Journal of Veterinary Science and Public Health

J. Vet. Sc. Public Health, v. 8, n. 1, p. 073-082, 2021

FETAL ULTRASOUND OF THE CENTRAL NERVOUS SYSTEM IN HUMAN AND VETERINARY MEDICINE: REVIEW

ULTRASSONOGRAFIA FETAL DO SISTEMA NERVOSO CENTRAL NA MEDICINA HUMANA E VETERINÁRIA: REVISÃO

Letícia Pavan[1*]; Beatriz Gasser[1]; Marjury Cristina Maronezi[1]; Priscila Silva[1]; Ana Paula Rodrigues Simões[1]; Luiz Paulo Nogueira Aires[1]; Ricardo Andrés Ramirez Uscategui[2]; Luciana Cristina Padilha-Nakaghi[1]; Marcus Antônio Rossi Feliciano[3]

1. Universidade Estadual Paulista – FCAV-Campus de Jaboticabal
2. Professor da Universidade Federal dos Vales do Jequitinhonha e Mucuri, MG
3. Professor da Universidade Federal de Santa Maria, RS
* pavan.leticia@yahoo.com.br
DOI: 10.4025/revcivet.v8i1.51416

RESUMO

A ultrassonografia é uma ferramenta frequentemente utilizada no pré-natal de fêmeas caninas, pois permite diagnosticar precocemente a gestação, avaliar a viabilidade fetal e estimar a idade gestacional de forma eficaz e não invasiva. A translucência nucal e o diâmetro transversal cerebelar são parâmetros ultrassonográficos de avaliação dos fetos humanos no primeiro e segundo trimestre gestacionais, respectivamente, mas ainda não descritos em veterinária. A translucência nucal está relacionada a malformações fetais e gestação de alto risco, enquanto a mensuração do cerebelo permite estimar a idade gestacional com maior precisão do que outros parâmetros biométricos em determinadas situações. A técnica de elastografia, por sua vez, foi aplicada recentemente em estruturas fetais, sendo que na medicina humana demonstrou correlação entre o desenvolvimento fetal e as modificações de rigidez das estruturas cerebrais.

Palavras-chave: cerebelo, cérebro, elastografia, translucência nucal

ABSTRACT

Fetal ultrasound of the central nervous system is a non-invasive examination that constitutes part of the prenatal care of women and is essential for the early diagnosis of anomalies and diseases common in this stage of development. Nuchal translucency (NT) and transverse cerebellar diameter (TCD) are ultrasonographic parameters to evaluate human fetuses in the first and second trimester of pregnancy, respectively, but not yet described in animals. NT is related to fetal malformations and high-risk pregnancies while TCD estimates gestational age with greater precision than other biometric parameters in certain situations. The elastography technique was recently applied to fetal structures and it demonstrated a correlation between development of human fetuses and stiffness changes in brain structures, which allowed the detection of anomalies. In veterinary medicine, evaluation of lung, liver and kidney tissue have been reported in order to estimate their maturation in domestic animals, while elastography of brain tissue has been used only in baboon fetuses.

Keywords: brain, cerebellum, elastography, nuchal translucency

INTRODUCTION

The first reports of ultrasonography of the fetal brain were performed in sheep and pigs, aiming to evaluate the heating induced by the technique, in order to investigate its safety for application in human fetuses (DUGGAN et al., 1995; HORDER et al., 1998). In canine fetuses, the first studies that evaluated cerebral ecobiometry measured the diencephalo-telencephalic vesicle, a portion of the brain, and correlated it with gestational days (BECCAGLIA and LUVONI, 2004; BECCAGLIA et al., 2008). Later, it was possible to identify, evaluate and monitor the development of brain mass and based on these analyzes, to earlier diagnose fetal malformations such as hydrocephalus (FELICIANO et al., 2013). From the development of more modern ultrasound devices and images of better quality and resolution, this practice has become viable to the clinical routine in veterinary obstetrics (DAVIDSON and BAKER, 2009).

In women, ultrasonography of the central nervous system (CNS) in prenatal care is widely used. In the first trimester of pregnancy, ultrasound measurement of the nuchal translucency (NT) is performed. Such evaluation is an effective method for screening trisomy 21 and other syndromes, establishing whether it is necessary to perform more invasive tests (amniocentesis and chorionic villus sampling), fetal echocardiography, in addition to suggest termination of pregnancy (NICOLAIDES et al., 2002). Another ultrasound measurement applied to human fetuses is the transverse cerebellar diameter (TCD), which, among its purposes, allows estimating gestational age with greater precision when compared to other biometric parameters (HOLANDA-FILHO et al., 2011).

