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Mini Review

Uterine Blood Flow Indices in Sheep during Pregnancy

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Introduction

To understand the different changes and events that occur in humans from conception until labour our experimental animal model is the ewe. Some studies use laboratory rodents, non-human primates and domestic ruminants as a model for research relevant to human pregnancies.[1] Sheep, humans and other higher primates have villous interdigitation, wherein the chorion has a tree-like branching pattern, and villi either fit into endometrial crypts or are they are directly bathed in maternal blood.[2] Furthermore, Pelage et al. demonstrated that the uterine vascularization of non-pregnant sheep is similar to that of women; so the sheep represents an appropriate animal model for experimental uterine artery embolization.[3] The previous authors analysed the anatomy of the uterine vascularature in non-pregnant ewes by following the tributaries and anastomoses of the middle uterine artery which is considered to be the main arterial supply for the uterine vasculature. As described in Figure 1, the origin of the uterine artery from the internal iliac artery was similar to that in women.[3,4]

Other studies were to analyze the uterine arterial blood supply in sheep recognized by the end the presence of pelvic anastomoses similar to those in women. The uterine artery originated from the internal iliac artery and then divided into dorsal and ventral branchs.[5] This pattern of division of the internal iliac artery was similar to that reported for women.[2,6] The pregnant sheep has been used to study the fetal-maternal communication. This may be attributed to the ability to surgically place and maintain catheters in both the maternal and fetal vasculature for repeated sampling of blood from pregnant ewes and their fetuses not under anesthesia.

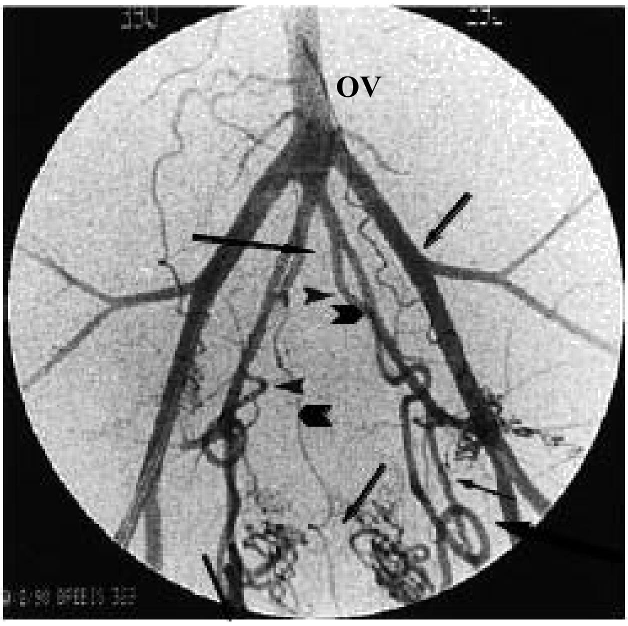

Figure 1: Uterine arteries in sheep: modified: utero-ovarian anastomosis (arrow), uterine arteries (arrowheads).[3]
UT: Uterine Artery; AO: Aorta; OV: Ovarian Artery; CI: Common Iliac Artery; EI: external Iliac Artery; II: Internal Iliac Artery; MS: Main Sacral Artery; UG: Urogenital Artery

Sheep represents an appropriate animal model to study uterine blood flow in women, because of the similarities of uterine vascularization and the existence of pelvic anastomoses in both non-pregnant sheep and women

Principles of Color Doppler Sonography Imaging

The use of doppler ultrasound during pregnancy provides a non-invasive method to study fetal, as well as maternal hemodynamics. Investigation of the uterine and umbilical arteries provides information on perfusion of the uteroplacental and fetoplacental circulations, respectively.[7]

The frequency of the ultrasound wave changes according to the relationship between the motion of both sender and receiver. Doppler first describe this phenomenon in 1842.[8] It was later known as the Doppler effect. Doppler described the application of this effect to both acoustics and optics, principally to the color of double stars and fluctuations in variable stars and novae. Vascular Doppler ultrasound is based on the Doppler effect which results from the scattering and reflection of ultrasound beams originating from the probe (Piezo-crystals) and moving to the reflecting object such as circulating red blood cells within blood vessels. A positive frequency is usually created when the object is moving toward the probe and vice versa. The difference in frequency between the released and returned signals is described as Doppler shift, which depends on the speed of the moving object. Processing of this Doppler shift can produce either a color flow display or a Doppler sonogram.[9-11]

