Evaluation of fetal exposure to external loud noise using a sheep model: Quantification of in-utero acoustic transmission across the human audio range

Pierre GÉLAT, PhD, Anna L DAVID, MD, PhD, Seyyed Reza HAQHENAS, PhD, Julian HENRIQUES, PhD, Aude THIBAUT de MAISIERES, MSc, Tony WHITE, MD, PhD and Eric JAUNIAUX, MD, PhD, FRCOG

From the Department of Mechanical Engineering, University College London, London, UK (Drs Gélat and Haqshenas); Department of Media, Communications and Cultural Studies, Goldsmiths, University of London, London, UK (Pr Henriques); Sonic Womb Productions Limited and Goldsmiths, University of London, London, UK (Mrs Thibaut de Maisieres); EGA Institute for Women's Health, Faculty of Population Health Sciences, University College London, London, UK (Prs Jauniaux and David), The Royal Veterinary College, London, UK (Mr White)

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Corresponding author: Eric Jauniaux, MD, PhD, FRCOG e.jauniaux@ucl.ac.uk

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Condensation: Measurement of in utero acoustic attenuation in fetal sheep across the audio range (100Hz–20kHz, at 6Hz intervals) revealed transmission of external noise sources by as little as 3 dB through the abdominal wall and uterine cavity.

Short version of title: Evaluation of fetal exposure to external sound sources.

AJOG at a glance:

- Why was the study performed There are no prior studies providing fine frequency measurement data of in-utero acoustic attenuation characteristics in the spectral width of the audio range, between 100 Hz and 20 kHz.
- What were the key findings Measurement of sound attenuation in the uterus of pregnant ewes shows that, at specific frequencies and relative to a given microphone location, the external noise source is attenuated by as little as 3 dB through the abdominal wall and uterine cavity.
- What does this add to what is known Measurement of the attenuation of acoustic sources through the abdominal wall indicates that significant frequency content above 10 kHz is transmitted inside the uterus suggesting that chronic loud noise exposure could have an impact on fetal development.

Abstract

Background: There is mounting evidence that neural memory traces are formed by auditory learning in-utero and that premature newborns are particularly sensitive to the intense, sustained noises or impulses sounds associated with the use of intensive care equipment. One area of critical importance is the determination of sound level exposure in-utero associated with maternal occupation. The attenuation factors provided by the abdomen and tissue as well as the routes by which the inner ear receives stimulation need careful consideration and investigation to provide prenatal protection from external sound levels and frequencies at which harm may be caused.

Objective: To measure how sound from external sound sources is transmitted inside the womb on a fetal sheep model in 6 Hz frequency steps between 100 Hz and 20 kHz, i.e. across most of the human audio range.

Study Design: We measured acoustic transfer characteristics in-vivo in six time-mated singleton pregnant Romney ewes (gestational age 103–130 days, weight 54–74 kg). Under general anaesthesia and at hysterotomy, a calibrated hydrophone was attached to the occiput of the fetal head within the amniotic sac. Two calibrated microphones were positioned in the operating theatre, close to the head and to the body of each ewe. Initial experiments were carried out on three pregnant ewes three days after transport recovery, to inform the data acquisition protocol. This was followed by detailed data acquisition of three pregnant ewes under general anaesthesia, using external white noise signals. Voltage

signals were acquired with two calibrated microphones, located near the head and the body of each ewe and with a calibrated hydrophone located in the amniotic fluid.

Results: Measurement of acoustic transmission through the maternal abdominal and uterine walls indicates that frequency contents above 10 kHz are transmitted into the amniotic sac, and that some frequencies are attenuated by as little as 3 dB.

Conclusion: This study provides new data about in-utero sound transmission of external noise sources, beyond physiological noise (cardiovascular, respiratory, and intestinal sounds) which help quantity the potential for fetal physiological damage resulting from exposure to high levels of noise during pregnancy. Fine frequency acoustic attenuation characteristics are essential to inform standards and clinical recommendations on exposure of pregnant women to noise. Such transfer functions may also inform the design of filters to produce an optimal acoustic setting for maternal occupational noise exposure, use of magnetic resonance imaging during pregnancy and for neonatal incubators.

Key Words: In-utero acoustics, Fetal ear, Fetal auditory system, Fetal sound exposure, Prenatal sound exposure, Noise pollution, Pregnancy, Hearing damage, Teratology, Occupational noise.

