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Evaluating devices for the measurement of auditory-evoked fetal movement

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Abstract

Determining normal and abnormal fetal function *in utero* in order to better predict which fetuses are at risk for adverse outcome is critical. However, the medical imaging tools that could assist with diagnosis are very expensive and rarely available in the developing world. In this study, we developed a prototype audio-motio-tachograph (AMTG), which measures fetal movements through the recording of abdominal wall deformations and tested it in Rwanda. First, we showed that AMTG detected fetal signals and that fetuses respond to complex acoustic stimuli. In order to improve the sensitivity of the device, we then measured whole abdominal wall deformations in an automated way using a lab-based 3D optical measurement system, in which fringes are projected and the deflections recorded with a camera. We found that abdominal wall deformations can be measured accurately with a non-invasive measurement apparatus. Overall, we conclude that wearable modalities provide a promising alternative assessment capacity in fetal research, especially in low income countries.

Keywords: Audio-motio-tachograph (AMTG), evoked fetal movements, fetuses, acoustic stimuli, wearable electronics, optical tomography

Co-Authorship Statement

The research presented in this thesis was a collaborative effort. My supervisors, Dr. Rhodri Cusack and Dr. Sandrine De Ribaupierre, provided feedback on all aspects. All data collection and the writing in this thesis were primary conducted by the author, Patrick Gatutsi. With the assistance of an electronics consultant, Shawn Nock, I aided in the design and the construction of the device.

Dr. Rhodri Cusack and Dr. Sandrine De Ribaupierre provided expert advice and supervision during all phases of this work including experimental design, assistance with data analysis and the editing of all chapters.

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3D	Three dimensions
AMTG	Audio-motio-tachograph
ATNAT	Amiel- Tison’s neurological assessment at term
CHUK	Centre Hospitalier et Universiatire de Kigali
CNS	Central nervous system
DDH	Developmental dysplasia of the hip
DAC	Digital-to-Analogue Converter
EEG	Electroencephalography
FHR	Fetal heart rate
fMRI	Functional magnetic resonance imaging
FMS	Fetal movement signals
GA	Gestational age
KANET	Kurjak’s Antenatal Neurodevelopmental Test
MATLAB	Matrix laboratory
MBT	Maternal breathing tracing
MEG	Magnetoencephalography
MRI	Magnetic resonance imaging
PCA	Principal component analysis
U/S	Ultrasound
USB	Universal Serial Bus
WHO	World Health Organization

Chapter 1 Introduction and literature review

1.1 Introduction

Assessing fetal function *in utero* to better predict which fetuses are at risk for adverse outcomes remains a great challenge in perinatal medicine. Due to the limitations of the ways in which fetal function can be measured, even the typical pattern of development is poorly understood. The assessment of the integrity and activity of the fetal central nervous system (CNS) has been an increasingly important area in obstetrics and pediatrics as a greater number of disorders are found to have a prenatal origin - the link between fetal life, well-being, and later neurodevelopmental outcome has been noticed by both clinicians and researchers(Milan Stanojevic et al., 2011; Milan Stanojevic, Zaputovic, & Bosnjak, 2012a). As the fetus is not directly accessible, medical imaging tools like ultrasound and MRI (Magnetic Resonance Imaging) can provide a way to track the development of the fetal brain. However, these resources are limited in many ways and still unavailable in low-income settings. Fetal behavior, broadly defined here as the interaction of a fetus with its environment (D. James, 1985), can also be measured. In particular, we focus on changes in fetal heart rate (FHR) and in fetal movement (Brändle et al., 2015; Kurjak et al., 2005; Kurjak & Luetic, 2010). These provide a way to indirectly assess brain function, by measuring changes in these behaviors in response to environmental stimuli. *In utero*, acoustic stimuli are the richest, and so we use these (Decasper, Lecanuet, & Granier-deferre, 2000). The degree or type of changes in FHR and fetal motor activity due to acoustic stimulation could potentially reflect changes in central nervous system and the health of the fetus. Recording evoked fetal movement and FHR has been suggested as a method of assessing fetal brain function and fetal well-being in general, which we review here. It has been carried out by employing different tools of measurements; from maternal perception of movement to medical imaging modalities. However, the existing measurement tools are limited in many ways and are expensive, which limits their utility in low-income settings. Therefore, the development of a sensitive tool for measuring fetal signals that is affordable is vital for fetal research. We focus on the potential of a wearable device that is mobile and will therefore allow recording for an extended period, to provide high sensitivity at low cost.

1.2 Neonatal brain function.

From neonatal studies, we now know that newborns just after birth can process some acoustic stimuli. This has been demonstrated by their preference for their mother's voice over that of the stranger (DeCasper & Fifer, 1980). One of the most used and well-known approaches for assessing neonatal reactions for external stimuli just after birth has been employed to measure the responsiveness to speech especially their mother's voice. For example, De Casper et al 1980 measured the ability of neonates younger than 3 days to discriminate recorded voices of their mother's over that of other females. In their study, shortly after birth, mother's voices of selected infants were recorded and were presented to them. They were in supine position with earphones secured over the ears and non-nutritive sucking nipple placed in the mouth. The nipple was held by an assistant who was not aware of the study and it was connected to a pressure transducer and recording equipment. A sucking period of 5 minutes before stimuli presentation was measured served as the baseline. Then, an interburst interval (IBI) or the time elapsing between the end of one burst of sucking and the beginning of the next before and during voice presentation was recorded. A preference for maternal voice was indicated by a greater IBI than the baseline contrary to nonmaternal voice, suggesting that newborns in their first day after birth recognize the sound of familiar voice(DeCasper & Sigafoos, 1983; DeCasper & Spence, 1986).

Using the same technique using a non-nutritive sucking nipple, Moon and his colleagues also examined the capacity and selective attention of the newborns to languages. Newborn whose mothers were monolingual speakers of English or Spanish were tested with audio recording of a female stranger speaking either Spanish or English. Their results showed that infants emitted longer average burst during their native language presentation. (B. S. Kisilevsky et al., 2009; Mampe, Friederici, Christophe, & Wermke, 2009a, 2009b; Mehler et al., 1988; C. Moon, Cooper, & Fifer, 1993; Soto, Edmonson, Cortes, & Vargas, 1993), indicating that infants have preference to their native languages.

These abilities and newborn behaviour in general are linked to later outcomes. This is exemplified in the work undertaken by Molfese and colleagues, using scalp recording with electro-encephalography (EEG). In their study, they examined auditory evoked electrical responses in newborns and later at 3 years, language performance, indicating that newborn responses to auditory stimuli can be used to predict later language development (Molfese & Molfese, 1985). Later their team found also that auditory event-related potentials recorded at birth can be used to predict dyslexia at 8 years old, suggesting that reading problems can be identified earlier and possible intervention should be given earlier than it is current possible (Molfese, 2000).

Another example of the importance of newborn behavior assessment in prediction of later cognitive abilities has been described previously (Leppänen et al., 2012). Leppanen and colleagues have used infant brain responses to investigate later neurocognitive processes related to phonology and other risk factors of later reading problems in infants with a dyslexic family background.

Early related potentials recorded in infancy were correlated to kindergarten age phonological processing and letter naming skills as well as reading and writing skills at school age(Leppänen et al., 2012). The evidence presented thus supports the idea that newborn behavior correlates with later cognitive outcomes.

These and other studies also demonstrate that there are a lot of sophisticated processing in newborns which may have origin in prenatal life but when and how these develop *in utero* has remained a great discussion in fetal medicine and research.

1.3 Fetal responsiveness

The presence of sophisticated auditory processing shortly after birth suggests that there may be fetal retention of acoustic experience and continuity from prenatal life into early postnatal life (M. Stanojevic, Kurjak, Salihagić-Kadić, & al., 2011; Milan Stanojevic, Zaputovic, & Bosnjak, 2012b). However, the approaches used for newborns of: non-nutritive sucking (in which infant sucks the pacifier attached to a computer that can detected changes in air pressure) (DeCasper & Fifer, 1980); head turning (which is a method of testing whether the infant can discriminate two or more sounds by turning the head towards the source sounds) (Zelazo, Weiss, Papageorgiou, & Laplante, 1989) are not available for use *in utero* because of inaccessibility of the fetus in its milieu.

The fetus is clearly able to respond to various external stimuli. There is evidence that fetuses respond with movement and heart rate changes to sound stimulation (Lester

Warren Sontag, n.d.). They react to their mother's voice by both heart rate and movement changes (Voegtline, Costigan, Pater, & DiPietro, 2013a). Their abilities to discriminate different sounds can be assessed by examining fetal movement and fetal heart rate changes (DeCasper, Lecanuet, Busnel, Granier-Deferre, & Maugeais, 1994; Lee & Kisilevsky, 2014; Voegtline, Costigan, Pater, & DiPietro, 2013b; Yan & Lee, 2010b). Other scientists have shown that the fetuses in third trimester can discriminate live and recorded maternal speech (Krueger, Cave, & Garvan, 2015).

The use of evoked fetal movement as the mean of assessing brain function and the ability of the human fetus to perceive, react and discriminate sounds has a long tradition and has been described since biblical times (New American bible, Luke 1:44). "*for as soon as the sound of your greeting reached my ears, the baby in my womb leaped for joy*, this is when Elizabeth heard Mary's greeting."

Scientifically, methods of measuring fetal behavior are by report of fetal movement by the mother, or observed objective methods such as ultrasound, MRI and other imaging tools, and have been investigated since the 1920s. For decades, one of the most popular ideas in fetal research is that most fetal sensory abilities few weeks before birth able to perceive *in utero*

Pieper (1925) showed that a sudden honking of an automobile horn within a few feet of the mother's abdomen in late pregnancy evoked marked fetal movement 20 to 30% of the time. Furthermore, Sontag and Wallace (1935) used a stopwatch to monitor FHR in 5 to 9 months old fetuses and observed that FHR acceleration was elicited by a vibration stimulus at 7 months. Additionally, mothers reported body movement in 71% of the fetuses tested (Lester Warren Sontag, n.d.). Continuing into the early 1980s, the development of medical technologies including ultrasound and fetal physiological monitoring tools enabled for more robust measures of FHR and fetal motion. Such innovations lead to the finding of increased FHR in response to the fetus' mother's voice and decrease FHR to the voices of strangers.

Fetuses near term have also shown the ability to remember sounds (Dirix, Nijhuis, Jongsma, & Hornstra, 2009). Chantal and colleagues assessed whether the fetuses in third trimester can learn and if they have memory. In their study, vibroacoustic stimuli was repetitively presented to the maternal abdomen and by using the habituation paradigm, they could assess fetal short-term memory at 10 minutes and later after 4 weeks. Their results showed that fetuses have a short- term memory from at least 30 weeks and have the ability to store some information up to 4 weeks later (Dirix et al., 2009), suggesting that intrauterine auditory environment plays a key role in shaping later auditory development.

All of the studies reviewed support the hypothesis that the fetuses in their last weeks *in utero* are not passive listeners rather they perceive acoustic information and react to them.

1.4 Fetal brain injury

The idea of investigating causes of central nervous system conditions *in utero* came after several decades when the search of these injuries was focusing chiefly on intrapartum and postpartum events.

Disruption of normal development of the brain during fetal life is now thought to contribute to the etiology of many neurological disorders that manifest later in life (Rees

& Inder, 2005). The mechanisms and causes of this disruption are numerous: prenatal events such as acute or chronic hypoxia, inflammatory and infective insults as well as intrauterine growth restriction are known to compromise brain development in fetuses with more consequences later in life including neurodevelopmental delay, long term neurological disorder such as cerebral palsy, epilepsy, learning difficulties, behavioural difficulties and psychiatric diagnoses.

For example, it is now known that many causes of cerebral palsy result from brain injury occurring prenatally rather than mismanaged delivery as it was previously considered. This evidence that much neurological impairment have their origins in prenatal life has been extensively found in many studies. Sonigo and colleagues in their study about prenatal diagnosis of fetal brain anomalies using MRI, have found that neonates who died from cerebral white matter damage within one neonatal week, 25 % had prenatal brain damage (Ellis, Goetzman, & Lindenberg, 1988; Sonigo, Rypens, Carteret, Delezoide, & Brunelle, 1998). Other scientists have provided strong evidence that most neurological conditions seen in the neonatal and infant period are not related to perinatal events rather the consequences of prenatal problems that can be identified by *in utero* fetal activity assessment. Squier (1991) found that most cases of brain damage are not the results of perinatal asphyxia events in full term infants but rather pregnancy related events(Squier & Keeling, 1991), suggesting that abnormal and disrupted brain development during gestation contribute to many neurological disorders that manifest throughout the entire lifespan.

Technical development in the field of medical imaging has made the study of fetal central nervous system possible in normal and diseased fetuses. Ultrasound has been used for more than 30 years to help diagnose fetal brain anomalies and the diagnosis of central nervous system injury and has a significant impact on the perinatal management as well as postnatal management of the newborn. Although the majority of obstetric sonographic examination is limited to number of fetuses, their positions, FHR and placental location, it is also possible to investigate even rare conditions *in utero*. Malinger and his team were able to diagnose malformations of cortical development by using ultrasound(G. Malinger et al., 2007; Volpe et al., 2006). Other structural defects(Hidalgo et al., 1982) and congenital cytomegalovirus (Gustavo Malinger et al., 2003)have been also detected.

Ultrasound imaging techniques have also revealed an association of fetal wellbeing, fetal size and body symmetry in pregnancy with infant neuromotor development, a marker of behavioural and cognitive assessment. The use of 4 dimensions ultrasonography has shown an important role in prenatal assessment of fetal neurobehavior and prediction of adverse neurological outcome (Kurjak et al., 2012). In their study,(Kurjak et al., 2012) they measured different isolated fetal movements (KANET) and examined all live born neonates postnatally using Amiel- Tison's neurological assessment at term(ATNAT) and found all cases with abnormal KANET have proved to be abnormal postnatally. Kurjak et al 2010 also used 4-D ultrasonography in both high risk and normal pregnancy, their results were consistent.

Although sonography has been considered as the primary technique for evaluating fetal development, its use in prenatal diagnosis of many brain disorders is limited. The use of magnetic resonance imaging for the study of the fetal brain has been gaining widespread acceptance based on the claim that it supplies higher diagnostic accuracy compared with ultrasound. MRI in fetal medicine has been suggested to be an adjunctive tool when a definitive diagnosis cannot be determined and when severe fetal brain injury is suspected(Griffiths et al., 2017; Simon et al., 2000). Diagnosis of some rare fetal conditions such as fetal stroke(Özduman et al., 2004) and neuronal migration disorders, tuberous sclerosis lesions(Sonigo et al., 1998) has been impossible until the use of magnetic resonance imaging

It has been shown to be possible to measure fetal cortical activation using fMRI. Using fMRI, Moore et al (2001) reported that temporal and frontal lobe activation in term fetuses respond to musical auditory stimuli (Moore et al., n.d.). Subsequently, Jardi and colleagues reported measurable neural activity in temporal lobe of the fetuses at 33 weeks of GA(Gestational Age) in response to acoustic stimuli(Jardri et al., 2012; Jardri, Pins, Houf, et al., 2008; Jardri, Pins, Houfflin-Debarge, et al., 2008) .

1.5 Fetal behaviour as an indicator of brain injury and fetal health

Evoked fetal responses, also known as fetal behaviour, are considered as indicators of fetal brain development, and have been used to study how brain functions emerge. The nature of the fetal response to stimuli is considered a measure of its well-being and has been the object of several previous studies.

Fetal behaviour has been used to assess the integrity of the fetal central nervous system at different stages of development and to extend newborn studies to fetal populations. Fetal movement has been used as indicators of fetal health status, with studies showing that decreased fetal movements may precede fetal demise (Concenço et al., 2017). Similarly, maternal perception of decreased fetal movements has been linked to poor neonatal outcomes including stillbirth, small for gestational age, fetal growth retardation and umbilical cord complications(Dutton et al., 2012; Warrander et al., 2012) and increased neonatal admissions(McCarthy, Meaney, & O'Donoghue, 2016).

In addition to being a guide to general fetal health, fetal movements are particularly important for another aspect; musculoskeletal development (Nowlan, 2015). Decreased fetal movement is associated with neuromuscular disorders such as multiple joint fusions, craniofacial malformations and thin hypo- mineralized bones(Miller & Hangartner, 1999; Rodriguez, Garcia-Alix, Palacios, & Paniagua, 1988). The field of fetal biomechanical research has used fetal activity in assessing musculoskeletal *events in utero* that occur later in neonatal life. There are a number of musculoskeletal conditions in which abnormal fetal movements (reduced or restricted) lead to an increase chance of fetal abnormality. Most common of these are the developmental dysplasia of the hip, arthrogryposis, congenital scoliosis(Jog, Patole, & Whitehall, 2002), fetal akinesia deformation sequences(Rodriguez et al., 1988), most of these conditions lead to life-long consequences of developmental skeletal disorders. In another example, developmental dysplasia of the hip (DDH) underlies 9% of all adult hip replacements (Beata & Andrzej, n.d.) and arthogryposis leads to early onset of osteoarthritis.