Doppler ultrasound has been used to measure the changes in frequency of echoes in order to calculate the speed of moving objects, such as measurement of the rate of blood flow through the heart and major arteries.[12] The first use of Doppler ultrasound technology was in the form of a continuous wave which assessed the Doppler shift within the ultrasound beam, but not the Doppler shift in a small defined area of distinct blood vessels. This Doppler was unable to assess flow direction or different velocities.[13-15] The next generation was the pulsed wave or range-gated Doppler, which provides information about the depth and velocities of blood flow.[16] Therefore, it can be used to evaluate specific blood vessels and provide color flow imaging. The targeted blood vessel is located first by continuous Doppler. The Pulsed Doppler is then used after adjustment of the gate exactly over the targeted blood vessel.[12]

The next advance in Doppler development was color Doppler sonography (Color Doppler imaging), which has the ability to visually assess blood flow velocities and perfusion in B-mode gray images.[17] Color imaging Doppler means that the instruments can impose color signals of blood flow on a gray-scale image (B-mode), the first two (continuous wave and pulsed wave) are known as spectral Doppler. The brightness of color pixels depends on the angle of insonation (Doppler insonation angle) between the ultrasound beam and the direction of flow in the blood vessel. This angle plays an essential role in the interpretation of Doppler parameters.[18]

The Doppler waveform represents changes in blood flow during one cardiac cycle. The pulse repetition frequency (PRF) of the ultrasound instrument must be at least half of the Doppler shift. When the beam angle and/or blood velocity is greater than half of the PRF, aliasing (an effect resulting in signals being indistinguishable) is the result. Aliasing is a common Doppler artefact in which the peak in the velocity waveform appears under the baseline. The explanation of this artefact is based on sending a second pulse from the transducer before receiving the first one (a result of incorrect Doppler angle and/or greater blood velocity than half PRF), with the result that the receiver cannot discriminate between signals from both pulses.[7]

Doppler frequency is increased with greater alignment of the insonation angle. Therefore, the angle should be as small as possible (15-60°). In contrast, with decreased ultrasound frequency, the Doppler frequency is also decreased.[11]

Anatomical View of the Uterine Vasculature in Sheep

The value of color Doppler ultrasonography in pregnant and non-pregnant animals depends mainly on the proper identification of blood vessels. Consequently, it is important to be familiar with the anatomy of the vasculature of the uterus in small ruminants. For sheep, the uterine vasculature has been described (Figure 1).[3,19] The main blood source is the uterine artery which is supported by uterine branches from both the ovarian and vaginal arteries, which form anastomoses with the ipsilateral uterine artery. The uterine arteries are derived from the internal iliac arteries which originate as a common trunk from the abdominal aorta and then divide into the right and left internal iliac arteries. The internal iliac artery of each side is divided into cranial and caudal branches. The cranial branch further divides into visceral branches to the pelvic organs, including the uterus.

Uterine artery

Three main types of vascular anastomoses are found in sheep. First, there is a transverse anastomosis between the right and left uterine arteries. The second one is found between the uterine and ovarian arteries, and the last one between the uterine and vaginal arteries. The uterine vessels are highly tortuos, which decreases with expansion of the uterus during pregnancy (Figure 2).[20,21]

Vaginal artery

It usually commences as a branch from the cranial internal iliac artery and is directed caudally to supply the caudal part of the cervix and the vagina.

