Open Access

Check for updates

Research Article

Journal of Veterinary and Animal Sciences
ISSN (Print): 0971-0701, (Online): 2582-0605
https://doi.org/10.51966/jvas.2025.56.4.631-635

Effect of progesterone receptor antagonists on the resistive index of the umbilical artery and foetal heart rate variations in whelping induction protocols#

Sriya K. Manoj[1], Shibu Simon[2], Choppillil Jayakumar[3], B. Bibin Becha[3], K. Magnus Paul[1] and Sangeetha S. Gireesh[4]

[1]Department of Animal Reproduction, Gynaecology and Obstetrics, [4]Department of Veterinary, Clinical Medicine, Ethics and Jurisprudence College of Veterinary and Animal Sciences, Mannuthy, Thrissur- 680 651, [2]University Veterinary Hospital, Kokkalai, Thrissur- 680 021, [3]Base Farm, Kolahalamedu, Idukki- 685501., Kerala Veterinary and Animal Sciences University Kerala, India.

Citation: Sriya, K.M., Simon, S., Jayakumar, C., Becha, B.B., Paul, K.M. and Gireesh, S.S. 2025. Effect of progesterone receptor antagonists on the resistive index of the umbilical artery and foetal heart rate variations in whelping induction protocols. *J. Vet. Anim. Sci.* **56** (4):631-635

Received: 11.09.2025 Accepted: 17.10.2025 Published: 31.12.2025

Abstract

This study assessed foetal heart rate (FHR) variations and umbilical artery resistive index (RI) as indicators of parturition timing in dogs undergoing induced whelping using two progesterone receptor antagonists, aglepristone and mifepristone. Sixteen pregnant bitches were divided into two groups receiving either aglepristone or mifepristone. Doppler ultrasonography showed that an FHR variation over 15 per cent, combined with an umbilical artery RI below 0.7 in the caudal foetus, predicted imminent whelping within 24 h. A higher RI above 0.75, 24 h after induction, was linked to dystocia and necessitated a caesarean section. Both aglepristone and mifepristone induced late-gestation changes similar to normal whelping signs, including FHR accelerations and decelerations, increased FHR variability, and decreased umbilical artery RI, with no significant difference between the two protocols. Monitoring FHR patterns and umbilical artery RI together provides a non-invasive and reliable method for predicting delivery timing and assisting with timely interventions during induced whelping; however, larger studies with more comprehensive neonatal outcomes are needed for validation.

Keywords: Foetal heart rate oscillations, umbilical artery resistive index, canine parturition prediction, progesterone receptor antagonists

Accurately predicting parturition in dogs remains challenging due to the natural variability in gestation length, which can span from 58 to 71 days—a 13-day window that makes breeding dates unreliable for estimating delivery (Kutzler *et al*., 2003). An effective method for predicting the exact timing of parturition in dogs would be highly valuable, as it allows for timely interventions to reduce or prevent reproductive losses. Two-dimensional ultrasonography provides only limited details on blood flow, so it is often combined with Doppler techniques for reproductive assessments in animals (Di Salvo *et al*., 2006; Miranda and Domingues, 2010).

#Part of M.V.Sc. thesis submitted to Kerala Veterinary and Animal Sciences University, Pookode, Wayanad, Kerala

**Corresponding author: sriyakmanoj@gmail.com, Ph. 8848403963*

Doppler ultrasonography evaluates maternal and foetal blood flow through major vessels, including the uteroplacental arteries, the umbilical cord and the foetal aorta (Di Salvo *et al*., 2006). It provides functional information on vascular dynamics, such as flow velocity, direction, and resistance (Nicolaides *et al*., 2000). The resistive index of the umbilical artery (RI of Uma) blood flow in canine foetuses during normal gestation steadily decreases, aiding placental and foetal tissue perfusion (Di Salvo *et al*., 2006; Simon *et al*., 2022b). Foetal heart rate (FHR) oscillations begin to increase about five days before delivery and become more noticeable as parturition approaches (Gil *et al*., 2014). Two parameters, HR Gradient and HR Variation, have been developed to analyse foetal heart rate changes (Giannico *et al*., 2015). Progesterone receptor blockers like aglepristone (RU 46534) and mifepristone (RU 38486) can safely induce labour in dogs when timed correctly, helping to achieve normal vaginal births and healthy puppies (Baan *et al*., 2005; Simon *et al*., 2017 and 2024). The current study proposes a more precise approach by combining Doppler-based FHR oscillations with the RI of Uma to accurately predict whelping time in induced whelping.