This literature emphasizes the role of fetal movement monitoring as a valuable means to assess different congenital anomalies. They also clearly indicate that there is a strong relationship between fetal responses and integrity of central nervous systems *in utero*.

Due to the present lack of technology to record neural activity in the womb and the inability to directly assess fetal brain function, fetal sensory abilities are examined by observing behavioral reactions. The appropriate methodology has to have sufficient sensitivity to determine if the stimulus and response are correlated. The pathway from hearing stimulus, to discriminating it or comparing it to a memory, to making a movement, necessarily involves the brain, and so would be expected to be a more sensitive measure of fetal brain function than movements in themselves.

1.6 Detecting fetal movement

It is of great importance to choose an appropriate approach to study fetal behavior. In developmental psychology and obstetrics, multiple methods have been employed to detect fetal movements from maternal perceptions to modern imaging techniques. Scientists and obstetricians rely on different methods for fetal movement monitoring which can be grouped and classified into active, passive and self-reported. Three were surveyed in the present study: maternal perception, ultrasound, MRI and wearable devices.

Firstly, maternal perception of fetal movement has been widely used to assess general fetal well-being (Raynes-greenow, Gordon, Li, & Hyett, 2013). Maternal perception of fetal movement is an important screening method for fetal wellbeing (Rådestad & Lindgren, 2012). Maternal perception of decreased fetal movement has been associated with poor pregnancy outcomes including stillbirth. Physiological studies of fetal activity have found associations between fetal movement and poor perinatal outcome. Maternal perception of decreased fetal movement has been *reported* in 15% of pregnancies during the third trimester and around 50% of women perceive a gradual reduction of fetal movement days before intrauterine death. Thus, early detection of reduced fetal movement has been considered as an opportunity for fetal health screening and continues to be used by women and clinicians. In some cases, especially when there is an impending intrauterine fetal death, fetal movement monitoring has shown to be more reliable as a pronounced decrease up to cessation of fetal movement occurred before fetal death *in utero* while fetal heart rates were still audible(Sadovsky & Polishuk, 1977).

On the other hand, maternal perception technique is in many ways limited, and many have concluded that maternal perception is modulated by irrelevant factors and should be discouraged (Frøen et al., 2008). Presence of some maternal fetal factors such as parity, gestational age, obesity and placental location may affect maternal perception of fetal movement which can alter the detection of a clinically significant reduction in fetal movement for some women. Furthermore, there is no widely accepted absolute definition of reduced fetal activity of alarm limits. Some women may also record passive fetal displacement, fetal breathing and Braxton Hicks's contractions as fetal movements (Hertogs, Roberts, Cooper, & Griffin, 1979). Maternal meals and maternal position changes may also alter maternal perception of fetal movements (Bradford, n.d.).

It has therefore been suggested that objective methods such as ultrasound and MRI are preferable to the maternal perception of movement. Ultrasound, an active method, uses high-frequency sound waves to generate an image of the fetus. Ultrasound has remained the main tool for assessing fetal movement in clinical care management and is used in some research contexts as well. It has allowed objective measurement of fetal movement responses to maternal specific stimuli such as maternal (B. S. Kisilevsky et al., 2009; Voegtline et al., 2013a), and non-speech stimuli (G. A. Ferrari et al., 2016).

Ultrasound observations of specific fetal movements has also enabled non-invasive study to investigate prenatal lateralization *in utero* (Reissland, Francis, Aydin, Mason, & Exley, 2014). The advent of ultrasound imaging has potentially broadened the knowledge about the CNS conditions *in utero*. An experimental demonstration of this effect was carried out by Talic(Talic et al., 2016). They used U/S to evaluate fetal behavior in assessing cerebral ventriculomegaly (Talic et al., 2012, 2016). It should be noted that all of these studies have measured the overall movement of the fetus, they were not testing evoked fetal movement.

While ultrasound serves as reference for fetal movement and a clinical standard tool, it has some limitations; in addition to being an expensive tool, it is very hard and almost impossible to fully display the fetus given the limited ultrasound beam especially in third trimester. Sound energy generates heat, and the World Health Organization (WHO) discourages frequent use of ultrasound imaging. Furthermore, the mechanical placement and orientation of the probe requires substantial expertise on the part of the operator – the sonographer - and can in itself elicit behavioral responses from the fetus (G. A. Ferrari et al., 2016). The images also require interpretation by the experienced sonographer, which increases cost, may lead to inconsistencies between sites, and reduces the availability in low-income settings.

A rarer method in clinical context for fetal monitoring is MRI, which requires expensive and bulky infrastructure, and is only available in hospitals with a high resource level and skilled personnel. The use of functional MRI in fetal research suggests a possible *in utero* fetal cortical activation to external stimuli. When visual stimuli was presented to near term fetuses, Fulford and colleagues found cortical activation in frontal (Jonathan Fulford et al., 2003) and fetal functional maturation(Jon Fulford & Gowland, 2009). Functional MRI has been also used to identify and localize cortical activation to sound in third term pregnancies (Jardri, Pins, Houf, et al., 2008). Moore et al (2001) reported observation of the temporal and frontal lobe activation in term fetuses in responses to musical auditory stimuli. (Moore et al., n.d.). The main disadvantage in using fMRI for auditory studies is the confounding effect of scanner noise, since any acoustic stimulus is superimposed on the noise of the MRI scanner. Imaging fetuses is still a challenge, data are difficult to acquire because of the techniques sensitivity to motion, and one cannot prevent fetuses to move in the uterus(Dubois et al., 2014). It is also an expensive method, which is a problem for clinical application outside rich settings.

Collectively, these studies outline a critical role in assessing fetal responses by different tools and their implications in fetal research.

1.7 Wearable device, fetal monitoring

Wearable devices have been popular in various fields from sport and fitness to health monitoring. Due to the high number of stillbirth which is a tragedy for parents and families with far reaching psychosocial impacts affecting over 2.6 million families worldwide annually, wearable devices have been important for fetal activity monitoring.

Over last decades, different devices have been built and evaluated for fetal movement monitoring: a piezosensor (Penders, Altini, Hoof, & Dy, 2015), electromagnetic device (Sadovsky, Mahler, Polishuk, & Malkin, 1973), and acceleration. Nishihara et al (2008) employed a capacitive acceleration sensor, and made recordings of the oscillations of the maternal abdominal wall. They were also recording micro-arousals evoked by fetal movement on mothers' EEG during their nocturnal sleep (Nishihara, Horiuchi, Eto, & Honda, 2008). Subsequently, they developed an accelerometer based fetal movement detector, that a pregnant woman could use to record fetal movement by herself at home over the long-term(Ryo, Nishihara, Matsumoto, & Kamata, 2012).

The field has gradually broadened. Mesbah et al 2011 designed an accelerometer based fetal activity monitor. Their device performance in detecting fetal movement was 59% with a specificity of 55% (Altini et al., 2016, 2017; Mesbah et al., 2011b). Al-Ashwal and colleagues have developed a sensor- based portable device for fetal kicking counting to prevent intrauterine fetal death which occurs mostly in last weeks of pregnancy. The device detected fetal movement based on the forces applied on the top of the sensor surfaces. However, its role was limited only to counting fetal kicks not in assessing responses to external stimuli (Al-Ashwal et al., 2016a)

These tools were developed to only monitor fetal movement an index of fetal well-being, and showed a promising role of wearable devices in pregnancy assessment and reduction of stillbirth, which remains high especially in low and middle -income countries.

According to WHO report, there are more than 25 stillbirths per live newborns in low-income countries. Publications that concentrate on designing devices have intended to focus on counting fetal movement rather than fetal responses to external stimuli which is very crucial in assessing the integrity and maturity of fetal central nervous systems.

1.8 Fetal monitoring in low income countries

The WHO recommends the use of ultrasound for gestation dating before 24 weeks, the early diagnosis of fetal malformation, and the enhancement of maternal pregnancy experience. Medical imaging tools like ultrasound and MRI are often not available, and continuous monitoring of fetal health is typically based on the traditional protocol of counting the fetal movements felt by the mother. Although the maternal perception is a relevant characteristic for the evaluation of the fetal health, this kind of monitoring is hard to accomplish and being subjective can induce errors due to mother’s anxiety and lack of concentration. In addition to scarcity of medical imaging in low and middle-income settings, there is an also ongoing personnel shortage which makes fetal medicine inefficient. One solution to overcome these problems lies in utilising and exploiting the wearable technologies.

1.9 Sound stimuli in fetal research

Hearing emerges in the third trimester, at approximately 26 weeks of gestation (Piontelli, n.d.), and unlike vision, the fetus has considerable exposure to complex sensory stimulation before birth. Hearing is one of the primary modalities of human beings for communicating and a prerequisite for the development of auditory receptive languages. Some studies have used the mother’s voice as a stimulus to elicit fetal movement

(Barbara S Kisilevsky et al., 2003) either through direct voicing or a recording (Krueger et al., 2015), on the grounds that it is the most repeatedly experienced stimuli *in utero* (C. M. Moon & Fifer, 2000) and more reinforcing (Decasper & Carstens, 1981). Other studies have used music (Arabin & Foundation, 2015; Olds, 1985; Schweitzerlaan, 2000) and father`s voice (D. K. James, Spencer, & Stepsis, 2002; B. S. Kisilevsky, Hains, Jacquet, Granier-Deferre, & Lecanuet, 2004; Yan & Lee, 2010a). Singing is also thought to be strongly engaging for newborns and has been employed in fetal research(Carolan, Barry, Gamble, Turner, & Mascarenas, 2011b). Lullabies are among the songs used in fetal and neonatal research for their calming benefit effect to neonates(Taheri, Jahromi, Abbasi, & Hojat, 2017), fetuses(Montemurro, 1996), as well as their mothers(Carolan, Barry, Gamble, Turner, & Mascarenas, 2011a; November, n.d.)Motivation for the current study

1.10 Motivation for the current study

Taken together, these projects demonstrate that fetuses discriminate sounds and voices. They also show that the fetus is able to learn prenatally and suggest fetal sensitivity to acoustic stimuli. These studies highlight that the fetus is not a passive listener, but can react and retain information from the uterine setting. These abilities are indicated by changes in fetal heart rate and movement in response to acoustic and auditory stimulation. Recording of fetal movement therefore can provide not only an assessment of CNS but also provide a potentially vital tool for routine monitoring of fetal well-being in general. It has particular potential in low-income settings. Currently, first-world hospitals and research laboratories have tools to assess fetal brain anatomy (ultrasound and MRI) and increasingly, measures of brain function (fMRI, MEG, EEG). But, all of these tools require expensive equipment typically costing between $50,000 to $5M and to operate them, specialists in disciplines such as radiology and computer science. Given the scarcity of healthcare and limited government health and research funding in low income countries like Rwanda, where more resources are allocated and invested in infectious diseases, providing timely assessment and preventive measures in prenatal assessment is often prohibitively expensive.

Our goal is to develop and evaluate a tool to measure fetal motion in response to auditory stimulation. At present the equipment needed to measure fetal motion has been expensive, immobile and intrusive. This has limited recording sessions to a few minutes, severely limiting the signal-to-noise possible. These challenges could be resolved by the emergence of wearable fabrics and technologies. We believe it is possible build a powerful device that can sense and record complex patterns of motion for less than $100. The aim of project was to design, build and evaluate a light-weight wearable device, low powered, safe and robust thus making it ideal for long term monitoring. The proposed non-invasive method is based on the concept that fetal movement causes maternal abdominal wall deformations, thus making it possible to assess fetal movement by abdominal wall changes. This device also has tremendous potential for the scientific study of developing brain functions. It is our hope that the future of our device will help us to extend our knowledge about fetal responsiveness and fetal brain function especially in low income settings.

Using our prototype device, the audio-motio-tachograph (AMTG), we aimed to probe cortical function by measuring sound-evoked changes in movement and to explore fetal abilities to discriminate different types of acoustic stimuli: with infant-directed singing, which is strongly engaging for newborns; lullabies without speech, but with a human voice and lullabies with no recognizable voice. This will test the integrity of the cortical complex sound processing which is a precursor of language. We also planned to test for fetal learning and memory, which is mediated by the fronto-parietal working memory network or the medial-temporal lobe long-term memory network, by comparing the responses to novel and familiar sounds. It is of interest to know whether the ability to process sounds holds true when complex sounds are used. After designing and constructing the prototype, we evaluated the device in healthy pregnant women with fetuses in third trimester when the majority of fetal fatalities in low risk pregnancy occur in Rwanda, where we think the device will be more efficient in detecting fetal movement and will have a useful contribution at a clinical level as well as at a research one in assessment of fetal brain responses.

The remaining part of this thesis is organized as follows: Chapter 2 presents the first experiment. This describes the design process for our wearable device, and the evaluation of it by collecting data from pregnant women in Rwanda in which we assess the responses of the fetus to complex sounds. Chapter 3 describes the second experiment, which aimed at gathering data to allow the design of an improved device by determining the optimal positioning and number of sensors for the next generation of AMTG. We used a static, lab-based piece of equipment to measure whole-abdomen deformations. Finally, the last chapter provides a general discussion in the context of the existing literature, and discusses limitations, and presents future directions for the field.

Chapter 2 Assessing evoked fetal movement with an audio-motio- tachograph

2.1 Background

MRI and other methods are currently being used by first-world hospitals to look at brain structure of the fetus, but these medical imaging resources are not available in low income settings. Even when they are available, they have limitations in measuring fetal responsiveness. fMRI in auditory studies poses the challenge of confounding effect of the scanner noise, and acquiring imaging data in fetuses is difficult because the technique is sensitive to motion (Dubois et al., 2014). A challenge with U/S is that it is requires a skilled operator, with the possibility of eliciting reactions due the movements of the operator (G. A. Ferrari et al., 2016). These make it difficult to acquire participants, and limit the duration of the time that data can be acquired, and affect the robustness of the result.

To overcome these limitations, a potential solution lies in the use of wearable technology. Fetal heart rate and fetal movement change in response to external stimuli, such as sound stimulation (Lester Warren Sontag, n.d.). Fetuses react to their mother’s voice (Voegtline et al., 2013a), discriminate different sounds (DeCasper et al., 1994; Lee & Kisilevsky, 2014; Voegtline et al., 2013b; Yan & Lee, 2010b), and discriminate live from recorded maternal speech (Krueger et al., 2015). Fetal movement has also been widely used to index fetal well-being, with studies showing that decreased fetal movement may precede fetal demise (Concenço et al., 2017). The response to sound could potentially be used to assess the integrity of the fetal central nervous system (horimoto et al., 1993).

As described in the introduction, over the last decades, wearable methods have been proposed for fetal movement monitoring: piezo-sensors (Penders et al., 2015), electromagnetic devices, and acceleration sensors (Sadovsky et al., 1973). A sensor-based portable device has also been documented that counts fetal kicking with the goal of preventing intrauterine fetal death, which occurs mostly in last weeks of pregnancy (Al-Ashwal et al., 2016a). The device detected fetal movement based on the forces applied on the top of the sensor surfaces. However, its role was limited only to count fetal kicks not in assessing responses to external stimuli (Al-Ashwal et al., 2016a). To our knowledge, measuring fetal responsiveness using a wearable device to monitor abdomen deformation has never been attempted. Therefore, the aim of the present study was to assess fetal responsiveness to acoustic stimulation that reflect fetal brain function using a prototype wearable, affordable device with a long recording period. To address this, we designed, built and evaluated a light-weight wearable device, which is low powered, safe and robust, thus making it ideal for long term monitoring. The proposed non-invasive method is based on the concept that fetal movement causes maternal abdominal wall deformations, thus making it possible to assess of fetal movement by abdominal wall changes. By using our prototype device, the AMTG, we also tested evoked fetal movement in healthy pregnant women of gestational ages ranging from 32 to 38 weeks,

This chapter will cover the description of the proposed solution for continuous fetal movement monitoring using a novel tool that uses abdominal wall deflections to detect fetal movement signals. It includes the architecture of the device. It also describes experimental testing to evaluate the device in pregnant women in Rwanda, the complex sounds we presented, the sensor signal processing and the results of the first experiment. It ends with a discussion along with conclusion.

