EFFECTS OF FREQUENT PRENATAL ULTRASOUND EXPOSURE ON RABBIT FOETAL GROWTH

BY

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A thesis submitted in fulfilment of the requirement for the degree of Master of Health Sciences (Medical Imaging)

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ABSTRACT

Given the advancement of the technology and the extensive use of ultrasound imaging in obstetric application, there may be an equivalent increase in the concerns pertaining to the potential biological consequences relative to the exposure. Thus, this research is designed to determine the effects arising from frequent prenatal ultrasound exposure on foetal development. This experimental study involved six pregnant rabbits, exposed to different number of ultrasound exposures at three stipulated gestational stages, early, mid, and late gestation. Exposures were performed daily for five days (protocol of five scans) and daily for two days (protocol of two scans). Ultrasound output parameters were kept constant (exposure duration = 10 minutes; frequency = 8.0 MHz; spatial-peak temporal-average intensity (I_{SPTA}) = 0.056 W/cm^2; acoustic output power = 0.06 W; mechanical index (MI) = 0.7). The measurements of foetal bi-parietal diameter (BPD), occipito-frontal diameter (OFD) and femur length (FL) were obtained 12 hours after the last exposure. The experiment was repeated with the same subjects for the next gestational stages. There were significant differences in foetal BPD between groups of different number of ultrasound exposures in early stage of pregnancy ($p < 0.05$), with a negative correlation ($p = 0.02$, $r_s = -0.84$). Number of exposures was found highly related to foetal BPD in early pregnancy ($p = 0.02$, $r^2 = 0.77$). There were also significant differences in foetal OFD between groups of different number of ultrasound exposures in early stage of pregnancy ($p < 0.05$), with a negative correlation ($p = 0.04$, $r_s = -0.72$). Number of exposures was found fairly related to foetal OFD in early pregnancy ($p = 0.04$, $r^2 = 0.64$). Foetal FL also reported significant differences between groups of different number of ultrasound exposures in mid stage of pregnancy ($p < 0.05$), with a negative correlation in both mid and late stages of pregnancy ($p = 0.02$, $r_s = -0.84$; $p = 0.00$, $r_s = -0.96$, respectively). Number of exposures was found highly related to foetal FL in both mid and late stages of pregnancy ($p = 0.02$, $r^2 = 0.78$; $p = 0.01$, $r^2 = 0.83$, respectively). Results suggested that the exposure to frequent prenatal ultrasound might be associated with the effects observed on foetal BPD, OFD and FL, which plausibly cause the incidence of intrauterine growth restriction (IUGR). Further investigation is needed to account for the underlying factors responsible for the observed changes.