Materials and methods

Sixteen pregnant dogs presented at University Veterinary Hospital, Kokkalai, and the Teaching Veterinary Clinical Complex, Mannuthy, were divided into two groups. Group I (n = 9) received a single subcutaneous dose of aglepristone (15 mg/kg), while Group II (n = 7) received mifepristone (3.5 mg/kg for large breeds and 5 mg/kg for small breeds) orally every 8 h for three doses, following Simon *et al.* (2022a). The treatments in Groups I and II began one day before the expected date of delivery (EDD-1), which was determined based on early pregnancy sonographic measurements. Both the inner chorionic cavity (ICC) diameter and crown–rump length (CRL) were used to estimate the average gestational age (GA). Bitches with GA ≤ 30 days were only included in this study and the EDD was calculated based on the GA (Simon *et al.,* 2024).

Transabdominal ultrasonography was performed using a My Lab Sigma (Esaote, Genoa, Italy) ultrasound system equipped with a multifrequency microconvex transducer (3–11 MHz). Bitches were positioned in left lateral recumbency without sedation.

Foetal heart rate patterns

Foetal heart rate (FHR) was assessed using pulsed-wave (PW) Doppler, with inter-beat intervals measured by digital callipers and calculations performed by the integrated software. FHR oscillations were evaluated by recording rate variations over 2–5-minute intervals. The FHR gradient (beats/min) was defined as the difference between the maximum and minimum recorded rates and FHR variation was expressed as a percentage of this gradient relative to the maximum heart rate (Gianicco *et al.,* 2015).

Umbilical artery RI

The RI of Uma (umbilical artery) was evaluated through cross-sectional scanning of the zonary placenta. Colour Doppler imaging was used to identify umbilical arteries at the mid-cord site of a free-floating umbilical cord. Standard settings included a gain of less than 40 per cent and an insonation angle of less than 15°. The sample volume (SV) was placed at the vessel's centre line before activating PW Doppler. Wave forms were only included if they showed three consecutive systolic peaks with consistent velocity and amplitude. Peak systolic velocity (PSV) and end-diastolic velocity (EDV) were measured in centimetres per second (cm/s). The resistive index (RI) = (PSV – EDV)/PSV was automatically calculated by the machine's software. Ultrasonographic monitoring began on EDD-1 and all animals underwent follow-up of Doppler examination 24 hours after the initial drug administration.

Statistical analysis

Statistical analysis was performed using SPSS software version 24.0. A repeated measures analysis of variance (ANOVA) was used to compare foetal heart rate (FHR) gradient, FHR variation and RI of Uma between groups and within groups at the EDD-1 and EDD time points.

Results and discussion

Foetal heart rate

The study observed a significant reduction in FHR in both groups within 24 h after treatment. Statistical analysis confirmed a significant decline in FHR within each group ($P < 0.05$), with no significant difference between the groups ($P > 0.05$). FHR decreased from 231.44 ± 2.43 to 203.69 ± 4.54 in Group I and from 229.86 ± 3.71 to 198.58 ± 4.18 in Group II after treatment (Table 1). The foetal heart rate and foetal-maternal heart rate (FHR/MHR) ratio increased from 35 days before birth, peaked

Table 1. Foetal heart rate (FHR) (bpm) (Mean ± SE) during EDD-1 (pre-treatment) and EDD (post-treatment)