Ovarian artery

It originates from the anteriolateral part of the abdominal aorta and supplies the ovary, the Fallopian tube through the Ramus tubarius and tip of the uterine horn through the Ramus uterinus.[21] Since the uterine vasculature in sheep is similar to that of women, the ewe is considered to be suitable animal model for research relevant to human gynaecology and obstetrics.[3]

The evaluation of color Doppler images recorded by color Doppler flow mode of ultrasound machine was first done via using a computerized image analysis method.[22-24] The images of cross sections of about the tissue under examination can be created and then transferred to PC where a specific program for analyses of blood vessels blood flow changes in certain predetermined area generally called "Region Of Interest (ROI)". Within this area the total area of the perfused areas and the total number of color pixels as a measure of blood flow using throughout software.[22,25] The analysis of the Doppler waves may be qualitative, semi-quantitative and quantitative done.[7] The assessments of Doppler sonography may be one of three: qualitative, semi-quantitative, and, finally, quantitative. The first one, qualitative, depends mainly on wave analysis as the presence or absence of end diastolic blood flow and its relation to the previous and next peak systolic blood flow. It also concerns the wave characteristics as above or under the baseline, in addition to increased and/or decreased end diastolic velocity of blood flow, either physiological or pathological.[22,26-28] The second, semi-quantitative, depends mainly on descriptions of blood flow indices, which are independent of the insonation angle. Measurements of the Doppler indices PI (pulsatility index) and RI (resistance index) include calculations of peak velocity (PV) and the time averaged maximum velocity (TAMV) values over the time of the cardiac cycle. These Doppler indices provide important information to enable the researcher or the clinician to understand the extent of vascular perfusion.[28] The quantitative analysis includes evaluation of blood flow parameters that require adjustment of the Doppler angle between Doppler beam and blood vessel, as well as the measurement of diameter of the target blood vessel to calculate blood flow volume, BFV.[29,30] Nowadays, there are some ultrasound machines that can assess the Doppler waves without transferring images to PC as used by Elmetwally et al.[20] All parameters are measured except for blood flow volume which requires manual adjustment of Doppler angle between Doppler beam and blood flow. In conclusion,

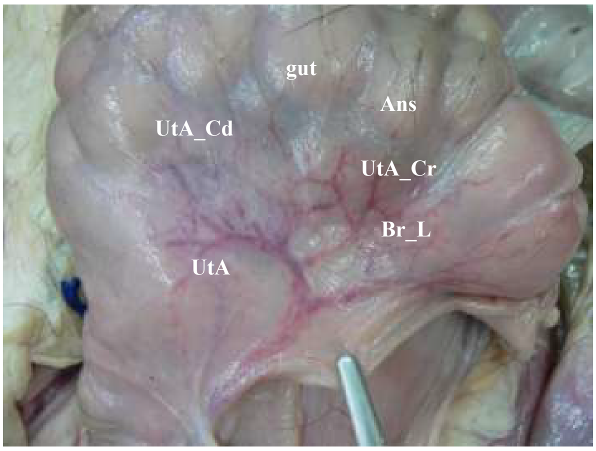

Figure 2: Uterine artery in a goat *in situ*.
(UtA: Uterine Artery, g_ut: gravid uterus, UtA_Cr: Cranial Branch of Uterine Artery, UtA_Cd: Caudal Branch of Uterine Artery, Ans: Anastomosis between Cranial and Caudal Branch of Uterine Artery, Br_L: Broad Ligament)

the Doppler indices provide measures of the resistance ratios to blood flow in the distal portion of the examined artery in the vascular bed. The higher the index value, the greater the resistance to blood flow in the respective vascular organ and vice versa.[7] The most regularly used color Doppler indices are described in schematic diagram “Figure 3: manipulation and orientation” modified from Elmetwally. The setting for the range of flow-velocity was adjusted to obtain the spectral graph, and a Doppler spectrum is generated across at least 3 to 5 uniform cardiac cycles and one the waves is used for spectral measurements.[5] The means for two to three measurements are used for statistical analysis. The important parameters (Figure 3) reported for Doppler evaluations of blood flow are defined as follows.

The resistance index (RI) is one of the most important indices of vascular perfusion of the tissue and it is recommended usually for low resistance vascular beds with continuous blood flow during diastole. It can be calculated using the following equation (RI=PSV-EDV/PSV).[31] The importance of the resistance index stems from its negative relationship with vascular perfusion. Namely, decreasing resistance increases vascular perfusion and vice versa.