Also in humans, the Virtual Touch Tissue Quantification (VTTQ) elastographic technique applied to fetal tissues was able to detect abnormalities in the development of the encephalic parenchyma (ZHENG et al., 2016). In baboons, it has been suggested that it would make it possible to estimate the maturation of fetal organs, including the brain (QUARELLO et al., 2015).

The aim of this study is to review NT and TCD, two measures of relevance already well established in women's prenatal care but not described in veterinary medicine, and also the application of elastography technique in fetal tissues, which is recent in both human and animal species.

CNS Embryology

The spinal cord and the brain constitute the CNS. The brain is located within the cranial cavity, surrounded by the cerebrospinal fluid and divided macroscopically into encephalon, cerebellum and brain stem. The cerebellum is positioned caudally to the brain and is composed by the lateral cerebellar hemispheres and the vermis, a median sagittal crest. Its functions are related to the balance and coordination of skeletal muscles (KÖNIG et al., 2016). The brain is proportionally larger in more advanced species in evolutionary history, whereas in humans the ratio between brain and body weight is 1:50, in dogs 1:200 and horses 1:800 (DYCE et al., 2010).

The nervous system originates from the ectoderm during embryonic period, which begins with uterine implantation in the dog, approximately 19 days after the peak of luteinizing hormone (LH), and ends when organogenesis is complete, approximately on the 35th day (PRETZER, 2008). In humans, this period is defined by the eight weeks following fertilization (O’RAHILLY and MÜLLER, 2012).

The neural plate is a thickening of the ectoderm that represents the primordial nervous system. It folds to form the neural tube, the anterior two-thirds of which develop into the brain (SINOWATZ, 2010). The three primary brain vesicles are the prosencephalon, the mesencephalon and the rombencephalon. The cerebral cortex originates from the telencephalon, a subdivision of the prosencephalon, while the cerebellum is derived from the metencephalon, which comes from the rombencephalon (DYCE et al., 2010).

Among the cells of the CNS, the last population to form is the cortical neurons of the brain and cerebellum. In early species such as bovine and equine, most of them are already formed at birth, while in dogs they continue to proliferate until the fourth month of life, and in humans until the third year (SINOWATZ, 2010).

CNS ultrasound of fetuses

Ultrasonography is a very important tool in prenatal care. In veterinary medicine, it is routinely used in bitches, as it allows early diagnosis of pregnancy, assess fetal viability and estimates gestational age in an effective and non-invasive way (NEPOMUCENO et al., 2013). During gestation of mares and cows, this technique also guarantees an early diagnosis, in addition to detect twin pregnancies and enables fetal sexing (GIMENES et al., 2013; BEKELE et al., 2016). In sheep, it has been described as the best method of gestational diagnosis because it is early, accurate, fast and safe (GANAIE et al., 2009).

To study cranial and cerebral development of canine fetuses, some important ultrasound parameters are the biparietal diameter (BPD), the characterization of brain mass, determination of brain volume indexes and vascularization (middle cerebral artery). These parameters allow predicting gestational age and evaluating the central nervous system of fetuses in bitches (TEIXEIRA et al., 2009; FELICIANO et al., 2013).

Before the 30th day, counted from the peak of LH, it is possible to identify in the ultrasound examination only an anechoic area of the head, without determining the structures (PRETZER, 2008). According to Feliciano et al. (2013), in one of the few reports about CNS ultrasound assessment of canine fetuses, ultrasound is applicable from the 30th day of gestation, when the brain mass begins to be visible in the skull in its sagittal and transverse sections.

NT and TCD are ultrasonographic parameters to evaluate human fetuses in the first and second trimester, respectively (MCLEARY et al., 1984; NICOLAIDES et al., 1992), but not described in animals.

NT is a subcutaneous accumulation of fluid in the posterior region of the neck of the fetuses (BAKKER et al., 2014). This measurement is obtained in a medium sagittal section and consists of the maximum thickness of the subcutaneous translucency over the cervical spine. The incidence of fetal abnormalities is related to this measure and includes trisomy 21, Turner syndrome and other chromosomal abnormalities, as well as malformations and genetic syndromes. TN values of 3 mm or more were defined as a marker for chromosomal abnormality in humans, which diagnosis was confirmed by amniocentesis or sampling of chorionic villi, both of them ultrasound guided (NICOLAIDES et al., 1992; MOLINA et al., 2006).