Group	FHR (beats/min) on EDD-1 (before treatment) (Mean ± SE)	FHR (beats/min) on EDD (24 h after treatment) (Mean ± SE)	P value
GI	$231.44^{a} \pm 2.43$	$203.69^{b} \pm 4.54$	<0.05
GII	$229.86^{a} \pm 3.71$	$198.58^{b} \pm 4.18$	

Means having different superscripts within a row (a-b) differ significantly at the 5 % level

at 20 days prepartum and then gradually decreased until delivery (Alonge *et al.,* 2016). The autonomic nervous system regulates foetal heart rates, with vagal control maturing earlier than sympathetic influence (Verdurmen *et al.,* 2013). Its decline in late gestation reflects vagal development and is linked to foetal weight (Frasch *et al.,* 2007). The foetal heart rate showed a decreasing trend as the bitch approached parturition.

FHR Oscillations, Gradient and variation

FHR oscillations were observed in the caudal-most foetus when the animal was assessed on both EDD-1 and on the EDD (Fig. 1). The range between the highest and lowest FHR recordings for this foetus increased from EDD-1 to EDD (Table 2). The exact timing of heart rate oscillations in canine foetuses could not be precisely determined (Gil *et al.,* 2014). Foetal heart rates in dogs are typically seen as FHR accelerations and decelerations during an impending whelping, (Gil *et al.,* 2014). Foetal HR accelerations and decelerations (Type I and II dips) are linked to uterine contractions and likely result from vagal stimulation caused by spinal or cranial compression. Higher foetal heart rate oscillations were observed starting at 72 h before birth, and all foetuses showed changes within the final 6 to 1 h antepartum (Gil *et al.,* 2014). These fluctuations may be related to foetal maturity, especially since litters can contain foetuses of varying ages (Tsutsui *et al.,* 2006).

The present study found that the FHR gradient showed significant differences between EDD-1 and EDD (Table 2), with no significant difference between the groups (P > 0.05). The mean FHR gradient in the caudal-most foetus significantly increased (P<0.05) from EDD-1 to EDD, rising from 17.44 ± 1.30 to 39.25 ± 3.87 in Group I, and from 19.29 ± 1.13 to 47.67 ± 3.39 in Group II (Table 2). Foetal heart rate oscillations were observed in a few foetuses 72–48 h before whelping, with most foetuses showing these changes within 24–12 hours prepartum (Thomas *et al.*, 2023). Post-treatment FHR gradient (FHRG) values in this study closely match those of Nayana (2024), who reported ranges of FHRG of 37 ± 4.09 to 53.29 ± 14.71 beats on the whelping day.

The mean FHR variation (%) of the caudal-most foetus increased from 7.35 ± 0.53 to 17.39 ± 1.38 in Group I and from 8.35 ± 0.48 to 21.55 ± 1.79 in Group II

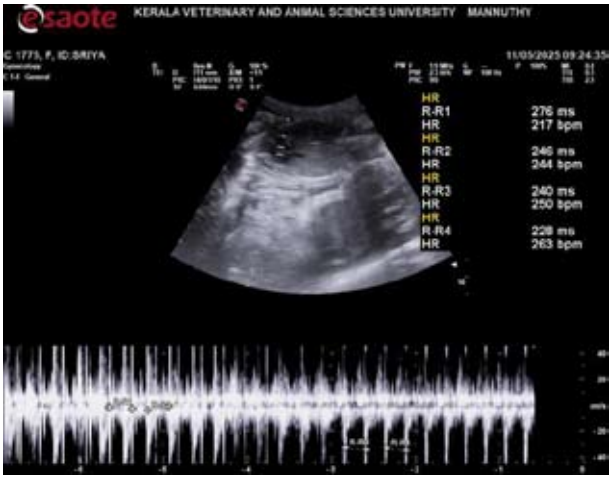

Fig. 1 Foetal heart rate oscillations observed during impending parturition assessed by PW Doppler