The pulsatility index (PI) can be calculated using the following equation (PI=PSV-EDV/TAMV).[32] Increases in PI indicate decreases in tissue perfusion and vice versa. As the relation of PI to RI is positive, one of these indices is assumed to be sufficient. The usefulness of PI and RI as Doppler indices in most color Doppler studies is that they are not affected by both Doppler angle and diameter of blood vessel, but are affected only by heart rate[11] As gestation advances, PI and RI decrease progressively, indicating an increase in fetal blood perfusion.[33] Furthermore, RI and PI are ratios of velocity measurements independent of Doppler angle.[5,20]

The systolic/diastolic ratio (S/D ratio) indicates the impedance of blood flow. A decrease in this ratio indicates an increase in blood perfusion of the target tissue (S is the maximum Doppler shift frequency and D is the minimum Doppler shift frequency).[34] This ratio is not often used, especially with the development of PI and RI measuring software.[35]

In order to evaluate the blood flow in small vessels, especially those that do not have collateral circulation and where there is difficulty in measuring the diameter, time averaged maximum velocity (TAMV) is usually used.[7] TAMV is calculated from time averaged maximum frequency shift over the cardiac cycle [TAMV=TAMVF*c/2Fx cos α, where c=ultrasound propagation speed, F=transmitted wave frequency and α=angle between ultrasound beam and blood flow direction].[36]

The blood flow volume (BFV) to the target tissue depends mainly on the mean velocity and the diameter of the target blood vessel. It can be calculated using the equation (BFV=Vel*A), where Vel is the time averaged maximum velocity during the cardiac cycle and A is the cross-sectional area of the target blood vessel which can be calculated from the vessel diameter and measured from B-mode images. From the vessel diameter, BFV can be calculated accurately by Doppler ultrasound when the diameter is ≥ 2 mm.[7] Three measurements should be taken using B-mode gray imaging for vessel diameter, and at least 3 to 4 cardiac cycle wave forms are needed to measure flow velocity. These measurements should also be associated with adjustment of the Doppler angle.

Development of Color Doppler Ultrasound Application in Sheep

Doppler ultrasonography has been used successfully for pregnancy diagnosis in women as early as 12 week of gestation. Further studies[37-39] determined the maternal, feto-placental and