2.2 Participant recruitment and procedures

The study was conducted from June 20th to August 20th, 2017 at Gahini Hospital, Rwanda, a district hospital serving a great part of the Eastern province of the country. At this hospital and in the rest of the health systems in low income settings in general, there is a shortage of skilled healthcare professionals and medical imaging modalities. Currently healthcare services at the health center level are mainly run by nurses and most of the antenatal services are carried out at this level. Pinard's stethoscope is the most common tool used to manually listen to the pattern and frequency of fetal heartbeat. Nurses use Leopold maneuver to assess fetal position as there is no U/S at these health centers. For antenatal care purposes, pregnant women have their first U/S only when they are referred to higher centers, mainly district hospitals. The small percentage of women who reach the district hospital for prenatal U/S are assessed by a general practitioner for fetal viability, fetal sex, number of fetuses, location of the placenta as well as fetal position. Our participants were among the few percentage who reach the district level.

After designing the prototype and piloting in London, Canada, the device was evaluated in pregnant women in Rwanda. All the participants gave written informed consent. The study was approved by ethics committees at Western University, Centre Hospitalier et Universitaire de Kigali (CHUK) and Gahini Hospital. Participants' medical files were used to obtain demographic and obstetric information, fetal presentation, and the location of the placenta. Some parameters were missing for some of the women medical file.

None were using medication. The mothers were also asked to stay still throughout the acquisition to reduce maternal movement artifacts.

Forty-two non-smoking women with healthy uncomplicated pregnancy carrying singleton fetuses between 32 and 38 weeks were recruited when coming for an antenatal care visit at Gahini Hospital, Rwanda. The mean with standard deviation of maternal age and gestational age was 27±5.8 years and 35±1.5 weeks, respectively. Seventeen of the participants were primigravidae (women who are pregnant for the first time) and 25 were multigravidae (who are or have been pregnant for at least a second time- see Table 1).

	Gestational age at testing (weeks)	Maternal age (years)	Gravida	Parity
Mean± SD	35.5±1.9	27.5±5.8	2.5±1.6	1.5±1.5
Max	38	40	9	7
Min	32	18	1	0

Table 1 Demographic and obstetrical data

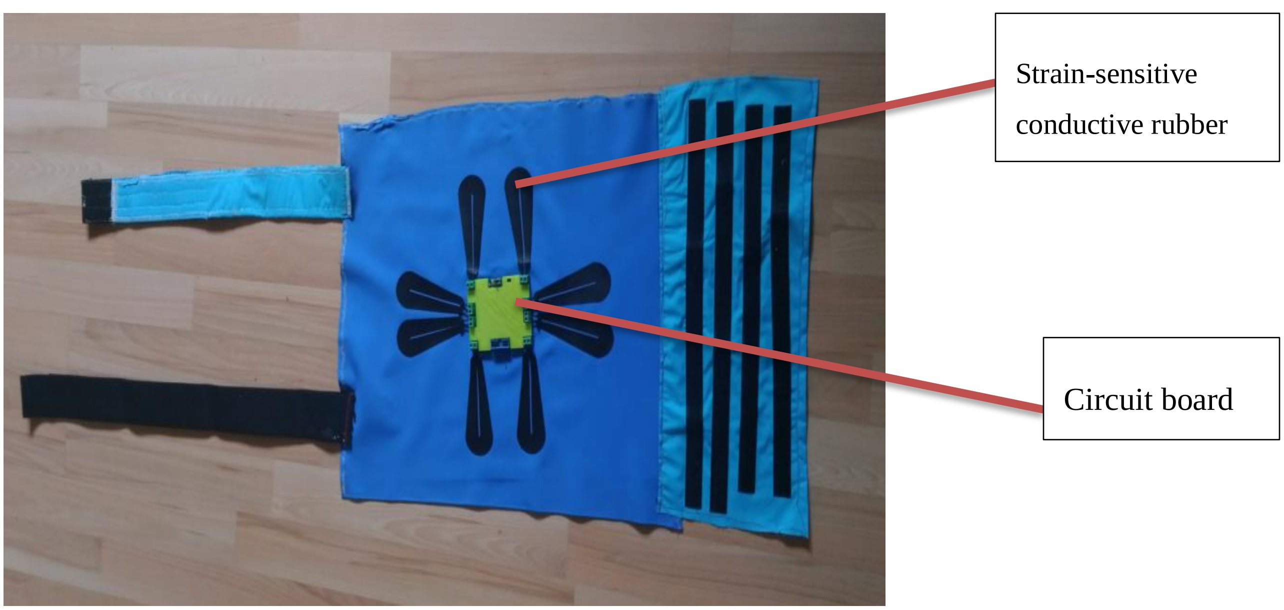
Initially, we acquired two sessions of 30 minutes but after analyzing the data from the first cohort of 27 participants, a problem was found which is that due to the limited memory capacity of the laptop, it began to slow down and drop samples from the acquisition beyond around 20 minutes. Unfortunately, it was assumed in the design of the software that the data acquisition would be robust, and so additional timing checks were not acquired. In later testing of the equipment, we could recreate the drift in timing after 20 minutes, but unfortunately there was sufficient jitter in the exact decline in performance that the data were not recoverable. In the first 27 subjects we therefore trimmed the two sessions to 15 minutes, and in the subsequent women, we acquired four trials of 15 minutes instead. Furthermore, the acquisition in one subject was shorter than 15 minutes, leaving us with 26 participants for the first cohort. 15 subjects were then acquired for the second cohort.

2.3 Materials

We developed a non- invasive and low cost-effective measurement system. The system was made of three parts: a fetal movement detector, stimuli presentation system and a recording system. With the help of an electronics consultant, Shawn Nock, we designed the AMTG. The device consisted of sensors made from rubber that were stretched by abdominal deformations. The fetal movement detecting system presented in this experiment was primarily based on the idea that fetal movement causes maternal abdominal wall changes that can be sensed by continuous recording deformations of maternal abdominal wall. The anterior abdominal wall is thin enough to be deflected, allowing any fetal movement especially in the third trimester when there is sufficient force to result in a deflection that can be measured on the abdominal wall surface.

Our prototype device (Fig 2-1A&B) that measures motion, consists of eight strain-sensitive conductive rubber sensors, sandwiched between two layers of elastic fabric that form a belt. It is bonded to the material using an iron-on fabric adhesive. Due to the variation in size and shape of the abdomen in pregnancy, the random nature of fetal movement, and our uncertainty about the shape of the deformations we would see, a high number of sensors was desired. However, the greater the number of sensors, the more complex the electronics, the greater the data storage that was required, and the more complex the device was to construct. We thus chose a compromise of 8 sensors, which could be amplified on a single, affordable chip. The sensors were connected into the circuit board, which measured the resistance in each sensor, and amplified the signal. The configuration of the sensors was chosen to be in a roughly radial form, as this was easy to construct, and we had no good evidence that another form would be better. For safety, the AMTG was low-voltage and powered by batteries. To simplify the circuitry of the prototype by avoiding the need for on-device digitization and storage, the signal was then passed through a cable to a digital-to-Analogue Converter (DAC) and then via a USB to a laptop, which stored the data.

A



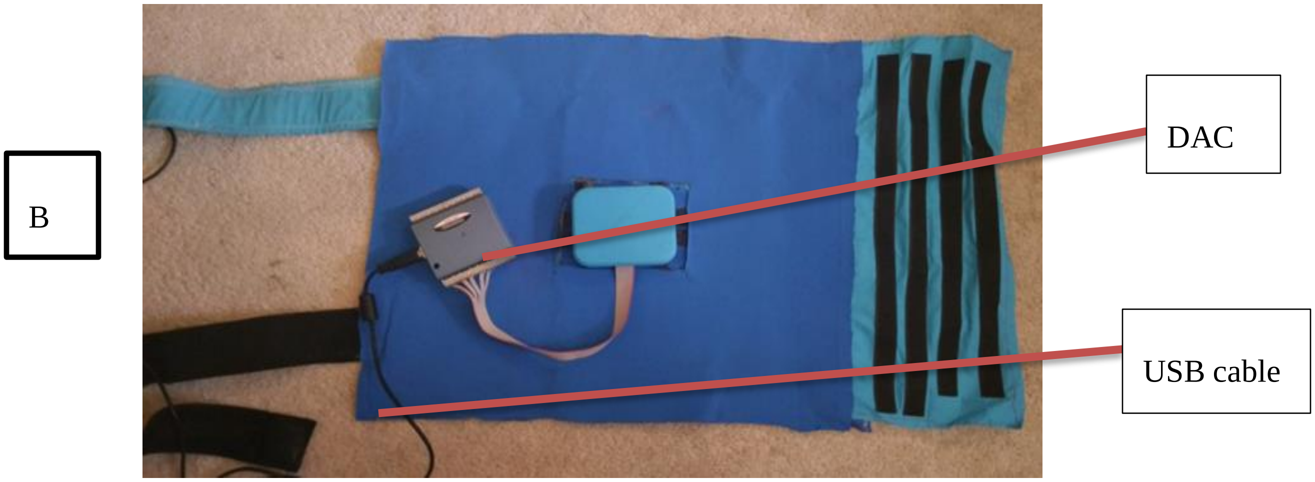


Figure 2-1 Proposed fetal movement device. (A) Construction of the device showing 8 conductive rubber sensors and the circuit board in the middle. (B) Final draft of AMTG, displaying a final draft of AMTG, displaying DAC (Digital-to-Analogue Converter) and USB(Universal Serial Bus) connection for recording.

To test for sound-evoked changes in movement, we designed a stimulation protocol to evaluate it, and implemented it in MATLAB. Sounds were presented to the fetus using commercially available “Belly buds “loudspeakers from the laptop (Fig 2-2A). They easily adhered to the maternal abdomen. They are safe effective tools to present audio stimuli including recorded voices, lullabies and stories to the fetus.

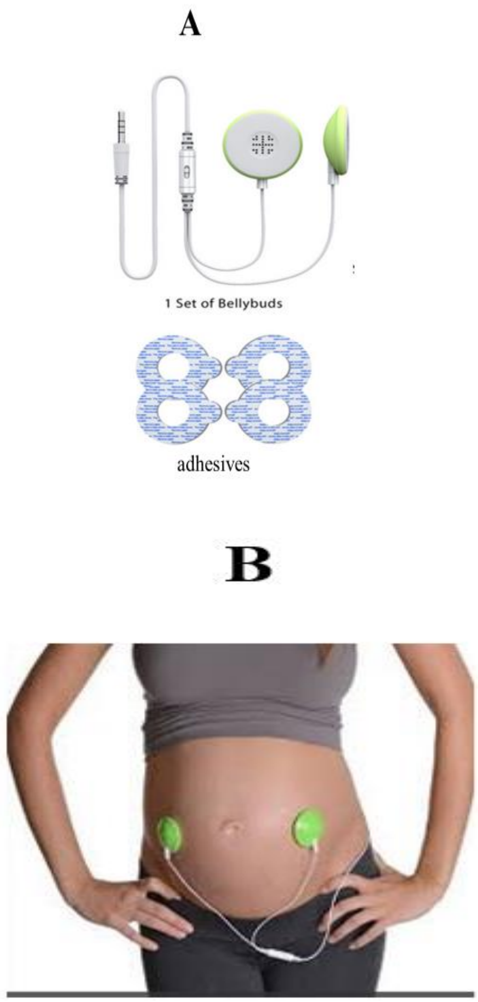


Figure 2-2 Sound presentation system. (A) A set of belly bud with a set of adhesives. (B)Belly buds on the maternal abdomen.

2.4 Study Design

Each woman rested quietly before the start of the experiment. To reduce digestive activity, they were asked to refrain from eating and drinking for at least 2 hours prior to the experiment. Lying on a bed in a semi-recumbent position, participants wore the AMTG on their abdomen. The AMTG with its 8 sensors covered the majority of anterior abdomen in an attempt to sensitively detect fetal activity. Using Belly buds, lullabies were presented to the fetus. The order of stimuli was counterbalanced across blocks and sessions to control for order effects.

In each block, three stimuli of 15 seconds each were presented followed by an inter-stimulus interval of 2 minutes and 15 seconds (Fig 2-3). There were 10 blocks in a 30-minute session, and 5 blocks in a 15-minute session. During data acquisition, women were given time to rest and relax after each session. In the first cohort, the experiment had 2 sessions of 30 minutes each whereas in the second one, session duration was changed to 15 minutes making 4 sessions in total. The duration of each session was changed due to the low capacity of the laptop however the duration of the experiment was not changed. Participants in both the first and second cohort were asked to mark fetal movement that they were aware of by pressing a button (Fig 2-4). The goal of this was to provide another way to validate that the device was detecting fetal activity.

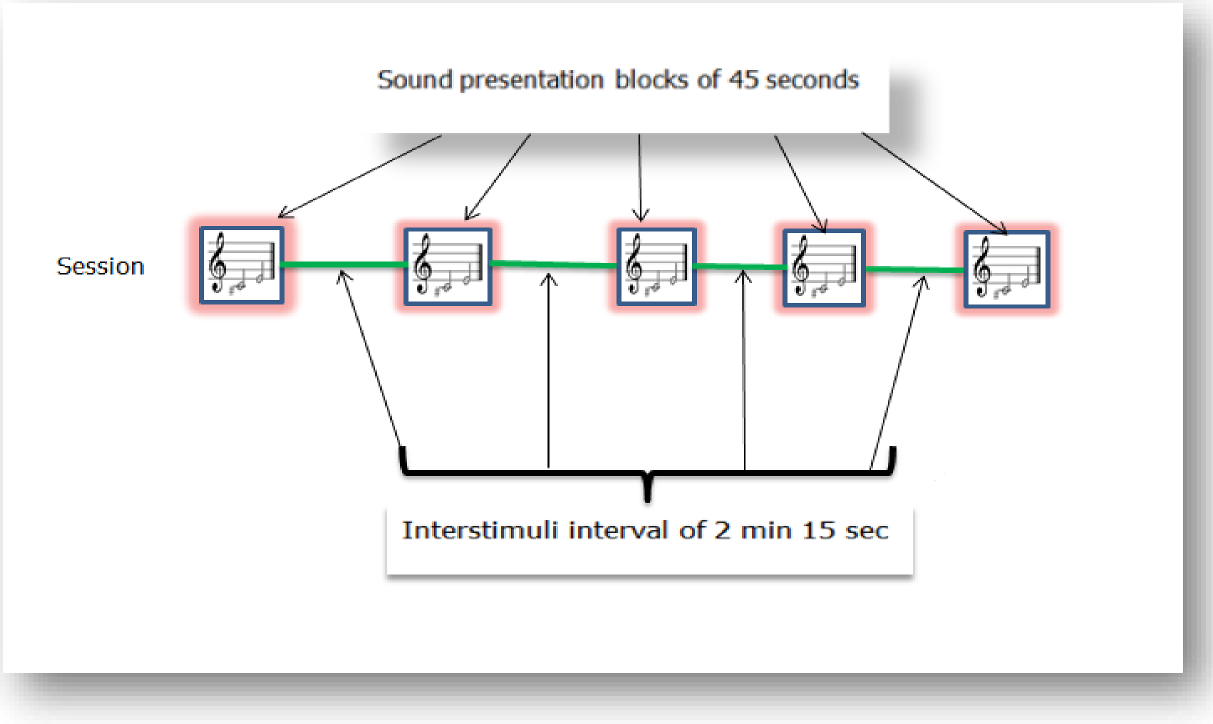


Figure 2-3 Sound presentation: Schematic of our experimental design regarding sound presentation for each session of the study. Sound blocks of 45 second long were presented with inter-stimulus intervals of 2 minutes and 15 seconds

Figure 2-4 Experiment set up: Participant in semi-recumbent position wearing the AMTG, holding a mouse in her right hand to mark fetal activity she perceived.

2.5 Stimuli

A fetus in the uterus in third trimester hears many different sounds. Their sources are internal, from activity of the mother, and external ones produced by sources of many kinds. In the current study we have used external stimuli; lullabies. The lullabies used were *Twinkle Twinkle Little Star, Mocking Bird, Rock a Bye Baby* and *Sunshine.* They were either sung or hummed by a Canadian woman. Each lasted for 15 seconds. They were presented with counterbalance order to avoid the order effect. They were equalized for average intensity level.

2.6 Signal pre-processing

We analyzed the data collected by the AMTG. Our device recorded movements that came from a mixture of sources, including maternal breathing, maternal posture adjustment, and fetal movement. Maternal movement or other artefacts would degrade the signal quality. However, these sources have different patterns in time, and so can be separated to some degree using a frequency analysis. Maternal breathing is fairly regular, although it may gradually shift in frequency with time. We therefore used a time-localised method of frequency analysis, called a *wavelet transform* (K. Englehart, Hudgins, Parker, & Stevenson, 1999; Kevin Englehart & Hudgins, 2001; Pavlov, Makarov, Makarova, & Panetsos, 2007). This allowed us to differentiate fetal movements signals (FMS) from maternal breathing tracing (MBT). Our goal was to use the wavelet transform to detect when the fetal movement occurred in relation to sound stimulation. We therefore divided the data into three minutes epochs, which were of 45 seconds of sounds presentation and 2 minutes 15 seconds of inter-stimulus interval (Fig 2-5). These epochs were then averaged, in a similar way to an event-related potential. analysis.