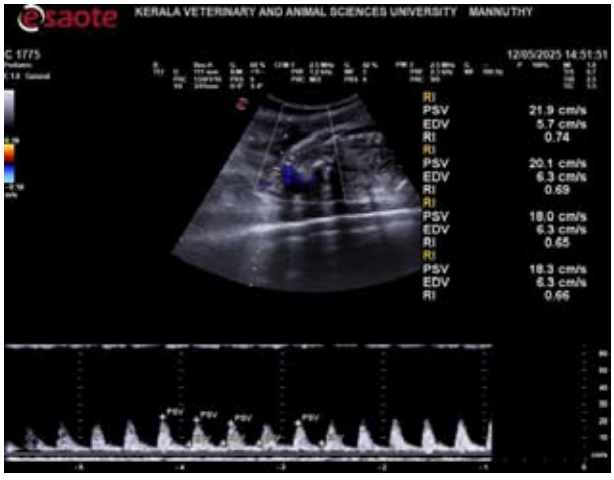

Fig. 2 Pulsed wave Doppler sonogram of the umbilical artery on the expected date of delivery

Table 2. FHR gradient (Mean ± SE) (beats) of the caudal-most foetus during EDD-1 (pre-treatment) and EDD (post-treatment)

Group	FHR gradient (bpm) on EDD-1 (pre-treatment) (Mean ± SE)	FHR gradient (bpm) on EDD (post-treatment) (Mean ± SE)	P value
GI	17.44^{b} ± 1.30	39.25^{a} ± 3.87	<0.05
GII	19.29^{b} ± 1.13	47.67^{a} ± 3.39	

Means having different superscripts within a row (a-b) differ significantly at the 5 % level

Table 3. FHR variation (%) of the caudal-most foetus during EDD-1 (pre-treatment) and EDD (post-treatment)

Group	FHR variation (%) EDD-1 (pre-treatment) (Mean ± SE)	FHR variation (%) EDD (post-treatment) (Mean ± SE)	P value
GI	7.35^{b} ± 0.53	17.39^{a} ± 1.38	<0.05
GII	8.35^{b} ± 0.48	21.55^{a} ± 1.79	

Means having different superscripts within a row (a-b) differ significantly at the 5 % level

Table 4. RI of the umbilical artery of the caudal-most foetus during EDD-1 (before treatment) and EDD (after treatment)

RI of Uma by ultrasonography	RI of Uma at EDD-1 (before treatment) (Mean ± SE)	RI of Uma EDD at (after treatment) (Mean ± SE)	P value
GI	0.72^{a} ± 0.01	0.64^{b} ± 0.18	<0.05
GII	0.70^{a} ± 0.01	0.64^{b} ± 0.02	

Means having different superscripts within a row (a-b) differ significantly at the 5 % level

when measured before treatment and 24 h after treatment (Table 3). The FHR variation (%) increased noticeably 24 h after treatment on the expected date of delivery (EDD), compared with pre-treatment measurements. Statistical analysis showed significant differences in these measurements within each group before treatment and 24 h after treatment, with no significant difference between groups (P >0.05). The FHR variation coefficient increased from 6.9 per cent (120–96 h prepartum) to 14.9 per cent (12–1 h prepartum) (Giannico *et al.,* 2016). The highest single-foetus heart rate variation observed in the present study was 29.1 per cent. Heart rate variation exceeded 30.67 per cent only in the 12–1 hour period before birth (Giannico *et al*., 2015). Nayana (2024) reported that mean FHRV on the day of whelping ranged from 16.88 ± 1.65 per cent in the mifepristone-induced group to 22.07 ± 4.81 per cent in the emergency caesarean group.