The ideal period for measuring NT is between the 10th and 14th weeks of gestation in humans (HYETT et al., 1997). Increased NT values suggest high-risk pregnancies, which may be related to spontaneous abortion, intrauterine death and structural abnormalities, mainly cardiac, even in karyotically normal fetuses. Therefore, it makes mandatory close monitoring of pregnancy, including fetal echocardiography (MICHAILIDIS and ECONOMIDES, 2001).

Gestational age influences the thickness of NT, so this measurement must be performed at the appropriate time. The risks to pregnancy are proportionally related to the degree of increase in NT. Although several reference values have been established over the years, it has been stipulated that measures greater than 3.5 mm should be considered elevated (BAKKER et al., 2014).

When NT reaches this thickness, the prevalence of fetal abnormalities and adverse pregnancy increases exponentially in euploid fetuses (SOUKA et al., 2005). Cardiac defects, diaphragmatic hernia, body-stalk anomaly, omphalocele and deformation sequence associated with fetal hypokinesis or akinesia are examples of malformations with greater prevalence in fetuses with increased NT than in the general population (SOUKA et al., 1998).

The same occurs with chromosomal defects, for which an overall incidence of 20% was reported for NT 3.5 to 4.4 mm, 50% for NT 5.5 to 6.4 mm and 75% when NT equal or greater than 8.5 mm. In addition, there is a different distribution of this measure in the different types of chromosomal defects. While in most fetuses with trisomy 21 the NT is less than 4.5mm, in those with trisomy 13 or 18 it is between 4.5 to 8.4mm. In fetuses with Turner syndrome, the TN is greater than or equal to 8.5mm (KAGAN et al., 2006).

The pathophysiology of increased NT remains undetermined, and the main hypotheses are based on heart failure or delayed development of the lymphatic system as possible causes of fluid accumulation in the cervical region (BAKKER et al., 2014). Some mechanisms already suggested for the increase in NT are abnormalities of the heart and great vessels, venous congestion in the head and neck, alteration in the composition of the extracellular matrix, abnormal development of the lymphatic system, neuromuscular disorders that compromise fetal movement and consequently lymphatic drainage, fetal anemia or hypoproteinemia and congenital infection (NICOLAIDES et al., 2002).

According to the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), BPD should be part of the fetal ultrasound routine in the second trimester of pregnancy to estimate gestational age. It consists of measuring the maximum width of the head in cross section, with detection of symmetrical cerebral hemispheres and the presence of a central and continuous hyperechoic line, which corresponds to the "falx cerebri" (SALOMON et al., 2011). In veterinary medicine, gestational ultrasound of dogs, cats and small ruminants includes the measurement of BPD with the same purpose (LÉGA et al., 2007; RAMOS et al., 2007; LAMM and MAKLOSKI, 2012).

However, in humans, it is known that BPD assessment has limitations in predicting gestational age when there is oligohydramnios, twin pregnancy, uterine anomalies and insinuation in the maternal pelvis at the end of pregnancy, among other conditions that lead to dolichocephaly or brachycephaly, changing the conformation of skull. In these cases, TCD is used as an alternative measure. Because the cerebellum is located in the posterior fossa, external pressures do not affect it, besides it is not dependent on the shape of the head. It can be initially differentiated by ultrasound in the 10th to 11th gestational week in women, but its examination becomes easier in the final third of the gestation (MCLEARY et al., 1984; GOLDSTEIN et al., 1987). Assessments made between the 13th and the 40th week of gestation in women found no significant differences in this parameter between male and female fetuses (HOLANDA-FILHO et al., 2011).

When diagnosing an apparently small fetus, it is difficult to determine whether it actually has growth retardation or if the estimated gestational age is incorrect. In this way, some fetal measures were evaluated in pregnant women with clinical suspicion of delayed intrauterine fetal growth, such as TCD, BPD, abdominal circumference and length of the femur. It has been shown that TCD was able to estimate gestational age more reliably than other biometric parameters and that it is possible to diagnose growth deviations by comparing these measures. The gestational age estimated by other parameters was two and a half weeks earlier than the actual age, while the age calculated by the TCD proved to be compatible with the age determined by the date of the last menstruation (REECE et al., 1987).

In addition to biometrics, it is important to note that techniques for assessing cerebellar echogenicity and the space of the retrocerebellar fluid are also used to detect pathologies in this structure. The normal cerebellar hemispheres are hypoechoic with echogenic borders. In humans, cerebellar malformations are common and most of them can be diagnosed only with ultrasound examination, which requires two plans for an adequate evaluation: the mid sagittal cut and the transversal cut (GAREL et al., 2011). Failure to demonstrate the cerebellum during the examination may also suggest malformations; some examples are cerebellar dysplasia, Arnold-Chiari malformation and Dandy-Walker cyst (MCLEARY et al., 1984). There are some reports of malformations similar to these in the canine, ovine, bovine, feline, swine and equine species (AKKER, 1962; KORNEGAY, 1986; RUSBRIDGE and KNOWLER, 2004).