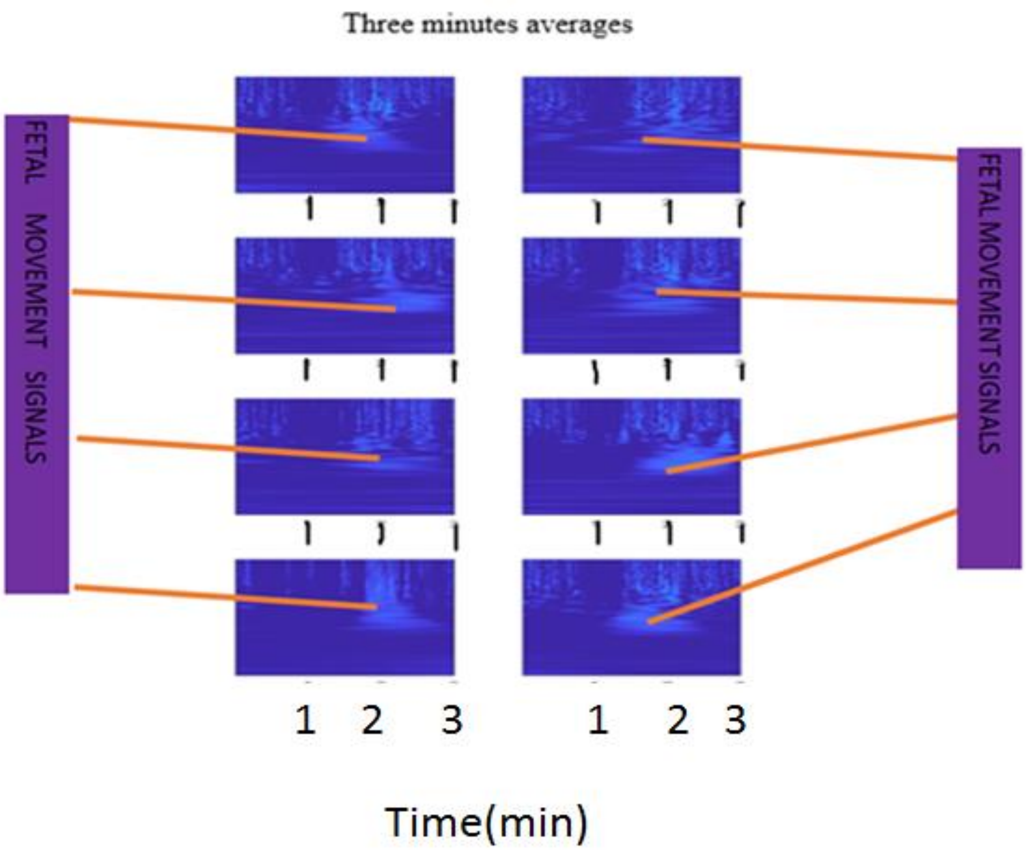


Figure 2-5 Three minute average: Three minute averages of eight sensors showing when fetal mobility occurs vis a vis sound presentation

In examining the wavelet power, we determined that the maternal breathing rate had a frequency higher than 0.2 Hz (i.e., inhalation and exhalation took less than 5 seconds). We therefore filtered them out by selecting frequencies lower than 0.2 Hz. To quantify total movement, which might be in many different directions, we then averaged power across frequency and channels.

2.7 Signal analysis and statistics

We also made a model of what the wavelet energy would look like if the fetus moved either at the start of the sounds of for the duration of them. The “block” and “onset” time courses (see Fig. 2-6, top) were wavelet transformed (Fig. 2-6, middle). The wavelet data were then filtered below 0.2 Hz (like the sensor data) and then summed across frequency to yield two time course predictions for the low-frequency energy wavelet signal to indicate if the fetus moved with a block or onset pattern (Fig 2-6, bottom). This model time course was then fitted with a regression model to the time courses for each session of each individual. The regression model was

$$sensor\_low\_frequency\_energy(time)=b1*block(time) + b2*onset(time) + c.$$

A value of the regression coefficients, *b1* and *b2*, were thus obtained for each subject, averaged and then tested across subjects using a sign test against zero.

As the sound timing was different for the two courses, two different models were used, but the betas were then pooled across both cohorts. Mean and standard errors across subjects were also calculated to assess when more fetal mobility occurred in relation to stimuli presentation.

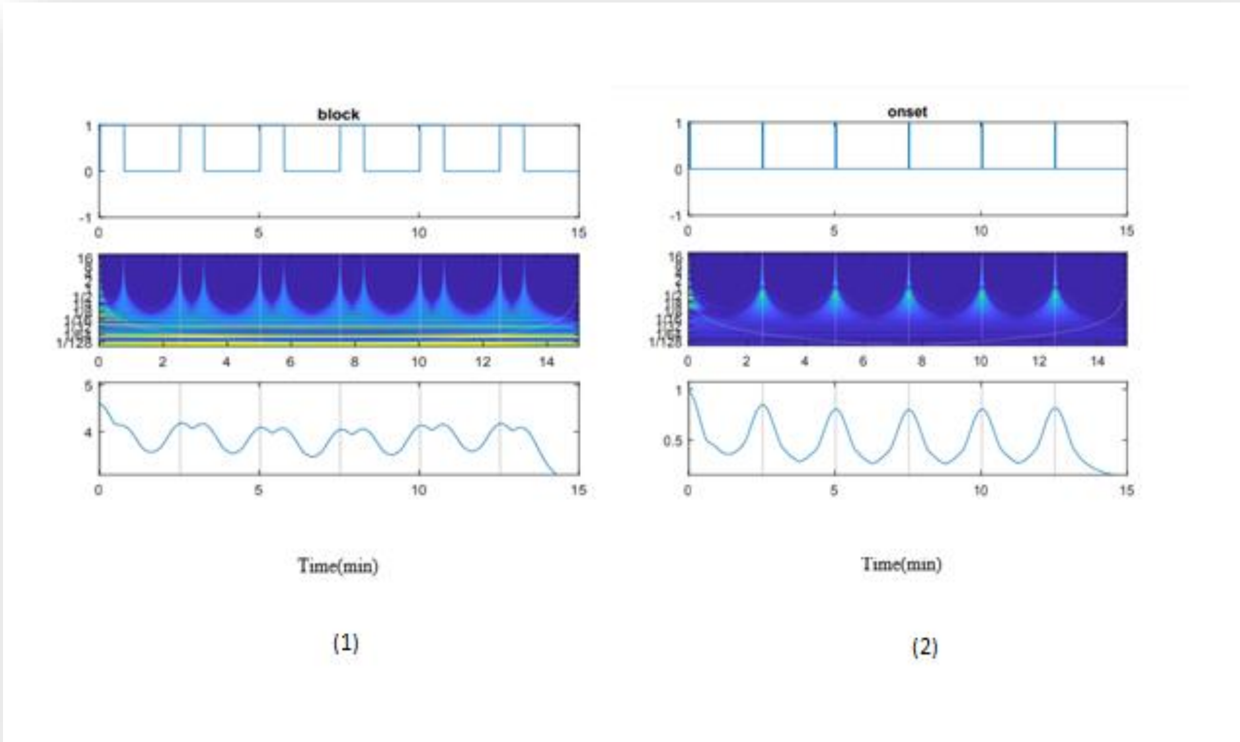


Figure 2-6 Wavelet model: Model showing how the wavelets look like if the fetus moves either at the start of the sounds (2) or for the duration of them (1).

2.8 Results

A total of 42 pregnant women made by 2 cohorts (first cohort, n= 27 and second cohort n=15) were recruited and tested at Gahini Hospital, Rwanda. The acquired data for one participant in the first cohort were incomplete and were not included in the analysis leaving the first cohort with 26 participants for analysis n=26. The summary of their demographic and obstetrical data is displayed in Table 1.

The device was sensitive to movement and detected maternal breathing (MBT) in most of our participants (Figs. 2-7 and 2-8). In some mothers, fetal movement (FMS) was perceived at the offset of sounds. There were also false positives, movements perceived by the women and not detected by the device. The explanation of this might be that false positive movements are the ones that occurred outside the sensors area.

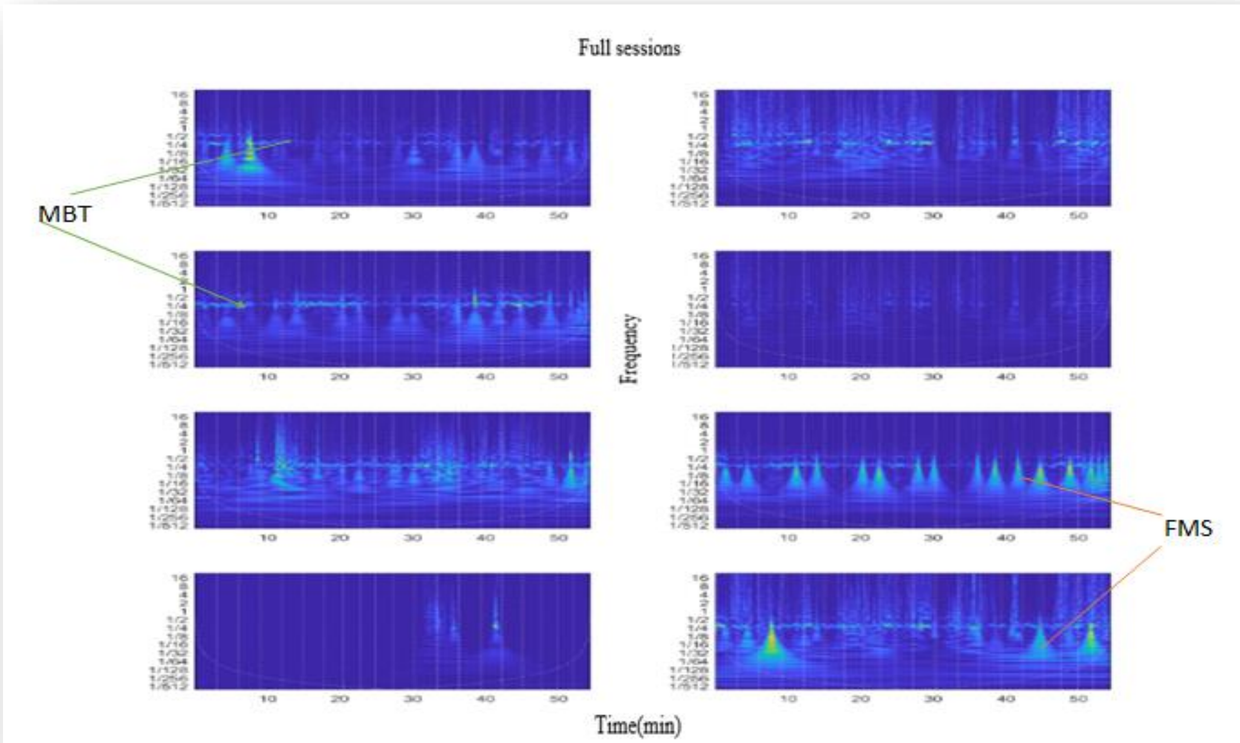


Figure 2-7 Signals from the AMTG, processed with a wavelet transform. Wavelet figure showing maternal breathing tracing (MBT) and fetal movement signals (FMS) for full sessions and for eight sensors.

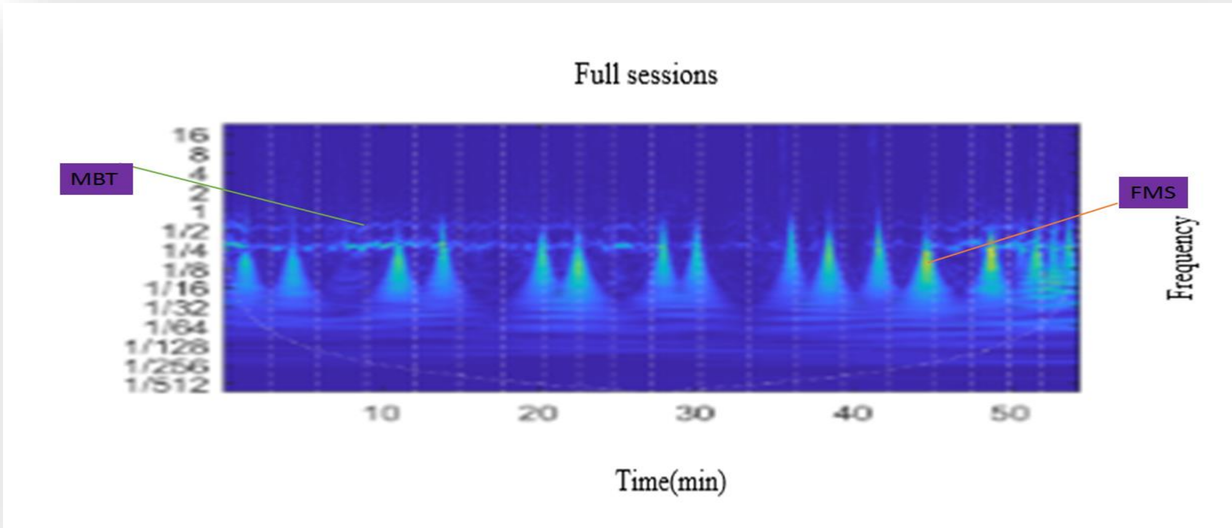


Figure 2-8 One sensor wavelet transform: Wavelet figure of one participant showing maternal breathing tracings (MTB) and fetal movements signals for one sensor.

In all participants, there was a strong respiratory signal from the mother. This was particularly evident in a Wavelet analysis of the time courses, with a signal at the characteristic frequency of breathing, throughout the testing period, (Fig 2-7). In many mothers, there was also a weaker but detectible fetal motion response, at the offset of the sounds (Fig 2-8). This suggests that maternal breathings and fetal movements can be isolated as independent components.

To study fetal signals separately from maternal breathing signals, we selected frequencies slower than 0.2 Hz. We then did a statistical analysis. The fetal movement and signals for individual subjects, the average across channels and sessions are shown in Fig 2-9A&B for both the cohort of 15 participants and of 26 participants. Data from

Figure 2-9 (A) for cohort of 26 can be compared with the data in Figure 2-9(B) which shows the same findings for the cohort of 15 participants.