Introduction

Anatomical studies have shown that the cochlea and peripheral sensory-end auditory organs of the human fetus are fully formed by 24 weeks.[1] Maturation of the auditory pathways of the central nervous system develop from the beginning of the third trimester of pregnancy, with significant activation to sound seen in the left temporal lobe of the fetal brain, confirming that sound processing occurs beyond the reflexive sub-cortical level.[2] Ultrasonographic observations of blink-startle responses to vibroacoustic stimulation are first elicited from 24 weeks of gestation, and are consistently present after 28 weeks[1] whereas maternal voice recognition in utero appears between 33 and 34 weeks of gestation.[3]

There is mounting evidence that neural memory traces are formed by auditory learning in-utero and auditory change detection is crucial for the development of the auditory system.[4,5] These development changes start from 27–28 weeks of gestation and are a prerequisite for language development.[4,5] Interpretation of acoustic and linguistic information on intrauterine recordings suggests that the prosodic features of speech (pitch contours, rhythm, and stress) are detectable by the fetus. Extensive prenatal exposure to a melody or to specific human speech induces neural representations that last for several months[4,5], and may contribute to language acquisition during the first year after birth. The hearing threshold or intensity at which neonates perceive sound at 27–29 weeks of gestation is approximately 40 dB[6], decreasing to a nearly adult level of 13.5 dB by 40-42 weeks of gestation, indicating continuing postnatal maturation of acoustic neural pathways.

Physiological auditory stimuli to which the fetus is exposed in-utero include both internal sounds, such as the maternal heartbeat, voice and other body sounds, as well as

external sounds that cross the different tissue layers of the maternal abdomen.[7] Sound is transmitted easily into the uterine environment.[8] In fetal sheep, exposure to intense broadband noise altered the fetal auditory brain stem response and damaged cochlea hair cells.[9] Noise levels over 100 dB, that are capable of damaging cochlea hair cells, have been recorded in adult intensive care units.[10] Excessive noise is implicated in intensive care psychosis, increased pain sensitivity and high blood pressure, poor recovery and higher risk of readmission. In 1997, the American Academy of Pediatrics Committee on Environmental Health expressed concern about the effect of high noise levels on the fetus and newborn and recommended further research.[11]

Fetal exposure to artificial environment noise has changed dramatically in the second half of the 20th century, in particular in urban areas. A systematic review using the World Health Organization (WHO) environmental noise guidelines for the European region found associations between environmental noise, specifically aircraft and road traffic noise and adverse birth outcomes including preterm birth and low birth weight.[12] The quality of the evidence was found to be low in particular, in older studies due to limitations in the recording technology. One of the most prevalent types of noise exposure in working women is occupational noise. A Swedish nationwide cohort study has shown an association between occupational noise during pregnancy and hearing dysfunction in children.[13] A more recent study by the same authors has also shown that full-time exposure to high levels of occupational noise during pregnancy is associated with slightly reduced fetal growth but not with premature birth.[14] The effect of intermediate occupational noise exposure (75–85 dBA) showed a small, but statistically increased risk for all studied birth outcomes, strengthening the evidence that pregnant women should not be subject to a long-

term exposure to levels >85 dBA of occupational noise during pregnancy. Other new sources of high sound levels for fetuses include magnetic resonance imaging (MRI), music concerts, and fetal stimulation musical devices.

Previous experiments in sheep and goats have indicated that intra-uterine noise is predominantly low-frequency[15], whereas energy above 0.5 kHz is attenuated by 40 to 50 dB.[8,16,17] Sheep experiments have also indicated that sounds in the environment of a pregnant woman penetrate the tissues and fluids surrounding the fetal head and stimulate the inner ear through a bone conduction route.[8] These data are limited by the quality of recording technology and access to computer models enabling the translation of animal data into human data. The aim of our study was to use state-of-the-art data acquisition systems and calibrated instrumentation to measure the in utero acoustic transfer characteristics on pregnant ewes to help quantify the potential for fetal auditory damage resulting from exposure to high levels of noise during pregnancy.

Materials and Methods

Two sets of experiments were carried out, each involving three time-mated pregnant Romney ewes (formally called Romney March sheep), weight range 54–74 kg carrying 103–130 days of gestation singleton fetuses, supplied by the Royal Veterinary College (Hertfordshire, UK). All procedures on animals were conducted in accordance with U.K. Home Office regulations and the Guidance for the Operation of Animals (Scientific Procedures) Act (1986). Ethics approval was provided by the animal studies committees of the Royal Veterinary College and the University College London, United Kingdom (Study reference: 2014-N-0050). General anaesthesia was induced with thiopental sodium