Elastography

In a complementary way to conventional ultrasound, elastography provides information on the elastic characteristics of the evaluated tissues by measuring the speed and direction of the propagation of shear waves, which directly correlates with tissue hardness (GENNISSON et al., 2013).

The technique is compared to a “virtual palpation” that allows to better locate and delimit lesions than ultrasonography. One of the elastographic methods is ARFI (Acoustic Radiation Force Impulse), which uses acoustic radiation forces that cause displacement in tissues. Elasticity is assessed qualitatively by the deformation that a given compression force causes in the tissue, creating an image known as an elastogram that is compared to the B-mode ultrasound image. In quantitative evaluation, the automatic speed measurement of the shear waves is made in the region of interest, which is chosen in the conventional ultrasound image (TRINDADE, 2013).

ARFI is a method of assessing tissue stiffness that has recently been used in the veterinary for the differentiation between benign and malignant mammary neoplasms of bitches (FELICIANO et al., 2017) and diagnosis of testicular diseases of dogs (FELICIANO et al., 2016). There are reference values for healthy tissues of the pancreas (AVANTE et al., 2015), adrenal glands (FERNANDEZ et al., 2017), spleen (MARONEZI et al., 2015), prostate and testicles (FELICIANO et al., 2015a) in the canine species. In the feline species, ARFI elastography was used in the testicular parenchyma (BRITO et al., 2015) and in mammary cancer (FELICIANO et al., 2015b).

Fetal elastography was first described in baboons, when liver, lung and brain stiffness was assessed in an attempt to validate the use of the technique in the prenatal period (QUARELLO et al., 2015). The applicability of this technique to evaluate fetal tissue development has been demonstrated in humans (ZHENG et al., 2016), baboons (QUARELLO et al., 2016), dogs (SIMÕES et al., 2018) and sheep (SILVA et al., 2018).

Zheng et al. (2016), who investigated the correlation between fetal development and stiffness of the thalamus, cerebellum, choroid plexus and cerebral parenchyma, first reported the cerebral elastography of human fetuses. The cerebral parenchyma was the only one to be significantly more rigid in the third trimester of pregnancy compared to the second trimester, and it was possible to correlate its shear speed with gestational age.

In humans, a preliminary study applied SWE elastography (Shear Wave Elastography) to fetal liver and lung tissue in order to verify its viability and reproducibility (MOTTET et al., 2019). By using the ARFI elastography in sheeps, it was observed that lungs and liver of fetuses undergo changes in their elasticity throughout pregnancy. The stiffness of the lung tissue decreases between the 16th and 21st weeks and the stiffness of the hepatic tissue increases between the 14th and 21st weeks, while the renal tissue does not undergo this modification (SILVA et al., 2018). In the last gestational week of bitches, the fetal liver tissue is more rigid than the lung tissue. However, it was not observed stiffness changes during this gestational period (SIMÕES et al., 2018).

CONCLUSION

The evaluations performed routinely during prenatal period of women (NT and TCD) and fetal elastography, this last one also performed in veterinary medicine, are non-invasive and promising methods to help determine the moment of delivery, diagnose malformations and monitor fetal development. Considering fetal CNS in veterinary medicine, the literature is scarce and therefore these techniques could be investigated.

Authors' contributions

Literature survey: Letícia Pavan, Priscila Silva, Ana Paula Rodrigues Simões, Luiz Paulo Nogueira Aires. Writing the text: Letícia Pavan, Beatriz Gasser, Marjury Cristina Maronezi. Correction: Luciana Cristina Padilha-Nakaghi, Ricardo Andrés Ramirez Uscategui, Marcus Antônio Rossi Feliciano.

Acknowledgment

To CNPq (National Council for Scientific and Technological Development) for research grant (process 131535/2018-8) and to FAPESP (São Paulo State Foundation Research) for thematic project (process 2017/14957-6).

REFERENCES

AKKER, S.V.D. Arnold-Chiari malformation in animals. **Acta Neuropathologica**, v.1, p.39-44, 1962.