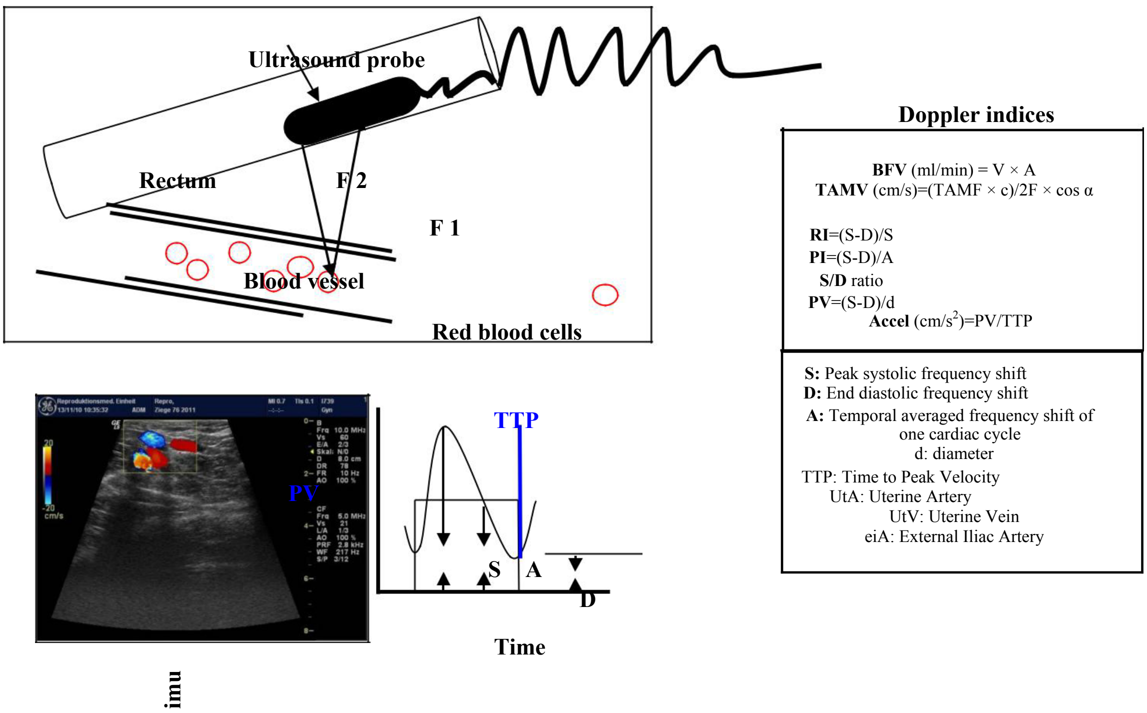

Figure 3: Manipulation and orientation of Doppler ultrasound probe and the different Doppler indices.[7,31,32,34]

umbilical blood flows and impedance of these blood flows. In human reproduction, a relationship was found between the maternal and umbilical blood flow and the intra-uterine fetal growth.[38,40]

Lindahl is considered to be one of the first researchers to use ultrasound based echo principles for pregnancy diagnosis in ewes between 60 and 80 days after conception.[41] Thereafter, Hulet used Doppler ultrasonography with an accuracy of 97% to 99% for pregnancy diagnosis in ewes between 75 and 92 days of gestation.[42] The basic principle of these Doppler investigations was to detect fetal heart beats, arterial pulsations or movements [of what???] in the caudal abdominal region of pregnant ewes. Detection of arterial pulsations or heart beats from both sides of the abdomen or in two different regions during the same scanning may indicate multiple pregnancies[43] and failure to detect pulsations, heart beats and fetal movement are indicators that the ewe is not pregnant.[44] Furthermore, there is a higher rate of accuracy in both single (82.6%) and multiple (92.9%) investigations by the Doppler method than by the real-time linear ultrasound scanning methods (68.2% and 66.7%, respectively) in pregnant ewes.[43] The earliest time at which pregnancy could be detected using external transducers with either the Doppler or A-scope technique was between 40 and 50 days after mating, but with some difficulties in determining the number of foetuses.[45]

A surgical feto-maternal model for Doppler sonographic measurements of the maternal middle uterine artery and fetal umbilical artery blood flow characteristics in ewes was developed by Soma et al.[46] Further, Doppler ultrasonic studies have been performed with the development of continuous wave Doppler ultrasonography and were used to study of some characteristics of the uterine artery or main vessels supplying placentomes and umbilical blood flow in ewes.[47,48] Blood flow parameters were used to differentiate between normal and abnormal pregnancies in small ruminants and in other animal species and women.[47,49] Also, they were used for determination of functional changes in female genitalia under the effect of cyclic hormones in women[26,50,51] and in animals.[5,29,36] As well, colour Doppler sonography has been used to study uterine artery blood flow postpartum in cows and small ruminants, respectively.[52,53]

Invasive color Doppler sonographic validation of uterine blood flow in pregnant sheep was performed using the transit-time ultrasonic perivascular flow probe method. The authors concluded that the uterine blood flow velocities reflect uteroplacental volume blood flow.[54,55]

Physiologically, the uterine and umbilical blood flows increases continuously during pregnancy to meet the increases in nutrient demand for fetal and placental growth.[56,57] The use of serial uterine blood flow volume measurements in pregnant sheep, from mid- to late-gestation, to describe the consequences of an induced intrauterine fetal growth restriction was studied by Wallace et al. using a perivascular Doppler flow probe attached to the uterine artery of the pregnant uterine horn from 83 days until 145 days of pregnancy.[58] Furthermore, colour Doppler indices of uterine artery Doppler indices were used to assess fetal risk during pregnancies.[59,60] Recently, colour Doppler ultrasound imaging was used to assess changes in uterine and umbilical blood flows throughout normal pregnancy in small ruminants.[5,20]

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