20 mg·kg^{-1} intravenously (Thiovet; Novartis Animal Health UK Ltd, Hertfordshire, UK) and after intubation, animals were maintained with 2–2.5% isoflurane in oxygen (Isoflurane-Vet; Merial Animal Health Ltd, Essex, UK) as previously described.[18] The number of fetuses and gestational age was confirmed using ultrasound examination of fetal size according to standard measurements.[19] The abdomen was sheared, cleaned with povidone iodine and draped. Laparotomy was performed using a midline incision below the umbilicus and the abdomen was opened in layers. In an area of myometrium away from placentomes, a 5 cm uterine incision was performed over the fetal head which was then exteriorized through the uterine incision.[20] Babcock clamps were used to compress the amniotic membrane against the uterine wall in order to minimize bleeding and reduce amniotic fluid loss. A calibrated hydrophone was sutured to the occiput of the fetal head and cabling was secured to the posterior aspect of the fetal neck using 2.0 Prolene (Ethicon, Ohio, USA). The distance between the hydrophone and the maternal skin was measured with ultrasound at 5–7 cm in all cases. This hydrophone features a flat frequency response (±1 dB) between 100 Hz and 20 kHz. The uterine incision was closed in two layers as described.[20] The cabling from the hydrophone was then exteriorized onto the ewe's right flank and secured to the skin. Antibiotics for infection prophylaxis and analgesia were given to the ewe at the end of the procedure as previously described[20]. The abdomen was then closed in layers. In the first set of experiments, one of the ewe was allowed to recover and sound experiments were conducted three days after transport in an open stable area. A companion sheep was always placed in the same stable area as the awake experimental animal. In the second experiments, the ewes were maintained under general anaesthesia until the end of the experiment. When sound experiments were completed, animals were

killed with an overdose of Pentobarbitone (Thiovet; Novartis Animal Health UK Ltd, Hertfordshire, UK). The preliminary experiments investigated whether the study carried out by Gerhardt et al.[8] could be replicated using modern hydrophones and digital recording technology. The preliminary experiments (Appendix 2) were needed to overcome the challenges of positioning the hydrophone inside the amniotic sac and were of a more qualitative nature than the main experiments (Appendix 3). The experimental setup is shown in Figure 1.

The Waveform Audio File Format (WAV) files corresponding to the hydrophone and microphone output voltage signals were imported into Matlab for signal processing. The methodology used to estimate the attenuation resulting from the maternal tissues and fluid is based on a transfer function estimate, whereby the frequency content of the hydrophone signals is compared with that of the microphone signals and frequency domain transfer characteristics derived. This data processing protocol is described in Appendix 3.

Results

Microphone and hydrophone signals

Figures 2 (a & b) show the microphone and hydrophone white noise excitation acoustic pressure signals obtained on ewe 2 for the 6th repeat of the main experiments, respectively. Calibration correction factors were applied. The signals were de-trended and then filtered with a bandpass filter with upper and lower −3 dB cut-off points at 100 Hz and 25 kHz, respectively.

From the acoustic pressure data displayed in Figure 2a, the sound pressure level (SPL) for each white noise burst was calculated using the RMS pressure value. On this

particular repeat, a logarithmic average of the 20 SPL values was found to be 106 dB at the head microphone location and 107 dB at the body microphone location. The ambient SPL inside the operating theatre, calculated from a logarithmic average of four repeat measurements each of 98 s duration, with the loudspeaker switched off, was found to be 72 dB at the head microphone location and 77 dB at the body microphone position. The background noise recorded by the amniotic sac hydrophone for corresponding measurements was found to be 96 dB. Since physiological noise (breathing, digestive noises, etc.) was reported by Gerhardt et al.[8] to be of the order of 50 dB, it is likely that this noise is a result of electromagnetic interference. This was indeed confirmed by looking at the spectral content of the signal. A logarithmic average of the SPL during the white noise excitation intervals was obtained as 102 dB. Assuming that the RF noise is not coherent with the white noise excitation signal, the SPL inside the amniotic sac is therefore 101 dB, i.e. only 5-6 dB lower than at the two operating theatre microphone locations.

Sound transmission inside the womb

For each repeat measurement, 20 transfer functions estimates were obtained, i.e. one for each white noise burst (see Appendix 3). Figures 3(a & b) show the microphone to hydrophone transfer function estimates, as a function of frequency between 100 Hz and 20 kHz. The mean together with the mean μ plus or minus the standard deviation σ is plotted, based on the data set comprising 80 transfer function estimates from the four repeat measurements. The above procedure was repeated to derive the corresponding microphone and hydrophone output signals for ewe 3.