AVANTE, M.L.; FELICIANO, M.A.R.; MARONEZI, M.C.; SIMÕES, A.P.R.; PAVAN, L.; VICENTE, W.R.R.; CANOLA, J.C. Acoustic Radiation Force Impulse (ARFI) Elastography in Healthy Canine Pancreas – Results Preliminary. In: 32nd World Veterinary Congress, 2015, Istambul. **Anais do 32nd World Veterinary Congress**, v.1, p.277-277, 2015.

BAKKER, M.; PAJKRT, E.; BILARDO, C.M. Increased nuchal translucency with normal karyotype and anomaly scan: What next? **Best Practice & Research Clinical Obstetrics and Gynaecology**, v.28, p.355-366, 2014. <DOI: 10.1016/j.bpobgyn.2013.10.004>.

BECCAGLIA, M.; FAUSTINE, M.; LUVONI, G.C. Ultrasonographic study of deep portion of diencephalo-telencephalic vesicle for the determination of gestational age of the canine foetus. **Reproduction in Domestic Animals**, v.43, p.367-370, 2008. <DOI: 10.1111/j.1439-0531.2007.00916.x>.

BECCAGLIA, M.; LUVONI, G.C.; Ultrasonographic study during pregnancy of the growth of an encephalic portion in the canine foetus. **Veterinary Research Communications,** v.28, p.161-164, 2004.

BEKELE, N.; ADDIS, M.; ABDELA, N.; AHMED, W.M. Pregnancy diagnosis in cattle for fertility management: a review. **Global Veterinaria**, v.16, n.4, p.355-364, 2016. <DOI: 10.5829/idosi.gv.2016.16.04.103136>.

BRITO, M.B.S.; FELICIANO, M.A.R.; COUTINHO, L.N.; SIMÕES, A.P.R; MARONEZI, M.C.; GARCIA, P.H.S.; USCATEGUI, R.R.; ALMEIDA, V.T.; CRIVELARO, R.M.; VICENTE, W.R.R. Elastography of Healthy Adults Felines Testes. **Acta Scientiae Veterinariae**, v.43, p.1-5, 2015.

DAVIDSON, A. P.; BAKER, T. W. Reproductive ultrasound of the bitch and queen. **Topics in Companion Animal Medicine**, v. 24, n. 2, p. 55-63, 2009. <DOI: 10.1053/j.tcam.2008.11.002>.

DUGGAN, P.M.; LIGGINS, G.C.; BARNETT, S.B. Ultrasonic heating of the brain of the fetal sheep *in utero*. **Ultrasound in Obstetrics & Gynecology**, v.21, n.4, p.553-560, 1995.

DYCE, K.M.; SACK, W.O.; WENSING, C.J.G. **Tratado de Anatomia Veterinária**. 4.ed. Tradução Rio de Janeiro: Elsevier, 2010. 834p.

FELICIANO, M.A.R.; MARONEZI, M.C.; BRITO, M.B.S.; SIMÕES, A.P.R.; MACIEL, G.S.; CASTANHEIRA, T.L.L.; GARRIDO, E.; USCATEGUI, R.R.; MICELI, N.G.; VICENTE W.R.R. Doppler and Elastography as complementary diagnostic methods for mammary neoplasms in female cats. **Arquivo Brasileiro de Medicina Veterinária e Zootecnia**, v.67, n.3, p.935-939, 2015b. <DOI: 10.1590/1678-4162-8114 >.

FELICIANO, M.A.R.; MARONEZI, M.C.; SIMÕES, A.P.R.; MACIEL, G.S.; PAVAN, L.; GASSER, B.; SILVA, P.; USCATEGUI, R.R.; CARVALHO, C.F.; CANOLA, J.C.; VICENTE, W.R.R. Acoustic radiation force impulse (ARFI) elastography of testicular disorders in dogs: preliminary results. **Arquivo Brasileiro de Medicina Veterinária e Zootecnia**, v.68, n.2, p.283-291, 2016. <DOI: 10.1590/1678-4162-8284>.

FELICIANO, M.A.R.; MARONEZI, M.C.; SIMÕES, A.P.R.; USCATEGUI, R.R.; MACIEL, G.S.; CARVALHO, C.F.; CANOLA, J.C.; VICENTE, W.R.R. Acoustic radiation force impulse elastography of prostate and testes of healthy dogs: preliminary results. **Journal of Small Animal Practice**, v.56, n.5, p.320-324, 2015a. <DOI: 10.1111/jsap.12323>.

FELICIANO, M.A.R.; NEPOMUCENO, R.M.; CRIVALERO, R.M.; OLIVEIRA, M.E.F.; COUTINHO, L.N.; VICENTE,W.R.R. Foetal echoencephalography and Doppler ultrasonography of the middle cerebral artery in canine fetuses. **Journal of Small Animal Practice**, v.54, n.1, p.149-152, 2013. <DOI: 10.1111/jsap.12038>.