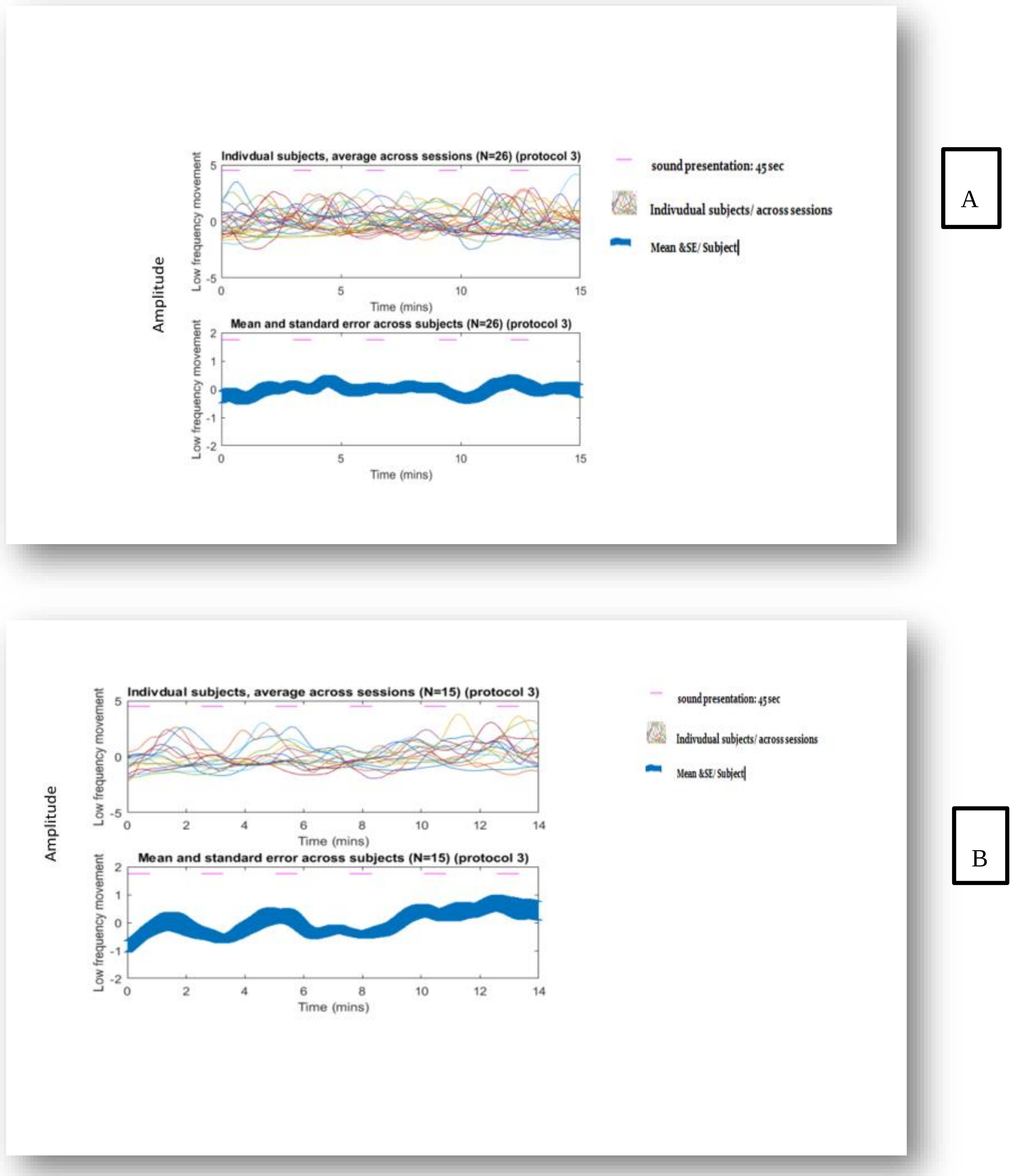
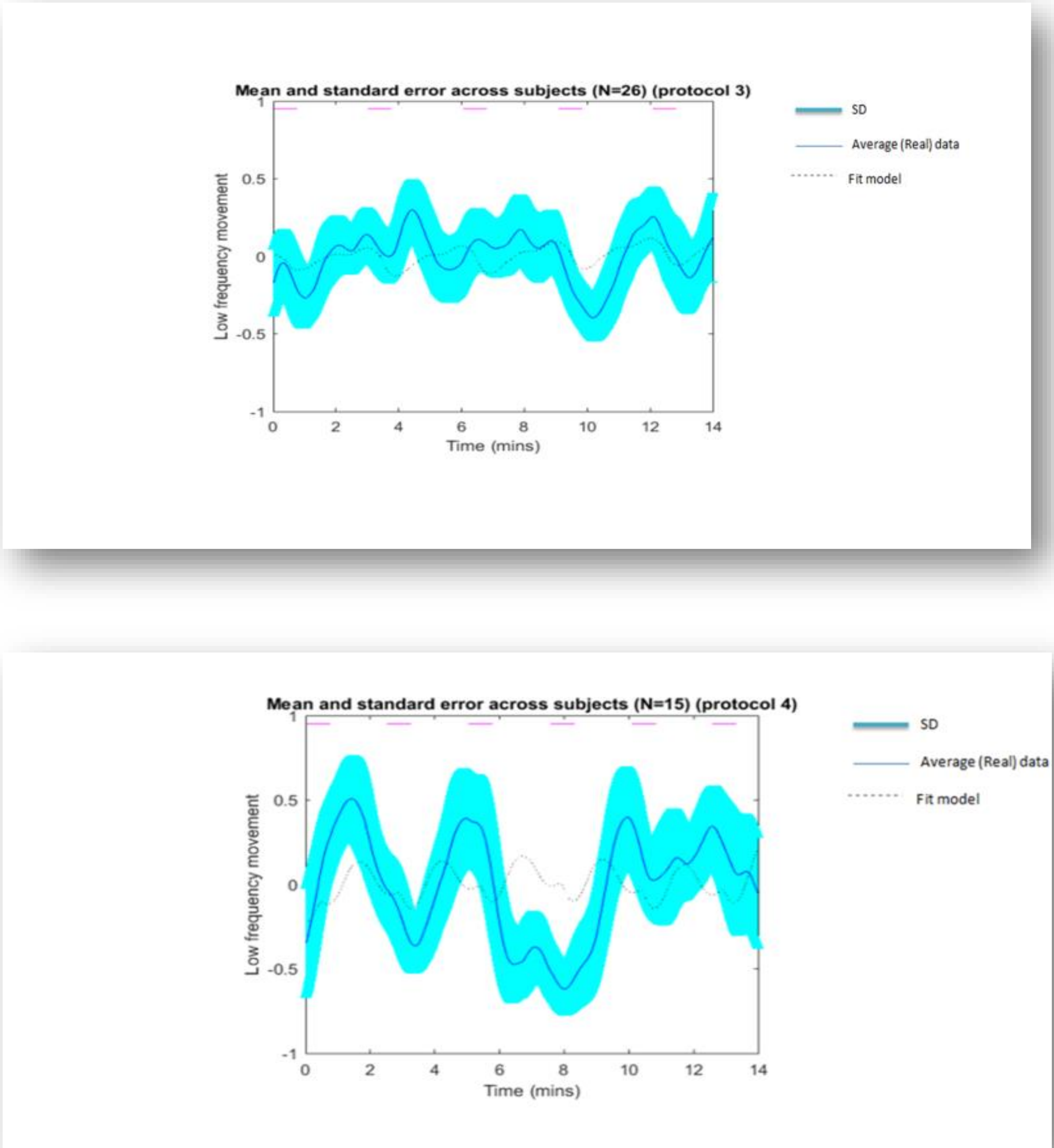


Figure 2-9 Fetal signal average: Fetal signals averaged across channels and sessions

for the individual subjects. (A) top graph shows individual subjects and when the sounds were presented, the bottom displays the mean and the standard errors across subjects for the first cohort (n= 26). (B) summarizes second cohort (n=15).

Fig. 2-9 A&B shows that fetal movements do not consistently correspond to the sounds. This finding pushed us to check if the fetus moved either at the start of the sounds or for the duration of them. Statistically, we used the regression model to derive a value of b1 and b2 for each participant. The statistic b1(block) was not significant and the statistic b2(onset) was significant $p < 0.05$, however, b1 and b2 were correlated. The results of this analysis, as shown Fig. 2-10 A&B, suggest that fetuses move less during or just after sounds.



A

B

Figure 2-10 Linear regression (A= First cohort, B= Second cohort). Figures displaying mean, standard error and linear regression. The blue line is the average

of real data with standard error shown in light blue. The dotted line shows the fit and the pink lines show when the sound was presented.

2.6 Discussion

The objective of the current study was to assess brain function in fetuses by recording their responses to sound stimulation using a prototype wearable, affordable device with a long recording period. Our results showed that the AMTG has promising potential in assessing evoked fetal responses even though it does not have sufficient signal-to- noise to be applied clinically. The proposed design was based on the detecting fetal motion through deformation of the abdomen.

Although prior studies have noted the potential of wearable tools for measuring fetal movement, none has used wearable device to measure fetal responsiveness to acoustic stimuli. The use of a wearable device in assessing fetal responses to acoustic stimulation with the capacity of long periods of recording can potentially be used to further understand markers of neurological integrity during fetal period. Thus AMTG will provide measurement tool for discovery of novel markers of a range of neurobiological diseases at the earliest possible stage for disease prevention and a timely manner for interventions. In parallel to predominant basic research, numerous studies on the prenatal assessment of neurobiological diseases carried out using different imaging modalities has revealed new resources for supporting the evidence of assessment of fetal motor behavior as a future marker of fetal neurobiology(Rutherford, 2018; Sami, 2018).

The current study has also found that fetuses move in response to sounds. This result ties with previous studies and is supported by the existing literature (Al-Ashwal et al., 2016b;

Altini et al., 2016, 2017; Boashash, Khlif, Ben-Jabeur, East, & Colditz, 2014; Mesbah et al., 2011b; Nishihara et al., 2008; Penders et al., 2015; Ryo et al., 2012; Stanger, Horey, Hooker, Jenkins, & Custovic, 2017). In the past, studies examined the reactions to lullabies mainly in infants (DeCasper & Carstens, 1981; Günes & Günes, 2012; Harkey, Casale, Pantelopoulos, & Zurcher, 2014; Loewy, Stewart, Dassler, Telsey, & Homel, 2013; Rand & Lahav, 2014). In this literature, lullabies have shown to calm infants, lull babies to sleep, simulate language development as well as strengthen the emotional bond between a parent and the child. Here we showed that unborn babies can also react to the same lullabies used in infant behavior and development research. Our results demonstrate that fetuses in their third trimester react to lullabies by moving less (Figs 2-10 A&B). These results go beyond previous reports, and show that a decrease in fetal movement occurs during and just after lullaby presentation. Prior studies that have also established the importance of lullabies in pregnancy for women and have demonstrated a role in assessing maturation of voice recognition, fetal memory and learning, reduction of stress, stimulating language.(Busnel, n.d.; Carolan et al., 2011b; C. M. Moon & Fifer, 2000; Parncutt, 2006).

Investigating the fetal CNS by assessing fetal responsiveness has been interpreted to be one of the approaches in studying rudimentary signs of motor behavior that could be more functional in the post-natal period helping the baby to accommodate to the external world (G. A. Ferrari et al., 2016). This indicates that fetal responsiveness could potentially be used as a clinical assessment tool for fetal well-being in general and fetal neurological status in particular (Amiel-Tison, Gosselin, & Kurjak, 2006; Antsaklis, Kurjak, & Izetbegovic, 2013; Birnholz, Stephens, & Faria, 1978; Olesen & Svare, 2004; Ryo et al., 2012)

In the current experiment, the analysis was more focused and limited to the changes of fetal movement in relation to a lullabies presentation in general; we concluded there was insufficient power to measure the difference between hummed and sung lullabies. This may be used to assess fetal abilities to discriminate music with voice and music without voice.

The AMTG, like many other wearable devices, captures different signals. Eliminating artifacts and separating signals of interest from others has been a challenge. We showed that the wavelet transform can be used as a technique to separate fetal signals from other non-fetal sources of motion. The same technique has been consistently used in previous fetal signal analysis and showed reliable results (Hasan, Reaz, Ibrahimy, Hussain, & Uddin, 2009; Kovács, Horváth, Balogh, & Hosszú, 2011; Winje et al., 2013). More work to improve the fetal signal processing by separating them from other signals as well as imbedding a processing system in the device is needed and crucial for better performance of the proposed measurement tool.

Together the present results support the idea that the use of wearable devices like AMTG in assessing fetal responses in low income countries is one of the solutions to overcome the scarcity of current imaging tools in these settings. However, for practical implementation, more work is needed to improve the AMTG.

The next chapter will therefore discuss the proposed solution to determine the optimal numbers of sensors and their location in order to make the next generation of the AMTG in principled design.

Limitation of the current experiment

Although this experiment shows the promise of a wearable device, at present, the signal to noise ratio is far from sufficient to be practical clinically. Therefore, our next goal was to design a better device. But the chief impediment here is that little is known about abdominal deformations due to fetal movement, and the sources of noise like maternal breathing. As we do not know the spatial and temporal characteristics of the signals we are trying to detect, and those we are trying to suppress, it is difficult to optimize the design in a principled way. The particular challenge is to design the optimal positioning and number of the sensors. To solve this, we planned to use a static, lab-based piece of equipment to measure whole-abdomen deformations. This would allow the principled design of the next generation of AMTG.

Because of the lack of some obstetric data such as the location of the placenta and fetal presentations for some of the participants, we could not investigate the performance of the device vis a vis the above- mentioned parameters. This could have been resolved by performing obstetrical ultrasound before acquiring data with AMTG.

2.9 Conclusion

In this experiment, we presented a novel system to measure evoked fetal responses using AMTG. The proposed approach provides non-invasive, low cost and long-term monitoring of fetal movement. We believe that AMTG has great potential for scientific studies of fetal brain function and will eventually be an important clinical tool, particularly in developing countries. However, the sensitivity is far from sufficient for clinical use. More work needs to be done to improve the device.

Chapter 3 Whole-field measurement of abdominal wall deformations: Fringe projection technique.

3.1 Introduction

In chapter two, we showed that the AMTG could detect fetal and maternal motion signals. However, the positions and the numbers of the sensors in the AMTG were somewhat arbitrary. The major problem in the design of a more sensitive device was the lack of an objective method of assessing whole abdominal wall deformation. In this chapter, we prososed a method of studying abdominal wall movements over a wider field of view and with a higher resolution. Our goal was to determine the number and the position of the sensors needed for the next AMTG generation. We also aimed at assessing and measuring evoked fetal movement by using the fringe projection technique. We used a static, lab-based piece of equipment to measure whole-abdomen deformations. We employed fringe projection which is an optical metrology technique that can measure the shape of a surface at high spatial and temporal resolution.

Broadly, this measurement approach consists of projecting patterns of stripes on a three-dimensionally shaped surface. Seen from an oblique angle, the pattern appears geometrically distorted due to the surface shape of the object. The distorted fringe pattern is recorded, typically by a camera and through computer analysis of the recorded images or videos, the object can be recreated in 3D space, with a high degree of precision.

The fringe projection system developed for this experiment was designed for profiling of dynamic changes. To illustrate the description of the method, we refer to Fig 3-1. The fringe pattern was composed of a sinusoidal grating created in MATLAB and projected onto the mother's abdomen, and the distorted fringe patterns due to the shape of the mother's abdomen and its changes over time were recorded in the form of a video obtained sequentially by a high definition webcam (1920x1080, 15 frames per second) that was offset from the axis of projection by approximately 20 degrees. The displacement of the stripes is then used for an exact retrieval of the 3D coordinates of any details on the abdomen including the shape estimate and its changes during sound presentation.

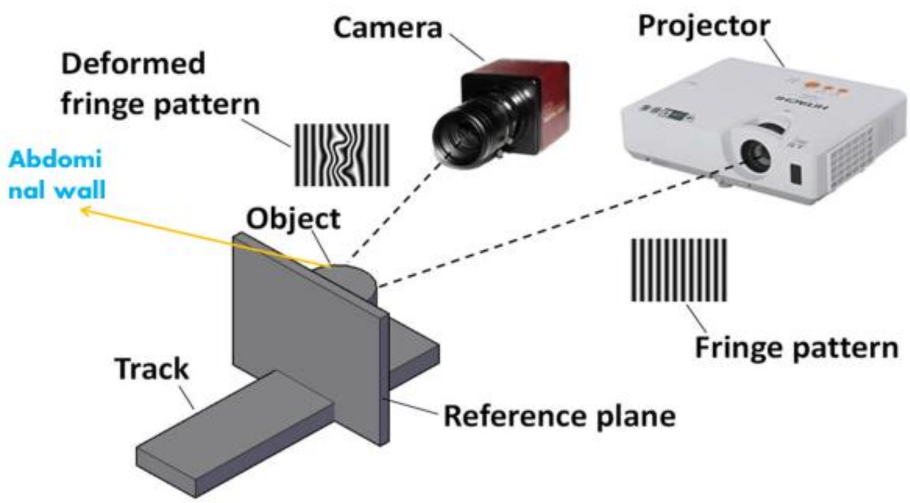


Figure 3-1 Fringe projection description: a schematic of a system for optical tomography fringe projection

As in chapter two, we aimed to measure the evoked fetal responses. Thus we again presented auditory stimuli to the fetus while the fringe patterns were being projected. Rather than using the belly buds, which would have obstructed measurement of the abdomen, we presented through speakers built in the projector. The sequence and the presentation design of the sounds were the same as those used in chapter 2.

3.1.1 Why fringe projection?

We employed fringe projection for its wide field of view, and high spatial and temporal resolution. It is contact free measurement and a fast and accurate technique. It does not pose health and safety risks. With fringe projection, it is possible to accurately measure the area over a wide range, from less than millimeter up to more than one meter. This technique suits the measurement of shape of the mother's abdomen due to its resolution, accuracy for precise detailed measurements.

3.1.2 Related works

The use of fringe projection for surface profiling is a well-developed method for optic metrology because it can generate rich three- dimensional (3D) surface profiles. Over the past several decades, optical sensing techniques have found numerous applications in different fields.

This approach has been very useful in various biomedical research; human body shape measurement in a normal condition (Lilley, Lalor, & Burton, 2000) and disease conditions such as the assessment of the pectus excavatum (W. Glinkowski et al., 2009), low back deformation measurement (W. M. Glinkowski et al., 2016; Hanafi, Gharbi, & Cornu, 2005), inspection of a wound (Barone, Paoli, & Razionale, 2011; Krouskop, Baker, & Wilson, 2002), skin topography measurement for the use of cosmetic, measurement of surface displacement (Li & Kofman, 2014), respiratory mechanisms and control of breathing in infants (Chen et al., 2010), patient beam position in imaging medicine and radiation treatment (Related, 1982) .