From the data in Figure 4a, the logarithmic average of the SPL for the 20 white noise bursts was found to be 107 dB for the body microphone and 109 dB for the head

microphone. The background SPL in absence of any loudspeaker excitation was found to be 72 dB at the body microphone locations and 77 dB at the head microphone location. These figures are comparable with those recorded with ewe 2 inside the operating theatre. The hydrophone inside the amniotic sac recorded a logarithmic average SPL of 103 dB over the 20 white noise bursts. The background noise recoded by the amniotic sac hydrophone for was found to be 98 dB. Hence the SPL recorded by the hydrophone is 102 dB when removing contribution from the noise, assuming that the latter is not coherent with the loudspeaker signal. This indicates that the SPL inside the amniotic sac is therefore only 5–7 dB lower than at the two operating theatre microphone locations. Again, this result is comparable to that obtained for ewe 2. Following the same procedure as for ewe 2, the transfer function estimates are displayed in Figures 5a and 4b, for both microphone locations.

Comment

Principal findings

Acoustic transfer characteristics measured on two pregnant Romney ewes between 100 Hz and 20 kHz at 6 Hz intervals, reveal that significant transmission of external noise sources occurs across much of the audio range. In one ewe, a hydrophone inserted inside the amniotic sac recorded a 4-dB attenuation between 200 Hz and 400 Hz, with respect to a microphone inside the operating theatre, placed near the body of the ewe. A common increase in the transfer characteristics above 8 kHz was observed in both ewes.

Strengths and limitations

A key strength of our study is that the excitation protocol uses a broadband loudspeaker to reproduce segments of white noise i.e. signal of equal intensity at different frequencies. This enabled us to evaluate with fine frequency resolution, the transfer of sound functions throughout most of the human audio range, from microphones located inside the operating theatre to a hydrophone located inside the amniotic cavity next to the fetal head. Furthermore, the use of the H_1 estimator (see Appendix 3) helps remove contamination from uncorrelated output noise, helping to overcome the poor signal-to-noise ratio of the hydrophone signals.

Differences in attenuation response trends are reported, depending on the animal, which are likely to be due to both variations in anatomy and in acoustic tissue properties. It is possible that such behaviour results from internal acoustic modes which are specific to the animal. We found that the microphone location may have an impact on the overall transfer function estimate (Figures 3 and 5). This is likely to be due to the complex acoustic environment inside the operating theatre.

Reflections on surfaces within the operating room, together with acoustic resonances will impact on the transfer function estimate. Ideally, such experiments would be better carried out in an anechoic room but such an undertaking would be technically very challenging. Depending on the position of the microphone inside the room, and with respect to the animal position on the operating table, the acoustic transfer characteristics between the loudspeaker and the microphone vary. The existence of anti-resonances in the transfer functions may in some cases be due to room modes which may be picked up more prominently at one microphone positions rather than another. For example, it is likely that the trough at around 750 Hz in Figure 3b results from a room resonance that is more

prominent at the location of the maternal head microphone than that of the body microphone.

Results in Context

Like previous authors, we have used the sheep model because of the similarities between the sheep and human fetus in size and uterus at term. Previous in-vivo experiments in the near-term ewe have indicated that of the external airborne sounds, only the low frequency (below 0.3 kHz) components reach the womb interior, and that frequencies above 0.5 kHz are attenuated by 40 to 50 dB.[7,8] Overall, previous studies show that low-frequency sound energy easily penetrates to the fetal head, with less than 5 dB attenuation for frequencies below 0.5 kHz, whereas higher frequencies are attenuated by up to 20 to 30 dB. The sound energy in amniotic fluid stimulates fetal hearing through a bone conduction route rather than through the external and middle ear systems[21]. Intrauterine sound recording in humans during labour after membrane rupture showed that low-frequency sounds (0.125 kHz) generated outside the mother were enhanced by an average of 3.7 dB.[22] There is a gradual increase in attenuation for increasing frequencies, with a maximum attenuation of 10.0 dB at 4.0 kHz but the interpretation of these data is difficult in the absence of amniotic fluid around the fetus.

The results of the present study indicate that at specific frequencies, the abdominal wall, together with overlying tissue and the amniotic fluid provide as little as 2–3 dB acoustic attenuation of external airborne sound inside the uterus environment at frequencies below 1 kHz, confirming the results of previous studies.[7,8] Above 1 kHz, the attenuation increases to 20–40 dB, depending on the animal and position of the external microphone. Above 10 kHz, the improved measurement protocol used in this study reveals that

significant external sound is transmitted in-utero and that attenuation is as little 3 dB at 11 kHz in one ewe. These results are in accordance with those of Lecanuet et al. who compared the characteristics of sound transmission between a similar sheep model and a non-biological plain rubber sphere[23] and support the hypothesis that internal resonances are responsible for the increase in in-utero sound transfer characteristics at frequencies above 10 kHz.