خلاصة البحث

رافق التطور التكنولوجي والاستخدام المكثف للتصوير بالموجات فوق الصوتية في الولادة مخاوف متعلقة بالعواقب البيولوجية المحتملة الناشئة من التعرض لهذه الموجات. وبالتالي فقد تم تصميم هذا البحث لتحديد الآثار الناشئة عن التعرض المتكرر للموجات فوق الصوتية قبل الولادة على نمو الجنين. اشتملت هذه الدراسة التجريبية على ستة أرانب حوامل تم تعريضها لكميات مختلفة من الموجات فوق الصوتية في ثلاث مراحل حمل محددة، وهي الحمل المبكر والمتوسط والمتأخر. تم تعريض الأرانب للموجات يوميًا لمدة خمسة أيام (بروتوكول مكون من خمس عمليات مسح) ويوميًا لمدة يومين (بروتوكول مكون من مسحين). كانت مقاييس مخرجات الموجات فوق الصوتية ثابتة على النحو التالي: مدة التعرض=10 دقائق؛ والتردد=8.0 ميجاهرتز؛ وشدة علاقة الذروة الحيزية بالمتوسط الزمني (I_{SPTA})=0.056 واط/سم^2؛ وطاقة المخرجات الصوتية = 0.06 واط ؛ والمؤشر الميكانيكي (MI)=0.7. تم الحصول على قياسات القطر الثنائي الجداري للجنين (BPD) والقطر القذالي الجبهي (OFD) وطول عظم الفخذ (FL) بعد 12 ساعة من التعريض الأخير. تم تكرار التجربة على نفس العينات لمراحل الحمل التالية. كانت هناك فروقا ملحوظة في قياسات BPD الجنينية بين المجموعات المعرضة لكميات مختلفة من الموجات فوق الصوتية في المرحلة المبكرة من الحمل ($p<0.05$) وذلك مع ارتباط سلبي ($p=0.02$، $r_s=-0.84$)، وتم اكتشاف أن كمية التعريض مرتبطة ارتباطا وثيقا بال BPD الجنيني في بداية الحمل ($p=0.02$، $r_s=0.77$). كانت هناك أيضًا فروقا ملحوظة في ال OFD الجنيني بين المجموعات المعرضة لكميات مختلفة من الموجات فوق الصوتية في المرحلة المبكرة من الحمل ($p<0.05$) مع ارتباط سلبي ($p=0.04$، $r_s=-0.72$)، وكانت كمية التعريض مرتبطة إلى حد ما بال OFD الجنيني في بداية الحمل ($p=0.04$، $r_s=0.64$). أظهرت أطوال عظام الفخذ FL الجنيني أيضًا فروقا ملحوظة بين المجموعات المعرضة لكميات مختلفة من الموجات فوق الصوتية في منتصف مرحلة الحمل ($p<0.05$) مع وجود ارتباط سلبي في كل من المراحل المتوسطة ($p=0.02$، $r_s=-0.84$) والمتأخرة من الحمل ($p=0.00$، $r_s=-0.96$). وُجد أن عدد حالات التعريض ارتبطت ارتباطًا وثيقًا بال FL الجنيني في كل من المراحل المتوسطة ($p=0.02$، $r_s=0.78$) والمتأخرة من الحمل ($p=0.01$، $r_s=0.83$). أشارت النتائج إلى أن التعرض المتكرر للموجات فوق الصوتية قبل الولادة قد يكون مرتبطًا بالتأثيرات التي لوحظت على قياسات BPD و OFD و FL الجنينية، والتي قد تسبب بشكل معقول حالات تقييد النمو داخل الرحم (IUGR). هناك حاجة إلى المزيد من التحقيق للأخذ بالعوامل الأساسية المسؤولة عن التغييرات الملاحظة.

APPROVAL PAGE

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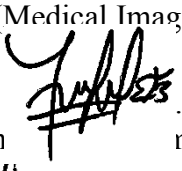

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DECLARATION

I hereby declare that this thesis is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

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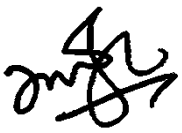
Signature .....  ..... Date .....09/10/2020.....

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Symbols

A	Amplitude
c	Speed of sound
cm	Centimetre
f	Frequency
Hz	Hertz
I	Intensity
I_{SPTA}	Spatial-peak temporal-average intensity
kHz	Kilohertz
MHz	Megahertz
mm	Millimetre
P	Power
r^2	Regression coefficient
r_s	Correlation coefficient
T	Period
Z	Acoustic impedance
ρ	Density of material
λ	Wavelength

LIST OF ABBREVIATIONS

Abbreviations

2D	2-dimensional
3D	3-dimensional
4D	4-dimensional
ACOG	American College of Obstetricians and Gynaecologists
AIUM	American Institute of Ultrasound in Medicine
ALARA	As Low As Reasonably Achievable
ANOVA	One-way Analysis of Variance
B-mode	Brightness mode
BMUS	British Medical Ultrasound Society
BPD	Bi-parietal diameter
DNA	Deoxyribonucleic acid
FDA	Food and Drug Administration
FL	Femur length
GD	Gestational day
HD	High-definition
HIFU	High-intensity focused ultrasound
HIV	Human immunodeficiency virus
HPV	Human papillomaviruses
I-ACUC	International Islamic University Malaysia Animal Care and Use Committee
IBM	International Business Machines Corporation
IIUM	International Islamic University Malaysia
IUGR	Intra-uterine growth restriction
KAHS	Kulliyyah of Allied Health Sciences
LIUS	Low-intensity ultrasound
MI	Mechanical index
MOH	Ministry of Health
NEMA	National Electrical Manufacturers Association
NRCP	National Council on Radiation Protection and Measurements
NZW	New Zealand White
O&G	Obstetrics and Gynaecology
ODS	Output display standard
OEM	Original Equipment Manufacturer
OFD	Occipito-frontal diameter

RIGs	Research Initiative Grants
RMC	Research Management Centre
SEM	Standard error mean
SPSS	Statistical Package for Social Sciences
TI	Thermal index
TPC	Touch, pampers and caress
TVS	Transvaginal sonography
WBC	White blood cell
WFUMB	World Federation of Ultrasound in Medicine and Biology
WHO	World Health Organisation