Owing to the advantages of low cost, lack of contact and non-invasiveness, fringe projection technique has also been discussed in the measurement of biological tissues in animals(Jiang et al., 2015). As a non-invasive method with no ionizing radiation, fringe projection was found to be beneficial over x-rays for follow up of scoliotic deformity in young adolescents who need intensive follow ups for many years (Pazos, Cheriet, Song, Labelle, & Dansereau, 2005).

To accurately design and measure different braces and prosthesis, fringe projection technique was used and proved to be a reliable method; development of facial prosthesis, personalized design and adjustment of spinal braces according to the patient specific trunk deformity (Fortin et al., 2007)

To measure the deformation and the topography of both living and inert objects, Marcelo et al. (Michalski, Rabal, & Garavaglia, 1986) have also used fringe projection, their result showed that this approach can be performed on a large object with the sensitivity in millimetric and submillimetric ranges making the fringe projection a good technique to accurately measure human body contours with an example of the assessment of abdominal wall changes (Michalski et al., 1986).

Another similar technique has been established to measure human body parts in motion using laser projection(Poredoš, Povšič, Novak, & Jezerš, 2015). Poredoš and his collegues used multiple laser projections instead of fringe projection to measure motion: a knee joint during leg motion, thoraco-abdominal and back deformation during breathing and the shape of a foot during walking(Poredoš et al., 2015). Together the above literature shows that the fringe projection technique suits for accurate measurement of changes of many different body parts.

In current experiment, we described the principle of the technique, the measurement of the whole abdominal deformations in healthy pregnant women in their third trimester, and how these change during sound presentation reflecting the evoked fetal movement.

3.1.3 Description of the method

The hardware consists of a projector, camera, and computer for control. The projector and the camera are aligned obliquely, separated by approximately 20 degrees. With suitable parameters and calibration of the system, the surface profile of the object of interest can be calculated.

There are a large number of fringe styles that can be used in this technique. The most popular are binary coded, triangular, sinusoid and trapezoid patterns. The choice of style of fringe goes with processing techniques and determines the quality of measurement. In this area of fringe projection technique, sinusoidal patterns are the most widely used compared to the other types due to its robustness against defocusing. A descriptive diagram is shown in the Fig 3-1

3.2 Method

3.2.1 Calibration system

In order to quantify surface deformation with fringe projection, calibration is needed. For this experiment, the reference plane (the wall) was first set and kept the same for all testing. To assess camera obliqueness from this plane, pieces of papers with 2 dimensional fringes were put on the outside corners of the screen (Fig.3.3) for the whole period of testing.

With the projector and the camera sitting on the table, the fringe patterns were projected on to the wall. To quantify the effect of displacements along the axis perpendicular to the wall, a solid piece of wood with known measurements, well finished with flat sides was used to measure the fringe pattern deflection. The wood was swept from the top to the bottom against the wall while the fringe patterns were being projected (Fig 3.2).

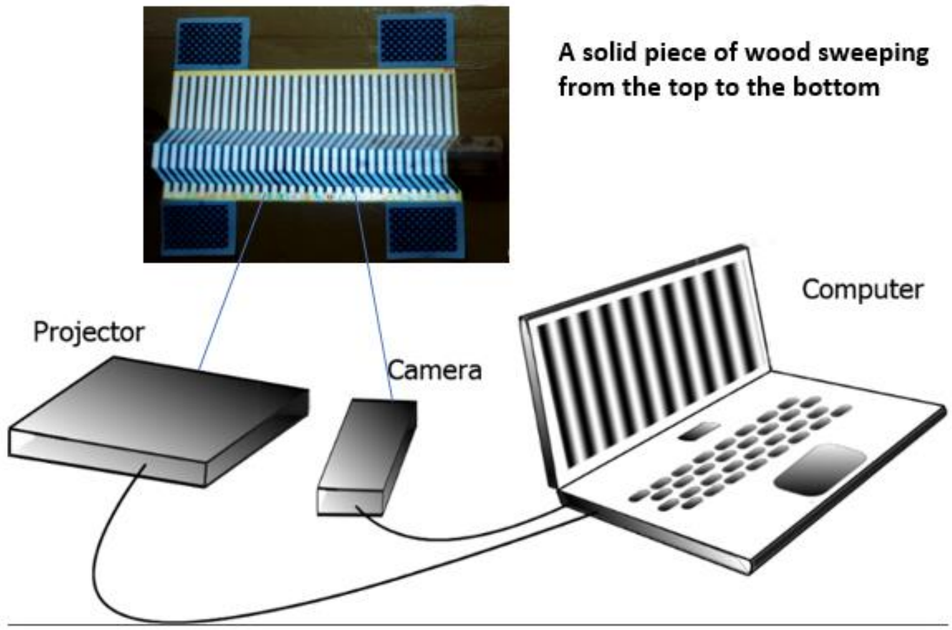


Figure 3-2 Calibration system: diagram displaying the calibration system, with the image on the top showing the wood sweeping against the projected fringe patterns.

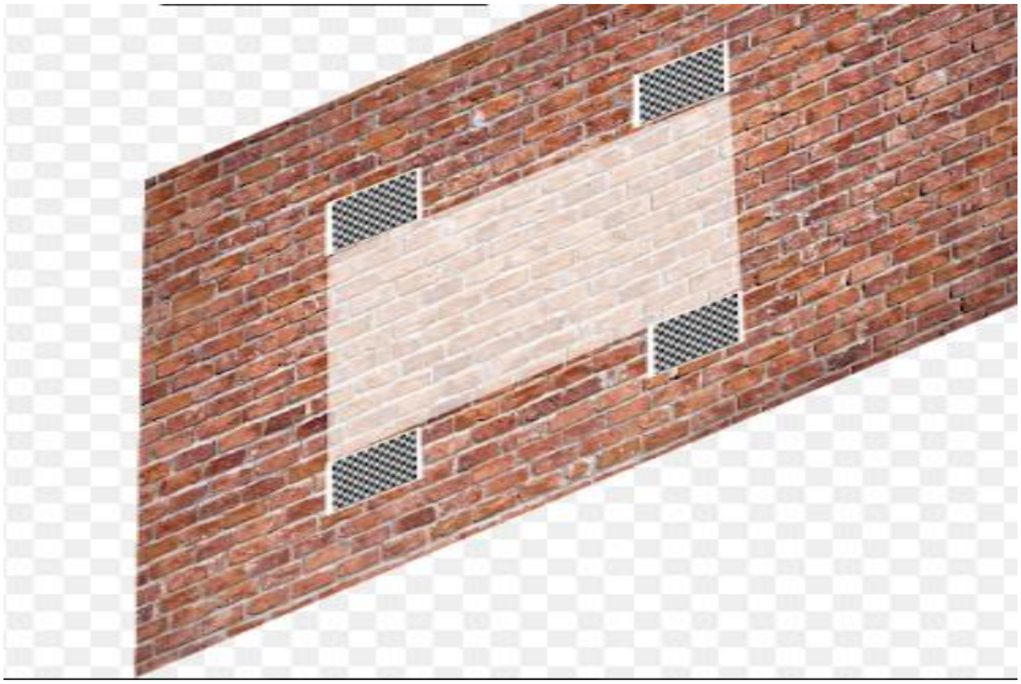
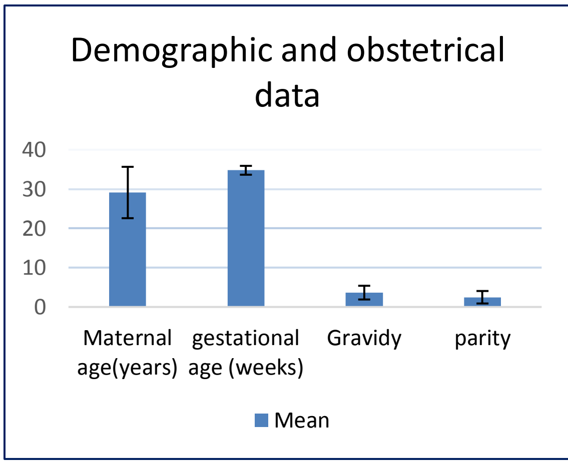


Figure 3-3 Reference plane. The diagram demonstrating the measurement of the wall/calibration system. 4 papers with 2 dimensional fringe patterns are positioned outside the corner of the screen.

3.2.2 Participants

After the calibration process, N=23 healthy pregnant women with a singleton pregnancy between 32 and 38 weeks of gestational age were recruited from Gahini Hospital, Rwanda for this experiment. Gestational age was determined from the last menstrual period. To participate in this study, pregnant women provided a written informed consent. The study was approved by the Research Ethics Committee of Gahini Hospital. They were recruited from prenatal information and follow up sessions. Their medical files were used to confirm that the participants did not have any medical conditions in the current pregnancy. To motivate their participation, they were compensated for their time at the rate of 3500Rwf/hour. In total, we collected data for 23 women over the course of one month(February 2018), however one was not analyzed due to missing data leaving

22 for analysis. No subjects voluntarily dropped out the study. Their mean maternal age and gestational age were 29 years and 34 weeks, respectively. Of the 22 participants (M=34.8 weeks, SD=1,1) included, 2 were 33 weeks GA, 8 were 34 of GA, 6 were 35 weeks GA, 4 were 36 weeks GA and 2 women were 37 weeks GA. Demographic and obstetrical data are summarized in the following graph.



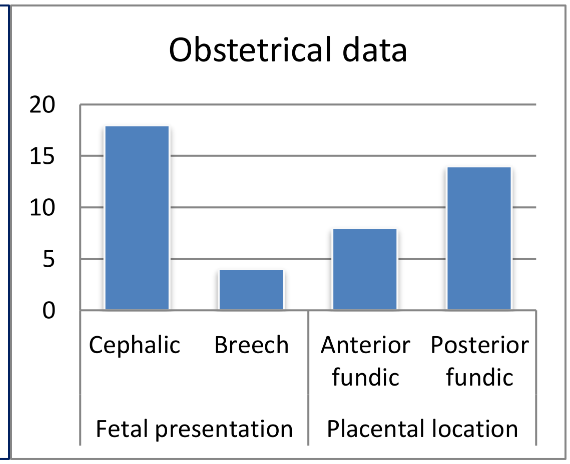


Figure 3-4 Demographic and obstetrical data

3.2.2 Materials

The measurement system consisted of a projection unit, which is a digital light processing projector (DBPOWER T20 LCD Mini projector) and the recording unit which is a Logitech C920 HD 1080p camera. The same projector was used to present sounds to the fetus via its built-in speakers. Both projector and the camera were connected to the laptop and they were separated from each other by 45 cm .The laptop stored the data and served as the source of the fringe pattern created in MATLAB and the sounds. A summarized measurement system is shown in Fig 3-5.

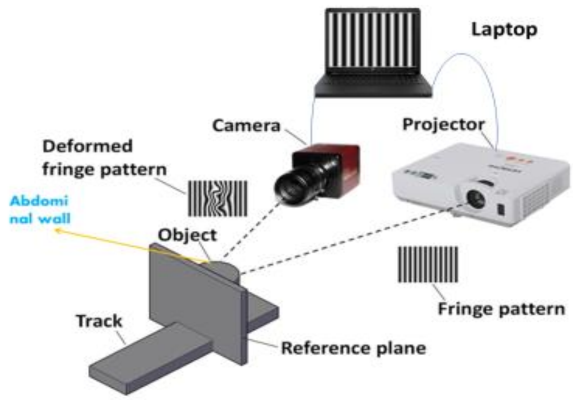


Figure 3-5 Measurement system: Diagram summarizing the measurement system consisting of laptop with fringe pattern on the screen connected to projector to display the stripe on the mothers abdomen, deformed fringe patterns are then recorded by the camera.

3.2.3 Sound stimuli

Four short segments of lullabies of 15 seconds in length each were used as sound stimuli. They were chosen for their known effect of strongly engaging newborns. The lullabies used in this experiment were *Twinkle Twinkle, Mocking bird, Rock a baby bye* and *Sunshine.* They were either sung or hummed by English women. To present the sounds, speakers built in to the projector were used.

3.2.4 Data collection procedure

Because the stability of the participant is important for measurement of the abdominal wall, participants were asked to sit, remain calm and still during testing. Any factors that could affect abdominal wall deformation such as coughing and moving during testing were noted. After getting a written informed consent to participate in the study, the participant sat on the chair 140 cm away from the projector and the camera with a bare abdomen. Fringe patterns of vertical parallel lines generated by MATLAB were projected onto both the reference plane (wall with 4 papers) and the participants' abdomens. At the same time, sound stimuli (lullabies) were presented to the fetus via speakers built in the projector. The camera then recorded the deformed fringe patterns. Each session was made of 15 minutes and after each session participants were given the time to rest and relax before completing the following sessions. In total, each participant underwent 4 sessions to complete the experiment, which lasted in total for one hour. All the videos were stored on a laptop for analysis.

3.2.5 Data pre-processing & Analysis

The data for this experiment were videos. The fringe projection could be clearly discriminated on the abdomen, but was difficult to detect on the clothing or surroundings. The first task was therefore to create a mask that delimited the area where the fringes were clearly discriminable. A semi-automatic tool provided with MATLAB was used, the Segmenter tool, which allowed the data to be loaded, analyzed and the results to be visualized. To draw the mask, we used an average of the magnitude of the signals with a spatial frequency similar to the fringes, in the 10 seconds after the sound was presented near the start of each session.

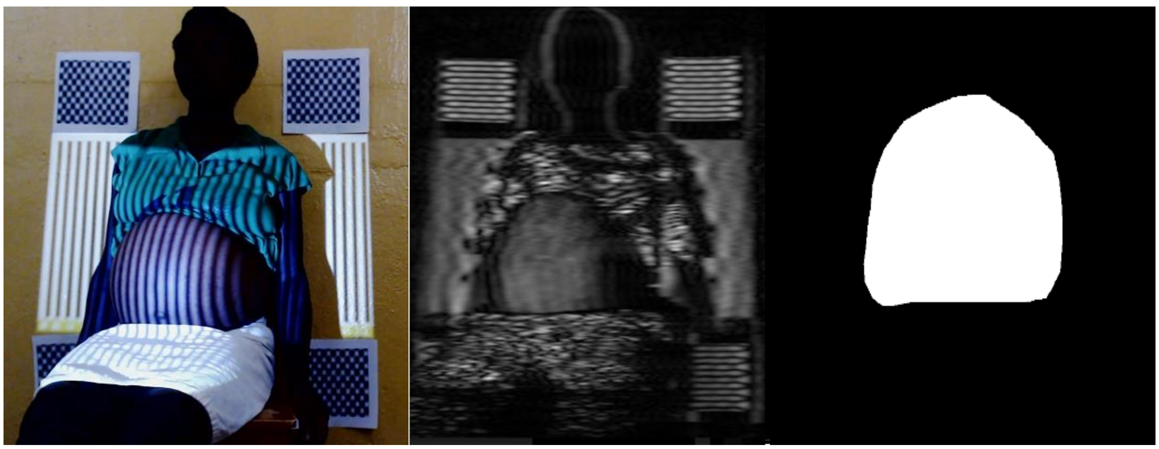
The next stage was a process called “demodulation”, in which the modulation of the higher spatial-frequency fringe pattern was converted map into a lower-spatial frequency map of displacement. Multiple algorithms were proposed to demodulate fringe patterns, such as a Fourier-transform based algorithm, phase stepping, digital phase locked loop, direct phase detection and wavelet transform method. We used the Fourier-transform method. Changes in displacement are encoded by changes in the phase (the angle) of the Fourier signal at each point in space. Like all phase signals, this is wrapped into the range -180 to 180 degree. To estimate the full shape of the abdomen, a phase unwrapping algorithm was used to find the mean estimate of the shape. To assess the abdominal wall changes over time, which can be measured by assessing changes the abdomen stick out, and points along a vertical line and horizontal line were chosen. Changes in abdominal wall was the position of y the axis which is how far the abdomen protrudes as a function of time (x axis) for a set of points sampled along a vertical and horizontal line through the center of the image.

Next, obtained traces along the vertical and horizontal lines were averaged. All traces were marked with the time of sound presentation. To separate maternal breathing signals from other signals, we again ran a wavelet transform and used a model, as in Chapter 2.

To perform the analyses, a high-performance computing cluster was needed. The total processing time needed was approximately 80 days of CPU time, which we performed in an Amazon-cloud based cluster in 8 hours.

3.3 Results

A total of N=23 healthy pregnant women were recruited at Gahini, Rwanda. One was lost due to technical difficulties and N=22 were included in the final analysis. A total of 1170 minutes (78 sessions) of data for video recordings during projection of stripe and sound presentation were analyzed. Subjects' average age was 29.1 years (SD=6.5) and their gestational age average was 34.8 weeks (SD=1.1). The summary of the participants 'characteristics are presented in Fig3-4.