Research implications

The possible fetal side effects associated with MRI include temperature increase due to radio frequency wave exposure, biological effects of a strong magnetic field and acoustic noise from time-variant gradients.[24] A large controlled study including 1737 early pregnancies has shown that exposure to MRI without gadolinium contrast during the first trimester of pregnancy compared with non-exposure is not associated with an increased risk of congenital anomalies, neoplasm or hearing loss from birth to age 4 years, however the risk of vision loss was higher for exposure between 5 and 10 weeks of gestation[25]. Prenatal exposure to MRI during the second or third trimester of pregnancy in a small cohort of 72 uncomplicated pregnancies is not associated with disturbances in functional outcomes or hearing impairment at preschool age.[26] These studies are retrospective and thus limited in the evaluation of actual noise fetal exposure.

Music devices designed for fetal acoustical stimulation have become increasingly popular over the last decade. Their usage is based on a pervasive myth, supported by a myriad of commercially-driven websites that playing music to your unborn fetus will enhance its cognitive abilities throughout its life. Jahn et al have recently evaluated the sound characteristics of three different music devices and have shown that sound pressure

levels are hardly detectable under attenuated conditions.[27] Their measurements were obtained in open air, using a pork uterus of 5 mm thickness covered by abdominal porcine tissue which is very different from the in-utero experimental conditions of the present study. We agree with Jahn et al that there is no evidence that, isolated auditory stimulation using loudspeakers with poor sound characteristics, may support the development complex multimodal maturation of the fetal sensory system. However, our data, obtained in a physiological uterine environment, indicate that some frequencies are attenuated by as little as 3 dB by the maternal abdominal and uterine wall. In addition, unlike the acoustic noise exposure associated with a regular 20–60 min MRI examination, music devices for fetal sound simulation are often use for several hours per day, therefore exposing the fetus to non-physiological sound. These findings highlight the need for further research into the potential negative impact of these devices, in particular when used internally.

Music devices have also been used in neonatal intensive care units (NICU) and unlike for their prenatal use have been associated with short- and long-term on preterm infant cognitive and emotional development.[28-30] However, a recent review[25] has shown that all recordings of maternal voice at sound levels are above NICU acceptable levels of 45dB, recommended by the American Academy of Pediatrics and that few of the findings on the positive effects of these recordings reached statistical significance. The integration of the in-vivo data of the present study into a computerised model together with available anatomical human data should enable us to develop a sound filter representative of the in utero physiological environment, which may then be integrated in a prototype womb-like incubator.

Conclusions

The results of the present study highlight the importance of acoustic studies during pregnancy and support the epidemiological evidence that pregnant women should not be long-term exposed to high level occupational noise. New sources of non-physiological external loud noise fetal exposure during pregnancy include those produced by medical equipment such as MRI and by musical devices designed for fetal acoustical stimulation. The latter are often used daily for many hours by parents-to-be without any evidence of benefit for the fetal development but with potential harm associated with chronic exposure to high level noise.

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Figure legends

Figure 1. Schematic of data acquisition setup involving the measurement of in utero sound attenuation in pregnant Romney ewes. An acoustic source was placed in the room and excited with bursts of white noise, generating spectral content between 100 Hz and 20 kHz. The sound was detected by the two microphones and the one hydrophone in the amniotic cavity and data transferred via cables to the computer.