FELICIANO, M.A.R.; USCATEGUI, R.A.R.; MARONEZI, M.C.; SIMÕES, A.P.R.; SILVA, P.; GASSER, B.; PAVAN, L.; CARVALHO, C.F.; CANOLA, J.C.; VICENTE, W.R.R. Ultrasonography methods for predicting malignancy in canine mammary tumors. **Plos One**, v.12, n.5, p.1-14, 2017. <DOI: 10.1371/journal.pone.0178143>.

FERNANDEZ, S.; FELICIANO, M.A.R.; BORIN-CRIVELLENTI, S.; CRIVELLENTI, L.Z.; MARONEZI, M.C.; SIMÕES, A.P.R.; SILVA, P.D.A.; USCATEGUI, R.R.; CRUZ, N.R.N.; SANTANA, A.E.; VICENTE, W.R.R. Acoustic radiation force impulse (ARFI) elastography of adrenal glands in healthy adult dogs. **Arquivo Brasileiro de Medicina Veterinária e Zootecnia**, v.69, n.2, p.340-346, 2017. <DOI: 10.1590/1678-4162-9131>.

GANAIE, B.A.; KHAN, M.Z.; ISLAM, R.; MAKHDOOMI, D.M.; QURESCHI, S.; WANI, G.M. Evaluation of different techniques for pregnancy diagnosis in sheep. **Small Ruminant Research**,

v.85, p.135–141, 2009. <DOI: 10.1016/j.smallrumres.2009.09.003>.
GAREL, C.; FALLET-BIANCO, C.; GUIBAUD, L. The fetal cerebellum: development and common malformations. **Journal of Child Neurology**, v.26, n.12, p.1483-1492, 2011. <DOI: 10.1177/0883073811420148>.
GENNISSON, J.L.; DEFFIEUX, T.; FINK, M.; TANTER, M. Ultrasound elastography: principles and techniques. **Diagnostic and Interventional Imaging**, v.94, p.487–495, 2013. <DOI: 10.1016/j.diii.2013.01.022>.
GIMENES, L.U.; ARAÚJO, R.R.; FERREIRA, J.C. Ultrassonografia do sistema reprodutor feminino de equinos. In: FELICIANO, M.A.R. et al. **Ultrassonografia na reprodução animal**. 1.ed. São Paulo: MedVet, 2013. Cap.4, p.69-90.
GOLDSTEIN, I.; REECE, E.A.; PILU, G.; BOVICELLI, L.; HOBBINS, J.C. Cerebellar measurements with ultrasonography in the evaluation of fetal growth and development. **American Journal of Obstetrics & Gynecology**, v.156, n.5, p.1065-1069, 1987.
HOLANDA-FILHO, J.A.; SOUZA, A.I.; SOUZA, A.S.R.; FIGUEROA, J.N.; FERREIRA, A.L.C.G.; CABRAL-FILHO, J.E. Fetal tranverse cerebellar diameter measured by ultrasound does not differ between genders. **Archives of Gynecology and Obstetrics**, v.284, p.229-302, 2011. <DOI: 10.1007/s00404-010-1644-5>.
HORDER, M.M.; BARNETT, S.B.; VELLA, G.J.; EDWARDS, M.J.; WOOD, A.K.W. *In vivo* heating of the guinea-pig fetal brain by pulsed ultrasound and estimates of thermal index. **Ultrasound in Obstetrics & Gynecology**, v.24, n.9, p.1467-1474, 1998.
HYETT, J.A.; PERDU, M.; SHARLAND, G.K.; NICOLAIDES, K.H. Increased nuchal translucency at 10-14 weeks of gestation as a marker for major cardiac defects. **Ultrasound in Obstetrics & Gynecology**, v.10, p.242-246, 1997.
KAGAN, K.O.; AVGIDOU, K.; MOLINA, F.S.; GAJEWSKA, K.; NICOLAIDES, K.H. Relation between increased fetal nuchal translucency thickness and chromosomal defects. **Obstetrics & Gynecology**, v.107, p.6-10, 2006. <DOI:10.1097/01.AOG.0000191301.63871.c6>.
KÖNIG, H.E.; MISEK, I.; MÜLLING, C. et al. Sistema Nervoso (Systema Nervosum). In: KÖNIG, H.E. e LIEBICH, H.G. **Anatomia dos animais domésticos: texto e atlas colorido**. 6.ed. Porto Alegre: Artmed, 2016. Cap.14, p.494-568.
KORNEGAY, J.N. Cerebellar Vermian Hypoplasia in Dogs. **Veterinary Pathology**, v.23, p.374-379, 1986.
LAMM, C.G.; MAKLOSKI, C.L. Current Advances in Gestation and Parturition in Cats and Dogs. **Veterinary Clinics: Small Animal Practice**, v.42, p.445–456, 2012. <DOI: 10.1016/j.cvsm.2012.01.010>.
LÉGA, E.; TONIOLLO, G.H.; OLIVEIRA, J.A.; RESENDE, K.T.; RODRIGUES, V. Determinação da idade fetal por meio da técnica ultra-sonográfica de fetometria e de morfologia fetal em cabras. **Arquivo Brasileiro de Medicina Veterinária e Zootecnia**, v.59, n.4, p.851-856, 2007. <DOI: 10.1590/S0102-09352007000400005 >.
MARONEZI, M.C.; FELICIANO, M.A.R.; CRIVELLENTI, L.Z.; SIMÕES, A.P.R.; BARTLEWSKI, P.M.; GILL, I.; CANOLA, J.C.; VICENTE, W.R.R. Acoustic radiation force impulse elastography of the spleen in healthy dogs of different ages. **Journal of Small Animal Practice**, v.56, n.6, p.393-397, 2015. <DOI: 10.1111/jsap.12349>.
MCLEARY, R.D.; KUHNS, L.R.; BARR JR, M. Ultrasonography of fetal