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND OF THE STUDY

Ultrasonography has become one of the most commonly used imaging procedures in medical practice, particularly in obstetrics and gynaecology (O&G) (Abramowicz et al., 2008) following the invention of ultrasound technology decades ago (Ter Haar, 2011). It began in the 1940s when a neurologist, Theodore Dussik together with his brother had transmitted the ultrasound beam through the human skull in attempts to diagnose brain tumours (Newman & Rozycki, 1998). Ever since Dussik's work, ultrasound has been the key investigation for diagnostic purposes due to the superior clinical benefits it imposes such that it is non-invasive (Hassani, 1974), with real-time imaging capability that is readily accessible at a lower cost (Hides, Richardson, & Jull, 1998).

It was in 1958 that an obstetrician, Ian Donald was acknowledged for his Lancet publication that enclosed the first ultrasound images of a foetus at fourteen weeks of gestation (Donald, Macvicar, & Brown, 1958). Donald contribution by incorporating the method of ultrasound scanning in O&G enabled the health care providers to assess the foetal growth during pregnancy, which then leads to the development of new criteria in diagnosing the early pregnancy (D′Cunha, 2014; Erjavic, 2018).

The enhancement in the quality of ultrasound equipment has relatively improved survival rates by reducing maternal and perinatal mortality (Wiafe, Odoi, & Dassah, 2011). A number of studies have identified that routine foetal examination

with ultrasonography in a low-risk population could detect several structural defects in earlier foetal stage (Chitty, Hunt, Moore, & Lobb, 1991; Eik-Nes, Salvesen, Okland, & Vatten, 2000; Whitworth, Bricker, Neilson, & Dowswell, 2010). Early pregnancy detection using ultrasound is favourable in a way that any congenital malformations or severe uterine abnormalities could be ruled out at the earliest possible time, thereby improving clinical decision making (Saari-Kemppainen, Karjalainen, Ylostalo, & Heinonen, 1990). In the absence of ultrasound imaging, the deformed foetus might unable to survive due to incapability in excluding early pregnancy anomalies, leading to poor pregnancy outcomes such as premature birth, stillbirth, low birth weight, as well as maternal mortality.

While the use of ultrasonography could be of benefit in obtaining a definitive diagnosis of a malformed foetus, it should be noted that the scanning might offer an abortion option to the pregnant mother. This value judgement must be weighed against the potential risks of false-positive morphologic diagnosis of malformation in order to avoid any termination of viable pregnancy. This matter of concern somehow could be alleviated with the revolutionary progress of high-resolution biophysical ultrasound equipment such as transvaginal sonography (TVS) that allowed detailed assessment of early pregnancy, hence reducing false-positive diagnosis while increasing diagnostic accuracy (Al-Memar, Kirk, & Bourne, 2015; Jauniaux, Johns, & Burton, 2005; Kaur & Kaur, 2011).

Advances in ultrasound technology have allowed the development of 3-dimensional (3D) and 4-dimensional (4D) ultrasound where they can easily be used in daily routine prenatal examinations (Merz, 2005). The use of 3D/4D ultrasonography as an adjunct modality to foetal 2-dimensional (2D) ultrasound has resulted in significant progress in the evaluation of foetal facial malformations (Kurjak,

Azumendi, Andonotopo, & Salihagic-Kadic, 2007). One of the recent achievements in 3D/4D ultrasound is the development of high-definition (HD) live ultrasound, which provides a realistic demonstration of foetal appearances such as facial expressions and behaviour (Kurjak, 2017). These technological advancements in ultrasound application enable not only an early congenital anomalies detection, but also a wide range of foetal malformations (Nawapun et al., 2018). By the end of the twentieth centuries, ultrasonography has become indispensable in O&G specialisation due to its extensive application in most hospitals worldwide as a part of routine antenatal care during pregnancy (Campbell, 2013).