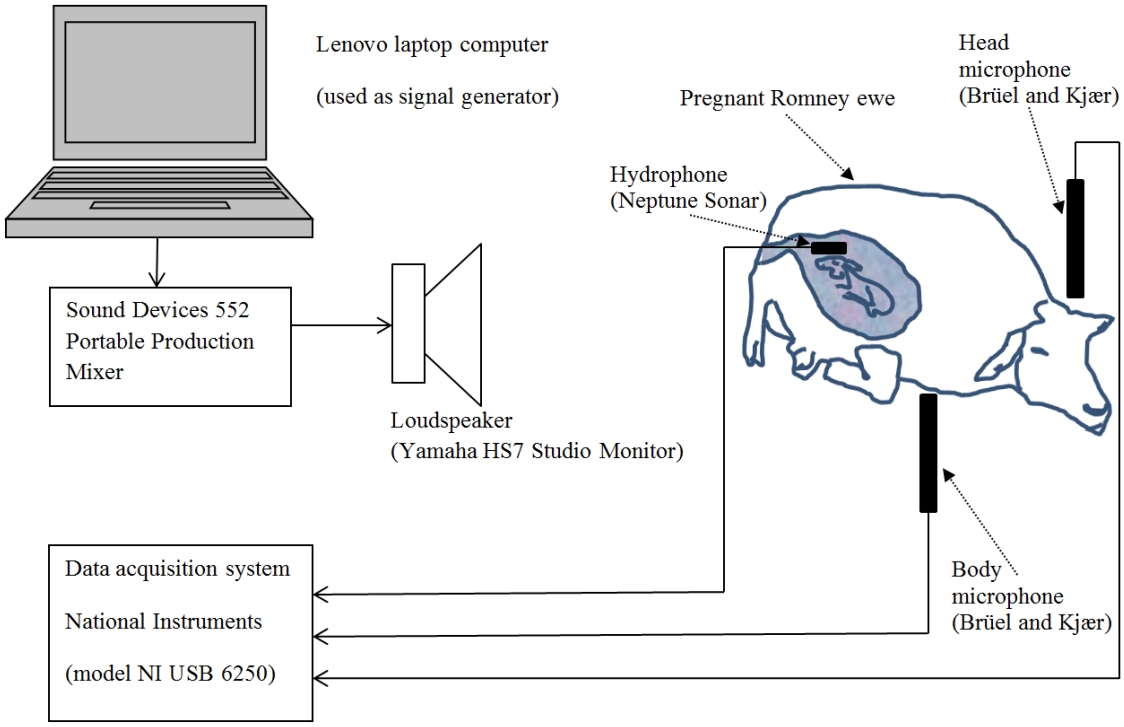
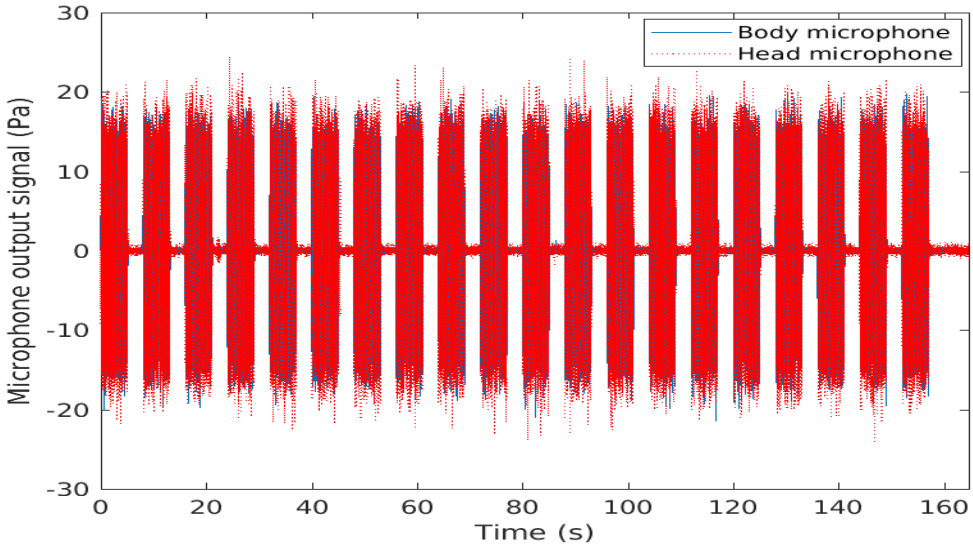


Figure 2. (a) Microphone output signals resulting from white noise burst excitation signal for ewe 2 (main experiment). (b) Amniotic sac hydrophone output signal resulting from white noise burst excitation signal for ewe 2. All signals are corrected for calibration factors.