Resistive index of the Umbilical artery

The RI of Umbilical artery (Uma) decreased from 0.72 ± 0.01 to 0.64 ± 0.18 in Group I, and from 0.70 ± 0.01 to 0.64 ± 0.02 in Group II, during pretreatment to 24 h after treatment, indicating reduced vascular resistance as whelping approached, with no significant difference between groups (P > 0.05). All bitches in the study displayed a biphasic waveform pattern. This finding was consistent with the studies by Di Salvo *et al*. (2006), Miranda and Domingues (2010), Simon *et al.* (2022b), Thomas *et al*. (2023) and Devarajan *et al*. (2025). The decline in umbilical artery RI during late gestation reflects decreased vascular resistance, which enhances placental and foetal visceral perfusion. This hemodynamic adaptation results from the maturation of placento-foetal circulation, foetal cardiovascular development, and maternal physiological factors (Coan *et al*., 2004; Mu and Adamson, 2006; Blanco *et al*., 2011; Simon, 2015). Diastolic blood flow increases during the final trimester, with no observed retrograde flow. As parturition approached, the RI of Uma decreased markedly, staying below 0.7 (range 0.61–0.7) during the final 12–6 h period (Fig. 2) and dropping to a low of 0.56 within the final 6–1 h window (Giannico *et al*., 2015). In the present study, the RI of Uma was below 0.7 for all foetuses examined on the EDD, except in two cases (where RI values were 0.75 and 0.78), which required caesarean section in Group I. This aligns with Giannico *et al.* (2015) and Thomas *et al.* (2023), who reported elevated umbilical artery RI values in dystocic dogs and dogs that underwent caesarean section due to dystocia, indicating foetal distress.

Based on the findings of the present study, it can be inferred that in induced whelping, an FHR variation greater than 15 per cent and an umbilical artery RI below 0.7 in the caudal-most foetus can predict parturition within 24 h, similar to the observations of Giannico *et al*. (2015), who proposed that higher FHR variation (>27.92%) with RI <0.7 could indicate delivery within 12 h in normal labour.

Conclusion

Monitoring FHR oscillations alongside the RI of Uma provided a valuable, non-invasive method to predict whelping in dogs. The current study suggested that in induced whelping, an FHR variation greater than 15 per cent and RI of Uma below 0.7 in the caudal-most foetus can forecast parturition within 24 h. Progesterone receptor antagonists, aglepristone and mifepristone, promote the expected late-gestation changes by decreasing the RI of Uma and FHR oscillations, with no significant differences observed between the two drugs. Although combining the RI of Uma and FHR variations provides useful indicators for predicting whelping, further research with more frequent serial Doppler evaluations, larger sample sizes, and neonatal outcome assessments is necessary to improve the accuracy of predictions.

References

Alonge, S., Mauri, M., Faustini, M. and Luvoni, G.C., 2016. Feto-maternal heart rate ratio in pregnant bitches: effect of gestational age and maternal size. *Reprod. Domest. Anim.* **51**: 688-692.

Baan, M., Taverne, M.A.M., Kooistra, H.S., De Gier, J., Dieleman, S.J. and Okkens, A.C., 2005. Induction of parturition in the bitch with the progesterone-receptor blocker aglepristone. *Theriogenology.* **63**: 1958-1972.

Blanco, P.G., Rodríguez, R., Rube, A., Arias, D.O., Tórtora, M., Díaz, J.D. and Gobello, C., 2011. Doppler ultrasonographic assessment of maternal and fetal blood flow in abnormal canine pregnancy. *Anim. Reprod. Sci.* **126**: 130-135.

Coan, P.M., Ferguson-Smith, A.C. and Burton, G.J., 2004. Developmental dynamics of the definitive mouse placenta assessed by stereology. *Biol. Reprod.* **70**: 1806-1813.

Devarajan, N.; Simon, S.; Jayakumar, C.; Aravind, A.; Sunil, B. and Mani, B.K. 2025. Doppler ultrasonographic evaluation of maternal and foetal blood flow in bitches approaching delivery by different whelping modes. *Indian J. Anim. Reprod.* **46**: 1.

Di Salvo, P., Bocci, F., Zelli, R. and Polisca, A., 2006. Doppler evaluation of maternal and fetal vessels during normal gestation in the bitch. *Res. Vet. Sci.* **81**: 382-388.