cerebellum. **Radiology**, v.151, p.439-442, 1984.
MICHAILIDIS, G.D.; ECONOMIDES, D.L. Nuchal translucency measurement and pregnancy outcome in karyotypically normal fetuses. **Ultrasound in Obstetrics & Gynecology**, v.17, p.102-105, 2001.
MOLINA, F.S.; AVGIDOU, K.; KAGAN, K.O.; POGGI, S.; NICOLAIDES, K.H. Cystic Hygromas, Nuchal Edema, and Nuchal Translucency at 11–14 Weeks of Gestation. **Obstetrics & Gynecology**, v.107, n.3, p.678-683, 2006.
MOTTET, N.; COCHET, C.; VIDAL, C.; METZ, J.P.; AUBRY, S.; BOURTEMBOURG, A.; ECKMAN-LACROIX, A.; RIETHMULLER, D.; PAZART, L.; RAMANAH, R. Feasibility of two-dimensional ultrasound shear wave elastography of human fetal lungs and liver: A pilot study. **Diagnostic and Interventional Imaging**, 2019. <DOI: 10.1016/j.diii.2019.08.002>.
NEPOMUCENO, A.C.; GARCIA, D.A.A.; BARROS, F.F.P.C.; COUTINHO, L.N.; FELICIANO, M.A.R. Ultrassonografia do sistema reprodutor feminino de pequenos animais. In: FELICIANO, M.A.R. et al. **Ultrassonografia na reprodução animal**. 1.ed. São Paulo: MedVet, 2013. Cap.3, p.41-67.
NICOLAIDES, K.H.; AZAR, G.; BYRNE, D.; MANSUR, C.; MARKS, K. Fetal nuchal translucency: ultrasound screening for chromosomal defects in first trimester of pregnancy. **BMJ**, v.304, p.867-869, 1992.
NICOLAIDES, K.H.; HEATH, V.; CICERO, S. Increased fetal nuchal translucency at 11-14 weeks. **Prenatal Diagnosis**, v.22, p.308-315, 2002. <DOI: 10.1002 / pd.308>.
O'RAHILLY, R.; MÜLLER, F. Prenatal development of the brain. In: TIMOR-TRITSCH, I.E. et al. **Ultrasonography of the prenatal brain**. 1.ed. New York: The McGraw-Hill Companies, 2012. Cap.1, p.1-13.
PRETZER, S.D. Canine embryonic and fetal development: A review. **Theriogenology**, v.70, p.300-303, 2008. <DOI: 10.1016/j.theriogenology.2008.04.029>.
QUARELLO, E.; LACOSTE, R.; MANCINI, J.; MELOT-DUSSEAU, S.; GORINCOUR, G. Feasibility and reproducibility of ShearWave elastography of fetal baboon organs. **Prenatal Diagnosis**, n.35, p.1112–1116, 2015. <DOI: 10.1002/pd.4655>.
QUARELLO, E.; LACOSTE, R.; MANCINI, J.; MELOT-DUSSEAU, S.; GORINCOUR, G. ShearWave elastography of fetal lungs in pregnant baboons. **Diagnostic and Interventional Imaging**, v.97, p.605-610, 2016. <DOI: 10.1016/j.diii.2015.11.019>.
RAMOS, A.K.M.; NEVES, J.P.; MCMANUS, C.; LUCCI, C.D.; CARNEIRO, H.C.R.; AMARAL, R.S. Avaliação dos parâmetros ecográficos de desenvolvimento gestacional em ovinos da raça Santa Inês. **Ciência Animal Brasileira**, v.8, n.3, p.537-543, 2007.
REECE, E.A.; GOLDSTEIN, I.; PILU, G.; HOBBINS, J.C. Fetal cerebellar growth unaffected by intrauterine growth retardation: a new parameter for prenatal diagnosis. **American Journal of Obstetrics & Gynecology**, v.157, n.3, p.632-638, 1987.
RUSBRIDGE, C.; KNOWLER, S.P. Inheritance of Occipital Bone Hypoplasia (Chiari Type I Malformation) in Cavalier King Charles Spaniels. **Journal of Veterinary Internal Medicine**, v.18, p.673-678, 2004.
SALOMON, L.J.; ALFIREVIC, Z.; BERGHELLA, V.; BILARDO, C.; HERNANDEZ-ANDRADE, E.; JOHNSEN, S.L.; KALACHE, K.; LEUNG, K.-Y.; MALINGER, G.; MUNOZ, H.; PREFUMO, F.; TOI, A. Practice guidelines for performance of