A B C

Figure 3-6 (A) Actual screenshot of one participant, (B) image of the one participant created by the mean of the first 10 seconds after the sound was presented. (C) A mask of relevant anatomical surface where stripes were clearly visible on the abdomen.

Figure 3-6A shows the actual screenshot of one of the participants; shows how the fringes were projected and that the stripes were clearly visible on the abdomen. Fig 3-6B presents the image of the participant obtained by averaging the first 10 seconds. This is an average of the magnitude demodulated data, which shows the strength of the fringe pattern at each point in the image. It shows the surface of interest (abdomen), other parts of the participant as well as the reference plan(wall). Fig 3-6C shows the corresponding mask of the anatomical surface of the abdomen where stripes were clearly visible.

Following demodulation and unwrapping, Fig 3-7 illustrates the shape estimate for one frame of one woman's abdomen. From the figures below the estimate shape are clear, but there is noise around the edges, and particularly at the bottom, where there was a loss of fringes.

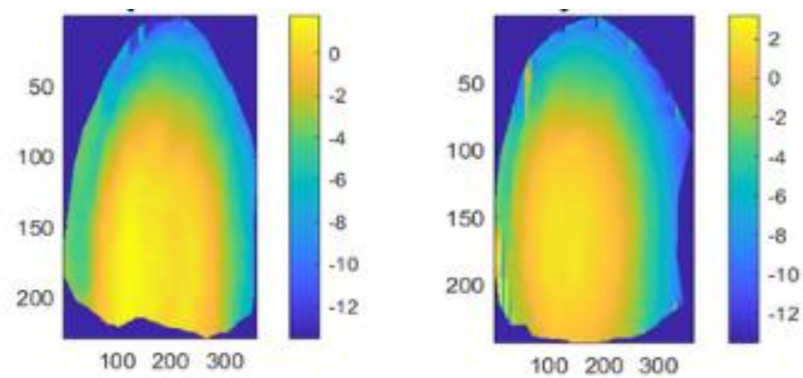


Figure 3-7 Shape estimate for the abdomen: Shape estimate for the abdomen that resulted from unwrapping phase for 2 different sessions

Changes of abdominal wall deformations

Using the signal processing steps described, the fringe projection technique detected changes of abdominal wall. The following figures show how the abdominal wall changes. These changes were assessed by looking at the variability in how the abdomen protrudes during the fringe projection and sounds presentations. To visualize this, displacement was sampled from 8 equally spaced positions along vertical and horizontal lines crossing the centre of the image. Fig 3-8 summarizes the results for the analysis of 3 sessions, and indicates that this technique identified changes in abdominal wall for both vertical and horizontal lines.

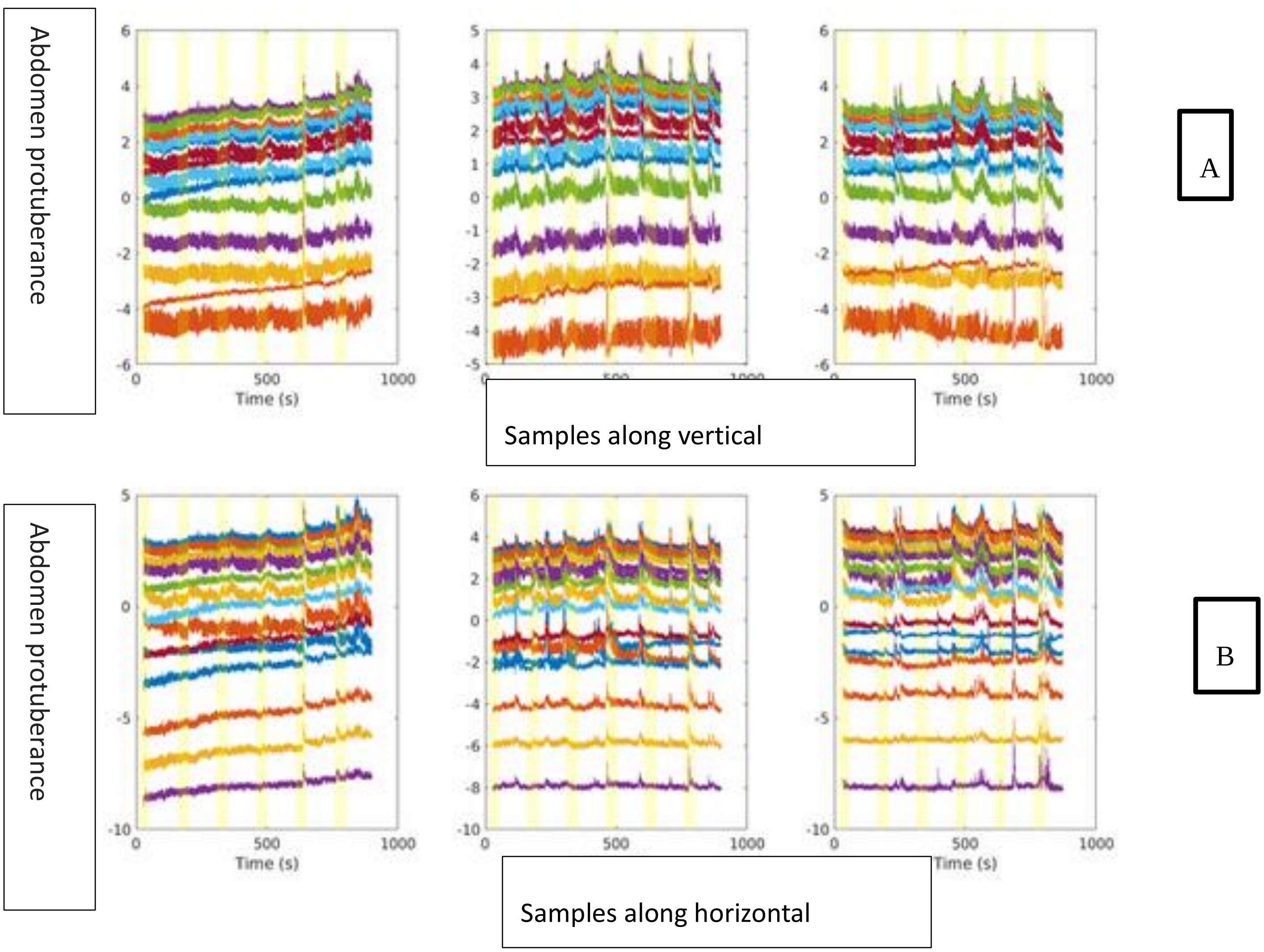


Figure 3-8 Changes of abdominal wall: Figures A&B show how the abdominal wall changes over time during fringe projections and sound presentation. (A) upper row shows how far the abdomen protrudes when in relation to sampled points along vertical line with overlaying

yellow bands showing when the sounds were presented, in 3 different sessions (B) lower row demonstrates the same changes in relation to sampled points along horizontal line.

Fig 3-9 shows the average amplitude of the traces which show changes in abdominal wall by means of fringe projections along with sound presentations. To account for the wide-range of differences in signals from different mothers, the amplitude values across the time series for each session were z-scored prior to averaging. The presented traces (averages) in the following figures were obtained by averaging sample points along the vertical (A) and horizontal lines (B). The figures also show when sounds were presented. As it can be seen, with the current analysis there is no relationship between the amplitude of changes in the abdominal wall deformations vis a vis when sounds were presented. In other words, the results, as shown in Fig 3-9 indicate that with the current analysis and approach, no detectable fetal response to sound was detected.

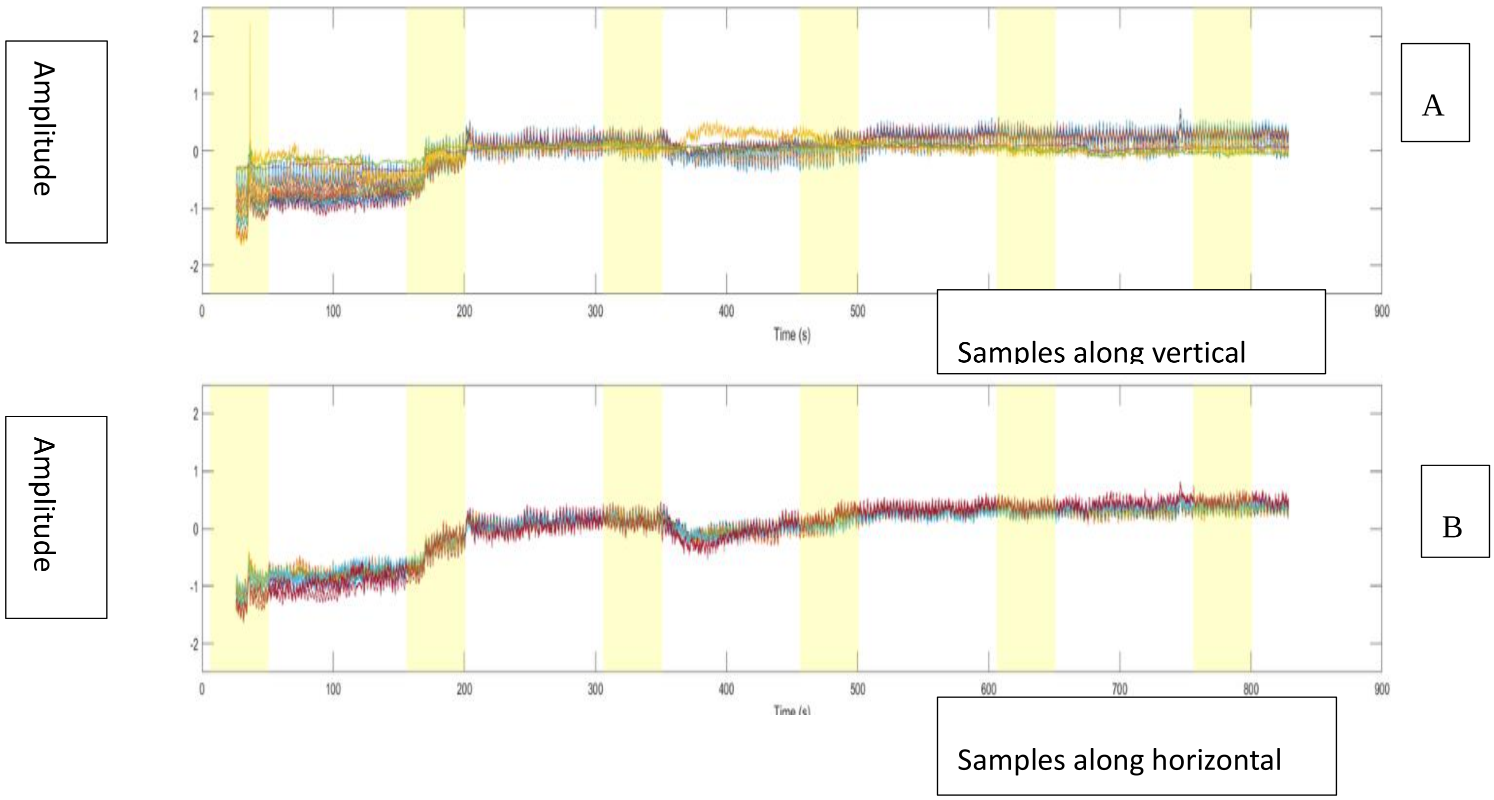


Figure 3-9 Average of abdominal wall changes: Average of traces that shows the changes of abdominal wall seen as how the abdomen protrudes in function of sampled points along vertical (A) and (B) horizontal lines. With Vertical yellow overlying lines showing when the sounds were presented.

Given the success of a wavelet-based method to separate maternal breathing from other signals in Chapter 2, we also applied and evaluated here. Fig. 3-10 shows an example wavelet transform, and shows the clear maternal breathing signal. This was apparent across all of the sessions examined, showing that the method was sensitive to abdominal movements.

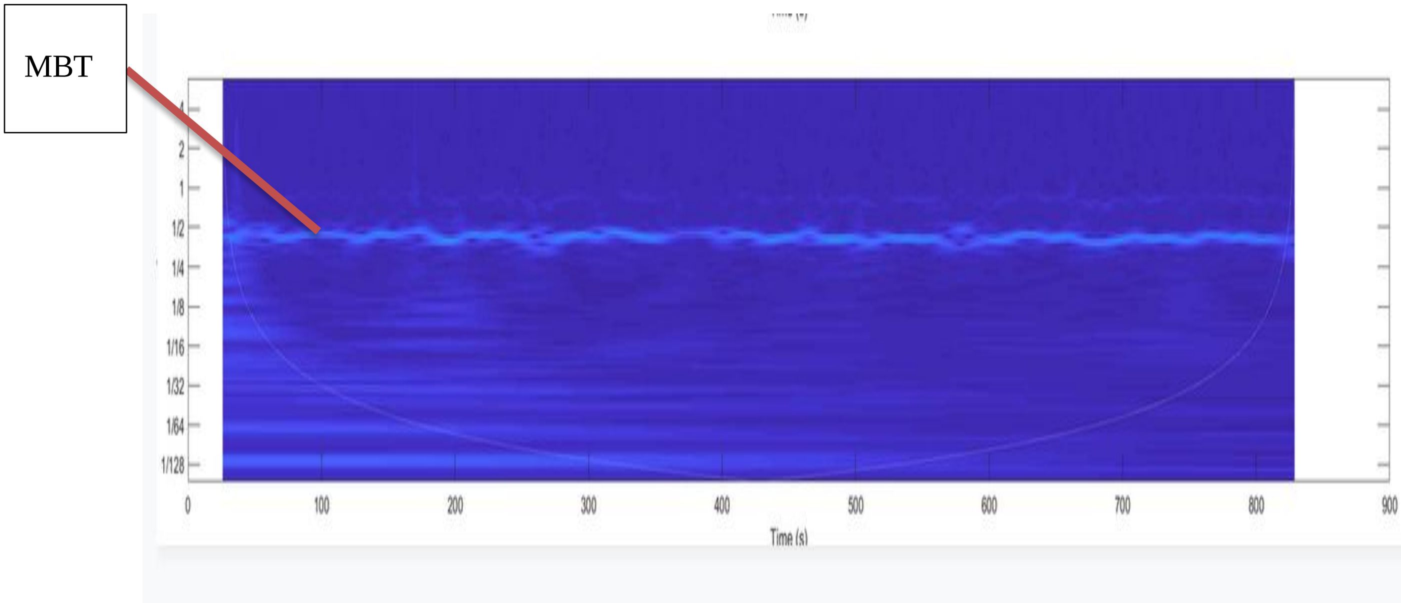


Figure 3-10 Wavelet transform: The figure of wavelet transform shows the maternal breathing signals

Denoising and similar regression analysis to that in Chapter 2 was performed. Unfortunately, it did not identify fetal movements. However, these date are rich and analysis will continue after the conclusion of the Masters.

3.4 Discussion

For the first time, fringe projection was applied to evaluate and measure abdominal wall changes over time in pregnant women. This experiment was conducted to better-determine the temporal and spatial patterns of displacemnet of the abdominal wall in pregnant women of 32 weeks of gestational age and above. The technique used in this experiment is known to provide accurate measurement of different objects, including some human surfaces. It was successful in providing a high-temporal and spatial resolution map without contact or interference with the natural changes in the abdominal wall. It is has the advantage of 3D measurement in pregnant women as it does not have risks of exposure to ionizing radiation. In addition to the advantages described above, this technique provides whole-field measurement with high resolution which can enable the evaluation of broad and specific changes of the anterior abdominal wall.

To investigate the potential of the proposed method in assessing changes of the abdominal wall in pregnancy, we tested 23 healthy pregnant women in their third trimester. To validate the method and to test if it can give reliable results, a simple but reliable calibration system was initially performed using wood (Fig 3-2 and Fig 3-3). Besides the initial calibration system at the beginning of the study, the same calibration procedure was performed daily to ensure all the measuring materials were not moved.

We demonstrated that fringe projection technique can be used to achieve high quality results in measuring abdominal wall deformation in the programmed principles in a very limited time and with a low-cost budget. To the best of our knowledge, we have presented the first method for measuring abdominal shape deformation in a human pregnant population using fringe projection technique. The system has no risk of ionizing radiation and would therefore be safe for use over extended periods of time as well as repetitive sessions.

The basic result that this technique can measure movement of the human abdomen is consistent with that of previous research showing that fringe projection can measure chest wall motion in subjects with and without pleural effusion (Chen et al., 2010), human body in motion enabling precise analysis of shape deformation (Poredoš et al., 2015), and respiratory rate and flow (Scalise et al., 2018). This literature supports the idea that fringe projection technique can provide a measurement system capable of real time measurement with a precise and nonintrusive analysis of shape deformation which has potential applications in the biomedical field.