Ultrasonography is acknowledged as the gold standard for gestational age dating pregnancies due to its relatively high sensitivity and specificity (Dietz et al., 2007; Macaulay, Buchmann, Dunger, & Norris, 2019). Ultrasound appeared very appealing to expectant parents (Garcia et al., 2002). Pregnant women have generally been found that they enjoyed the use of ultrasound modality for their own reassurance (Bricker et al., 2000; Gudex, Nielsen, & Madsen, 2006) along with the desire to find out the health status and well-being of the baby (Bashour, Hafez, & Abdulsalam, 2005; Ugwu, Osungbade, & Erondu, 2009). These are some of the reasons that encourage pregnant women to obtain repeated prenatal scans that may lead to the increasing demand for commercial ultrasound services among pregnant women (Roberts, Griffiths, Verran, & Ayre, 2015). It should be remembered that wider access to obstetric ultrasound may increase the risk of inappropriate use of such services. Overuse of obstetric ultrasonography especially for commercial interests rather than health benefits is a major concern that should not be ignored.

Nonetheless, even if ultrasound has become the modality of choice for pregnancy examination and proven to offer benefits more than harm, there is always a

need to weigh the perceived benefits obtained against any possible risk. The key point is that, there are options given to pregnant mothers. Most view that experience of having ultrasound examination is one of the gratified parts in the journey of parenthood. Therefore, it is the duty of health practitioners to provide the expectant parents with appropriate information so that they are well-informed before accepting the offer to ultrasound examination. In that context, any "keepsake ultrasound", in which the service is accustomed for non-diagnostic purposes can be avoided.

1.2 STATEMENT OF RESEARCH PROBLEMS

Routine ultrasound refers to the ultrasound examination conducted regularly for every pregnant women in order to ensure the best medical conditions for both mother and foetus throughout pregnancy (Wiafe et al., 2011). Routine obstetric scanning has long been an essential part of routine antenatal care in most developed countries (Garcia et al., 2002). Such practice continues to evolve to become one of the most important growths in obstetric centre worldwide (Gammeltoft & Nguyên, 2007; Vangeenderhuysen, Abdellahi, & Isselmou, 2002). As of 2016, the World Health Organisation (WHO) has recommended a minimum of eight antenatal visits for women with uncomplicated pregnancies (Mchenga, Burger, & Von Fintel, 2019). In Malaysia, it is recommended by the Ministry of Health (MOH) for healthy pregnant women to have seven to ten antenatal visits during pregnancy depending on the gravidity (MOH, 2013). In relation to the recommended visiting schedules, it is important to note that each visits does not necessarily includes prenatal ultrasound examination.

Following the world health antenatal care guidelines, the MOH Malaysia recommends that all pregnant women should have access to first prenatal scan or also

known as dating scan before 24 weeks of pregnancy as a part of antenatal care with the aim to assess the gestational age (MOH, 2013). According to Perinatal Society of Malaysia (1996) in the Guideline on the Use of Ultrasound in Pregnancy, pregnant women should have an ultrasound examination at about 20 weeks of gestation. While the guidelines for dating scan are well-established both globally and locally, the information on how frequently ultrasound examination should be performed during pregnancy remains limited. The term 'frequent' is generally understood to mean something that happens repetitively. It is commonly used in various context to describe the repeated occurrence of an event. In the context of this current study, the term 'frequent' will be used in its broadest sense to refer to multiple ultrasound exposures given prenatally during pregnancy.

As the ultrasound application evolves, concern over the safety, practicality and necessity of frequent ultrasound exposure in pregnancy keep growing. The concern raised regarding frequent exposure of prenatal ultrasound during pregnancy because, with the promising ultrasound techniques and application, parents are more likely to take the examination routinely even without an obvious clinical indication. Studies have been undertaken on account of growing concern to discover the potentially damaging effects of ultrasound exposure. Loads of existing evidences revealed that ultrasound produces biological effects either directly or indirectly, which can cause changes to the tissue exposed (Abramowicz et al., 2008; Izadifar, Babyn, & Chapman, 2017; Newnham et al., 2004; Shankar & Pagel, 2011; Sikov, Collins, & Carr, 1984). However, the evidence supporting studies related to frequent prenatal ultrasound is far from comprehensive. Although studies have recognised the potential biological effects of prenatal ultrasound, research has yet to systematically explore the influence of frequent use of ultrasound on developing foetus. There is a current paucity of high-

quality research specifically relating to frequent prenatal ultrasound exposure.