the routine mid-trimester fetal ultrasound scan. **Ultrasound in Obstetrics & Gynecology**, v.37, p.116-126, 2011. <DOI: 10.1002/uog.8831>.

SILVA, P.D.A.; USCATEGUI, R.A.R.; SANTOS, V.J.C.; TAIRA, A.R.; MARIANO, R.S.G.; RODRIGUES, M.G.K.; SIMÕES, A.P.R.; MARONEZI, M.C.; AVANTE, M.L.; MONTEIRO, F.O.B.; VICENTE, W.R.R.; FELICIANO, M.A.R. Acoustic radiation force impulse (ARFI) elastography to asses maternal and foetal structures in pregnant ewes. **Reproduction in Domestic Animals**, v.54, p.498-505, 2018. <DOI: 10.1111/rda.13384>.

SIMÕES, A.P.R.; FELICIANO, M.A.R.; MARONEZI, M.C.; USCATEGUI, R.A.R.; BARTLEWSKI, P.M.; ALMEIDA, V.T.; OH, D.; SILVA, P.E.S.; SILVA, L.C.G.; VICENTE, W.R.R. Elastographic and echotextural characteristics of foetal lungs and liver during the final 5 days of intrauterine development in dogs. **Animal Reproduction Science**, v.197, p.170-176, 2018. <DOI: 10.1016/j.anireprosci.2018.08.025>.

SINOWATZ, R. Development of the central and peripheral nervous system. In: HYTTEL, P. et al. **Essentials of domestic animal embryology**. 1.ed. Philadelphia: Saunders Elsevier, 2010. Cap.10, p.120-162.

SOUKA, A.P.; KAISENBERG, C.S.; HYETT, J.A.; SONEK, J.D.; NICOLAIDES, K.H. Increased nuchal translucency with normal karyotype. **American Journal of Obstetrics and Gynecology**, v.192, p.1005-1021, 2005. <DOI:10.1016/j.ajog.2004.12.093>.

SOUKA, A.P.; SNIJDERS, J.M.; NOVAKOV, A.; SOARES, W.; NICOLAIDES, K.H. Defects and syndromes in chromosomally normal fetuses with increased nuchal translucency thickness at 10–14 weeks of gestation. **Ultrasound in Obstetrics & Gynecology**, v.11, p.391-400, 1998.

TEIXEIRA, M.J.; SOUZA, D.M.B.; MELO, K.C.M.; WISCHRAL, A. Estimativa da data do parto em cadelas rottweiler através da biometria fetal realizada por ultrassonografia. **Ciência Animal Brasileira**, v.10, p.853-861, 2009.

TRINDADE, Ana F.P. **Aplicação Clínica - Avaliação da técnica Acoustic Radiation Force Impulse**. 2013. 107 f. Dissertação (Mestrado em Engenharia Biomédica) – Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, Lisboa.

ZHENG, X.Z.; WUL. J.; TAN, X.Y. A novel approach to assessing fetal tissue stiffness using virtual touch tissue quantification. **Medical Ultrasonography**, v.18, n.1, p.70-74, 2016. <DOI: 10.11152/mu.2013.2066.181.xzi>.