dystocia due to prolonged gestation, uterine inertia and foetal oversize. A veterinarian is at crossroads when presented with a complaint of failure of initiation of delivery even after completing 65 days after the first multiple matings. Moreover in small litter pregnancies, there may be inadequate cortisol release from the foetus to induce prostaglandin F2α production by the endometrium for luteolysis, which in turn initiates parturition (Pretzer, 2008). Inadequate stimulus to initiate the parturition cascade result in extended duration of pregnancy and possible dystocia from relative foetal oversize causing over stretching of uterine myometrium and primary uterine inertia (Pretzer, 2008 and Smith, 2012).Consequently, induction of whelping becomes inevitable. But, it is critical to ensure that foetus has attained, its maximal gestational age prior to delivery (Lopate, 2008).

Antiprogestins block the actions of endogenous progesterone. Mifepristone strongly binds to progesterone receptors and thus act as antagonist to progesterone functions (Spitz and Bardin, 1993). Prostaglandin E_1, misoprostol accelerated the cervical dilatation soon after using antiprogestin, aglepristone in bitches treated for termination of pregnancy (Agaoglu *et al*., 2011). The present study hence aimed to determine the efficacy and safety of mifepristone in combination with anterior vaginal administration of misoprostol to induce whelping in canine high risk pregnancies with small litter size.

Materials and Methods

The study was carried out in twelvedogs of different breeds presented to the University Veterinary Hospital, KVASU, Kokkalai and Mannuthy, Thrissur, with history of not exhibiting any signs of parturition even after attaining 63 days from last breeding date. The animals were subjected to detailed clinico-gynaecological examination and pregnancy status with three or fewer fetuses was confirmed by radiographic evaluation. Trans abdominal sonography using real time B-mode ultrasound scanner was performed to assess the foetal viability and gestational age (GA)

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of the foetus. Six bitches that attained a GA of 62±2 days on sonography were subjected to medical induction of whelping using mifepristone orally at a dose rate of 5mg/kg body weight (BW) twice daily for two consecutive days, in association with anterior vaginal administration of 400µg misoprostol 24 h following the first dose of mifepristone. Six bitches radiographically confirmed of three or fewer fetuses were pursued during their natural whelping process. Serum progesterone and cortisol estimation was carried out prior to initiation of treatment and on initiation of whelping. The data obtained during the study were subjected to statistical analysis using SPSS 24.0 version software.

Results and Discussion

Induction response in the dogs treated with mifepristone along with vaginal administration of misoprostol was 100 per cent. The mean duration of pregnancy on the day of treatment calculated from the last day of breeding ranged between 60 to 63 days with a mean (±SE) of 61.67±0.42 days in induced group. For the dogs in spontaneously whelping group (control group) the calculated gestation period on the day prior to whelping from last breeding ranged between 63 to 67 days with a mean (±SE) of 64.33±1.50 days. Similarly Polster (2006) also reported longer gestation duration in dogs with single pup (64.0days) followed by litter size of 2 to 6 pups (62.3 days). The treatment provided was without any impending signs of whelping even on sonographic GA determination of 61±1 days. All dogs initiated whelping within 72 hours (h) of start of treatment. The success rate observed in the present study was higher than the reports of 83.33% by Vander-Weyden *et al*. (1989) and 80% by Nohr *et al*. (1993). This could be attributed to the fact that they reported success rates with mifepristone alone, while in this study, the cent percent success rate could be due to combination treatment of mifepristone followed by misoprostol. The time taken for initiation of whelping after first dose of treatment in induced group ranged from 24.5 to 46 h with a mean (±SE) of 35.58±3.54 h and in control group, the time taken for initiation of whelping after initial presentation of animals ranged from 52 to 71 h with a mean (±SE) of 62.33±2.78h. Similar observations on the initiation of parturition following mifepristone administration was reported as 26 to 78 h by Vander Weyden *et al*. (1989) and 26 to 40 h by Nohr *et al*. (1993). The time interval from initiation of whelping to the delivery of the entire litter in treatment group was a mean (±SE) of 152.50±49.66 min and in control group, it had a mean (±SE) of 165.00±49.44 min. The decreased time interval to complete the whelping process in treatment group compared to control group could be attributed to the combined effect of both mifepristone and misoprostol in augmenting the uterine contractions and thereby whelping process. This effect of combination therapy in completing the delivery within a short interval was proved in dogs by Agaoglu *et al*. (2011) also.

The mean progesterone levels before treatment was 4.34±0.68 ng/ml and showed decrease in progesterone levels with mean of 2.71±0.41 ng/ml after treatment. An increased circulating plasma progesterone concentration in the treatment group at the time of whelping has also been reported by Fieni *et al*. (2001) who explained on the basis of increasing binding of progesterone receptors by progesterone antagonists in place of natural hormone. The mean cortisol levels before treatment was 28.11±6.68 ng/ml and increase in cortisol levels with mean of 61.56±5.17 ng/ml after treatment. As reported by Concannon *et al*. (1977), maternal cortisol concentration fluctuated within the normal range during the last week of gestation (15-25 ng/ml) with elevated levels on the day before parturition (40-80 ng/ml). The per cent of neonates viable at birth were 92.31 (12 out of 13), and 53.85 (7 out of 13) in induced group and spontaneously whelping group respectively.

Jayakumar *et al*. (2017) stated that, incidence of still births during spontaneous whelping was highest in canine pregnancy with small litter size. The higher live birth rate (92.31 %) in the treatment group could be attributed to the effect of mifepristone in

increasing the cortisol secretion from partial blocking of pituitary glucocorticoid receptors and increased ACTH and thereby foetal lung maturation. Also, Lopate (2008) reported that due to the zonary nature of the canine placenta, once a foetus exceeds its due date by more than 2 days, it will demand more nutritional support than the placenta is able to provide, resulting in intrauterine foetal death. None of the bitches exhibited any side effects after administration of mifepristone and misoprostol.

The present study established the clinical efficacy and safety of combined mifepristone and misoprostol treatment in high risk canine pregnancy with small litter size as noticeable from an effective induction response, high live birth rate, reduced gestation period, lack of side effects and satisfying neonatal survival rate.

Table 1. Comparison of the efficacy of treatment protocol for induction of whelping with control group

Parameters	Treatment group (n=6)	Control group (n=6)
Mean GA assessed by ultrasound (days)	61.63±0.42	62.67±0.55
Mean GA assessed by last breeding date to parturition/ whelping (days)	61.67±0.42	64.33±1.50
Mean gestational length from ultrasound measurement to date of whelping	63.04±0.76	65.09±0.92
Mean gestational length from last date of breeding to date of whelping	63.14±0.76	66.92±0.69
Time of delivery of first pup (hours)	35.58±3.54 (Range 24.5 to 46)	62.33±2.78 (Range 52 to 71)
Duration of whelping (minutes)	152.50±49.66 min	165.00±49.44
Nature of whelping	Vaginal delivery (n=6)	Vaginal delivery (n=5) Caesarean section (n=1)
Number of puppies born alive	12 out of 13 (92.3%)	7 out of 13 (53.8%)
Puppies survival upto 2 weeks	11 out of 12 (91.6%)	6 out of 7 (85.7%)

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