Frasch, M.G., Müller, T., Wicher, C., Weiss, C., Löhle, M., Schwab, K., Schubert, H., Nathanielsz, P.W., Witte, O.W. and Schwab, M., 2007. Fetal body weight and the development of the control of the cardiovascular system in fetal sheep. *J. Physiol.* **579**: 893-907

Giannico, A.T., Gil, E.M.U., Garcia, D.A.A. and Froes, T.R., 2015. The use of Doppler evaluation of the canine umbilical artery in prediction of delivery time and fetal distress. *Anim. Reprod. Sci.* **154**: 105-112.

Gil, E.M.U., Garcia, D.A.A., Giannico, A.T. and Froes, T.R., 2014. Canine fetal heart rate: do accelerations or decelerations predict the parturition day in bitches? *Theriogenology.* **82**: 933-941.

Kutzler, M.A., Mohammed, H.O., Lamb, S.V. and Meyers-Wallen, V.N., 2003. Accuracy of canine parturition date prediction from the initial rise in preovulatory progesterone concentration. *Theriogenology.* **60**: 1187-1196.

Miranda, S.A. and Domingues, S.F.S., 2010. Conceptus ecobiometry and triplex Doppler ultrasonography of uterine and umbilical arteries for assessment of fetal viability in dogs. *Theriogenology.* **74**: 608-617.

Mu, J. and Adamson, S.L., 2006. Developmental changes in hemodynamics of uterine artery, utero-and umbilicoplacental, and vitelline circulations in mouse throughout gestation. *Am. J. Physiol. Heart Circ. Physiol.* **291**: H1421-H1428.

Nayana, D. 2024. Influence of modes of whelping on transfer of maternal bacterial microbiota to newborn puppies. Ph.D. thesis, Kerala Veterinary and Animal Sciences University, Pookode, 211p.

Nicolaides, K.H., Rizzo, G. and Hecher, K., 2000. *Placental and fetal Doppler.* (1st Ed.). The Parthenon Publishing Group, New York, pp. 35–66.

Simon, S. 2015. Conceptus echobiometry and Doppler ultrasonographic assessment of maternal and foetal blood flow in canine pregnancy. Ph.D. thesis, The Gandhigram Rural Institute- Deemed University, Gandhigram, 205 p.

Simon, S., Bhai, L.K., Nair, R.S. and Abubaker, S.P.S. 2017. Clinical efficacy of whelping induction protocol using mifepristone in advanced pregnant bitches. *Int. J. Sci. Res.* **6**: 1510-1513.

Simon, S., Emadudeen, N., Thomas, R. and Hind, A. 2022a. Critical management of canine pregnancies by early ultrasonographic prediction of whelping date and induction of whelping with mifepristone on prediction day. *47th World Small Animal Veterinary Association Congress*, 29th – 31st October, 2022. Lima, Peru. Abstract No.452.

Simon, S., Ramanathan, A. and Ghosh, K.N. 2022b. Doppler ultrasonographic assessment of maternal and foetal blood flow in canine pregnancy and its application in the critical management of gestation. *Indian J. Anim. Res*. **56:** 811-821.

Simon, S., Emadudeen, N., Devarajan, N., Thomas, R. and Hind, P.A. 2024. Predicting whelping day with early pregnancy ultrasonography and induction of parturition using mifepristone on the expected delivery date in bitches. *Indian J. Anim. Res.* Online First. https://doi.org/10.18805/IJAR.B-5432

Thomas, R., Jayakumar, C., Paul, K.M., Aravind, A. and Gleeja, V.L. 2023. Whelping prediction using foetal heart rate variations and umbilical artery resistivity index in late gestation. J. Vet. Anim. Sci. **54**:1000-1004

Tsutsui, T., Hori, T., Kirihara, N., Kawakami, E. and Concannon, P.W., 2006. Relation between mating or ovulation and the duration of gestation in dogs. *Theriogenology.* **66**: 1706-1708.

Verdurmen, K.M., Renckens, J., van Laar, J.O. and Oei, S.G., 2013. The influence of corticosteroids on fetal heart rate variability: a systematic review of the literature. Obstet. Gynecol. Surv. **68**: 811-824. ■