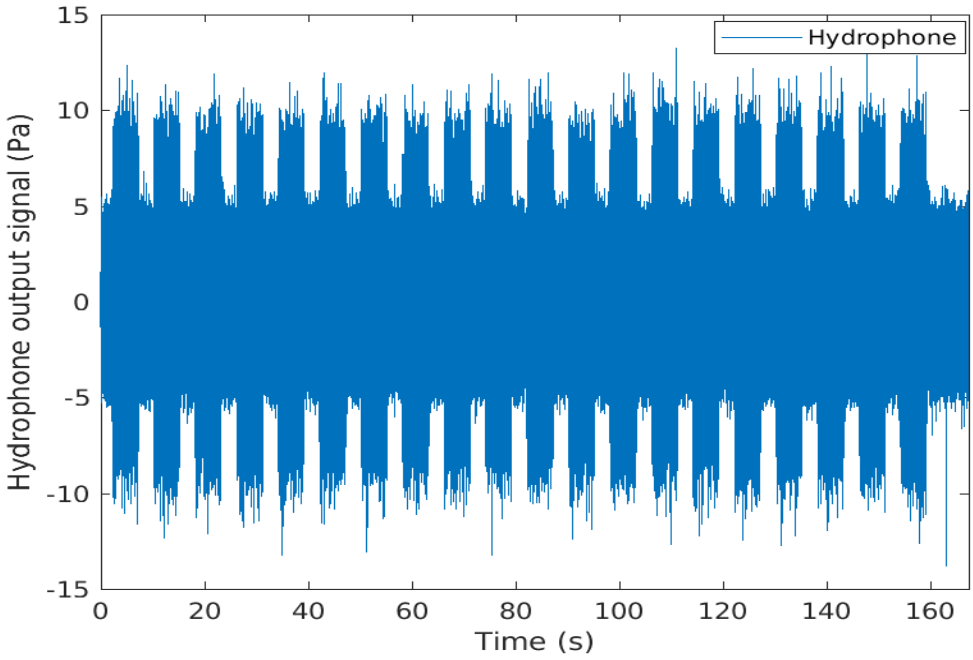


Figure 3. (a) Body microphone to amniotic sac hydrophone transfer characteristics for ewe 2 (main experiments). (b) Head microphone to amniotic sac hydrophone transfer characteristics for ewe 2 (main experiment).

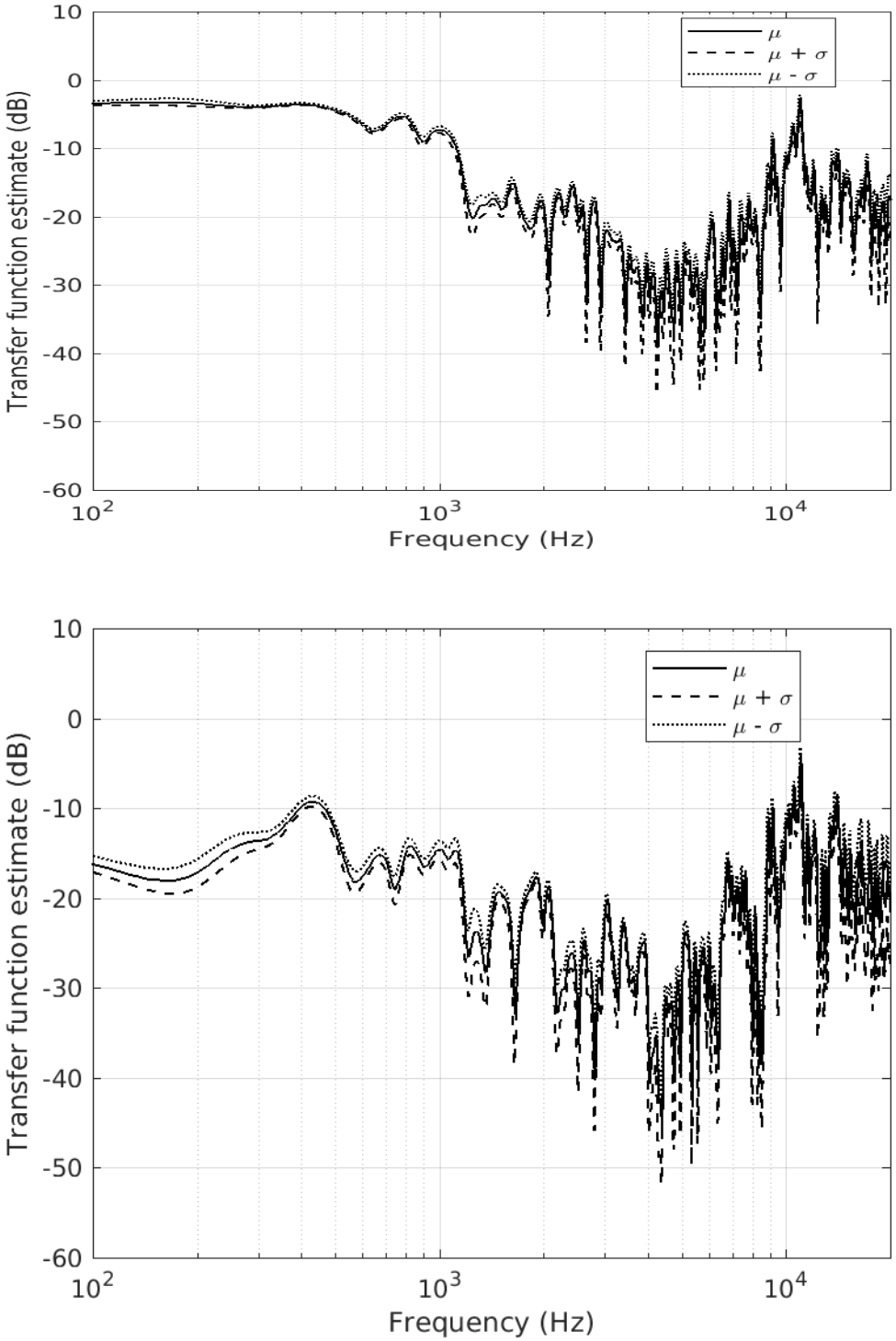


Figure 4. (a) Microphone output signals resulting from white noise burst excitation signal for ewe 3 (main experiment). (b) Amniotic sac hydrophone output signal resulting from white noise burst excitation signal for ewe 3 (main experiment). All signals are corrected for calibration factors.