A randomised controlled study reported that foetus exposed with multiple (five) ultrasound exposures showed an elevation about one third in intra-uterine growth restriction (IUGR) as compared to those exposed with single exposure (Newnham, Evans, Michael, Stanley, & Landau, 1993). However, the incidence of growth restriction was unexplained. The evidence that IUGR is associated with frequent ultrasound exposure is weak and inconclusive. Analysis of newborn biometry on the previous study concluded that, if there is an effect of frequent prenatal ultrasound exposure on foetal IUGR, the mechanism is probably to be the effect on bone development rather than placental insufficiency (Evans, Newnham, Macdonald, & Hall, 1996). Childhood follow-up studies to 8 years of age showed insignificant differences in childhood growth and development suggesting that growth after birth was not affected by frequent ultrasound exposure (Macdonald, Newnham, Gurrin, & Evans, 1996; Newnham et al., 2004).

Even though ultrasound is commonly well-recognised as a safe imaging modality, there is no guarantee of its absolute safety. Just because there is no proof that ultrasound poses any adverse biological effects at diagnostic levels, does not mean that harm is absent. It should be noted though, that the level of awareness and knowledge pertaining potential bio-effects of prenatal ultrasound among health practitioners, by and large, were fairly poor (Bagley, Thomas, & Digiacinto, 2011; Elolemy, Almuwannis, Alamiri, & Alkhudair, 2015; Moderiano, McEvoy, Childs, & Esterman, 2017; Piscaglia et al., 2009; Sheiner & Abramowicz, 2008). Therefore, we cannot disregard the idea that the interaction between ultrasound as a form of energy and biological tissues has the potential to cause damage to living tissues.

1.3 PURPOSE OF THE STUDY

Given the uprising technology of ultrasound machine and the wide services available at both public and private facilities, there may be an equivalent increase in the concerns about the potential biological effects arise from the exposure. Apart from that, there is a big possibility that the number of routine ultrasound practice would also grow in accordance with the increase in the services provided. In response to the predicted possible concern, a study was set up to discover the issue further. This research attempted to investigate the effects arising from prenatal ultrasound exposures given repeatedly to rabbit foetus during pregnancy. To the best of our knowledge, the effects of prenatal ultrasound on foetal biometry have rarely been examined. Thus, the purpose of the present study was to evaluate these effects on biometric measurements in rabbit foetus exposed prenatally to ultrasound. The study employed rabbit as subject due to its ideal characteristic as an animal model in the research of human reproductive system (Fischer, Chavatte-Palmer, Viebahn, Santos, & Duranthon, 2012). The study focused on the changes in the measurements of foetal biometry following frequent ultrasound exposures.

1.4 OBJECTIVES OF THE STUDY

1.4.1 General Objective

The general objective of this study is to determine the effects of frequent prenatal ultrasound exposure on rabbit foetal growth.

1.4.2 Specific Objectives

The specific objectives of this study are:

1. To investigate the effects of frequent prenatal ultrasound exposure on rabbit foetal biometry measurements, specifically in bi-parietal diameter (BPD), occipito-frontal diameter (OFD) and femur length (FL).
2. To evaluate the relationship between frequent prenatal ultrasound exposure and rabbit foetal biometry.

1.5 RESEARCH QUESTIONS

1. Is there any significant change in rabbit foetal biometry when exposed to frequent ultrasound exposure?
2. Is there any relationship between frequent ultrasound exposure and rabbit foetal biometry?

1.6 RESEARCH HYPOTHESES

H1 Frequent prenatal ultrasound exposure has an effect on rabbit foetal bi-parietal diameter (BPD), occipito-frontal diameter (OFD), and femur length (FL).

H2 Frequent prenatal ultrasound exposure is related to the changes in rabbit foetal bi-parietal diameter (BPD), occipito-frontal diameter (OFD), and femur length (FL).

1.7 SIGNIFICANCE OF THE STUDY

This study explored the impact of frequent prenatal ultrasound exposure towards rabbit foetal development. It is important to highlight the safety issues pertaining to prenatal ultrasound owing to the considerable body of literature explaining potential bio-effects of ultrasound to human tissues despite ambiguous evidence of its harmful effects at the diagnostic level. Besides, the practices of its non-medical usage continue to alert caution with the use of ultrasound during pregnancy. This necessitates a thoughtful and up-to-date study regarding the potential risks of having frequent prenatal ultrasound exposure in order to bring out medical benefits higher than potential harm.

1.8 LIMITATIONS OF THE STUDY

There are several important limitations identified in this study. The most important limitation lies in the fact that the source of ultrasound exposure used in this study is limited to the available equipment at the time and setting of the study. Thus, the effects investigated are only depending on the acoustic potency of the equipment,