In the present study we did not determine in numbers the magnitude changes of the abdominal wall but we have demonstrated graphically that the minimal movement of the anterior abdominal wall can be detected as it can be seen in Fig 3-8 and Fig 3-9, they are rapid and short, it is easy to miss them. Therefore, any approach in the measurement of these changes needs to be more precise. In line with previous studies, our findings support the idea of that fringe projections technique can provide a reliable approach when dealing with precise measurement. This has been supported in different studies; Michalski et al found that fringe projection technique is a precise measurement with a tolerance of a millimeter and submillimeter ranges with potential applications in establishing criteria for positioning human bodies (Michalski et al., 1986). Moreno and colleagues have insisted in their work that fringe projection should be an alternative measurement approach in health care because of its promising applications in evaluating and quantification of some parts of the human body in a more accurate way, as well as being a faster and more economic technique (Moreno Yeras, González Peña, & Junco, 2003). The same idea has seen in previous studies examining chest wall kinematics and patterns of breathing during speech in COPD patients (Binazzi, Lanini, Gigliotti, & Scano, 2013); chest wall motion measurement for respiratory volume evaluation (Chen et al., 2010), precise measurement of respiration rate and flow (Scalise et al., 2018) and monitoring respiratory mechanisms during breathing as well as correcting breathing irregularity(Povšič, 2012). All of these demonstrate that the presented technique shows potential and a wide range of application in the clinical field as an alternative assessment tool. The ability to measure regional abdominal volume changes can also be used to assess fetal movement in pregnant women. This contactless measurement provided by this method can also be a good alternative in cases of patients with burns when the body surface area is damaged.

In the past, studies examined the potential fringe projections technique in reconstructing surfaces and surface profiles in general of human bodies, this approach was found to be reliable in reconstructing the surface of some different parts of the human body; topographic analysis of the low back in spinal deformity(Pazos et al., 2005), anterior chest deformity in general(Shochat, Csongradi, Hartman, & Rinsky, 1981) and assessment of pectus excavatum(W. Glinkowski et al., 2009). Here we showed that fringe projection technique can be used to reconstruct the anterior surface of the abdomen in pregnant women. Our results demonstrate that shape estimate for the anterior surface of the abdomen can be reconstructed (Fig 3-7) using the proposed technique. Shape estimates were retrieved well except on lower edges where fringes were lost due to the unwrapping phase technique. The loss of fringes can also be explained by bad lighting as well as use of one camera with possible inability to capture all the projected patterns area.

As the aim of this experiment, estimate shape for the anterior part of abdomen in pregnant women will allow us to determine the position and the number needed for the improvement of the AMTG in order to cover the abdomen at the maximum. Although this experiment did enable us to assess the overall changes of the anterior abdominal wall, for example due to maternal breathing, the current analysis was not able to distinguish fetal movement from other signals that were seen as changes of abdominal wall deformations. Detecting fetal movement was made more challenging by the fact that changes of abdominal wall deformations seen in Fig 3-9 were not correlating with the sound presentation blocks. Identifying evoked fetal movements will need a further analytic algorithm.

To increase the specificity of the system, work is in progress to make another algorithm that will allow us to differentiate fetal movement from other signals as well as the assessment of the performance of this technique with regards to detection of evoked fetal responses mainly fetal movement. Better results are hoped from this analysis.

This experiment also opens up fringe projection as a new tool in assessing evoked fetal movements. We believe that our approach will enable fast and accurate measurements of evoked fetal movement which can be deducted from abdominal wall deformities in pregnant women. We also continue to believe that the long-term monitoring of evoked fetal movement may provide valuable information on the integration of central nervous systems.

The system presented in this experiment has limitations. This includes bad lighting conditions as the interfering light in the testing room can negatively affect the fringe projections, image acquisition and the results. It is preferable and advisable to have the control of the light sources, including light from outside and light from the ceiling fixtures.

The other challenge that fringe projection studies have, lies in natural minimal movements that can be made by the participant during testing. These movements interfere with the accuracy of surface reconstruction but when the system calibration is well set, minimal movements can only cause neglected inaccuracy.

3.5 Conclusions

This experiment established a promising novel application of fringe projection for measuring whole abdominal deformation and surface profile in pregnant women. The non-contact abdominal wall measurement system developed in this experiment has been shown to be an alternative tool for measuring surface area and deformations of the abdominal wall. We also explored possibilities and the contribution of fringe projection in assessing changes evoked fetal movements. While our approach was able to assess changes of abdominal deformations, more analyzing algorithms are needed to retrieve evoked fetal movements.

In future, we will use the data from the fringe experiment to design the next iteration of the device. The device will then be evaluated on a larger number of participants before it is of clinical use. Additionally, the device will be employed as a measurement tool in other developmental fetal research.

Chapter 4 General discussion

The assessment of movement can be used for follow up and monitoring of general fetal well-being in clinical settings and to study and monitor function of neonates as a marker of neurological integrity (F. Ferrari et al., 2011; Hamer, Bos, & Hadders-Algra, 2016; Olsen et al., 2016; Ploegstra, Bos, & de Vries, 2014; van Iersel, Bakker, Jonker, & Hadders-Algra, 2009), and as prognostic tool to identify infants with neurodevelopmental disabilities (Burger & Louw, 2009; Manacero, Marschik, Nunes, & Einspieler, 2012)

The aim of the current study was to assess fetal responsiveness which reflect brain function by using a novel measurement method. Our goal was to use this to detect fetal responses to acoustic stimulation through continuous recording of abdominal wall changes for a long period using a prototype wearable, affordable device. This method shows potential in low income settings where there is a scarcity of current imaging tools as well as high skilled personnel in imaging and computer science domains.

The measurements in both experiments were conducted on the basis of continuous recordings of the abdominal wall deformations while complex sounds were being presented to the fetus in third trimester within healthy conditions. While further evaluation is required, this early experience suggests that AMTG may provide a means of detecting brain functions in fetuses especially in low income settings. Additionally, the current study also suggested that fringe projection could serve as a measurement tool for detection of abdominal wall deformations which might be used as a reflection of fetal movement. The presented method utilizes affordable approaches with the capacity of longer recording time. This makes the presented methodology an objective one with potential benefit in low income countries and in the context of fetal research in general including its possible potential clinical applications. Contrary to other methods of neuroimaging in fetal population, during a measurement based on AMTG and fringe projection, the patient/participant is not exposed to harmful effects and there are no contraindications to frequent repetitions of the testing.

To carry out the current study using AMTG, we designed and constructed a prototype. The device was made of eight strain sensitive conductive rubber sandwiched between two layers of elastic fabrics. Both fabrics and sensors were sensitive to minor changes thus making recording of deformations of the abdomen possible. To evaluate this, women wore the device on the abdomen as a belt and sounds were presented via belly buds. We found that AMTG can detect motion in the third trimester in response to acoustic stimulation, indicating the usage and importance of wearable devices in evoked fetal movement which is the reflection of brain functions in fetuses.

Aligning with prior studies, we showed that the solution of fetal movement detection with a long period of recording lies in the use of wearable technology in research and clinical context(Borges, Barroca, Velez, & Lebres, n.d.; Penders et al., 2015). This has been shown by the use of accelerometer-based fetal movement detectors(Al-Ashwal et al., 2016a; Altini et al., 2016, 2017; Bhong & Lokhande, 2013; Boashash et al., 2014; Mesbah et al., 2011a; Nishihara, Ohki, Kamata, Ryo, & Horiuchi, 2015). However, these proposed devices for continuous objective monitoring of fetal movements focused on quantitative measurement of fetal movement in general, and they did not measure evoked fetal movements.

The use of current medical imaging such as U/S and fMRI in fetal research has a caveat: several studies have used a short period of recording resulting in large differences in results as well as variable clinical outcomes. Thus, a longer period of recording in the present study may allow us to get more important fetal information during the gestational period as well as long- term neurodevelopmental status.

We showed that evoked fetal movement which reflects brain functions in fetus can be investigated by continuous measurement of abdominal wall deformations with an affordable device that has a long period of recording compared to current expensive imaging modalities in fetal research such as U/S and MRI.

Signals generated by most wearable fetal movement detectors are a mixture of several signals from different sources and are analyzed according to their frequency, power and the source. We showed the potential of wavelet transform to segregate fetal signals from maternal artifact signals.

Seeing that AMTG can detect fetal movement in response to acoustic stimulation, we then investigated the evoked fetal movements change during complex sounds stimulation. To do this, we used linear regression and found that fetuses move less during or just after sound presentation. The interpretation of this result will be that the calming effect of lullabies seen in children(Günes & Günes, 2012) and preterm infants (Taheri et al., 2017) is also present in near term fetuses.

It is worth noting that comparison of fetal responsiveness to sound stimuli between studies is not practical because of the difference in methodologies. These differences include types of sound stimuli (reading passage, singing, vibroacoustic), the means of delivery of the stimuli (recorded, live sound) and the difference in time of recording (short, long period of recording) as well. All these differences contribute towards the heterogeneous findings in this area.

Despite differences, there are some shared common findings. The main one is that fetuses in third trimester are not passive listeners but rather respond to external sound stimuli by a change in their mobility with some showing a decrease and others an increase in fetal movements.

To carry out this study, we employed lullabies as a sound stimulus; we also employed wavelet transform analysis which has been used in many other different studies to dissociate fetal movement from other unwanted signals. We found that regardless of the age, fetuses from 34 weeks respond to lullabies. This finding is important and suggests that evoked fetal movement analysis has the potential to serve as a biomarker of CNS integrity. The effects and reactions of the fetuses to lullabies have a paucity of studies. However lullabies have been shown to have beneficial effects on preterm infants such as keeping neonate oxygen saturation and other vital signs in normal range (Jabraeili, Sabet, MustafaGharebaghi, Asghari Jafarabadi, & Arshadi, 2016) suggesting that lullabies can positively affect vital signs in preterm infants due to their calming effect. While all 4 lullabies used in this study elicited change in fetal movements, we did not investigate differences between lullabies. It is possible that these stimuli were too soporific to evoke fetal motion, and that possibly higher tempo stimuli would evoke a larger response.

As previously mentioned, the AMTG at the current stage is far from clinical efficiency for use. We then proposed in experiment two, a method of measuring abdominal deformations in a principled way in order to further improve the AMTG as the basic principle lies in detection of evoked fetal movement through abdominal deformation. We established a novel method to assess whole abdominal deformation using a fast, economic and accurate technique called "fringe projection". This technique requires a projection unit, recording device and a storage unit.

It is envisaged that the method presented in the current study would be of most value in the detection of evoked fetal movement; one way of assessing brain function in fetuses, especially in low income settings where there is a huge shortage of imaging modalities. The use of AMTG constitutes a promising advancement of wearable devices in the detection of evoked fetal movement especially for long periods of recording. It is low cost, and sensitive to small movements, making it a possible alternative to current imaging modalities.

There are some limitations when assessing fetal brain functions: The biggest challenge in studying fetal responsiveness in general is that parameters of sound stimuli have been neither measured nor normalized which may impact the responses with possible consequences on the interpretations of the findings.

There is still a need to improve the device in order to make it more handy and wearable. In addition to improving overall sensitivity, more understanding of evoked fetal movement and further explorations to classify normal and pathological findings are needed. Detailed investigation of evoked fetal movement with extended period of recording will help develop a comprehensive understanding of the maturation of the CNS, assessing some neurobiological disorders at the earliest stages, which are now being diagnosed in later life.

4.1 Conclusion

The current study evaluated a new approach of assessing fetal responsiveness to acoustic stimuli which reflects brain function. It can be stated that the assessment of brain function in fetuses *in utero* is feasible in third trimester by means of wearable devices. The method described may make it possible by measuring evoked fetal movement through continuous monitoring of abdominal wall changes. We developed a novel prototype device which is capable of measuring evoked fetal movement through continuous recording of abdominal wall deformations.

It can also be concluded that fringe projection technique provided a way of studying the whole abdominal wall changes in order to increase the specificity of the device. Taken together, we provided a promising alternative and affordable tool for potentially measuring evoked fetal responses that may be suitable for addressing the basic questions regarding periods of recording and affordability of continuous evoked fetal movement especially in low income facilities.

The application of this method within fetal research and clinical practice represents a growing area of inter-disciplinary collaboration, which may lead to a greater understanding of the development of the nervous system in fetuses at high risk of motor impairment and other neurodevelopmental disorders as well.

The approach of evoked fetal movement in clinical and scientific studies can only be enhanced if the measurement tool has the ability to record for an extended period of time. It has to be simple, safe and affordable to be applicable and important in low income facilities. The reliable and well-designed system to study fetal responsiveness should have the potential to discriminate between the abdominal wall deformations due to fetal movements and that due to maternal noise.

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Appendix A Ethics approval Notice, CHUK, Rwanda

CENTRE HOSPITALIER UNIVERSITAIRE
UNIVERSITY TEACHING HOSPITAL

Quality Health Care
Training & Research

Ethics Committee / Comitéd'éthique

April 28th, 2017 **Ref.: EC/CHUK/347/2017**

Review Approval Notice

Dear Patrick Gatutsi, Stephen Rulisa and Rhodri Cusack,

Your research project: ***"Antenatal determination of fetal brain function using an audio-motio-tachograph."***

During the meeting of the Ethics Committee of University Teaching Hospital of Kigali (CHUK) that was held on 28/04/2017 to evaluate your protocol of the above mentioned research project, we are pleased to inform you that the Ethics Committee/CHUK has approved your protocol.

You are required to present the results of your study to CHUK Ethics Committee before publication.

PS: Please note that the present approval is valid for 12 months.

Yours sincerely,

<<University teaching hospital of Kigali Ethics committee operates according to standard operating procedures (Sops) which are updated on an annual basis and in compliance with GCP and Ethics guidelines and regulations>>.

Appendix B Ethics Approval Notice, Gahini, Rwanda

REPUBLIC OF RWANDA

EASTERN PROVINCE
KAYONZA DISTRICT
GAHINI HOSPITAL
BP.75 RWAMAGANA

Approval Notice

Dear Patrick Gatutsi, Stephen Rulisa and Rhodri Cusack,

I am pleased to inform you that your research project "***Antenatal determination of fetal brain function using an audio-motio-tachography***" has been approved

You are required to present the results of your study to Gahini Hospital before publication.

PS: Please note that the present approval is valid for 12 months

Yours sincerely,

Gahini, June 18th 2017

Appendix C Ethics Approval Notice/ Amendments, Gahini, Rwanda

REPUBLIC OF RWANDA
MINISTRY OF HEALTH
KAYONZA DISTRICT
GAHINI HOSPITAL
PO BOX 75 RWAMAGANA
E-mail : gahinih@yahoo.fr / hopitagah@gmail.com

Ethics Approval Notice/ Amendment

Principal Investigator: Prof. Rhodri Cusack
Co-Investigators: Dr. Patrick Gatutsi, Dr. Stephen Rulisa.
Protocol title: Antenatal determination of fetal brain function using an audio-motio-tachography
Ethics approval date: June 18th 2017 **Expiry date:** June 18th 2018

This is to notify you that Gahini hospital has reviewed and granted the approval to the amendments on the approved research title and date noted above.

The ethics approval shall remain valid until the expiry date noted above assuming timely and acceptable responses to the Gahini Hospital directory's periodic requests for the surveillance and monitoring information.

Yours sincerely,

Gahini, December 15th,2017

Appendix D Ethics Approval Notice/ Western University

Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Full Board Initial Approval Notice

Principal Investigator: Dr. Rhodri Cusack
Department & Institution: Social Science\Psychology,Western University

Review Type: Full Board
HSREB File Number: 108919
Study Title: Antenatal determination of fetal brain function using audio-motio-tachograph

HSREB Initial Approval Date: April 03, 2017
HSREB Expiry Date: April 03, 2018

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Data Collection Form/Case Report Form	Research team data collection form	2017/01/11
Instruments	PARmed-X for Pregnancy tool AMTG 22MARCH2017	2017/03/22
Advertisement	108919 CusackLabPosterforAMTG clean version march 22nd2017	2017/03/22
Other	108919 script debriefing AMTG march 22 2017	2017/03/22
Letter of Information & Consent	LONDON_LOIANDCONSENT AMTG22MARCH2017 CLEAN VERSION	2017/03/22
Western University Protocol	108919 Clean	2017/03/22

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Western University, Research, Support Services Bldg., Rm. 5150
London, ON, Canada N6G 1G9 t. 519.661.3036 f. 519.850.2466 www.uwo.ca/research/ethics

Curriculum Vitae

Name:	Patrick Gatutsi
Post-secondary Education and Degrees:	University of Rwanda, College of Medicine and Health Sciences Kigali, Rwanda 2010-2015 MBBS
	The University of Western Ontario London, Ontario, Canada 2016-Present M.sc
Honours and Awards:	Queen Elizabeth II Diamond Jubilee Full Scholarship 2016-2018
Related Work Experience	Teaching Assistant The University of Western Ontario 2017