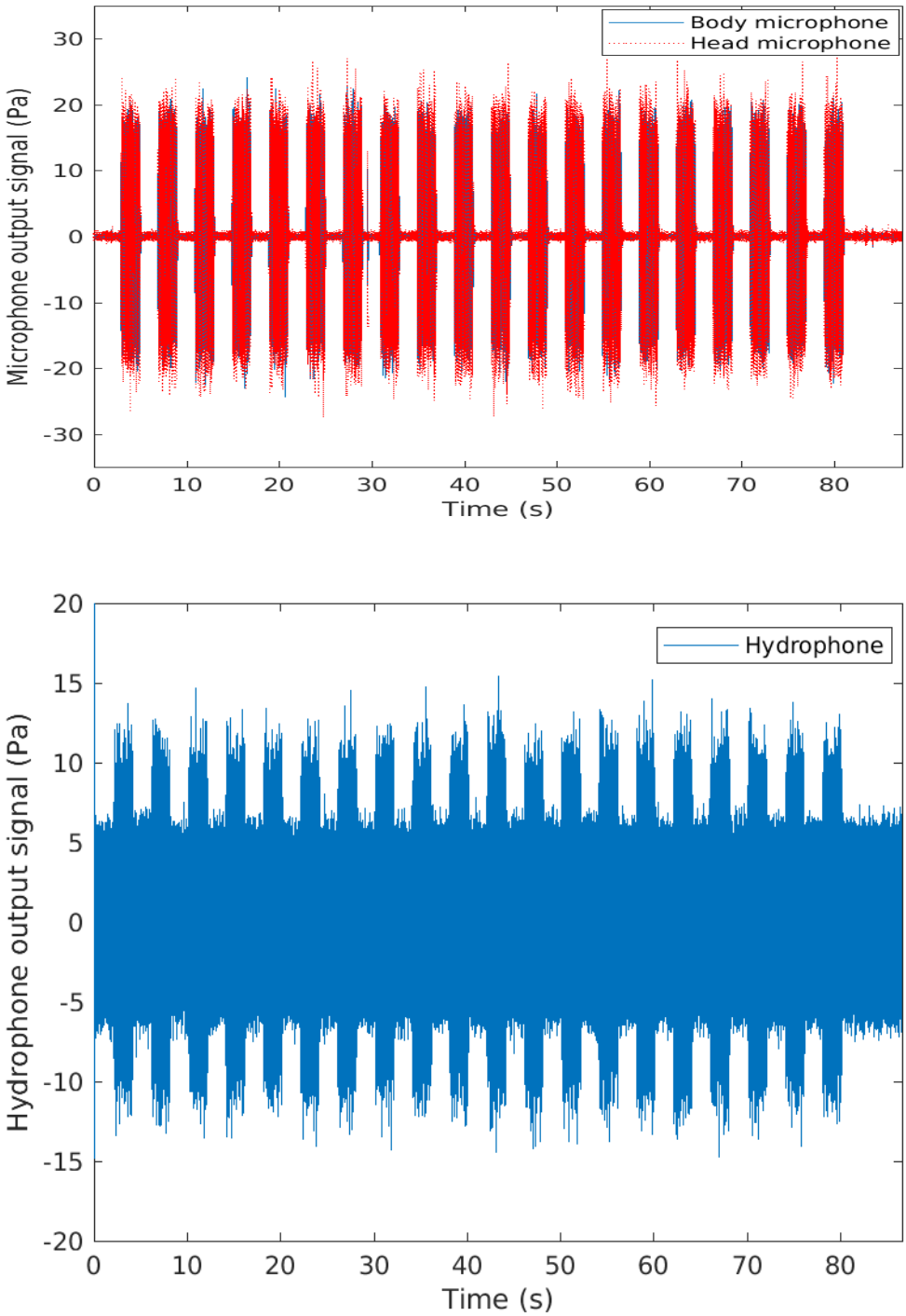


Figure 5. (a) Body microphone to amniotic sac hydrophone transfer characteristics for ewe 3 (main experiment). (b) Head microphone to amniotic sac hydrophone transfer characteristics for ewe 3 (main experiment).